


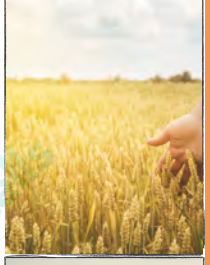


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The body receives almost 100% of the nutrients that are extracted from rye grass pollen. Sold to more than 50 countries on 6 continents around the world for more than 50 years, Swedish researchers have found that research studies. extracted from rye pollen contains Substances that are essential for the creation of new life in the plant family and are fundamental in the food chain. It is a natural anabolic steroid.

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Natural Choice Nutraceuticals

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Our premium natural extracts originate from meticulously selected flower pollen found in "Rye." These extracts undergo a unique proprietary production process crafted by Graminex L.L.C. in Ohio, United States. This exclusive process encompasses every stage, from cultivation and harvesting to the creation of high-quality natural extracts, specifically G60 and G63, derived from GBX flower pollen particles. Graminex holds the sole rights to this process and maintains adherence to strict pharmaceutical production standards in alignment with the World Health Organization's requirements.

Our extracts are renowned for their world-class production standards, boasting ORAC certification for exceptionally high antioxidant concentration and CAP-e Test accreditation, which signifies outstanding absorption into red blood cells. Over more than five decades, we have consistently refined and improved our product's efficacy.

Registered as a "NUTRACEUTICAL" or "nutritional therapy," Pollitin addresses issues at the cellular level, offering antibacterial properties and reinforcing immunity. By delivering essential nutrients tailored to various bodily systems, it equips the body to effectively combat abnormal cells. Our dedication to research is exemplified by over 150 certifications from medical and pharmaceutical institutions.

Moreover, Pollitin is not only a national achievement but a global triumph, available in over 50 countries. Our exclusive patented production process sets us apart as the sole producer of this unique formulation globally, rendering it impossible for anyone else to replicate our success in extracting and utilizing these flower pollen particles.

Pollitin - สารอาหารบำบัดเซลล์อ

สารสกัดธรรมชาติคุณภาพสูง สกัดจากเกสรดอกไม้จาก “ข้าวไรย์” ที่มีสูตรลับเฉพาะของ บริษัท (Graminex L.L.C.) ที่รัฐโอไฮโอ้ ประเทศสหรัฐอเมริกา ในการปลูก เก็บ และผลิตสกัดธรรมชาติคุณภาพสูง G60, G63 จากอณูละอองเกสรดอกไม้ GBX, Graminex® เอกสิทธิ์เฉพาะของบริษัท Graminex เท่านั่นที่ผลิตได้เพียงเจ้าเดียวในโลก อยู่ภายใต้การควบคุมมาตรฐานการผลิตยา ตามข้อกำหนดขององค์การอนามัยโลก

จนเราได้รับการรับรองมาตรฐานการผลิตระดับโลกระดับเดียวกับการผลิตยาเพราะ Pollitin ได้รับรองการทดสอบค่า ORAC หรือ ค่าระดับความเข้มข้นของสารต้านอนุมูลอิสระที่สูงมาก และ CAP-e Test หรือค่าความสามารถในการดูดซึมเข้าสู่เม็ดเลือดแแดงในระดับที่สูงจนได้รับ

การขึ้นทะเบียนเป็น “NUTRACEUTICAL” หรือ “โภชนเภสัช สารอาหารบำบัดระดับเซลล์” ที่สามารถแก้ไขปัญหาฟื้นฟูได้ลึกถึงระดับเซลล์ มีฤทธิ์ฆ่าเชื้อแบคทีเรีย และมีผลเสริมสร้างภูมิต้านทานเมื่อเซลล์ต่างๆ ได้รับสารอาหารที่เหมาะสมตามระบบต่างๆ ในร่างกาย ส่งผลให้ร่างกายสามารถต่อสู้กับ เซลล์ที่ผิดปกติภายในร่างกายได้ถึง 95% และยังได้รับรองมาตรฐานการผลิตและประสิทธิภาพจากองค์กรต่างๆ มากมายระดับโลก รวมไปถึงยังได้รับรางวัลการันตีอีกมากมายจาก เอกสิทธิ์สูตรลับพิเศษเฉพาะของ Graminex ทำให้สินค้ามีคุณภาพและเกิดผลลัพธ์ที่ดีและน่าเชื่อถือ จนได้รับการยอมรับระดับสากลอีกด้วย

ตลอดระยะเวลากว่า 50 ปี เราได้มีการวิจัยพัฒนาประสิทธิภาพอย่างต่อเนื่อง มีการวิจัยจากสถาบันทางการแพทย์และเภสัชกรรมรับรองมากกว่า 150 การวิจัย เรามีความภูมิใจอย่างมากในการเป็นผู้ผลิตหนึ่งเดียวของโลกที่ได้ครอบครอง ถือลิขสิทธิ์เอกสิทธิ์กระบวนการผลิตและสูตรเฉพาะ G60 และ G63 จากละอองเกสรดอกไม้ชนิด GBX ที่ไม่มีใครสามารถทำได้ ส่งผลให้ Pollitin เป็นที่ยอมรับจากคนจำนวนมากใน 6 ทวีป 50 ประเทศทั่วโลก และได้รับผลตอบรับที่ดีจากผู้บริโภคในการซื้อซ้ำสินค้าอย่างต่อเนื่องมากกว่า 50 ปี

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TOPPIC

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Findings on Prostatitis through the "Pollen Extract G63" of Graminex Company

Hiromi Yokoyama Naofumi Suzuki Yoshimi Nishimura
(Kanda New Medical Clinic)

Pollen, containing a rich source of nutrition (amino acids, minerals, and vitamins), represents the emergence of the next generation of plant substances with not yet fully understood hidden action that should not be overlooked. Pollen formulations have been used for the last 35 years in urology (enlargement of the prostate, prostatitis) treatment. This has been administered for a long time with peace of mind and without harmful effects as an alternative to pharmaceuticals for the improvement of both prostatitis and the associated indeterminate complaints. Moreover, this has seen as the welcome birth of supplements in improving associated symptoms. This time, we are reporting on study findings and the improvement effect obtained in the treatment of prostatitis with the supplement pollen extract.

Objective and Method

At this Clinic, 13 patients visiting the clinic for prostatitis treatment agreed to receive administration. The degree of improvement was determined based upon the IPSS score (International Prostate Symptom Score). The period of administration was from 1 month to three months. The pollen extract used in the trial was produced by Graminex Company in Ohio, USA from the pollen of raw materials such as rye, corn, and timothy hay (referred to as Phlegm pratense in Japan) which were cultivated without using agrochemicals or genetically modified varieties. However, a slight amount of pollen from timothy weeds (referred to as Phleum pratense in Japan) was also included. The pollen which has a double hull is not digested or absorbed even when ingested since it has strong resistance to acid and heat (cannot be destroyed even at 300°C).Graminex Company using a special technology is able to separately extract G60 (water soluble nutrition component) and GFX (lipid soluble component) and we received the product G63 which is a 20:1 combination of G60 and GFX. The dosage was 6 tablets per day; three tablets each after breakfast and dinner. One 250 mg tablet contains 62.5 mg of pollen extract. (The daily quantity .... 375mg as pollen extract)

Results

The trial study was stopped for 2 subjects among the 13 participants (one subject was stopped because his PSA value had increased prior to the start of administration and one was stopped because he was taking Gaster for epigastric distress before administration started but symptoms did not improve), and one other subject was eliminated from the effect determination since the IPSS was not filled in after administration.

Graminex Prostatitis Therapy Trials ... Prostatitis

Name	Age	Progress	IPSS	Perineal pain	Erection Ejaculation Difficult	Pain during urination	Change
S. K	56	Before	25	None	None	None	
		After 1 month	24	None	None	None	Morning erections increased.
S. T	73	Before	17	None	None	None	

		After 1 month	13	None	None	None	
I. Y	74	Before	12	None	occasionally	occasionally	
		With PSA - Therapy Trial stopped No related cause					
O. T	65	Before	8				
		After 3 months	3				Painful urination improved, did not have to go to the toilet at night
N. K	57	Before	11	None	Always	None	
		After 1 month	11	None	at times	None	Nocturia (night urination) (3~4 times)
		After 2 months	6	None	None	None	Nocturia (night urination) (2~3 times)
		After 3 months	9	None	None	None	Daytime urination, urinate freely
I. T	62	Before	10	pain at times	occasionally difficult	None	
		After 1 month	8	pain at times	occasionally difficult	None	A little improvement of perineal pain
		After 3 months	8	pain at times Difficult	occasionally	None	No particular change In symptoms, Watching the drop of of PSA
M. T	73	Before	18	None	None	None	
		After 1 month	14	None	None	None	
		After 3 months	14	None	None	None	
S. I	68	Before	7	None	None	None	
		After 1 month	5	None	None	None	Urination
S. M	61	Before	27				
		After 1 month		No IPPS record			improved a little,
T. M	71	Before	17	None	No Erection	None	Concomitant administration of Gastar (20)
				Reverse flow			Related cause unknown
U. T	62	Before	_ _ _	None	None	None	
		After 1 month	14	at times painful, At times difficult		None	
M. H	74	Before	15	None	None	None	
		After 1 month	6	None	None	None	rather improved
S. T	71	Before	24	None	always difficult	pain at times	
		After 1 month	17	None	difficult at times	pain at times	Pain is improving

Conclusion

The Average subject age was 66.1 ± 5.7, and 9 out of 10 patients saw improvement with a drop in IPSS score. The average IPSS was 15 before and administration, dropping to an IPSS average of 11 after administration. Additionally, improved patients evidenced an improving trend in their symptoms of perineal pain, erection, ejaculation difficulty, and pain during urination.

Discussion

Reshaping of the inflamed portion becomes necessary in the case of bacterial and non-bacterial inflammation of the prostrate occurring. Pollen extract makes possible rapid recovery since it contains plentiful amino acids and co-enzymes that work with the vitamins and mineral which are required for the repair of cells. Additionally, it is can be considered that the prostrate function also recovers since the zinc and selenium which are necessary for the Prostrate are also included in the extract.

Safety

There was an example of the medical trial being stopped for 2 subjects. As previously mentioned, the trial was stopped because of the high PSA

value and treatment was changed to another method. And, the other case was stopped because Gaster was taken for epigastric distress before administration started but symptoms did not improve. Based upon examination by stomach camera, reflux esophagitis and erosive gastritis were evidenced and a causal relationship with pollen extract could not be recognized.

There were no other symptoms of particular note and this supplement can be administered long term with peace of mind.

7/29/2005

Clinical evaluation of Cernilton in benign prostatic hypertrophy

Hayashi J, Mitsui H, Yamakawa G, Suga A, Kai A, Shimabukuro T, Yanagi K, Fujisawa S, Takihara H, Kaneda Y, et al

Twenty patients with benign prostatic hypertrophy were treated with Cernilton, 6 tablets a day for an average of 13.2 weeks. Subjective effectiveness was observed in the improvement of sense of residual urine (92%), retardation (86%), night frequency (85%), strain on urination (56%), protraction (53%) and forceless urinary stream (53%). The overall subjective effectiveness was 80% of patients, and the overall objective effectiveness was 54% of patients. Night frequency, residual urine volume and tidal urine volume were improved significantly. The overall effectiveness was 80%. No side effects were observed.

PMID: 2421560, UI: 86183472
Hinyokika Kiyo 1986 Jan;32(1):135-41

Clinical evaluation of cernilton in the treatment of the benign prostatic hypertrophy

Horii A, Iwai S, Maekawa M, Tsujita M

Cernilton was given clinically to 30 patients with benign prostatic hypertrophy. Cernilton was given orally at least for 12 weeks at a daily dose of 6 tablets in three divided doses. The overall clinical efficacy on subjective symptoms was 80%, and that on objective signs, 43%. During the administration period of Cernilton, no serious untoward effects were observed in either the clinical or laboratory findings. It is, therefore, suggested that, from the clinical point of view, Cernilton is a useful and safe drug in the treatment of benign prostatic hypertrophy.

PMID: 2412423, UI: 85303710

Hinyokika Kiyo 1985 Apr;31(4):739-46

Graminex® Flower Pollen Extract™ - A microbiological digest

We often speak of Graminex® Flower Pollen Extract™ as a microbiological digest, and therefore it may be appropriate to explain what this expression means.

As you already know Graminex® Flower Pollen Extract™ is produced by extraction from the raw-material pollen using a non solvent manufacturing process. Graminex is currently the only manufacturer using non solvent technology to produce Flower Pollen Extracts eliminating residual solvents in the final product.

Hereby only type-pure pollen is used. Before the extraction it has been stabilized and purified through a special treatment. A number of selected plants give their pollen to the production of different Graminex® extracts. These plants have been chosen after acute dermal, oral and genetic toxicology assay were completed.

The extraction of the pollen grains presents certain problems. Each grain is a biological unit with a complete set of different substances necessary for the creation of new life. These substances are well protected by the sheath, which is very resistant and can stay unchanged for thousands of years even if the grains have fallen unprotected on the ground. However, the sheath is provided with hilums, germinal openings, covered by a membrane, which can be dissolved.

The non solvent extraction method used by Graminex can easiest be described as follows. After having removed the membrane with a proprietary process using no solvents, the content of the grains is flushed out through the hilums. The husks are then removed. This is done so carefully that the extract is never heated to more than 400C. The extract received is called Graminex® Flower Pollen Extract™. Through this treatment such substances that are toxic or harmful, e.g. allergens and other high-molecular substances, are broken down .and eliminated Therefore, as a rule, our products can be used also by people otherwise allergic or hypersensitive to pollen.

During the processing high-molecular substances, that are difficult to absorb and often irritating, are reduced to low-molecular substances, i.e. each molecule contains less atoms, e.g. protein is reduced to peptides and amino acids. These low - molecular substances are harmless and can quickly be absorbed in the blood so that the body immediately can benefit by them. This is the reason for the quick effect of the Graminex® preparations and also an explanation to the fact that relatively small amounts are needed for a good effect.

Almost nothing gets lost, but the whole amount of Graminex® Flower Pollen Extract™ is active as distinguished from usual foodstuff or Synthetic substances of a more complicated composition. In those cases the body can sometimes have difficulties to utilize the substances, e.g. calcium and vitamin preparations. Even if large quantities are supplied, the body can have difficulties in utilizing necessary substances.

Some of the conditions determinative for the body's ability to utilize different substances are known. Thus, already more than 100 years ago, Justus von Liebig could phrase his classic "Minimum Law" in which he pronounced that very often a substance, from which is added too little, can be determining for how all added nourishment is absorbed. Thus it is possible to increase the body's ability to utilize supplied nourishment by providing for the body reasonable demands for nutrient substances of different kinds.
This can, however, many times be difficult, as we are creatures of habit and prefer to eat what we like, even if we thereby perhaps miss some substances that our body really need.

By a daily supply of Graminex® Flower Pollen Extract™ in PollenAid™ or any of the Graminex products, the body gets guaranteed all the substances necessary for life and it will also be possible for the body to

utilize all nourishment in the food. The body can, thanks to Graminex® Flower Pollen Extract™, utilize vitamins and other important substances present in the daily food. In this way Graminex® Flower Pollen Extract™ normalizes the functions of the body and increases health and resistance against diseases.

Identification of a Prostate Inhibitory Substance in a Pollen Extract

Fouad K. Habib, Margaret Ross, Ari Lewenstein, Xin Zhang, and Jean Claude Jaton
University Department of Surgery, Western General Hospital, Edinburgh, Scotland (FKH., M.R.); Cernitin SA, Lugano, Switzerland (A.L.); and Department of Medical Biochemistry, University of Geneva, Switzerland (X.Z., J.C.J.)

ABSTRACT: Recently, much attention has focused on the treatment of BPH with the pollen extract, Cernilton. The present investigation was designed to identify the active component in this agent which might be responsible for the symptomatic relief of BPH as previously reported [1,2]. Sequential purification of the active component present in the pollen extract was carried out by a combination of dialysis, gel filtration, and reverse phase chromatography. To monitor the biological activity of each of the purified fractions, a biological assay employing the human prostate cancer cell line DU145 was undertaken.

While we have identified a number of constituent components in the pollen extract, only one fraction designated V-7 (FV-7) maintained a strong inhibitory effect on the growth of DU145 cells. The inhibition was time- and dose-dependent, and the concentrations of FV-7 required to reduce the cell numbers by 50% (IC_{50}) after 2 days of exposure was 5 µg/ml. FV-7 was also inhibitory towards the primary culture of prostate stroma and epithelial cells, with the stroma/fibroblast showing greater sensitivity towards the HPLC-purified component. However, it should be noted that this inhibitory activity measured in the primary culture cells was only achieved at higher concentrations of FV-7. Preliminary characterization of the active ingredient identified FV-7 as DIBOA which is a cyclic hydroxamic acid. FV-7 and DIBOA induce similar inhibitory effects on the growth of DU145 cells.

KEY WORDS: BPH, primary culture, Cernilton, fraction V-7, DIBOA

INTRODUCTION

Attention has recently focues on an extract from rye pollen which was found to be most effective in the treatment of prostate diseases with no untoward side effects [1-3]. The pollen extract know as “Cernitin” is obtained by microbial digestion of the pollen followed by extraction with water and an organic solvent in a two-step process. Two fractions are consequently obtained: “T-60,” containing the water-soluble substances and accounting for more than 80% of the total extracted material and “GBX,” containing the fat-soluble substances. The two fraction T-60 and GBX are mixed in the final product designated “Cerniton” in a ration of 20:1 respectively.

Earlier studies on the water-soluble fraction, T-60, have shown that T-60 was inhibiting the growth of prostate cancer cell lines and primary cutlures from BPH specimens [4,5]. In the primary cultures, the inhibition was time- and concentraction-dependent, with the fibroblast stomal component showing greater sensitivity to the pollen extract than the epithelial cells derived from the same BPH tissue [5].

The results from the in vitro studies seem to be backed up by pharmacological and clinical data. Pharmacological investigations have demonstrated a significant reduction ($P<0.05$) in the ventral and dorsal lobes of rat prostates after Cernitin was administered orally for 21 days [6]. Furthermore, in a double-blind placebo-controlled study, there was a significant decrease in residual urine in patients with Cernilton ($P<0.025$) and in the antero-posterior and transverse diameters of the prostate on ultrasound ($P<0.025$) following 6 months’ treatment [2].

In an attempt to identify the growth inhibiting factor in T-60, fractionation was carried out

employing gel filtration and reverse phase chromatography. The eluted fractions were subsequently tested for their inhibiting effects on the prostate cancer cell line (DU145), and the active fractions singled out for further characterization and comparison with a known synthetic compound. Finally, the biological activity of the identified active substance was tested in primary cultures from BPH specimens.

MATERIALS AND METHODS

Chemicals and Purification Procedures

Cernitin T-60 was a gift from Cernitin SA, Lugano, Switzerland. The purification of the active compound present in T-60 was carried out by a combination of dialysis, gel filtration, and reverse phase chromatography steps. Details of the fractionation steps and of the chemical properties of the constituent product are the subject of a separate report [7; manuscript in preparation]. However, a brief summary of the strategy used is outlined in Figure 1. The synthesis of the active DIBOA compound was carried out by Professor U. Burger, Department of Organic Chemistry, University of Geneva, as detailed previously [8].

Cell Culture

To monitor and evaluate the biological activity of each of the purified fractions detailed in Figure 1, a biological assay employing the human prostate cancer cell line DU145 [9] was undertaken. This was based on the earlier experiments which demonstrated an inhibition in DU145 growth following exposure to the pollen extract [4]. The conditions employed for the growth of these cells have previously been described [4,10,11].

Primary Culture of Prostate Epithelial and Fibroblast Cells

Human BPH epithelial and fibroblast cells were cultured from prostate chips removed by transurethral resection. The epithelial and fibroblast cells were released from prostate tissue following overnight digestion in collagenase solution (600 IU/ml in 5% FCS RPMI 1640), and sub- and primary cultures were grown by plating onto plastic culture flasks and incubated at 37°C in a 95% air and 5% CO_2-humdified atmosphere. By using this system it was possible to establish and serially culture pure populations of both epithelial and fibroblast cells in well-defined media as detailed previously [5,12,13]. Verification of the cultures as prostatic fibroblast and epithelial cells has been confirmed by immunocytochemical staining employing a variety of antibodies, and also by phase contrast microscopy as described in our earlier work [5].

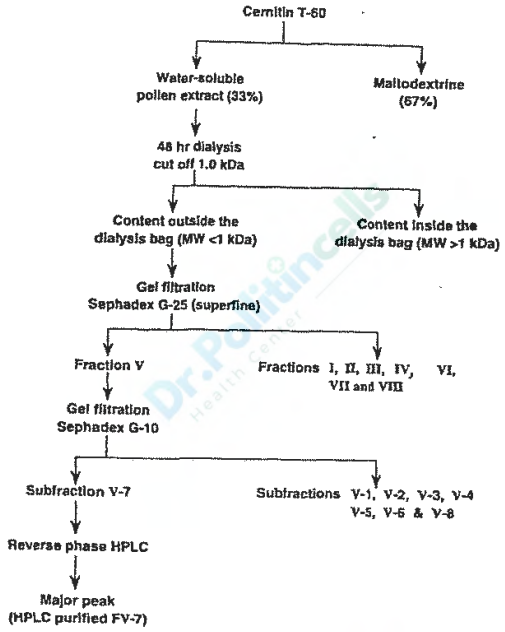


Fig. 1. Details of the fractionation steps and the strategy employed to isolate and purify the active ingredients in Cernitin T-60.

Cell Growth and Thymidine Incorporation

Cell growth was monitored using thymidine incorporation, backed up well cell counting using the trypan blue exclusion method. Confluent DU145 as well as stroma and epithelial cells from 75-cm^2 tissue culture flasks were harvested and plated at a density of 1.5 x 10^3 cells/well in 96-well plates. After plating the cells, the Cernitin fractions (1-100 µg/ml) were added for periods of up to 6 days, with media changes on day 3; control wells received no pollen extract fractions. Following the incubation, cells were plated with thymidine and harvested, and radioactivity was counted as published previously [5,10,11]. The patterns obtained were also confirmed by cell count using the trypan blue exclusion method. In parallel experiments, the activity of the synthetic DIBOA compound was tested for its effects on the growth of DU145 cells and compared to the activity of the natural component isolated from Cernitin T-60.

Statistical Analysis

Differences between control and test groups were examined for statistical significance by Student's *t* test.

RESULTS

Localization of the Active Ingredients in Cernitin T-60

At each step of the purification procedure (Fig. 1), aliquots of the fractionated substances were removed and tested for their DU145 inhibitory activity. Dialysis of the water-soluble component demonstrated that the activity was merely confined to the diffusate with an apparent molecular weight < 1 kD; the inert dialysate was therefore discarded. The diffusate was subsequently lyophilized and chromatographed one G-25 column yielding eight well-resolved fractions, of which only fraction V (FV) exhibited potent inhibitory activity (Fig. 2; Table 1). FV was, in turn, eluted on a G-10 chromatography column resulting in eight subfractions of which only subfraction 7 (FV-7) manifested a significant inhibitory activity towards the DU145 cells (Fig. 3; Table 1). Further purification of subfraction FV-7 was carried out on a reverse-phase high-performance chromatography column resulting in one major peak which was strongly inhibitory towards DU145 cells (Fig. 4). This peak accounted for approximately 90% of the material loaded on the HPLC column [7].

The biological potency of each of the active fractions was compared to the starting T-60 material, and the IC50 for each fraction was determined (Table 1). It is apparent from the data in Table 1 that the potency of the active substances increases markedly with each purification step, yielding a final product (FV-7) which is roughly 200 times more active than the starting T-60 product, and showing inhibitory activity at concentrations as low as 5 µg.ml (Table 1).

Effect of Fraction FV-7 on DU145

The results depicted in Figure 4 demonstrate the impact of increasing concentrations of FV-7 (Fig. 4a) and DIBOA (Fig, 4b.) on the growth of DU145 cells at different days of incubation. While both FV-7 and DIBOA at 1µg/ml demonstrated no effect on cell growth, increasing the concentration of either FV-7 or DIBOA to 10 µg/ml induced a strong inhibitory effect which was significantly different from control values ($P<0.001$) even after one day of exposure to either compound. However, the inhibitory activity of the natural product at 10 µg/ml appeared to be slightly more potent than that of the synthetic compound. Futher incubation of the cells for longer periods and/or with higher concentrations of the extract totally inhibited growth and depleted cell numbers.

Effects of Fraction FV-7 on Primary Culture of Prostate Epithelia and Fibroblast Cells

In addition to the studies on DU145, we have also examined the impact of the HPLC-purified FV-7 at various concentrations on the growth of primary culture of prostate epithelial and fibroblast cells obtained from patients with BPH. These studies were carried out over a period of 6 days.

The results depicted in Figure 5a,b demonstrate that FV-7 maintains a time- and concentration-dependent effect on both stroma and epithelial cells. At concentrations of 1 µg/ml, FV-7 stimulated DNA synthesis in the epithelial cells, including a 300% increase in thymidine incorporation ($P<0.001$) after 5 days' exposure. However, a dose-dependent decrease in DNA synthesis was also noted with concentrations >1 µg/ml. This was particularly evident in FV-7 at concentrations of 100 µg/ml, with the inhibition of the epithelial cells increasing with time of exposure and demonstrating an 80% inhibition following 4 days' treatment ($P<0.001$).

Experiments with primary culture of fibroblast cells yielded similar results to those described for the epithelium. Initially at a low concentration of FV-7 (1 µg/ml), the fibroblast cells were stimulated and thymidine incorporation increase by 90% after 5 days; treatment ($P<0.001$). However, at concentrations >10 µg/ml, FV-7 inhibited the growth of the fibroblast cells, with maximum inhibition being reached after 4 days' exposure.

DISCUSSION

The commercial preparation, Cernilton, contains a pollen extract of which the water-soluble fraction, designated Cernitin T-60, is exceeding heterogeneous and comprises mainly low

TABLE I. Identification of the Biologically Active Products in Cernitin T-60 Following Fractionation

Method for fractionation	Active fraction[a]	Weight of active fraction (% of T-60)	IC_{50}[b]
Initial product	T-60	100	1.0 mg/ml
Dialysis (cut off <1 kD)	Diffusate	60	0.8 mg/ml
Sephadex G-25	Fraction V	3.6	100 µg/ml
Sephadex G-10	Fraction V-7	0.3	10 µg/ml
Reverse phase HPLC	Fraction V-7 (HPLC-purified)	0.2	5 µg/ml

[a]As monitored by the DU145 cell proliferation test.
[b]Concentrations of active ingredient causing 50% growth inhibition of DU145 after two days of exposure.

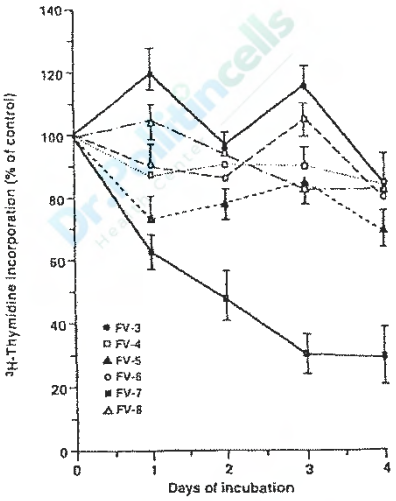


Fig. 3. Growth of the androgen-insensitive DU145 human prostate cell line following treatment with subfractions of FV (100 µg/ml). Experiments were carried for periods of up to four days, and the results are expressed as the percentage of ^3H thymidine incorporated relative to the untreated control. Each point is the mean of three separate experiments, each run eight times. Bars represent coefficient of variation.

molecular weight components, most of which have not yet been identified. All of the biological investigations to date have been conducted using the whole unfractionated Cernitin T-60 extract. This extract was recently reported to inhibit in vitro the growth of various prostatic cancer cell lines and primary cultures of fibroblast and epithelial cells [4-5]. The main objective of the present investigation was to extend those studies by identifying the active agent(s) present in the pollen extract, and to investigate the biological activity of the pure substance(s).

The strategy of combining the biological assays with the fractionation techniques enabled us to pinpoint the precise component responsible for inhibiting the prostate growth in vitro. The fraction designated FV-7 was shown to be inhibitory at a concentration as low as 5 µg/ml, and this is closely comparable to the concentrations of most other drugs used in in vitro assays. It was also of interest to note that FV-7 accounts for only 0.3% (w/w) of the total T-60 pollen extract, a value based on the combined material recovered from all fractions following the initial lyophilization. However, because of the losses incurred after every fractionation step, estimated at around 30% for each of the gel permeation chromatography and HPLC steps, it would be more realistic to assume that the concentration of FV-7 in the whole pollen extract may be close to 1% (w/w). Such a percentage is compatible with the growth inhibition data obtained with T-60 where inhibition >50% was recorded in the presence of 1 mg/ml of the original material [4].

The inhibitory effects of FV-7 on prostatic tumor cell growth appear to be dose- and time-dependent. After the initial exposure to FV-7, DU145 cells stop growing and dividing, an effect which can persist for at least nine days. Following reverse-phase HPLC, purified FV-7 at concentrations as low as 10 µg/ml induced significant inhibition of the DU145 cells, even after two days' exposure. The structure of FV-7 has been elucidated by mass spectrometry and nuclear magnetic resonance. The bulk of FV-7 (over 95%) was identified as DIBOA (2,4-dihyroxy-2H-1,4-benzoxazine-3(4H)-one; Fig. 6), a cyclic hydroxamic acid [7] which was originally found in most members of the Gramineae family of plants [14]. Up to now, the physiological properties of DIBOA had not been clearly elucidated, although its role as a phytotoxic agent has been suggested [15,16]. Furthermore, several laboratories have evaluated the antitumor activity of hydroxamic acid. It has

been shown that these may act as inhibitors of ribonucleotide reductase activity [17-19], but whether this is their mode of action in the human prostate still remains to be established. However, it was interesting to note that the inhibitory activities of FV-7 towards the prostate DU145 cells mimicked those of the synthetic DIBOA.

Although the usage of immortal cell lines has been most helpful in identifying the active inhibitory agent in the Cernitin T-60, their use is somewhat limited because of: a) the neoplastic nature of the continuous cells, while Cernilton is prescribed purely for BPH [3]; b) immortal cell lines are identical clones and do not therefore take account of the morphological heterogeneity of the prostate [20]; and c) continuous cell lines may undergo phenotypic changes and this might render them distinctive from the cells of origin [21]. In view of these limitations, we have decided to continue our work with the HPLC-purified Cernitin T-60 subfraction FV-7, employing the well-established primary cultures of epithelial and fibroblast cells form human hyperplastic prostates [5,12-13]. Those studies were facilitated by our abilities to establish and serially culture pure populations of epithelial and fibroblast cells in a well-defined serum-free medium [5].

The results outlines in this manuscript demonstrate that the HPLC-purified subfraction FV-7 acts on both epithelial and stromal cells in a dose-dependent fashion. At low concentrations, we have observed a stimulatory

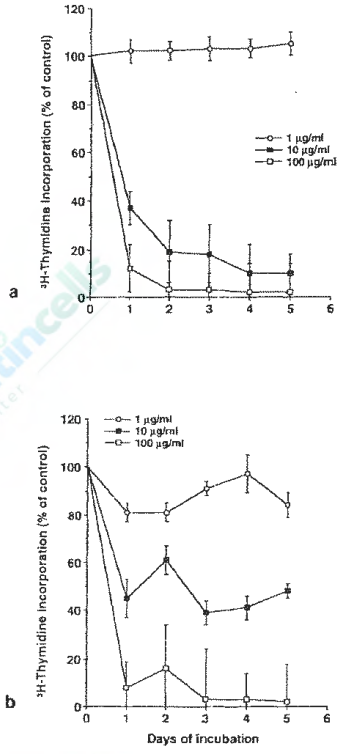


Fig. 4. The effect of time of exposure (1–6 days) to FV-7 (HPLC-purified, 1–100 µg/ml, **a**) and DIBOA (1–100 µg/ml, b) on DNA synthesis in the androgen-insensitive *DU145* prostate cell line. The data are expressed as percent of ^{3}H-thymidine incorporation relative to the untreated control. Each point represents the mean of three separate experiments, each run eight times. Bars represent coefficient of variation.

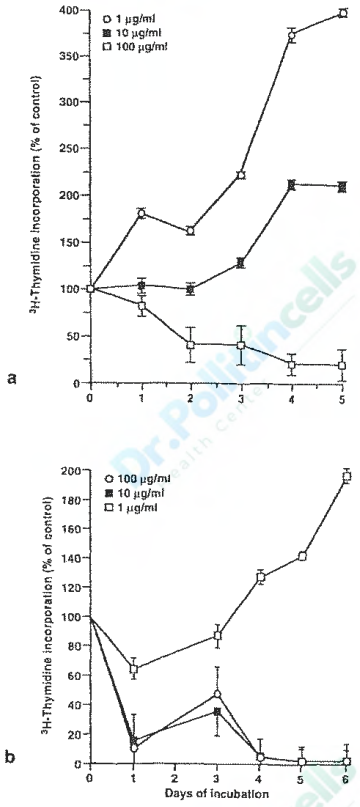
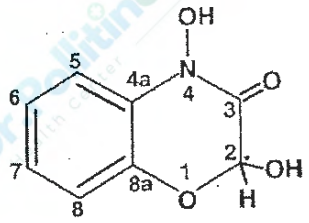


Fig. 5. The effect of HPLC-purified FV-7 at various concentrations on the cell growth of primary culture of epithelial **(a)** and fibroblast **(b)** cells. The data is normalized relative to the untreated control (100%), and each point represents the mean of three separate experiments, each run eight times. Bars represent coefficient of variation.



DIBOA

Fig. 6. The structure and formula of DIBOA (2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one).

effect, but this is totally reserved at higher concentrations when the active factor induces an inhibitory effect on both cell types. The reasons for the initial stimulation of DNA synthesis at the lower doses of FV-7 (<1 µg/ml) is not very clear, but it is significant that similar patterns have been observed with other herbal medicines [22] and may be related to an increase in cells in the A_0 or D_3 regions of the cell cycle [23] at the lower doses of FV-7. Additional studies are currently underway to elucidate the exact mechanism(s) responsible for this phenomenon. However, the stroma cells appear to be far more sensitive to exposure to this factor than the epithelium, which requires 10 times the concentrations of FV-7 to induce a comparable inhibitory effect. Since the human BPH is predominantly a stromal hyperplasia, the greater susceptibility of the stromal component to the Cernitin factor highlights the potential usefulness of this drug in the management of BPH. Efforts are now directed at identifying its mode of action and at the possibility that this is mediated via growth factors known to induce BPH pathogenesis [24].

ACKNOWLEDGEMENTS

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Clinical effect of Cernilton in chronic prostatitis

Suzuki T, Kurokawa K, Mashimo T, Takezawa Y, Kobayshi D, Kawashima K, Totsuka Y, Shiono A, Imai K, Yamanaka H

Twenty-five patients with chronic prostatitis were given Cernilton tablets. Improvement of subjective symptoms and objective findings was noted in 96.0% and 76.0% of the cases. Sonographic findings in the prostate showed 33-100% improvement in four objective items. No side effects were observed in any case after Cernilton medication. Cernilton was judged to be an effective drug for chronic prostatitis

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In vitro Evaluation of the Pollen Extract, Cernitin T-60, in the Regulation of Prostate Cell Growth

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Summary—Nine human-derived cancer and non-cancer continuous cell lines were employed to evaluate the relative *in vitro* activity of the pollen extract, Cernitin T-60. Responses of the cell lines to the drug were assessed by measuring growth and cell survival as determined by cell count. The results demonstrated that of the 9 continuous cell lines tested, only those derived from the human prostate were growth inhibited by the pollen extract, whereas the non-prostate derived cells exhibited variable degrees of resistance to the T-60. The selectivity of the drug for the prostate cell lines was even more pronounced in the hormone- independent models, suggesting that there might be a place for the pollen extract in the control of abnormal growth in hormone-insensitive cells.

In spite of the considerable advances in our understanding of the processes leading to the growth and proliferation of the human prostate, the management of prostate diseases still remains a major clinical problem (Chisholm, 1989). Cancer of the prostate is the second most common cause of death due to cancer in males in the United Kingdom (Cancer Research Campaign, Factsheet 10.1, 1988) and the death rate is increasing. Clearly, the traditional forms of treatment such as surgery at the primary site, orchiectomy, hormone treatment and radiation are not as effective as Huggins might have originally perceived (Huggins and Hodges, 1941) and there is now every reason to find an alternative form of treatment.

Recently, there have been several reports suggesting that the pollen extract, Cernilton, is an effective agent in the treatment of prostate disease (Ito *et al*., 1986; *Buck et al.,* 1989). The pollen extract is a preparation produced by AB Cernelle in Sweden and is essentially a microbial digestion of a mixture of pollens which have been extracted first in water and subsequently with an organic solvent (Kimura *et al*., 1986).

In an attempt to assess the selectivity and specificity of these pollen extracts, we undertook a number of experiments to compare the *in vitro* activity of Cernilton towards a wide range of human-derived cancerous and non-cancerous continuous cell lines of prostate and non-prostate origin. We confined our experiments to the water soluble fraction T-60 component, which, accounts for approximately 60% of the pollen extract. In addition, we also undertook a few experiments on benign hyperplastic prostates to test the impact of the pollen extract on testosterone metabolism and the binding of androgens to their receptors.

Materials and Methods

Chemicals
Cernitin T-60 was a gift from AB Cernelle, Helisingborg, Sweden.

Tissues
Specimens of benign prostatic hyperplasia (BPH), obtained by transurethral resection, were transferred to the laboratory and either used immediately or snap frozen in liquid nitrogen and stored at -70° C.

Cell cultures
The epithelial and fibroblastic cell lines were all derived from human cancerous and non-cancerous tissue and details of their sources are given in Table 1. Of the 3 human prostate

cancer cell lines investigated, the LNCaP model is the only one which is hormonally responsive (Horosewicz *et al*., 1983), whereas the other 2 cell lines, the DU145 (Stone *et al.,* 1978) and the 1013L (Williams, 1980) were all hormone-insensitive. All cell lines were maintained at 37° C under a humidified atmosphere at 5% CO_2 and 95% air in 75cm^2 tissue culture flasks (Corning, New York, USA). The culture medium used was RPMI-1640 (Gibco, Paisley) supplemented with 10% (v/v) fetal calf serum, 20 mM HEPES, penicillin (100 units/ml), streptomycin (100 µg/ml) and 1% (v/v) L-glutamine. At each transplant, cells from the confluent monolayer were removed by trysinisation (trypsin 0.05%, EDTA 0.025%, Gibco) and suspended at 5x10^4 cells/ml in the growth medium.

Growth assays

Dose-response curves of Cernitin T-60 treatment were determined using the following method. Triplicate determinations for each treatment were performed in 24 well culture plates (Cell-Cult, Sterilin, Teddington). Each well was seeded with 5x10^4 cells and incubated overnight in the medium under incubation conditions as described above for routine cell culture. The following day, the T-60 stock solution was serially diluted in supplemented RPMI 1640 medium to yield concentrations of 1-4 mg/ml. Controlled cultures receive medium alone. For the dose-response curve studies, the cells were exposed to Cernitin T-60 for a total period of 4 days, with changes of freshly diluted T-60 in medium every 2 days. For the time course study, cells were treated in the presence and absence of T-60 for 1, 2, 3, or 4 days. Experiments were terminated by the removal of cells from the monolayer by 2 successive trypsinisations and the pellets of harvested cells were subsequently suspended in 0.5 ml of Dulbecco A Medium (Oxoid Ltd, Basingstoke). The counting of cells was achieved on a haemocytometer slide after a 1-2 dilution with trypsin/ glutamine.

Nuclear androgen receptors

Method used for the preparation of nuclear fractions and measurements of androgen receptors followed those previously published (Habib *et al*., 1986). For androgen receptor determinations, the competition binding assay was with 17α-methyl-^{3}H-methyltrienolone (R1881) in the presence of triamcinolone acetonide. Dissociation constants (Kd) and number of binding sites were determined by the Scatchard (1949) method.

Assay for 5a -reductase activity

5α-reductase was assayed at 37° C by following the conversion of (^{3}H) testosterone to (^{3}H) dihydrotestosterone and (^{3}H) 3α)β) androstanediol as previously detailed Habib *et al*., 1985).

Results

The effect of T-60 on cell growth

Proliferation curves of the hormone-sensitive and hormone-insensitive prostate cell lines in

Table 1 Details of Cell Lines

Cell line	*Tumour type*	*Source*	*Cell/well*	*Duration of drug exposure (days)*
HEP	Cancer of the larynx	Gifts from Dr Mary Norval, University Medical School, Edinburgh	5×10^4	1–4
CHANG	Cancer of the liver		5×10^4	1–4
HEF	Human embryo fibroblast		5×10^4	1–4
RT112	Cancer of the bladder	Dr J. R. W. Masters, Department of Pathology, St Paul's Hospital, London	5×10^4	1–4
SUZA	Cancer of the testis		5×10^4	1–4
DU145	Cancer of the prostate	Gifts from Dr D. Mickey, Department of Urologic Research, University of North Carolina, USA	5×10^4	1–4
1013L	Cancer of the prostate		5×10^4	1–4
LNCaP	Cancer of the prostate	Gift from Dr J. S. Horoszewicz, Department of Medical Virology and Oncology, Roswell Park Memorial Hospital, Buffalo, USA	5×10^4	1–4
MCF-7	Cancer of the breast	Gift from Dr W. R. Miller, Department of Clinical Surgery, University Medical School, Edinburgh	5×10^4	1–4

the absence and presence of increasing concentrations of T-60 for periods of up to 4 days are shown in Figure 1. Although the growth of each of these prostate cell lines was slowed following the addition of the pollen extract, the results show that the inhibition was much more marked in the case of the androgen-insensitive cell lines. Indeed, at 1mg/ml the pollen had no effect on the growth of the LNCaP cells, which exhibited an identical profile to that of the control, whereas the androgen-insensitive 1013L and DU145 cells demonstrated significant inhibition, particularly on day 4. By contrast, at the higher pollen concentrations (4mg/ml) the growth of all 3 prostate cell lines was arrested and the cell numbers were rapidly depleted with the time of exposure. After 4 days, cell counts had been reduced by an average of 94% compared with controls.

Parallel experiments on the non-prostate derived cell lines showed no response to pollen extract (1mg/ml) even after 4 days' exposure (Fig. 2). However, at the higher concentrations (4mg/ml) the pollen induced some inhibition with the HEF and RT112 cells ($P < 0.01$) following a 4-day incubation (Fig. 2), although this was not as marked as in the prostate cells. Significantly, none of the other non-prostate derived cells showed any significant response ($P > 0.5$).

The effect of T-60 on androgen metabolism and steroid receptors

We also tested the impact of increasing concentrations of Cernitin T-60 (0-10mg/ml) on the 5α-reductase activity of tissue obtained from 6 separate BPH patients. As demonstrated in Table 2, there was no change in the activity of the enzyme with increase in T-60 even at concentrations as high a 10mg/ml.

Table 2 Effect of T-60 Concentrations on 5α - Reductase Activity of the Human Benign Prostate

Patient no.	T-60 concentration (mg/ml) 0	0.75	2	10
1	1.44 ± 0.2*	1.34 ± 0.23	1.38 ± 0.12	1.25 ± 0.09
2	1.55 ± 0.18	2.08 ± 1.10	0.98 ± 0.12	1.58 ± 0.29
3	6.29	6.98 ± 2.72	8.46 ± 1.29	9.89 ± 0.89
4	2.21 ± 0.15	2.18 ± 0.19	—	2.23 ± 0.23
5	2.98 ± 0.52	3.18 ± 0.21	4.45 ± 0.56	—
6	2.58 ± 0.26	2.4 ± 0.24	2.32 ± 0.04	2.28 ± 0.65

* Values expressed in pmol/mg protein/min ± SD.

Table 3 Effect of Cernitin T-60 (4mg/ml) on Nuclear Androgen Receptor Measurements in 6 BPH Specimens

Treatment	K_d (nmol/l ± SD)	Binding site (fmol/g tissue ± SD)
Control	2.95 ± 0.60	84.4 ± 27.5
T-60 added	2.80 ± 0.57	78.8 ± 32.1

In addition, we undertook several experiments to measure nuclear androgen receptor levels in the absence and presence of the pollen extract at 4mg/ml. The results summarized in table 3

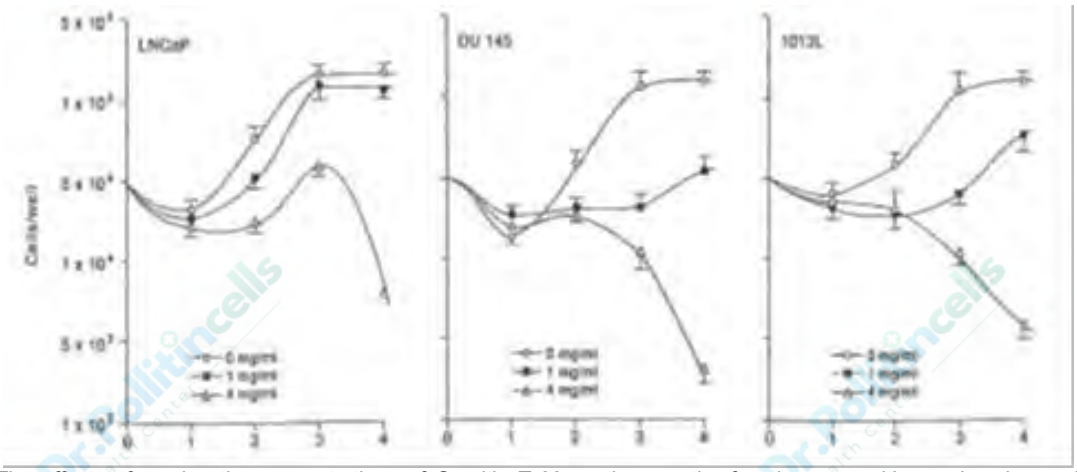

Fig 1. The effects of varying the concentrations of Cernitin T-60 on the growth of androgensensitive and androgen insensitive prostate cell lines. Each point represents the mean ± SD of 3 separate experiments each run 6 times.

indicate that there was no significant difference between the control and test groups with regard to the number of binding sites (P> 0.5) and dissociation constants (p> 0.5).

Discussion

These data represent the first report of the *in vitro* evaluation of the water-soluble fraction of the pollen extract, Cernitin T-60, using a panel of human prostate tumor-derived continuous cell lines. In addition, parallel in vitro experiments were also undertaken on 6 other cell lines derived from non-prostatic sources essentially to assess the specificity and efficacy of pollen extract.

Attempts to minimize variations between experiments were made by standardizing experimental conditions with regard to the same medium, fetal calf serum concentrations, and narrow range of cell passages. Furthermore, we observed a little variation in drug response with repeated experiments for each particular cell line. Nonetheless, the results of this study suggest that the responses induced were varied and these were predominantly a function of the cell lines: high in the case of the prostate, low or non-existent in the non-prostate derived cells. Of interest also is the heterogeneity in responses of the prostate cell lines to the agent. The hormone-insensitive cells demonstrated a greater sensitivity to the pollen extract than the androgen-dependent line and this was particularly evident at the lower pollen concentrations.

We are not yet sure of the mechanism of action of this drug but quite obviously it is not mediated via the androgen delivery system of the cell, since the pollen had no effect on either the 5α-reductase activity of the tissues or its steroid receptors. There have also been reports suggesting that Cernilton might be a potent inhibitor of the cyclo-oxygenase and lipoxygenase enzymes which are needed for leukotriene and prostaglandin synthesis (Loschen, personal communication) but these reports have not been extended to the prostate and will require verification.

However, it is gratifying to note that the selectivity of the pollen extract for the prostate, as demonstrated in the present study, was also supported by the work carried out by Ito *et al*. (1986). Following an intake of Cernilton over a period of 21 days, the rats in the latter study showed significant reductions in the weight of the ventral and dorsal prostate but there was no change in any of the other major organs.
Following these encouraging results, a double-blind trial was undertaken on a group of patients with BPH, the results of which are described by Buck *et al*. (1990).

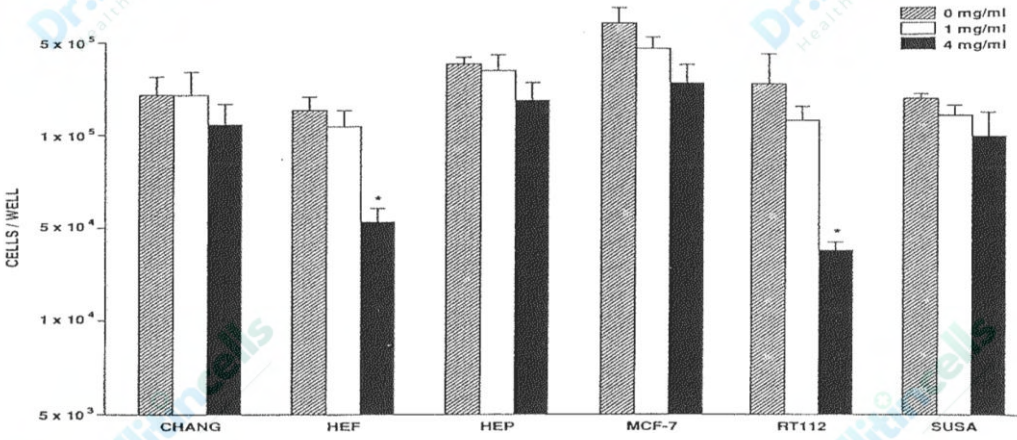

Fig. 2 The effect of Cernitin T-60 on the growth of 6 non-prostate derived cell lines after 4 days' exposure to the drug. Results are the mean ± SD of 3 separate experiments each run 6 times (P> 0.01).

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Inhibition of Growth of Human Benign Prostatic Hyperplasia by Cernilton N in the Nude Mouse Model

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1989

Introduction

In spite of the high incidence of benign prostatic hyperplasia (BPH) a conservative therapy for this disease has still not been established (1,2). The reasons for this are the following: On the one hand, the symptomatology in patients with BHP is due to various different factors, which leads to uncertainty regarding the objective parameters to be considered in clinical trials (2); also, all clinical investigations of the treatment of BPH present the problem of a high placebo effect. On the other hand, the aetiology of prostatic hyperplasia is still unexplainable, due to lack of suitable experimental models (2,3). This makes the search for casual factors on which to base a conservative therapy difficult.

At present, mainly phytotherapeutic agents are used for conservative treatment up to Stage II of the disease according to the classification of Vahlensieck (4, 5). We have established the heterotransplantation of human BPH tissue into the nude mouse as a model for the evaluation of the aetiology of BPH and of drug therapies and their mechanisms (6). Within the framework of these investigations we have studied the plant-based preparation Cernilton N in this model, since in a clinical trial it had been possible to show a significant effect with Cernilton N in comparison with placebo (7). The aim of these first investigations is to answer the question whether a significant effect on the growth of a hormonally stimulated BPH can be demonstrated in our model.

Materials and Methods

All the NMRI nu/ nu mice are kept in a special laboratory, under sterile conditions with a constant relative humidity of 55% and a constant temperature of 27 C. They receive a standard diet of Altromin (Lage) and water.

The human BPH tissue is obtained, by the transvesical prostatectomy, from two patients with BPH.

The tissue is cut into small pieces under sterile conditions and reference tissue is kept on one side for the histological assessment.

Within one hour, pieces measuring 3x3x3 mm are transplanted into both sides of the thorax of the mice.

The test animals are three-month-old male NMRI nu/ nu mice, orchiectomized one day previously.

At the same time, silicone implants with 5-alpha-dihydrotestosterone (DHT) and oestradiol (E_2) are implanted subcutaneously, for hormonal stimulation of the tissue, as described by Steenbrugge (8).

Three groups, each of 4 animals (= 8 tumours), are formed per tumour-line. Groups II and III receive the silicone implants with DHT (serum level for DHT: 8.0 ng/ ml) and E_2 (serum level for E_2: 400 pg/ ml) for the hormonal stimulation. Group I serves as control (serum levels of DHT and E_2 below the measurable levels):

The mice of Group I are also treated with the pollen extract, Cernilton N (Extract. pollinis sicc. 2.5:1), in the dose of 10 mg/25 g body weight, twice a week, p.o., through stomach tube. Based on body weight, this dosage is equivalent to 50 times the dosage in humans (in order to obtain a speeded up effect). The size of the tumours is measured once a week, with a calliper. Their volume is calculated by means of the formula,

length of tumour x width of tumour $^2/_2$, as described earlier (9).

After 2 months the animals are sacrificed and the tissue removed for histological examination.

The human character of the tissue is checked by semi-quantitative determination of the human LDH isoenzymes (electrophoresis), also 2 months after the heterotransplantation.

Statistical analyses are performed by and independent investigator, whereby the t-test is used for comparison of mean values in 2 comparative groups and a one-way analysis of variance for comparison of the mean values in 3 comparative groups.

Results

In all cases the BPH tissue was histologically vital two months after transplantation, with no signs of necrosis or rejection.

In group I (control group) the volume of the tumours did not change significantly during the two months in the body of the mouse.

In the other two groups the volume of the transplanted tumours increased in the course of the two months. In comparison with the control group this increase in volume is statistically significant ($p < 0.05$). The increase observed in Group III (treatment-group) is, however, significantly less than that in Group II ($p < 0.008$).

The volumes of the transplanted prostate tissue before and two months after transplantation are shown in Table 1 and the growth curves are presented in Figure 1.

All the transplanted prostate-tissue preparations show an epidermoid metaplasia. A difference between the two groups with hormonal stimulation could not be demonstrated histologically.

Discussion

A statistically significant inhibition of growth through the application of Cernilton N can be demonstrated for human BPH in the nude mouse model. This result concurs with the results of the clinical trial (7). On the other hand, however, it must be born in mind that the transferability of these findings to man is limited. The doses of the stimulant hormones on the one hand and of the therapeutic agent on the other, which are used in order to achieve the speeding-up effect, are both unphysiologically high. Also, in man the size of the prostate alone is insufficient to explain the whole pathological picture (2).

A conclusion regarding a possible mechanism of action cannot be drawn on the basis of our results. Also the histological picture, due to the lack of differences between groups, provides no information on the mechanism of the inhibition of growth of the tumour. However, an inhibition of the enzymes, 5-alpha-reductase and aromatase, can be excluded, since the end-products of the biochemical reactions catalyzed by these enzymes are substituted.

The model described here is nevertheless suitable, through further investigations of the prostate tissue, to contribute to clarification of the mechanisms of action.

Cernilton N is capable, under experimental conditions, of exerting an objectively evaluable effect on the growth of human BHP tissue.

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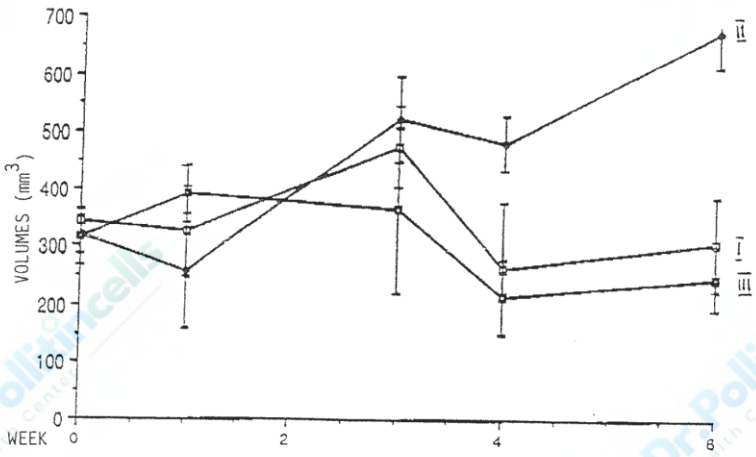
Table 1: Volume of BPH – Mean values (MV) Sunday 29.4.90, 20.36 hrs

Time	Group I MV	Group II MV	Group III MV	Group I s	Group II s	Group III s	p
Baseline	343.0	318.3	315.9	6.1	32.7	48.7	0.940
1st week	324.8	256.0	390.4	78.1	99.5	50.8	0.076
3rd week	473.5	522.2	363.1	72.8	75.0	141.9	0.046
4th week	282.8	479.8	213.8	112.5	48.0	63.7	0.008
6th week	307.0	673.0	246.3	79.3	58.4	54.0	0.001

Figure 1 : Volume of the benign prostatic hyperplasia after heterotransplantation



= Group I (Hormonal stimulation + Cernilton N)
= Group II (Hormonal stimulation)
= Group III (Control group)

Inhibition of the Arachidonic Acid Metabolism by an Extract from Rye Pollen

G. Loschen, L. Ebeling

Introduction

Clinical studies with a defined pollen extract preparation document its symptomatic efficacy in patients with benign prostatic diseases. In patients with benign prostatic hyperplasia (BPH) a significant reduction in nocturia and residual urine is observed (4,8). The continued improvement in symptoms (5) and a significant reduction in the anteriorposterior diameter of the prostate after six months of treatment (8) suggest a permanent pharmacological influence on pathophysiological alterations induced by the underlying disease. In patients with chronic non-bacterial prostatitis a significant improvement in symptoms or even a symptom-free status is achieved as it is in patients with prostatodynia. Furthermore, a reduction or even normalization of the white cell count in prostatic secretions has been documented (7).

Despite the fact that prostaglandins have been demonstrated for the first time in the prostate, and despite the fact that the entire group of substances received its name based on their increased presence in the prostate gland (10), little is known as of yet about their function in this particular organ. What is known, however, is that prostaglandins and leukotriens play an important role in inflammatory reactions (11). Furthermore, an etiologic role in the development of BPH has been suggested (1).

The majority of the known mediators of inflammation arise from the membrane-bound arachidonic acid. Their intracellular release by activation of phospholipases facilitates their enzymatic metabolism in a cascade of pharmocologically very potent reaction products. The biosynthesis of the eicosanoid-derived inflammatory mediators, which according to present pharmacological knowledge are of importance for the understanding of the pathologic alterations on a molecular level, is initiated by two enzymes: cyclo-oxygenase and 5- lipoxygenase.

The therapeutic effectiveness of many drugs can be explained by their interactions with enzymes that are responsible for individual steps in the metabolism of arachidonic acid (11). The clinical effectiveness of the pollen extract in benign prostatic diseases therefore leads to the question, whether, and to what extent this extract influences the biosynthesis of prostaglandins and leukotriene in vitro.

Material

The examined pollen extract is produced by AB Cernelle, Engelholm (Sweden). It consists predominantly (greater than 90 %) of rye pollen (Secale cereale L.) as well as two other quantitatively relatively unimportant types of pollen. The exact composition can be obtained from the manufacturer. The pollen is extracted initially with water and thereafter with acetone.
For the experiment discussed herein the water-soluble (wPE) and fat-soluble (fPE) fractions which were standardized for their content in α-amino-acids (18.3 % w/w) and for phytosterols (1.1 % w/w) were tested separately. The experiments were conducted in the research laboratories of Grünenthal GmbH, Aachen, Germany.

^{14}C-marked arachidonic acid and the radioactive-marked metabolites of arachidonic acid (PGF_2; PGE_2; LTB_4; 5-HETE) were purchased from Amersharn Buchler (Braunschweig, Germany). For the thinlayer chromatography, silica gel G 60 plates with fluorescent indicators and concentration zone were purchased from E. Merck, Darmstadt, Germany.

The thin-layer radiochromatography analyses were performed with the linear analyzer LB 2870, Berthold Company, Wildbad, Germany.

RBL-1 cells (rat basophilic leukemia cells) were donated by Prof. P. *Piper*, Royal College of Surgeons, London. The medium for RBL-1 cells consisted of Eagles Medium, newborn calf serum, and fetal calf serum, L-glutamin, and a mixture of penicillin and streptomycin, and was purchased from Gibco, Karlsruhe, Germany.
The cells were grown in spinner flasks (Bellco Glass Inc, Vineland, New Jersey, USA).

Lyophilized seminal vesicle microsomes were freshly obtained from slaughtered rams (Julius Kind OHG, Grevenbroich, Germany).

The Ca-Ionophor A 23 187 was purchased from Calbiochem, Frankfurt / Main, Germany.
Indomethacin was purchased from Merck, Sharp and Dohme, Rahway, NJ (USA), and Naproxen from Syntex, Palo Alto, CA (USA). All other solutions and reagents not described were either purchased from Boehringer Mannheim, Mannheim, E. Merck, Darmstadt, or Sigma, München, Germany.

Methods

Measurement of the Prostaglandin Biosynthesis (Cyclo-oxygenase activity)

25 µl lyophilized microsomes from ram seminal vesicle (1.8mg protein/m/l) are suspended in 975µl calcium phosphate buffer (50mmol/l, pH 7.5), and incubated in the presence of test substances together with 20 µmol/l ^{14}C-arachidonic acid (150,000cpm/ml) for 10 minutes at room temperature.

The incubation reaction is stopped with 20 µl acetic acid and is extracted with 2ml of ethyl acetate. The extract is then compressed under N_2 and separated on silica gel plates with a concentration zone in a solvent mixture of ether: hexan: acetic acid (50:50:1). This solvent is not suitable to separate the Prostaglandins but rather to quickly separate the non-metabolized arachidonic acid from its cyclo-oxygenase products. If a separation of the formed prostaglandins is desired, a solvent mixture of ether acetate: acetic acid = 99:1 (3 consecutive separations) is recommended.

The radioactivity distribution on the plate is measured thereafter using the TLC linear analyzer (Berthold Company). The radioactivity of the formed cyclo-oxygenase products (starting peak) and the non-metabolized arachidonic acid (front peak) are calculated as a percentage of the total radioactivity. Measurements are performed in triplicates and the means and standard deviations of the radioactive cyclo-oxygenase products are plotted against the logarithm of the test substance concentration. The concentration of test substance which leads after graphical interpolation to a 50% inhibition of the radioactive cyclo-oxygenase products is noted as IC_{50}-value. Naproxen is used as a positive control of inhibition and is measured in each experiment to determine the IC_{50} value. The responding volume of the solvent for the test substances is used as blank (20 µl ethanol).

Measurement of Leukotriene Biosynthesis (5-Lipoxygenase Activity)

To search for inhibitors of the leukotrien biosynthesis, cell cultures of RBL-1 cells (rat basophilic leukemia cells) are particularly well suited.

RBL-1 cells are centrifuged for 20 minutes at 400 x g and are adjusted with potassium phosphate buffer (50mmol/ l; pH 7.4) to a cell count of 1.5 x 10^7 cells/ ml.

Indometacin (10µmol/l), the tested substance in various concentrations, ^{14}C-arachidonic acid (20µmol/l cold plus approximately 100,000cpm radioactive arachidonic acid with a specific radioactivity of 56 mCi / mmol) and the Ca-Ionophor A 23 187 (20 µmol/l) are added to 1 ml of this cell suspension. After an incubation time of five minutes the assay is acidified with 20 µl of acetic acid and thereafter extracted twice with ethyl acetate. The extract is compressed under N_2, then again resuspended with 20 µl ethyl acetate, and placed on silica gel thin-layer chromatography plates. The separation of the radioactive reaction products follows with two different solvents at 4 °C.

In the first solvent (ether: hexan: acetic acid=50:50:1) the plates are developed twice in immediate succession. In the second solvent (ethyl acetat:iso-octan: H_20: acetic acid=110: 50:10:20; upper phase) the plates are only developed to approximately half the height of the

plate. The radioactivity distribution is measured with the Berthold linear analyzer. 5-HETE and the LTB_4-Isomers (with a common peak) are separated by these two solvents from arachidonic acid, other monoHETEs (12-HETE and 15-HETE), and phospholipids and triglycerides. The 5-HETE peak and LTB_4 peak (in the mixture of isomers of various LTB_4 isomers) are integrated with a TLC-Linear analyzer (Berthold Company) and are expressed as a percentage of the total radioactivity. Measurements are done in triplicate and means as well as standard deviations are plotted on semi-logarithmic paper against the inhibitor concentration. The IC_{50} value is graphically calculated by interpolation. In each experiment the IC_{50}-value for nordihydroguaiaretic acid (NDGA) is measured as a positive control. An equal volume of the used solvent for the test substances is used as blank.

Lyophilized microsomes from ram seminal vesicles are prepared according to the method of *van der Ouderraa* et al. (16). RBL-1 cells are grown in spinner flasks according to the instructions by *Isersky* et al. (12). The protein concentrations are measured according to the *Lowry* et al. method (13).

Results

The effect of both the fat-soluble (fPE) and water-soluble (wPE) pollen extract fractions on the biosynthesis of prostaglandins from radioactively marked arachidonic acid catalyzed by the cyclo-oxygenase in ram seminal vesicle microsomes is shown in Fig. 1.

Under identical conditions ^{14}C-marked arachidonic acid was incubated in the presence of 5mg/ml water-soluble pollen extract (wPE, lowest chromatogram), 20µm/ ml fat-soluble pollen extract (fPE, second radio-chromatogram from bottom), 10 µmol / l Naproxen (non-steroidal anti-inflammatory agent and cyclooxygenase inhibitor), as well as 20 µl ethanol (solvent of the utilized test substances) and were incubated with ram seminal vesicles microsomes as the source for the enzyme.

After extraction of the radioactive reaction products and the subsequent thin-layer chromatography separation, two radioactive peaks are obtained. The starting peak contains the different cyclo-oxygenase products (Prostaglandin E_2, F_2, D_2, G_2, H_2), which are

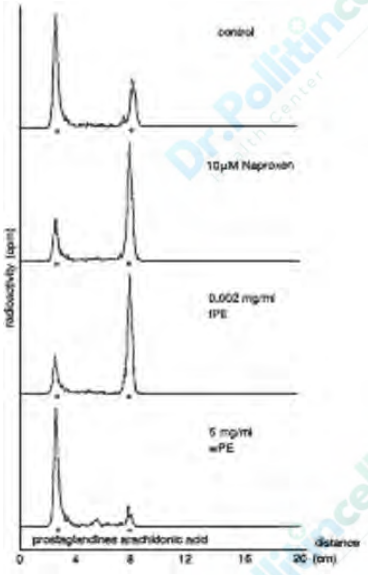


Fig. 1 Effect of the fat-soluble (fPE) and water-soluble (wPE) pollen extract fractions on the prostaglandin biosynthesis from radioactive-marked arachidonic acid in ram seminal vesicle microsomes in comparison to a non-steroidal anti-inflammatory agent (Naproxen).

not further separated with the chosen solvent. The front peak contains the rest of the non-metabolized arachidonic acid. A correlative comparison of the four radio-chromatograms shows that the fat-soluble pollen extract in a concentration of 20 µg/ml inhibits the biosynthesis of prostaglandins from arachidonic acid to approximately the same extent as the non-steroidal anti-inflammatory agent and cyclooxygenase inhibitor Naproxen in a concentration of 10 µmol/l.

The water-soluble pollen extract shows no significant inhibition of prostaglandin biosynthesis up to a contraction of 5 mg/ml in comparison to the control.

In a similar manner, the concentration-dependent inhibition of prostaglandin biosynthesis by the fat-soluble pollen extract was measured (Fig. 2). Graphical interpolation resulted in an estimated 50 % inhibition of prostaglandin biosynthesis from arachidonic acid by the fat-soluble pollen extract at a concentration of only 5 µg/ml.

In a similar fashion, the effect of both pollen extract fractions on the biosynthesis of leukotriens from arachidonic acid was investigated. We utilized cell cultures from rat

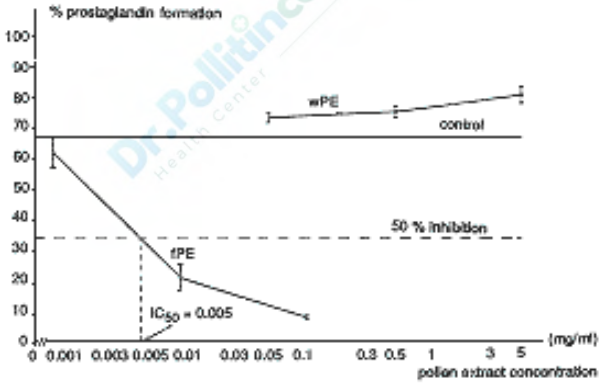


Fig. 2 Determination of the IC_{50}-value for inhibition of prostaglandin biosynthesis (cyclo-oxygenase activity) from arachidonic acid ($\bar{x}$ ± SD) in ram seminal vesicle microsomes by the fat-soluble (fPE) pollen extract fraction (n = 3, related to the pollen extract concentration). 100% prostaglandin formation corresponds to a complete metabolism of 20µmol/ 1 ^{14}Carachidonic acid.

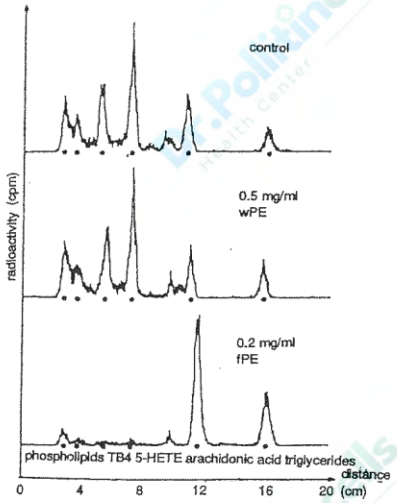


Fig. 3 Effect of the fat-soluble (fPE) and water-soluble (wPE) pollen extract fractions on the leukotriene biosynthesis from radioactive-marked arachidonic acid in rat basophilic leukemia cells (RBL-1 cells).

basophilic leukemia cells (RBL-1 cells) as the source for the enzyme 5-lipoxygenase, which catalyzes the biosynthesis of leukotriens from arachidonic acid.

The effect of both pollen extract fractions on the leukotriene biosynthesis is initially again shown inthe thin-layer radiochromatography (Fig. 3).

Under identical conditions RBL-1 cells were incubated in the presence of water-soluble (0.5 mg / ml) and fat soluble (0.2mg/ml) pollen extract together with the Ca-Ionophor A 23 187 and radioactive arachidonic acid. The three radio-chromatograms shown in Fig. 3 result after extraction of the radioactive reaction products and thin-layer chromatography separation. In the presence of fat-soluble pollen extract (fPE, bottom chromatogram) the enzymatic activity of 5-lipoxygenase is practically completely inhibited. The water-soluble pollen extract, however, shows no significant inhibition of the 5-lipoxygenase reaction (formation of 5-HETE and leukotriene B_4-Isomers) in comparison to the control even if a 2.5-fold higher concentration (0.5 mg / ml) is utilized.

A 50 % inhibition of the leukotrien biosynthesis (5-lipoxygenase activity) is reached under these experimental conditions at a concentration of 0.08 mg / ml fat-soluble pollen extract (see Fig. 4). With the water-soluble pollen extract the leukotrien biosynthesis could not be inhibited in concentrations up to 5 mg / ml (data not shown).

To judge the inhibitor effect of both pollen extract fractions on the prostaglandin and leukotrien biosynthesis in a therapeutic manner, the IC_{50}-values for some known steroidal and non-steroidal anti-inflammatory agents were measured under the same conditions. Since the concentration of both pollen extract fractions cannot be expressed as a molar concentration, the concentration of the tested anti-inflammatory agents were converted from molarity to mg / ml to allow a better comparison of in vitro effectiveness. In Table 1 the IC_{50}-values for the inhibition of leukotriene and prostaglandin biosynthesis are summarized. Table 1 demonstrates that the fat-soluble pollen extract fraction expressed as mg / ml inhibits the prostaglandin and leukotrien biosynthesis in vitro more than acetyl salicylic acid does, and equally as strongly as the non-steroidal anti-inflammatory agent diclofenac.

Discussion

The goal of this study was to test the effect of a defined pollen extract on the prostaglandin and leukotrien biosynthesis in vitro to develop a pharmacodynamically plausible hypothesis for its clinical effectiveness in patients with chronic prostatitis, BPH, and prostatodynia (also called prostate congestion [23]).

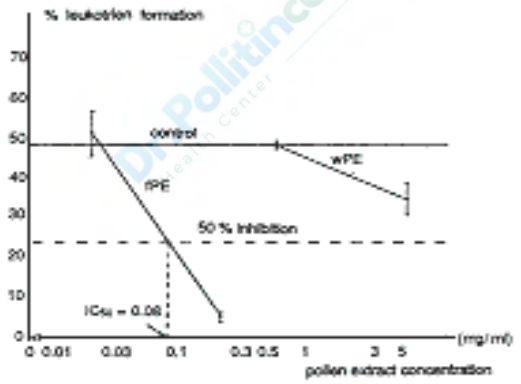


Fig. 4 Determination of the IC_{50}-value for the inhibition of leukotriene biosynthesis (5-lipoxygenase activity) from arachidonic acid ($\bar{x}$ ± SD) in rat basophilic leukemia cells (RBL-1 cells) by the fat-soluble (fPE) pollen extract fraction (n = 3, related to the pollen extract concentration). 100 % leukotrien formation corresponds to a complete metabolism of 20µmol/ $1^{14}C$- arachiclonic acid.

To determine prostaglandin and leukotrien biosynthesis, thin-layer chromatography was utilized and the radioactivity distribution of the formed cyclo-oxygenase and 5-lipoxygenase products as well as the non-metabolized arachidonic acid was investigated in ram seminal vesicles microsomes and RBL-1-cells.

The TLC documentation of the cyclo-oxygenase activity in this screening method is reliable and complete if influences on the metabolism of cyclo-oxygenase are tested. Among the chemical-analytical methods of measurements for the influence on the 5-lipoxygenase pathway of the arachidonic acid cascade, thin-layer radiochromatography considers the sum of 5-HETE and the LTB_4 isomers as representative for the 5-lipoxygenase products formed and does not capture peptidol leukotriens. This method is valuable in screening for 5-lipoxygenase inhibitors if intact cultivated RBL-1 cells are utilized. To avoid theundesirable metabolism of arachidonic acid by the cyclo-oxygenase, indometacin is utilized in a sufficient inhibitory concentration. This does not affect the 5-lipoxygenase pathway.

The results document an inhibitory effect on the prostaglandin and leukotrien biosynthesis in vitro by the fat-soluble pollen extract. The inhibition ofcyclo-oxygenase predominates. The inhibition of both cyclo-oxygenase and 5-lipoxygenase is dose dependent and the graphically determined IC_{50}-values are approximately equal to those of diclofenac. The water-soluble pollen extract fraction, however, did not show a significant inhibitory effect on the arachidonic acid cascade in vitro.

Clinically the pollen extract has resulted in a reduction of pathologically increased white cell counts in prostatic secretions in patients with chronic non-bacterial prostatitis, with a concomitant decrease in dysuria and discomfort or pain in the inguinal, perineal, or genital area (7). In BPH and concomitant prostatic congestion, which also exhibits histological evidence for chronic inflammation and interstitial edema and the congestion of secretions in prostatic tissues (9,23), the symptomatic effect of the pollen extract leads to an improvement in the voiding dysfunction (4,5,7,8).

If the chronic inflammatory or congestive changes found in these benign prostatic conditions are considered as the pathophysiologically relevant substrate of the subjective complaints (5,23), the therapeutic effectiveness of the pollen extract could be the result of an intraprostatic inhibition of both the prostaglandin and leukotrien biosynthesis and a subsequent anti-edematous and anti-leukotactic effect of the fat-soluble fraction according to our in vitro results.

Furthermore, other effects, not primarily related to inflammation, are possibly relevant for the therapeutic mechanism of the pollen extract. The prostaglandin-modulated contraction of smooth muscle cells (19) resulting in coordinated voiding by bladder and urethral smooth muscle might also be influenced by an inhibition of the cyclo-oxygenase. Therefore a relaxation of the prostatic urethra could also explain urodynamic improvements after treatment with pollen extract such as the reduction in residual urine and the improvement in average and peak urinary flow rate (4,5,7,8) (these parameters are found to be abnormal in patients with benign prostatic diseases (6,14,18)). Concerning the 5-lipoxygenase inhibition, no indications for a relaxation of the SRS-A (slow reacting substance of anaphylaxis)-induced contraction in vivo are available.

A further possible pharmacological effect of the pollen extract in patients with BPH could be a prophylactic or pathophysiologically relevant effect concerning hormonal or immunological

Tab. 1 Effect of the fat-soluble (fPE) pollen extract fraction on the prostaglandin and leukotrien biosynthesis in direct comparison with other anti-inflammatory agents.

Test substance	IC_{50}-value 5-lipoxygenase (µmol/l)	(mg/ml)*	IC_{50}-value Cyclo-oxygenase (µmol/l)	(mg/ml)*
Pollen extract	–	0.08	–	0.005
Naproxen	215	0.0495	8	0.0018
Diclofenac	220	0.0623	26	0.0074
Indometacin	240	0.0859	0.35	0.0002
Acetyl salicylic acid	> 500	> 0.090	375	0.0675
Paramethasone	> 100	> 0.053	> 500	> 0.267

* For a better comparison of the inhibitory effects, the IC_{50}-values of the anti-inflammatory agents were also expressed in mg/ml.

metabolic processes in the prostate. Prostaglandins and leukotriens are suspected of being involved in the etiology and pathogenesis of BPH as a result of eicosanoid-dependent dysregulations (1,17). A dose-dependent inhibition of the 5α-reductase and the 3α- and 3ß-hydroxysteroid-dehydrogenase which regulate the intraprostatic testosterone metabolism in the epithelium and stroma of BPH homogenates has been documented in vitro for the fat-soluble pollen extract fraction (*M. Krieg*, personal communication, publication in preparation). Whether and to what extent these results may be connected to our findings and to what extent these results are of pharmacological importance in humans has to be tested in further studies.

Treatment with ß-sitosterin, a phytosterol also contained in rye pollen (21), has led to a decrease in the prostaglandin concentration in BPH tissue (24) and in the prostatic secretion of BPH patients (2). Concerning the discussed pharmacodynamical effects of the fat-soluble pollen extract fraction with a ß-sitosterin content of 8.3 % (w/w), these in vivo results do not allow any further conclusions since data concerning the above-mentioned metabolic parameters were not measured. The documentation of inhibition of the phospholipase A_2 by free fatty acids (3), which are also contained in the fat-soluble pollen extract fraction (30 %; w/w) merely demonstrates that a pharmacological effect on the production of arachidonic acid from phosphatides with subsequently reduced substrate for cyclo-oxygenase and 5-lipoxygenase is possible.

Concerning the use of non-steroidal anti-inflammatory agents for benign prostatic diseases, not much is known with the exception of an unsuccessful treatment of non-bacterial prostatitis with ibuprofen (400 mg po tid over 90 days) in a pilot study (22). Clinical experiences with the pollen extract in other typical indications for non-steroidal anti-inflammatory agents are also lacking. A comparison of desirable effects on the basis of in vivo studies is therefore not possible. Side effects associated with a generalized prostaglandin deficiency such as damage to the gastric mucosa (15), as it is characteristic for cyclo-oxygenase inhibition (11), has not been reported after the use of pollen extracts in humans. The side effects known to occur in humans after the use of nonsteroidal anti-inflammatory agents are therefore not seen in the treatment with the pollen extract. Gastrointestinal complaints can occur (4, 5), however, but their incidence is rather rare and the intensity of these side effects is mild or moderate.

In drug extracts a number of different chemical compounds are contained some of which, in the case of the pollen extract, ß-sitosterin and free fatty acids, are pharmacologically effective. Therefore a clear determination of the clinical relevant substance or substances and their bioavailability is often not possible. This is particularly true for the pollen extract since even the water-soluble fraction has shown a significant growth inhibition of cultivated prostate cells in experimental studies (*F K. Habib*, Edinburgh, personal communication, publication in preparation). The possible explanations for the different side effect profiles of pollen extract and non-steroidal anti-inflammatory agents are therefore limited.

If identical conditions are assumed, the clinically

utilized daily dosages of pollen extract (fat-soluble fraction) and diclofenac are 12 and 50 mg, respectively, which inhibit in vitro the prostaglandin and leukotrien biosynthesis in an equivalent fashion. Considering in addition the reduction of the production of arachidonic acid by the free fatty acid of the pollen extract, and the inverse relationship between orally taken dose and relative serum concentration as has been demonstrated for diclofenac (20), it is evident that the pharmacologically necessary dose of the pollen extract is comparatively low.

If one assumes a mechanism of action for the fat-soluble pollen extract fraction that is not completely or partially independent in relation to the eicosanoids, it seems reasonable to assume that the pollen extract in the usual dosage does not inhibit local prostagiandin biosynthesis in the mucosal cell layer of the gastrointestinal tract to an extent that it would cause undesirable side effects. At the same time, however, in the prostate and/ or periurethrally, a therapeutically necessary concentration may be reached. The chronic form of congestive and inflammatory processes in benign prostatic conditions which can be treated with a lower concentration of drugs in comparison to the acute inflammatory processes is another indicator for this hypothesis.

Our in vitro experiments concerning the influence of a pollen extract on the arachidonic acid cascade require animal experiments and pharmacological confirmation in humans to determine the value of the assumed therapeutic mechanisms of action, namely anti-congestive, anti-inflammatory, relaxant, and antiproliferative. This does not affect the possible relevance of the water-soluble pollen extract fraction for clinical effectiveness.

In summary we conclude that the in vitro inhibition of the prostaglandin and leukotriene biosynthesis by the fat-soluble pollen extract fraction offers a pharmacologically plausible explanation for the clinical effectiveness and the underlying mechanism in the therapy of benign prostatic conditions with the pollen extract.

Summary

A standardized extract mainly from rye pollen (Cernilton®N) was tested in vitro on the inhibition of prostaglandin and leukotrien synthesis. The determination of the prostaglandin and leukotrien synthesis from labelled arachidonic acid was done in microsomes of ram seminal vesicles and in rat basophilic leukemia cells (RBL-1 cells). The water-soluble and fat-soluble extract fraction from the whole pollen extract were tested separately. The radio-TLC separation of the reaction metabolites showed a dose-dependent inhibition of the cyclo-oxygenase and the 5-lipoxygenase activity by the fat-soluble pollen extract fraction. The IC_{50}-values of 0.005 mg/ml and 0.08 mg/ml, respectively, were similar to those of diclofenac, which was also tested. The water-soluble fraction showed no effect on this test system. According to these in vitro results and clinical experience with the pollen extract so far, its therapeutic efficacy on benign prostate diseases is best explained by the anticongestive, anti-inflammatory effect of the fat-soluble fraction. Due to the different actions of prostaglandins and leukotriens, relaxant and antiproliferative effects are also conceivable.

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* Published in Arzneim.-Forsch./Drug Res. 41 (1), Nr. 2 (1991) 162-167. 1 Cernilton®; composition: 23 mg pollen extract consisting of 20 mg water-soluble and 3 mg fat-soluble extract fractions.
Pharma Stroschein (licensed by Cernitin ™ SA, Lugano, Switzerland), Hamburg.

Pharmacological Studies on Cernilton, a New Remedy for Prostatitis and Prostatomegaly (2)

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I. Introduction

CERNILTON contains two major ingredients, Cernitin T-60 (T-60) and Cernitin GBX (GBX) mixed at a ratio of 20:1. The drug is clinically effective in the treatment of prostatomegaly.

In the present study acute toxicity test was carried out with CERNILTON (Cer) with a view to determine the LD_{50} in rats and mice and observe symptoms produced at a large dose. Subacute toxicity test was carried out with Cer, T-60 and GBX in rats and chronic toxicity test with Cer. Observations were made on physical development and general toxic symptoms. Liver function test, pathohistological examinations and other tests were also carried out.

II. Methods of Tests

1. *Acute Toxicity Tests of T-60, GBX and Cer*

Method: Animals used were Donryu strain rats (bodyweight 150-180 g) and ddN strain mice (bodyweight 20-25 g) of both sexes at 6-8 weeks of age, each group consisting of 5-10 animals. The sample drugs were given by three routes: oral, subcutaneous (only males), and intraperitoneal (only males). Following medication, animals were observed hourly for 6 hours and then only daily 7 days as to acute toxic symptoms and presence of death. Dead animals were subjected to laparotomy and the thoracic and abdominal organs were macroscopically observed. The LD_{50} was calculated on the basis of the total number of deaths in 7 days by means of the Probit method. T-60 and Cer were dissolved or suspended in 1% CMC and GBX was suspended in olive oil. The volume was so adjusted that the animals would receive 20 ml/ kg by oral route, 10 ml/ kg by the subcutaneous route, and 5 ml/ kg by the intraperitoneal route.

Dose (Table 1): According to the report by Tor Magnusson, the LD_{50} of T-60 is 5g/ kg by intraperitoneal route in mice. The dose levels were set up on the basis of this report.

2. *Subacute Toxicity Tests of T-60, GBX and Cer*

Donryu strain rats of both sexes weighing about 80g were used. The animals were raised under controlled conditions (room temperature 25±1°C, humidity 55±5%) and a total of 12 groups was set up, each group consisting of 10 males and 10 females. Four groups of animals were used for each sample drug. Sample drugs were given by the oral route with the aid of a gastric sound, once daily over a period of 35 days.

The dose levels were determined on the basis of the data obtained by Tor Magnusson as well as the results obtained in our laboratory concerning the LD_{50} of T-60, GBX and Cer. It was also taken into consideration that chronic toxicity test was to be carried out.

T-60 and Cer were suspended in 1% CMC solution. Concentrations were so adjusted that the maximum daily volume would be 4 ml/100g for T-60 and 2 ml/100g for Cer. Original solution (specific gravity 0.94) was used for GBX.

Observations were made on the following items: a) body weight: Determined daily until the end of administration. b) Food consumption: Determined for 10 days after the 25th day of administration. c) Observation of toxic symptoms: Daily until the end of administration. d) Blood test: Blood was collected from 10 animals (5 males, 5 females) in each group before administration and on the 30th day of administration. RBC count, hemoglobin value (cyanmethemoglobin method), WBC count, and WBC percentage were determined. e) Urine: Urine was collected from 10 animals (5 males, 5 females) in each group before administration and at the end of administration. Sugar, protein and urobilinogen were examined with Uristix (Ames Co.). The volume and color of urine were also examined. f) Liver function test: BSP excretion test was performed by Gaebler's method prior to autopsy at the end of administration. Hepatosulphalein was injected in doses of 10 mg/ kg into the vein of a hind limb and the amount of excreted dye was measured after 5 min. In addition, serum GOT and GPT levels were measured using ESGOT testing agent. g) Total cholesterol, total protein, blood sugar: Total protein was measured simultaneously with liver function test. Blood sugar was measured by Somogyi-Nelson's method and cholesterol level by Zak-Henly's method. h) Autopsy: 1) Macroscopic observation of organs: Major organs. 2) Weight: Hypophysis, thymus, heart, liver, kidneys (bilateral), adrenal glands (bilateral), spleen, prostate, testis (unilateral), epididymus (unilateral) and spermatocyst. 3) Pathohistological examinations: Brain, lungs, heart, liver, spleen, kidneys, stomach, intestine, pancreas, thymus, adrenal, spermatocyst and bone marrow. Each organ was fixed with 10% formalin solution and embedded in paraffin. It was then sliced and stained with hematoxylin eosin for microscopic observations.

3. *Chronic Toxicity test of Cer*

The conditions of animal breeding and method of administration were the same as in the subacute toxicity test. The drug was given for 180 days. Five dose groups were set up on the basis of the results obtained in the subacute toxicity test. T-60 was first dissolved in 1% CMC solution, after which GBX was added and mixed well with a homogenizer. The drug was so adjusted in concentration that the maximum volume would be 1ml/100g.

Items of observation were as follows. a) Body weight. b) Food consumption. c) Toxic symptoms. d) Blood test. e) Urine test. f) Liver function test. g) Total cholesterol, total protein, blood sugar. h) Autopsy.

III. Results

1. Acute Toxicity Tests of T-60, GBX and Cer
A. Observation of toxic symptoms and death
a. Rats

1) *T-60 administration groups*

a) Oral route: Though varying in intensity, symptoms were similar in all groups, regardless of sex. Animals crouched immediately after administration. Piloerection and decreased activity ensued. None, however, died and all the animals returned to normal after 6-24 hours.

b) Subcutaneous route: Symptoms were essentially the same as those observed in a) in all five groups. However, animals screamed for 5-10 seconds as if complaining of pain when injected subcutaneously. Subcutaneous induration was present at the site of injection for three days and then disappeared. Death occurred in no cases even by this route.

c) Intraperiotoneal route: Crouching, piloerection, decreased activity, and apprehension were noted. In survivals these symptoms disappeared after 6-12 hours, but in dead cases the symptoms did not disappear and the animals died after 24 hours in the state of natural death.

2) *GBX administration groups*

a) Oral route: Crouching, piloerection and decreased activity were seen from about 3 min after administration, but no specific symptoms

were shown. All animals recovered after 6 hours and survived.

b) Subcutaneous route: Death occurred in no cases, and symptoms were same as those seen in a). The site of injection presented swelling and induration as in the case of T-60, but they disappeared in about 5 days.

c) Intraperitoneal route: Death occurred by the third day. Symptoms noted were crouching, decreased activity and slight tremor. In the 1.95 and 2.34g/ kg dose groups, where all animals survived, the symptoms disappeared after 24 hours.

3) *Cer administration groups*

a) Oral route: Crouching, piloerection, decreased activity, and apprehension occurred from about 2 min after administration, but no specific toxic symptoms were seen. All animals recovered and returned to normal after 24 hours. Death was not noted.

b) Subcutaneous route: Symptoms were similar to those observed in a) and no specific toxic symptoms were disclosed. Some cases developed slight inflammation at the site of injection which lasted 3 days. Screaming lasting several seconds was noted at the time of injection, but death occurred in no cases.

c) Intraperitoneal route: Besides the symptoms observed in a) and b), slight general tremor was noted. In survivals the animals recovered after 12-24 hours, while in dead cases the symptoms persisted and the animals died within 24 hours. No further deaths, however, occurred during the 7 days of observation.

b. Mice

1) *T-60 administration groups*

a) Oral route: Difference due to sex was not noted. Intensity of symptoms varied somewhat with doses, but generally symptoms were same as those observed in rats. In other words, piloerection, decreased activity and tremor were noted, but they disappeared after 24 hours. In dead cases these symptoms were marked and animals died within 24 hours.

b) Subcutaneous route: For a few seconds after administration the animals ran about within the cage as if complaining of pain. Activity decreased somewhat more by this route than by the oral route, though it returned to normal after 6 hours. Death occurred between the 24th and 72nd hours of administration. Inflammation manifested at the site of injection in all cases as in rats, but likewise it disappeared in about 72 hours.

c) Intraperitoneal route: In dead cases in the large dose group, the animals developed piloerection, crouching, tremor of extremities and eventually died. In survivals symptoms as piloerection, decreased activity, and slight tremor were noted, but they disappeared after 6 hours.

2) *GBX administration groups*

a) Oral route: As with T-60 administration, symptoms were same in both sexes and slightly varied in intensity with doses. Namely, piloerection and decreased activity occurred immediately after administration, and in the large dose group slight general tremor was noted. Some cases developed diarrhea which lasted about 48 hours. Dead cases were all noted within 24 hours.

b) Subcutaneous route: In the large dose group the animals jumped around in the cage immediately after administration, showed piloerection, crouching, and staggering after one minute and died after 24-72 hours. In the small dose group these symptoms appeared too, but they disappeared after 48 hours. Inflammation at the site of injection was more marked than with T-60 administration but disappeared after 4 days.

c) Intraperitoneal route: Piloerection, decreased activity, and slight tremor appeared immediately after administration. Death occurred in some cases after 24-120 hours. Recovery

was slow in survivals but they returned to normal by the 6th day.

3) *Cer administration groups*

a) Oral route: Symptoms were similar to those observed with T-60. Piloerection, decreased activity, and tremor were seen. Death occurred within 24 hours. These symptoms also occurred in survivals but they disappeared after 6 hours.

b) Subcutaneous route: As with oral administration, piloerection, decreased activity and tremor appeared. However, they were of slighter degree than with subcutaneous injection of T-60. Death occurred within 48 hours.

c) Intraperitoneal route: In the large dose group, the same tremor as seen with T-60 administration appeared and death ensued. In survivals in the small and medium dose groups, piloerection, decreased activity, and slight tremor all appeared, but they disappeared within 10 hours.

B. LD_{50} (Table 2)

The LD_{50} in rats was not obtainable by the oral and subcutaneous routes because all animals survived even at the maximum permissible dose. However, by the intraperitoneal route, the toxicity of the sample drugs was considerably high. The LD_{50} was 7.58g/ kg for T-60, 3.31 for GBX, and 6.66 for Cer. GBX was the most toxic while T-60 and Cer were approximately of the same degree.

In mice the LD_{50} was successfully obtained by routes. As a result, it was found that GBX was the least toxic by the subcutaneous route. On the other hand, by the intraperitoneal route, GBX was the most toxic of all sample drugs. Of the three routes, the intraperitoneal route was the most toxic while the oral and subcutaneous routes were approximately of the same degree.

2. Subacute Toxicity Tests of T-60, GBX and Cer

A. Body weight and death (Figs. 1,2,3)

a. T-60 administration groups

1) Control group: The control group receiving 1% CMC solution at a dose of 40ml/ kg showed normal weight increases both in males and females.

2) T-60 6.0g/kg group: The males showed normal weight increases at the control group and registered a greater weight increase than the control group throughout the period, with a difference of about 14 g at the end of administration. In females weight decrease was noted around the 25th day of administration, but as a whole they showed the same weight increase tendency as the control group. Death occurred in one male and one female, on the 23rd and 24th day, respectively.

3) T-60 12.0g/kg group: Weight increase in males slowed down transiently from about the 20th day, but generally the tendency was the same as that of the control group. Females showed a greater weight increase than the control throughout the period, with a difference of about 5g on the 30th day of administration. The difference, however, was not statistically significant. Death occurred in one male and one female on the 33rd and 21st day respectively.

4) T-60 24.0g/kg group: Males showed a greater weight increase than the control group up to the 20th day as in the previous two groups, but from about the 25th day weight increase slowed down markedly, with practically no weight increase shown up to the end of administration. The body weight on the 30th day was about 30g less than that of the control group, thus with a significant difference between the two groups. In females weight increase slowed down from about the 20th day, the body weight being lower than that of the control group by about 5g on the 30th day. Death occurred in 2 males (9, 32nd day) and 3 females (26, 20, 32nd day).

b. GBX administration groups

1) Control group: The control group receiving 1% CMC solution at a dose of 10 ml/kg showed normal weight increases both in males and females.

2) GBX 5.0g kg group: Both males and females showed normal weight increases, and the body weight at the end of administration was about the same as that of the control group. Death occurred in one male on the 33rd day.

3) GBX 10g/kg group: In males weight increase slowed down from about the 20th day, and the body weight was about 30g lower than that of the control group in the 30th day, with significant difference. Females showed normal weight increases. The bodyweight at the end of administration was little different from that of the control group.

4) GBX 20g/kg group: In males weight increase slackened more than in the previous 3 groups, and although it subsequently recovered, the body weight on the 30th day was about 40g lower than that of the control group. The difference was of significance. In females, contrarily, weight increase progressed quite favourably and the body weight was about 12g higher than of the control group on the 30th day. Death occurred in one male (14th day) and 3 females (6, 9, 32nd day).

c. *Cer administration groups*

1) Control group: The control group, which was given 20ml/kg of 1% CMC solution, showed normal weight increases in both sexes as the control groups of T-60 and GBX. Death occurred in one male, but this was due to an error in administration.

2) Cer 6.3g/ kg group: Both males and females showed exactly the same weight increase as the control group up to the 20th day, but then it was slightly inhibited. Difference in body weight, however, was noted at the end of administration in comparison with the control group. One male died on the 34th day.

3) Cer 12.6g/kg group: Males had a slightly greater weight increase than the control group from about the 15th day, with a difference of about 5g on the 30th day of administration. Females showed exactly the same weight increase as the control group, with no difference in body weight at the end of administration. Death occurred in 2 males (22, 34th day) and one female (31st day).

4) Cer 25.2g/kg group: Weight increase slowed down from about the 5th day in both sexes lasting until the end of administration. In males, although there was no weight decrease, the difference with the control group reached as much as 20g on the 30th day. In females, a transient weight decrease was noted on the 30th day, and the difference with the control group at the end of administration was about 16g, with significant difference. Death occurred in no cases.

B. *Food consumption (Table 3)*

Food consumption tended to decrease in both males and females with all sample drugs as compared with that in the control group. This tendency was particularly marked in the T-60 24.0g/kg, GBX 20.0g/kg, and Cer 25.2g/kg groups where the food consumption was only about half that of the control group.

C. *Observation of toxic symptom*

a. *T-60 administration groups*: In the 12.0g/kg and 24.0g/kg groups, piloerection, soft feces and depression appeared from about the 15th day. In addition, mild tremor of forelimbs, salivation, face-washing and coughing appeared every day 5-10 min after administration, disappearing gradually after 10 min with animals coughing repeatedly. Toward the end of administration, tremor of forelimbs intensified with a longer recovery time required, and in all cases loss of appetite, emaciation and piloerection were noted persistently.

b. *GBX administration groups*: From about the 15th day, in addition to the aforementioned symptoms of piloerection and soft feces, forward opening of forelimbs was noted in the 10.0g/kg and 20.0g/kg groups, beginning from immediately to 5 min after administration. From about 5-10 min after administration salivation, face-washing, tremor of forelimbs, searching behaviour, and coughing appeared, and

animals, after repeating face-washing and severe tremor of forelimbs, moved toward recovery after 30-40 min of administration. In the 20.0g/kg group there was found mixed in soft feces something whose colour was indicative of the sample drug. Loss of appetite, emaciation and depression were markedly observed in the latter period of administration.

c. *Cer administration groups*: In the 12.6g/kg and 25.2g/kg groups about two-thirds of the animals showed salivation, face-washing, chronic tremor of forelimbs and coughing about 10 min after administration from about the 20th day. These symptoms continued for about 20 min and then gradually improved. In the 25.2g/kg group several animals developed searching behaviour. It gradually improved after the animals repeated coughing and face-washing. Furthermore, loss of appetite, emaciation, piloerection, and soft feces were persistently observed until the end of administration.

D. Blood tests (Table 4, 5, 6)
a. T-60 administration groups

1) RBC: RBC was slightly decreased in the experimental groups as compared to that in the control group. Significant difference was noted between the T-60 24.0g/kg and control groups in both sexes.

2) Hemoglobin: Hemoglobin was decreased in the experimental groups as compared to that in the control group. The males of all groups and the females of the 12.0g/kg and 24.0g/kg groups showed significant difference from the control group.

3) WBC: WBC showed no marked changes in males. In females it increased more in the experimental groups than in the control group, with significant difference noted in the cases of 12.0g/kg and 24.0g/kg groups.

4) WBC percentage: Neutrophiles, basophiles, acidophiles and lymphocyte were all within normal limits in distribution, and no morphologically abnormal cells were disclosed.

b. *GBX administration groups*

1) RBC: RBC showed no marked changes in the experimental groups as compared to that in the control group on the 30th day.

2) Hemoglobin: Hemoglobin decreased in the females of the 10.0g/kg group as compared to that in the control group, with significant difference. No marked changes were noted in the other groups.

3) WBC: In males all experimental groups showed a decreasing tendency in comparison to the control group, with significant difference in the case of the 20.0g/kg group. In females no such tendency was revealed.

4) WBC percentage: WBC percentage showed no specific abnormalities, and no morphologically abnormal cells were disclosed.

c. *Cer administration groups*

RBC, hemoglobin, WBC and WBC percentage as determined on the 30th day show no marked changes in the experimental groups as compared to those in the control group. Morphologically abnormal cells were not revealed.

E. *Urine tests*

Toward the end of administration sugar was detected in the Cer 25.2g/kg group and protein and urobilinogen in the GBX 20.0g/kg group, in 3-4 cases each, but the levels were not significantly high. Results obtained both before and after administration showed no abnormalities. Comparison between the experimental and control groups also showed no abnormalities. The urinary volume tended to increase in the experimental groups. The color tone was normal.

F. Liver function test (Tables 7, 8, 9)
a. T-60 administration groups

1) BSP excretion test: In males BSP excretion was delayed in the experimental groups in comparison to that in the control group, with

significant difference noted in the cases of the 6.0g/kg and 12.0g/kg groups. No such delay was seen in females.

2) Transaminase: In males GOT and GPT were lower in the experimental groups than in the control group, with significant difference in the cases of the 6.0g/kg and 24.0g/kg groups, the former both in GOT and GPT and the latter in GOT. In females both GOT and GPT showed no significant difference between the experimental and the control group.

b. GBX administration groups

1) BSP excretion test: The experimental groups showed no tendency of delayed excretion in both sexes in comparison to the control group. Rather, excretion was somewhat delayed in the control group.

2) Transaminase: GOT showed no difference between the experimental and control groups in both sexes. GPT was slightly raised in the experimental groups in both sexes, with significant difference from the control in the cases of the females of the 5.0g/kg group.

c. Cer administration groups

1) BSP excretion test: In males excretion tended to delay in all experimental groups with increase in dosage, but no significant difference was noted from the control. In females, delayed excretion was not revealed at all.

2) Transaminase: In males both GOT and GPT were lower in the experimental groups than in the control group, with significant difference in the cases of the 12.6g/kg and 25.2g/kg groups, the former in GPT and the latter in both GOT and GPT. In females both GOT and GPT were lower in the 6.3g/kg and 25.2g/kg groups. In the 12.6g/kg group GOT and GPT tended to rise, but the difference was not significant from the control.

G. Total cholesterol, total protein, blood sugar (Tables 7, 8, 9)

a. *T-60 administration groups*: Total cholesterol was raised in the males of the 12.0g/kg and 24.0g/kg groups compared to that in the control group. It was found lowered in the females of the 24.0g/kg group, with significant difference from the control. Blood sugar tended to rise with increase in dosage in females and total protein registered a significantly high value in the males of the 24.0g/kg group. Otherwise, there was no difference from the control.

b. *GBX administration groups*: Total cholesterol was lowered in the females of the 10.0g/kg group, with significant difference from the control. Otherwise, there was no difference between the experimental and control groups in both sexes. Blood sugar was higher in the experimental groups in both sexes, with significant difference in the cases of 5.0g/kg group (males), 10.0g/kg group (females), and 20.0g/kg group (both sexes) and 10.0g/kg (females) groups than in the control group, with significant difference.

c. *Cer administration groups*: Total cholesterol tended to increase in the experimental groups in both sexes as compared to that in the control group. The difference was significant in the case of the 25.2g/kg group (males). Blood sugar was lower in the 6.3g/kg and 12.6g/kg groups in both sexes than the control but was higher in the 25.2g/ kg group in both sexes. The difference, however, was not significant. Total protein in the experimental groups showed no difference from the control in both sexes.

H. Autopsy

a. *Macroscopic observation of organs*: No specific changes were disclosed in the thoracic, abdominal, and endocrinological organs. Smear specimens of the seminal vesicle, epididymus and testis showed no abnormalities. It is unlikely that the testicular function was impaired.

b. Organ weight (Tables 10, 11, 12, Fig. 4)
1) T-60 administration groups

a) Hypophysis: The weight showed no marked variations between the experimental and

control groups. A higher weight than the control with significant difference, however, was noted in the males of the 12.0g/kg group and the females of the 24.0g/kg group.

b) Thymus: The weight was lower in the males of the 24.0g/ kg group and the females of the 12.0g/kg and 24.0g/kg groups than the control, each with significant difference.

c) Heart: The weight tended to be decreased in the high-dose groups in both sexes. In the 24.0g/kg group it was decreased in both sexes, with significant difference from the control.

d) Liver: There was no difference between the experimental and control groups in both sexes.

e) Kidney: Here, too, the weight tended to be decreased in the high-dose groups in both sexes, with significant difference bilaterally between the 24.0g/kg and control groups in males.

f) Adrenal gland: In males the weighy tended to increase in the experimental groups as compared to that in the control group, with significant difference in the cases of the 12.0g/kg group (bilateral) and the 24.0g/kg group (left). In females the weight was little affected except that it was slightly increased in the 6.0g/kg group.

g) Spleen: Except that the weight was decreased in the 24.0g/kg group in both sexes, there was no marked difference between the experimental and control groups.

h) Prostate: The weight decreased as the dosage was increased, and significant difference was noted between the control and the 12.0gkg and 24.0g/kg groups.

i) Testis, epididymus: None of the experimental groups showed difference with the control group.

j) Seminal vesicle: The weight was higher in the 6.0g/kg group than the control, but was lower in the 24.0g/kg group with significant difference.

2) *GBX administration groups*

a) Hypophysis: The weight was increased in the males of the 10.0g/kg group, with significant difference from the control. Otherwise, no difference was revealed between the experimental and control groups in both sexes.

b) Thymus: In males, the weight tended to decrease as the dose was increased, while in females the decreasing tendency was evident.

c) Heart: In males the weight was lower in the 20.0g/kg group, with significant difference from the control, but in females it was rather increased in all experimental groups.

d) Liver: The weight tended to be increased in the experimental groups in both sexes, but none of the groups showed any significant difference with the control group.

e) Kidneys: In males the weight tended to decrease as the dosage was increased, and significant difference was noted between the 20.0g/kg and the control groups (left). In females, contrarily, the weight increased with dosage, with significant difference from the control in the case of the 20.0g/k group (left).

f) Adrenal glands: The weight increased with dosage in experimental groups in both sexes. In the 20.0g/kg group significant difference was noted from the control in the left kidney in both sexes. In the right kidney, the males of all experimental groups showed significant difference from the control.

g) Spleen: In males the weight tended to decrease with increase in dosage. In females an increasing tendency was noted, but neither showed significant difference from the control.

h) Prostate: The weight was lower in the experimental groups than the control, but not so evidently as in the T-60 administration groups. The relation to dosage was not clear.

i) Testis, epididymus: The weight of the testes in the 20.0g/kg group and that of the epididymus in the 5.0g/ kg and 10.0g/kg groups were lower than the control, with significant difference.

j) Seminal vesicle: the weight was lower in all the experimental groups, with significant difference from the control in the case of the 20.0g/kg group.

3) *Cer administration groups*

a) Hypophysis: The weight was increased in the males of the 12.6g/kg and 25.2g/kg groups in the females of the 6.3g/kg group, with significant difference from the control.

b) Thymus: It weighed less in the females of the 25.2 g/kg group than in the control group, with significant difference. Otherwise, there was no difference between the experimental and control groups in both sexes.

c) Heart: None of the experimental groups showed great difference from the control group in both sexes.

d) Liver: The weight tended to increase with dosage in the experimental groups in both sexes. The difference between the 25.2g/kg group and the control was significance in both sexes.

e) Kidneys: As in the liver, the weight tended to increase with dosage in both sexes in the experimental groups, and the 25.2g/kg showed significant difference from the control.

f) Adrenal glands: The weight was increased in experimental groups in both sexes except in the 6.3g/kg group. Significant difference was noted from the control in the 6.3g/kg (right, both sexes), 12.6g/kg (bilateral, both sexes) and 25.2g/ kg (bilateral, both sexes) groups.

g) Spleen: Except that the weight was lower in the females of the 25.2g/kg group, with significant difference from the control, no great difference was noted between the experimental and control groups.

h) Prostate: The weight was higher in the experimental groups but with no significant difference. A correlation between dosage and weight was not revealed.

i) Testis: the weight increased as the dosage was increased in the experimental groups, with significant difference in the cases of the 12.6g/kg and 25.2g/kg groups.

j) Epididymus: No difference was shown between the experimental and control groups.

k) Seminal vesicle: All experimental groups showed a higher weight, but with no significant difference.

4) *Weight of prostate per 100g of body weight (Fig. 4)*

a) T-60 administration groups: As the dosage was increased, the weight tended to decrease in the experimental groups, with significant difference from the control in the cases of the 12.0g/kg and 24.0g/kg groups.

b) GBX administration groups: With increase in dosage, a slight weight-increasing tendency was noted in the experimental groups, but the difference was of no significance.

c) Cer administration groups: The weight was slightly higher in the experimental groups, but with no significant difference.

c. Pathohistological observations
1) T-60 administration groups

a) Control group

(1) Prostate: The parenchyma of the prostate was composed of glandular ducts. The ducts had no clear-cut basal membranes and the interior surface was covered with glandular epithelium. The width of the ducts varied greatly depending on the height of the ducts. For convenience' sake the letters X and Y will be used here, the former indicating narrow glandular ducts and the altter wide ducts. There appearded three types of glandularducts: X ducts, dilated X ducts, and Y ducts. Seminal

ductules with abundant polynucleic gigantic cells, which seemed to be Sertoli's cells, were found in some areas. Otherwise, there were no abnormal findings.

(2) Liver: Venous congestion and slight deposit of fat droplets were seen. No other abnormal findings were obtained.

No abnormalities were found in the other organs.

b) T-60 6.0g/kg group

(1) Prostate: Findings varied from case to case, some consisting of only Y ducts and others X and dilated X ducts.

(2) Testis: Marked degeneration of seminal ductules and atrophic seminal ductules rich in gigantic cells were seen in a small number of cases.

(3) Liver: Fat deposit, diffuse cellular atrophy, and cellular dissociation were noted. They were severe in degree.

(4) Hypophysis: Congestion was disclosed in a small number of cases.

c) T-60 12.0g/kg group

(1) Prostate: Similar findings were obtained in all cases. It consisted mainly of X ducts, mixed with dilated X ducts.

(2) Testis: No specific findings were obtained.

(3) Liver: The changes were particularly evident in females and atrophied liver cells and pimelosis were markedly seen. In a small number of cases pimelosis was quite marked, and moreover intrasinusoidal congestion was associated.

(4) Kidney: Congestion and urinary cast were noted in about half the cases.

(5) Hypophysis: Marked congestion and congestive edema was seen in a small number of cases.

d) T-60 24.0g/kg group

(1) Prostate: Slight degeneration of ducts was noted in about half the cases. Findings, however, were not uniform, some cases consisting of X and Y ducts and others dilated X or Y ducts.

(2) Testis: Hypoplasia of seminal ductules and necrosis due to coagulation of sperms were noted in a small area in all cases.

(3) Liver: Atrophy of cells and scattered fatty droplets were shown in about half the cases. Marked congestion was noted in a few cases.

(4) Kidneys: A moderate degree of congestion was shown in all cases. Otherwise, there were no specific findings.

(5) Pancreas: Localized vacuolation or pimelosis of the acinus was observed in a small number of cases.

(6) Hypophysis: All cases showed slight congestion.

(7) Thyroid: In many cases colloid was thin (some cases devoid of it) and the epithelium was vacuolated.

2) GBX administration groups

a) Control group

(1) Prostate: In all cases it consisted of X ducts and dilated X ducts. In a small number of cases Y ducts were also noted.

(2) Testis: No abnormal findings.

(3) Liver: Very slight cellular dissociation, congestion and scattered fatty droplets were shown in a small number of cases.

No changes were disclosed in the other organs.

b) GBX 5.0g/kg group

(1) Prostate: In many cases Y ducts were somewhat abundantly noted, but generally the findings were similar to those in the T-60 6.0g/kg group.

(2) Testis: No specific findings.

(3) Liver: Diffuse cellular atrophy and fatty droplets were observed.

(4) Kidney: No specific findings.

(5) Hypophysis: Congestion was seen in all cases.

No specific findings were obtained in the other organs.

c) GBX 10.0g/kg group

(1) Prostate: Findings were similar in all cases. The prostate consisted mainly of X ducts, and dilated X ducts were few.

(2) Testis: No specific findings.

(3) Liver: Atrophy of cells and deposit of fat droplets were noted as in the T-60 12.0g/kg group. They were less marked than those in the T-60 administration groups but more marked than those in the Cer administration groups.

(4) Hypophysis: Congestion or congestive edema was seen in about half the cases.

d) GBX 20.0g/kg group

(1) Prostate: Some cases consisted of X and dilated X ducts while others consisted mainly of Y ducts.

(2) Testis: No specific findings.

(3) Liver: Cellular dissociation and localized cellular atrophy were noted in many cases, but fat scarcely appeared.

(4) Kidney: No specific findings.

(5) Hypophysis: Somewhat marked congestion was disclosed in about half the cases.

(6) Thyroid: The colloid was thin and the epithelium was vacuolated.

3) Cer administration groups

a) Control group

(1) Prostate: The prostate consisted of X ducts in about half the cases. In the other half it consisted of X ducts and dilated X ducts.

(2) Testis: No specific findings.

(3) Liver: Slight congestion and deposit of fatty droplets were noted in all cases.

(4) No specific findings.

(5) Hypophysis: Acidophilic cells were slightly increased in a small number of cases.

No specific changes were shown in the other organs.

b) Cer 6.3g/kg group

(1) Prostate: In many cases it consisted of X ducts and dilated X ducts, while in some cases Y ducts were markedly observed.

(2) Testis: Slight hypoplasia of sperms was shown in a small number of cases.

(3) Liver: In about half the cases deposit of fatty droplets and diffuse cellular atrophy were slightly noted.

No specific changes were seen in other organs.

c) Cer 12.6g/kg group

(1) Prostate: It consisted of X ducts in all cases, mixed with Y ducts in a few cases. Slight degeneration or disappearance of glandular ducts was noted in most cases, but the degree was slight. The stroma showed no abnormalities.

(2) Testis: Seminal ductules suggestive of hypoplasia of sperms were locally noted immediately below the capsule.

(3) Liver: Slight cellular atrophy, dissociation of cell cords, and deposit of fatty droplets were seen.

(4) Kidney: Slight congestion of the cortico-medullary border zone and glomeruli and urinary casts occurred in about half the cases.

(5) Hypophysis: Increased acidophilic cells were seen in a small number of cases.

d) Cer 25.2g/kg group

(1) Prostate: In most cases X ducts were dilated, some with degeneration or disappearance of the glandular epithelium. The degree of change varied with cases. Y ducts were generally scarce.

(2) Testis: Seminal ductules suggestive of hypoplasia of sperms were disclosed in a small number of cases, but degeneration or necrosis was not observed. Generally findings were scarce.

(3) Liver: Slight cellular atrophy and deposit of scattered fatty droplets occurred in about half the cases.

(4) Kidney: Only slight congestion of glomeruli was noted in about half the cases, and the renal tubules showed no changes at all.

(5) Hypophysis: Only acidophilic cells were slightly increased.

(6) Thyroid: The colloid was thin and sometimes absent, and the epithelium was vacuolated in many cases.

3. Chronic Toxicity Test of Cer
A. Body weight and death (Fig. 5)

a. Control group: The control group, which received 10ml/kg of CMC solution, showed normal weight increases in both sexes.

b. Cer 1.6g/kg group: In males the body weight was greater than the control, by about 20g on the 30th day and by about 35g on the 105th day. Thereafter, it decreased transiently. After the 135th day increase and decrease occurred alternately and the difference with the control at the end of administration was about 12g. In females weight increase became somewhat unsteady after the 135th day and the body weight slightly decreased after the 165th day. However, the tendency was the same as that of the control as a whole. Death occurred in one male and one female, on the 134 and 166th day respectively.

c. Cer 3.2g/kg group: The body weight in males showed no decrease up to the 165th day and was about 20g greater than the control. After the 165th day it slightly decreased so that the difference with the control was only about 5g at the end of administration. In females, the body weight ceased increasing after the 105th day and then slightly decreased after the 165th day. At the end of administration it was about 10g smaller than the control. One male died on the 117th day.

d. Cer 6.3g/kg group: As in the previous two groups, the males showed normal weight increase up to the 165th day without weight decrease, and the body weight was about 20g greater than the control. However, toward the end of administration the body weight decreased slightly so that the difference with the control ended up with about 14g. In females, the weight increase slowed down after the 105th day and the body weight at the end of administration was about 1.5g smaller than the control. One male died on the 165th day.

e. Cer 12.6g/kg group: The males showed a slower weight increase than the control and the three previous groups. This tendency was intensified after the 105th day and the body weight at the end of administration was about 40g smaller than the control with significant difference. In females, the body weight ceased increasing after the 120th day. On the contrary, it tended to decrease and the difference with the control at the end of administration was about 16g, though with no significant difference. Death occurred in 2 males, on the 124th and 164th day.

B. Food consumption (Table 13)

The food consumption decreased from about the second month in the 12.6g/kg group (both sexes) and from about the fourth month in the 6.3g/kg group (both sexes). The other groups showed no great difference with the control, but

generally the consumption tended to decrease as the dosage was increased.

C. Observation of toxic symptoms

The toxic symptoms were nearly the same as those observed in the subacute toxicity test. In the 1.6 and 3.2g/kg groups, beginning from about the 90th day, there occurred immediately after administration face-washing, coughing and slight general tremor in about one-third of the cases lasting about 15 min. At the time of recovery the animals were slightly in sedation. The intensity of symptoms did not change until the end of administration. Piloerection was also noted. Generally speaking, the intensity of symptoms was stronger in males. In the 6.3g/kg and 12.6g/kg groups the same symptoms as seen above appeared from about the 70th day and tremor of forelimbs, searching behavior, coughing, face-washing and salivation from about the 100th day. The symptoms lasted about 15 min and then gradually moved toward recovery. Toward the end of administration loss of appetite, emaciation and piloerection occurred in all cases and alopecia in one male.

D. Blood tests (Tables 14, 15)

a. WBC: No marked difference was noted between the experimental and control groups when comparison was made before administration, on the 90th day and 180th day. Nevertheless, the number was found to be smaller than the control in the males of the 6.3g/kg group on the 180th day and in both sexes of the 12.6g/kg group, all with significant difference.

b. Hemoglobin: Except that the males of the 6.3g/kg group were smaller in number than the control with significant difference on the 90th day, there was no difference between the experimental and the control groups in both sexes at all time periods.

c. WBC: Some difference was noted between the experimental and the control groups before administration and on the 90th day in both sexes, but the difference was not significant. On the 180th day, however, the males of all experimental groups showed a smaller value than the control, with significant difference in the cases of the 1.6g/kg, 3.2g/kg and 12.6g/kg groups. In females, WBC was slightly increased in all experimental groups, but no significant difference was noted.

e. WBC percentage: As in the subacute toxicity test, the results showed no marked difference in cell distribution between the experimental and control groups at all time periods. No morphologically abnormal cells appeared.

E. Urine tests

No abnormal findings were obtained in sugar, protein, and urobilinogen. The urinary volume, however, tended to increase in the experimental groups.

F. Liver function test (Table 16)

a. BSP excretion test: No tendency of excretion delay was noted in the experimental groups in both sexes as compared to the control. In the females of the 3.2g/kg group the excretion was even faster than the control.

b. Transaminase: GOT and GPT were not increase with dosage in the experimental groups in both sexes, but GPT in the males of the 3.2g/kg group showed a higher value than the control and GOT in the females of the 12.6g/kg group a lower value, each with significant difference was noted.

G. Total cholesterol, total protein, blood sugar (Table 16)

a. Total cholesterol: There was no definite tendency noted. In males the 3.2g/kg and 6.3g/kg groups showed the same value as the control, the 1.6g/kg group a lower than the control, and the 12.6g/kg group showed a slightly higher value than the control, but no significant difference was noted.

b. Total protein: The males of the 1.6g/kg and 3.2g/kg groups showed a lower value than the

control, with significant difference. In females, there was no difference between the experimental and the control groups.

c. Blood sugar: Males generally showed a higher value than the control in all groups, but the correlation to dosage was not evidenced. However, in females, the value tended to increase with dosage and significant difference from the control was noted in the 3.2, 6.3, and 12.6g/kg groups.

H. Autopsy

a. Macroscopic observation of organs: In a few cases in the 6.3g/kg and 12.6g/kg groups there was noted a chronic inflammatory picture in the lung. Otherwise, no macroscopic changes were noted in the thoracic, abdominal or endocrine organs. Smear specimens of the seminal vesicle, epididymus and testis showed no abnormalities. It is unlikely that the function of the testis was impaired.

b. Organ weight (Table 17, Fig. 6)

1) Hypophysis: The weight was lower in the males of the 12.6g/kg group and in the females of all experimental groups than the control, with significant difference.

2) Thymus: The weight tended to decrease with increase in dosage in all experimental groups in both sexes, with significant difference from the control in the cases of the 6.3g/kg (males) and 12.6g/kg (both sexes) groups.

3) Heart: Except that the females of the 1.6g/kg group were greater than the control, there was no difference between the experimental and control groups.

4) Liver: Males showed no difference between the experimental and control groups, but the females of the experimental groups were generally greater than the control, with significant difference.

5) Kidney: It weighed less in the males of the 12.6g/kg group in the bilateral kidneys than the control, with significant difference. Otherwise, there was no difference between the experimental and control groups.

6) Adrenal gland: Generally, the weight tended to increase in the experimental groups in both sexes, with significant difference from the control in the cases of the 1.6g/kg (females), 3.2g/kg (males) and 6.3g/kg (males) groups.

7) Spleen: In males, the weight was decreased in the 12.6g/kg group, with significant difference from the control. The other three groups showed a slightly higher weight than the control. In females, all experimental groups showed a higher weight than the control, and the weight tended to increase, with dosage. The difference with the control was significant in the cases of the 3.2g/kg, 6.3g/kg and 12.6g/kg groups.

8) Prostate: It weighed less in all the experimental groups, and furthermore the weight tended to decrease as the dosage was increased. The difference with the control was significant in the cases of the 3.2g/kg, 6.3g/kg, and 12.6g/kg groups. Even in terms of weight per 100g of body weight, the tendency was of the same and significant difference was noted in the 3.2g/kg, 6.3g/kg, and 12.6g/kg groups.

c. Pathohistological findings
1. Control group

a) Prostate: The glandular ducts folded and were covered with relatively high epithelium which was slightly protruding like papilloma. They were composed of two types of ducts, one type of being a narrow lumen (hereinafter abbreviated as X) and the other being a wide lumen with low epithelium (hereinafter abbreviated as Y). Marked widening of lumen was seen in some Y ducts and the epithelium underwent squamous metaplasis in response to the widening. However, falling-off or disappearance of the epithelium was not observed.

b) Testis: The pictures of seminal ductules varied slightly with cases depending on the stage of spermatogenesis, such as delayed

spermatogenesis (hereinafter abbreviated as C), homogenous coagulation (D), numerous Sertoli's cells (E), and transitory impairment of maturation of sperms (F). Degeneration of spermatoblasts (G) was not found at all.

c) Liver: Slight dissociation and partial atrophy of liver cells with fatty droplets were disclosed in a small number of cases. But generally lesions were scarce. Congestion occurred in no cases.

d) Kidneys: Deposit of basophilic crystals in the area between the cortex and medulla, slight congestion of stroma or urinary casts were observed in a small number of cases.

e) Spleen: The pulp slightly coarse, and the blood volume varied with cases.

f) Thymus: The medulla was wide and the cortex developed well, but the cellular density was coarse in many cases.

g) Adrenal gland: In general, the cortex was of uniformly light staining and in some cases distinction of different layers was rather difficult. Severe congestion was also seen in the area between the cortex and medulla in some cases.

h) Thyroid: Colloid was thin. The epithelium was entirely within normal limits.

i) Hypophysis: Acidophiles increased in number in many cases. The organ was slightly edematous, and hemorrhage was seen in a few cases.

No specific findings were obtained in the heart, lungs, brain, pancreas, digestive tracts, bone marrow and ovary.

2) Cer 1.6g/kg group

a) Prostate: The epithelium of X ducts was vacuolated and fell off at time. On the other hand, Y ducts showed marked squamous metaplasia in a few cases, but the difference with the control was not significant.

b) Testis: The findings C, D, E and F were seen sporadically in the normal seminal ductules.

c) Liver: Slight but wide-spread atrophy of liver cells, associated with irregularly-sized nuclei, was seen in a small number of cases. Congestion and fatty droplets were noted sporadically.

d) Kidney: Mild congestion and urinary casts were found in the greater majority of the cases in both sexes. In females, concentric round or irregularly-shaped basophilic crystals, which had been seen in the control group, were found in the parenchyma in the cortico-medullary border area.

e) Spleen: The pulp was congestive and coarse and was deficient in cells in general.

f) Pancreas: Partial atrophy and vacuolation of the acinus and mild edema of stroma were seen in a small number of cases.

g) Thymus: The parenchyma was coarse and the cortical cells also under-developed in a small number of cases. Cellular necrosis was found in one case.

h) Adrenal gland: In the greater majority of cases the fat was deficient and the cortex was uniformly of light staining. In a few cases there occurred severe congestion in the zonal cortex.

i) Thyroid: In most cases it lacked colloid and the epithelium underwent squamous metaplasia at times.

j) Hypophysis: In males acidophiles increased, but in females it consisted chiefly of main cells.

k) There was no great difference between the control and experimental groups in regard to other organs; brain, heart, lungs, digestive tracts, ovary and bone marrow.

3) Cer 3.2g/kg group

a) Prostate: Falling-off or degeneration of epithelium of X ducts was seen in many cases. In general, X ducts were slightly enlarged and Y ducts rather decreased.

b) Testis: The findings C, E, F were seen more frequently in this group than in the previous two groups. However, they were not so severe as to cause dysfunction.

c) Liver: Findings were similar to those seen in the 1.6g/kg group. Atrophy of liver cells, congestion, and deposit of fatty droplets were seen in a few cases.

d) Kidney: The basophilic crystals seen in the 1.6g/kg group were noted in all females, but none in males. Mild congestion and swelling of main tubules were found in nearly all cases. Granule-form deposit was present in Bowman's capsule in a few cases.

e) Spleen: The lymphatic tissue was decreased. The pulp was coarse and deficient in cells. Congestive edema was seen in a few cases.

f) Heart: Histocytes somewhat increased in the pericardium forming small cell foci. In one case they penetrated into the myocardium and in another case they formed round cellular infiltration in the myocardium.

g) Thymus: Both cortex and medulla were coarse and lacked cellular density.

h) Adrenal gland: Congestion was generally noted in females. In males congestion was not evident, and the cortex was of light staining and lacked fat.

i) Thyroid: Scanty colloid. The epithelium was somewhat atrophied and vacuolated in many cases.

j) Hypophysis: As in the 1.6g/kg group, acidophilic cells were increased in males while in females it consisted chiefly of main cells.

No specific findings were obtained in other organs as lungs, digestive tracts, pancreas, ovary and bone marrow.

4) Cer 6.3g/kg group

a) Prostate: Y ducts were fewer than X ducts. In X ducts, some cases were with necrosis of hyaline degeneration of the epithelium, others with stenotic ducts or higher epithelium, while still others with vacuolation or falling-off of epithelium. Y ducts under marked squamous metaplasia. An intermediate type between X ducts and Y ducts was also seen. The stroma was not affected very much, although serious infiltration was seen in some.

b) Testis: All the findings C, D, E and F were observed in mature seminal tubules corresponding to the stages of spermatogenesis. In most cases the tubules were normal and completely free from disturbances interfering with spermatogenesis.

c) Liver: Mild diffuse atrophy of liver cells was seen in a few cases, and the degree was somewhat stronger than that in the 3.2g/kg group. The severity of congestion varied with cases, but was not necessarily stronger than that in the previous three groups.

d) Kidney: Deposit of basophilic crystals was noted in the corticomedullary border area in females. In males this was not noted at all. Turbid swelling, degeneration or necrosis of the epithelium of the renal tubules occurred in no cases.

e) Spleen: The pulp was enlarged and in some cases it became coarse due to congestive edema. Reticulum cells, hematopoietic cells or giant cells were sparse, and deposit of hemosiderin was not evident.

f) Heart: Histocytes and round cells infiltrated beneath the pericardium and then through the stroma to the superficial layer of the myocardium. This was found in one case.

g) Pancreas: Sporadic small acinous atrophy and vacuolation or fatty degeneration of the epithelium was seen in a few cases.

h) Thymus: Serous infiltration of the cortex and medulla was seen over a wide area in a few males. In females the parenchyma was dense in all cases and hemorrhage occurred in no cases.

i) Adrenal gland: Severe congestion and dissociation of cortical cells were found in a few cases. Generally fat was scanty.

j) Thyroid: In general colloid was scanty. Vacuolar swelling and falling-off of the epithelium were seen in some cases.

No specific changes were seen in the brain, hypophysis, lungs, digestive tracts, ovary and bone marrow.

5) Cer 12.6g/kg group

a) Prostate: The findings were nearly the same as those in the 6.3g/kg group. In some cases the epithelium of X ducts completely degenerated and disappeared retaining only the basal membrane, in some other cases vacuolar degeneration and atrophy of the epithelium was noted, and in still other cases Y ducts underwent squamous metaplasia of the epithelium.

b) Testis: Degenerative cells of findings C, D, E, F and G of seminal tubules appeared somewhat more in this group than in the 6.3g/kg group. Of these, seminal tubules with coagulative necrosis and slight calcification (D) and those which consisted of only Seltori's cells (E) were relatively abundantly noted. Nevertheless, most seminal tubules were normal and such marked degeneration as indicating loss of testicular function occurred in no cases.

c) Liver: Diffuse liver atrophy occurred somewhat more frequently in this group than in the 6.3g/kg group. Irregularly-sized nuclei, congestion, and deposit of fatty droplets were extensively noted. Moreover, they were severe in degree.

d) Kidneys: Congestion was considerably severe in both sexes. Turbid swelling of main renal tubules was noted in some cases, and in females basophilic crystals were noted in all cases.

e) Spleen: Lymphatic follicles were slightly atrophied and the pulp was edematous. Giant cells and hemosiderin were not particularly evident.

f) Pancreas: Partial vacuolation of the acinus and fatty droplets occurred in a few cases, the degree being about the same as that in the 6.3g/kg group.

g) Adrenal gland: In males the blood and fat were scarce and the cortex was of light staining. Contrarily, in females, the organ was congestive and contained abundant fat.

h) Hypophysis: Main cells comprised the greater part of the parenchyma and acidophilic cells were sparse. Cells were generally full and congestion was only sporadically seen. In one case a large follicle consisting of mucoid epithelium was noted.

No specific changes were noted in other organs as brain, heart, lungs, digestive tracts, thyroid, ovary, and bone marrow.

IV. Summary

Acute, subacute and chronic toxicity tests were carried out with T-60, GBX and Cernilton using rats and mice, and the following results were obtained.

1. Acute toxicity test

The LD_{50} as determined in Donryu stain rats was high with each sample drug, and there was no difference between sexes. The lethal dose was the smallest by the intraperitoneal route with all sample drugs, whereas the LD_{50} was unobtainable by the oral and subcutaneous routes. In ddN strain mice the results were the same. As in rats, the lethal dose was the smallest by intraperitoneal route, although the sensitivity was somewhat higher than in rats. By

the oral and subcutaneous routes, GBX showed the lowest toxicity both in rats and mice. The toxicity was of the same degree both with T-60 and Cer and symptoms manifested at an early period. By the subcutaneous route, GBX exhibited the strongest toxicity both in rats and mice. The toxic symptoms seen with T-60 and Cer at a large dose were piloerection and depression occurring from immediately after to 10 min. after administration and tremor and gait disturbance after 10-30 min. In death cases these symptoms lasted 1-3 hours. Such symptoms also occurred in survivals, but they were rather slight in degree and the animals recovered in about 24 hours. With GBX no specific symptoms occurred and only piloerection, depression, emaciation, local swelling and enduration were noted by the oral and subcutaneous routes. By the intraperitoneal route slight tremor was noted additionally. In death cases food consumption and body weight decreased and animals died in 2-6 days after showing emaciation.

2. Subacute toxicity test

With T-60 suppression of weight increase appeared at a dose of 24.0g/kg in both sexes, with significant difference noted between the males and the control. Death also occurred in a few cases at this dose. With GBX suppression of weight increase occurred evidently in the males of the 10.0g/kg and 20.0g/kg groups, with significant difference from the control. Death occurred in a few cases in each of the 10.0g/kg and 20.0g/kg group. With Cer there was no marked influence noted in either sex, but in the 25.2g/kg group suppression of weight increase occurred in both sexes, with significant difference from the control in the case of females. Death occurred in 2-3 cases in each group.

Toxic symptoms were the same with all sample drugs.

General toxic symptoms appeared from the 15-20th day. Salivation, face-washing, coughing, tremor of forelimbs, and searching behavior occurred 5-20 min after administration lasting 10-20 min, and then from about 30-40 min after administration the animals gradually moved toward recovery after repeating the symptoms of coughing, face-washing, and slight tremor of forelimbs. Toward the end of administration loss of appetite, emaciation, piloerection and depression were markedly observed in all large-dose groups.

RBC, hemoglobin and WBC counts showed significant difference between experimental and control groups at times with T-60 and GBX, but not with Cer.

Results of BSP excretion test were similar with both T-60 and Cer. Namely, excretion was delayed only in males. With GBX delayed excretion was not revealed. GOT and GPT were not raised with any of the sample drugs. Total cholesterol in the T-60 administration groups and blood sugar and total protein in the GBX administration groups were higher than the control with significant difference. In the Cer administration groups total cholesterol slightly increased. Blood sugar was not found related to dosage.

In organ weight some changes were noted in the hypophysis in the Cer administration groups. The weight of the thymus tended to decrease in the experimental groups with all sample drugs. At a large dose the difference with the control was considerably great. The weight of the liver tended to increase with dosage in the GBX and Cer administration groups. It decreased, however, in the T-60 administration groups. The kidney weight increased with dosage in both sexes of the T-60 administration groups and the males of the GBX administration groups. Contrarily, it decreased in the females of the GBX administration groups and both sexes of the Cer administration groups. With regard to the adrenal gland, the weight increased with dosage in both sexes in all administration groups except in the females of the T-60 administration groups. The spleen showed no definite tendency. At a large dose, however, all administration groups showed a lower weight than the control in both sexes except in the

females of the GBX administration groups. The prostate decreased in weight as the dosage was increased in the T-60 and GBX administration groups. In the Cer administration groups the weight was greater than the control. In terms of weight per 100g of body weight, a decreasing tendency was noted in the T-60 administration groups and an increasing tendency in the GBX administration groups. In the Cer administration groups it increased slightly more than the control, but with no significant difference. The weight of the testis showed a decreasing tendency in the GBX administration groups and an increasing tendency in the Cer administration groups. The weight of the spermatocyst was decreased in the T-60 and GBX administration groups and increased in the Cer administration groups.

Pathohistological findings at a small dose were as follows. The prostate showed no great difference among the various groups receiving T-60, GBX, and Cer. The difference with the control was not great either, and there was no tendency of the development of the glandular ducts being suppressed. The testis and liver showed pathological changes in the T-60 and Cer administration groups, but not in the GBX administration groups. The kidney showed no changes with any of the sample drugs.

At a medium dose, Cer produced some changes in the glandular ducts of the prostate. With T-60 and GBX no specific changes were produced. The glandular ducts consisted mostly of high epithelium in all administration groups receiving T-60, GBX and Cer. The testes showed no changes with T-60 and GBX. However, spermatogenesis was slightly suppressed with Cer. In the liver Cer produced the least changes, followed by GBX and T-60 in that order. The kidney was not changed with GBX. The changes were approximately of the same degree and same frequency with Cer an T-60. In the hypophysis acidophilic cells were increased with Cer.

At a large dose, the prostate was composed of high epithelium in many cases in the Cer administration groups. In the T-60 and GBX administration groups dilated ducts were found mixed. Degeneration of X ducts was seen with all sample drugs. In the Cer administration groups, in particular, it occurred in nearly all cases, although the degree was about the same as that in the T-60 and GBX administration groups.

The testis was affected more in the T-60 administration groups than in the other administration groups. In the GBX administration groups it was not affected at all. The findings of the liver varied greatly among the three administration groups, the Cer administration groups showing less findings than the T-60 administration groups and the GBX administration groups showing no difference with the control group. The kidney, too, was little affected by the administration of GBX. However, congestion was seen with Cer and T-60, which occurred far more frequently with the latter. In the hypophysis congestion did not occur with Cer, but instead acidophilic cells were increased. With administration of T-60 and GBX, congestion was noted.

It can be said from the foregoing that hyperplasia of the prostate was suppressed somewhat more strongly with Cer than with T-60 and GBX, but the liver, kidney and other organs were less affected with Cer than with T-60.

3. Chronic toxicity test

In the large-dose group receiving 12.6g/kg, the animals showed normal weight increases as the control group in both sexes except that the weight increase was suppressed after the 100th day of administration. Death occurred in 1-2 cases in each group but no animals died due to drug poisoning. With administration of Cer, face-washing, coughing and general tremor of light degree were noted in the 1.6g/kg and 3.2g/kg groups from immediately after to 15 min after administration beginning from about the 90th day. In the 6.3g/kg and 12.6g/kg groups the foregoing symptoms manifested from about the 70th day; from about the 100th day tremor of forelimbs, searching behavior, coughing, face-

washing, and salivation occurred. Toward the end of administration loss of appetite, emaciation and piloerection were markedly noted in the 12.6g/kg group in both sexes. RBC and WBC counts, hemoglobin value, and WBC percentage all showed no marked alterations except that RBC and WBC counts were found increased or decreased around the 180th day in the males of the 1.6g/kg, 3.2g/kg, and 12.6g/kg groups. The urinary volume was somewhat increased, but otherwise no abnormalities were noted in urine in the experimental groups. BSP excretion and transaminase activity, too, showed no great difference between the experimental and control groups. Blood sugar was increased with dosage and significant difference was noted from the control in the case of females in the 3.2g/kg, 6.3g/kg, and 12.6g/kg groups. Total cholesterol was increased with significant difference from the control in the males of the 12.6g/kg group. Total protein was decreased in the males of the 1.6g/kg and 3.2g/kg groups, with significant difference from the control. Macroscopically, no specific changes were found in the organs. The weights of the hypophysis, prostate, thymus, adrenal gland, and spleen were decreased, especially that of the prostate which was only about 2/3 of the control.

Pathohistologically, specific findings were obtained in the prostate and testis. In the case of the prostate, when continuous administration was carried out at a small dose (1.6g/kg), the epithelium of the glandular ducts vacuolated or fell off. At a medium or large dose (3.2-12.6g/kg) degeneration, necrosis or atrophy of the epithelium occurred in many cases. Changes in the seminal ductules in the testis varied considerably. At a medium dose (3.2g/kg) thre occurred delayed spermatogenesis, increased Sertoli's cells, and suppression of maturation of spermatid. In the 6.3g/kg group, in addition to these, degeneration of spermatid was abundantly seen. In the 12.6g/kg group calcification as well as coagulative necrosis of seminal ductules was noted in many cases. In all groups, however, the seminal ductules were not all degenerated; rather, a great majority of ductules presented normal pictures. Smear specimens of the seminal vesicle, testis and epididymus showed no abnormalities, and it was unlikely that the function of the testis was impaired.

The liver showed congestion, deposit of fatty droplets and cellular atrophy in a few cases in the 1.6g/kg group. These changes intensified slightly with dosage and occurred in many cases in the 12.6g/kg group. In the kidney deposit of basophilic crystals was noted in the cortico-medullary border zone in many cases, including the control group. The signification of this manifestation is not clear. Congestion was noted in the control groups as well as in the experimental groups. In the experimental groups, however, it increased in intensity and frequency as the dosage was increased, and in the 12.6g/kg group turbid swelling of renal tubules was disclosed in some cases. Changes were also noted in other organs as the heart, lung, thymus, pancreas, and thyroid, but they were not considered due to administration of the drug since they were also noted in the control group and since the dose-response correlation was not established.

V. Discussion and Concluding Remarks

The LD_{50} of Cer, T-60 and GBX as determined in rats and mice was very large by the oral route. Moreover, toxic symptoms disappeared within a short period of time. The influence on symptoms, development, blood, and organ weight varied little with the sample drugs. However, considering that sugar was detected in the urine in the Cer 25.2g/kg group and that the blood sugar level was raised in the T-60 24.0g/kg and Cer 25.2g/kg groups, continuous administration at a large dose may cause disturbance in the metabolism of sugar. Pathohistological findings at a large dose were degeneration of the epithelium of glandular ducts, hypoplasia of sperms in the testis, fat deposit in the liver, atrophy and congestion of liver cells, and congestion and urinary casts in the kidney. Taking all findings into consideration, the influence on the prostate was the strongest

with Cer and other organs were the strongest with T-60. In chronic toxicity test where rats were used, the findings were nearly the same as those seen in the subacute toxicity test. Deposit of basophilic crystals was noted in the kidney and turbid swelling in the epithelium of the renal tubules. In the pancreas partial vacuolation, pimelosis, and atrophy of the acinus were shown, but as they were also seen in the control group, they may bear some connections with the aforementioned rise in blood sugar level.

As seen above, prolonged and missive administration of Cer may cause specific disturbances in the prostate, testis, liver, and kidney and as functional disturbance rise in blood sugar level. Yet, it must be remembered that disturbances would occur only when the drug is administered at the high dosage of 6.3g/kg or 12.6g/kg, which is about 800-1,200 times the normal human dose. On the other hand, the maximum safety dose in rats is about 3.2g/kg, or about 400 times as much as the normal human dose. From all these it is concluded that the toxic symptoms will not likely to manifest in the form of side-effects on clinical levels.

Tab. 1 Dosegs of acute toxicity.

Animal	Route	Sex	T 60	GBX	Cer
			Dose (g/kg)	Dose (g/kg)	Dose (g/kg)
Donryu rats	p.o.	♂	17.92—34.40	20.74—43.00	18.84—27.09
		♀	17.02—34.40	20.74—43.00	18.84—27.09
	s.c.	♂	7.20—14.95	12.00—21.74	10.89—15.69
		♀	——	——	——
	i.p.	♂	5.50—11.40	1.95— 6.99	3.65—13.07
		♀	——	——	——
ddN mice	p.o.	♂	25.05—39.70	39.70—79.50	31.50—46.12
		♀	17.90—44.60	33.71—83.97	18.84—39.00
	s.c.	♂	4.15—21.50	13.50—48.58	9.98—17.68
		♀	——	——	——
	i.p.	♂	3.98—20.10	1.13— 2.81	4.00—14.54
		♀	——	——	——

Tab. 2 LD 50 of T-60, GBX and Cer

( ) shows fiducial limits

animal	route	sex	Cernitin T 60	Cernitin GBX	Cernilton"
Donryu rats	p.o.	♂	34.40g/kg <	43.00g/kg <	27.01g/kg <
		♀	34.40g/kg <	43.00g/kg <	27.01g/kg <
	s.c.	♂	14.95g/kg <	20.74g/kg <	15.69g/kg <
		♀	——	——	——
	i.p.	♂	7.58g/kg (7.14— 8.04)	3.31g/kg (2.99— 3.66)	6.66g/kg (6.02— 7.35)
		♀	——	——	——
ddN mice	p.o.	♂	31.90g/kg (30.38—33.50)	55.45g/kg (49.30—62.25)	37.78g/kg (36.35—39.27)
		♀	27.75g/kg (26.66—28.89)	52.25g/kg (50.21—54.38)	27.61g/kg (26.54—28.71)
	s.c.	♂	9.47g/kg (8.78—10.21)	26.13g/kg (24.47—27.92)	13.06g/kg (12.51—13.63)
		♀	——	——	——
	i.p.	♂	8.31g/kg (7.63— 9.07)	1.72g/kg (1.64— 1.81)	6.94g/kg (6.33— 7.61)
		♀	——	——	——

Tab. 3 Food consumption during T-60, GBX, and Cernilton administration (35 days).

sample	T-60				GBX				Cernilton			
	control	6.3 g/kg	12.6 g/kg	25.2 g/kg	control	6.0 g/kg	12.0 g/kg	24.0 g/kg	control	5.0 g/kg	10.0 g/kg	20.0 g/kg
dose	18.35	14.80	14.31	8.00	17.80	14.19	17.80	7.69	19.67	16.97	14.81	12.67
	15.72	12.95	12.25	7.8	14.90	14.00	16.00	7.94	15.42	13.10	14.13	13.44

(g/animal/day)

Tab. 4 Changes in blood picture during 35 days of Cernitin T-60 administration (p.o.).
(average of five cases)

Sex	Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Baso-phile %	Acido-phile %	Neutrophile % staff	Neutrophile % segment	Lympho-cytes %	Mono-cytes %	Others %
♂	before	control	6.29±0.37	9.8±0.43	7.86±0.73	0.2	1.0	1.0	22.4	73.8	1.6	0
		6 g/kg	4.86±0.29	10.0±0.60	7.18±0.62	0	2.2	1.6	27.2	65.6	3.4	0
		12 g/kg	5.62±0.60	9.1±0.36	6.84±0.66	0.2	2.0	1.4	20.0	72.8	3.6	0
		24 g/kg	5.42±0.32	10.6±0.47	7.96±0.46	0.4	2.2	1.6	25.2	67.6	3.0	0
	after 35 days	control	7.13±0.47	13.8±0.25	9.7 ±0.31	0.2	0.8	1.4	26.4	69.0	2.2	0
		6 g/kg	6.11±0.26	12.4±0.45*	8.80±0.33	0.2	0.4	2.0	23.6	70.8	2.8	0.2
		12 g/kg	6.55±0.27	12.2±0.41*	10.12±0.48	0.2	1.2	1.4	22.0	73.2	2.0	0
		24 g/kg	5.80±0.23*	12.7±0.23*	8.80±0.33	0	3.0	1.4	29.0	64.4	2.2	0
♀	before	control	5.49±0.27	9.6±0.35	7.16±0.66	0.2	0.6	1.4	27.0	68.8	2.0	0
		6 g/kg	5.35±0.33	10.1±0.24	7.22±0.90	0.2	1.0	1.2	23.6	71.0	3.0	0
		12 g/kg	5.25±0.26	9.1±0.36	6.86±0.50	0.2	2.0	1.2	18.8	75.6	2.2	0.2
		24 g/kg	4.87±0.33	9.0±0.37	7.04±0.41	0	0.4	0.8	31.0	62.8	4.8	0
	after 35 days	control	6.96±0.28	13.8±0.26	7.64±0.71	0	0.8	1.4	24.8	69.2	3.8	0
		6 g/kg	6.92±0.40	13.8±0.61	9.18±0.48	0	2.8	1.2	25.4	70.0	2.6	0
		12 g/kg	6.17±0.27	12.6±0.39*	10.76±0.85*	0	1.8	1.0	26.8	67.8	2.6	0
		24 g/kg	5.95±0.34*	12.5±0.39*	9.19±0.47*	0	1.4	1.8	22.2	72.0	2.6	0

± : standard error * : $P < 0.05$ significant

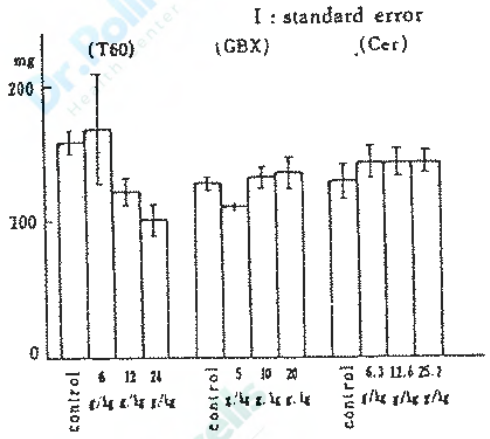

Fig. 4 Average prostate weight after 35 days T-60, GBX and CERNILTON administration (p. o.)
(Prostate weight/100 g body weight)

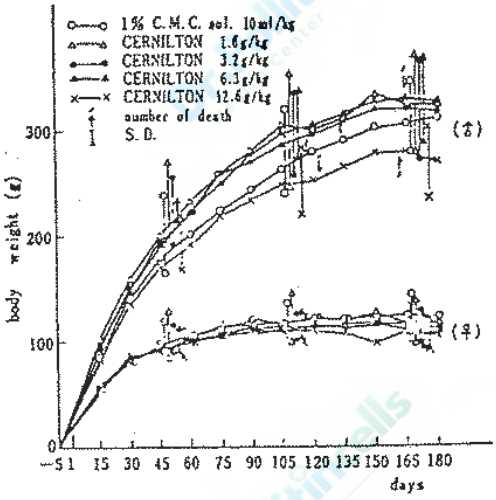

Fig. 5 Body weight increase in rats receiving CERNILTON daily for 180 days (p. o.)

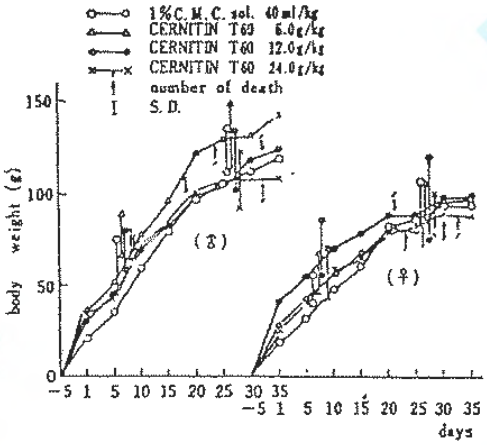

Fig. 1 Body weight increase in Rats receiving T-60 daily during 35 days. (p.o.)

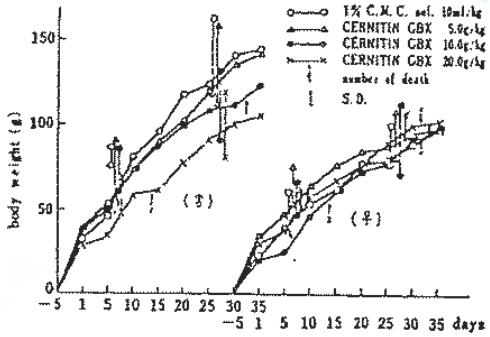

Fig. 2 Body weight increase in rats receiving GBX daily during 35 days (p. o.)

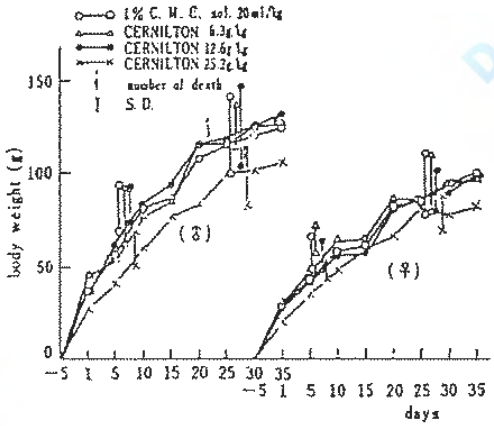

Fig. 3 Body weight increase in rats receiving CERNILTON daily during 35 days (p. o.)

Tab. 5 Changes in blood picture during 35 days of Cernitin GBX administration (p.o.)
(average of five cases)

Sex	Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Baso-phile %	Acido-phile %	Neutrophile %		Lympho-cytes %	Mono-cytes %	Others %
								staff	seg-ment			
♂	before	control	5.44±0.23	8.6±0.48	7.44±0.65	0.2	1.4	1.4	29.6	63.2	4.0	0.2
		5 g/kg	5.09±0.10	7.9±0.30	7.54±0.49	0	1.4	1 2	23.4	68.4	3.6	0
		10 g/kg	4.52±0.14	9.4±0.68	7.80±0.31	0.2	1.0	1.4	23.6	70.6	3.2	0
		20 k/kg	5.22±0.18	9.8±0.33	7.82±0.57	0.2	0.8	0.8	31.6	62.0	4.4	0.2
	after 35 days	control	6.01±0.20	12.5±0.30	10.38±0.25	0	1.8	1.0	27.2	66.6	2.8	0
		5 g/kg	6.07±0.40	12.5±0.26	9.98±0.94	0	2.4	1.6	22.2	72.0	1.6	0.2
		10 g/kg	5.80±0.20	12.5±0.30	9.62±0.67	0	0.8	2.4	24.0	70.4	2.4	0
		20 g/kg	5.89±0.56	12.8±0.34	8.72±0.56*	0.2	0.8	1.2	28.6	67.2	2.0	0
♀	before	control	5.95±0.16	9.5±0.41	6.40±0.25	0.4	2.0	1.6	21.4	70.0	3.4	0.2
		5 g/kg	5.32±0.45	8.0±0.27	7.64±0.48	0	1.4	0.6	14.4	70.4	5.0	0.2
		10 g/kg	6.08±0.34	9.2±0.42	6.24±0.50	0	1.6	1.0	23.8	70.4	3.2	0
		20 g/kg	5.04±0.22	10.4±0.41	7.56±0.38	0.2	0.6	2.6	27.6	64.0	4.8	0.2
	after 35 days	control	5.95±0.19	13.4±0.39	10.94±0.79	0	1.2	1.4	21.4	74.0	2.0	0
		5 g/kg	6.07±0.26	13.0±0.14	11.20±0.52	0.2	1.0	1.4	21.0	74.6	1.8	0
		10 g/kg	6.23±0.26	11.8±0.27*	8.94±0.51	0	2.0	1.6	26.4	67.6	2.2	0.2
		20 g/kg	6.27±0.25	12.5±0.43	9.42±0.53	0	1.0	0.6	21.0	75.6	1.8	0

± : standard error * : $P < 0.05$ significant

Tab. 6 Changes in blood picture during 35 days Cernilton administration (p.o.)
(average of five cases)

Sex	Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Baso-phile %	Acido-phile %	Neutrophile %		Lympho-cytes %	Mono-cytes %	Others %
								staff	seg-ment			
♂	before	control	5.57±0.16	10.3±0.57	9.92±0.79	0	0.8	1.2	30.6	65.6	3.8	0
		6.3 g/kg	5.70±0.28	9.2±0.30	8.18±0.23	0	0.8	1.6	24.0	70.0	3.6	0
		12.6 g/kg	5.61±0.47	10.3±0.46	8.68±0.43	0	0.8	1.4	24.6	69.2	3.8	0
		25.2 g/kg	5.04±0.22	10.4±0.41	8.56±0.38	0	0.8	0.8	23.4	74.8	1.8	0
	after 35 days	control	6.56±0.34	13.0±0.14	10.10±0.56	0	1.6	1.2	28.4	66.6	2.2	0
		6.3 g/kg	6.10±0.34	13.0±0.14	9.86±0.50	0	2.0	1.4	25.4	68.8	2.4	0
		12.6 g/kg	6.06±0.21	12.6±0.19	9.98±0.51	0.2	1.4	2.0	28.6	65.8	2.0	0
		25.2 g/kg	7.13±0.47	13.8±0.25	9.70±0.31	0	0.6	1.6	26.6	67.8	3.4	0
♀	before	control	5.65±0.20	10.0±0.53	8.56±0.88	0	0.6	1.2	25.8	68.8	3.6	0
		6.3 g/kg	6.11±0.52	9.0±0.15	8.00±0.54	0.2	0.8	1.4	26.4	69.0	2.2	0
		12.6 g/kg	5.96±0.14	10.7±0.83	7.42±0.44	0	0.8	1.6	27.0	67.0	3.6	0
		25.2 g/kg	5.19±0.25	9.7±0.44	7.18±0.21	0	1.2	1.4	26.2	68.2	3.0	0
	after 35 days	control	6.18±0.22	13.2±0.14	8.76±0.47	2.0	0	0.8	28.4	66.6	2.2	0
		6.3 g/kg	6.67±0.24	13.5±0.26	9.88±0.70	0	1.2	1.0	25.6	69.6	2.6	0
		12.6 g/kg	5.86±0.14	13.2±0.32	9.18±0.53	0	1.6	0.4	20.4	74.8	2.8	0
		25.2 g/kg	6.96±0.28	13.8±0.26	7.64±0.71	0	2.0	0.8	22.4	72.2	2.6	0

± : standard error

Tab. 7 Hepatic function on 35 th day of T-60 administration (p.o.)

Sex	Dose	BSP (%)	Transaminase (Karmen unit)		Cholesterol (mg/dl)	Blood suger (mg/dl)	Total protein (g/dl)
			GOT	GPT			
♂	control	10.4±3.8	91.8±6.0	31.3±2.2	49.7±3.4	95.6±32.5	7.1±0.3
	6 g/kg	20.5±3.0*	70.5±2.2*	24.0±1.4*	55.9±2.9	72.7± 3.8	7.4±0.2
	12 g/kg	20.5±1.7*	78.3±2.7	28.0±1.3	70.6±4.6*	69.8±26.1	7.6±0.2
	24 g/kg	13.1±2.8	68.3±0.6*	25.0±3.6	64.0±2.7*	112.8± 3.4	8.0±0.1*
♀	control	12.1±1.4	71.2±2.4	25.6±0.6	58.3±4.9	88.5±16.5	7.6±0.2
	6 g/kg	12.6±1.5	70.3±3.5	24.3±1.5	56.0±3.6	55.7± 0.6	7.4±0.1
	12 g/kg	8.2±2.0	67.0±4.4	25.5±1.8	51.1±1.9	133.4±12.6	7.8±0.1
	24 g/kg	8.8±2.8	71.0±5.6	31.3±7.1	40.0±3.2*	100.4±36.6	7.6±2.5

± : standard error * : P <0.05 significant

Tab. 8 Hepatic function on 35 th day of GBX administration (p.o.)

Sex	Dose	BSP (%)	Transaminase (Karmen unit)		Cholesterol (mg/dl)	Blood suger (mg/dl)	Total protein (g/dl)
			GOT	GPT			
♂	control	23.7±2.7	85.4±3.3	28.4±1.9	54.2±4.1	72.8± 1.8	7.4±0.2
	5 g/kg	9.2±2.1*	92.0±3.0	31.3±4.3	56.5±1.6	141.4±14.5*	7.8±0.1*
	10 g/kg	14.1±3.1*	84.8±6.0	29.0±1.8	60.5±1.9	124.9±17.9	7.5±0.1
	20 g/kg	7.8±5.0*	78.8±0.8	29.0±1.5	57.1±3.1	136.9±12.9*	7.2±0.2
♀	control	8.0±1.3	73.8±4.1	22.8±0.8	50.2±3.6	76.8± 6.0	7.0±0.2
	5 g/kg	5.6±1.0	74.5±7.3	29.5±1.0*	49.2±2.6	100.9±12.1	7.7±0.2*
	10 g/kg	4.2±1.0*	66.0±2.6	25.7±1.5	36.6±3.8*	129.0± 8.1*	7.7±0.2*
	20 g/kg	6.0±1.5	70.3±3.8	26.5±3.0	40.4±1.8	133.4± 9.1*	7.5±0.2

± : standard error * : P <0.05 significant

Tab. 9 Hepatic function on 35 th day of Cernilton administration (p.o.).

Sex	Dose	BSP (%)	Transaminase (Karmen unit)		Cholesterol (mg/dl)	Blood suger (mg/dl)	Total protein (g/dl)
			GOT	GPT			
♂	control	10.4±3.8	91.8±6.0	31.3±2.2	49.7±3.4	95.6±32.5	7.1±0.3
	6.3 g/kg	15.1±3.8	78.8±3.3	28.8±1.9	51.5±2.8	56.2±11.4	7.8±0.1
	12.6 g/kg	14.0±4.4	78.5±2.9	24.0±0.8*	55.3±5.5	59.4± 6.8	7.5±0.2
	25.2 g/kg	18.0±6.6	71.0±1.2*	26.8±1.5*	60.8±6.0	111.8± 5.8	7.6±0.1
♀	control	12.1±1.4	71.2±2.4	25.6±0.6	58.3±4.9	88.5±16.5	7.5±0.5
	6.3 g/kg	7.6±1.1*	68.4±4.2	23.2±1.2	66.2±3.6	76.5±14.6	7.6±0.1
	12.6 g/kg	7.5±1.9	77.3±4.6	26.3±1.6	63.7±6.4	72.8±14.1	7.7±0.1
	25.2 g/kg	9.4±2.2	63.8±3.8	21.3±1.3	74.8±4.6*	117.1± 7.3	7.4±0.4

± : standard error * : P <0.05 significant

Tab. 10 Average organ weight after 35 days

Sex	Dose	Hypophisis (mg)	Thymus (mg)	Heart (mg)	Liver (g)	Kidney (mg)	
						L.	R.
♂	control (8)	9.0±0.3	323.9±32.5	818.3±39.0	6.90±0.41	808.5±39.0	817.4±34.7
	6 g/kg (9)	9.4±0.8	374.0±42.4	924.0±30.1*	7.74±0.39	922.9±27.2*	879.7±31.7
	12 g/kg (9)	10.9±0.4*	335.1±19.1	878.9±23.8	6.90±0.25	795.7±24.5	807.9±19.3
	24 g/kg (7)	8.7±0.4	218.6±20.6*	715.9±23.3*	6.58±0.21	678.1±18.4*	674.6±21.6*
♀	control (10)	12.0±0.5	437.7±33.0	754.1±19.3	6.59±0.32	730.3±26.2	738.4±25.4
	6 g/kg (9)	10.7±1.8	440.4±26.4	812.7±28.8	6.38±0.16	778.0±31.1	752.3±37.5
	12 g/kg (9)	11.2±0.8	327.3±23.8*	713.3±24.5	6.58±0.24	744.9±35.8	733.4±37.6
	24 g/kg (7)	18.1±1.9*	347.0± 9.1*	655.9±28.1*	6.03±0.44	686.3±30.6	659.4±30 3

± : standard error * : P<0.05 significant ( ) : number of cases

Tab. 11 Average organ weight after 35 days

Sex	Dose	Hypophisis (mg)	Thymus (mg)	Heart (mg)	Liver (g)	Kidney (mg)	
						L.	R.
♂	control (10)	8.5±0.5	359.3±18.4	904.7±29.0	7.22±0.30	901.2±27.1	860.5±24.8
	5 g/kg (9)	7.8±0.5	338.8±28.6	901.2±30.0	8.21±0.25*	885.1±33.1	863.2±29.6
	10 g/kg (8)	9.8±0.4*	347.9±14.3	878.9±34.7	8.29±0.26*	877.0±31.3	860.3±36.6
	20 g/kg (9)	8.6±0.9	298.4±26.1	794.7±30.9*	8.83±0.29*	828.9±21.5*	806.2±26.7
♀	control (10)	12.4±2.7	408.6±10.0	765.0±24.5	6.61±0.39	756.8±34.6	737.4±16.4
	5 g/kg (9)	12.8±1.0	383.2±33.3	794.6±26.2	7.74±0.35*	731.2±30.3	716.9±34.2
	10 g/kg (7)	12.7±1.1	388.9±24.6	782.6±27.2	8.10±0.24*	838.1±32.6	816.9±26.9
	20 g/kg (7)	12.6±0.5	384.1±21.1	837.0±39.2	8.81±0.51*	917.3±41.0*	837.0±33.3

± : standard eror * : P<0.05 significant ( ) : number of cases

Tab. 12 Average organ weight after 35 days

Sex	Dose	Hypophisis (mg)	Thymus (mg)	Heart (mg)	Liver (g)	Kidney (mg)	
						L.	R.
♂	control (9)	9.0±0.3	323.9±32.5	818.3±39.0	6.90±0.41	808.5±39.0	817.4±34.7
	6.3 g/kg (9)	9.7±0.4	343.0±13.2	886.2±20.1	7.07±0.12	858.8±20.6	836.2±17.0
	12.6 g/kg (8)	10.1±0.4*	328.6±18.3	834.8±31.1	7.43±0.30	888.1±25.9	849.5±35.7
	25.2 g/kg (10)	11.2±0.4*	353.5±17.7	851.5±29.5	10.40±0.31*	1043.4±32.6	1035.7±30.0*
♀	control (10)	12.1±0.8	403.6±19.5	735.3±22.9	6.59±0.27	730.3±23.1	738.4±38.2
	6.3 g/kg (9)	15.6±1.1*	419.1±50.1	788.7±28.8	6.79±0.23	752.0±22.6	761.3±34.4
	12.6 g/kg (9)	14.4±1.3	385.1±24.0	789.0±29.3	6.76±0.22	763.0±26.7	751.0±26.4
	25.2 g/kg (10)	10.9±0.4	280.1±14.0*	709.0±15.8	9.24±0.30*	814.2±29.3	760.8± 8.4

± : standard error * : P<0.05 significant ( ) : number of cases

Cernitin T-60 administration (p.o.).

Adrenal (mg)		Spleen (mg)	Prostate (mg)	Testis (mg)	Epididymis (mg)	Seminal vecicle (mg)
L.	R.					
15.9±1.4	16.8±1.0	492.8±43.7	390.7±38.0	1029.4±29.6	434.3±28.3	695.6±101.2
20.3±1.9	17.2±2.0	588.2±20.2	405.6±40.1	1014.5±54.1	429.9±18.2	842.2±132.8
21.2±1.6*	20.6±1.0*	485.3±25.5	273.0±16.9*	1009.7±75.0	463.1± 9.9	649.4± 20.2
20.1±0.9*	19.1±0.9	419.0± 5.7	209.4±28.2*	1014.0±45.0	411.6±51.6	467.9± 29.1*
33.2±0.5	32.5±1.2	426.5±50.7				
38.8±1.6*	39.3±1.8*	467.6±25.9				
31.9±2.4	31.0±2.3	494.0±41.4				
32.1±1.6	28.3±3.0	338.9±36.6				

Cernitin GBX administration (p.o.).

Adrenal (mg)		Spleen (mg)	Prostate (mg)	Testis (mg)	Epididymis (mg)	Seminal vecicle (mg)
L.	R.					
13.7±1.2	11.5±1.1	553.5±28.2	306.7±18.1	1072.7±26.7	504.2± 9.6	741.2±74.0
16.0±0.5	14.2±0.5*	491.0±19.3	271.9±14.5	1068.6±45.4	404.8±12.4*	618.6±55.1
16.5±0.7	15.0±0.8*	477.1±27.6	300.0±24.7	1049.0±37.3	428.8±10.3*	645.8±45.3
19.1±0.8*	17.0±0.7*	432.1±77.4	280.0±28.3	1002.0±20.3*	501.8±51.4	408.1±17.8*
34.8±1.8	34.9±1.4	504.6±29.2				
38.2±1.4	39.7±3.8	532.7±40.0				
34.9±2.3	37.7±3.1	507.0±31.6				
42.6±3.0*	38.4±2.1	543.0±21.6				

Cernilton administration (p.o.).

Adrenal (mg)		Spleen (mg)	Prostate (mg)	Testis (mg)	Epididymis (mg)	Seminal vecicle (mg)
L.	R.					
15.9±1.4	16.8±1.0	492.8±43.7	290.7±38.0	1029.4±29.6	434.3±28.3	695.6±101.2
14.8±0.8	14.1±0.8*	488.4±13.8	322.6±22.1	1053.4±23.3	433.9± 8.0	715.3± 50.2
19.8±0.5*	19.5±0.5*	533.1±31.2	322.8±23.6	1115.6±24.3*	481.6± 9.7	894.3± 55.3
27.7±0.4*	27.1±0.3*	474.0±23.6	320.2±19.7	1150.4±30.2*	460.2±14.6	864.6± 56.8
34.2±1.6	28.8±1.7	474.0±29.1				
33.3±2.4	34.6±1.7*	537.7±49.7				
40.7±2.2*	38.7±1.0*	451.6±21.9				
39.3±1.2*	41.3±1.5*	392.3±15.6*				

Tab. 13 Food consumption during Cernilton administration (180 days). (g/animal/day)

Sex	Dose \ Months	before	1	2	3	4	5	6
♂	control	14.92	16.01	20.00	18.90	20.40	20.03	19.81
	1.6 g/kg	16.58	20.20	22.09	20.94	21.03	21.43	19.10
	3.2 g/kg	15.82	19.32	19.64	21.95	20.65	18.57	18.19
	6.3 g/kg	16.54	18.84	19.04	19.56	17.76	17.79	14.40
	12.6 g/kg	15.38	15.85	14.85	16.03	14.00	15.10	14.19
♀	control	13.92	14.22	13.68	12.66	13.13	10.39	12.41
	1.6 g/kg	13.66	14.06	13.57	12.62	12.76	13.50	12.87
	3.2 g/kg	13.68	14.39	12.38	11.85	11.76	12.17	12.14
	6.3 g/kg	14.40	14.79	12.19	11.48	11.27	10.99	11.41
	12.6 g/kg	14.14	13.24	10.23	10.16	10.14	9.70	8.91

Tab. 14 Changes in blood picture during 180 days Cernilton administration (p.o.). (male rats)

Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Baso-phile %	Acido-phile %	Neutrophile staff	Neutrophile seg-ment	Lympho-cytes %	Mono-cytes %	Others %
before	control	6.53±0.44	10.6±0.28	12.80±0.10	0	1.2	1.0	31.2	62.8	3.8	0
	1.6 g/kg	7.35±0.27	10.3±0.35	11.84±0.82	0	2.2	1.0	30.0	65.4	3.2	0.2
	3.2 g/kg	6.87±0.37	10.6±0.26	10.84±0.98	0	1.4	1.2	28.8	66.4	2.2	0
	6.3 g/kg	6.80±0.84	10.1±0.38	10.28±1.03	0	1.2	1.6	31.0	62.2	3.8	0.2
	12.6 g/kg	7.03±0.34	9.8±0.24	10.36±0.71	0	1.0	0.8	25.2	70.0	3.0	0
after 90 days	control	7.57±0.24	13.4±0.31	10.42±1.35	0.2	3.6	0.8	27.6	66.4	1.4	0
	1.6 g/kg	7.40±0.26	13.3±0.25	10.36±0.71	0.2	2.0	0.8	25.0	71.6	0.4	0
	3.2 g/kg	8.01±0.36	13.1±0.08	9.36±1.24	0.2	2.8	1.0	22.8	71.0	2.2	0
	6.3 g/kg	7.89±0.23	12.3±0.23*	8.86±0.60	0	1.6	2.2	28.2	77.6	2.4	0
	12.6 g/kg	8.23±0.28	13.2±0.17	12.3 ±0.90	0.2	3.2	0.6	28.0	65.8	3.0	0.2
after 180 days	control	7.11±0.52	11.6±0.78	12.00±0.55	0	1.8	1.6	30.2	64.8	1.6	0
	1.6 g/kg	6.91±0.52	12.6±0.96	7.98±0.28*	0	1.6	1.0	30.4	65.8	1.2	0
	3.2 g/kg	7.07±0.24	12.6±0.44	9.30±0.70*	0	1.8	1.0	25.6	69.6	1.8	0.2
	6.3 g/kg	6.55±0.41	12.8±0.32	10.64±1.06	0	1.2	0.4	29.8	66.2	2.4	0
	12.6 g/kg	6.54±0.49	12.5±0.69	9.52±0.76*	0.2	1.2	0.8	22.6	72.6	2.6	0

± : standard error * : $P < 0.05$ significant

Tab. 15 Changes in blood picture during 180 days Cernilton administration (p.o).
(female rats)

Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Baso-phile %	Acido-phlie %	Neutrophile %		Lympho-cytes %	Mono-cytes %	Others %
							staff	seg-ment			
before	control	7.35±0.43	11.6±0.35	12.00±0.99	0	2.4	1.0	25.2	67.2	4.0	0.2
	1.6 g/kg	7.35±0.52	11.8±0.36	10.44±0.87	0	2.6	1.2	32.4	59.2	4.6	0
	3.2 g/kg	6.94±0.44	11.2±0.36	8.28±0.38	0	0.8	1.2	24.8	69.8	3.2	0.2
	6.3 g/kg	6.84±0.34	10.9±0.13	10.44±0.53	0	2.2	1.2	20.0	73.4	2.8	0.4
	12.6 g/kg	6.64±0.48	10.9±0.42	12.08±1.25	0.4	2.6	1.0	25.4	67.0	3.6	0
after 90 days	control	7.12±0.55	12.0±0.40	11.00±1.39	0	2.2	0.6	26.0	68.0	4.0	0
	1.6 g/kg	7.95±0.27	11.2±0.23	10.46±0.36	0	3.4	0.2	29.0	65.4	2.0	0
	3.2 g/kg	8.39±0.25	12.3±0.55	10.84±0.60	0.6	2.2	0.4	28.2	65.8	2.8	0
	6.3 g/kg	8.09±0.35	12.3±0.34	8.70±0.67	0	1.6	0.2	22.2	72.0	4.0	0
	12.6 g/kg	7.53±0.23	12.1±0.35	11.20±0.81	0	4.6	0	28.2	65.2	2.0	0
afte 180 days	control	7.19±0.15	13.2±0.50	8.24±0.62	0	0.8	1.4	38.0	58.6	1.0	0.2
	1.6 g/kg	7.37±0.35	14.5±0.57	9.44±0.38	0	1.2	0.6	24.0	72.6	1.6	0
	3.2 g/kg	7.42±0.42	12.4±0.28	9.48±0.73	0	2.2	0.6	28.2	68.0	1.0	0
	6.3 g/kg	6.57±0.33	12.7±0.26	10.16±0.77	0	1.6	1.6	31.4	63.2	2.2	0
	12.6 g/kg	6.03±0.32*	12.6±0.34	9.50±0.64	0.2	4.8	1.8	28.0	65.6	2.0	0

± : standard error * : $P < 0.05$ signficant

Tab. 16 Hepatic function on 180 th day Cernilton administration (p.o.)

Sex	Dose	BSP (%)	Transaminase(Karmen unit)		Cholesterol (mg/dl)	Blood surger (mg/dl)	Total protein (g/dl)
			GOT	GPT			
♂	control	46.7±4.3	70.2± 7.2	41.4±6.3	96.4± 4.6	84.4±19.2	8.6±0.2
	1.6 g/kg	55.9±3.8	75.8± 2.1	31.5±1.0	68.1± 3.4*	108.5± 7.6	7.9±0.1*
	3.2 g/kg	50.7±8.0	64.8± 1.8	28.5±1.3	80.5±10.0	95.1± 6.4	7.8±0.2*
	6.3 g/kg	46.5±4.3	85.8± 6.5	33.8±5.3	93.7±10.7	97.8± 6.3	8.4±0.1
	12.6 g/kg	47.6±4.4	67.8± 4.2	34.0±4.1	144.2±20.2*	113.5± 8.9	8.9±0.3
♀	control	50.4±7.2	80.6± 5.7	29.2±0.8	120.1±10.6	88.3± 3.8	8.9±0.3
	1.6 g/kg	44.5±7.0	74.8± 4.1	28.0±1.1	106.8± 8.6	80.6± 8.4	9.1±2.8
	3.2 g/kg	29.7±1.9*	87.2±13.6	40.0±7.7*	106.2± 8.8	100.0± 2.3*	8.8±2.1
	6.3 g/kg	41.5±4.4	66.8± 5.5	21.8±5.7	99.7± 7.9	163.0±13.4*	8.3±0.2
	12.6 g/kg	50.2±4.2	64.6± 2.5*	35.0±3.8	140.0± 8.3	169.8±12.0*	9.0±0.1

± : standard error * : $P < 0.05$ significant

Tab. 17 Average organ weight after 180 days Cernilton administration (p.o.)

Sex	Dose	Hypophisis (mg)	Thymus (mg)	Heart (mg)	Liver (g)	Kidney (mg)		Adrenal (mg)		Spleen (mg)	Prostate (mg)
						L.	R.	L.	R.		
♂	control (10)	11.5 ±0.5	302.2 ±13.6	1333.5 ±66.9	11.09 ±0.47	1488.9 ±69.3	1427.2 ±61.9	21.9 ±1.0	22.6 ±0.9	755.1 ±56.4	753.8 ±69.0
	1.6 g/kg (9)	12.6 ±0.6	277.5 ±14.1	1419.3 ±38.7	11.66 ±0.49	1396.8 ±65.1	1336.9 ±59.8	23.6 ±0.9	24.0 ±1.1	774.4 ±29.9	659.9 ±75.5
	3.2 g/kg (9)	10.3 ±1.1	250.4 ±22.3	1457.4 ±28.2	11.42 ±0.37	1468.1 ±42.7	1410.9 ±40.2	26.9 ±1.8*	28.1 ±1.1*	794.6 ±52.7	500.8 ±37.3*
	6.3 g/kg (9)	11.0 ±0.4	237.9 ±25.3*	1469.6 ±25.3	11.67 ±0.31	1543.1 ±32.9	1491.8 ±21.8	25.6 ±1.1*	23.1 ±1.1	797.8 ±32.8	491.4 ±45.1*
	12.6 g/kg (8)	9.6 ±0.5*	189.5 ±16.8*	1264.3 ±32.5	10.37 ±0.35	1303.3 ±53.1*	1211.6 ±39.3*	23.4 ±1.4	22.9 ±1.8	562.4 ±16.5*	403.8 ±35.3*
♀	control (10)	14.4 ±1.4	196.8 ±12.1	824.1 ±15.7	6.71 ±0.34	784.7 ±31.0	784.9 ±27.8	27.9 ±0.7	28.5 ±1.2	460.0 ±21.0	
	1.6 g/kg (9)	11.1 ±0.4*	200.7 ± 3.8	907.4 ±35.2*	7.09 ±0.28	811.5 ±23.6	852.1 ±70.8	32.4 ±1.4*	33.2 ±1.3*	504.0 ±15.8	
	3.2 g/kg (10)	11.2 ±0.4*	195.8 ±10.4	888.3 ±28.2	9.27 ±0.26*	870.4 ±30.6	837.8 ±21.4	29.2 ±1.1	27.4 ±1.3	543.4 ±22.2*	
	6.3 g/kg (10)	11.2 ±0.4*	179.0 ± 9.2	822.9 ±12.3	7.01 ±0.13	769.4 ±16.2	763.2 ±19.9	29.7 ±0.9	30.3 ±0.8	542.2 ±21.4*	
	12.6 g/kg (10)	10.4 ±0.3*	163.3 ± 8.5*	863.1 ±21.3	7.19 ±0.20	770.5 ±25.2	771.5 ±18.7	28.2 ±0.5	25.5 ±1.1	607.0 ±45.0*	

±: stadard error *: $P < 0.05$ significant ( ): number of cases

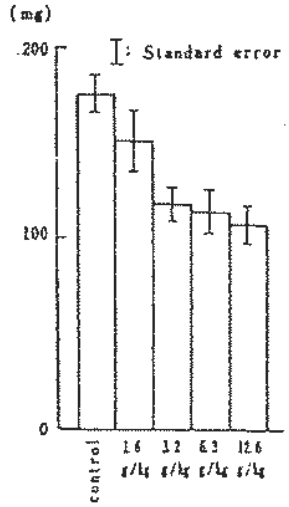

Fig. 6 Average prostate weight after 180 th day CERNILTON administration (p. o.) (prostate weight/100 g body weight)

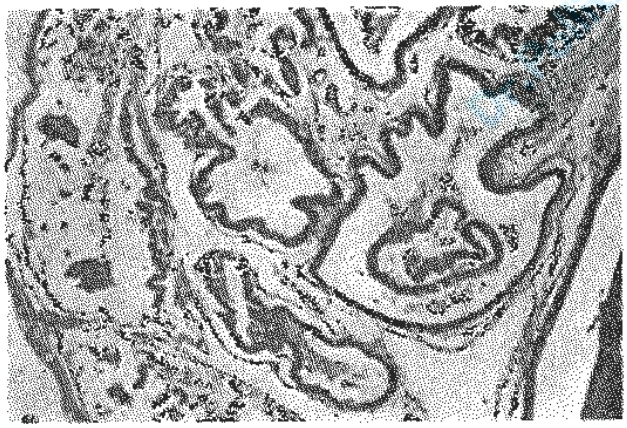

Photo 1. Prostate. Cernilton 12.6g/kg group, male (survival). Glandular ducts A (signifying Undilated glandular ducts with relatively thick epithelium which creased and protruded in the ducts like papilloma) were slightly dilated and the epithelium partially fell off and disappeared.

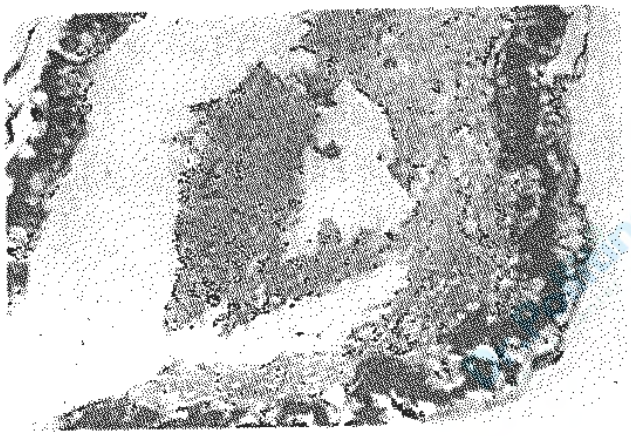

Photo 2: Prostate. Cernilton 12.6g/kg group, male (dead, 124th day). Glandular ducts B (signifying markedly dilated glandular ducts whose epithelium underwent squamous metaplasia) were partially but markedly atrophied in the epithelium.

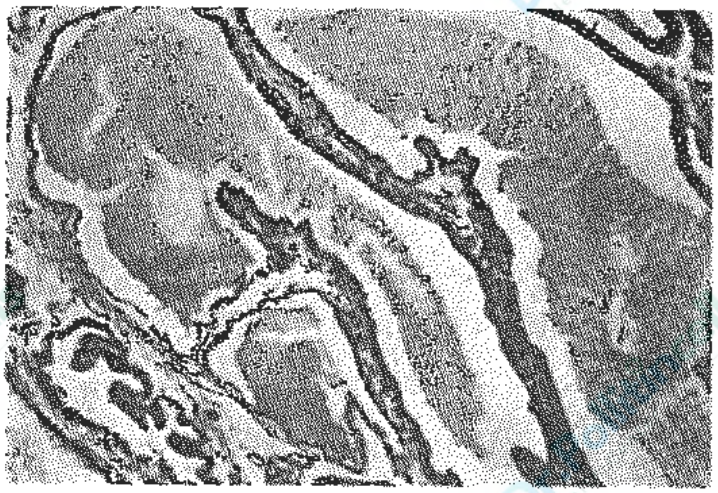

Photo 3. Prostate. Cernilton 12.6g/kg group, male (survival). Glandular ducts A were extensively degenerated and atrophied.

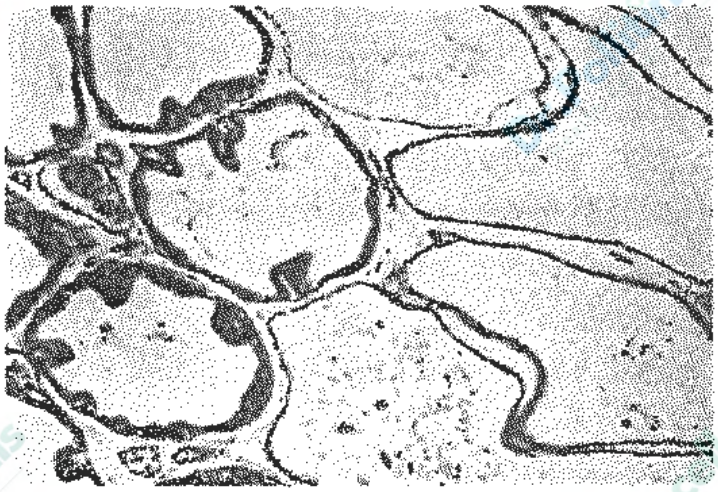

Photo 4. Prostate. Cernilton 12.6g/kg group, male (survival). Extensive vacuolation of the epithelium.

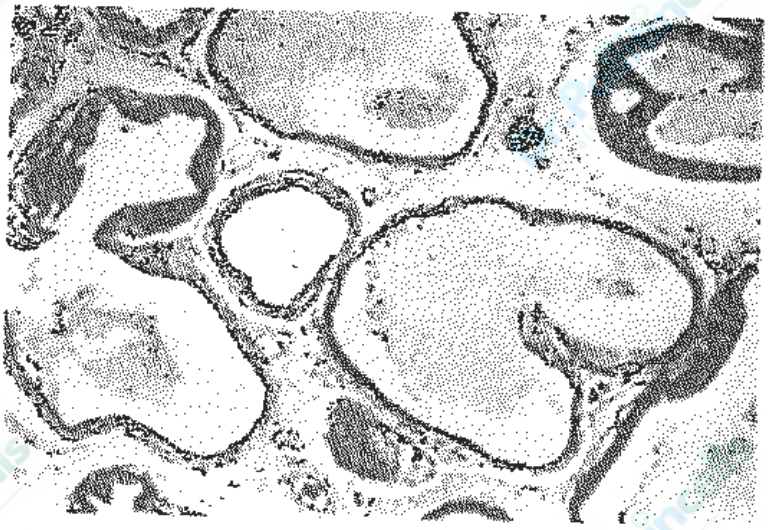

Photo 5. Prostate. Cernilton 12.6g/kg group, male (survival). Glandular ducts A were slightly dilated. Adjacent to them were dilated ducts that lost epithelium.

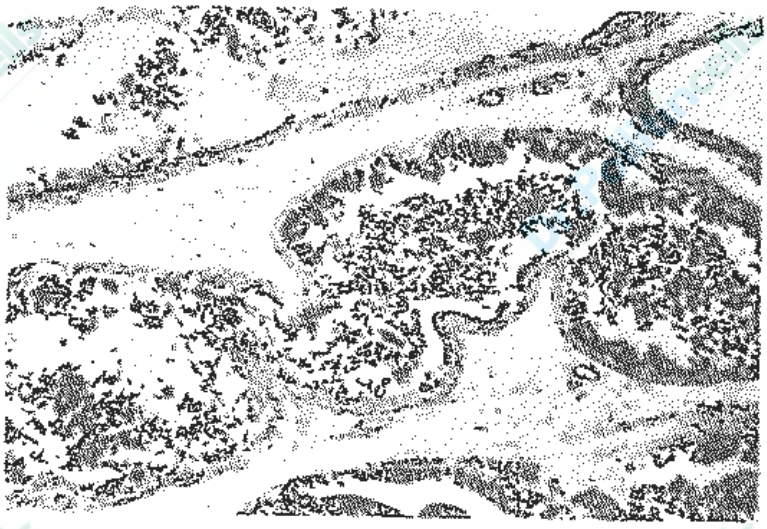

Photo 6. Prostate. Cernilton 6.3g/kg group, male (survival). Glandular ducts that lost most of the internal integument of the epithelium.

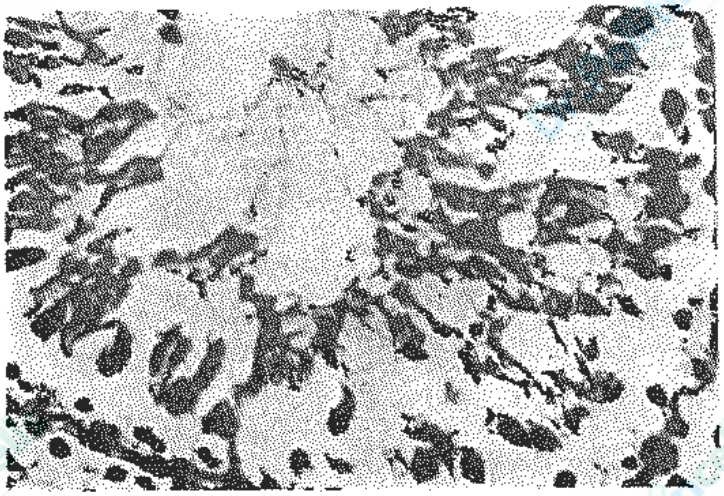

Photo 7. Testis. Cernilton 12.6g/kg group, male (survival). Spermatids showed hypoplasia and only Sertoli's cells were conspicuously seen. Suppression of naturation was of course noted.

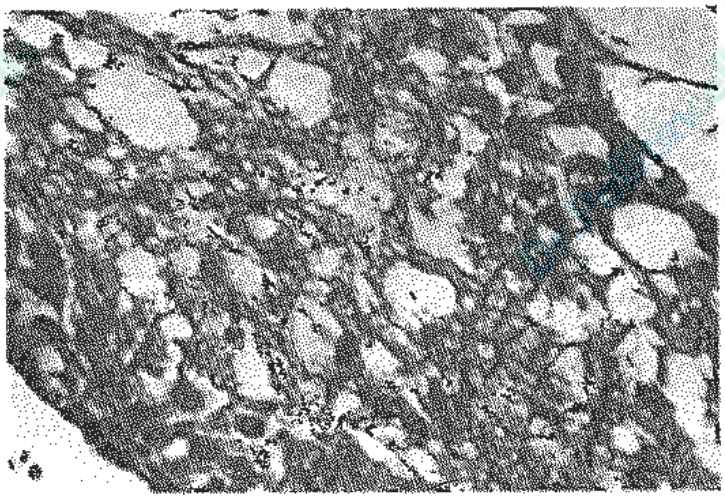

Photo 8. Testis. Cernilton 12.6g/kg group, male (survival). Maturation of spermatids was suppressed and the ducts underwent coagulative necrosis.

Phytotherapeutic Agents in the Treatment of Benign Prostatic Hyperplasia

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Curr Urol Rep. 2000 Aug;1(2):103-9.

The rationale and efficacy of phytotherapeutic agents in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) are continuously debated. While plant extracts are prescribed and reimbursable treatment options in Europe, they are officially classified merely as dietary supplements in the United States. The most commonly used preparations originate from the species Serenoa repens, Pygeum africanum, hypoxis rooperi, pinus, picea, urtica dioica, and secale cereale (rye pollen). Combination extracts derived from two or more plants are also used. Various components have been suggested to be active, and different mechanisms of action are being supposed. Open trials and some short-term randomized studies, suggesting safety and efficacy have been reported. However, if stringent criteria of evidence-based medicine are applied, the data are inconclusive. Therefore, the 4th International Consultation on BPH and the recent German guidelines have not (yet) recommended phytotherapy for the management of symptomatic BPH.

Publication Types:
• Review
• Review, Tutorial
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Phytotherapy for benign prostatic hyperplasia

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Abstract

Objective

To systematically review the existing evidence regarding the efficacy and safety of phytotherapeutic compounds used to treat men with symptomatic benign prostatic hyperplasia (BPH).

Design

Randomized trials were identified searching MEDLINE (1966±1997), EMBASE Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. The studies were included if men had symptomatic benign prostatic hyperplasia, the intervention was a phytotherapeutic reparational one or combined, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Key data were extracted independently by two investigators.

Results

A total of 44 studies of six phytotherapeutic agents (Serenoa repens, Hypoxis rooperi, Secale cereale, Pygeum africanum, Urtica dioica, Curcubita pepo) met inclusion criteria and were reviewed. Many studies did not report results in a method allowing meta-analysis. Serenoa repens, extracted from the saw palmetto, is the most widely used phytotherapeutic agent for BPH. A total of 18 trials involving 2939 men were reviewed. Compared with men receiving placebo, men taking Serenoa repens reported greater improvement of urinary tract symptoms and flow measures. Serenoa repens decreased nocturia (weighted mean difference .WMD. 20:76 times per evening; 95% CI . 21:22 to 20.32; n . 10 studies) and improved peak urine flow.WMD . 1:93 ml s21; 95% CI . 0:72 to 3.14, n . 8 studies). Men treated with Serenoa repens rated greater improvement of their urinary tract symptoms versus men taking placebo (risk ratio of improvement. 1:72; 95% CI . 1:21 to 2.44, n . 8 studies). Improvement in symptoms of BPH was comparable to men receiving the finasteride. Hypoxis rooperi (n . 4 studies, 519 men) was also demonstrated to be effective in improving symptom scores and flow measures compared with placebo. For the two studies reporting the International Prostate Symptom Score, the WMD was 24.9 IPSS points (95% CI . 26:3 to 23.5, n . 2 studies) and the WMD for peak urine flow was 3.91 ml s21 (95% CI . 0:91 to 6.90, n . 4 studies). Secale cereale (n . 4 studies, 444 men) was found to modestly improve overall urological symptoms. Pygeum africanum (n . 17 studies, 900 men) may be a useful treatment option for BPH. However, review of the literature has found inadequate reporting of outcomes which currently limit the ability to estimate its safety and efficacy. The studies involving Urtica dioica and Curcubita pepo are limited although these agents may be effective combined with other plant extracts such as Serenoa and Pygeum. Adverse events due to phytotherapies were reported to be generally mild and infrequent.

Conclusions

Randomized studies of Serenoa repens, alone or in combination with other plant extracts, have provided the strongest evidence for efficacy and tolerability in treatment of BPH in comparison with other phytotherapies. Serenoa repens appears to be a useful option for improving lower urinary tract symptoms

and flow measures. Hypoxis rooperi and Secale cereal also appear to improve BPH symptoms although the evidence is less strong for these products. Pygeum africanum has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no convincing evidence supporting the use of Urtica dioica or Curcubita pepo alone for treatment of BPH. Overall, phytotherapies are less costly, well tolerated and adverse events are generally mild and infrequent. Future randomized controlled trials using standardized preparations of phytotherapeutic agents with longer study durations are needed to determine their long-term effectiveness in the treatment of BPH.

Keywords: Phytotherapy, Benign prostatic hyperplasia, Randomized controlled trials, Systematic reviews, Meta-analysis, Public health nutrition: 3(4a), 459±472 459

Phytotherapy or the use of plant extracts for treatment of lower urinary tract symptoms (LUTS) consistent with benign prostatic hyperplasia (BPH) was first described in Egypt in the 15th century BC1. Phytotherapy is common in Europe and is increasing in the Western Hemisphere. In 1998, the sale of botanical medications in the United States was $1.5 billion per year and the use of phytotherapeutic compounds increased nearly 70% among US adults 2,3. About 30 phytotherapeutic compounds are used for the treatment of BPH (Table 1). Phytotherapeutic agents represent nearly half the medications dispensed for treatment of BPH in Italy, compared with 5% for alpha-blockers and 5% for 5a-reductase inhibitors 4. In Germany and Austria, phytotherapy is the first-line treatment for mild to moderate lower urinary tract symptoms and represents more than 90% of drugs prescribed for treatment of BPH. In the United States, phytotherapies for BPH are available as nonprescription dietary supplements. Nearly a quarter of men attending a United States urology clinic who had previously treated BPH indicated they had used phytotherapeutic agents for self-treatment of urinary tract symptoms 5.

Phytotherapies are often promoted to ‘maintain a healthy prostate’ and as natural and harmless treatment of BPH symptoms. Despite their popularity with the public there has been reluctance among many practitioners to routinely recommend these products. This is because of uncertainty regarding their efficacy and safety 6,7. Most phytotherapeutic compounds are unlicensed and do not require evidence of efficacy, safety or purity. There have been over 40 published randomized controlled trials evaluating the efficacy of phytotherapy for symptomatic BPH in approximately 5000 men. Many more trials are in progress and should provide needed evidence regarding the role of phytotherapeutic products.

Systematic reviews of the existing literature provide a systematic assembly of the results of primary investigations using strategies that limit bias and random error 8. Systematic reviews efficiently integrate unmanageable amounts of information and provide results that allow for rational decision making. They can establish whether findings are consistent and generalized or whether findings vary by subsets. If clinically and statistically appropriate, a quantitative summary (meta-analysis) can be performed resulting in statistical pooling of results and enhancement of the estimates of therapeutic effects and risk estimates. This is especially helpful when a large number of small trials have been conducted or when results from comparable studies provide differing results. Systematic reviews also identify gaps in existing evidence and make recommendations for future research to close these scientific and clinical gaps. Phytotherapeutic compounds Serenoa repens (saw palmetto) background the most widely used phytotherapeutic agent for BPH is the extract of the dried ripe fruit from the American dwarf palm plant, saw palmetto, Serenoa repens (also known by its botanical name as Sabal serrulata). Serenoa repens has been approved in France and Germany for treatment of BPH. Berries from saw palmetto were first used by the American Indians in the southeast United States in the early 1700s to treat testicular atrophy, erectile dysfunction, and prostate gland swelling or inflammation 1. The medicinal value of Serenoa repens for relief of prostate gland swelling has been reported since the 1800s. The mechanism of action of Serenoa repens has been investigated in several in vitro or indirect in vivo studies and has not been definitively defined. The mechanism may include alteration of cholesterol metabolism, antioestrogenic, anti-androgenic (including 5a-reductase inhibitor activity), anti-inflammatory

effects, and a decrease in available sex hormone binding globulin 9±12.

Results of studies a systematic review and meta-analysis of randomized trials assessed the existing evidence regarding efficacy and safety of Serenoa repens in men with symptomatic BPH 13. Studies were identified through a search of MEDLINE (1966±1997), EMBASE, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. Randomized trials were included if participants had symptomatic BPH, the intervention was a preparation of Serenoa repens alone or in combination with other phytotherapeutic agents, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Two investigators independently extracted key data on design features, subject characteristics, therapy allocation and outcomes of the studies. A total of 18 studies involving almost 3000 men were identified and analysed 14±31 (Tables 2±5). Many studies did not report results in a method that permitted quantitative meta-analysis. Sixteen trials were double blinded, 14 were placebo controlled and four involved Serenoa repens in combination with other phytotherapeutic agents. The average study duration was 9 weeks (range 4±48 weeks) and the average age of enrollees was 65 years.
Baseline characteristics regarding prostate volume, urine flow rates and symptom scale scores were comparable with previous trials evaluating pharmacologic management of BPH. The available data indicate that Serenoa repens (alone or in combination with other phytotherapeutic agents) improves urinary symptoms and flow measures (Figs 1±3). Compared with placebo, saw palmetto improved urinary symptom scores by 28% and nocturia by 25% (the weighted mean difference .WMD.20:76 times per evening; 95% CI . 21:22 to 20.32; n . 10 studies). Peak urine flow was improved by 24% (WMD . 1:93 ml s21; 95% CI . 0:72 to 3.14, n . 8 studies), mean urine flow by 28% (2.22 ml s21; data not shown), and residual urine volume by 43% (222.05 ml; data not shown). Men taking Serenoa repens were more likely to report improvement in urinary symptoms than men taking placebo (73.6% vs. 50.9%; risk ratio . 1:76). Adverse effects were generally mild and comparable with placebo. Compared with finasteride17,30, saw palmetto provided similar responses in urologic symptom scores (0.37 International Prostate Symptom Score (IPSS) points), nocturia (20.20 times per evening) and flow measures. Saw palmetto was associated with a lower rate of erectile dysfunction than finasteride (1.1% vs. 4.9%; P , 0:001) and reduced neither prostate size nor prostate specific antigen (PSA) levels. Critics have stated that comparing saw palmetto with finasteride might be showing equivalency to placebo. However, previous trials and meta-analyses have demonstrated that finasteride provides symptomatic improvement in men with prostate glands .40 g, a size comparable to those enrolled in this study 32,33.

The treatment effect sizes noted with saw palmetto were comparable to effects reported with other pharmacologic agents, such as finasteride. However, the results should be viewed cautiously. Studies utilized different doses and preparations of Serenoa repens (including combination preparations). The most extensively investigated preparation of Serenoa repens is manufactured in France and sold as Permixon. The most commonly reported dosage was 160 mg twice per day. Many studies did not report outcome data in a consistent fashion. Only three studies reported validated urologic symptom scales. Trials were of short duration with only two studies having follow-up of at least phytotherapy for benign prostatic hyperplasia 463 6 months' duration. Therefore, it is not known whether Serenoa repens prevents long-term complications of BPH such as acute urinary retention or the need for surgical intervention. The only trial comparing Serenoa repens with alpha-blockers lasted less than 3 weeks, making a comparison impossible. Finally, it is possible that study results were not reported if there were no improvements in symptoms or flow measures (publication bias). There are two placebo-controlled studies involving 298 men that were scheduled for completion in 1998. However, their results have not yet been reported. Summary Extracts from the saw palmetto plant, Serenoa repens, provide modest improvement in urinary symptoms and flow measures. Compared with finasteride Serenoa repens produces similar improvements in symptoms and flow measures, has fewer adverse treatment effects and costs less. The long-term safety and efficacy of Serenoa repens and its ability to prevent complications from BPH are not known. Standardized preparations are often not available. Publication of ongoing trials is

encouraged and initiation of long term studies compared with alpha-blockers would be useful. Hypoxis rooperi (South African star grass, bsitosterol) Background Phytosterol extracts derived from the South African star grass, Hypoxis rooperi, are popular. The resumed active constituent is b-sitosterol. Beta-sitosterol contains a mixture of phytosterols, with smaller amounts of other sterols, bonded with glucosides 1. Additionally, the quantity of bsitosterol- bD-glucoside is often reported. The product is sold under the trade names Harzol or Azuprostat. Although the mechanism of action of b-sitosterols is not known it may be related to cholesterol metabolism or anti-inflammatory effects (via interference with prostaglandin metabolism) 1.

Results of studies for randomized controlled trials evaluated b-sitosterol in 519 men with symptomatic BPH34±37 (Table 3). All were 464 TJ Wilt et al. double-blinded and lasted between 4 and 26 weeks. Three trials used non-glucosidic b-sitosterols in doses ranging from 30 mg to greater than 120 mg per day 34,35,37. The other trial utilized a preparation that contained 100% bsitosteryl- b-D-glucoside (0.15 mg twice a day) 36. The average age of participants was 65 years. Men had moderately severe BPH (mean baseline IPSS score . 15:2; peak urine flow . 10:2ml s21; prostate size . 49 cc.: Beta-sitosterol provided statistically significant improvements in urinary symptom scores and flow measures (Figs 4 and 5). In the two studies reporting the IPSS score, the WMD compared with placebo was 24.9 points (95% CI . 26:3 to 23.5, n . 2 studies) (35% improvement). The WMD for peak urine flow was 3.91 ml s21 (45% improvement) and for residual volume the WMD . 228:62 ml (95% CI . 0:91±6:90; n . 4 studies) (29% improvement). Betasitosterol did not reduce prostate size and the trial using 100% b-sitosteryl- b-D-glucoside (WA184) did not show improvement in urinary flow rates. Adverse events were infrequent and mild. Withdrawal rates were less than 10% and did not differ from placebo.

An extract from South African star grass, b-sitosterol, improved urologic symptoms and flow measures. However, the existing evidence is limited to trials of short duration, relatively few patients studied and lack of standardized b-sitosterol preparations. Their long term effectiveness, safety and ability to prevent BPH complications are not known. Secale cereale (rye-grass pollen) Background Rye pollen extract is prepared from the rye-grass, Secale cereale. It is used by millions of men worldwide and is a registered pharmaceutical throughout Western Europe, Japan, Korea and Argentina 38. In the United States, Cernilton is used as a nutritional supplement by approximately 5000 men 39. One dose contains 60 mg of Cernitin T60, a water-soluble pollen extract fraction, and 3 mg of Cernitin GBX, an acetone soluble pollen extract fraction 38. The acetone-soluble fraction was found to contain b-sterols 40. In vitro studies suggest that Cernilton may have anti-androgenic effects, relax urethral smooth muscle tone and increase bladder muscle contraction, or may act on the alpha-adrenergic receptors and relax the internal and external sphincter muscles 41±43.

Phytotherapy for benign prostatic hyperplasia 467 Results of studies A total of 444 men have been enrolled in two placebo-controlled .n . 163. and two comparative trials lasting from 12 to 24 weeks 44±47 (Table 4). Three studies were double-blinded 44,45,47. The mean age of participants was 69 years. Differences in the control agents and methods of reporting results did not permit all studies to be combined in a meta-analysis. However, three studies reported symptom scores or measured symptom Improvement 45±47. Nocturia was reported in three studies 44,45,47 and all studies reported peak urine flow and residual urine volume. Data from all studies were consistent with improvement in symptoms and urinary flow. Cernilton improved ‘self-rated urinary symptoms’ versus placebo and Tadenan, an extract from Pygeum africanum 46. Almost 70% men taking Cernilton reported symptom improvement compared with 29% taking placebo. Obstructive and irritative symptom scores improved from baseline by 60% in men taking Cernilton compared with 40% with Tadenan. Cernilton reduced nocturia compared with placebo and Paraprost, a pharmacologic treatment used primarily in Japan containing 265 mg of L-glutamic acid, 100 mg of Lalanine and 45 mg of aminoacetic acid 47. Versus placebo, there was a two-fold improvement in the percentage of men reporting improvement in nocturia (63% vs. 31%) 44,45.

Compared with Paraprost, Cernilton reduced nocturia by 0.40 times per evening. The only adverse event reported was mild nausea. Although the results suggest that Cernilton

provided modest benefit there are limitations to the evidence. The longest treatment duration was 24 weeks. Only one study reported results from a standardized and validated urologic symptom scale. While the manufacturer suggests two to four tablets or capsules daily, the dosages and standardization of preparation were not usually reported. The most frequently reported amount was two Cernilton capsules three times per day.

Summary

The evidence suggests that an extract from rye-grass pollen, Cernilton, is well tolerated and modestly improves urologic symptoms. However, trials were of short duration, enrolled relatively few patients, and lacked standard product preparation. Additionally, there was infrequent use of validated symptom scale scores. It does not improve urinary flow measures and the long-term safety and effectiveness is not known.

Pygeum africanum (African plum)

Background

Traditionally, the bark of the African plum tree (Pygeum africanum) was collected and powdered, then drunk as a tea to improve genito-urinary symptoms. Purified bark extracts have been used throughout Europe for the past 30 years. The postulated active components include phytosterols, especially b-sitosterols, pentacyclic triterpenoids and esters of long-chain fatty alcohols. Pygeum africanum extract may suppress LUTS by reducing bladder hyperreactivity, decreasing inflammation, and protecting against abnormal prostate growth 48. A 1995 review identified 12 double-blind, placebo controlled studies involving 717 men with BPH 46, 49±63 (Table 5). Most studies used a Pygeum extract under the trade name Tadenan with doses ranging from 75 to 200 mg day 21. All studies were at least 16 weeks in duration. More than half the studies measured peak urinary flow and all but one measured urinary frequency. Standardized and validated symptom scores were not utilized and there was no pooled estimate of treatment effect size or adverse events. The majority of studies noted an improvement in nocturia compared with placebo.

An ongoing double-blind placebo-controlled study is evaluating Tadenan (100 mg and 400 mg) in 750 men with symptomatic BPH. The primary endpoint is a mean reduction in the IPSS score between baseline and 6 months. However, the results have not been reported. In five small-scale studies involving 183 men, P. africanum was compared with active drug or therapy 50,57,63. Two studies involved plant extracts (sitosterin and extract of Radix urticae urtae) 50. The results Fig. 5 Effect of b-sitosterol on peak urine flow vs. placebo 468 TJ Wilt et al. indicate that Pygeum reduced nocturia more than comparators in the 3 studies reporting this endpoint. However, in two of these studies there were no statistical comparisons. Since the publication of this review there have been two additional trials utilizing Pygeum. One was a study utilizing a combination of Pygeum with Urtica and is discussed in the section on Urtica 59. The other trial demonstrated that Pygeum was less effective than Cernilton in improving 'self-rated urinary symptoms' 46. Obstructive and irritative symptom scores improved from baseline by 60% in men taking Cernilton compared with 40% in men taking Tadenan.

Summary

Extracts from the African plum tree, Pygeum africanum may be a useful treatment option for BPH. However, inadequacies in the reporting of outcomes limit the ability to estimate its safety and efficacy. An ongoing trial should provide much needed information on the short-term effectiveness and tolerability of Pygeum africanum.

Urtica dioica (stinging nettle)

Background

Extracts from roots of the stinging nettle are often used in Germany for the treatment of BPH. The extracts contain a mixture of water- and alcohol-soluble compounds with extraction procedures varying from company to company. Proposed mechanisms of action include inhibition of prostatic growth factor including blocking the conversion of testosterone to dihydrostersterone 1. Results of studies There have been five randomized trials evaluating stinging nettle. Three of these involved combinations with other phytotherapeutic agents (Pygeum and Sabal), making it difficult to evaluate the efficacy of stinging nettle alone 26,30,59. Furthermore, one of these studies merely compared two different doses of a

combined extract of Urtica and Pygeum59. The report by Sokeland compared a combination of Sabal and Urtica (PRO 160/120) extract with finasteride and placebo30. This trial lasted 12 weeks and evaluated 543 men. Compared with finasteride there were no differences in IPSS scores (24.8 vs. 25.8 IPSS points), peak urine flow or residual urine volume. More adverse events were associated with finasteride, including more cases of erectile dysfunction, diminished ejaculation volume, and headaches. Compared with placebo, the combination of Sabal±Urtica (Prostagutt) improved IPSS scores by 17% (23.5 IPSS points) 26. One placebo-controlled study lasting 3 months compared a liquid preparation of stinging nettle with placebo in 41 men with BPH64. An improvement in IPSS scores was noted in men taking stinging nettle. However, because of unacceptable taste this preparation has been removed from the market. Another placebo-controlled trial examined the effectiveness of Urticae extract capsules65. Although improvements in peak urine flow and total voided volume were reported, there was no difference in urologic symptoms. Additionally, 24% of men (6/25) taking Urticae withdrew from the study; half of them due to unspecified side effects.

Summary

Evidence from randomized trials suggests combination preparations of Urticae appear to provide some benefit for treatment of lower urinary tract symptoms, although stinging nettle extracts alone do not appear to be beneficial. Additional randomized controlled trials need to be conducted before Urticae can be recommended as an effective option for the treatment of LUTS.

Curcubita pepo (pumpkin seed)

Results of studies

There has been only one small-scale randomized trial of short duration that has evaluated the efficacy of pumpkin seed extracts16. This study evaluated 55 men, lasted for 12 weeks and utilized a preparation that included pumpkin seed, Curcubita pepo, and Sabal serrulata (Curbicin 160 mg three times a day). Compared with placebo, Curbicin improved self-rating of urinary symptoms (85% noted improvement vs. 11% taking placebo) and nocturia. Residual urine volume was reduced by 31% (42.5 cc) compared with only 6.5% (7.6 cc) with placebo. Because the study utilized a combination preparation the reported improvement in urologic symptoms and flow measures cannot be clearly attributed to pumpkin seeds.

Summary

There is no convincing evidence that extracts of pumpkin seed alone improve urologic symptoms or flow measures. They may provide improvement in urinary symptoms and flow measures when used in combination with Sabal serrulata. Randomized controlled trials need to be conducted. Recommendations and conclusions Should physicians recommend plant extracts for treatment of BPH? Despite their popularity and the existence of over 40 randomized controlled trials involving nearly 5000 men, the available data do not yet provide clear evidence of efficacy for most phytotherapeutic products. Extracts of saw palmetto (Serenoa repens) (alone or in combination with other phytotherapeutic products) have the strongest evidence for efficacy and tolerability. They appear to be a useful option for improving lower urinary tract symptoms and flow measures. Rye-grass pollen (Secale cereale) and South African star grass (Hypoxis rooperi, b-sitosterol) also appear to improve symptoms and are well tolerated. However, the evidence is Phytotherapy for benign prostatic hyperplasia 469 less strong for these products. African plum tree bark (Pygeum africanum) has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no convincing evidence supporting the use of pumpkin seed (Curcubita pepo) or stinging nettle (Urtica dioica) extracts alone for treatment of BPH. They may be effective in combination with other phytotherapeutic products. The widespread use of phytotherapy attests to the popularity of plant extracts for treatment of BPH symptoms. They cost less and are better tolerated, at least in the shortterm, than either alpha-blockers or finasteride. However, if the primary goal is to reduce symptoms, alpha-blockers such as doxazosin, tamsulosin, alfuzosin or terazosin seem to be a better choice than finasteride and probably phytotherapy. Additionally, plant extracts have not yet been demonstrated to reduce complications from BPH or the need for surgical intervention in comparison with interventions such as

finasteride33. The Committee on Other Medical Therapies of the Fourth International Consultation on BPH concluded that: most plant extract preparations have different components; it is not known what mechanisms of action demonstrated in vitro might be responsible for clinical effects; short-term randomized studies suggest clinical efficacy for some preparations; and studies were usually inadequate due to the methodology utilized, small numbers and short duration of study. Of greatest importance is the completion of additional high quality studies of long duration to fully evaluate the efficacy and safety of phytotherapeutic products for treatment of BPH6. Until completion of these studies and/or regulation of these products the lack of universal definitions, practices, and standards within the supplement industry place the onus on the physician to judge product quality and efficacy. Manufacturers/companies of plant extracts often use different extraction processes. There is no evidence that the extract from one manufacturer is equivalent to that of another.

Additionally, since the active ingredient(s) are not known, it is possible that one product might have clinical efficacy while another does not. Each company's product must be tested to evaluate clinical efficacy and bioactivity. The following recommendations have been made for assessing quality measures (these do not directly address clinical efficacy or safety) in selecting high-quality and reliable preparations of phytotherapeutic products manufactured in the United States66. 1. The manufacturer tests raw ingredients for purity and potency prior to inclusion in a product. 2. The product is manufactured in a pharmaceutically licensed facility registered with the Food and Drug Administration. 3. The product's ingredients meet the applicable United States Pharmacopoeia (USP) standards. 4. All finished products are analyzed for purity and potency following production by an independent laboratory using established methods to ensure that the product meets label claims and is of good quality. In some cases, this information can be found on product labeling. All reputable manufacturers will keep certificates of laboratory results for each finished batch of product on file. These should be available to physicians and pharmacists on request.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Cernilton for Benign Prostatic Hyperplasia

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Background

Benign prostatic hyperplasia (BPH), nonmalignant enlargement of the prostate, can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH has been growing steadily. Cernilton, prepared from the rye-grass pollen Secale cereale, is one of the several phytotherapeutic agents available for the treatment of BPH.

Objectives

This systematic review aims to assess the effects of Cernilton on urinary symptoms and flow measures in men with benign prostatic hyperplasia (BPH).

Search Strategy

Trials were searched in computerized general and specialized databases (MEDLINE, EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting manufacturers and researchers.

Selection Criteria

Trials were eligible if they were: (1) randomized controlled trials or controlled clinical trials comparing Cernilton with placebo or other BPH medications in men with BPH; and (2) included clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements.

Data collection and analysis

Information on patients, interventions, and outcomes was extracted by at least two independent reviewers using a standard form. Main outcome measure for comparing the effects of Cernilton with placebo and standard BPH medications were the change in urologic symptoms scales. Secondary outcomes included changes in nocturia as well as urodynamic measures (peak and mean urine flow, residual volume, prostate size). Main outcome measure for side effects was the number of men reporting side effects. MAIN RESULTS: 444 men were enrolled in 2 placebo-controlled and 2 comparative trials lasting from 12 to 24 weeks. Three studies used a double-blind method although treatment allocation concealment was unclear in all. Cernilton improved "self rated urinary symptoms" (percent reporting satisfactory or improving symptoms) versus placebo and Tadenan. The weighted risk ratio (RR) for self-rated improvement versus placebo was 2.40 [95% CI = 1.21, 4.75], and the weighted RR versus Tadenan was 1.42 [95% CI = 1.21, 4.75]. Cernilton reduced nocturia compared with placebo and Paraprost. Versus placebo, the weighted RR was 2.05 [95% CI = 1.41, 3.00], and versus Paraprost, the WMD was -0.40 times per evening [95% CI = -0. 73, -0.07]. Cernilton did not improve urinary flow rates, residual volume or prostate size compared to placebo or the comparative study agents. Adverse events were rare and mild. The withdrawal rate for Cernilton was 4.8% compared to 2.7% for placebo and 5.2% for Paraprost.

Reviewer's Conclusions

The Cernilton trials analyzed were limited by short duration, limited number of enrollees, gaps in reported outcomes, and unknown quality of

the preparations utilized. The comparative trials lacked a proven active control. The available evidence suggests Cernilton is well tolerated and modestly improves overall urologic symptoms including nocturia. Additional randomized placebo and active-controlled trials are needed to evaluate the long-term clinical effectiveness and safety of Cernilton.

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Phytotherapy in Chronic Prostatitis

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Abstract

Chronic prostatitis is a very common condition that is poorly understood and has a significant impact on quality of life. Given the lack of proven efficacy of conventional therapies, such as antibiotics, it is not surprising that patients have turned with increasing frequency to phytotherapy and other alternative treatments. Although alternative therapies are plentiful, few have been subjected to scientific scrutiny and prospective controlled clinical trials. This review will cover phytotherapies commonly used in prostatitis patients and focus in detail on those with published data. These treatments include zinc, cernilton (flower pollen), quercetin, and saw palmetto. Although many of these therapies appear promising in small preliminary studies, phytotherapy requires the same scientific criteria for validation and acceptance as do conventional medical therapies.

Article Outline

All prostatitis researchers can agree that patient and physician dissatisfaction over the management of this disease is high. It is not surprising, therefore, that patients often seek alternative forms of therapy. Phytotherapy, the use of plant-derived or "herbal" products, is gaining popularity in North America and is already the treatment of choice for many chronic conditions in Europe and Asia. Advantages of phytotherapy include (1) unique mechanisms of action, (2) typically low side-effect profiles, (3) low cost, and (4) a high level of acceptance by patients. A large disadvantage of phytotherapy in the United States is lack of US Food and Drug Administration (FDA) oversight, and indeed, consumer watchdog groups have found that many herbal preparations do not contain what is claimed on the label. Other disadvantages include (1) unknown drug interactions (sometimes leading to catastrophic results[1]), (2) no side-effect data collection, and (3) meaningless labels (to circumvent FDA regulations), such as "supports prostate health" or "promotes normal bladder function."

Alternative herbal-based therapies are prevalent and popular in urologic disease in general and prostatic disorders in particular. Typical herbal therapies recommended for benign prostatic hypertrophy (BPH) with some clinical evidence of efficacy include saw palmetto (*Serenoa repens*), stinging nettle (*Urtica dioica*), and *Pygeum africanum*.[2] Flower pollen extract (Cernilton) has also been used with less evidence of efficacy for BPH. [3] Given the overlap of lower urinary tract symptoms between BPH and chronic prostatitis, these agents, either alone or in combination in "prostatic health" formulations, have also been recommended for men with prostatitis.

In patients with documented recurrent bacterial prostatic infection (category II), prolonged antibiotics remain the mainstay of therapy. Prolonged antibiotic use can alter intestinal flora, and use of probiotics (live beneficial bacteria) may reduce the incidence of gastrointestinal side effects.[4] Many men with category II prostatitis have recurrent urinary tract infections, and there is considerable interest in cranberry juice to treat cystitis in women, although randomized placebo-controlled data are lacking. [5] Cranberry juice may reduce *Escherichia coli* adherence and biofilm load in uroepithelial cells.[6] There are no published data on the efficacy of cranberry juice in prostatic infections, however, and it is possible that the acidity of the product could actually exacerbate symptoms. Zinc was one of the first factors with an antimicrobial effect to be identified in seminal plasma. [7] The initial discovery that many men with chronic bacterial prostatitis have low levels of zinc in the semen has led to the long-standing

recommendation for zinc supplements in men with all forms of prostatitis. Unfortunately, oral intake of zinc does not appear to increase zinc levels in semen. [8] There are no published clinical trials that demonstrate the efficacy of zinc supplements for either treating or preventing prostatitis.

Category III (chronic pelvic pain syndrome [CPPS]) is the most common and enigmatic prostatitis syndrome. In the absence of infection, there is evidence for an inflammatory or autoimmune component to CPPS in some patients. Even in the absence of visible white blood cells, expressed prostatic secretions and semen of men with CPPS have elevated levels of inflammatory cytokines and oxidative stress.[9, 10, 11 and 12] Phytotherapy has been used most commonly in this category of prostatitis, and evidence for efficacy is actually more compelling than for other standard therapies.

Cernilton, an extract of flower pollen, has been used in prostatic conditions for its presumed anti-inflammatory and antiandrogenic effects. In a small open-label study, 13 of 15 patients reported symptomatic improvement.[13] In a larger more recent open-label study, 90 patients received 1 tablet of cernilton N 3 times daily for 6 months. [14] Patients with complicating factors (prostatic calculi, urethral stricture, bladder neck sclerosis) had minimal response, with only 1 of 18 showing improvement. In the "uncomplicated" patients, however, 36% were cured of their symptoms and 42% improved. Symptomatic improvement was typically associated with improved uroflow parameters, reduced inflammation, and a decrease in complement C3/coeruloplasmin in the ejaculate. Side effects in studies of cernilton for BPH and prostatitis have been negligible.

Quercetin is a polyphenolic bioflavonoid commonly found in red wine, green tea, and onions.[15] It has documented antioxidant and anti-inflammatory properties and inhibits inflammatory cytokines implicated in the pathogenesis of CPPS, such as interleukin-8. [16] In a preliminary small open-label study, quercetin at 500 mg 2 times daily gave significant symptomatic improvement to most patients, particularly those with negative expressed prostatic secretions cultures. [17] This was followed by a prospective, double-blind, placebo-controlled trial of quercetin 500 mg 2 times daily for 4 weeks using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) as the primary endpoint. [18] Patients taking placebo had a mean improvement in NIH-CPSI from 20.2 to 18.8, and those taking quercetin had a mean improvement from 21.0 to 13.1 (P = 0.003). In all, 20% of patients taking placebo and 67% of patients taking the bioflavonoid had an improvement in symptoms of ≥25%. A third group of patients received Prosta-Q (Farr Cabs, Santa Monica, CA), a commercial formulation containing quercetin with bromelain and papain, digestive enzymes known to increase the intestinal absorption of quercetin. In this group, 82% had a significant improvement in symptoms.

Saw palmetto is the most commonly used phytochemical for lower urinary tract symptoms and BPH, and indeed, some of the clinical studies with entry criteria based on symptoms likely included patients with CPPS. There have been no published studies of saw palmetto use in CPPS. A poster presented at the 2001 American Urological Association meeting compared therapy with saw palmetto or finasteride in CPPS patients for 1 year.[19] Although there was some improvement seen in the finasteride group, there was no improvement in the saw palmetto group.

Traditional Chinese medicinal therapies typically use acupuncture and herbal preparations. There are some publications with English abstracts that suggest significant improvement with this approach, although it is difficult to interpret formulation composition, entry criteria, and endpoint measures.[20]

In summary, phytotherapy shows much promise for prostatitis patients. In category II, probiotics can reduce the gastrointestinal side effects of prolonged antibiotic use. In category III, cernilton and quercetin have documented effects in both patient-reported improvement and improvement in biochemical markers of inflammation. Zinc, saw palmetto, and other agents used in BPH, such as stinging nettle and *Pygeum africanum*, do not have evidence for efficacy in CPPS. It is important that these phytotherapeutic approaches, and others, such as traditional Chinese medicine, be evaluated in prospective, randomized placebo-controlled trials with defined entry criteria and

validated endpoints.

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Phytotherapy of BPH with Cernilton® N

Results of a controlled clinical study

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Introduction

In a controlled clinical study in patients suffering from benign prostatic hyperplasia (BPH) the efficacy and the benefit/risk ratio of Cernilton® N is documented and its importance for the (long-term) treatment of this condition is discussed.

Treatment with phytopharmalogical preparations is well established in the therapeutic spectrum of benign prostatic hyperplasia and, on the basis of its high benefit/risk ratio, is recognized as a possible symptomatically oriented medication. Follow-up controls carried out within the framework of phytotherapy ensure that the indication for conservative treatment is regularly checked and, if necessary, revised. In view of the epidemiological knowledge concerning the comparatively rare indication of surgical intervention [2, 11] and the differentiated evaluation of TUR [7, 13], phytotherapeutic agents are used in BHP, preferably in the initial stages of the disease [2, 15,18].

Based on the positive therapeutic experience with Cernilton N in benign prostatic diseases [6], we performed a clinical study in BHP patients in Stages II and III of the disease over a treatment period of 24 weeks, in which the standardized pollen-extract preparation Cernilton N[1] was investigated, according to a double-blind trial design, versus placebo, with separate follow-up phases for the two groups. The results of the double-blind phase have already been published [3].

This study, carried out in collaboration with 6 practising urologists in a representative patient population, documents the therapeutic efficacy of Cernilton N, which is attributed to the anticongestive and antiinflammatory effects of the pollen extract.

Patients and method

With regard to the basic characterization of this clinical trial [3] it has to be established that the results of the double-blind study are confirmed in the trial population evaluated, and are therefore presented in the summarized pre/post comparison of Phase I. As an extension to the biometric methods, the variance analysis for the split-plot design of the time-points before the treatment, after Phase I and after Phase II is used.

The breakdown of BPH into Stages II and III was classified according to Vahlensieck [18] and the intensity of the disorders of miction according to the FDA recommendation [4]; the measurements of urinary flow are represented with reference to the urine volume, by means of the Uroflow Index [14].

Following the double-blind phase the active-drug and placebo groups were treated with Cernilton N, according to an open trial design, whereby this follow-up phase also covers a 12-week study period. Due to discontinuation of the treatment (urine retention/TUR, lost capsules), premature withdrawal of the treatment (freedom from symptoms) in Phase I and non-inclusion of 7 patients in the follow-up phase, a total of 92 patients could be included in the biometric analysis. Of these, 45 patients were treated first with active drug and then with Cernilton N, and 47 patients first with placebo and then with Cernilton N.

During Phase II neither the physicians nor the patients were informed which medication

(placebo or active drug) had been given during Phase I, or with what general result, in order to avoid any subsequent effect on the trial results at the final control examination after 24 weeks. Deviations from the treatment plan occurred due to discontinuation or interruption of the treatment in three cases. The medication for concomitant diseases was changed in Phase II, in comparison with Phase 1, in one case.

Results

The comparative groups are homogeneous and their inclusion data correspond to those for the double-blind study [3]. The clinical symptomatology of BPH patients is determined by the leading symptom, nycturia, which was reported by almost all the patients. Concomitant diseases, mainly diseases of the cardiovascular system and metabolic diseases were present in 54.3%, and concomitant medication, principally cardiovascular preparations and antidiabetics, was reported in 41.3% of the patients.

In the double-blind phase, statistically significant differences are documented in regard to nycturia, diuria (frequent urination during the day; pathological: >4 times a day), feeling of residual urine, volume of residual urine and overall assessment by the physician and the patient (Table 1).

Follow-up phase: Placebo - Cernilton N

In comparison with the findings at the end of the double-blind and follow-up phases, after the change-over from the 12-week placebo medication to the also 12-week Cernilton N therapy the following changes were observed.

The response, defined as asymptomatic or improved status following initially pronounced symptoms or findings, shows, for all the parameters studied, a marked increase in the number of patients in whom a regression of the symptomatology was recorded (Tables 2 and 3).

In the urodynamic parameters, a significant reduction of the residual urine volume (Fig. 1) and a further increase in the Uroflow Index values, from 0.79±0.27 to 0.97±0.25 (under placebo: from 0.70±0.31 to 0.79±0.27) were observed. Correspondingly, the overall assessment of the treatment as "very good" or "good", by the physician and by the patient, is documented more frequently after the follow-up phase: in 63.8% and 66.0% of the cases, respectively (after the double-blind phase: 13.6% and 27.3%, respectively).

Follow-up phase: Active drug -Cernilton N

In the patients treated firstly with active drug (Cernilton N), the positive changes in the clinical symptoms, palpation findings and urodynamic test parameters observed after the subsequent 12 weeks' treatment with Cernilton N (Phase II), in comparison with the findings after Phase I, are slight when compared with the corresponding results in the placebo-Cernilton N group (Fig. 1).

In the overall assessment of the treatment, after the active drug phase (Phase I) "very good" or "good" assessments by the physician and the patient were made in 58.1% and 72.1% of the cases, respectively, and after the subsequent Cernilton N medication (Phase II) in 62.2% and 62.2% of the cases, respectively. The results after the total 24-week treatment period were assessed as poor by the patient in 4.4% of the cases and by the investigating physician in 13.3% of the cases.

Comparison of the treatment-groups

The findings concerning nocturia and volume of residual urine demonstrate that the therapeutic results under Cernilton N in the placebo-Cernilton N group correspond to those obtained under active drug (Fig. 1). In regard to the time-point of the effect on the following clinical symptoms and parameters, considerable differences were observed between the two treatment-groups: nycturia ($P = 0.051$), diuria ($P = 0.039$), feeling of residual urine ($P = 0.013$), enlargement of the prostate ($P = 0.046$) and congestion of the prostate ($P = 0.030$). In each case the earlier time-point was observed in the active drug-Cernilton N group.

In Phase I the residual urine volume decreases significantly more markedly under active drug ($P = 0.001$); in Phase II there is a marked reduction ($P = 0.002$) in the placebo-Cernilton N group. After Phase II the tolerability of Cernilton N is assessed as "good" in 86 cases (93.5%) and as "satisfactory" in 6 cases (6.5%). Unwanted effects, given as pressure over the stomach and nausea, are recorded in 3 cases.

Discussion

The results of this controlled clinical study confirm the effectiveness of the pollen-extract preparation Cernilton N in benign prostatic hyperplasia (BPH). Clear differences are demonstrated in favour of Cernilton N for nycturia, diuria, feeling of residual urine and residual-urine volume and, in the comparison between the treatment-groups, also for enlargement of the prostate and congestion of the prostate. Also, in the comparison of the therapeutic results under active drug with those under Cernilton N following initial placebo medication, an almost parallel course is to be observed. In regard to dysuria, pathological urge to urinate, malaise and the uroflow parameters, no statistically significant differences are to be observed.

In the patients treated with placebo in Phase I, marked improvement of miction is observed in the follow-up phase. In regard to certain of the parameters investigated, in particular diuria and feeling of residual urine, the continuous treatment with Cernilton N leads to freedom from symptoms. For the leading symptom, nycturia, improvement is obtained in three-quarters of all the patients.

In regard to the urodynamic test parameters, the findings for the residual-urine volume show a stable course in the follow-up phase, after an initially marked reduction under active drug. The Uroflow Index also shows a continuous increase whereby, in spite of increased miction volume [8, 9, 14], the flow time and flow-increase time are reduced.

The continuous therapeutic efficacy of Cernilton N in regard to the clinical symptomatology and the urodynamics, which also concurs with the results of a six-month, placebo-controlled, double-blind study with pollen extract in patients with comparatively advanced BPH [5], is reflected by the positive assessment of the treatment by the investigating physician and by the patient in over 80% and 90% of the cases, respectively.

The clinical relevance of changes in the congestion and inflammation of the prostate in BPH [2, 3, 12, 17, 18] is confirmed by the results of this clinical study, if a causal relationship with the irritative symptoms, and partly also with the obstructive symptoms, is assumed. In this respect the differential diagnosis based on the urodynamics refers to the importance of the hyperactivity of the detrusor muscle, whereby the residual urine is also considered as a parameter of the performance of this muscle [9]. Assuming that the action of Cernilton N is based on anti-oedematous effects, which lead to normalization of pathological changes in the neural supply, this is also suggested by the parallel improvements in the irritative symptoms and the residual-urine volume. Furthermore, an inhibitory effect of orally administered Cernilton N on the hormonally stimulated growth of heterotransplants of BPH can be demonstrated in the nude-mouse model [19]. For a definitive evaluation of its clinical, human pharmacological relevance, more extensive studies are necessary.

Phytotherapy in BPH is characterized by a high benefit-risk ratio whereby, especially in disorders of frequency of miction, controlled long-term treatment is justified in view of the restrictive surgical indication [2, 7, 9, 11, 13, 18]. Although the clinical relevance of the treatment as an alternative to surgical intervention is not demonstrated [10], the main benefit is rather the improvement obtained in the subjectively experienced disturbance of miction. Therefore new drug developments [1, 16] need to be equally as effective as surgical intervention, unless tolerability equivalent to that of the phytotherapeutic agents is guaranteed.

Summary

In a controlled clinical study the efficacy and tolerability of the pollen-extract preparation, Cernilton N, were studied in patients with BPH in Stages II and III (according to Vahlensieck) in 6 urology practices. In the 12-week Phase I of the trial Cernilton N was studied according to a double-blind design versus placebo, and in the subsequent Phase II (follow-up), also of 12 weeks, according to an open trial design in the two comparative groups. The evaluation, carried out in 92 patients, shows significant differences between active drug and placebo after the end of the double-blind phase, which level out at the end of the follow-up phase after the change-over to Cernilton N in the group which received placebo during Phase I. The tolerability of Cernilton N is assessed as "good" in 93.5% of the cases and as "satisfactory" in 6.5%. These results of a study in a representative patient population demonstrate the good efficacy of Cernilton N in BPH in Stages II and III of the

disease over a period of 24 weeks and documents the continuous therapeutic benefit of the pollen extract, which makes possible an effective long-term treatment of BPH.

Conclusions for medical practice

The continuous therapeutic efficacy of Cernilton N makes low-risk long-term therapy possible. Antihormonally acting drugs have an equivalent benefit-risk ratio. Anticongestive therapy will continue to be the principal approach in the conservative treatment of BPH.

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Table 1. Results of a double-blind study: significant differences in favour of Cernilton N in clinical symptomatology, urodynamics and overall assessment of the therapy

Parameter	Active drug	Placebo	Significance (*P* value)
Clinical symptomatology			
	Response (%)		
Nycturia	66.7	37.2	0.011
Diuria	61.9	37.0	0.023
	Freedom from symptoms (%)		
Diuria	45.2	15.2	0.003
Feeling of residual urine	38.2	3.8	0.005
Urodynamics			
	Volume		
Residual urine			
- before Phase I (ml; $\bar{x}\pm s$)	54.5±24.9	51.9±32.0	
- after Phase I (ml; $\bar{x}\pm s$)	28.9±19.7	44.9±28.6	0.001
- reduction (%)	47.0	13.5	
Overall assessment			
	Proportion of patients (%)		
Investigating physician			
- very good	20.9	2.3	
- good	37.2	11.4	0.001
Patient			
- very good	25.6	2.3	
- good	46.5	25.0	0.001

Table 2: Response of the symptoms and improvement of the palpation findings under placebo and subsequent Cernilton N therapy

Response (%)		
Symptom	Phase I (placebo)	Phase II (Cernilton N)
- Nycturia	37.2	68.2
- Diuria	37.0	60.9
- Feeling of residual urine	46.2	65.4
- Dysuria	52.0	76.0
- Urge to urinate	62.2	84.2
- Malaise	44.4	74.1
Palpation findings, improved (%)		
Prostate	Phase I (placebo)	Phase II (Cernilton N)
- Enlargement	12.1	40.4
- Congestion	62.1	72.4

Table 3: Freedom from symptoms and negative palpation findings under placebo and subsequent Cernilton N therapy

Freedom from symptoms (%)

Symptom	Phase I (placebo)	Phase II (Cernilton® N)
- Nycturia	14.0	38.6
- Diuria	15.2	50.0
- Feeling of residual urine	3.8	42.3
- Dysuria	36.0	60.0
- Urge to urinate	32.4	60.5
- Malaise	33.3	74.1

Palpation findings, negative (%)

Prostate	Phase I (placebo)	Phase II (Cernilton® N)
- Enlargement	2.1	14.9
- Congestion	37.9	62.1

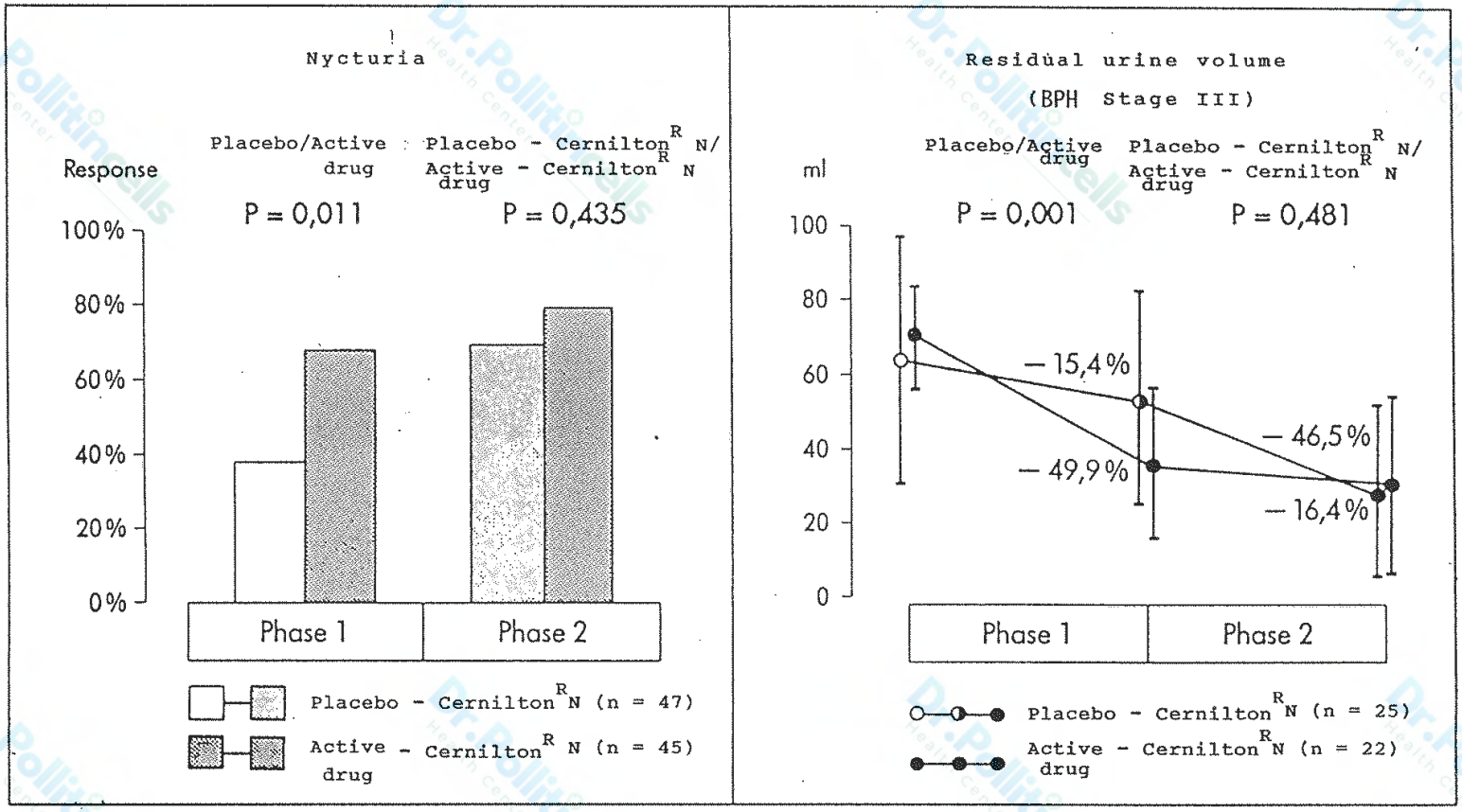

Fig.1: Comparison of the treatment-groups, placebo-Cernilton N and active drug-Cernilton N. Significant differences in the double-blind phase level out after subsequent Cernilton N therapy in the follow-up phase. Parallel course under active drug in comparison with Cernilton N with initial placebo medication in the double-blind phase. Significantly different (P = 0.008) course of the residual-urine volume over both phases in the two treatment-arms.

Possibilities and Limitations of Phytotherapy for Benign Prostatic Hyperplasia (BPH)

Results of Treatment with Cernilton® N for Stages 1-3 according to Alken (or II-IV according to Vahlensieck)

D. Bach, L. Ebeling

Introduction

Surgical treatment (transurethral resection or open surgical enucleation of the adenoma) of benign prostatic hyperplasia (BPH) is still the only curative therapy and therefore the "gold standard" for the treatment of BPH. Other treatment modalities have to be judged according to this standard. Despite all improvements in surgical technique and modern anesthesiology, a perioperative mortality rate of 0.2% and an increased delayed mortality due to cardiovascular diseases remains a significant risk factor (19). Furthermore, other possible complications of surgery such as urinary incontinence, erectile impotence, or retrograde ejaculation are not acceptable to some patients.

Despite extensive investigation into the endocrinological control of the growth of the prostate, the etiology of the pathological enlargement of this gland has not yet been definitely resolved. As a target organ for male steroid hormones, the prostate is under the influence of dihydrotestosterone and 17ß-estradiol, which act in particular synergistically on the growth of the fibromuscular stroma. This explains why antiandrogens may be useful in the treatment of BPH (4,20). Because of the adverse effects of antiandrogens such as disturbances of libido and erectile function as well as gynecomastia, this therapeutic principle has thus far not been utilized widely, and is only used for certain patients such as those at prohibitive surgical risk. Other treatment attempts such as the inhibition of the enzyme 5alpha-Reductase require further studies concerning efficacy and adverse effects (14).

The importance of phytotherapeutic drugs with a low side effect profile has consequently increased in regard to the conservative treatment of BPH, which at least in Germany is mainly the responsibility of nonhospital-affiliated physicians. In recent years a standardized pollen extract (Cernilton ®N[1]) has been investigated (5,6,9) and utilized. This pollen extract has also been utilized to treat prostatic congestion and/or prostatodynia and non-bacterial prostatitis without proven pathogens (8). The anticongestive effect of the pollen extract in the treatment of BPH should be considered as a clinically relevant therapeutic principle.

To examine the value of treatment of BPH with phytotherapeutic drugs in clinical practice, a study was conducted in BPH patients to determine efficacy and tolerance of the pollen extract in the various stages of disease.

Patients and Methods

Patients

Over the course of one year, 208 practicing physicians documented their treatment experiences using Cernilton® N in 1,933 patients with BPH. Because of missing follow-up examinations or premature termination of either treatment or documentation not related to the treatment with Cernilton®, data on only 1,894 patients were available for analysis. An additional 96 cases which were not classified in regard to the stage of the disease were also excluded from the analysis. In seven of these patients treatment was terminated after the 12th week.

The patient material included therefore 1,798 patients with consecutive treatment over 24 weeks (2 tablets orally 3 times daily). In 1,661 patients pretreatment evaluations and evaluations after 12 and 24 weeks of treatment were available, while in 29 patients data were available for the pretreatment evaluation and after 24 weeks of treatment with Cernilton® N. In 51 patients the treatment was terminated because of symptomatic improvement (N = 11), lack of efficacy (N = 7), surgery (N = 27), untoward side effects (N = 4) or urinary tract infections (N = 2). In 57 cases treatment was terminated without a specified reason. Overall, therefore, 108/ 1,798 (6%) of the patients terminated treatment prematurely in the study population, as opposed to 115 / 1,894 (6.1 %) in the entire patient population.

The patients were staged according to *Alken*. Nine hundred and ten patients (50.6 %) were in stage 1, 770 patient (42.8 %) in stage 2, and 118 patients (6.6 %) in stage 3. The average age for these three groups was 60.0, 67.6, and 71.6 years, respectively. Overall, 59.1 % of patients had been pretreated, usually with other phytotherapeutic drugs used in BPH over an average duration of 21.2 (stage 1), 32.5 (stage 2), and 46.8 months (stage 3). This pretreatment was judged as "successful" in 52.0 % of stage 1 patients, 42.6 % of stage 2 patients and 30.4 % of stage 3 patients. Concomitant diseases existed in 812 (45.2 %) of the patients. Cardiovascular diseases (57.4%), endocrine and metabolic diseases (22.8%), and urological diseases (11.0 %) were most common. Among the urological diseases, prostatitis and bladder cancer were the most common.

To further describe the voiding disturbances, data such as age at the first manifestation, specific symptoms (irritative versus obstructive), intensity of the symptoms over time (constant versus variable, either increasing or decreasing), and incidence of episodes of acute urinary retention were documented.

Methods

Clinical evaluation was conducted prior to initiation of therapy as well as after 12 and 24 weeks of treatment. Irritative and obstructive symptoms (nocturia, frequency, feeling of incomplete emptying, urgency, delayed voiding, prolonged voiding time, weak urinary stream, and post-void dribbling) were classified as either mild, moderate, or severe.

Size and congestion of the prostate were evaluated by digital rectal examination (DRE). Residual urine volume was determined by ultrasonography. The documentation of residual urine was optional, and flow rate parameters were not documented at all since several of the participating physicians were family physicians and general practitioners who often did not have the means to perform residual urine or, in particular, flow rate measurements.

According to the design of the study, a statistical analysis was conducted using minimum, maximum, median, and mean values, standard deviation (STD), and frequency distributions. To compare frequency distribution across the various stages of BPH, the X^2 test was used. For the comparison of means, a simple analysis of variance was employed, and for the comparison of mean time effectiveness profiles, split plot variance analysis was utilized.

Results

Voiding Disturbances and Findings on DRE

The distribution of obstructive and irritative voiding symptoms at the time of entry into the study is tabularized in Table **1**. Data concerning age at first manifestation and type of voiding symptoms as well as their course are listed in Table **2**. While in stage 1 BPH nocturia and frequency are the dominating symptoms, prolonged voiding time and a weak urinary stream are most common in stage 2, and in particular in stage 3 BPH. Post-void dribbling was of particular importance in patients with stage 3 BPH. Prostatic congestion increased significantly with increasing stages. As expected, a more pronounced enlargement of the prostate was found in patients with stages 2 and 3.

Parameter	BPH 1 (N = 910)	BPH 2 (N = 770)	BPH 3 (N = 118)
Nocturia	43.6%	65.2%	79.8%
Frequency	53.8%	60.3%	77.9%
Feeling of incomplete emptying	20.9%	45.2%	69.8%
Urgency	26.4%	30.3%	49.5%
Delayed voiding	31.1%	62.3%	85.3%
Prolonged voiding	34.2%	70.1%	90.5%
Weak stream	38.7%	74.3%	88.8%
Postvoid dribbling	26.3%	44.0%	74.6%
Prostate enlargement	32.1%	86.1%	89.5%
Prostate congestion	28.1%	43.2%	63.0%

Tab. 1 Moderate to severe intensity of voiding symptoms and findings at digital rectal examination (DRE) in 1,798 patients with BPH. [The frequency of symptoms and DRE findings differ significantly between the three stages. ($p<0.001$).]

Of interest was the significantly different average age at the first manifestation of the voiding symptoms. In patients with stage 1, it was eight years earlier than in stage 3. If one takes the average age of the patient into account, symptoms have been present prior to treatment for 3.5 years in stage 1 patients, for 5.7 years in stage 2 patients, and for 7.1 years in stage 3 patients. If one excludes the possibility that the data obtained from older patients become relatively imprecise, these results can only be explained by an age-dependent dynamic course of progression of the disease process of BPH.

Irritative symptoms dominated in patients with stage 1, while in stages 2 and 3 obstructive symptoms were more common. However, in the advanced stages, often both irritative and obstructive symptoms were found equally common. Fluctuation of the intensity of the symptoms was particularly characteristic for patients with stage 1 BPH, while in patients with stages 2 and 3 a progression of the symptoms and a higher incidence of episodes of acute urinary retention was evident.

In regard to the findings on DRE and the voiding symptoms, the treatment with Cernilton ® N did not yield a significant difference in the response rates (range from 68% - 83%) between stages 1 and 2 (Table **3**). However, if one compares the therapeutic efficacy in stages 1 and 2 with respect to the symptom-free status concerning nocturia and the obstructive voiding symptoms as well as the DRE concerning the prostatic size, a significant difference in favor of stage 1 was found (Table **3**). For patients with stage 3 BPH, a response rate between 28% and 63% was found, while a symptom-free status was found in 0 - 15% of patients (Table **3**).

Unchanged positive symptoms and/or prostatic congestions (Non-responder) were found between 16.8% and 28.7% for patients with stage 1, 19.8% and 31.2% for patients with stage 2, and between 33.3% and 52.7% for patients with stage 3 BPH. Unchanged positive symptoms were found more commonly in the obstructive symptom category. Considering these findings, the comparison between the different stages yielded significant differences ($p < 0.001$) for all parameters, with a weaker effect in particular for stage 3 patients and in comparing stage 1 with stage 2. Worsening of the status in up to 6.4% of the patients was found particularly in patients with stage 3 BPH.

An analysis of the time course showed for all parameters - with the exception of the size of the prostate - an increase in the rate of patients with a symptom-free status in regard to voiding symptoms and prostatic congestions at 24-week evaluation in comparison with the 12-week evaluation. The incremental rate of improvement between 12 and 24 weeks of treatment was 13 % to 24 % for stage 1, 10 % to. 25 % for stage 2, and 1 % to 17 % for stage 3. There was no principle difference detected between stages 1 and 2. Fig. **1** illustrates the time course of one of the symptoms (nocturia) for the different stages of the disease throughout the treatment period. The mean severity index for this symptom is shown.

Tab. 2 Characteristic of voiding symptoms in the three stages of BPH.

Parameter		BPH 1	BPH 2	BPH 3	Comparison of Stages
Age at first manifestation (years)	$\bar{x}$	56.5	61.9	64.5	$p < 0.001$
	SD	10.2	8.7	8.0	
o not available		35	26	4	
Type of complaints					
o Mainly irritative		58.5%	29.7%	14.8%	
o Mainly obstructive		29.4%	42.5%	55.7%	
o Irritative and obstructive		11.8%	27.1%	28.7%	$p < 0.001$
o not available		8	10	3	
Clinical course (multiple listings)					
o Sometimes more, sometimes less		51.0%	32.5%	23.7%	$p < 0.001$
o Variable symptoms		47.8%	37.9%	22.0%	$p < 0.001$
o Increasing symptoms		31.9%	54.3%	73.7%	$p < 0.001$
o Episodes of retention		4.1%	9.9%	38.1%	$p < 0.001$
o not available		10	7	2	

Tab. 3 Overall treatment response rates (R) and symptom-free or negative DRE status (S) after treatment with Cernilton® N in percent (rounded) of patients who initially had symptoms or findings on DRE.

Parameter	Patients (N) Stage 1/2/3	BPH 1 R (%)	BPH 1 S (%)	BPH 2 R (%)	BPH 2 S (%)	BPH 3 R (%)	BPH 3 S (%)
Nocturia	727/719/111	76	43	73	21	57	5
Frequency	746/693/108	82	48	89	34	63	12
Feeling of incomplete emptying	469/605/101	83	64	79	47	56	15
Urgency	449/454/ 83	79	60	79	56	59	33
Delayed voiding	645/701/111	72	46	73	27	54	5
Prolonged voiding	629/711/113	72	40	70	20	47	2
Weak stream	736/737/112	71	37	70	17	46	4
Postvoid dribbling	592/651/109	72	49	68	37	55	15
Prostatic enlargement	802/746/111	29	13	33	3	28	–
Prostatic congestion	504/495/ 74	75	55	68	38	51	16

Residual Urine

Significant improvements in the amount of residual urine were noted under treatment with Cernilton® N in patients with stages 1 and 2. A comparison between pre-treatment and post-treatment values in patients who had initially at least 20 ml of residual urine revealed a mean decrease of 32.7ml (51 %) for stage 1, 43.1 ml (45 %) for stage 2, and 18.5 ml (13 %) for stage 3.

A time-course analysis in these patients showed for stages 1 and 2 a continuing decrease of the amount of residual urine under treatment. However, in patients with stage 3 BPH a worsening was noted at 24 weeks after an initial improvement (Fig.**2**). Analysis of variance revealed a significant difference when comparing the different stages of the disease (p=0.016). In patients with stage 2 BPH in comparison with stage 1, a more significant decrease of the residual urine volume was achieved after 24 weeks of treatment. In stage 1, 39.6 % of the patients with an initial residual urine volume of >20 ml had a residual urine volume of ≤20 ml at 24 weeks, while 25.0 % of patients with stage 2 achieved the same result. In patients with stage 3 BPH the residual urine volume was at the end of the treatment still significantly elevated. The degree of obstruction in this stage apparently does not allow a significant quantitative change of residual urine volume during treatment.

Adverse Effects

Adverse effects were noted in 15 patients for an incidence of 0.8 %. Except for two cases without specific documentation, the adverse effects were mainly gastrointestinal symptoms (stomach pain, pressure sensation, nausea, diarrhea, and indigestion). Treatment was terminated because of adverse effects after 12 weeks in four patients.

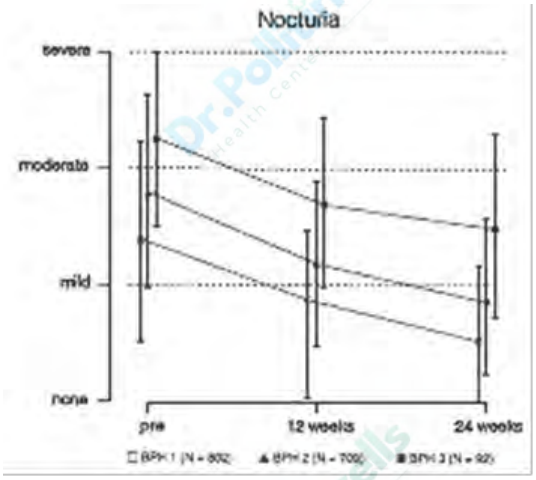

Fig.1 Nocturia (average intensity, $\bar{x} \pm SA$) during 24 weeks of treatment in patients with stages 1, 2 and 3 BPH with Cernilton® N. The intensity of the symptom decreases throughout the treatment in all three stages.

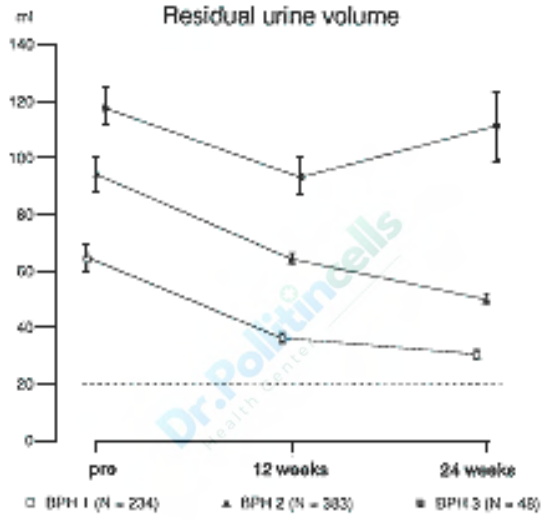

Fig.2 Residual urine volume ($\bar{x}$±SEM) during 24 weeks of treatment in patients with stages 1, 2, and 3 BPH with Cernilton® N. Continuing decrease of residual urine volume in stages 1 and 2, and a worsening after initial improvement during the first 12 weeks in stage 3 patients are observed.

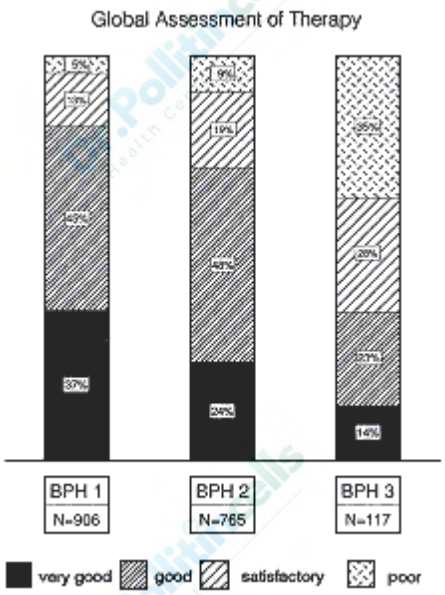

Fig. 3 Overall assessment of the efficacy of Cernilton® N in 1,788 patients with BPH by physicians stratified by stage.

Global Assessment of Efficacy and Tolerance

Independent of the stage of the disease, tolerance was judged to be good in over 99 % of patients. There were statistically significant differences in the judgment of the treating physicians concerning the efficacy across the three stages (Fig. **3**). The subjective assessment of the patients showed in principal a similar distribution of the results, but was overall somewhat more favorable when compared to the physicians' judgment. While the treatment result in patients with stages 1 and 2 BPH was judged as positive in over 90 %, it was judged as poor in 35 % of patients with stage 3. The main reasons for the treatment failure were advanced stage of the disease, need for surgery, psychogenic problems, bacterial prostatitis, and non-compliance of the patient.

Discussion

Reports in the urological literature document that several so-called conservative treatment options for BPH compete for both physicians and patients with BPH. Results following balloon dilation of the prostate, insertion of urethral spirals or stents made of surgical steel mesh in the prostatic urethra, thermotherapy, and drug treatment have been reported. Balloon dilation (15), insertion of spirals (11,18), or stents, (24), improved micturition only temporarily. Thermotherapy has apparently not yet reached practical applicability in the treatment of BPH (7,13,16,21).

If all these methods fail, oftentimes transurethral or suprapubic catheterization is a method of last resort. However, patients usually do not tolerate a permanent catheter over a long duration. This leaves the different drug treatments amongst which the low-risk phytotherapeutic drugs have a permanent place (2).

The use of these drugs is justified by good treatment results documented in case reports, open-label clinical studies, or prospective placebo-controlled double-blind studies. Criticism has been raised stating that the number of placebo-controlled studies is too low to prove the efficacy of the treatment (10). The placebo effect, which has to be taken into account with all drug treatments, is superimposed over the actual drug effect, and therefore no clear determination as to the efficacy of these drugs can be made.

However, concerning , the pollen extract preparation, Cernilton ® N, experimental *in vitro* and *in vivo* data, and clinical documentation of effectiveness are available. An inhibition of the prostaglandin and leukotriene synthesis (17), an inhibition of the enzymes 5alpha-Reductase, 3alpha- and 3ß-Hydroxysteroid-dihydroxygenase (22), an anti-proliferative effect on BPH cells (12), as well as on BPH heterotransplants (23), and a significantly better efficacy of verum as compared to placebo in regard to nocturia, residual urine, and the global assessment of the treatment results have been reported (5,9). The following discussion therefore aims at the question of the clinical relevance and the indication for the use of phytopharmaca in the treatment of BPH.

The present report details the observation made by 208 practicing physicians during the treatment of 1,933 BPH patients with Cernilton ® N. Under the conditions of routine clinical practice, it can be shown that

irritative and obstructive voiding symptoms, prostatic congestion, and the residual urine volume are significantly improved, depending on the stage of the disease.

When comparing the results with those of controlled clinical trials, the response rates and the percentage of patients who achieve a symptom-free status or whose clinical findings become negative are higher in the present report. This may be explainable by the patient selection necessary for clinical studies. However, except for the symptom of frequency, which may be judged differently because of inconsistencies in its definition, there are no principal differences and therefore the data of the present study remain valid.

Concerning the symptoms, it is noted that the irritative symptoms show the largest margin of improvement, and patients with stage 1 BPH obtain the most benefit. Since irritative and obstructive symptoms are often equally common in patients with stage 2 BPH, these subjective voiding symptoms also improve significantly in patients with stage 2 BPH.

The clinical course of the voiding symptoms indicates that with the progression of the disease, obstructive symptoms increase and become more important in comparison to irritative symptoms. In regard to the therapeutic effect, this results in a lower percentage of patients achieving a symptom-free status in those men with stage 2 disease. In this group, prostatic congestion is also usually more pronounced.

In contrast to this, the residual urine volume decreases both absolutely and relatively more in patients with stage 2 disease than in patients with stage 1 disease. This may explain the relatively small differences in the global assessment of the therapeutic results stratified by these stages of the disease. The course over 24 weeks of treatment indicates that the residual urine decreases in particular in patients with stage 2 BPH between week 12 and 24. The percentage of patients with improved or symptom-free status further increases during the second half of the treatment course. These results document therefore a relatively better efficacy of the treatment in stages 1 and 2 BPH during long-term therapy.

The clinical relevance of a therapeutic strategy is significantly impacted by the improvement of the quality of life as defined by the patient. The improvement of the voiding dysfunction is reflected in the overall global subjective assessment of the therapeutic result by the patient. If curative surgery is not medically indicated - this has to be decided for each individual patient - and an immediate surgical intervention independent of the stage of the disease is not necessary given the availability of continued monitoring of the patient (3), the results of the present study indicate that patients with stage 1 and 2 BPH according to *Alken* or stage II or III according to *Vahlensieck* represent a classical target group for the treatment with phytotherapeutic drugs. The impact of the treatment on prostatic congestion and associated inflammation is thereby the main focus of this treatment regimen (1).

The treatment of BPH with phytotherapeutic drugs is well tolerated and represents a treatment option with few risks. Therefore, a treatment trial may be justified even in patients with stage 3 BPH until the time of definite surgical treatment. In more than one-half of these patients some improvement in symptoms and a minor decrease in the amount of residual urine can be achieved. Phytotherapeutic drugs are not suitable for long-term treatment of patients at prohibitive surgical risk.

Summary

To examine the possibilities and limitations of phytotherapy for benign prostatic hyperplasia (BPH) a 24-week treatment trial using the pollen extract preparation Cernilton® Nwas conducted. Based on 1,798 cases a significant improvement in voiding symptoms, palpable prostatic congestion, and residual urine could be documented in stages 1 and 2. In patients with stage 3, the improvement in voiding symptoms was rather limited, as expected. When comparing the results after 12 and 24 weeks of treatment, a continuing improvement of all parameters during the second 12 weeks of treatment was noted.

The drug was tolerated well in over 99% of patients. The efficacy in stages 1 and 2 was judged to be satisfactory, good or very good by over 90% of the patients. Because of the lack of conservative treatment alternatives for patients with BPH, treatment with phytotherapeutic drugs with their associated minimal risks is recommended as one of the prime treatment modalities for patients with BPH who are under continued medical care and monitoring. Until surgery, a treatment trial is also justified in patients with stage 3.

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Prostatitis

Pygeum africanum

A tropical African evergreen tree.

Administration of extracts of the bark (standardized to contain 14% beta-sitosterol and 0.5% n-docosanol) may be beneficial at a dosage of 50 to 100 mg twice daily.

Experimental Study

18 pts. with benign prostatic hypertrophy or chronic prostatitis and, simultaneously, sexual disturbances, received an extract of *Pygeum africanum* (Tadenan®, Roussel Pharma) 200 mg daily. After 60 days, the extract had improved all the urinary parameters that were investigated. Also, sexual behavior was reported to be improved despite a lack of change in the levels of sex hormones or in nocturnal penile tumescence and rigidity. No side effects were observed (*Carani C, Salvoli V, Scuteri A, et al. [Urological and sexual evaluation of treatment of benign prostatic disease using Pygeum africanum at high doses.] Arch Ital Urol Nefrol Androl 63(3):341-5,1991) (in Italian).*

Combination Treatment

Flower Pollen Extract

Administration of standardized extract of flower pollen (Cernilton®) may be beneficial.

Note: In vitro studies suggest that Cernilton® is a potent cyclo-oxygenase and lipoxygenase inhibitor and a smooth muscle relaxant (Buck AC, Rees RW, Ebeling L. Treatment of chronic prostatitis and prostatodynia with pollen extract. Br J Urol. 64(5):469-9, 1989).

Experimental Study

90 pts. with chronic prostatitis received Cernilton N one tablet 3 times daily. After 6 mo., in the 72 patients without complicating factors (urethral strictures, prostatic calculi or bladder neck sclerosis), 56 (78%) had a favorable response; 26 (36%) were cured of their signs and symptoms, and 30 (42%) improved significantly with an increase in flow rate, a reduction in leukocyturia in the post-prostate massage urine and a decrease in complement C3/ceruloplasmin in the ejaculate. In the 18 pts. with complicating factors, however, only 1 pt. showed a response; thus complicating factors should be considered in pts. who fail to respond to treatment within 3 months. The extract was well tolerated by 97% of pts. *(Rugendorff EW, Weidner W, Ebeling L, Buck AC. Results of treatment with pollen extract (Cernilton N) in chronic prostatitis and prostatodynia. Br J Urol. 71(4):433-8, 1993).*

Experimental Study

25 pts. with chronic prostatitis received Cernilton tablets. Improvement of subjective symptoms and objective findings was noted in 96% and 76%, respectively. Sonographic findings showed 33-100% improvement in 4 objective parameters. No side effects were observed *(Suzuki T, Kurokawa K, Mashimo T, et al. [Clinical effect of Cernilton in chronic prostatitis.] Hinyokika Kiyo. 38(4):489-94, 1992) (in Japanese).*

Experimental Study

13/15 pts. with chronic prostatitis and prostatodynia with a mean duration of 3.3 yrs. were treated with Cernilton 2 tabs twice daily. 7 had complete and lasting symptom relief, while 6 had marked improvement. Most pts. who responded (11/13) did not start to show improvement until 3 mo. after starting treatment,

and symptoms recurred in 2 pts. who stopped treatment. No adverse reactions were seen (*Buck AC, Rees RW, Ebeling L. Treatment of chronic prostatitis and prostatodynia with pollen extract. Br J Urol. 64(5): 496-9, 1989*).

Experimental Study

32 pts. with chronic prostatitis received Cernilton 6 tabs daily. After an average of 6 weeks, improvement of subjective symptoms and objective findings was noted in 74.2% and 65.6%, respectively. The effective rate was 75%. No subjective side effects or abnormal changes in laboratory data were observed *(Jodai A, Maruta N, Shimomae E, et al. [A long-term therapeutic experience with Cernilton in chronic prostatitis.] Hinyokika Kiyo. 34(3):561-8, 1988) (in Japanese).*

Experimental Study

Based on a grading system using both objective and subjective measures of 14 pts. with non-gonorrheal prostatitis and urethritis given Cernilton 4 tabs daily, it was 'effective' in 10 (71%) and 'slightly effective' in 3 (21%). Of 16 pts. given placebo it was 'effective' in 7 (44%) and 'slightly effective' in none. Subjective symptoms disappeared in 10 pts. (71%) and diminished in 4 (29%) while the rest had some degree of improvement in the Cernilton group. In the placebo gp., subjective symptoms disappeared in 5 pts. (31%), diminished in 2 (13%), and worsened in 2 (13%). In the Cernilton group, there was normalization of the urinary sediment in 5 pts. (36%) improvement in 1 (7%), persistence of the abnormal state in 2 (14%), exacerbation in 1 (7%), and continuation of the normal state in 4 (29%) (the result in 1 pt. is unknown). In the placebo gp., there was normalization in 3 pts. (19%), improvement in 2 (13%), persistence of the abnormal state in 3 (13%) and persistence of the normal state in 8 (50%). For the Cernilton gp., urinary bacteria following prostatic massage disappeared in 3 pts. (21%), failed to change in 2 (14%), and remained normal in 9 (64%). For the placebo gp., bacteria disappeared in 1 pt. (6%), failed to change in 2 (13%), reappeared in 1 (6%) and remained normal in 12 (75%). There were no notable subjective or objective side effects *(Ohkoski M, Kawamura N, Nagakubo I. [Clinical evaluation of Cernilton in chronic prostatitis.] Rev Med Suiza. 2(16):436-9. 1970)(in Spanish).*

See Also

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Alternative medications for benign prostatic hyperplasia available on the Internet: a review of the evidence for their use

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Introduction

The number of people seeking alternative medications to treat disease is increasing; indeed, this was the subject of study conducted by Eisenberg *et al* in 1993 [1] who reported that there were 425 million visits to providers of alternative treatment during 1992 in the USA. This number has probably increased since then. These alternative therapies are sold as nutritional supplements for numerous illnesses, ranging from treatments for the common cold to those for depression. As with other specialties, there is now an abundance of alternative therapies for urological conditions. It is estimated that in the USA 30-90% of patients seen by urologists for putative BPH may be taking some form of alternative therapy for the condition [2-4]. Access to these agents has become easier with the increased use of the internet by these patients.

An internet search using the words 'alternative treatments for BPH' as a search term revealed >1000 sites offering help and advice about BPH. On reviewing these sites there were several available alternative therapies, available via the Internet, for treating BPH:

- *Serenoa repens (Saw Palmetto berry extract);*
- *Hypoxis rooperi (South African star grass);*
- *Pygeum africanum (African plum);*
- *Cucurbita pepo (pumpkin seeds);*
- *Urtica dioica (Stinging nettle);*
- *Secale cerale (Rye pollen);*
- *Flaxseed oil;*
- *Lycopene;*
- *zinc;*
- *β-sitosterol;*
- *selenium.*

Each of these substances can be bought singly but much more common are the various combined 'prostate health' products. Some combination products list numerous ingredients, but the amount of each ingredient varies among products, and therefore if a combination product is selected the patient is required to undertake much painstaking reading of the labels.

Despite the increased use of these products both in Europe and the USA, most urologists have little understanding or knowledge of them. There is also limited evidence of their efficacy [4]. In this article we review the evidence which supports their widespread use by current urological patients.

Serenoa repens (Saw palmetto berry extract)

This agent is derived from the olive-sized berries of the saw palmetto tree and is the most popular phytotherapeutic agent used in the treatment of BPH. The exact mechanism of its action has not been confirmed, although numerous mechanisms have been proposed. These include an anti-inflammatory effect, anti-androgenic activity, inhibitory effect on type 1 and 2 isoenzymes of 5α reductase, and

inhibition of prolactin and growth factor-induced cell proliferation. The *in vitro* studies to determine its mechanism of action mainly used supraphysiological dosages, leaving the significance of these studies open to debate [4-6].

Lowe *et al.* [7] conducted a meta-analysis which set out to review all placebo-controlled trials using the 'Permixon' brand of saw palmetto. There were seven such studies, each short duration, i.e. <3 months, reporting an improvement in symptoms, although the only symptom common to all of the studies was nocturia. There was also an improvement in urine flow when compared with placebo, although this was apparently limited.

The most widely quoted study of 'Permixon' saw palmetto was a comparison with finasteride, a 5α reductase inhibitor, and involved 1098 patients in a 6-month double-blind, randomized controlled study. Both symptom scores and urinary peak flow rate were improved to a similar extent in both groups. The differences were significant when compared with baseline for both drugs. However, there was no placebo group in this trial and therefore the improvements reported might simply have been the result of a placebo effect.

***Pygeum africanum* (African plum)**

In traditional African medicine a tea made from the powdered bark of this tall evergreen tree is drunk to control urinary disorders in men. Today, this supplement is commonly used in France, known more commonly under its trade name of Tadenan. It is frequently sold in combination with saw palmetto and other agents as part of pills for 'male health'.

Tadenan has been shown to have several effects, including inhibition of fibrolast growth factors, antioestrogenic effects, inhibition of chemotactic leukotrienes and other 5 lipo-oxygenase metabolites [4,8].

Breza *et al* [9] evaluated this agent in a recent 2-month open-label trial using a daily dosage of 100 mg. Using the IPSS they reported a 40% reduction in scores and an improvement in mean peak urinary flow rates (10.97 mL/s at baseline to 13.07 mL/s at the end of the study). This was an uncontrolled study, only suggesting a benefit from Tadenan, and obviously no other conclusions can be made. Unfortunately, there are no recent placebo-controlled clinical studies using Tadenan.

***Hypoxis rooperi* (South African star grass)**

This agent contains mainly β-sitosterol, which is thought to be the major active component, with other sterols being detected in lesser amounts [4,5]. The extract of star grass is marketed as Harzol. *In vitro* studies with Harzol show that it enhances the production and secretion of plasminogen activators in isolated epithelial cells. In prostate stromal cell cultures there are also increased levels of TGF-β1 when conditioned with β-sitosterol. TGF-β1 is a differentiation factor and induces apoptosis. These *in vitro* studies have not been verified *in vivo* and they have not been shown to be clinically relevant [4].

This drug has been studied in a double-blind placebo-controlled trial [10]; 200 patients were randomized to receive a placebo or a preparation of phytosterol. In both groups there were symptomatic improvements over baseline measurements and the difference was greater in the phytosterols group. These authors also reported a larger improvement (by 4.1 mL/s) in peak urinary flow rate in those treated with Harzol than in the placebo group. At the 18-month follow-up the group initially given the placebo were given Harzol; they then had improvements which were comparable with the group initially treated with Harzol. Interestingly, the beneficial effect of Harzol continued over the next 12 months regardless of whether the patient stopped Harzol or was given the placebo [11].

***Urtica dioica* (stinging nettle)**

There are at least 16 different preparations of this extract taken from the roots of the stinging nettle. The roots contain a mixture of lectins, phenols, sterols and lignins. Despite its widespread use in Germany for treating BPH there are limited clinical data about its efficacy for this condition. Two double-blind placebo-controlled studies were conducted >10 years ago, but with few patients and in trials <3 months, the data produced were of little value.

***Secale cerale* (rye pollen)**

The commercial preparation 'Cernilton' is pollen prepared from several plants found growing in countries such as Sweden and Switzerland. This drug is available across Europe and is manufactured by microbial digestion of the pollen. As with many alternative medications the mechanism of action remains unclear. Several mechanisms have been proposed, including an improvement in detrusor activity, inhibition of 5α reductase activity, and an influence on androgen metabolism in the prostate [5].

A study reported in 1996 [4] compared Cernilton with Tadenan over a 4-month period; there was no placebo group in the study. No conclusions can be drawn from this study as the efficacy of Tadenan has, as yet, not been confirmed. Despite this, the authors [4] reported a better response, in terms of symptom scores, residual volumes and peak flow rates, with Cernilton. Clearly, a double-blind placebo-controlled trial is required.

Soy

Environmental factors such as diet are thought to influence the causes of BPH. The underlying rationale for this comes from epidemiological data showing that the incidence of BPH is much lower in the Orient than in the Western world. This difference is not solely caused by genetic differences, as the incidence of BPH increases in those who migrate from the Orient to the USA [12]. When Western and Oriental diets are compared a major difference is the high intake of soybean products in the latter. Genistein is derived from soybean and is a major ingredient of tofu; it is also an active oestrogen, with a high affinity for the oestrogen receptor. Geller et al. [13] studied the effects of genistein on human BPH tissue *in vitro*, showing a dose-dependent decrease in the growth of this tissue. These promising results support a possible role for soy products in managing BPH, although further study is required.

Trace elements

Trace elements such as zinc and selenium are often marketed for their beneficial effects in management of BPH. Although there is no evidence to support the efficacy of such trace elements they are still widely taken by patients.

Combination pills

Many of the above extracts are sold as combination pills. One such combination is 'Prostagutt forte', which is a combination of *Serenoa repens* and *Urtica dioica*; it is widely used although there are no data to support increased efficacy with combination products. This combination pill was compared with finasteride in 489 randomized patients in a 48-week trial; there were no statistically significant differences in the IPSS and peak urinary flow rates between the groups. Unfortunately, because there was no placebo group, no valid conclusions can be made from this study.

Combination pills remain popular, although in many the amount of saw palmetto varies considerably, with some actually containing very little. Despite the lack of evidence for them, there is still widespread use of these products.

What advice should be given to patients?

Lowe et al. [4] reported that should a patient wish to try an alternative medication for BPH, then their advice would be for the patient to select the least expensive one available and trial it for 1 month. If the agent 'does not work', then they should try another brand for a month, even trying a third. Lowe et al. felt that if there was no change after 3 months then the patient would be best advised to take conventional medication. We concur with this advice and also suggest that the patient should be made aware that the alternative medications that they might be taking have not been subjected to the same rigorous clinical trials that 'conventional' drugs are, and that several of these alternative drugs remain 'unknown quantities'.

In summary, patients are now resorting to alternative medications for BPH with increasing frequency. One of the main reasons for this is the increasing public awareness of these previously 'unknown' products, through the expansion of health-food shops but particularly through the increasing use of the Internet by patients.

From this review it is apparent that although the use of these medications is increasing, understanding about them and the mechanisms of action are not increasing at the same rate. Although some of the studies cited here have shown promising results, randomized controlled trials containing many patients followed for long

periods are needed. This will allow the initial results reported with these alternative medications to be validated or refuted. Only then will urologists be able to confidently and safely recommend these products to patients.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Alterations in the Intraprostatic Hormonal Metabolism by the Pollen Extract Cernilton®N

Sabine Tunn, M. Krieg

Introduction

A number of hypotheses have been implicated in the etiology of benign prostatic hyperplasia (BPH). The most important theories are: (1) an alteration of the androgen metabolism in BPH if compared to the normal prostate (NPR) leading to an accumulation of the biologically highly active androgen 5α-dihydrotestosterone (DHT) predominantly in the stroma; (2) a change in the androgen-estrogen ratio in favor of estrogens; (3) and an alteration in the intraprostatic interaction between stroma and epithelium [for an overview see (3)]. Such variable hypotheses do not allow a unified therapeutic concept for BPH.
For the medical treatment of BPH a variety of substances are utilized such as GnRH analogues, which reduce peripheral androgen and estrogen concentration (5,8), 5α-reductase inhibitors, which lower the intraprostatic DHT concentration (14), or aromatase inhibitors, which lower the peripheral estrogen concentration (12).

Besides these substances influencing the hormonal milieu, phytopharmaca are also utilized to treat patients with BPH who do not have indications for surgery. These drugs, such as the pollen extract Cernilton®N, lead to a subjective improvement in the patient's symptoms. The effect is supposedly based on an improvement in the inflammation or congestion of the prostate. To what extent these drugs influence the intraprostatic hormonal milieu is not known. We were interested in the question whether and to what degree phytopharmaca influence the intraprostatic androgen metabolism and may exert their effects by a change in the intraprostatic DHT content. To this end we characterized the main enzymes of the androgen metabolism (5α-reductase, 3α- and 3β-hydroxysteroid oxidoreductase) in the epithelium and stroma of the human prostate, and tested the in vitro influence of the phytopharmacon Cernilton®N on these enzymes.

Materials and Methods

The activity of DHT-metabolizing enzymes (5α-reductase, 3α-HSO_{red}, 3β-$HSOR_{red}$) was determined in mechanically separated epithelial and stromal fractions from 10 normal and 20 hyperplastic prostate glands. To this end aliquots of the tissue homogenates were incubated with at least 4 different concentrations of the individual substrates (either exclusively in ^{3}H-labelled or ^{3}H-labelled and unlabelled form: testosterone to measure the 5α-reductase in concentrations from 14 to 600 nM, DHT to measure 3α- and 3β-$HSOR_{red}$ in concentrations from 100 to 4860 nM). After addition of a co-factor NADPH-regenerating system (5 mM glucose-6-phosphate, 0.6 U glucose-6-phosphate dehydrogenase) the reaction was started with the co-factor NADPH (5α-reductase: 0.5 mM; 3α- and 3β-$HSOR_{red}$: 1.5 mM) and the mixture incubated for 15 min at 37° C. To determine the effect of the pollen extract, epithelial and stromal fractions of three of the hyperplastic prostates were incubated with various concentrations (49;246;493µg/ml) of the water-soluble (wPE) or fat-soluble (fPE) fractions of the extract, mixed well and then submitted to the same procedure as described above. After the reaction was stopped by the addition of either, and following extraction, the steroids were separated by HPLC (reversed phase, stationary phase: Lichrosorb RP 18, mobile phase: acetonitrile: H_20 = 50:50). Quantification was performed by measuring the radioactivity in the individual chromatographic fractions (substrate and various metabolites).

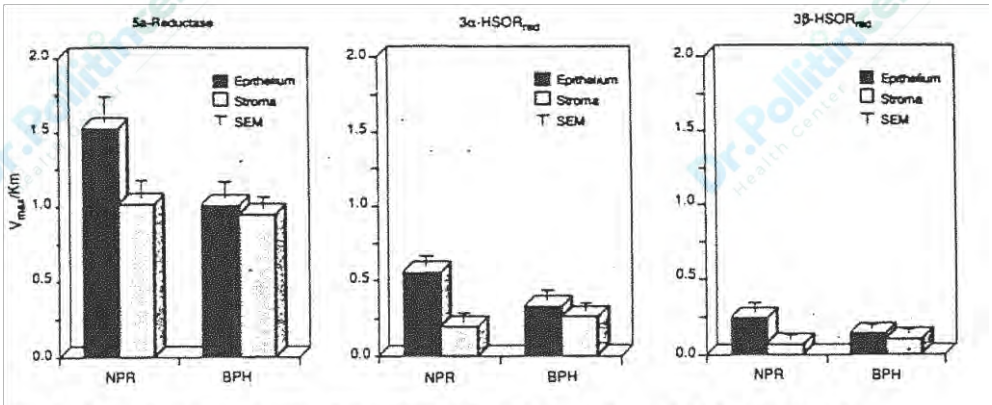


Fig. 1 Mean potential capacities (Vmax/Km) of 5α-reductase, 3α- and 3β-hydroxysteroid oxidoreductase (3α- and 3β-HSOR$_{red}$) in epithelium and stroma of 10 normal (NPR) and 20 hyperplastic (BPH) prostate glands.

The enzymatic activity was determined from the distribution of the radioactivity in these fractions. The specific activity of the labelled substrate, the ratio between labelled and unlabelled substrate, the incubation time, the protein concentration, and the blanks were utilized for the calculation. All assays were performed in duplicate.

Proteins were measured according to Lowry (6). The kinetic parameters Km and Vmax were calculated from the Lineweaver-Burk plot using regression analysis (least square method). The Student's t-test was utilized to determine significant differences between the means.
$P < .05$ was considered significant.

Results and Discussion

In the human prostate many androgen-metabolizing enzymes are present (see Fig. 1 in the chapter, ,,Hormone Metabolism in the Human Prostate"). The potential capacities of these enzymes vary greatly as our own published (10,11) and unpublished results show. The DHT-forming 5α-reductase and the DHT-removing 3α- and 3β-hydroxysteroid oxidoreductases (3α- and 3β-HSOR$_{red}$) have the highest potential capacity and therefore the greatest biological significance. It can therefore be assumed that these three enzymes are mainly responsible in the regulation of the intraprostatic DHT level.

Androgen Metabolism in the Normal and Hyperplastic Human Prostate

The potential capacity of an enzyme is expressed by the ratio Vmax / Km (10). In Fig. 1 the mean potential capacities for 5α-reductase, 3α-HSOR$_{red}$ and 3β-HSO$_{red}$ in epithelium and stroma of normal and hyperplastic prostates are shown. The 5α-reductase in the epithelium of normal prostate tissue has the highest potential capacity, where it is significantly higher than in the stroma, and also higher than in stroma or epithelium in hyperplastic prostate tissue. In the stroma there are no significant differences between NPR and BPH. The potential capacity of the 3α-HSOR$_{red}$ is significantly lower than that of the 5a-reductase, and the capacity of the 3β-HSOR$_{red}$ is again significantly lower than that of the 3α-HSOR$_{red}$. Both DHT- removing enzymes have significantly higher capacities in the epithelium of normal prostate tissue than in the stroma, and than in the epithelium and stroma of BPH tissue. The potential capacity of the 3α-HSOR$_{red}$ in NPR stroma is minimally lower, and that of the 3β-HSOR$_{red}$ even significantly lower than in BPH stroma.

A comparison of the potential capacities of the DHT-forming 5α-reductase and the DHT removing 3α-HSOR$_{red}$ and 3β-HSOR$_{red}$ allows the conclusion that there is no higher accumulation of DHT in BPH as compared to NPR. This conclusion is, however, only valid under the assumption of similar mean testosterone concentrations in men with normal and hyperplastic prostates. These results of the potential capacities therefore do not support the DHT accumulation hypothesis for BPH, but rather support the recently published data on DHT concentrations in normal prostate tissue (13,15) which demonstrated a higher concentration of DHT in normal prostate tissue removed immediately after death than in BPH tissue.

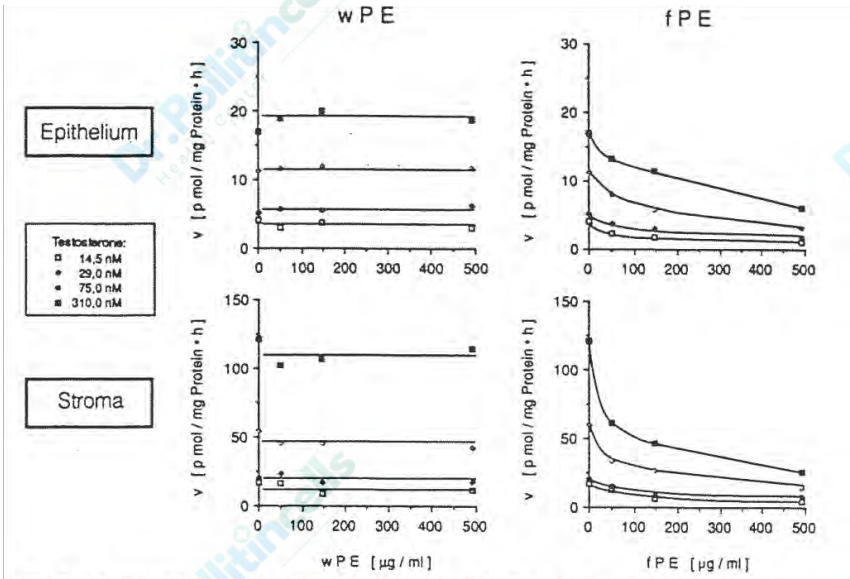


Fig. 2 Influence of the water-soluble fraction (wPE) of the pollen extract (left column) and the fat-soluble fraction (fPE) of the pollen extract (right column) on the enzyme activity (v). The activity of 5α-reductase in the epithelium (upper row) and stroma (lower row) is shown as an example. The enzyme activities were measured at different concentrations of the substrate testosterone (14.5–310 nM) and varying concentrations of wPE and fPE (49–493 µg/ml incubation mixture). All measurements were done in duplicate.

Alteration of the Intraprostatic Androgen Metabolism by the Pollen Extract Cernilton®N

To determine the effect of the pollen extract Cernilton®N on the enzymes of the intraprostatic androgen metabolism, the activities of the DHT-forming 5α-reductase and the DHT-metabolizing 3α-$HSOR_{red}$ and 3β-$HSOR_{red}$ were measured in epithelium and stroma of three hyperplastic prostates with varying concentrations of substrates as well as different concentrations of the water-soluble (wPE) and fat-soluble (fPE) fraction of the pollen extract. The activity of the 5α-reductase was not affected by wPE in a concentration range from 49 to 493 µg / ml incubation mixture in epithelium or stroma (Fig. 2). The activities of 3α-$HSOR_{red}$ and 3β-$HSOR_{red}$ were similarly not affected by this substance within the same concentration range (data not shown). However, fPE demonstrated in epithelium and stroma an inhibitory effect on the 5α-reductase (Fig. 2). The formation of DHT from testosterone is therefore significantly inhibited by the addition of fPE to the incubation mixture. Additionally, fPE also inhibited the activity of 3α-$HSOR_{red}$ and 3β-$HSOR_{red}$ in epithelium and stroma (data not shown). Therefore the metabolism of DHT to 5α-androstanediol is also diminished. The fat-soluble extract of another phytopharmacon (Serenoa repens B, Permixon®) was also found to inhibit the activity of 5α-reductase and 3α-$HSOR_{red}$ in human foreskin fibroblasts (9). This would indicate that nonspecific acting ingredients of such fat-soluble extracts are responsible for the inhibition of the enzymes.

To determine the kinetic mechanisms of the inhibitory effect of fPE, the enzyme activities were plotted for the different substrate and inhibitor concentrations in a double-logarithmic plot according to Lineweaver-Burk as shown exemplarily for the 3α-$HSOR_{red}$ in epithelium and stroma in Fig. 3. For all enzymes, 5α-reductase, 3α-$HSOR_{red}$ and 3β-$HSOR_{red}$, it was found in epithelium and stroma that the presence of fPE in the incubation mixture of the tissue homogenate did not change the Km, but that the Vmax changed corresponding to the concentration. Therefore the fPE acts as a non-competitive inhibitor of these enzymes, or in other words, the ingredients of the fat-soluble fraction do not bind at the active center for testosterone or DHT, but at another location, thereby altering the turnover number.

In Fig. 4 the mean potential capacities (ratio Vmax / Km) for the three enzymes in epithelium and stroma of the three hyperplastic prostates are depicted without (Fig. 4 A) and with (Fig. 4

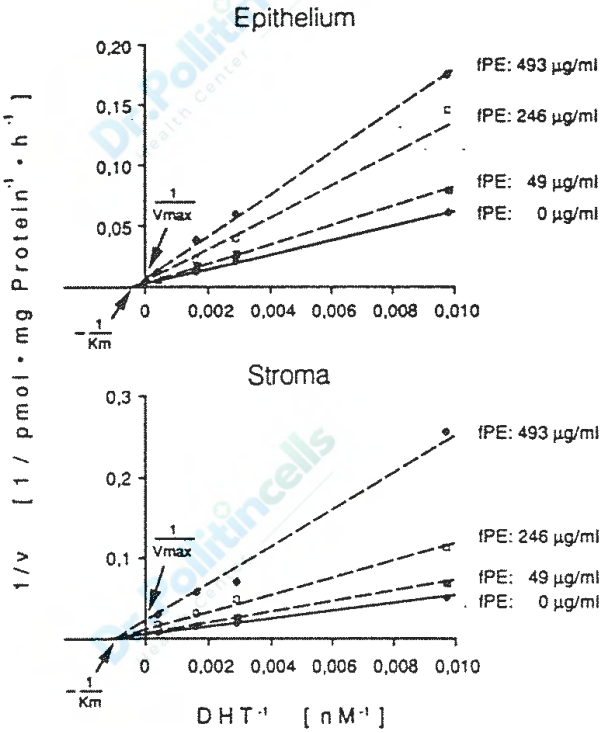
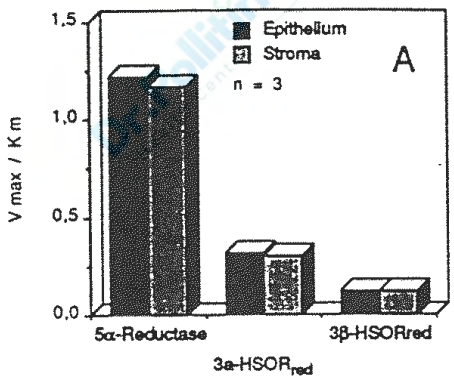


Fig. 3 Inhibition of the enzyme activity (v). The inhibition of the 3α-$HSOR_{red}$ by different concentrations (49–493 µg/ml incubation mixture) of the fat-soluble fraction (fPE) of the pollen extract as a function of the concentration of the substrate DHT in epithelium and stroma of a hyperplastic prostate is shown as an example (double logarithmic plot according to Lineweaver-Burk).

B) additional fPE (493 µg / ml incubation mixture). It is easily seen that the potential capacities of the 5α-reductase as well as the 3α- and 3β- $HSOR_{red}$ in epithelium and stroma are drastically reduced, but that the inhibitory effect of the fPE on the three enzymes is different. The mean potential capacity of the 3α-$HSOR_{red}$ is more inhibited in both compartments than that of both 5α-reductase and 3β-$HSOR_{red}$.

To estimate the expected changes in DHT content after in vitro incubation with fPE, the mean potential capacities of the three enzymes without additional fPE were assumed to be 1.0, and the percent activity after addition of the highest concentration of fPE (493 µg / ml incubation mixture) was calculated. The mean percentage activity of 5α-reductase after addition of fPE is shown next to the mean percentage activity of the DHT metabolizing enzymes 3α- and 3β-$HSOR_{red}$ (Fig. 5). It can be seen that the activity of the 3α-$HSOR_{red}$ in particular in the stroma, but also in the epithelium is more inhibited than that of the 5α-reductase, while the inhibition of the 3β-$HSOR^{red}$ is similar to that of the 5α-reductase. The different reaction of the enzymes may be explained by the different intracellular localization. The 3α-$HSOR_{red}$ is equally distributed between cytosol and cytosolic membranes, while the 3β-$HSOR_{red}$ is mainly membrane-bound (1). The 5α-reductase is exclusively found in the perinuclear and microsomal membranes (2,4,7). Although our studies were conducted in a cell-free milieu, the membrane-bound enzymes are probably surrounded by membrane particles and should be only minimally influenced by fat-soluble extract.

Since these in vitro studies showed a stronger inhibition of the DHT catabolism compared to the DHT formation by the fat-soluble fraction of the phytopharmacon Cernilton®N, a lowering of the intraprostatic DHT level in tissue homogenates after fPE administration cannot be expected. On the contrary, an accumulation of DHT results, which should be similar to that in the normal prostate, however, at a generally lower activity level. This comparison is only valid under the condition that similar amounts of the fat-soluble extract are incorporated in the epithelial and stromal cells without being metabolized, and that these extracts reach the enzymes 5α-reductase, 3α- and 3β-$HSOR_{red}$ - which are located in different subcellular compartments - in similar concentrations. To make statements about the capacity of the



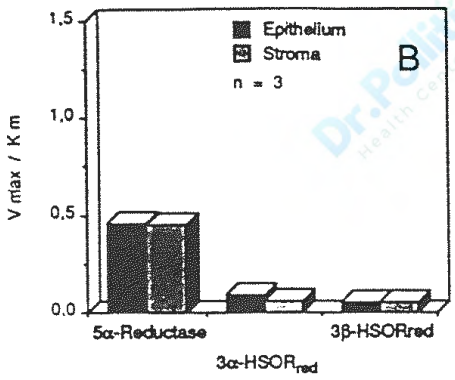


Fig. 4 Mean potential capacity (Vmax/Km) of 5α-reductase, 3α- and 3β-HSOR$_{red}$ in epithelium and stroma of three hyperplastic prostates without addition of fat-soluble fraction (fPE) of the pollen extract (A) and after addition of 493 µg fPE per ml of incubation mixture (B). All Vmax and Km values determined by Lineweaver-Burk plots.

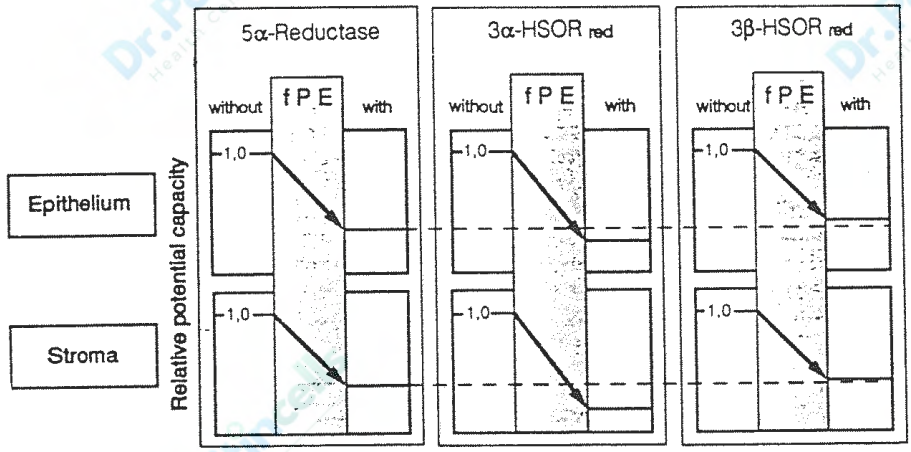


Fig. 5 Mean potential capacity (5a-reductase, 3α-HSOR$_{red}$ and 3β-HSOR$_{red}$) without (left columns) and after addition (right columns) of fat-soluble fraction (fPE) of the pollen extract in epithelium (upper row) and stroma (lower row) of three hyperplastic prostates. The potential capacities without additional fPE were assumed as 1.0, and the percentage remaining potential capacity after addition of fPE was calculated. The dotted lines indicate the relative potential capacities of the 5a-reductase in epithelium and stroma after addition of fPE.

pollen extract to influence androgen metabolism in vivo, further studies of androgen metabolism have to be conducted in prostate glands of patients who have been treated for a defined period of time with the pollen extract.

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Quantitative Evaluation on the Effectiveness of Cernilton® on Benign Prostatic Hypertrophy

H. Takeuchi et al. (Endocrinological Dept., Faculty of Medicine, Tokyo Medical & Dental University) (Hinyok Kiyo, Volume 27, No. 2, February 1981)

Introduction

Prostatomegaly is a very common disease in elderly men. It consists of a glandular, proliferative change occurring in the interior of the bladder and urethra. There are histopathological features, with proliferation not only of the glandular tissue but also of muscle and connective tissue. From the pathological point of view this is not genuine neoplasia but hyperplasia: the gland retains its normal exocrine function. The aetiology of the enlargement is still not certain, but a model experiment on dogs has shown that androstanediol secreted by the testes is involved, with estradiol as an accelerating factor.

This fact strongly suggests the participation of the endocrine function of the testes in the genesis of the disease.

The characteristics of an enlargement of this kind are also important from the therapeutic point of view. For example, if there is hormone imbalance with reduced sexual activity, the secretions accumulate in the tissue of the enlarged gland, leading to so-called “congestive prostatism”, with the formation of what is virtually a cyst. Therefore if the secretions are suitably eliminated the entire prostate gland will shrink.

From the clinical point of view prostatomegaly is a nodular proliferation (adenoma), which is located mainly in the right and left lobes of the prostate gland and pushes the latter outwards, not only forming a capsule, but also pressing it down and flattening it out. This increases urethral resistance during micturition and leads to various subjective symptoms; moreover there is obstruction of the lower urinary tract, with secondary effects on the bladder and upper urinary tract, finally leading to systemic symptoms. However, there is not necessarily any relation between the degree of obstruction and the size of the adenoma; there tends to be a closer relationship with either the site of enlargement, oedema of surrounding tissue, or infections complications. Frequency, which is regarded as an early symptom of this disease, or delayed and prolonged micturition, narrowing of the stream of urine, decline in ejaculatory power etc., which are regarded as symptoms of irritation, appear at an early stage, depending on the site of enlargement. On the other hand, there are not a few cases where the disease remains at the stage of “silent prostatism”, even with a prostatomegaly of 10-20g. Clinical problems of this kind, in conjunction with the above-mentioned pathological and physiological characteristics, suggest the possibility of some palliative method of treatment for the disease as opposed to the conventional prostatectomy. This would not be merely symptomatic but directed towards the eradication of the cause.

If this position is adopted, not only the basic problem of reduction of the adenoma, but also accessory problems of oedema of the neck of the urinary bladder accompanying the adenoma, stasis of the prostatic secretion and infections complications will form the object of therapy. At the moment hormones, plant or animal organ extracts etc. are regarded as effective against this disease. However, not only the mode of action but also the usefulness of such preparations is still under review.

Although the pollen preparation Cernilton®, which has long been regarded as useful against prostatitis mainly in Northern Europe, has been regarded as indicated for prostatomegaly, both for its effect against inflammation and its action in inhibiting the growth of the prostate gland (2), there have been few studies of its actual use and effectiveness against prostatomegaly (3, 4). The present study is concerned with 25 cases of prostatomegaly chosen at random from patients assessed as not requiring an immediate operation, and investigates the preparation's effectiveness both from the point of view of subjective symptoms and from a physical examination of prostate gland, with the aim also of throwing some light on its mode of action.

Subjects of Investigation and Method

(A) Subjects: the subjects were 25 cases chosen at random from patients with prostatomegaly at the Endocrinological Department of the Faculty of Medicine, Tokyo Medical & Dental Hospital. The following were the exclusion criteria when selecting these cases:

1. Those not complaining of difficulty in micturition;
2. Those at stage III or later of the disease; with a residual urine volume of more than 250 ml;
3. Those receiving some other preparation for prostatomegaly up to one week before the start of the trial;
4. Patients with complications, such as mental disorder, neurological disease (neurogenic bladder, including diabetes);
5. Patients with urethral stricture;
6. Patients with hardening of the neck of the urinary bladder;
7. Patients with the complication of cancer of the prostate gland;

(B) Method and period of administration of the preparation: Cernilton was administered 3 times a day orally, 2 tablets at a time, for 3 months continuously. Concurrent drugs were given as little as possible: when complications made this inevitable only drugs were allowed which were judged to have no effect on prostatomegaly.

(C) Test items: Before and after the 3-months trial period and at suitable intervals during the trial subjective symptoms were ascertained and objective data investigated according to the following schedule:

a) Enquriy into subjective symptoms: The items investigated in the enquiry into subjective symptoms and the gist of questions were as follows

1. Frequency of micturition during day and at night;
2. Whether or not acute poor stream was present;
3. Prolonged micturition:
   (i) comes out smoothly
   (ii) takes some time
   (iii) takes a very long time
4. Delayed micturition:
   (i) very frequent, as when young
   (ii) sometime between each
   (iii) a long time between each
5. Staining during micturition:
   (i) micturition is usually possible without being particularly aware of it;
   (ii) sometimes it is not possible to micturate unless one consciously puts an effort into the abdomen;

	(iii) micturition is not possible unless one continually puts an effort into it during the act.
6. Decline in vigor of urine stream:	(i) the thickness and force of the stream are no different from when the patient was young; (ii) the stream is weak, or intermittent; (iii) it comes out only in drops and hardly at all.
7. Feeling of residual urine	(i) Nil (ii) Present slightly (iii) Present

b) Enquiry into objective symptoms: The items of the objective enquiry were as follows

1. Findings on rectal examination;
2. Measurement of residual urine;
3. Ultrasonic planigram method (using an Aloka ECHO VISION SSD-120, a planigram of the prostate was obtained via the rectum and used to measure the maximal antero-posterior diameter of the prostate (in cm), maximal transverse diameter (cm) and length (cm), also obtaining the presumed weight of the prostate (g));
4. Measurement of urine flow (using a DISA 2100 URO system, a curve was drawn of the urine flow per second, and the maximum flow rate, MFR ml/ sec, average flow rate (ml/ sec), micturition volume (ml), micturition time (sec) and residual urine volume (ml) were calculated) ;
5. Urethral pressure profile (UPP) (using a DISA 2100 URO system, a curve was drawn of the UPP and the maximum urethral pressure (cm H_20), maximum urethral closure pressure (MUCP cm H_20) and prostatic profile length (PPL cm) were obtained, also calculating the prostatic urethral resistance (PUR g/cm) integrated within the PPL range on the basis of the PPL curve and MUCP standard curve).

c) General tests: The following were also investigated in the general tests:-

1. Hematology: red cell count, white cell count, platelet count, hematocrit (Ht = %), haemoglobin (Hb = g/ dl), leukocyte differential (eosinophils, basophils, band cells, segmented neutrophils, lymphocytes, monocytes).
2. Serum chemical tests: GOT (U/L), GPT (U/L), alkaline phosphatase (U/L), acid phosphatase (K. A. units), BUN (mg/ dl), creatinine (mg/ dl), total protein (TP= g/ dl), cholesterol (mg/ dl), triglyceride (mg/ dl), Na (mEq/ l), K (mEq/1), Cl (mEq/l), P (mg/ dl), Ca (mg/dl).
3. Urological tests: protein, sugar ½ estimated amount and deposit.

d) Assessment of effectiveness: The assessment of the effectiveness of Cernilton in relation to subjective and objective symptoms accompanying Prostatomegaly was according to the following standards:

1) Assessment of effectiveness against subjective symptoms: after 3 months of treatment the patient was questioned regarding changes before and after the treatment in the six items mentioned in the gist of the enquiry, namely frequency of micturition (especially at night), prolonged micturition, delayed micturition, straining during micturition, decline in force of urine stream and feeling of residual urine, and an assessment was made on a scale of 3 grades: improvement, no change and deterioration. On the basis of these findings a total assessment was then made of:

(i) markedly effective, where there was no item which had deteriorated and 4 or more items had improved.
(ii) effective, where there was no item which had deteriorated and 1-3 items had improved.
(iii) no change, where there was no change in any item, and
(iv) ineffective, where even though there were improved items there was deterioration even in only one item.

2) Judgement of effectiveness against objective symptoms: when it was found in the objective findings that the difference between pre- and post-trial values for the 4 items of: residual urine, prostate weight ascertained by the ultrasonic planigram method, maximum flow rate (MFR) obtained by uroflowmetry, and urethral resistance obtained from the UPP, was 50% in the case of residual urine and more than 20% for the other items, this was assessed as improvement or deterioration, “no change” being cases where the figure was within these limits. The following total assessment was then made:-

(i) markedly effective, where there were 2 or more items on the improvement side;
(ii) effective, where there was 1 more item on the improvement side;
(iii) no change, where there was the same number of deterioration and improvement items, or where all items showed no change;
(iv) ineffective, where the deterioration items were more numerous.

3) Method of overall evaluation of therapeutic effectiveness: the therapeutic effectiveness of this preparation in prostatomegaly as regards subjective and objective symptoms was assessed by the following criteria:-

(i) markedly effective, where the findings both for subjective and objective symptoms were markedly effective or effective;
(ii) effective, where the findings were markedly effective or effective for subjective symptoms but no change for objective symptoms;
(iii) ineffective, where either subjective symptoms or objective symptoms or both were ineffective.

e) Statistical evaluation: The numerical values for the test items of the objective findings and general tests were summed for all patients for each item; the t value was ascertained by each of the differences between pre- and post-trial values, and a two-way test of significance at the 5% level was conducted using a table of t values.

Trial Findings

The age of subjects of the test ranged from 53 to 77, the average age being 67 (S. D. = 6 years). 6 cases had previously received drug treatment for prostatomegaly – either a vegetable extract or a Gestageno hormone preparation. No effectiveness was found with either of these preparations. Complications notified were 1 each of emphysema, cardiac insufficiency and hypertension; during the course of testing 2 cases of prostatic calculus, 1 of prostatitis and 1 of cystitis came to light.

The chief complaints of the 25 subjects were difficulty of micturition 18 (72%), frequency (20%) and residual urine sensation 2 (8%). 3 cases (12%) had experienced acute poor stream in the past. Enquires revealed that all cases had had some difficulty in micturition, whose details are shown in Table 1: beginning with the most frequent 96% had prolonged micturition, 92% had delayed micturition, 84% had nocturnal frequency, 68% had a decline in the force of the urine stream, 68% experienced strain during micturition and 32% had a feeling of residual urine.

The preparation was administered with relative precision: apart from 1 case where acute poor stream occurred, an operation was indicated and the preparation was terminated in month 2, all cases continued taking it for 3 months or more. No cases received any concurrent drugs.

A) Therapeutic effectiveness of Cernilton against subjective symptoms

Although there was some fluctuation in the effect against subjective symptoms during the course of administration of the preparation, the impression at the end of 3 months treatment could be classified fairly well into the 3 grades of: improvement, no change and deterioration. Table 2 lists cases of improvement for the various symptoms: starting from the high effectiveness rate end, the figure was 54% for prolonged micturition, 50% for nocturnal micturition, 50% for residual urine sensation, 47% for decline in force of urine stream, 41% for straining during micturition and 22% for delayed micturition. As an overall judgment of these findings, one could hardly say that the effectiveness of the preparation against subjective symptoms was outstanding, although the start of emission of urine did improve and there was a relative improvement in the force of flow. The feeling of residual urine, frequency and other symptoms of irritation of the bladder neck were alleviated. However, this does not mean that there was any marked shortening of the time required for micturition. It would appear that this was due to an increase in diurnal urinary volume due to a decrease in the frequency of micturition.

The overall assessment of the effectiveness of this preparation against subjective symptoms was: markedly effective, 2 cases (8%); effective, 14 cases (56%); no change, 5 cases (20%); and ineffective, 4 cases (16%). The efficiency rate was assessed as 64% (Table 6).

B) Therapeutic effectiveness of Cernilton against objective symptoms

Table 3 summarizes the pre-test and post-trial figures for various measurement values in the objective findings.

a) Residual urine volume: in 15 out of 25 cases (60%) residual urine was detected after the start of the trial in amounts of 10-90ml (33±25ml). At the end of the trial 1 case had a fresh occurrence of acute poor stream; apart from inserting an indwelling urethral catheter, there was no occurrence of residual urine and in 3 out 15 cases it disappeared, in 3 cases it lessened and in 2 cases it increased. The volume of residual urine in the 15 cases at the end of the trial ranged from 0 to 120 ml (28±26ml). The t value was 0.38, and there was no significant difference in the residual urine volume after the trial (Table 3).

b) Ultrasonic planigram method: The findings of measurement of the prostate gland by the ultrasonic planigram method showed that the antero-posterior diameter before the trial was 2.0-3.8 cm (2.6±0.5cm); this tended to increase slightly to 2.5-3.6 cm (3.0±0.4 cm) after the trial. The findings were similar for transverse diameter and length: the transverse diameter before the trial had been 3.2-4.5 cm (3.8±0.5cm), and this tended to increase slightly to 3.6-4.4 cm (4.0±0.4 cm) and length from 3.0-5.0 cm (3.9±0.6 cm) to 3.5-5.0 cm (4.2±0.6 cm). this also affected the weight: where this had been 11.7-44.9 g (23.7±10.4 g) before the trial, it had increased to 20.9-56.6 g (31.2±14.8 g) after it. However, these figures were not statistically significant.

c) Uroflowmetry: The urine flow curve, maximum flow rate (MFR), average flow rate, volume passed, time of urination, residual urine etc. were measured by this method, but since apart from MFR the measurement levels were greatly influenced by the urine volume in the bladder during measurement they were excluded from the investigation. The MFR was 3.6-15.7 ml/sec (8.7±4.3 ml/sec) before the test and tended to increase: figures for after the test were 7.6-15.1 ml/sec (11.8±3.5 ml/sec). The t value was -1.90 and the significance level was under 10%: although this

does not come within the standard 5% of the two-way test, in a one-way test as to whether the urine flow rate increases over the course of the trial, it would come within the 5% figure and would be significant. Consequently, although this difference is not clearly evident, the indications are that Cernilton tends to increase the flow of urine. This is also connected with the number of subjects, but would appear to be a problem related to the length or shortness of the trial period.

d) U.P.P.: The prostatic profile length (PPL) was 2.5-6.6 cm (4.2±1.3 cm) before the trial and tended to decrease slightly after the trial to 2.9-4.3 cm (3.4±3.5cm). The maximum urethral closure pressure (MUCP) was 35-120 cmH_20 (92±23 cmH20) before the trial and clearly decreased after the trial to 45-85 cmH20 (58±19 cmH_20). The t value here was 2.71, with significance at the 5% level. The prostatic urethral resistance (PUR) showed a wide distribution of 7-57 g/cm (28±14 g/cm) before the trial and a clearly lower value of 8-14 g/cm after it (12±3 g/cm). This corresponds to the decline in MUCP: t=2.17 ($P<0.05$), and here too this can be described as a significant decline.

e) Overall assessment of effectiveness against objective symptoms: the following is a summary of findings before and after the administration of Cernilton of organic measurements of the prostate by the ultrasonic planigram method and of functional measurements from residual urine, uroflowmetry and UPP.

The size of the prostate gland itself did not decrease during the trial period of 3 months but on the whole rather tended to increase, with the result that the character of the disease in question was not checked. However, since there were no controls to whom Cernilton was not administered, it is not impossible that the rate of growth of the organ in question slackened. However, the measurements of the functional effects of prostatomegaly on the mechanism of urination showed a general trend for the better. This took the form of a decline in the prostatic profile length (PPL) in the urethral plane and a decrease in urethral closure pressure, indicating a reduction in urethral resistance and an improved urine flow rate. From this it may be presumed that there was release from a state of constriction due to some factor from the bladder neck to the external sphincter of the bladder. It would appear most appropriate to regard this as an elimination of the oedema and inflammation of the area in question or else of the stasis of prostatic secretions, and the mode of action of Cernilton relates to this point.

Table 6 shows the overall assessment findings for the effectiveness of this preparation against objective symptoms. They were: markedly effective, 0 cases (0%); effective, 9 cases (36%); no change, 13 cases (42%); and ineffective, 3 cases (12%).

C) Effect of Cernilton on general test findings:

Tables 4 and 5 summarize the haematological and serum chemical test findings for before and after the Cernilton trial.

a) Hematological tests: There was only one case that showed a white cell count before the trial of 12,800 and both before and after the trial showed red cell, white cell and platelet counts, also Ht and Hb levels, more than 10% outside the normal range. The same patient had a complication of cystitis. In the white cell differential, band cells tended to be common and segmented neutrophils infrequent both before and after the trial: remembering that all the counts were done by the same technician, there may have been some problems in assessment. In any case, if a comparison is made of pre-trial results, band cells tend to decrease and lymphocytes to increase and the

statistical significance of this cannot be denied. As regards other constituents, no abnormal values or variations were observed either before or after the trial.

There appears to be a possibility that the increase in lymphocytes was connected with the immune action of the preparation, and the assessment was that this cannot be disregarded.

b) Serum chemical tests: Abnormal values for serum constituents were 2 cases of a slight rise in GOT and GPT (less than twice normal), 3 cases of a rise in BUN (23-25 mg/dl) and Cr (1.4-1.6 mg/ dl) and 5 cases of a rise in triglyceride (181-233 mg/dl), the number of patients involved being 8. In no other case was there more than 10% variance from normal in the test items. Furthermore, also including patients who showed abnormal values, no variations exceeding 10% were found in any patient or test item in the comparison of pre- and post-trial findings. However, acid p-ase and triglyceride showed a general tendency to decrease and Cl to increase.

The tendency for acid p-ase to decrease would seem to be significant in the consideration of the inhibitory effect of this preparation on the prostate gland. If this preparation is regarded as having the effect of reducing triglyceride, this is useful information, quite apart from this trial. The fact that a pre-trial level of 101 mEq/ l Cl became 109 mEq/l after the trial is a considerable change, suggesting that there is an effect in stabilizing the blood electrolyte levels.

c) Urological tests: No abnormal findings were made apart from an increase in white cells in the deposit before and after the trial in one case.

D) Overall assessment of therapeutic effectiveness of Cernilton against prostatomegaly

The therapeutic effectiveness of Cernilton against Prostatomegaly is shown in Table 6: a high rate of effectiveness of 64% was shown against subjective symptoms, but the improvement in objective findings was not outstanding at 36%. In the assessment of the two combined there were 8 cases of markedly effective (32%) and 8 of effective (32%), giving an effectiveness rate of 64%. There was almost complete agreement between the improvement in subjective and objective findings: the 9 cases where there was effectiveness against objective symptoms all showed an improvement in subjective symptoms – markedly effective or effective. In 2 cases there was deterioration in both subjective and objective findings, and in 3 cases there was deterioration in one or the other, with the other unchanged. Therefore in no instance did a case where there was effectiveness against subjective symptoms become unchanged or ineffective in the overall assessment.

General Discussion

Cernilton consists of “Cernilton pollen extract” extracted from a mixture in certain proportions of the pollen of 8 plant species grown in South Sweden. The allergens are dissolved and removed, and the constituents are water-soluble Cernitin T-60 (T-60) and oily Cernitin GBX (GBX). The component ratio of the former to the latter is 20 to 1 and 1 tablet of Cernilton contains 63 mg of the preparation.

The pharmacological effect of Cernilton, as reported by Ishikawa et al.[5] and Ozaki et al.[6], can be summarized as follows. In animal (rat) experiments no abnormal symptoms were exhibited even with 20 times the human dose: however with…*units there were difficulties in walking, and when the dose was repeated face-washing, coughing and tremor throughout the body. Both T-60 and GBX, after a temporary rise in blood pressure, led to a dose-dependent fall in blood pressure and respiratory stimulation, which was more marked with T-60. Against smooth muscle GBX brought about an acceleration of spontaneous movements and T-60 also caused twitching. There was an inhibitory effect from both preparations against croton oil oedema after 1 and 24 hr, against ovalbumin oedema from GBX after 24 hr and by the filter

paper pellet method from T-60. Large doses of Cernilton brought about impairment of liver function, increase in suprarenal gland weight, weight loss of prostate gland and thymus gland and interference with sperm production. Degenerative atrophy of the epithelium was noted in the prostate gland. T-60 had this effect but not GBX. Cernilton had the effect of increasing total cholesterol and blood sugar in the serum and reducing total protein. According to Kimura et al.[7)], the antigenicity or immunogenicity of both drugs is either extremely slight or nil.

In view of the above facts it can be stated that the characteristic pharmacological effect of Cernilton is a relatively marked anti-inflammatory action, with hardly any side effects worthy of note; moreover it works rather specifically against the prostate gland, combining this with an inhibitory effect. However, one can hardly say that there is any satisfactory evidence to support the finding that this preparation has a specific effect against prostatitis. Consequently our view before the present trial was that one should not expect any great therapeutic effectiveness against prostatomegaly. Nevertheless, the clinical findings obtained in this trial provided ample evidence for the usefulness of the preparation against prostatomegaly.

Organic measurements of the prostate gland by the ultrasonic planigram method showed that the administration of Cernilton could not completely reduce its size (Fig. 1), but the functional measurements of the effect of the prostate gland on the urination mechanism showed that Cernilton reduced the length of the urethra occupied by the prostate gland and also reduced the urethral closure pressure and markedly reduced the urethral resistance as a whole (Fig. 2). This indicates an organic change in the interior of the posterior urethra from the bladder neck to the external sphincter. Although no detailed proof could be obtained, this probably involved an elimination of the inflammatory oedema in this area and of accumulated secretions in the prostatic duct. Apparently because of this, the urine flow rate increased and the subjective symptoms of irritation of the bladder neck decreased markedly. Thus the findings of this trial provided objective data to support the traditional view that the preparation improves subjective symptoms.

It cannot be concluded from the above results that prostatomegaly is radically reduced and eliminated with a resultant cure by administering the preparation, but it can be said that it is a quite useful symptomatic treatment for this disease. Although the majority of cases of prostatomegaly do not cause serious disease, they do involve quite distressful subjective symptoms for the patient, and treatment would be adequate which would lead to their eradication for a certain time. In this sense a lack of side effects is the most important property, and a condition is that there should of course be no inhibition of liver, kidney and heart functions, nor of testicular function. During this trial none of the 25 patients complained of subjective side effects, nor were there any signs thereof in the various tests. The normalization of the left shift in the white cell differential and of a high serum triglyceride level would tend to be rather in the patient's favour.

It has been shown above that Cernilton has no side effects and was effective against 64% of cases of prostatomegaly. Although its mode of action could be conjectured along general lines, would it not be possible to make an estimate of its usefulness before treatment in each individual case? It was therefore decided to ascertain the correlation coefficient between the various objective measurements and the degree of improvement of subjective symptoms with a scale of: markedly effective = 4, effective = 3, no change = 2, and ineffective = 1, and the figures obtained were residual urine 0.34, prostate gland weight – 0.42, MFR – 0.02 and urethral resistance – 0.21. i.e. the preparation was found to be effective whatever the objective findings, meaning that the therapeutic effectiveness of the preparation could not be predicted on the basis of tests such as these. Thus it would appear to be indicated to administer the preparation to all patients: either over a long period with the aim of improving the subjective symptoms of patients where an immediate operation is not indicated or for a certain time just before an operation with the aim of improving urinary function.

The effectiveness rate of this preparation against prostatomegaly, 64%, if compared with the 91% reported by Akasaka[4], and the 10 out of 12 cases reported by Ineda (83%)[5], is much lower but is the same as the 63% of Kimura et al.[8] (5 out of 8 cases) and the 69% of Taguchi et al.[9]. This is also because of the different standards used in judging effectiveness by these authors, and no sweeping statement can be made. In any case the finding that this preparation is effective against subjective symptoms accompanying prostatomegaly is common to all these authors.

Summary and Concluding Remarks

When 6 tablets per day of Cernilton were administered to 25 cases of prostatomegaly the following findings were made:

1. The improvement of subjective symptoms was most striking for prolonged micturition difficulty (54%), followed by nocturnal frequency (50%) and then residual urine sensation (50%), decline in force of urine stream (47%), straining during urination (41%), delayed micturition (22%).
2. The effectiveness for subjective symptoms as a whole was: markedly effective 8%, effective 56%, no change 20% and deterioration 16%, with an effectiveness rate of 64%.
3. As regards residual urine, there were many cases where this decreased but also some where it increased: on average pre-treatment 32.5±25.0 ml became post-treatment 27.9±25.6, with no significance in the change.
4. In the measurements of the prostate gland by the ultrasonic planigram method there was a slight tendency for antero-posterior diameter, transverse diameter and length to increase, while the weight increased from a pre-treatment 23.7±10.4 g to a post-treatment 31.2±14.8 g, so that it can be concluded that this preparation does not cause the prostate gland to shrink.
5. Where the maximum urine flow rate before treatment by the uroflowmetry method had been 8.7±4.3 ml/sec, this became 11.8±3.5 ml/sec after treatment, so that it was clearly established that this preparation improves urine flow.
6. In the measurements by the urethral pressure profile method the length of the prostatic urethra decreased as a result of administering this preparation. The maximum urethral closure pressure also decreased, and there was a significant drop in the urethral resistance from a pre-treatment 28±14 g/cm to a post-treatment 12±3 g/cm.
7. The effectiveness of this preparation against objective symptoms was assessed as: markedly effective 0 cases (0%), effective 9 cases (36%), no change 13 cases (42%) and ineffective 3 cases (12%).
8. On the basis of haematological and serum chemical tests, no changes could be detected indicating any harm inflicted by this preparation on the human body.
9. No subjective or objective side effects at all were noted.

On the basis of the above findings it can be assumed that Cernilton removes the oedema of the urethral mucosal surface from the bladder neck to the external sphincter which accompanies prostatomegaly, and so improves urination and alleviates the irritation experienced subjectively in the bladder neck. In view of the complete absence of observed side effects, it is concluded that this preparation is indicated for all cases of prostatomegaly and that its effectiveness can be relied on.

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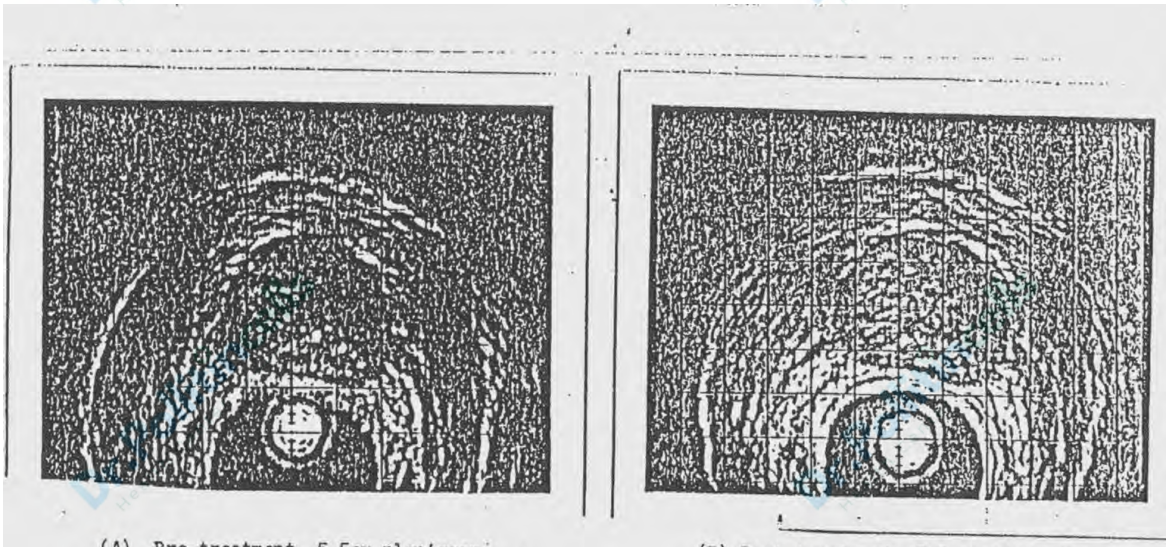

(A) Pre-treatment 5.5cm planigram

Antero-posterior diameter	3.2 cm
Transverse diameter	4.2 cm
Length	4.0 cm
Weight	33.3 g

(B) Post-treatment 5.5 cm planigram

Antero-posterior diameter	3.2 cm
Transverse diameter	4.3 cm
length	4.0 cm
Weight	31.4 g

Fig. 1. Changes in prostate gland planigrams of prostatomegaly patients after receiving Cernilton

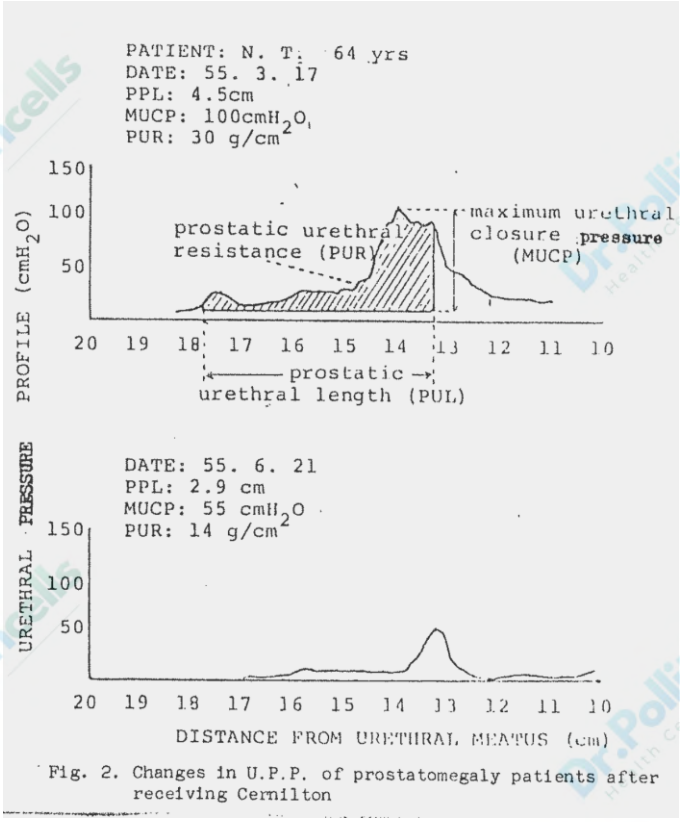

Fig. 2. Changes in U.P.P. of prostatomegaly patients after receiving Cernilton

Table 1. Subjective symptoms in 25 prostatomegaly cases

Type and degree of subjective symptoms		Number of cases (%)
Nocturnal frequency	more than 4 times	5 cases
	2 - 3 times	16 (84%)
	0 - 1 time	4
Prolonged micturition	++ (3)	2
	+ (2)	22 (96%)
	- (1)	1
Delayed micturition	+ (2)	23 (92%)
	- (1)	2
Straining in micturition	++ (3)	1
	+ (2)	16 (68%)
	- (1)	8
Decline in force of urine stream	++ (3)	2
	+ (2)	15 (68%)
	- (1)	8
Residual urine sensation	++ (3)	1
	+ (2)	7 (32%)
	- (1)	15

Table 2. Effectiveness of Cernilton against subjective symptoms of prostatomegaly

Subjective symptoms	Number of cases	Number of cases who improved	Effectiveness rate
Nocturnal frequency	20	10	50%
Prolonged micturition	24	13	54
Delayed micturition	23	5	22
Straining in micturition	17	7	41
Decline in force of urine stream	17	8	47
Residual urine sensation	8	4	50

Table 3. Effectiveness of Cernilton against objective symptoms of prostatomegaly

Type of objective symptoms		Pre-treatment	Post-treatment	t value (result of 2-way test)
Residual urine volume (ml)		32.5 ± 25.0	27.9 ± 25.6	0.38
Ultrasonic planigram method :	antero-posterior diameter (cm)	2.6 ± 0.5	3.0 ± 0.4	- 1.32
	transverse diameter (cm)	3.8 ± 0.5	4.0 ± 0.4	- 0.74
	length (cm)	3.9 ± 0.6	4.2 ± 0.6	- 0.10
	weight (g)	23.7 ± 10.4	31.2 ± 14.8	- 1.25
Uroflowmetry :	MFR (ml/sec)	8.7 ± 4.3	11.8 ± 3.5	- 1.90 ($p<0.10$)
U.P.P. :	PPL (cm)	4.2 ± 1.3	3.4 ± 0.6	1.27
	MUCP (cmH_2O)	92.0 ± 23.0	58.0 ± 19.0	2.71 ($p<0.05$)
	PUR (g/cm)	28.0 ± 14.0	12.0 ± 3.0	2.17 ($p<0.05$)

Table 4. Change in haematological valves after administering Cernilton

Test item		Pre-treatment value	Post-treatment value	t value (result of 2-way test)
Red cell count X 10^4		460.9 ± 38.4	449.4 ± 44.9	0.61
White cell count		6900.0 ± 2500.0	6600.0 ± 1300.0	0.27
Platelet count X 10^4		25.7 ± 6.8	27.7 ± 3.6	- 0.67
Ht (%)		42.1 ± 2.5	41.0 ± 3.8	0.81
Hb (g/dl)		14.5 ± 0.9	13.9 ± 1.3	1.37
White cell differential	eosinophils	2.0 ± 1.4	3.0 ± 3.3	- 0.80
	basophils	0.89 ± 0.78	0.60 ± 0.89	0.63
	band cells	30.3 ± 6.9	18.4 ± 6.2	3.20 (p<0.05)
	segmented cells	34.9 ± 11.9	30.4 ± 10.3	0.68
	lymphocytes	29.7 ± 10.2	42.2 ± 11.3	- 2.12 (p<0.10)
	monocytes	5.6 ± 2.4	5.4 ± 2.6	0.11

Table 5. Changes in seven chemical tests after administration of Cernilton

Test		Pre-treatment level	Post-treatment level	t value (result of 2-way test)
GOT	(U/l)	22.0 ± 8.0	26.0 ± 14.0	- 0.86
GPT	(U/l)	23.0 ± 14.0	30.0 ± 30.0	- 0.77
Alkaline p-ase	(U/l)	82.0 ± 22.0	85.0 ± 21.0	- 0.31
Acid p-ase	(K.A.U.)	2.9 ± 0.5	2.6 ± 0.4	1.41
BUN	(mg/dl)	16.0 ± 4.0	15.0 ± 5.0	0.30
Cr	(mg/dl)	1.1 ± 0.2	1.1 ± 0.1	- 0.20
TP	(g/dl)	7.1 ± 0.4	0.9 ± 0.4	1.29
Cholesterol	(mg/dl)	189.0 ± 44.0	199.0 ± 51.0	- 0.49
Triglyceride	(mg/dl)	135.0 ± 55.0	122.0 ± 52.0	0.52
Na	(mEq/l)	141.0 ± 2.0	141.0 ± 2.0	- 0.29
K	(mEq/l)	4.1 ± 0.3	4.0 ± 0.5	0.30
Cl	(mEq/l)	104.0 ± 2.0	106.0 ± 3.0	- 2.32 (p<0.10)
P	(mg/dl)	2.7 ± 0.5	2.6 ± 0.2	0.45
Ca	(mg/dl)	9.1 ± 0.5	8.9 ± 0.4	0.99

Table 6. Therapeutic effectiveness of Cernilton against prostatomegaly

Degree of therapeutic effectiveness	Subjective symptoms	Objective symptoms	Total assessment
markedly effective	2 cases (8%)	0 cases (0%)	8 cases (32%)
effective	14 (56%)	9 (36%)	8 (32%)
no change	5 (20%)	13 (52%)	4 (16%)
ineffective	4 (16%)	3 (12%)	5 (20%)
total	25 (100%)	25 (100%)	25 (100%)

Randomized Trial of a Combination of Natural Products (Cernitin, Saw Palmetto, B-Sitosterol, Vitamin E) on Symptoms of Benign Prostatic Hyperplasia (BPH)

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Abstract

Because benign prostatic hyperplasia (BPH) is relatively common, it is important to discover safe and effective means to treat this often debilitating perturbation. Accordingly, we examined the effectiveness of a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) in treating symptoms of BPH. We undertook a randomized, placebo-controlled, double-blind study. Patients were enrolled from 3 urological practices in the USA. 144 subjects were randomized for study. 17 subjects eventually withdrew, leaving 70 patients in the test group and 57 in the placebo group to complete the study. Inclusion criteria consisted of a diagnosis of BPH, no evidence of cancer, and a maximal urinary flow rate between 5 and 15 ml/second. Patients received either placebo or the combined natural products for 3 months. Evaluations were performed via the American Urological Association (AUA) Symptom Index score, urinary flow rate, PSA measurement, and residual bladder volume. Nocturia showed a markedly significant decrease in severity in patients receiving the combined natural products compared to those taking placebo ($p<0.001$). Daytime frequency was also lessened significantly ($p<0.04$). When the average individual total AUA Symptom Index score in the test group was compared to that in the placebo group at the end of the study, the difference proved highly significant ($P<0.014$). PSA measurements, maximal and average urinary flow rates, and residual volumes showed no statistically significant differences. When taken for 3 monts, a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) compared to placebo can significantly lessen noturia and frequency, and diminish overall symptomatology of BPH as indicated by an improvement in the total AUA Symptom Index score. The combination of natural products caused no significant adverse side effects.

Key Words: Benign Prostatic Hyperplasia, Natural means to treat; Nocturia, Natural means to teat; Frequency, Natural means to treat; Cernitin; Saw Palmetto; B-Sitosterol

Introduction

Despite availability of numerous positive reports, it is not generally recognized in the USA that certain natural products can overcome many troublesome symptoms emanating from benign prostatic hyperplasia (BPH) [1]. Three natural products possessing such potential are: a collection of pollens called cernitin [2-11], saw palmetto (*Serenoa repens*) [12-18], and B-sitosterol [19,20]. Some antioxidants, such as vitamin E, are also believed to be helpful in the treatment [1].

Virtually all studies on the effects of natural agents have been performed in Europe and Asia. This may be the principal reason behind the poor recognition in the USA of the therapeutic benefits of natural products in alleviating symptoms of BPH. Therefore, we undertook a multicenter, randomized, placebo-controlled, double-blind study in the USA to determine how a combination of these products might influence common perturbations of BPH. Our major objectives were to assess both subjective criteria (American Urological Association Symptom Index) and objective criteria (average and maximal urinary flow rates, post void residual urinary volume in the bladder, and PSA score) comparing natural products to placebo over 90 days. To accomplish this, we examined a combination of cernitin, saw palmetto, B-sitosterol, and vitamin E. The first 3 components have been found singly in clinical studies to possess the potential to benefit the often debilitating symptoms caused by BPH [1].

Materials and Methods

Plan

As depicted in Fig. 1, 144 subjects were enrolled at the 3 sites (Washington, DC; Florida; and Idaho) in this multicenter clinical trial. Patients for study were solicited through advertisements in local newspapers and from patient data bases in the investigators' urology practices. 17 subjects eventually withdrew, leaving 70 patients in the test group and 57 in placebo group to complete the study. After signing informed consent in the presence of the principal investigator or his designee at the site, patients received a numbered bottle of pills from the study coordinator at each site. Care was taken so that the pill forms of placebo and test could not be identified by sight, smell or taste. Only the clinical monitor at a separate site from where the studies took place possessed the code, so that neither the doctors nor patients were aware of what was being given or taken.

Inclusion criteria consisted of the following. A diagnosis of BPH was necessary. There was to be no evidence of cancer by digital rectal and/or PSA examinations. The maximal urinary flow rates were to be between 5 to 15 ml /second for a voided volume in excess of 100 ml. The patient had to read, speak, and clearly understand English, and written informed consent to participate in the trial had to be obtained. These studies were approved by separate Institutional Review Boards (IRB) for each of the 3 locations.

Exclusion criteria consisted of an age greater than 80 years; the presence of any tumor, malformation, or infection of the genitourinary tract; any severe concomitant medical condition that would make it undesirable in the clinician's opinion for the subject to participate in the trial or would jeopardize compliance with the trial protocol; severe laboratory abnormalities at baseline according to the WHO recommendations for grading of acute and subacute toxicity (Grade 2-4); medical treatment for BPH with finasteride (Proscar) within the last 3 months and all other medical treatment for BPH within the last 4 weeks; and patients currently being treated with antibiotics for genitourinary tract infections.

Study Design

The study design included a 3-month participant commitment to adhere to the following schedule. The patients were to take 2 pills of the combined natural products or placebo each day over 90 days. The test group received a total daily dose of cernitin 378 mg, saw palmetto complex and phytosterols (saw palmetto fruit standardized to 40% to 50% free fatty acids and B-sitosterol standardized to 43%) 286 mg, and vitamin E 100 IU. They were to make 3 clinic visits.

- Visit 1 (Baseline)
- Visit 2 (Day 45)
- Visit 3 (Day 90)

Procedures

The following procedures were performed on each study participant:

1. Physical Examination (Visits 1 and 3)
2. Laboratory Evaluation (Visits 1-3)
3. American Urological Association (AUA) Symptom Score (Visits 1-3)
4. Urinary flow evaluation (Visits 1-3)
5. Post void residual bladder volume (Visits 1-3)

Analytical Approaches

The target sample size was projected by evaluating previous clinical trials using cernitin for the treatment of BPH which were conducted outside the United States [3,4,6,8,911]. Cernitin clinical trials with similar outcome measures, demonstrating statistically significant findings averaged n=55.5. Since one half of the studies were open label, conservative action dictated at least doubling the "n" to ensure adequate statistical power. The randomization unit was a cluster method. A stratification with minimization procedure by site was used to increase the likelihood of a balanced distribution. Data were analyzed by FutureTech, Inc. of Boise, Idaho. The analyses examined the changes in individuals of all study variables over the course of the study comparing the test group receiving cernitin, saw palmetto, B-sitosterol, and vitamin E to the placebo group. Two statistical analyses were conducted on each question or parameter. The first analysis used a general linear model

PROFILE OF A RANDOMIZED CONTROLLED TRIAL

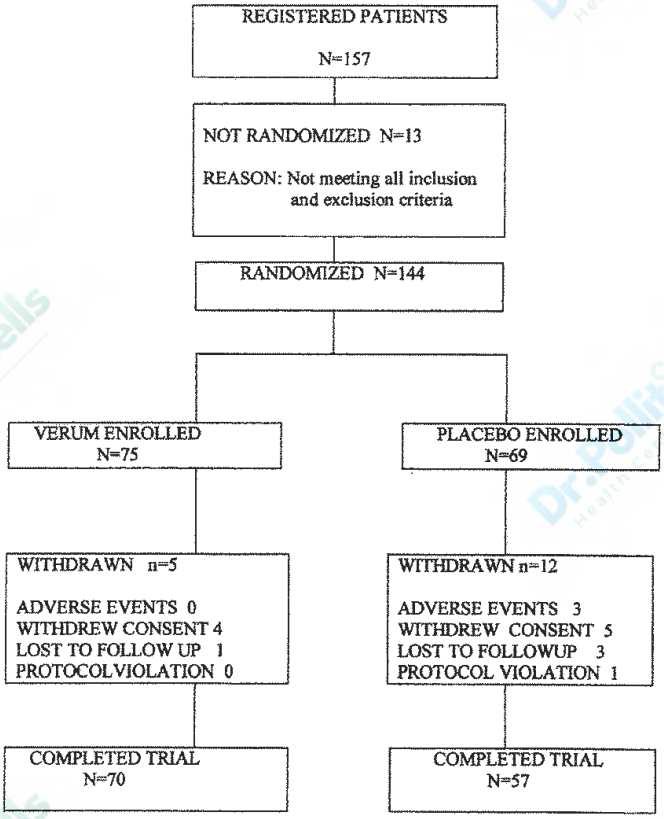

Figure 1. Progress through the various stages of the trial, including flow of participants and withdrawals.

mixed measures analysis of variance (Mixed ANOVA). This analysis takes into account the relative amount of change between groups over time. Of particular interest is the group by time interaction. This is indicative of a difference between the test (active) group and the placebo group from baseline to 45 day to 90 day assessments. Such an analysis will reveal significant differences between baseline and 90 day assessments as well as 45 day to 90 day assessments. The second analysis used the independent t-test on change scores (i.e., day 90 score – baseline score). The absolute amount of change was analyzed. For both analyses, statistical significance was set at $p<0.05$.

Results

As shown in Fig. 1, 144 patients of the 157 registered were eventually randomized – 75 to the test group and 69 to the placebo group. Five of 75 (6.7%) test patients did not complete the study, whereas 12 of 69 (17.4%) failed to complete the study in the placebo group. The information on the randomized patients who remained and withdrew before completing the study are depicted in Fig. 1. All the adverse events severe enough to cause termination, i.e., 3, occurred in the placebo group. One patient in the placebo group was removed from the study for protocol violation. Five patients in the test group either withdrew consent or were lost to follow-up compared to 8 patients in the placebo group. Concerning all adverse events listed in Table 1, 7 (10%) occurred in the test group and 9 (16%) in the placebo group. Interestingly, flatulence was reported by 3 in the test group, but the only 2 patients complaining of gastrointestinal distress were in the placebo group.

The questions asked in the American Urological Association (AUA) Symptom Index are listed in Table 2, and the scoring system for the first 6 questions is described just below them. Note that question 7 is slightly different from the first 6 questions in that the number of trips to the bathroom during the night is being sought. Table 3 depicts the mean AUA scores and the statistics performed by Mixed ANOVA at the 3 time points. Results from Question #7 concerning nocturia showed that there was a markedly significant decrease in severity in patients receiving the test substances compared to those taking placebo ($p<0.001$). Daytime frequency (question 2) was also lessened significantly in the test group compared to placebo ($p<0.04$). When the average individual total AUA Symptom Index score in the test group was compared to that in the placebo group, the difference proved highly significant ($P<0.014$). Table 4 shows the average changes in the AUA Symptom Index parameters between the test and placebo groups over the 90 days of study. Again, nocturia ($P<0.001$), frequency ($p<0.031$) and total AUA score ($P<0.009$) improved significantly in test compared to placebo groups.

Table 5 provides the data for the objective measurements. The PSA scores, maximal and average urinary flow rates, and residual volumes showed no statistically significant differences when comparing the test and placebo groups.

Discussion

Benign prostatic hyperplasia (BPH) presents a difficult, widespread problem [1,21]. Common symptoms of obstructive BPH are often disabling and include a weak urinary stream, a sense of incomplete bladder emptying, difficulty initiating urination, frequency, nocturia, urgency, and poorly controlled stopping and starting of the urinary stream (Table 2). Previously, treatment options for prostate enlargement focused primarily on surgery. However many adverse symptoms attributed to the operative procedure may persist after surgery -- post urination dripping, severe incontinence, and even a decline in sexual function. Because of the potential for these significant side effects, prescription drugs are often chosen by many as initial therapy against BPH, especially when the symptoms are mild or moderate.

Table 1. Adverse events

Event	Verum	Placebo
Flatulence	3	0
Lower abdominal rash	0	1
Dizziness	0	1
Headache	1	1
Nausea/GI distress	0	2
Urinary tract infection	1	0
Ear infection	0	1
Lumbar spine surgery (spur)	0	1
Herpes zoster	1	0
Elevated blood pressure	0	1
Chest pain	0	1
Right arm laceration	1	0

Table 2. American urological association symptom index

Question 1. Emptying. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Question 2. Frequency. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?

Question 3. Hesitancy. Over the past month or so, how often have you found that you stopped and started again several times when you urinated?

Question 4. Urgency. Over the past month or so, how often have you found it difficult to postpone urination?

Question 5. Weak Stream. Over the past month or so, how often have you had a weak urinary stream?

Question 6. Straining. Over the past month or so. how often have you had to push or strain to begin urination?

For questions 1–6, score:

0 for not at all
1 for less than 1 time in 5
2 for less than half the time
3 for about half the time
4 for more than half the time
5 for almost always

Question 7. Nocturia. Over the last month or so, how may times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning? (0, 1, 2, 3, 4, or 5)

Sum of scores from 7 questions indicate severity of BPH:

0–7 = mild prostatism
8–18 = moderate prostatism
19–35 = severe prostatism

Finasteride prevents production of dihydrotestosterone (DHT) from testosterone by inhibiting the activity of the conversion enzyme, 5-alpha reductase. This is important, because DHT is associated with BPH [22]. However, the beneficial effects of finasteride lasts only as long as the drug is being taken and must be given for many months before finasteride can be assessed as to effectiveness. Further, a decreased libido is an unwanted side effect in some men [23]. Another class of drugs has also been used to treat BPH. Alpha blockers are employed to relax the muscle tissue of the prostate in order to relieve the pressure around the urethra [24]. By relaxing the smooth muscles in the prostate, these agents essentially open the bladder and urethra and allow easier flow. However, adverse reactions can be serious and include chest pain, light-headedness, weakness, fast and/or irregular heartbeat, shortness of breath, nasal congestion, swelling of the extremities, and impotence [25].

Recently, many have turned to the use of natural products to overcome or at least ameliorate symptoms of BPH. The public often prefers natural compounds, because of a perception that they have fewer serious side effects compared to drugs. Among the natural agents most widely used outside the USA are a defined pollen mixture called cernitin (rye, timothy, corn), saw palmetto, and B-sitosterol. Various agents used to lessen free radical formation such as vitamin E have been reported to be useful additions as well. In the present investigation, we examined an over-the-counter product with the trade name Cernitin AF™ containing the aforementioned agents.

We carried out a multicenter, randomized, double-blind, placebo-controlled study on 70 patients in the test group and 57 patients in the placebo group to determine how patients with BPH would respond to the combination of natural products. A markedly significant beneficial response was noted by the lessening of nocturia, frequency, and overall AUA Symptom Index scores, even when assessed by different statistical methodologies (Tables 3 and 4). Although there was a general improvement of symptomatology associated with taking placebo, the improvements from the combined natural products compared to placebo in some parameters were dramatic: nocturia 258%, $p < 0.001$; frequency 242%, $p = 0.040$; and overall AUA Symptom Index score 90%, $p = 0.009$.

Table 3. Mean scores from the American urological association symptom index

Q#	Parameter	Baseline	Day 45	Day 90	p
Q1	Emptying	2.37/2.30	1.91/1.98	1.58/1.62	ns
Q2	Frequency	3.34/2.82	2.54/2.29	2.48/2.57	0.040[1]
Q3	Hesitancy	2.72/2.42	1.98/2.21	1.72/1.86	ns
Q4	Urgency	2.57/2.46	2.05/2.10	1.94/2.23	ns
Q5	Weak stream	3.62/3.35	3.01/2.66	2.48/2.57	ns
Q6	Straining	1.70/1.83	1.12/1.57	1.00/1.20	ns
Q7	Nocturia	2.58/2.47	1.95/2.07	1.61/2.19	<0.001[1]
Q1–7	Total AUA score	18.9/17.7	14.6/15.0	12.7/14.5	0.014[1]

Means (70 verum and 57 placebos) for baseline, 45 days and 90 days are shown. First number in the group represents mean of verum group at the time indicated. the second is mean of placebo group at the time indicated. Statistics by Mixed ANOVA.
[1] = statistically significant examining Time × Group Interaction.

Table 4. Change in AUA symptom index over 90 days (70 patients on verum and 57 on placebo)

AUA Questions	Verum	Placebo	% Improvement[1]	p
Emptying				
Question 1	–0.783 ± 0.171	–0.702 ± 0.182	+12%	0.748
Frequency				
Question 2	–0.855 ± 0.185	–0.250 ± 0.207	+242%	0.031[2]
Hesitancy				
Question 3	–0.971 ± 0.194	–0.589 ± 0.205	+65%	0.181
Urgency				
Question 4	–0.594 ± 0.164	–0.232 ± 0.260	+156%	0.225
Weak stream				
Question 5	–1.174 ± 0.186	–0.804 ± 0.208	+46%	0.186
Straining				
Question 6	–0.696 ± 0.169	–0.643 ± 0.195	+8%	0.838
Nocturia				
Question 7	–0.971 ± 0.119	–0.271 ± 0.118	+258%	<0.001[2]
Total AUA score				
Question 1–7	–6.171 ± 0.766	–3.241 ± 0.774	+90%	0.009[2]

Mean ± SEM is shown for 70 patients in the verum group and 57 patients in the placebo group.
– = improvement in symptoms, + = worsening of symptoms (Based on scale 0–5, being worst)
[1]Indicates % improvement in verum score over placebo
[2]Statistically significant by unpaired t test.

Table 5. Objective criteria for cernitin AF study after 90 days

	Verum		Placebo	
	Baseline	After 90 days	Baseline	After 90 days
Bladder volume (ml)	58.9 ± 11.4	57.5 ± 12.8	59.6 ± 12.8	40.7 ± 10.4
PSA (units)	2.6 ± 0.3	2.6 ± 0.4	1.9 ± 0.3	2.6 ± 0.7
AFR (ml/min)	6.0 ± 0.4	6.0 ± 0.5	6.1 ± 0.5	6.8 ± 0.5
MFR (ml/min)	11.2 ± 0.8	11.8 ± 0.7	12.1 ± 0.9	13.1 ± 1.0

Means ± SEM are shown for 70 patients in the verum group and 57 patients in the placebo group.
AFR = average flow rate, MFR = maximal flow rate.

To derive an even greater understanding of the significance of the effect on nocturia, we focused on patients with the greatest distress, i.e., those who at the beginning of the study micturated 3 or more times during the night. Of the 33 patients taking the combined natural products, 29 of 33 (88%) showed improvement in the AUA Symptom Index compared to 14 of 24 patients

(58%) receiving placebo (p=0.004). The decrease of -1.145 + 0.103 (SEM) in the test group means that the patients micturating 3-4 times a night, on an average, were now more apt to void only twice a night. We did a similar analysis on frequency. In those patients having frequency (as defined by Question 2 in table 2) 3 times or greater during the day, 32 of 47 (68%) test patients showed some improvement, whereas only 15 of 34 (44%) placebo patients reported improvement (p=0.013). The decreased frequency of -1.362 + 0.203 (SEM) in the test group meant that the average frequency of 4 decreased below 3. Residual urinary volume in the bladder, average and maximal flow rates, and PSA were not significantly different between test and placebo groups at the end of the 3 month treatment period. No significant adverse side effects were discerned in those taking the combined natural products.

Of the natural compounds involved in this study, perhaps the least is know about defined pollen extract referred to as cernitin. We are unaware of any other major study carried out in the USA on this agent. Therefore, we will discuss cernitin in more detail than the other natural products. In 1967, Ohkoshi, Kawamura and Nagakubo of Keio University reported that cernitin was effective in the treatment of 30 patients with chronic nonbacterial prostatitis and prostadynia [7]. Takeuchi investigated both subjective and objective effects of cernitin on 25 men with BPH and reported favorable results, especially for nocturia, in 64 per cent [8]. In 1986, a field study of 2,289 patients being treated by 170 urologists was undertaken [2]. Cernitin improved symptoms in 64 to 82 percent, in contrast to a low rate of adverse reactions found in 2.9 per cent of cases. In a double-blind, placebo-controlled study performed in 1988 in collaboration with 6 practicing urologist, Becker and Ebeling [3] examined 48 patients taking cernitin and compared them with an equal number of patients receiving placebo over a 12 week interval. Nocturia was claimed by 97% of the patients as a symptom of their disorder. There was a significant improvement using cernitin compared to placebo in nocturia, i.e., 69% vs. 37% (p<0.005). Not only the sensation of residual urine but the actual volume of residual urine was significantly reduced by the flower pollen extract. Mild nausea was reported in one patient.

Cernitin has a number of physiological effects that could benefit BPH. It has an anticongestive-antiinflammatory action which could lessen external pressure on the urethra [1]. These effects may be due to inhibition of prostaglandin and leukotriene biosynthesis. It has been noted that the activities of 5-lipoxygenase and cyclo-oxygenase enzymes are markedly reduced and the arachidonic cascade is interrupted by cernitin [25]. Additional pharmacological effects reported for the pollen preparation are: inhibition of prostate cell growth in animals, influence on contractility of bladder and urethral smooth muscle as well as diaphragms of animals, and an influence on the metabolism of dihydrotestosterone [26].

Saw palmetto (*Serenoa repens*) is an extract of the pulp and seeds of a dwarf, scrubby palm tree native to the West Indies and the Atlantic coast of the United States. It is generally accepted that saw palmetto works, at least in part, by the same major mechanism as finasteride, i.e., preventing the conversion of testosterone to DHT [12]. However, saw palmetto not only lowers the rate of DHT formation, but blocks the ability of DHT to bind to cells, preventing the action of hormone on receptors [13]. In addition, *Serenoa repens* may prevent severe inflammatory responses via a dose-related effect on the arachidonic acid cascade through a double blocking of cyclo-oxygenase and lipoxygenase pathways [27]. In one study examining 110 subjects, it decreased night time urination by 45 percent, increased urinary flow rate more than 50 percent, and reduced the amount of urine left in the bladder after urination by 42 per cent [18]. In other large trials, improvement in prostatic symptomatology was readily noted and saw palmetto even compared favorable with Hytrin (alpha blocker)

and/or Proscar (finasteride) in affecting the symptomatology of BPH when these agents were compared head to head. [14-18].

B-sitosterol is a phytopharmacological agent containing many phytosterols [19,20]. In a randomized double blind study reported in the Lancet [20], 200 patients with symptoms of BPH from 8 private urological practices were treated for 6 months with either 20 mg of B-sitosterol or placebo. At the end of 6 months, modified Boyarsky scores decreased statistically in the B-sitosterol-treated group compared to the placebo group. Reduction took place in the prostatic volume, the quality of life score improved, the peak urine flow increased, the mean voiding time and the urinary volume retention also improved from the initial scores in the sterol group, whereas no changes were noted in the placebo group. Importantly, no severe adverse reactions were attributed to B-sitosterol.

In light of the subjective findings, it is not clear why changes in objective criteria were not seen in the present study. However, this is not unusual. Examination of other BPH clinical studies reveals a lack of consistent findings among both subjective and objective parameters even in those investigations deemed positive through overall assessment [1-21]. PSA is not known to change in response to saw palmetto intake [12-18] and has been shown only once to decrease in the case of cernitin usage [9]. Buck et al [6] found no change in urinary flow rates in response to cernitin, but Braeckman found significant change in his investigation of saw palmetto [17]. Both the former citations reported significant changes in residual urine volume. Considering everything, we believe that our subjective changes are real and indicate a definite benefit from the use of this combination of natural products despite the lack of objective support.

Conclusion

We cannot state with certainty whether we could have accomplished the same results in our study by using only one or 2 of the ingredients present in the combination of natural products. Cernitin [1-11], saw palmetto [12-18], and B-sitosterol [19,20] have been shown to be effective, at least to some extent, when used individually. Because each agent has slightly different actions and different time frames of action, it seemed wise initially to examine a combination to determine clinical utility. Accordingly, we know from our results that a combination of cernitin, saw palmetto, B-sitosterol and vitamin E provided significant relief from some of the most irritating symptoms resulting from BPH. Further studies directly comparing combinations with individual components must be carried out in the future. In summary, this combination of natural products when taken over 3 months significantly lessened nocturia and frequency, diminished overall symptomatology of BPH as indicated by the improvement in the total AUA symptom index scores while causing no significant adverse side effects.

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Clinical evaluation of cernilton in the treatment of the benign prostatic hypertrophy

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Cernilton was given clinically to 30 patients with benign prostatic hypertrophy. Cernilton was given orally at least for 12 weeks at a daily dose of 6 tablets in three divided doses. The overall clinical efficacy on subjective symptoms was 80%, and that on objective signs, 43%. During the administration period of Cernilton, no serious untoward effects were observed in either the clinical or laboratory findings. It is, therefore, suggested that, from the clinical point of view, Cernilton is a useful and safe drug in the treatment of benign prostatic hypertrophy.

PMID: 2412423, UI: 85303710

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Randomized Trial of a Combination of Natural Products (Cernitin, Saw Palmetto, B-Sitosterol, Vitamin E) on Symptoms of Benign Prostatic Hyperplasia (BPH)

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Abstract

Because benign prostatic hyperplasia (BPH) is relatively common, it is important to discover safe and effective means to treat this often debilitating perturbation. Accordingly, we examined the effectiveness of a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) in treating symptoms of BPH. We undertook a randomized, placebo-controlled, double-blind study. Patients were enrolled from 3 urological practices in the USA. 144 subjects were randomized for study. 17 subjects eventually withdrew, leaving 70 patients in the test group and 57 in the placebo group to complete the study. Inclusion criteria consisted of a diagnosis of BPH, no evidence of cancer, and a maximal urinary flow rate between 5 and 15 ml/second. Patients received either placebo or the combined natural products for 3 months. Evaluations were performed via the American Urological Association (AUA) Symptom Index score, urinary flow rate, PSA measurement, and residual bladder volume. Nocturia showed a markedly significant decrease in severity in patients receiving the combined natural products compared to those taking placebo ($p<0.001$). Daytime frequency was also lessened significantly ($p<0.04$). When the average individual total AUA Symptom Index score in the test group was compared to that in the placebo group at the end of the study, the difference proved highly significant ($P<0.014$). PSA measurements, maximal and average urinary flow rates, and residual volumes showed no statistically significant differences. When taken for 3 monts, a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) compared to placebo can significantly lessen noturia and frequency, and diminish overall symptomatology of BPH as indicated by an improvement in the total AUA Symptom Index score. The combination of natural products caused no significant adverse side effects.

Key Words: Benign Prostatic Hyperplasia, Natural means to treat; Nocturia, Natural means to teat; Frequency, Natural means to treat; Cernitin; Saw Palmetto; B-Sitosterol

Introduction

Despite availability of numerous positive reports, it is not generally recognized in the USA that certain natural products can overcome many troublesome symptoms emanating from benign prostatic hyperplasia (BPH) [1]. Three natural products possessing such potential are: a collection of pollens called cernitin [2-11], saw palmetto (*Serenoa repens*) [12-18], and B-sitosterol [19,20]. Some antioxidants, such as vitamin E, are also believed to be helpful in the treatment [1].

Virtually all studies on the effects of natural agents have been performed in Europe and Asia. This may be the principal reason behind the poor recognition in the USA of the therapeutic benefits of natural products in alleviating symptoms of BPH. Therefore, we undertook a multicenter, randomized, placebo-controlled, double-blind study in the USA to determine how a combination of these products might influence common perturbations of BPH. Our major objectives were to assess both subjective criteria (American Urological Association Symptom Index) and objective criteria (average and maximal urinary flow rates, post void residual urinary volume in the bladder, and PSA score) comparing natural products to placebo over 90 days. To accomplish this, we examined a combination of cernitin, saw palmetto, B-sitosterol, and vitamin E. The first 3 components have been found singly in clinical studies to possess the potential to benefit the often debilitating symptoms caused by BPH [1].

Materials and Methods

Plan

As depicted in Fig. 1, 144 subjects were enrolled at the 3 sites (Washington, DC; Florida; and Idaho) in this multicenter clinical trial. Patients for study were solicited through advertisements in local newspapers and from patient data bases in the investigators' urology practices. 17 subjects eventually withdrew, leaving 70 patients in the test group and 57 in placebo group to complete the study. After signing informed consent in the presence of the principal investigator or his designee at the site, patients received a numbered bottle of pills from the study coordinator at each site. Care was taken so that the pill forms of placebo and test could not be identified by sight, smell or taste. Only the clinical monitor at a separate site from where the studies took place possessed the code, so that neither the doctors nor patients were aware of what was being given or taken.

Inclusion criteria consisted of the following. A diagnosis of BPH was necessary. There was to be no evidence of cancer by digital rectal and/or PSA examinations. The maximal urinary flow rates were to be between 5 to 15 ml /second for a voided volume in excess of 100 ml. The patient had to read, speak, and clearly understand English, and written informed consent to participate in the trial had to be obtained. These studies were approved by separate Institutional Review Boards (IRB) for each of the 3 locations.

Exclusion criteria consisted of an age greater than 80 years; the presence of any tumor, malformation, or infection of the genitourinary tract; any severe concomitant medical condition that would make it undesirable in the clinician's opinion for the subject to participate in the trial or would jeopardize compliance with the trial protocol; severe laboratory abnormalities at baseline according to the WHO recommendations for grading of acute and subacute toxicity (Grade 2-4); medical treatment for BPH with finasteride (Proscar) within the last 3 months and all other medical treatment for BPH within the last 4 weeks; and patients currently being treated with antibiotics for genitourinary tract infections.

Study Design

The study design included a 3-month participant commitment to adhere to the following schedule. The patients were to take 2 pills of the combined natural products or placebo each day over 90 days. The test group received a total daily dose of cernitin 378 mg, saw palmetto complex and phytosterols (saw palmetto fruit standardized to 40% to 50% free fatty acids and B-sitosterol standardized to 43%) 286 mg, and vitamin E 100 IU. They were to make 3 clinic visits.

- Visit 1 (Baseline)
- Visit 2 (Day 45)
- Visit 3 (Day 90)

Procedures

The following procedures were performed on each study participant:

1. Physical Examination (Visits 1 and 3)
2. Laboratory Evaluation (Visits 1-3)
3. American Urological Association (AUA) Symptom Score (Visits 1-3)
4. Urinary flow evaluation (Visits 1-3)
5. Post void residual bladder volume (Visits 1-3)

Analytical Approaches

The target sample size was projected by evaluating previous clinical trials using cernitin for the treatment of BPH which were conducted outside the United States [3,4,6,8,911]. Cernitin clinical trials with similar outcome measures, demonstrating statistically significant findings averaged n=55.5. Since one half of the studies were open label, conservative action dictated at least doubling the "n" to ensure adequate statistical power. The randomization unit was a cluster method. A stratification with minimization procedure by site was used to increase the likelihood of a balanced distribution. Data were analyzed by FutureTech, Inc. of Boise, Idaho. The analyses examined the changes in individuals of all study variables over the course of the study comparing the test group receiving cernitin, saw palmetto, B-sitosterol, and vitamin E to the placebo group. Two statistical analyses were conducted on each question or parameter. The first analysis used a general linear model

PROFILE OF A RANDOMIZED CONTROLLED TRIAL

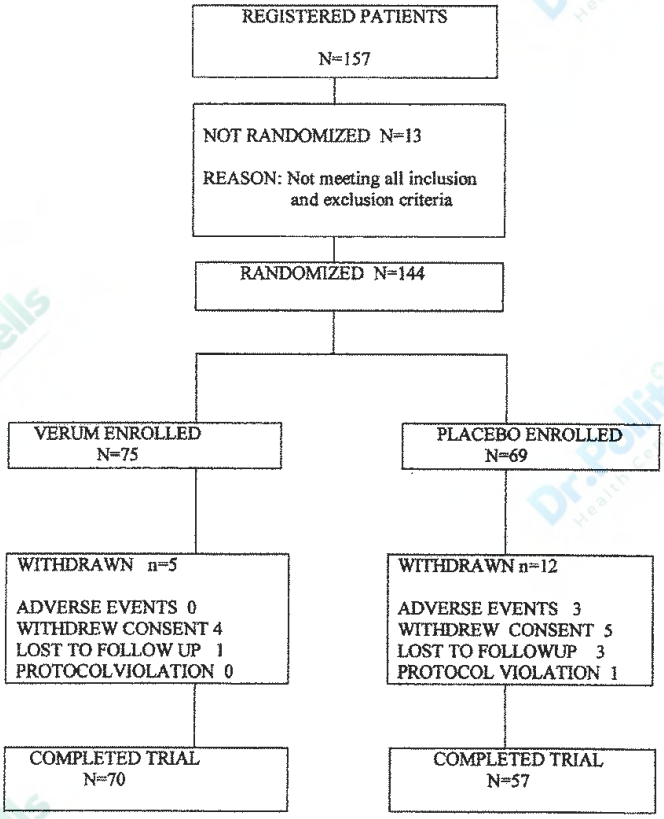

Figure 1. Progress through the various stages of the trial, including flow of participants and withdrawals.

mixed measures analysis of variance (Mixed ANOVA). This analysis takes into account the relative amount of change between groups over time. Of particular interest is the group by time interaction. This is indicative of a difference between the test (active) group and the placebo group from baseline to 45 day to 90 day assessments. Such an analysis will reveal significant differences between baseline and 90 day assessments as well as 45 day to 90 day assessments. The second analysis used the independent t-test on change scores (i.e., day 90 score – baseline score). The absolute amount of change was analyzed. For both analyses, statistical significance was set at $p<0.05$.

Results

As shown in Fig. 1, 144 patients of the 157 registered were eventually randomized – 75 to the test group and 69 to the placebo group. Five of 75 (6.7%) test patients did not complete the study, whereas 12 of 69 (17.4%) failed to complete the study in the placebo group. The information on the randomized patients who remained and withdrew before completing the study are depicted in Fig. 1. All the adverse events severe enough to cause termination, i.e., 3, occurred in the placebo group. One patient in the placebo group was removed from the study for protocol violation. Five patients in the test group either withdrew consent or were lost to follow-up compared to 8 patients in the placebo group. Concerning all adverse events listed in Table 1, 7 (10%) occurred in the test group and 9 (16%) in the placebo group. Interestingly, flatulence was reported by 3 in the test group, but the only 2 patients complaining of gastrointestinal distress were in the placebo group.

The questions asked in the American Urological Association (AUA) Symptom Index are listed in Table 2, and the scoring system for the first 6 questions is described just below them. Note that question 7 is slightly different from the first 6 questions in that the number of trips to the bathroom during the night is being sought. Table 3 depicts the mean AUA scores and the statistics performed by Mixed ANOVA at the 3 time points. Results from Question #7 concerning nocturia showed that there was a markedly significant decrease in severity in patients receiving the test substances compared to those taking placebo ($p<0.001$). Daytime frequency (question 2) was also lessened significantly in the test group compared to placebo ($p<0.04$). When the average individual total AUA Symptom Index score in the test group was compared to that in the placebo group, the difference proved highly significant ($P<0.014$). Table 4 shows the average changes in the AUA Symptom Index parameters between the test and placebo groups over the 90 days of study. Again, nocturia ($P<0.001$), frequency ($p<0.031$) and total AUA score ($P<0.009$) improved significantly in test compared to placebo groups.

Table 5 provides the data for the objective measurements. The PSA scores, maximal and average urinary flow rates, and residual volumes showed no statistically significant differences when comparing the test and placebo groups.

Discussion

Benign prostatic hyperplasia (BPH) presents a difficult, widespread problem [1,21]. Common symptoms of obstructive BPH are often disabling and include a weak urinary stream, a sense of incomplete bladder emptying, difficulty initiating urination, frequency, nocturia, urgency, and poorly controlled stopping and starting of the urinary stream (Table 2). Previously, treatment options for prostate enlargement focused primarily on surgery. However many adverse symptoms attributed to the operative procedure may persist after surgery -- post urination dripping, severe incontinence, and even a decline in sexual function. Because of the potential for these significant side effects, prescription drugs are often chosen by many as initial therapy against BPH, especially when the symptoms are mild or moderate.

Table 1. Adverse events

Event	Verum	Placebo
Flatulence	3	0
Lower abdominal rash	0	1
Dizziness	0	1
Headache	1	1
Nausea/GI distress	0	2
Urinary tract infection	1	0
Ear infection	0	1
Lumbar spine surgery (spur)	0	1
Herpes zoster	1	0
Elevated blood pressure	0	1
Chest pain	0	1
Right arm laceration	1	0

Table 2. American urological association symptom index

Question 1. Emptying. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Question 2. Frequency. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?

Question 3. Hesitancy. Over the past month or so, how often have you found that you stopped and started again several times when you urinated?

Question 4. Urgency. Over the past month or so, how often have you found it difficult to postpone urination?

Question 5. Weak Stream. Over the past month or so, how often have you had a weak urinary stream?

Question 6. Straining. Over the past month or so. how often have you had to push or strain to begin urination?

For questions 1–6, score:

0 for not at all
1 for less than 1 time in 5
2 for less than half the time
3 for about half the time
4 for more than half the time
5 for almost always

Question 7. Nocturia. Over the last month or so, how may times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning? (0, 1, 2, 3, 4, or 5)

Sum of scores from 7 questions indicate severity of BPH:

0–7 = mild prostatism
8–18 = moderate prostatism
19–35 = severe prostatism

Finasteride prevents production of dihydrotestosterone (DHT) from testosterone by inhibiting the activity of the conversion enzyme, 5-alpha reductase. This is important, because DHT is associated with BPH [22]. However, the beneficial effects of finasteride lasts only as long as the drug is being taken and must be given for many months before finasteride can be assessed as to effectiveness. Further, a decreased libido is an unwanted side effect in some men [23]. Another class of drugs has also been used to treat BPH. Alpha blockers are employed to relax the muscle tissue of the prostate in order to relieve the pressure around the urethra [24]. By relaxing the smooth muscles in the prostate, these agents essentially open the bladder and urethra and allow easier flow. However, adverse reactions can be serious and include chest pain, light-headedness, weakness, fast and/or irregular heartbeat, shortness of breath, nasal congestion, swelling of the extremities, and impotence [25].

Recently, many have turned to the use of natural products to overcome or at least ameliorate symptoms of BPH. The public often prefers natural compounds, because of a perception that they have fewer serious side effects compared to drugs. Among the natural agents most widely used outside the USA are a defined pollen mixture called cernitin (rye, timothy, corn), saw palmetto, and B-sitosterol. Various agents used to lessen free radical formation such as vitamin E have been reported to be useful additions as well. In the present investigation, we examined an over-the-counter product with the trade name Cernitin AF™ containing the aforementioned agents.

We carried out a multicenter, randomized, double-blind, placebo-controlled study on 70 patients in the test group and 57 patients in the placebo group to determine how patients with BPH would respond to the combination of natural products. A markedly significant beneficial response was noted by the lessening of nocturia, frequency, and overall AUA Symptom Index scores, even when assessed by different statistical methodologies (Tables 3 and 4). Although there was a general improvement of symptomatology associated with taking placebo, the improvements from the combined natural products compared to placebo in some parameters were dramatic: nocturia 258%, $p < 0.001$; frequency 242%, $p = 0.040$; and overall AUA Symptom Index score 90%, $p = 0.009$.

Table 3. Mean scores from the American urological association symptom index

Q#	Parameter	Baseline	Day 45	Day 90	p
Q1	Emptying	2.37/2.30	1.91/1.98	1.58/1.62	ns
Q2	Frequency	3.34/2.82	2.54/2.29	2.48/2.57	0.040[1]
Q3	Hesitancy	2.72/2.42	1.98/2.21	1.72/1.86	ns
Q4	Urgency	2.57/2.46	2.05/2.10	1.94/2.23	ns
Q5	Weak stream	3.62/3.35	3.01/2.66	2.48/2.57	ns
Q6	Straining	1.70/1.83	1.12/1.57	1.00/1.20	ns
Q7	Nocturia	2.58/2.47	1.95/2.07	1.61/2.19	<0.001[1]
Q1–7	Total AUA score	18.9/17.7	14.6/15.0	12.7/14.5	0.014[1]

Means (70 verum and 57 placebos) for baseline, 45 days and 90 days are shown. First number in the group represents mean of verum group at the time indicated. the second is mean of placebo group at the time indicated. Statistics by Mixed ANOVA.
[1] = statistically significant examining Time × Group Interaction.

Table 4. Change in AUA symptom index over 90 days (70 patients on verum and 57 on placebo)

AUA Questions	Verum	Placebo	% Improvement[1]	p
Emptying				
Question 1	–0.783 ± 0.171	–0.702 ± 0.182	+12%	0.748
Frequency				
Question 2	–0.855 ± 0.185	–0.250 ± 0.207	+242%	0.031[2]
Hesitancy				
Question 3	–0.971 ± 0.194	–0.589 ± 0.205	+65%	0.181
Urgency				
Question 4	–0.594 ± 0.164	–0.232 ± 0.260	+156%	0.225
Weak stream				
Question 5	–1.174 ± 0.186	–0.804 ± 0.208	+46%	0.186
Straining				
Question 6	–0.696 ± 0.169	–0.643 ± 0.195	+8%	0.838
Nocturia				
Question 7	–0.971 ± 0.119	–0.271 ± 0.118	+258%	<0.001[2]
Total AUA score				
Question 1–7	–6.171 ± 0.766	–3.241 ± 0.774	+90%	0.009[2]

Mean ± SEM is shown for 70 patients in the verum group and 57 patients in the placebo group.
– = improvement in symptoms, + = worsening of symptoms (Based on scale 0–5, being worst)
[1]Indicates % improvement in verum score over placebo
[2]Statistically significant by unpaired t test.

Table 5. Objective criteria for cernitin AF study after 90 days

	Verum		Placebo	
	Baseline	After 90 days	Baseline	After 90 days
Bladder volume (ml)	58.9 ± 11.4	57.5 ± 12.8	59.6 ± 12.8	40.7 ± 10.4
PSA (units)	2.6 ± 0.3	2.6 ± 0.4	1.9 ± 0.3	2.6 ± 0.7
AFR (ml/min)	6.0 ± 0.4	6.0 ± 0.5	6.1 ± 0.5	6.8 ± 0.5
MFR (ml/min)	11.2 ± 0.8	11.8 ± 0.7	12.1 ± 0.9	13.1 ± 1.0

Means ± SEM are shown for 70 patients in the verum group and 57 patients in the placebo group.
AFR = average flow rate, MFR = maximal flow rate.

To derive an even greater understanding of the significance of the effect on nocturia, we focused on patients with the greatest distress, i.e., those who at the beginning of the study micturated 3 or more times during the night. Of the 33 patients taking the combined natural products, 29 of 33 (88%) showed improvement in the AUA Symptom Index compared to 14 of 24 patients

(58%) receiving placebo (p=0.004). The decrease of -1.145 + 0.103 (SEM) in the test group means that the patients micturating 3-4 times a night, on an average, were now more apt to void only twice a night. We did a similar analysis on frequency. In those patients having frequency (as defined by Question 2 in table 2) 3 times or greater during the day, 32 of 47 (68%) test patients showed some improvement, whereas only 15 of 34 (44%) placebo patients reported improvement (p=0.013). The decreased frequency of -1.362 + 0.203 (SEM) in the test group meant that the average frequency of 4 decreased below 3. Residual urinary volume in the bladder, average and maximal flow rates, and PSA were not significantly different between test and placebo groups at the end of the 3 month treatment period. No significant adverse side effects were discerned in those taking the combined natural products.

Of the natural compounds involved in this study, perhaps the least is know about defined pollen extract referred to as cernitin. We are unaware of any other major study carried out in the USA on this agent. Therefore, we will discuss cernitin in more detail than the other natural products. In 1967, Ohkoshi, Kawamura and Nagakubo of Keio University reported that cernitin was effective in the treatment of 30 patients with chronic nonbacterial prostatitis and prostadynia [7]. Takeuchi investigated both subjective and objective effects of cernitin on 25 men with BPH and reported favorable results, especially for nocturia, in 64 per cent [8]. In 1986, a field study of 2,289 patients being treated by 170 urologists was undertaken [2]. Cernitin improved symptoms in 64 to 82 percent, in contrast to a low rate of adverse reactions found in 2.9 per cent of cases. In a double-blind, placebo-controlled study performed in 1988 in collaboration with 6 practicing urologist, Becker and Ebeling [3] examined 48 patients taking cernitin and compared them with an equal number of patients receiving placebo over a 12 week interval. Nocturia was claimed by 97% of the patients as a symptom of their disorder. There was a significant improvement using cernitin compared to placebo in nocturia, i.e., 69% vs. 37% (p<0.005). Not only the sensation of residual urine but the actual volume of residual urine was significantly reduced by the flower pollen extract. Mild nausea was reported in one patient.

Cernitin has a number of physiological effects that could benefit BPH. It has an anticongestive-antiinflammatory action which could lessen external pressure on the urethra [1]. These effects may be due to inhibition of prostaglandin and leukotriene biosynthesis. It has been noted that the activities of 5-lipoxygenase and cyclo-oxygenase enzymes are markedly reduced and the arachidonic cascade is interrupted by cernitin [25]. Additional pharmacological effects reported for the pollen preparation are: inhibition of prostate cell growth in animals, influence on contractility of bladder and urethral smooth muscle as well as diaphragms of animals, and an influence on the metabolism of dihydrotestosterone [26].

Saw palmetto (*Serenoa repens*) is an extract of the pulp and seeds of a dwarf, scrubby palm tree native to the West Indies and the Atlantic coast of the United States. It is generally accepted that saw palmetto works, at least in part, by the same major mechanism as finasteride, i.e., preventing the conversion of testosterone to DHT [12]. However, saw palmetto not only lowers the rate of DHT formation, but blocks the ability of DHT to bind to cells, preventing the action of hormone on receptors [13]. In addition, *Serenoa repens* may prevent severe inflammatory responses via a dose-related effect on the arachidonic acid cascade through a double blocking of cyclo-oxygenase and lipoxygenase pathways [27]. In one study examining 110 subjects, it decreased night time urination by 45 percent, increased urinary flow rate more than 50 percent, and reduced the amount of urine left in the bladder after urination by 42 per cent [18]. In other large trials, improvement in prostatic symptomatology was readily noted and saw palmetto even compared favorable with Hytrin (alpha blocker)

and/or Proscar (finasteride) in affecting the symptomatology of BPH when these agents were compared head to head. [14-18].

B-sitosterol is a phytopharmacological agent containing many phytosterols [19,20]. In a randomized double blind study reported in the Lancet [20], 200 patients with symptoms of BPH from 8 private urological practices were treated for 6 months with either 20 mg of B-sitosterol or placebo. At the end of 6 months, modified Boyarsky scores decreased statistically in the B-sitosterol-treated group compared to the placebo group. Reduction took place in the prostatic volume, the quality of life score improved, the peak urine flow increased, the mean voiding time and the urinary volume retention also improved from the initial scores in the sterol group, whereas no changes were noted in the placebo group. Importantly, no severe adverse reactions were attributed to B-sitosterol.

In light of the subjective findings, it is not clear why changes in objective criteria were not seen in the present study. However, this is not unusual. Examination of other BPH clinical studies reveals a lack of consistent findings among both subjective and objective parameters even in those investigations deemed positive through overall assessment [1-21]. PSA is not known to change in response to saw palmetto intake [12-18] and has been shown only once to decrease in the case of cernitin usage [9]. Buck et al [6] found no change in urinary flow rates in response to cernitin, but Braeckman found significant change in his investigation of saw palmetto [17]. Both the former citations reported significant changes in residual urine volume. Considering everything, we believe that our subjective changes are real and indicate a definite benefit from the use of this combination of natural products despite the lack of objective support.

Conclusion

We cannot state with certainty whether we could have accomplished the same results in our study by using only one or 2 of the ingredients present in the combination of natural products. Cernitin [1-11], saw palmetto [12-18], and B-sitosterol [19,20] have been shown to be effective, at least to some extent, when used individually. Because each agent has slightly different actions and different time frames of action, it seemed wise initially to examine a combination to determine clinical utility. Accordingly, we know from our results that a combination of cernitin, saw palmetto, B-sitosterol and vitamin E provided significant relief from some of the most irritating symptoms resulting from BPH. Further studies directly comparing combinations with individual components must be carried out in the future. In summary, this combination of natural products when taken over 3 months significantly lessened nocturia and frequency, diminished overall symptomatology of BPH as indicated by the improvement in the total AUA symptom index scores while causing no significant adverse side effects.

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Report on the clinical evaluation of “Cernilton” preparation in cases of chronic prostatitis

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Gustav-Ricker-Hospital
Urological Clinic

Director: Prof. Dr. med. habil. G. W. Heise

The trial treatment of nine patients has been in progress since April 1965. Preparations of “Cernilton” in tablet form were placed at our disposal for these trial experiments by the Berlin Institute of Medicine.

Nine cases of clinically established prostate diseases, i.e. prostatitis, were treated. The following symptoms were observed in all instances:

9 cases of micturition disturbances
9 cases of cohabitation difficulties
9 cases of leukocytes in the ejaculate

All the patients were found to suffer from lowered libido and painful orgasms, and six of them exhibited manifestations of impotence. The practice of coitus interruptus was denied in all cases. In three cases the diagnosis was confirmed by histological excision, which revealed adenomatosis of the prostate with leukocyte infiltration. Haemospermia was detected in five cases.

Cultures of ejaculates from all nine cases revealed two cases of haemorrhagic ejaculates, two cases of greenish streptococci, two cases of haemolytic streptococci and one case of Peseudomonas aeruginosa. Apathogenic bacteria were found in three cases. All the ejaculates contained leukocytes and bacteria. Two cases with haemorrhagic discharges were observed, and a previous history of venereal infection (gonorrhea) was reported for two patients. One patient exhibited a predisposition to allergy.

Suicide had previously been attempted by two patients and grave depressive manifestations were observed in four others.

No pathological changes in the kidneys, urethra, or bladder could be established, i.e. no calculus, pyelonephritis or malformations could be confirmed.

Comprehensive re-examinations undertaken in 1966, revealed that all the patients had responded with a definite improvement. The following conclusions could be drawn from the use and evaluation of the drug to date:

In agreement with the findings of other investigators, it is apparent that scientific exactitude in the treatment of this subject is not possible.

In establishing criteria for cure or improvement, the following tests were undertaken:

1. Urine examination
2. Ejaculate examination
3. Examination of bacterial culture of ejaculate

4. Subjective report by the patient
5. Palpation findings

Chronic prostatitis is understandably difficult to define, since a considerable diversity of changes can take place in the prostate, that cannot always be definitely differentiated from each other. The diagnosis is thus best confirmed by histological examination. Biopsy specimens were therefore used in two cases. In the other cases, the material examined was the ejaculate and not the product of stripping, which had been studied by other investigators. As mentioned above, non-pathogenic bacteria were found in all cases, as well as large numbers of leukocytes.

As the test group consisted of no more than nine patients, no purpose could be served by grouping with relation to venereal disease. It may however be mentioned that, at the end of the treatment, previous infection of the urinary tract was of no fundamental importance.

In contrast to the observation period of 3 months, practiced by many of the West German workers, our own observations were carried over three years.

1. In all the nine cases, the ejaculate examinations showed the ejaculates to be free from leukocytes and bacteria after a protracted course of one Cernilton tablet taken three times daily.
2. Cultivated specimens of ejaculate and urine did not reveal the presence of pathogenic bacteria.
3. All the patients exhibited a considerable improvement both mentally and physically, with the result that some of the patients discontinued medication with Cernilton during the final 6-12 month. Only in three cases is Cernilton still being taken (3 x 1 tablets daily), but even these patients experience both physical and mental well-being.

The appearance of discharges has ceased, cohabitation difficulties no longer occur and pains radiating to the perineum and sacral region have disappeared.

Micturition disturbances could no longer be observed, neither could side-effects of after-effects following treatment with Cernilton be confirmed.

In conclusion it may be said that treatment of nine patients with one Cernilton tablet taken three times daily for a period of two years and longer brought about a healing of the condition, and that the pollen preparation Cernilton is a very suitable agent in the treatment also of severe and stubborn cases of chronic prostatitis. It would be a commendable advance if treatment with this pollen preparation were to become incorporated into recommended therapeutic praxis.

Results of Treatment with Pollen Extract (Cernilton® N) in Chronic Prostatitis and Prostatodynia

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Summary— We report the results of a prospective study with the pollen extract, Cernilton® N, in a dose of 1 tablet *tid* for 6 months for the treatment of chronic prostatitis syndrome in 90 patients. The factors documented before and after 3 and 6 months' treatment were digital rectal examination (DRE) of the prostate, uroflowmetry, bacterial studies, leucocyte counts in urine and measurement of complement C3/coeruloplasmin in the seminal fluid.

The patients were divided into 2 groups: those without associated complicating factors (CFs) (n=72) and those with complicating factors, i.e. urethral strictures, prostatic calculi, bladder neck sclerosis (n=18). In the group without CFs, 56 (78%) had a favourable response; 26 (36%) were cured of their symptoms and signs and 30 (42%) improved significantly with an increase in flow rate, a reduction in leukocyturia in post-prostate massage urine (VB3) and a decrease in complement C3/coeruloplasmin in the ejaculate. In the patients with CFs only 1 patient showed a response. Complicating factors should be considered in patients who fail to respond to treatment within 3 months. Cernilton® N was well tolerated by 97% of patients.

Controversy surrounds the aetigology and clinical significance of the painful prostate and the diagnosis of chronic prostatitis and prostatodynia is seldom based on sound diagnostic criteria (Drach, 1980). Even when the diagnosis of chronic bacterial or non-bacterial prostatitis and prostatodynia has been reached, the results of treatment are ofter disappointing (Pfau, 1986).

Clinical studies with the pollen extract, Cernilton® N (A.B. Cernelle, Sweden), have revealed symptomatic improvement in prostatic inflammatory disease and benign prostatic hyperplasia (Denis, 1966; Ebeling, 1986; Becker and Ebeling, 1988, 1991; Buck *et. al.,* 1989, 1990). We present the results of a prospective study on the efficacy of Cernilton® N in the treatment of chronic non-bacterial prostatitis and prostatodynia.

Patients and Methods

Ninety patients aged from 19 to 90 years (mean 47.2±SD 17.6) with symptoms of prostatitis of at least 1 year's duration, in whom bacterial localization studies were negative, were entered into the study. Thirty patients had had at least 2 previous episodes of bacterial prostatitis and/or urinary tract infection treated with antibiotics, but were entered into the study during an infection-free period.

The diagnosis was based upon bacterial localization studies of pre- and post-massage urine samples and expressed prostatic secretion (EPS) (Meares and Stamey, 1968). Leucocyte counts in the sediment from the first voided 10 ml of urine (VB1), mid-stream urine (VB2) and first voided 10 ml of after massage (VB3) were performed using a counting chamber and calculating the number of leucocytes/µl (MD-Kova-system^{R}) Sieck, 1983).

Additional investigation (ultrasonography, voiding and/or retrograde cystourethrography and endoscopy) revealed other pathology in 18 patients. These complicating factors were bladder neck sclerosis (10), urethral strictures (5) and extensive prostatic calcification (3). Eight patients had undergone a previous transurethral or open prostatectomy (7 for benign prostatic hyperplasia (BPH) and 1 for chronic prostatitis).

Forty-four patients (49%) had received treatment with various drugs, including antibiotics, anti-inflammatory agents and other empirical remedies, during the 3 months prior to entering the trial; 37 patients had improved.

Cernilton® N (Pharma Stroschein (liscensed by Cernitin SA, Lugano, Switzerland; Hamburg, Germany) was given in a dose of 1 tablet *tid* and in most cases treatment was continued for 6 months. The following factors were recorded before treatment and after 3 and 6 months' therapy: (i) symptoms of discomfort and pain were graded as absent, mild, moderate and severe; (ii) nocturia, frequency and dysuria were scored according to Boyarsky *et al.* (1977); (iii) the findings of rectal palpitation of the prostate; (iv) uroflowmetry; (v) leucocyturia in VB2 and VB3; (vi) bacteriuria; (vii) complement C3 and coeruloplasmin in the ejaculate (scored semi-quantitatively combining the values of complement C3/coeruloplasmin/dl according to a modified scheme of Blenk and Hofstetter (1975) as follows; 1 =<1.5 mg/negative; 2=1.5-<2 mg/ <0.5 mg; 3=2-4 mg/ 0.5-1 mg; 4=3-8 mg/>1-3 mg).

Complement C3 and coeruloplasmin were determined after the ejaculate had been liquefied and centrifuged for 5 min at 11,266 U/min resp. at 10,500 g. The radial immunodiffusion of the supernatant sample was performed with LC-Partigen^R C 3c and LC-Partigen^R plates (Behringwerke AG, Marburg, Germany). In addition to the sample, a control from calibrated standard serum was placed on the plates (dilution 1:20 for complement C3, dilution 1:11 for coeruloplasmin). The amount of complement C3 and coeruloplasmin was calculated from the diameter of the samle precipitate according to the calibration curve from calibrated standard serum of complement C3 and coeruloplasmin (Behringwerke AG, Marburg, Germany).

A "cure" was defined as a complete response with a return to normal of all factors, an "improvement" as a partial symptomatic and objective response and "no improvement" as persistence of symptoms or signs or deterioration. The biometrical evaluation was performed by descriptive analysis of the factors before and after treatment as well as a comparison of changes at 3 months and 6 months. The following tests were used: (i) the *t* test for related samples for a comparison of uroflow measurements; (ii) the Wilcoxon matched-pairs signed-rank test using chi^2 approximation for comparison of the leucocytes in VB3; (iii) the sign test for the scored complement C3/coeruloplasmin in the ejaculate; (iv) the Pawlik corrected contingency coefficient for qualitative and the Spearman rank correlation coefficient for quantitative correspondence between the changes of leucocyturia in VB3 and the peak urine flow rate.

Results

At the commencement of the study the patients' clinical symptoms were maily moderate or mild; the prostate was enlarged in 56% and tender in 94%. On the basis of significant differences at initial presentation and the response to treatment the patients were separated into 2 groups: those without (n=72) and those with (n=18) complicating factors. Complement C3 in the ejaculate was >1.5 mg/dl in all cases.

Symptoms

Almost all of the patients complained of frequency and dysuria, while pain was present in about two-thirds. Patients with associated CFs responded poorly to treatment, whereas in those without CFs the symptoms were markedly reduced after 6 months' treatment (Table 1).

In patients without CFs the prostate reverted to a normal size in 15/39 cases; its consistency improved in 37/68 cases and it was no longer tender on palpation in 47/71 cases after treatment. These signs worsened in 5 patients. The findings on palpation of the prostate in the group with associated CFs were either unchanged or had deteriorated.

Table 1 Response to Treatment in 72 Patients without Complicating Factors

Symptom	*Cured (%)*	*Improved (%)*	*No.*
Discomfort	68	9	53
Pain	69	12	49
Nocturia	56	30	54
Frequency	49	26	72
Dysuria	52	12	69

Uroflowmetry

In contrast to the patients with CFs, where all uroflow parameters became worse, there was a significant improvement in the time to peak flow and increased voided volume in the patients without CFs (P<0.05). Micturition and flow time remained unchanged. In patients with CFs the peak urine flow rate showed a slight decrease from 11.9±3.9 to 10.5±2.6 ($\bar{x}$±SD). In patients without CFs the mean peak flow rate before treatment was 15.9±SD 5.2 ml/s; this increased to 19.0±SD 7.2 ml/s at 3 months (P<0.001) and to 23.9±SD 10.6 ml/s at 6 months (P<0.001; comparing 6 with 3 months: P<0.001).

Leucocyturia in VB3 (L-VB3)

In patients with CFs the L-VB3 increased from a median of 80 to 185 leucocytes/µl (P<0.001). Comparing the number of leucocytes before and after treatment in patients without CFs the L-VB3 decreased from a median of 50 to 20 leucocytes/µl (P<0.001). In these patients the pre-treatment mean leucocyte count fell from 85±SD 89.9 leucocytes/µl to 69.1±SD 121.8 at 3 months and to 42.2±SD 62.6 leucocytes/µl at 6 months (control vs 3 vs 6 months P<0.001; comparing 6 with 3 months: P<0.001). The individual changes documented separately as pre and post values at different baseline levels of leucocyturia, *i.e.* <50, 50-99, 100-1000 leucocytes/µl, are shown in Figure 1.

L-VB3 and PUFR (peak urine flow rate)

Correlation of the changes in L-VB3 with the PUFR in patients without CFs showed that the leucocyte count decreased in 52 cases while the PUFR increased, but the PUFR fell in 3 patients. An increase in L-VB3 occurred together with a decrease in PUFR in 8 cases and an increase in PUFR in 9 cases. There was a highly significant negative correlation between L-VB3 and PUFR (CC corr= 0.720; r= -0.56). Because of the wide distribution pattern of the leucocytes in VB3, individual differences between the baseline values and the control after treatment were ranked separately for L-VB3 and PUFR according to the definition of rank 1 as the strongest increase plotted as the combined ranks of the individual changes for both parameters (Fig.2).

Complement C3/coeruloplsmin

Patients without CFs showed a decrease in complement C3/coeruloplasmin in the ejaculate after 3 months (P<0.001) and a further decrease after 6 months (P<0.001; comparing 6 with 3 months: P=0.005). Patients with CFs showed an increase in these indices of inflammation (P=0.07) (Table 2).

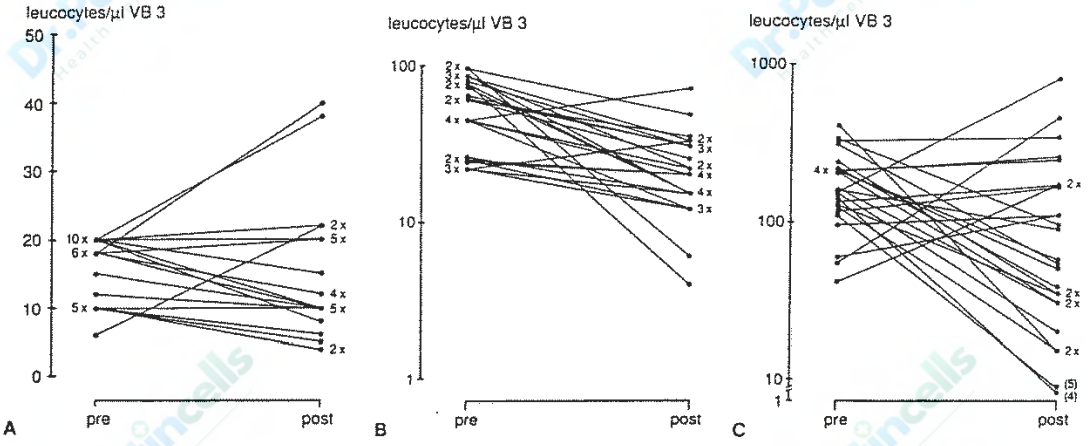

Fig. 1 Individual courses of leucocyturia in VB3 in 72 patients without complicating factors, plotted separately according to baseline values (pre: < 50, 50–99, 100–1000 leucocytes/µl) or control (post) values. The numbers on the left and right sides of the lines refer to the number of patients with the corresponding baseline or post-treatment value, *e.g.* 10 × in Figure 1A represents 10 patients with the same baseline value of 20 leucocytes/µl VB3. The numbers (5) and (4) in Figure 1C represent the post-treatment values of leucocytes/µl VB3 in 2 patients which are not assessable from the Figure owing to the broken axis of ordinate.

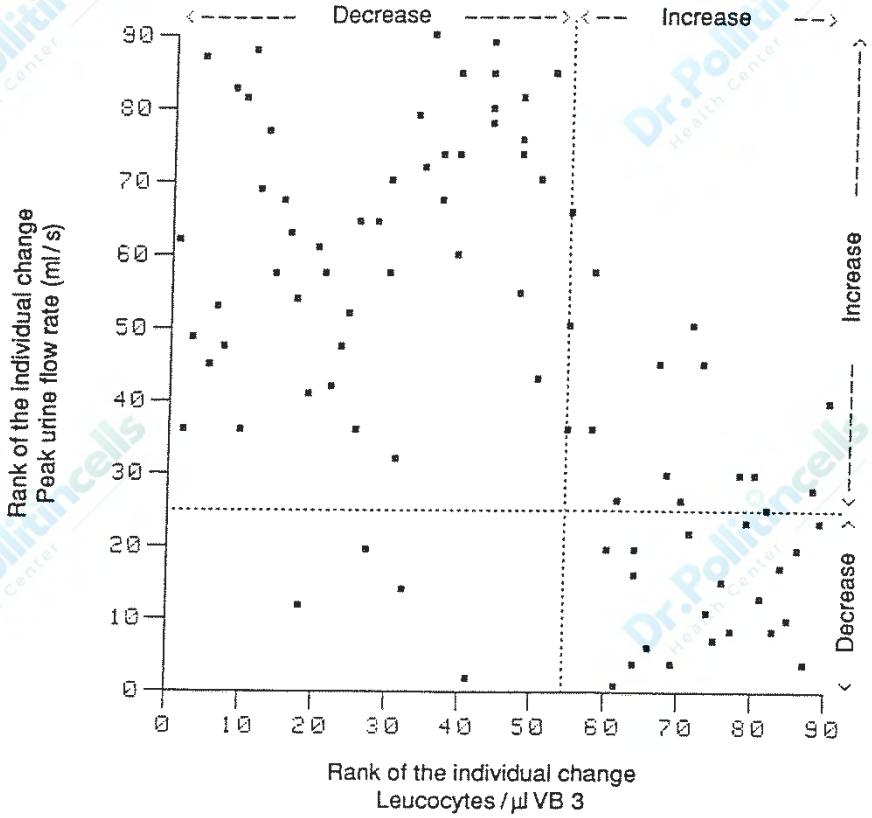

Fig. 2 Scattergram of the combined ranked individual changes in leucocyturia in VB3 (L-VB3) and peak urine flow rate (PUFR) in 90 patients with chronic prostatitis syndrome comparing the values before and after treatment. High inverse qualitative (CC_{corr} = 0.720) and quantitative (r_s = 0.565) correlation between the changes of L-VB3 and PUFR. Rank 1 = strongest decrease, rank 90 = strongest increase, parallel lines to ordinates = no change (conversion point).

Table 2 Complement C3/coeruloplasmin/dl Ejaculate before and after 3 ($P < 0.001$) resp. 6 Months ($P < 0.001$; $P = 0.005$ comparing 6 with 3 months) of Treatment in Patients without Complicating Factors and before and after Treatment in Patients with Complicating Factors (CF) ($P = 0.07$)

	No CF			*With CF*	
Complement C3/coeruloplasmin	*Pre* No.	*3 months* No.	*6 months* No.	*Pre* No.	*Post* No.
< 1.5 mg/negative	—	3	11	—	—
1.5–< 2.0 mg/< 0.5 mg	8	36	40	4	—
2.0–< 4.0 mg/< 0.5–1 mg	46	30	13	11	9
3.0–< 8.0 mg/< 1–3 mg	17	2	5	1	7
Missing values	1	1	3	2	2

Assessment of efficacy

There was an overall clinical response in 56/72 patients (78%) without CFs; 26 of these (36%) were cured of symptoms and signs and the remainder (42%) were improved. In 16 patients (22%) there was no response. In patients with CFs only 1 improved and the remaining 17 showed no response. Treatment was discontinued in 12 paitents because of an ineffective response or clinical deterioration. The most frequent cause of deterioration was symptomatic bacteriuria (83%) and these

patients were treated with antibacterial therapy. CFs were present in 67% of all patients in whom treatment was discontinued.

Treatment was well tolerated by 97% of patients. Three complained of a mild to moderate degree of meteorism, heartburn or nausea which did not require discontinuation of treatment.

Discussion

Cernilton® N was found to be effective in the treatment of patients with chronic non-bacterial prostatitis and prostatodynia. Patients with complicating factors due to incidental lower urinary tract pathology (e.g. bladder neck sclerosis, urethral stricture or extensive prostatic calcification) failed to respond and a high percentage of these developed bacteriuria.

Complement C3 in the ejaculate is regarded as an extremely sensitive index of an inflammatory process in the prostate or adnexae (Blenk and Hofstetter, 1991), even in patients with minor and/ or focal pathological changes within the gland that do not necessarily lead to an increase in the number of leucocytes in the expressed prostatic secretion or the VB3. Comparison of the baseline values of complement C3/coeruloplasmin and L-VB3 showed a high concentration of complement C3 in the ejaculate even in patients with a low leucocyte count in VB3 (i.e. prostatodynia). The decline in the complement C3/coeruloplasmin values with pollen extract in these patients suggests that inflammation of oedema may also be a feature of prostatodynia (di Trapani et al., 1988; Vahlensieck and Dworak, 1988).

Barbalias (1992) reported an increase in the maximum urethral closure pressure (MUCP) in patients with the prostatitis syndrome resulting in a simultaneous diminution in urinary flow rates. It is suggested that local inflammation may irritate adrenergic endings and cause a high MUCP. Our finding of an inverse correlation between inflammation and uroflow supports this hypothesis and the decrease in complement C3 leads us to speculate that local irritation may also be responsible in patients with prostatodynia. Takeuchi et al. (1981) reported a significant decrease in the MUCP from 92±SD 23 to 58±SD 19 cm H_2O with a reduction in the prostatic profile length and prostatic urethral resistance with pollen extract in patients with BPH. The concluded that this finding may be related to the eradication of oedema and inflammation in the periurethral area.

Cernilton® N is an extract from several pollens. Its pharmacological action could be ascribed to inhibition of the cyclo-oxygenase and 5-lipoxygenase enzyme in the biosynthesis of prostaglandins and leucotrienes as demonstrated by the *in vitro* studies of Loschen and Ebeling (1991). A dose-related inhibition of noradrenaline-induced contractions of the rat and mouse urethra with pollen extract has been observed (Kimura et al., 1986; Nakase et al., 1988). In addition, extract of pollen was shown to inhibit the growth of the rat prostate and immortal prostate cancer cell lines in culture (Ito et al., 1986; habib et al., 1990). From this broad spectrum of pharmacodynamic activity it is difficult at the present time to define a precise mode of action.

This study has shown a progressive improvement in the clinical course of patients with chronic prostatitis and prostatodynia over a 6-month period. This confirms the observation of Buck et al. (1989) that a 3-month period treatment with pollen extract is required before significant improvement occurs. This favourable response indicates that Cernilton® N has an important therapeutic role in the treatment of these conditions. Futher studies are necessary to elucidate its precise mode of action.

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Effects of pollen extract EA-10, P_5 on chronic prostatitis or infertility with chronic prostatitis

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KEY WORDS: prostatitis; infertility; free radicals; pollen

ABSTRACT

AIM: To determine the drug action mechanism of pollen extract EA-10, P_5 on the treatment of chronic prostatitis (CP) or infertility with CP. **METHODS:** Malondiadehyde (MDA), super oxide dismutase (SOD), and nitrogen monoxide (NO) were measured by biochemical assay, and zinc content was assayed by atomical spectrophotography in the pre-treatment and post-treatment of CP or infertility with CP. **RESULTS:**Compared with control group, leukocytes in expressed prostatic secretion (LEPS), MDA, and NO were increased, and zinc content and SOD were decreased significantly in the pre-treatment of CP. After the treatment, LEPS was improved, and MDA and NO were reduced, while zinc content were increased apparently and the alteration of SOD was not evident *(*P>0.05). In the pre-treatment of infertility with CP, LEPS, MDA, NO, sperm viability, and seminal leukocytes were obviously higher and seminal plasma SOD, zinc content, and sperm motility were obviously lower than those in control group. After the treatment, LEPS, sperm motility, and sperm viability were improved, MDA, NO, and seminal leukocytes were decreased, SOD and zinc content were increased markedly. **CONCLUSION:** There was inter-correlation between oxygen free radicals (OFR) and occurrence, development, and recovery of CP; Change of OFR may be involved in the drug action mechanism of EA-10, P_5 in the treatment of CP or infertility with CP.

INTRODUCTION

Chronic prostatitis (CP) is one of the most common diseases in andrology. Its therapeutic efficacy is not very satisfactory. Recent studies showed that CP might defect semen quality. Thus, it is significant to make an investigation of pathogenesis and medication of CP.

Oxygen free radicals (OFR) which causes tissue damage by lipid peroxidation (LPO)[1], includes mainly superoxide anion (O_2), hydrogen peroxide (H_2O_2), hydroxy free radical (·OH), and nitrogen monoxide (NO). LPO has yielded several types of secondary free radicals and a large number of reactive compounds (including MDA), resulting in the destruction of cellular portion. Of course, cells are equipped with various antioxidants, such as vitamin E, vitamin C, glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and so on. These can scavenge supernumerary OFR and protect organism from cytotoxic effect of OFR[2,3]. In addition, there was apparent negative correlation between semen OFR level and semen quality, but with the increasing of semen OFR level and prolonging of contact time between OFR and sperm, sperm vital force would obviously decrease[4,5]. Studies also showed seminal MDA might be increased apparently in chronic bacterial prostatitis, resulting in the influence of sperm vitality and sperm motility[6,7]. These data indicated that OFR played an important role in pathogenesis of CP and infertility.

EA-10, P_5 is regarded as a satisfactory drug in the treatment of CP. At present, it is still unknown that whether OFR, antioxidase, and zinc content in semen will be regulated in the

treatment of CP or infertility with CP by EA-10, P_5. Therefore, we investigated whether EA-10, P_5 could inhibit LPO, and thus to obtain the primary conclusion about drug action mechanism of EA-10, P_5 in our treatment.

MATERIALS AND METHODS

Population

All 68 cases of CP (group I) and 63 cases of infertility with CP (group II) were divided into two groups, which were then subdivided into three treatment subgroups respectively (group A: EA-10, P_5 + Roxithromycin, group B: EA-10, P_5 alone, and group C: Roxithromycin alone). Twenty cases who were normal healthy donors of proven fertility were used as control group. The treatment period was four weeks. Group A received EA-10, P_5 (product from Sweden Pharmacia Allergon AB, 375 mg/pill) and roxithromycin (150 mg/pill) twice daily. Group B-C received respectively EA-10, P_5 and Roxithromycin twice daily. During the treatment, all 131 cases were treated with sitzing bath in hot water and controlled diet (wine and pungent diet prohibited).

Semen samples and treatment

Semen samples were obtained from all cases by masturbation after 3 d of abstinence. Samples were incubated for 20 min in 37 ºC warm bath box. Firstly, regular semen analysis and seminal MDA content were analyzed after semen has been liquefied completely; Secondly, liquefied semen was centrifuged at 1000×*g* for 10 min, and seminal plasma was used to determine the content of NO and SOD. Finally, surplus seminal plasma was frozen at -20 ºC until further use for zinc content assay.

Determination of seminal MDA content and SOD activity

Seminal MDA content was determined by thiobarbituric acid (TBA) method [8]. SOD activity was measured as the inhibition of nitroblue tetrazolium reduction due to superoxide anion generation by xanthine plus xanthineoxidase [9].

Zinc and NO content in seminal plasma assay

Zinc content was assayed by a method based on atomical spectrophotography [10]. The NO concentration was estimated by a method based on nitrite salt response with sulfanilamide to from diazole, which could appear purplish red color reacting with naphthalene ethylenediamine in the acid conditions. The absorbance of 530 nm was measured [11].

Semen parameters

All semen analysis adopt with color quality analysis system of WLJY-9000, which was devised by skill trade Company Weili Peking. All parameters were settled down to refer to standard of World Health Organization (WHO)[12].

Statistical

Date were expressed as mean ±SD and analyzed with *t*-test. Value of $P<0.05$ was considered to be statistically significant.

RESULTS

Changes in symptom and LEPS in CP or infertility with CP

After the treatment by EA-10, P_5 + Roxithromycin, EA-10, P_5 alone, and roxithromyc alone in CP or infertility with CP, remissive rate of symptom was 92 %, 66.67 %, 68.17 %, and 90 %, 61.91 %, 63.64 %, while

Tab 1. Changes in symptom and LEPS in different treated groups of CP. $^bP<0.05$ *vs* EA-10, P_5+Roxithromycin groups.

Treatment	Case	Symptom improved		LEPS improved	
		Efficiency	Percent/%	Efficiency	Percent/ %
EA-10, P_5+Roxithromycin	25	23	92	22	88
EA-10,P_5	21	14	66.67^b	12	57.14^b
Roxithromycin	22	15	68.17^b	13	59.09^b

Tab 2. Changes in the symptom and LEPS in different treated groups of infertility with CP. $^{b}P<0.05$ *vs* EA-10, P_5 +roxithromycin groups.

Treatment	Case	Symptom improved		LEPS improved	
		Efficiency	Percent/%	Efficiency	Percent/%
EA-10, P_5+roxithromycin	20	18	90	17	85
EA-10,P_5	21	13	61.91^{b}	11	52.38^{b}
Roxithromycin	22	14	63.64^{b}	12	54.55^{b}

effective rate of LEPS was 88 %, 57. 14 %, 59.09 %, and 85 %, 52. 38 %, 54. 55 %, respectively. Therapeutic efficacy in group A was significantly higher than that in group B or C *(*P<0. 01) (Tab 1, 2).

Changes in LEPS, MDA, SOD, Zinc content, and NO in CP

Compared with control group, LEPS, MDA, and NO were increased, while zinc content and SOD were decreased significantly in the pretreatment *(*P<0.01). After the treatment, LEPS and zinc content were improved, while MDA and NO were decreased apparently *vs.* pre-treatment *(*P<0.01), but there was no obvious alteration of SOD *(*P>0.05) (Tab 3).

Changes in LEPS, MDA, SOD, Zinc content, NO, and semen parameters in infertility with CP

In the pre-treatment, LEPS, MDA, NO, sperm viability, and seminal leukocytes were obviously higher and SOD, zinc content, and sperm motility were obviously lower than those in controlled group *(*P<0.01). After the treatment, LEPS, SOD, zinc content, sperm motility, and sperm viability were improved and MDA, NO, and seminal leukocytes were decreased significantly (P<0.01). Compared with the pre-treatment, MDA levels and seminal leukocytes were reduced significantly in group A than these in group B or C in the post-treatment *(*P<0.01) (Tab 4).

DISCUSSION

In this test, we have used EA-10, P_5 and roxithromycin to treat CP and infertility with CP. Roxithromycin has a good effect to chlamydia besides much of Gram-negative bacteria [13]. Therapeutic efficacy was lower in our works than that in literature. But our therapeutic efficacy was still satisfactory. We considered that the reason may be as follows: (1) Chronic bacterial prostatitis may be selected in all the chosen cases, which might influence therapeutic efficacy of EA-10, P_5. (2) The treatment period was shorter compared with that illustrated in literature. In addition, we have found that therapeutic efficacy in group A was better than

Tab 3. Changes in LEPS, MDA, SOD, Zn^{2+} content, and NO in different treated groups of CP. Mean±SD. $^{b}P<0.05$, $^{c}P<0.01$ *vs* control. $^{d}P>0.05$, $^{f}P<0.01$ *vs* pre-treatment at the same group. $^{h}P<0.05$ *vs* EA-10, P_5+Roxithromycin group.

	Control (n=20)	EA-10,P_5+Roxithromycin (n=25)		EA-10,P_5 (n=21)		Roxithromycin (n=22)	
		pre-treat	post-treat	pre-treat	post-treat	pre-treat	post-treat
LEPS /Hp	3.4±2.1	25±16^{b}	5.0±2.8^{f}	23±13^{b}	7±4^{f}	25±14^{b}	7±4^{f}
MDA/μmol·L^{-1}	4.1±1.1	8.3±1.9^{c}	4.3±1.4^{f}	8.3±1.7^{c}	5.4±1.6^{bfh}	8.4±1.8^{c}	5.2±1.2^{bfh}
Zn^{2+}/mmol·L^{-1}	2.3±0.6	1.2±0.4^{b}	1.8±0.5^{f}	1.2±0.5^{b}	1.6±0.5^{f}	1.2±0.4^{b}	1.6±0.5^{f}
SOD/kU·L^{-1}	920±119	850±118^{b}	851±122^{d}	838±110^{b}	840±113^{d}	829±120^{b}	831±123^{d}
NO/μmol·L^{-1}	4.6±1.6	63±20^{c}	39±16^{bf}	63±20^{c}	45±18^{bf}	63±21^{c}	47±18^{bf}

in

Tab 4. Changes in LEPS, MDA, SOD, Zinc content, NO, and Semen parameters in different treated groups of infertility with CP. Mean±SD. $^{a}P>0.05$, $^{b}P<0.05$, $^{c}P<0.01$ *vs* control. $^{d}P>0.05$, $^{e}P<0.05$, $^{f}P<0.01$ *vs* pre-treatment at the same group. $^{h}P<0.05$ *vs* EA-10, P_5+Roxithromycin groups.

	Control (n=20)	EA-10,P_5+Roxithromycin (n=25)		EA-10,P_5 (n=21)		Roxithromycin (n=22)	
		pre-treat	post-treat	pre-treat	post-treat	pre-treat	post-treat
LEPS/Hp	3.4±2.1	23±13^{c}	6±4^{f}	23±12^{c}	7±5^{f}	23±12^{c}	6±4^{f}
MDA/μmol·L^{-1}	4.1±1.1	9.2±1.6^{c}	5.5±2.1^{f}	9.1±1.9^{c}	7.5±2.4^{beh}	9.1±1.7^{c}	7.2±2.5^{beh}
Zn^{2+}/mmol·L^{-1}	2.3±0.6	1.1±0.4^{c}	1.6±0.4^{bf}	1.1±0.4^{c}	1.5±0.4^{bf}	1.1±0.3^{c}	1.4±0.4^{bf}
SOD/kU·L^{-1}	920±119	653±115^{c}	736±125^{bf}	663±91^{c}	727±104^{bf}	660±97^{c}	722±109^{bf}
NO/μmol·L^{-1}	4.6±1.6	78±20^{c}	55±18^{bf}	76±27^{c}	63±27^{bf}	77±25^{c}	61±21^{bf}
10^{9}×Sperm density/L^{-1}	76±24	82±49^{a}	79±46^{ad}	79±42^{a}	77±41^{ad}	80±41^{a}	79±40^{ad}
Sperm motility/%	75±12	37±14^{c}	46±14^{bf}	38±17^{c}	43±19^{bf}	37±16^{c}	43±18^{bf}
Sperm viability/%	14±8	36±14^{c}	24±10^{bf}	34±14^{c}	28±11^{bf}	34±13^{c}	28±11^{bf}
10^{9}×Seminal leukocytes/L^{-1}	0.5±0.3	1.6±0.9^{c}	0.7±0.4^{af}	1.6±0.8^{c}	0.9±0.4^{bf}	1.6±0.8^{c}	0.9±0.5^{bf}

group B or C. This indicated that EA-10, P_5 should be used together with effective antibiotic in the treatment of CP.

Some studies have proved that OFR was related to occurrence and development of CP[3- 4,14]. In our studies, MDA was higher and SOD was lower significantly in the pre-treatment of CP than those in the control group, which suggested that there be an increase of OFR, a decrease of antioxidation, and reinforce a of LPO. But MDA was decreased after the treatment, indicated that OFR was scavenged massively and LPO was obviously inhibited.

Similarly, MDA was higher and SOD was lower significantly in pre-treatment of infertility with CP than those in the control group, which suggested that oxidation be increased and antioxidation be decreased in semen. At the same time, we discovered that sperm motility was declined and sperm viability was raised significantly. But after the treatment, MDA was decreased and SOD was increased significantly than those in the pre-treatment *(*P<0.01), accompanying with improvement of sperm motility and sperm viability apparently. This indicated that LPO was inhibited and antioxidation was reinforced. From the result above, we believed that EA-10, P_5 could reduce LPO and enhance antioxidation in the treatment of CP or infertility with CP.

In our treatment, antibiotic and EA-10, P_5 were used not only to cure CP but also to improve semen quality. We found that EA-10, P_5 had an effect on weakening oxidative stress and increasing antioxidation in protatic secret and semen. This suggested that change of OFR may be involved in the drug action mechanism of EA-10, P_5 in the treatment of CP or infertility with CP. At present, it is known that ferulic acid was an antioxidant containing phenolic hydroxy[15]; and P_5, one of valid portion in pollen extract EA-10, P_5, may have anti-oxidative effect owing to providing phenolic hydroxy too. Nevertheless this view still needs to be confirmed by more investigation.

It was reported that zinc content in prostatic secretion and semen was higher than in other organ and body fluid, which showed that zinc played an important role in keeping function of prostate and other accessory sex glands. Our studies showed that zinc content was increased accompanying with improvement of an illness state. EA-10, P_5 can enhance zinc content in seminal plasma, which may be related to improve local circumstance.

In summary, all these results could provide us with a possible therapeutics approach to treat infertility with CP. In order to improve therapeutic efficacy, anti-infection and anti-oxidation should be adopted in the treatment of CP or infertility with CP.

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Chronic Prostatitis

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Chronic prostatitis, which is one of the most common diseases with which the adult male is afflicted [1, 2], covers a wide range of symptoms originating in the prostate. Gartman [3] collected 178 of these symptoms related to the strategic position of the prostate to the urinary, genital and gastro-intestinal tract. A classification based on histological appearance by Swinney [14] divides the clinical heterogeneous group of chronic prostatitis in a true inflammatory group, a group with no evidence of inflammatory changes and a third small group of granulomatous prostatitis first described by Tanner and McDonald [5]. A new extract Cernitin (2) was introduced in 1959 by Ask-Upmark [6] in the therapy of this syndrome. This paper gives the preliminary results in small group of patients treated with this product in combination with a study of some constituents of prostatic fluid in this disease.

Methods and materials

Thirty one patients with a presumptive diagnosis of chronic prostatitis were considered potential candidates for admission to the study. The presumptive diagnosis was based on a careful history after which the patients underwent complete urological evaluation. This evaluation included weight and height, general and neurological findings, rectal findings with touch diagrams, residual urine, hemogram, serum phosphatase and lactic dehydrogenase (LDH), sedimentation rate, urinary sediment, urine and prostatic secretion cultures and antibiograms and urography. Prostatic secretion was obtained through massage of the prostate.

In several selected instances cystometry, transrectal prostatic biopsy and cysto-urethroscopy were performed. After this evaluation all patients with present urologic abnormalities or infections were excluded from the study and treated following standard urological concepts. The other patients, ten in total, which had received four days of sulfatherapy during the urological manipulations were treated with vitamins for a total period of six weeks. After this period a new urinesediment and urineculture was obtained. When these results were negative and when the syndrome of chronic prostatitis, <<a contradictio in terminis in this case>> was still present, Cernitin therapy was started. Four tablets were given in the morning for a total of twelve weeks to seven patients. After six weeks and at the end of the therapy the prostate was again massaged. Where prostatic secretion could be obtained total protein, LDH and acid phosphatase were determined and compared to similar determinations in the serum. Pherograms of protein and the isozymes of LDH and acid phosphatase were also determined. The total LDH and phosphatase were determed by the procedure of Berger and Broida [7] and Sigma technique [8] respectively. Total protein was determined by the biuret method [9]. The protein and enzyme pherograms were carried out according to a microelctrophoretic technique previously described [10] with modifications for the isozymes of LDH [11] and acid phosphatase [12]. The repeated touch diagram of the prostate attempted to define size, consistency, sensitivity and discernible longitudinal sulcus [13]. This rectal examination and massage in order to obtain prostatic fluid, executed after voiding, to clear the urethra, was the only form of treatment besides extract. Moderate restriction of alcohol was also advised.

A second group of five patients hospitalized for cerebral commotion was utilized as a control group to the remaining seven patients.

Results

In the group of seven patients with a syndrome compatible with chronic prostatitis but where no evidence of infection was detected, the following data were obtained.

The mean age was 36 (22-44). Slight urinary problems were present in each instance which was mainly the reason for their reference. These included frequency (4), urgency (4), hesitation (2), discomfort when urinating (7). None of them complained of urethral discharge. Three of them complained of loss of sexual desire and four had regular pain in one of the testicles, groin, or perineum. Five of them had some signs of neuropsychiatric irritability including anxiety, nervousness, and fatigue. All laboratory studies were normal in the seven patients including serum and acid phosphatase and LDH. The serum LDH isozymes were normal in each sample. The prostatic secretion obtained in five patients and which could only be collected in three cases after receiving therapy, was colorless in all instances. Acidity, total protein, total acid phosphatase, and total LDH determined in nine instances, are shown in table I. Quantitated pherograms of protein, LDH and acid phosphatase (Fig. 1, 2, 3) from these samples are shown in table II.

The average size of the touch diagram exceeded the normal size (2 a 3 cm wide, 2.5 cm long and 2 cm thick at the heaviest point) in five out of seven patients combined with softer consistency and tenderness in at least one out of three occasions of rectal examination. Transrectal biopsy of the prostate performed in two instances revealed fibrosis in both and lymphocytic infiltration in one occasion.

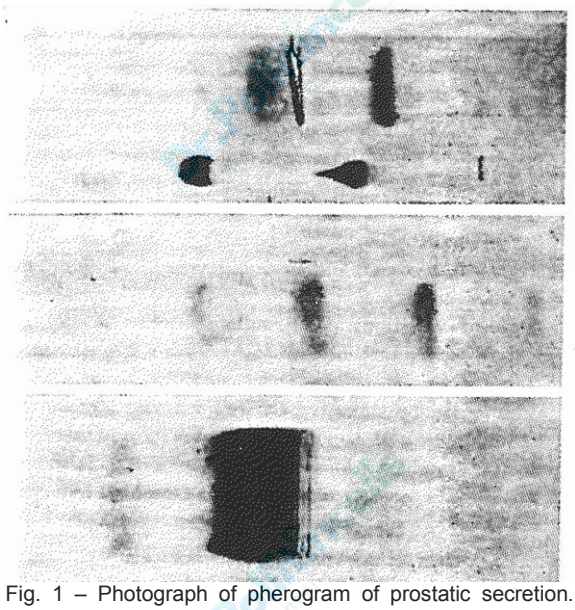

Fig. 1 – Photograph of pherogram of prostatic secretion. Three main fractions are clearly visible.
Fig. 2 – Photograph of LDH enzymogram of prostatic secretion. Five fractions are visible with a predominance of the middle fractions.
Fig. 3 – Photograph of acid phosphatase activity after electrophoretic separation by Gomori technique. Two fractions are present. The fraction to the left is albumin visualized by precipitation.

Following therapy, improvements of symptoms occurred in all seven patients. Therapy was discontinued in three of them. The other four still admitted slight abnormalities on close questioning and were kept on continuous therapy. In two out of three patients the sexual desire improved with disappearance of the symptoms. In the control group of five patients all laboratory investigations were normal. Rectal massage provided only two instances enough fluid for examination. The laboratory results obtained in these patients are presented in table I and II.

Discussion

A bacterial chronic prostatitis is a clinical syndrome which is vaguely defined, comprising a variable set of characteristic symptoms and findings on rectal examination of the prostate. Its only objective evidence is the histological aspect of deformed acini by an excess of fibromuscular

TABLE I

Values of total LDH, acid phosphatase and total protein in serum and prostatic secretion in patients with chronic prostatitis syndrome, * after six weeks of treatment, ** after twelve weeks of treatment and in a control series. Acidity of prostatic secretion is added in the last column.

Patients	Total LDH		Acid phosphatase		Total proteins		Acidity (Prostatic secretion)
	BB	Units	BB	Units	g %	g %	
R.T.	240	7.400	0.63	2.000	7.2	0.8	6.5
	—	*8.600	—	1.600	—	0.9	6.5
	—	**7.800	—	1.900	—	1.3	6.8
W.V.	320	9.200	0.53	1.600	6.8	1.5	6.7
	—	*6.800	—	1.800	—	0.8	6.5
M.H.	220	4.250	0.45	800	7.5	3.6	6.4
F.F.	200	6.700	0.53	1.750	7.1	1.8	6.2
	—	*7.200	—	1.900	—	1.1	6.5
M.F.	300	5.700	0.20	1.800	6.7	0.9	6.6
Controls							
L.P.	320	6.300	0.56	1.600	7.6	0.9	6.3
J.W.	180	8.250	0.49	1.500	6.8	2.4	6.5
A.P.	140	4.800	0.32	2.400	7.1	1.3	6.6

TABLE II

Representative example of quantitated electrophoretic study of prostatic secretion of one patient (W.V.)

Proteins	Fraction I	Fraction II	Fraction III
	15 %	38 %	47 %

LDH Isozymes	I	II	III	IV	V
	7.26 %	28.30 %	35.37 %	22.94 %	6.13 %

Acid Phosphatase	Fraction I	Fraction II
	86 %	14 %

stroma. This feature however is difficult to assess in a small surgical specimen which excludes the prostatic biopsy from the normal clinical evaluation of these patients. The aetiology is unknown and hypothesis range from psychomatic and autoimmune diseases. Therapy of course is not well defined and various measures including repeated prostatic massage to verbalization of symptoms have all been advocated [3]. A new form of treatment was studied by Leander, G. [14] and Jönson, G. [14] consisting of the oral administration of an extract of pollen, Cernitine, with no bacteriostatic or bacteriocidal effect *in vitro* and mainly consisting of amino-acids, vitamins, and unknown steroids. Therapeutic relief was obtained in a large variety of patients with chronic prostatitis including bacterial and abacterial cases. These results can be compared to the symptomatic relief by amino-acid therapy in benign prostatic hypertrophy as reported by Damrau [15].

A successful clinical result was obtained with Cernitine in a group of patients with abacterial prostatitis. It should be noted however that the extensive questioning and investigation in these cases might already relief some of these patients from their symptoms [16] and larger series will have to prove any statistical therapeutic effect of Cernitin against placebo. It can be conceived that Cernitin may have similar symptomatic relief effect in cases of true inflammatory prostatitis in combination with adequate chemotherapy. No adverse or side effects were noted in any patient. Attempts were made to determine biochemical parameters for the clinical diagnosis of chronic prostatitis by the determination of total serum LDH and acid phosphatase, serum LDH isozymes and acidity, total protein, total LDH, acid phosphatase and the pherogram of the proteins and the isozymes of LDH and acid phosphatase in the prostatic secretion as compared to a control group. These attempts were futile as shown in table I and II.

It showed also that no substantial difference occurred in any of these parameters after Cernitine therapy.

However, several interesting observations could be made concerning the results of the prostatic secretion. All obtained specimen had an acid reaction in contradiction to reports in the literature [17] where alkalinity of the prostatic secretion in described as a regular observation in chronic prostatitis. The total protein content of the prostatic secretion ranged between 0.89 mg percent to 3.6 mg% which are somewhat higher than the figures of Mann [18]. Electrophoretic separation of these proteins provided an identical pherogram both in diseased and control patients with three main fractions (Fig. 1). These fractions have been earlier described by Nylander [19]. No significant variations were noted in these fractions between the two groups as compared to previous reports of Soanes [20, 21]. This may be due to the absence of infection in these experiments since leukocytes or bacterial contamination may be responsible for the alteration of the protein spectrum in these reports. The total LDH activity and acid phosphatase activity were marked in both groups and can be compared to the recently provided figures of Grayhack (22). The activity of LDH isozymes was mostly divided between the three middle fractions (Fig. 2). Five fractions were present in every instance. No relation of any particular enzymatic shift could be noted in relation to age, disease or therapy. The acid phosphatase of the prostatic secretion was composed of several fractions. We were able to obtain two fractions (Fig 3) in three instances, one main fraction in the a region, one smaller fraction in the b region. This phenomenon was already reported by Estborn [23] but received no further attention. Further investigation seems in order to study this duplicity of phosphatase in relation to the importance of this enzyme in clinical urology.

Conclusions

Seven patients with clinical syndrome of abacterial chronic prostatitis were treated with Cernitine. Subjectif relief was obtained in all cases. Statistical evaluation by double blind studies is necessary for definite evaluation. Attempts for determination of biochemical parameters in this disease regarding protein, LDH and acid phosphatase determinations were completely negative.

Summary

Seven patients suffering from the clinical syndrome of <<abacterial chronic prostatitis>> according to their symptoms and rectal examination were treated with Cernitin (Cernilton, AB Cernelle, Sweden) for twelve weeks. Relief of symptoms was complete in three marked in four. Further experiments for statistical evaluations are mandatory.

The study of protein, lactic dehydrogenase, and acid phosphatase in serum and prostatic secretion established no parameters for diagnostic or therapeutic evaluation.

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Clinical effect of Cernilton in chronic prostatitis

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Twenty-five patients with chronic prostatitis were given Cernilton tablets. Improvement of subjective symptoms and objective findings was noted in 96.0% and 76.0% of the cases. Sonographic findings in the prostate showed 33-100% improvement in four objective items. No side effects were observed in any case after Cernilton medication. Cernilton was judged to be an effective drug for chronic prostatitis

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Clinical Evaluation of Cernilton in Adenoma of the Prostate

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Frequently the urologist is confronted with patients suffering from adenoma of the prostate who, for certain reasons, cannot in the immediate future be submitted to any sort of surgical treatment.

A significant number of such cases having been confirmed in our Urology Service at the Italian Hospital in Buenos Aires, it was decided to determine what effect CERNITIN exerted in this type of condition.

CERNITIN is a microbiological extract of dried pollen obtained under optimum conditions of standardization.

This extract contains various active principles: 21 difference amino-acids, lipids, saccharides, phospholipids, a minute percentage of oestrogens, enzymes, DNA, RNA, vitamins (not vitamin B_{12}) and minerals.

As long ago as 1960, Ask-Upmark of Sweden was reporting that CERNITIN was effective in the treatment of prostatitis. The mode of action of CERNITIN has not yet been determined, but what can be considered proven is a decongestant effect with a marked specific affinity for prostatic tissue, and a capacity to improve defense mechanisms against infection and inflammation in general.

Although the mode of action of CERNITIN is not yet clear, the following are, briefly, some of the theories and investigations which have taken place, which will surely in the future help to elucidate it:

1. From experiments conducted by Sir Alic-Isaac it appears that CERNITIN may be able to augment the production of INTERFERON (a protein produced by the cells for defense against viruses.)
2. Cernitin may have a stimulant effect upon the THYMUS, and it is already known that this gland plays an important role in the body's defences against infections.
3. Finally we report an article in Acta Chemica Scandinavica Vol. 24, 1970 – pp.3672, in which Dr. Kvanta mentions the fact that he has proved that CERNITIN has an inactivating effect upon STREPTOLYSIN (a toxin produced by streptococci).

From all these observations and facts it would appear that CERNITIN may take effect by means of a combination of different modes of action.

Materials and methods

100 patients were included in this investigation divided into 4 Groups (see diagram) according to their symptomatology.

Group 1: Patients who presented with minimal prostatism; that is, with commencing dysuria, slight polyuria, nocturia once or twice, clear abacterial urine and no residual urine.

Rectal examination revealed a prostate normal as to size, shape and consistency.

Group 2: Patients who presented with prostatism and increased dysuria and polyuria, both by day and by night, clear urine, residual urine of 60 c. c., and slight bacteriuria

Rectal examination: enlarged prostate with the features of an adenoma.

Group 3: Patients who present with marked dysuria, burning on micturition, a feeling of hypogastric fullness, nocturia, cloudy urine, bacteriuria of more than 150.000 colonies per millilitre and residual urine of 150 to 250 c.c.

Rectal examination: enlarged prostate with loss of median sulcus, smooth surface and elastic consistency.

Group 4: Patients consist of some with a large volume of residual urine and others with a total acute retention of urine, with pyuric cloudy urine, sometimes blood-stained. Their general condition is only fair.

The age of the 100 patients varied between 55 and 70 years.

Dosage and Results

The most frequently-used dose of Cernilton was 6 tablets daily, taken before meals (Giúdice), or else 3 or 4 tablets daily taken in the morning (Toro) both over a prolonged period.

Rearing in mind the symptomatology, urinalysis and the absence or presence of residual urine (Groups 1 and 2) we preferred to prescribe 4 tablets daily for 3 weeks, followed by a pause of 10 days and then continuing up to a total dosage of 100 tablets.

In this group of 40 patients we noticed, within a few days of starting the treatment, an improvement in their symptoms, and their total disappearance after the full dosage mentioned had been taken.

With regard to Groups 3 and 4, the treatment followed was 6 to 8 tablets a day up to a total of 100. We also prescribed antibiotics after appropriate urine culture. In this group of 60 patients, within a few days of the commencement of treatment, we observed a great improvement in the symptoms, mainly in frequency and nocturia.

10% of these patients showed no response to the treatment given.

Secondary Effects

In all the cases treated we encountered no allergic reactions, gastritis or hepatic intolerance. Some patients complained of abdominal distension, which improved with reduction of dosage. These side-effects were insignificant, and did not modify the final results.

Conclusions

Cernilton appears to have a decongestant and antiphlogistic effect upon the prostate gland, for which reason the subjective and objective symptomatology disappears or improves, which fact persuades us to continue with this treatment. The advantages of this preparation lie in its harmlessness and the possibility of carrying out prolonged courses of treatment.

	Group 1	Group 2	Group 3	Group 4
Number of cases	15	25	38	22
Average age	55-70	55-70	55-70	55-70
Urinalysis	Abacterial	Abacterial	Urinary infection	Urinary infection more than 100.00 colonies
Symptoms	Commencing dysuria Polyuria		Dysuria, polyuria, burning on micturition, nocturia	Incomplete or complete retention or urine. Hematolpyuria

Note: We are using Cernilton in acute and chronic prostato-cystitis, chronic urethritis and the cystitis syndrome in the female.

In view of the few cases so far treated, we have not yet reached a definitive conclusion.

Clinical evaluation of Cernilton in benign prostatic hypertrophy

Hayashi J, Mitsui H, Yamakawa G, Suga A, Kai A, Shimabukuro T, Yanagi K, Fujisawa S, Takihara H, Kaneda Y, et al

Twenty patients with benign prostatic hypertrophy were treated with Cernilton, 6 tablets a day for an average of 13.2 weeks. Subjective effectiveness was observed in the improvement of sense of residual urine (92%), retardation (86%), night frequency (85%), strain on urination (56%), protraction (53%) and forceless urinary stream (53%). The overall subjective effectiveness was 80% of patients, and the overall objective effectiveness was 54% of patients. Night frequency, residual urine volume and tidal urine volume were improved significantly. The overall effectiveness was 80%. No side effects were observed.

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Clinical evaluation of Cernilton in chronic prostatitis

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1. Introduction

Chronic prostatitis and spermatocytosis are known to have long persistence of subjective symptoms. The diseases are not fully defined yet, and it is speculated that many of the cases classified as falling in these diseases are of primary psychosomatic origin.

As early as 1960 Ask-Upmark of Sweden reported that a pollen preparation was effective in the treatment of prostatitis. Though its mechanism of action is not known, the preparation is considered to prevent growth of bacteria and exert roborant and desensitizing actions.

The purpose of this trial was to study the effectiveness of Cernilton, a pollen preparation used for treatment of prostatitis in Europe, by a double blind test using placebos.

2. Composition

Pollen species used in Cernilton are:

Timothy	26 %
Maize	26 %
Rye	40 %
Pine	5 %
Orchard grass	2 %
Alder	1 %

One Cernilton tablet contains:

Cernitin GBX	3 mg
Cernitin T60	60 mg
Calcium gluconate	70 mg
Lactose	70 mg
Calcium hydrogen phosphate	140 mg
Alginic acid	10 mg
Potato starch	20 mg
Pigment	3 mg
Talc	20 mg

One placebo contains:

Lactose	180 mg
Avicel (microcrystal cellulose)	60 mg
Dextrin	152 mg
Carbon wax	20 mg
Pigment	3 mg

3. Subjects and Method of Administration

The subjects were selected from among the patients with prostatitis and non-gonorrheal urethritis visiting the Outpatient Clinic. Those with acute inflammatory symptoms were excluded.

Administration was made once daily, 4 tablets in the morning. Patients with even-numbered dates of birth were given Cernilton while those with odd-numbered dates were given placebos. Administration was made in such a way that neither patients nor physicians would know which was given.

4. Grading System and Criteria of Evaluation

A. Grading System

1. Subjective Symptoms
   Disappearance……...2 points
   Some improvement……1 point

2. Number of leukocytes in urine after massage of prostate
   Less than 15 in one visual field (magnified 100 times)……normal
   Decrease from above 15 to normal…….2 points
   Decrease by more than 15……1 point

3. Number of bacteria in urine after massage of prostate
   Disappearance…….. 2 points
   Number decreased……1 point

4. Other findings
Decreased hardness of prostate……1 point
Improvement of leukocytosis…….1 point
Disappearance of comma shreds….1 point

B. Criteria of Evaluation
Effective: Cases with a total of 3 or more points or with normal findings in all items.
Slightly Effective: Cases with a total of 1-2 points.
Ineffective: Cases with no points

5. Therapeutic results

Cernilton was given in 17 cases. Of these, the clinical courses were followed in 14 cases, and the results were: “effective” in 10 cases, “slightly effective” in 3 cases, and “ineffective” in 1 case. Placebos, on the other hand, were given in 21 cases, and the clinical courses were followed in 16 cases, with “effective” in 7 cases and “ineffective” in 9 cases.

In subjective symptoms, disappearance was noted in 10 cases and subsidence in 4 cases in the Cernilton group, with all cases showing some sort of improvement. In the placebo group, disappearance was seen in 5 cases, subsidence in 2 cases, no-change in 7 cases, and exacerbation in 2 cases. The results show a great difference, but it must be emphasized that objective evaluation of subjective symptoms is all but impossible.

The findings in urinary deposits after the massage of the prostate were, in the Cernilton group, normalization in 5 cases, improvement in 1 case, persistence of abnormal state in 2 cases, exacerbation in 1 case, and persistence of normal state in 4 cases; result was unknown in one case because the urine was not examined. In the placebo group, normalization was noted in 3 cases, improvement in 2 cases, persistence of abnormal state in 3 cases, and persistence of normal state in 8 cases; exacerbation was not noted.

The findings in bacteria in the urine after the massage of the prostate were: disappearance in 3 cases, no-change in 2, and persistence of normal state in 9 in the Cernilton group and disappearance in 1 case, no-change in 2, reappearance in 1, and persistence of normal state in 12 in the placebo group.

6. Cases

Several cases are illustrated below.

Case 1. 26. Effective
Chief Complaints: heavy pressure sensation in the lower abdomen and abnormal sensation in the penis.

Findings and Treatment:
March 24: Prostate normal on palpation. No tenderness. Deposits of urine examined after massage of prostate. RBC8- 10/1GF. WBC slightly increased/ 1GF. Epithelial cells 3-4/ 1GF. Culture of bacteria, negative. Peripheral blood examined. WBC 5300. Hemogram, slight shift to the left. Administration of Cernilton started.

April 1: 32 tabs of Cernilton given in 8 days with persistence of chief complaints. Medication continued.

April 12: 60 tabs of Cernilton given in 15 days. Abnormal sensation in the penis disappeared (29 days).

May 21: 116 tabs of Cernilton given. Heavy pressure sensation in the lower abdomen subsided. No tenderness. Deposits of urine reexamined after massage of prostate. RBC not found. WBC 8-10/1 GF. Epithelial cells 5 6/1 GF. Culture of bacteria, negative. No side-effects.

Remarks: The chief complaints persisted for a long time, but urinary findings were markedly improved.

Case 2. 23. Effective.
Chief complaints: Initial voiding pain.

Findings and Treatment:
March 24: Prostate normal in size and

hardness, but tenderness present. Examination of urinary deposits after massage of prostate: RBC 10-13/ 1 GF, WBC 20-30/ 1GF, cocci positive.

April 2: Chief complaints, left untreated for a week, persisted without improvement. Administration of Cernilton started.

May 31: 56 tabs of Cernilton given in 14 days. Chief complaints subsided on the 6th day. Prostate normal. Tenderness disappeared. Examination of urinary deposits after massage of prostate: RBC 1/2 – 3GF, WBC 5-6/ 1GF, culture of bacteria negative.

June 14: 112 tabs of Cernilton given in 14 days. Medication discontinued.

Remarks: This is a case in which both subjective and objective symptoms have disappeared.

Case 3. 27. Effective.
Chief complaints: Sense of urinary retention.

Findings and Treatment:
March 25: Findings in urine and prostate both within normal limits. Slight tenderness seen. Administration started.

April 1: 28 tabs of Cernilton given in 7 days without improvement of chief complaint. Urinary findings after massage of prostate: RBC (-), WBC 5-8/ 1GF, epithelial cells 1/1 – 2GF, culture of bacteria negative.

April 15: 140 tabs of Cernilton administered in 35 days, with improvement of chief complaint.

April 28: 196 tabs of Cernilton in 49 days. Chief compliant disappeared completely. Medication withdrawn. No side-effects.

Remarks: This is a case in which only subjective symptoms were found. In all three cases, the initial effect appears to have taken place after administration of more than 10 days.

Case 9. 23. Cernilton effective, placebo ineffective.

Chief complaint: Sense of urinary retention.

Findings and Treatment:
Dec. 3: Induration found in right lower part of prostate. E.coli 56540/ ml revealed after massage. Urocydal and Wintomylon given.

March 28: Anti-inflammatory agents and antibiotics had no effect, though given for 4 months. Slight voiding pain appeared. Induration still noted in the prostate. Pseudomonas 5600/ ml noted in urine after massage of prostate. Examination of peripheral blood: WBC 5000, hemogram no shift to the left. Administration of placebo started to observe the course.

April 11: 56 placebo tablets given in 14 days. Total voiding pain somewhat exacerbated.

May 23: 168 placebo tablets given in 42 days. Total voiding pain subsided but sense of urinary retention persisted. Induration noted in prostate. Examination of urinary deposits after massage of prostate: RBC(-), WBC 10 11/ 1FG, St. epidermis 6 160/ml. Administration of Cernilton started.

June 13: 84 tablets of Cernilton administered in 21 days. Voiding pain disappeared and sense of retention subsided.

July 4: 168 tablets of Cernilton in 42 days. Subjective symptoms all disappeared and induration not palpable.

Remarks: This is a case which has been completely cured with Cernilton. The patient was not informed of the change of drugs during the treatment.

Case 10. 47. Cernilton effective, placebo ineffective.

Chief Complaint: Dull pain in the perineum.

Findings and Treatment:
March 17: Prostate somewhat enlarged with

tenderness. Examination of urinary deposits after massage of prostate: RBC (-), WBC 1 2/ 1GF, epithelial cells 1/ 1GF, culture of bacteria negative. Administration of Cernilton started.

April 4: 68 tabs of Cernilton administered in 17 days. Chief complaint and tenderness disappeared and prostate became normal in size. Medication withdrawn.

April 27: Chief complaint recurred. Prostate normal in size. Examination of urinary deposits after massage of prostate: RBC (-), WBC 1-2/ 1GF, bacteria negative. Administration of placebo started.

May 13: 56 placebo tablets given in 14 days with no improvement of chief complaint. Placebo withdrawn.

7. Side Effects

No complaints compatible with side-effects were noted among the cases studied (Cernilton group 17 cases, placebo group 21 cases). Neither were abnormal objective symptoms noted, in the cases where clinical courses were followed.

Reportedly, Cernilton must be administered in the morning as it produces a caffeine-like action. This, however, was observed in none of our cases. Case 12 mistakenly took the drug in the afternoon for some days, but he said he did not suffer from insomnia at all. One of the authors, too, had 4 tablets at 10 o' clock every night for 5 days; and he did not experience excitement or insomnia, either. This may be a matter of individual susceptibility. Yet, our impression is that the drug is not necessarily one to be taken in the morning.

8. Discussion

There are no definite criteria for diagnosis of prostatitis at present. On the contrary, the presence of chronic prostatitis itself is sometimes doubted. Generally, positive finding in the culture of bacteria and increase in the number of leukocytes in urinary deposits after the massage of the prostate, are the criteria used for diagnosis of chronic prostatitis, through diagnosis based solely on tenderness has also been employed since old times.

On the other hand, it comes gradually to be known that chronic prostatitis is often attributable to allergy. It was Stewart and Wray who first described pathological changes of allergic prostatitis, and many cases of eosinophilic granulomatous prostatitis have since been reported. In some cases asthma is claimed associated. Since Cernilton has the actions of desensitization and increasing physical resistance, as well as bacterial and bacteriostatic actions, it can be expected to exert considerable effects on pathological changes of allergic prostatitis, granting that the mechanism of action is not precisely known.

The cases of prostatitis selected for the present study were mainly diagnosed on the basis of subjective symptoms and findings on palpation. Thus, many cases showed no abnormal findings in the secretion of the prostate or in the urine. Care, however, was taken to select only such cases as would comply with the diagnostic criteria laid down by Campbell in his text-book. Naturally, some cases of psychosomatic origin were included. On the other hand, the cases where placebos proved effective were not necessarily of psychosomatic origin. A good number of them can be considered to have healed spontaneously. Yet the fact that the rate of effectiveness was higher than 90% in Cernilton group as against below 50% in the placebo group, suggests that the there must have been cases where Cernilton was indicated. This is supported by the significant difference of effects registered in the two cases where both Cernilton and placebos were employed and further by the fact that improvement of subjective symptoms was more difficult to obtain in the placebo group.

Cernilton was administered over periods ranging from 10 to 56 days, but no side-effects were noted. It is considered that a longer period of administration is possible. The onset of effect was rather slow, taking place in 7-10 days. Therefore, administration should at least be maintained for

two weeks. Recurrence of symptoms was noted in two cases after withdrawal of the drug. Since the drug is experimentally confirmed to cause little toxicity, maintenance of medication even after disappearance of symptoms is advisable.

More describes that chronic prostatitis is found in more than 35% of male adults over the age of 35, while, according to another report, it is found in 85% of male adults over the age of 30. The participating factors are trauma, drinking and car-driving, and the incidence may even increase in future. In most cases bacteria are either totally absent or only sparsely detected, and thus positive use of antibiotics is not justified. On the other hand, long-term administration of anti-inflammatory drugs does not always result in improvement of symptoms. In this sense, the pollen preparation Cernilton points to a new approach. It may not be effective in all cases of chronic prostatitis, but it certainly can be effective in many such cases, especially those of allergic origin. For treatment of acute prostatitis, however, it is desirable to use antibiotics since Cernilton does not possess potent bactericidal action. Finally, it is reported that the drug is to be carefully administered to patients allergic to pollen.

Conclusions

Cernilton and placebos have been used for treatment of chronic prostatitis and following results obtained:

1. Of a total of 14 cases in the Cernilton group, 10 cases were effective and 3 cases slightly effective.
2. Results obtained in the placebo group were much less favourable, effective in 7 cases and ineffective in 9 cases.
3. Side-effects were observed in none of the 38 cases studied.

Table 1. Cernilton Group

No.	Age	Dosage tab. × time	Adm. Days	Combined Drugs	Effects	Subjective symptoms	After Massage of Prostate: Urinary findings	After Massage of Prostate: Bacteria in Urine	Remarks
1.	26	4 × 1	43	—	Effective	+ + → +	+ + → —	—	Tenderness of prostate disappeared.
2.	23	,,	28	—	,,	+ + → —	+	+ → —	,,
3.	27	,,	49	—	,,	+ + → —	—	—	Same patient as No. 9 in Table 2.
4.	33	,,	10	—	,,	+ + → —	+ → ±	+ → —	
5.	38	,,	21	—	,,	+ + → —	—	—	
6.	44	,,	56	Uracydal 21 days before Cernilton	,,	+ + → —	+ + → —	—	
7.	32	,,	42	—	,,	+ + → —	—	—	Recurred after withdrawal.
8.	34	4 × 1 2 × 1	7 28	—	,,	+ + → —	—	—	
9.	23	4 × 1	42	Placebos 42 days before Cernilton	,,	+ + → ±	+ → —	—	Same patient as No. 9 in Table 2.
10.	47	,,	24	—	,,	+ + → —	+ → —	—	Later changed to placebo same patient as No. 10 in Table 2.
11.	57	,,	21	—	Slightly effective	+ + → —	?	—	Ureteral calculus subsequently found and treatment changed.
12.	61	,,	56	Panvitan 3 tabs daily	,,	+ + → —	+ +	+	Induration of prostate disappeared.
13.	52	,,	10	Antibiotics	,,	+ + → +	+ → —	+	Hypertrophy of prostate associated.
14.	37	,,	14	—	Ineffective	+ + → +	+ → + +	—	Same patient as No. 16 in Table 2.

Table 2. Placebo Group

No.	Age	Dosage tab. × time	Days Adm.	Combined Drugs	Effects	Subjective symptoms	After Massage of Prostate: Urinary findings	After Massage of Prostate: Bacteria in Urine	Remarks
1.	38	4 × 1	49	—	Effective	+ + → +	+ → —	+ → —	
2.	60	,,	28	—	,,	+ + → —	+ + → +	—	
3.	53	,,	7	—	,,	+ + → —	+ + → +	—	
4.	31	,,	14	—	,,	+ + → —	—	—	
5.	33	,,	35	—	,,	+ + → —	+ → —	—	
6.	41	,,	21	—	,,	+ + → —	—	—	
7.	25	,,	42	—	,,	+ + → —	+ + → —	—	
8.	27	,,	27	—	Ineffective	+ +	—	—	Vaginal trichomonas found transitorily in urine.
9.	23	,,	42	—	,,	+ +	+	+	Same patient as No. 9 in Table 1. Subsequently changed to Cernilton.
10.	47	,,	14	Cernilton 24 days before placebo	,,	— — → +	— —		Same patient as No. 10 in Table 1.
11.	21	,,	28	—	,,	+ +	—	—	
12.	29	,,	14	—	,,	+ +	—	—	
13.	42	,,	7	—	,,	+ +	—	— → +	
14.	60	,,	28	—	,,	+ +	+	—	
15.	33	,,	21	—	,,	+ +	+	—	
16.	52	,,	10	—	,,	+ → + +	—	+	Same patient as No. 16 in Table 1.

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前立腺肥大症に対するセルニルトンの臨床効果

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CLINICAL EVALUATION OF CERNILTON IN THE TREATMENT OF THE BENIGN PROSTATIC HYPERTROPHY

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Cernilton was given clinically to 30 patients with benign prostatic hypertrophy. Cernilton was given orally at least for 12 weeks at a daily dose of 6 tablets in three divided doses. The overall clinical efficacy on subjective symptoms was 80%, and that on objective signs, 43%. During the administration period of Cernilton, no serious untoward effects were observed in either the clinical or laboratory findings. It is, therefore, suggested that, from the clinical point of view, Cernilton is a useful and safe drug in the treatment of benign prostatic hypertrophy.

Key words: Benign prostatic hypertrophy, Cernilton

緒　　言

前立腺肥大症は，ごくありふれた泌尿器科領域の疾患のひとつであり，最近の高齢化社会への移行とあいまって，増加の傾向がいちじるしい．

本症の主症状は，腺腫ならびに間質組織の良性増殖により惹起される排尿困難などであり，その成因については内分泌学的因子―とくに Androgen ―の関与が定説化している[1]が，その病態についての詳細はあきらかではない．本症の治療は，これまで外科的手術療法が主体であったが，最近保存的療法も薬剤の開発にともない，大きな位置を占めている．われわれは，そのような薬剤のなかで，非ホルモン剤であるセルニルトンを前立腺肥大症患者に投与し，投与前後における自覚的症状ならびに他覚的所見の変化について観察した．セルニルトンは，8種類の植物花粉より抽出したエキスを含有する薬剤で，1錠中にセルニチンポーレンエキス 63 mg を含有する．その薬理学的機作の詳細はあきらかではないが，排尿促進作用，抗浮腫作用，消炎作用を有する[2,3]と報告されている．以下に前立腺肥大症患者を対象としてセルニルトンを投与して得た臨床成績について報告する．

対象ならびに方法

1．対象

対象とした患者は，当科外来を受診し，前立腺肥大症と診断されたもの30名である．排尿障害を有するものを対象とし，尿道狭窄，膀胱頸部硬化症，ならびに尿路感染症を有するものは除外した．

2．用法・用量

Table 1.

症例No.	年齢(歳)	Güyon分類	主訴	病歴期間	効果判定までの投与期間(週)	自覚的症状 夜間頻尿 前	夜間頻尿 後	遷延性排尿 前	遷延性排尿 後	尋延性排尿 前	尋延性排尿 後	排尿時のいきみ 前	排尿時のいきみ 後	尿線の勢い 前	尿線の勢い 後	残尿感 前	残尿感 後	患者の印象	判定
1	73	I	頻尿	V	4	2	1	2	2	2	2	2	2	1	1	1	1	4	4
2	68	I	排尿困難	V	12	0	0	2	2	2	2	2	2	2	2	2	2	4	4
3	62	I	尿道不快感，残尿感	i	8	3	4	2	1	1	1	1	1	1	1	1	1	4	4
4	85	II	排尿困難	VI(5年)	6	4	3	2	1	3	2	3	2	2	2	3	1	2	2
5	68	II	残尿感	VI(5年10月)	15	0	0	1	1	2	1	1	1	2	1	2	1	3	3
6	74	I	頻尿	V	7	4	2	2	2	2	1	2	2	1	1	1	1	3	3
7	75	II	排尿困難	V	4	2	3	1	1	2	1	1	1	2	1	2	1	2	2
8	69	II	残尿感	VI(−)	4	4	2	2	1	2	2	2	1	2	1	2	1	2	2
9	54	I	頻尿	IV	20	2	1	2	1	2	2	2	1	2	1	1	1	2	2
10	53	I	頻尿	IV	8	2	1	2	1	2	1	2	1	2	1	1	1	2	2
11	72	II	排尿困難	V	4	2	2	2	1	2	2	2	2	2	2	2	1	3	3
12	76	I	夜間頻尿	V	4	12	7〜8	2	1	2	1	2	2	2	1	1	1	2	2
13	66	II	排尿困難 尿閉	I	5	2	1	2	2	2	1	2	2	2	2	3	2	2	2
14	64	I	排尿困難	IV	8	4〜5	3〜2	3	2	3	2	3	2	3	2	3	1	3	3
15	62	II	排尿困難	III	4	2〜3	4	2	2	2	2	1	1	2	2	1	1	4	4
16	64	I	頻尿	IV	8	4〜5	1	3	2	2	2	3	2	2	2	3	1	2	2
17	60	II	排尿困難	IV	2	4	2	2	2	2	1	1	1	1	1	3	2	3	3
18	71	II	排尿困難	V	20	2	1	3	2	2	2	3	2	2	2	2	2	4	4
19	68	II	排尿困難 頻尿	V	8	3〜4	2〜3	2	1	2	1	2	1	2	1	1	1	1	1
20	64	II	頻尿 残尿感	II	4	3	2	2	1	3	2	2	1	2	2	3	1	2	2
21	54	II	排尿困難	—	8	3〜4	—	2	1	3	2	2	1	2	2	2	1	2	2
22	67	II	排尿困難，頻尿	I	8	4〜5	1〜2	2	1	2	1	2	1	2	1	3	1	1	1
23	76	II	排尿困難，頻尿，残尿感	IV	8	5〜6	3〜4	3	2	3	2	3	2	3	2	3	1	2	2
24	78	III	尿閉	—	12	尿閉	3〜4	尿閉	2	尿閉	2	尿閉	2	尿閉	2	尿閉	2	2	2
25	73	II	排尿困難 夜間頻尿	VI(5年)	8	1	3	2	2	2	2	2	2	2	2	2	1	4	4
26	64	I	排尿困難，残尿感，夜間頻尿	VI(2年2月)	12	3	2	2	1	2	2	2	2	2	2	2	2	3	3
27	67	II	排尿困難	VI(2年1月)	12	4	2	2	1	2	2	2	1	2	2	2	1	3	3
28	53	II	排尿困難，残尿感	IV	6	バルーン留置	0	3	2	3	2	3	2	2	2	3	1	2	2
29	72	I	排尿困難	VI(2年1月)	8	0	1	2	1	2	1	2	1	2	1	2	1	3	3
30	47	II	排尿困難	IV	8	0	1	3	1	3	2	3	2	3	2	3	1	1	1

Table 2.

症例 No.	年齢(歳)	Güyon 分類	主訴	病歴期間	効果判定までの投与期間(週)	他覚的所見 直腸内触診 前	直腸内触診 後	残尿量(mℓ) 前	残尿量(mℓ) 後	U 前立腺部延長 前	U 前立腺部延長 後	U 膀胱内突出 前	U 膀胱内突出 後	C Thumann法 A(cm) 前	C Thumann法 A(cm) 後	G Thumann法 B(cm) 前	G Thumann法 B(cm) 後	G Thumann法 前立腺重量(g) 前	G Thumann法 前立腺重量(g) 後	判定	副作用	総合判定
1	73	I	頻尿	V	4	2	2	0	0	1	1	1	1	4.8	4.6	4.0	4.2	21.3	21.3	4	(−)	4
2	68	I	排尿困難	V	12	2	2	0	0	2	2	2	1	5.6	5.0	4.8	4.6	35.2	27.6	3	(−)	3
3	62	I	尿道不快感，残尿感	I	8	1	1	0	0	2	1	2	1	4.2	4.0	4.0	3.8	17.2	14.8	4	(−)	4
4	85	II	排尿困難	VI(5年)	6	1	1	30	40	2	2	1	2	4.0	4.5	4.5	5.0	19.2	26.8	5	(−)	3
5	68	II	残尿感	VII(5年10月)	15	3	3	10	6	4	4	5	5	4.5	4.8	5.8	6.2	34.1	41.6	4	(−)	4
6	74	I	頻尿	V	7	1	1	0	0	2	2	2	2	3.5	3.6	3.8	4.0	12.2	13.7	4	(−)	3
7	75	II	排尿困難	V	4	3	2	60	55	4	4	4	4	4.5	4.6	5.0	5.2	26.8	29.4	4	(−)	3
8	69	II	残尿感	VI(−)	4	2	2	10	5	2	2	2	2	4.0	4.0	4.0	3.8	16.0	14.8	4	(−)	3
9	54	I	頻尿	IV	20	2	2	5	0	2	2	2	1	3.0	3.5	3.0	3.0	6.8	8.6	4	(−)	3
10	53	I	頻尿	IV	8	2	2	0	0	2	2	2	2	4.2	3.8	4.0	4.1	17.2	15.4	4	(−)	3
11	72	II	排尿困難	V	4	2	2	10	25	3	3	3	3	4.5	5.0	4.0	4.0	19.2	22.8	5	(−)	4
12	76	I	夜間頻尿	V	4	2	2	15	10	2	2	1	2	4.0	4.0	3.2	4.2	11.7	17.2	4	(−)	3
13	66	II	排尿困難，尿閉	I	5	2	3	40	30	4	4	4	4	6.0	5.5	6.0	6.0	54.0	47.5	3	(−)	2
14	64	I	排尿困難	IV	8	2	2	0	0	2	2	2	2	5.8	6.0	5.0	5.2	39.4	33.2	4	(−)	4
15	62	II	排尿困難	III	4	2	3	20	30	4	4	4	4	6.5	6.5	6.0	6.5	61.0	68.7	4	(−)	4
16	64	I	頻尿	IV	8	2	2	0	0	2	2	2	2	4.5	4.8	3.6	4.2	16.6	22.8	4	(−)	3
17	60	II	排尿困難	IV	2	1	1	0	0	1	1	1	1	3.0	3.0	3.0	3.5	6.8	8.6	4	(−)	3
18	71	II	排尿困難	V	20	2	3	60	90	2	3	3	3	5.0	5.5	4.0	4.5	22.8	31.3	5	(−)	4
19	68	II	排尿困難，頻尿	V	8	2	2	40	0											1	(−)	1
20	64	II	頻尿，残尿感	II	4	2	1	50	0											2	(−)	2
21	54	II	排尿困難	—	8	3	2	50	0	2	1	2	1							2	(−)	2
22	67	II	排尿困難，頻尿	I	8	3	2	40	0	2	1	2	1							1	(−)	1
23	76	II	排尿困難，頻尿，残尿感	IV	8	3	3	110	20	3	2	3	2							2	(−)	2
24	78	III	尿閉	—	12	3	3	尿閉	40											2	(−)	2
25	73	II	排尿困難，夜間頻尿	VI(5年)	8	2	2	35	70	2	2	2	2	6.5	6.0	6.0	6.0	61.0	54.0	4	(−)	4
26	64	I	排尿困難，残尿感，夜間頻尿	VI(2年2月)	12	2	2	40	0	2	2	2	2	5.6	5.8	5.7	5.0	45.1	39.4	3	(−)	3
27	67	II	排尿困難	VI(2年1月)	12	3	3	35	60	4	4	3	3	5.5	5.0	6.5	6.3	54.0	45.1	3	(−)	3
28	53	II	排尿困難，残尿感	IV	6	2	2	50	0	3	3	3	3	7.0	6.5	6.5	6.0	76.9	61.0	3	(−)	2
29	72	I	排尿困難	VI(2年1月)	8	2	2	0	0	2	2	2	2	3.0	3.5	4.0	4.0	10.7	13.2	3	(−)	3
30	47	II	排尿困難	IV	8	4	3	100	58	4	3	4	3	6.5	6.0	6.0	5.5	61.0	47.5	2	(−)	2

セルニルトン1回2錠を1日3回食後に経口投与した．他の薬剤は併用せず，最低12週間連続投与した．

3．判定項目ならびに判定基準

自覚的症状は，遷延性排尿困難，再延性排尿困難，排尿時のいきみ，尿線の状態，残尿感につき，その程度を3段階に分類した．そして，セルニルトン投与による自覚的症状の変化を著効から悪化までの5段階にわけた．主治医による効果判定も同様に5段階に分類した．他覚的所見については，投与前後における直腸内触診による前立腺の大きさ，残尿量，膀胱尿道造影の各項目における変化について観察した．また測定しえた症例については，尿流量測定，尿道抵抗曲線の各パラメーターの投与前後の値を比較した．これらを総合して他覚所見の改善の程度を5段階に分類した．自覚的症状と他覚的所見の改善度を合わせて総合判定をおこない，著効から無効までの4段階に分類した．以下にわれわれの得た成績につき報告する．

成　　績

1．自覚的症状に対する効果（Table 1.）

1）遷延性排尿困難に対する効果

遷延性排尿困難については，スムーズに出るを1，やや時間がかかるを2，非常に時間がかかるを3，とした．この分類により1段階以上改善したものは21例であり，2段階以上改善したものは2例であった．

2）再延性排尿困難に対する効果

再延性排尿困難については，若い時と同様であるを1，やや時間がかかるを2，非常に時間がかかるを3，とした．投与後1段階以上改善したものは18例，2段階以上改善したものは1例であった．

3）排尿時のいきみに対する効果

とくに意識しなくても普通に排尿できるを1，ときどき意識して腹に力を入れねば排尿できないを2，排尿の間いつも力まないと尿が出ないを3，とした．投与後1段階以上改善したものは17例，2段階以上の改善を示したものは1例であった．

4）尿線の状態に対する効果

尿線の状態については，若い時と変わらないを1，弧を描かずに途中で切れることがあるを2，排尿開始時から滴状であるを3，とした．投与後1段階以上改善したものは13例，2段階以上改善したものは1例であった．

5）残尿感に対する効果

残尿感については，なしを1，ややありを2，ありを3，とした．投与後1段階以上改善したものは19例，2段階以上改善したものは9例であった．

Table 3. 自覚症状に対する効果

症　　状	症例数	改善例	非改善例	悪化例	有効率(%)
遷延性排尿	28	21	7	0	75.0
再延性排尿	29	18	11	0	62.1
排尿時のいきみ	25	17	8	0	68.0
尿線の勢い	26	13	13	0	50.0
残　尿　感	22	19	3	0	86.4

Table 4. Güyon 分類有効例数（率）

Güyon分類	症例数	自覚症状判定
Ⅰ	11	8 (72.7)
Ⅱ	18	15 (83.3)
Ⅲ	1	1 (100.0)

6）夜間頻尿に対する効果

夜間頻尿について，回数のあきらかな減少を見たものは6例であった．

2．自覚的症状についての小括

自覚的症状の変化は Table 3. のとおりで，残尿感に対する効果がもっとも高く，86.4%の改善率であった．以下遷延性排尿困難に対し75%，排尿時のいきみに対し68%，再延性排尿困難に対し62.1%，尿線の状態について50%の有効率を示した．また Güyon 分類別にみた有効率はⅢ度の1例に対する 100% は除き，Ⅱ度に対し83.3%の有効率を示したのは注目されると思われる（Table 4.）．自覚的症状に対する効果判定は患者の印象では改善が80%，不変が20%であった．主治医による判定でも同様であった（Table 8.）．

3．他覚的所見に対する効果（Table 2.）

他覚的所見における判定項目として，1）直腸内触診による前立腺の大きさ，2）残尿量，3）尿道膀胱造影における前立腺膨隆部の横径（A），前立腺部尿道長（B），Thumann 法による前立腺重量，4）尿流量測定における排尿量，平均排尿量，最大排尿量，5）尿道抵抗曲線における (1)前立腺部尿道長 (2)最大尿道閉塞圧 (3)前立腺部尿道圧 ならびに6）膀胱内圧の各項目を設定し，セルニルトン投与前後における検査値の変化を検討した．

1）直腸内触診による前立腺の大きさ

触診による前立腺の大きさは，鳩卵大から鶯卵大の5段階に分類した．投与前鳩卵大は4例，小鶏卵大は18例，鶏卵大は7例，超鳩卵大は1例であった．投与後縮小を認めたものは5例であった．逆に大きくなったもの3例で，不変22例であった．

2）残尿量

投与前に残尿を認めたものは21例で，その平均残尿

量は 40.5 ml であった．投与後は平均残尿量 25.7 ml と減少を認めた．また，カテーテル留置の一応の指標と考えられる残尿量 50 ml につき，それ以上の群とそれ以下の群につき残尿量の変化を検討した．投与前残尿量が 50 ml 以上あったものは 8 例で，平均残尿量は 68.6 ml で，投与後 32.9 ml と統計学的に有意の差で減少を認めた．8 例中 3 例は投与後残尿を認めなかった（Table 7.）．

3）尿道膀胱造影

尿道膀胱造影斜位像につき　(1) 腺腫の膀胱内突出 (2)前立腺部尿道の延長　を測定項目として，1．正常，2．軽度変化，3．中等度変化，4．やや高度変化，5．高度変化，の 5 段階に分類し，セルニルトン投与前後の値を比較した．

(1)　前立腺腫の膀胱内突出

投与前の判定では，正常 4 例，軽度変化13例，中等度変化 5 例，やや高度変化 4 例，高度変化 1 例であった．投与後，軽度変化が正常に復したもの 5 例，中等度変化が軽度になったもの 1 例，やや高度変化が中等度変化になったもの 1 例であった．改善したものは合計 7 例，30.4％の改善率であった．

(2)　前立腺部尿道の延長

投与前の判定では，正常 2 例，軽度変化16例，中等度変化 3 例，やや高度変化 6 例であった．投与後，軽度変化が正常に復したもの 3 例，中等度変化が軽度となったもの 1 例，やや高度変化が中等度となったもの 1 例，合計 5 例，20％の改善率であった．

(3)　前立腺腫の膀胱内突出部横径（A）

投与前に計測しえた症例は24例であった．投与前平均値は 4.82±0.24 cm で，投与後は 4.81±0.21 cm とあきらかな差は認めなかった．

(4)　前立腺部尿道長（B）

投与前に計測しえた例数は前項と同じ24例であった．投与前平均値は 4.68±0.23 cm で，投与後は 4.78±0.20 cm とやはりあきらかな差は認めなかった．

4）尿流量測定（Table 5.）

Table 5.　尿流量測定成績一覧

(n=16)

症例 No.	排尿量（ml） 前	排尿量（ml） 後	平均排尿量(ml/sec.) 前	平均排尿量(ml/sec.) 後	最大排尿量(ml/sec.) 前	最大排尿量(ml/sec.) 後
15	150	160	2.9	3.2	12.9	10.8
16	220	190	3.8	4.4	20.0	18.0
17	210	200	4.2	4.0	26.3	24.5
18	100	80	1.8	1.5	7.6	7.0
19	195	178	3.7	8.9	10.6	16.9
20	150	200	3.1	4.9	8.9	12.6
21	150	300	3.4	6.0	7.0	12.7
22	260	230	4.0	9.3	9.0	20.1
23	100	200	2.6	4.7	8.5	12.0
24	0 (尿閉)	200	0 (尿閉)	3.3	0 (尿閉)	7.3
25	85	32	1.4	2.5	4.3	5.8
26	195	207	4.6	8.3	7.2	12.5
27	75	139	3.2	3.0	5.7	7.0
28	191	280	2.5	5.0	5.0	7.0
29	174	152	3.2	3.1	5.3	6.1
30	199	292	3.3	5.1	7.1	9.5
$\bar{x}\pm SE$	153.4 ±16.64	190.0 ±17.68	2.98 ±0.288	4.83 ±0.573	9.09 ±1.574	11.86 ±1.385
		NS		P<0.01		P<0.01

Table 6.

(n=6)

症例 No.	前立腺部尿道(cm)		最大尿道閉塞圧($\frac{cm}{H_2O}$)		前立腺部尿道抵抗(g/cm)		膀胱内圧(cmH_2O)	
	前	後	前	後	前	後	前	後
25	5.0	3.5	80	40	30	20	118	87
26	4.5	4.0	70	64	60	44	80	116
27	6.0	5.5	40	80	20	30	127	84
28	4.0	4.0	110	90	42	40	66	80
29	3.5	3.5	44	90	20	30	74	91
30	5.0	5.0	66	40	60	38	116	116
$\bar{X}$	4.67	4.25	68.3	67.3	38.7	33.7	96.8	95.7
± SE	±0.357	±0.335	±10.45	±9.48	±7.51	±3.56	±10.77	±6.60
	NS		NS		NS		NS	

Table 7. 投与前残尿量 ≧50 ml の症例における残尿量の変化

(n=8)

症例 No.	残尿量(ml)	
	前	後
7	60	55
18	60	90
20	50	0
21	50	0
23	110	20
24	尿閉	40
28	50	0
30	100	58
$\bar{X}$ ± SE	68.6±9.62	32.9±11.83
	0.01<P<0.05	

但し、有意差検定では症例No.24を除く。

(1) 総排尿量

測定しえた症例数は16例で，総排尿量の平均値は，投与前 153.4±16.6 ml，投与後では，190.0±17.7 ml と増加する傾向にあった．

(2) 平均排尿量

セルニルトン投与前の平均排尿量は，平均 2.98±0.29 ml/sec. であり，投与後は 4.83±0.57 ml/sec. と前後において，統計学的に有意な改善を認めた．

(3) 最大排尿量

セルニルトン投与前の最大排尿量の平均値は，9.09±1.57 ml/sec. であり，投与後は，11.86±1.39 ml/sec. と有意に改善した．

5) 尿道抵抗曲線 (Table 6.)

計測しえた群が6例と数少ないため統計学的な検討はやや困難ではあるが，成績は以下の通りであった．

(1) 前立腺部尿道長

投与前の尿道長平均値は 4.67±0.36 cm で，投与後は 4.25±0.34 cm と短くなる傾向にあった．

(2) 最大尿道閉塞圧

セルニルトン投与前の平均値は 68.3±10.5cmH_2O から投与後 67.3±9.5 cmH_2O と低下する傾向が認められた．

(3) 前立腺部尿道抵抗

セルニルトン投与前の前立腺部尿道抵抗の平均値は 38.7±7.5 g/cm で投与後は 33.7±3.6 g/cm と低下する傾向を示した．

6) 膀胱内圧 (Table 6.)

計測しえた症例は6例で，投与前の平均値は 96.8±10.8 cm H_2O，投与後 95.7±6.6 cm H_2O と，膀胱内圧に対するセルニルトンの効果は認めなかった．

4．他覚的所見についての小括 (Table 8.)

他覚的所見に対する効果は，著明改善から悪化までの5段階に分類した．今回対象となった30例につき，主治医による効果判定は，著明改善2例，中等度改善5例，軽度改善は6例であり，有効率は 43% であった．

効果判定

効果判定は，1．自覚的症状に対する効果判定を患者ならびに主治医によりおこない，2．他覚的所見に対する主治医判定の3者を考慮して総合判定をおこな

Table 8.

(n=30)

自覚症状に対する効果						他覚所見			総合判定			
患者の印象			症状判定			判定						
改善	不変	悪化	改善	不変	悪化	改善	不変	悪化	著効	有効	やや有効	無効
24	6	0	24	6	0	13	14	3	2	7	13	8
(80%)	(20%)	(0%)	(80%)	(20%)	(0%)	(43%)	(46%)	(10%)	(73%)			

った．

1．自覚的症状に対する効果判定

1）患者判定によるもの

遷延性排尿困難，再延性排尿困難，排尿時のいきみ，尿線の状態，残尿感の5点についての患者の総合的印象による効果判定では，著明改善3例，中等度改善13例，軽度改善が8例で，有効率は80%であった．

2）主治医判定によるもの

主治医判定によるものでは，著明改善が3例，中等度改善が13例，軽度改善8例と，改善率80%を示した．

2．他覚的所見に対する効果判定

主治医による効果判定では，著明改善2例，中等度改善5例，軽度改善6例と有効率は43%であった．

3．総合判定

前述の1．と2．を総合した判定は，著効から無効までの4段階に区分した．結果として，総症例30例のうち，著効2例，有効7例，やや有効13例，無効8例であった．有効率は73%と比較的高率であった．

考　　察

前立腺肥大症は，泌尿器科外来を訪れる患者のうちでも，比較的大きな割り合いを占める疾患であり，現在増加しつつある疾病と考えられる．その発症要因については，数多くの説があるが，現在では内分泌異常によるとの説が大勢を占めていると思われる．そのため本症病態下のホルモン動態ならびにホルモン受容器の解析がおこなわれている[4~6]．治療については外科的療法がさまざまな方法で活発におこなわれている．しかし高齢者の発症が多く，また当該年齢層に各種合併症の頻度も高いことより，保存的治療も数多くおこなわれているのが現状と思われる．保存的治療に用いられる薬剤も，前述した内分泌学的環境の変化によるとする立場から，男性ホルモンが一時使用されたが前立腺癌に promoting factor として働くことが知られており，現在はほとんど使用されない[7]．女性ホルモン製剤は現在数多く使われているが，副作用に直面することもまれではない．

Table 9.　鶏卵大以上の前立腺重量の変化

(n=8)

症例 No.	Thumann 法 (g) 前	後
13	54.0	47.5
14	39.4	33.2
15	61.0	68.7
25	61.0	54.0
26	45.1	39.4
27	54.0	45.1
28	76.9	61.0
30	61.0	47.5
$\bar{x}\pm$ SE	56.55±4.035	49.55±4.044
	$P<0.05$	

今回われわれが検討したセルニルトンは，非ホルモン製剤の範疇に入り，副作用は全例に認めなかった．セルニルトンについて，投与による自覚的症状に対する有効率は80%であるが，他覚的所見に対する有効率は43%と解離が認められる．その原因についての詳細は不明であるが，アジア地域における前立腺肥大症は，外科的被膜との癒着が強いことは知られており[8]，セルニルトンの持つ抗浮腫作用ならびに消炎作用がなんらかの点で有利に働いているものと思われる．しかし，尿道膀胱造影における各項目の変化，直腸内触診における腺腫の大きさの変化，前立腺部尿道長の変化からうかがえるように，セルニルトンは前立腺腫に対する本質的な効果は有していないと思われる．ただ直腸診で鶏卵大以上であったものについて，Thumann 法[9]により前立腺重量を推定した場合，縮小する傾向を認めたのは興味あることと思われるが，今後症例を

かさねて検討する必要があろう (Table 9.).

ま と め

1．前立腺肥大症患者30症例につき，セルニルトン6錠分3投与を12週間連続しておこない，その前後の自覚的症状，他覚的所見の変化について観察した．

2．自覚的症状については，80%の改善率を認めた．

3．他覚的所見については，43%の有効率を認めた．

4．特記すべき副作用は認めなかった．

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Clinical evaluation of Cernilton in the treatment of the benign prostatic hypertrophy

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Cernilton was given clinically to 30 patients with benign prostatic hypertrophy. Cernilton was given orally at least for 12 weeks at a daily dose of 6 tablets in three divided doses. The overall clinical efficacy on subjective symptoms was 80%, and that on objective signs, 43%. During the administration period of Cernilton, no serious untoward effects were observed in either the clinical or laboratory findings. It is, therefore, suggested that, from the clinical point of view, Cernilton is a useful and safe drug in the treatment of benign prostatic hypertrophy.

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Effect of Cernitin pollen-extract on the Sex-hormone-induced Nonbacterial Prostatitis in Rats

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Cernitin pollen-extract (Cernilton®, CN-009) is a preparation made from eight kinds of pollen. The active components are water-soluble (T60) and fat-soluble (GBX) fractions. CN-009 has been used for the treatment of chronic prostatitis in Europe and Japan. To study the action of CN-009 on the prostatitis, we examined the effect of CN-009 on the sex-hormone-induced nonbacterial prostatitis in rats.

Aged Wistar rats (10 months old) were castrated and then injected 17*β*-estradiol (0.25 mg/kg, s.c.) for 30 days. These treatments reduced the weight of prostate and induced the inflammation and epithelial cell dysfunction of the lateral prostate lobe in the rats. Testosterone (2.5 mg/kg, s.c.) injected for the last 14 days of the treatment of 17*β*-estradiol to the rats restored markedly the estradiol-induced prostatitis. Those changes were similar to the findings reported by others. CN-009 was administered orally for the last 14 days of the treatment of 17*β*-estradiol to the rats. The administration of 378 mg/kg of CN-009 did not change in the prostatic histopathological findings, while 1260 mg/kg of CN-009 increased the number of intracellular secretory granules of epithelial cells and diminished weakly the invasion of inflammatory cells into the lumen or the stroma in the prostatic gland.

These results suggest that CN-009 may recover the prostatic epithelial cell dysfunction and have the mild anti-inflammatory properties.

Key Words: Cernitin pollen-extract, Cernilton, CN-009, Aged Wistar rat, Castration, Sex-hormone-induced nonbacterial prostatitis

Title	前立腺肥大症に対するセルニルトン錠の臨床的検討
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前立腺肥大症に対するセルニルトン®錠の臨床的検討

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CLINICAL EVALUATION OF CERNILTON ON BENIGN PROSTATIC HYPERPLASIA

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and Shunsaku TSUJIMURA
From the Department of Urology, Nagoya City University Medical School
(*Director: Prof. K. Ootaguro, M.D.*)

Twenty-two patients whose average age was 67 years and who had benign prostatic hyperplasia of stage I and II were treated with Cernilton for more than 4 weeks.

Subjective symptoms were excellently improved and the improvement rate was over 85% in all of the evaluated symptoms of dysuria. In the overall evaluation, 18 out of 22 patients were rated as moderately improved or better, 2 were slightly improved and 2 remained unaltered. Aggravation of the symptoms was found in none of the patients.

Objective findings such as residual urine volume and urinary flow rate were improved in 3 patients, although the shrinkage of the prostate was not observed on rectal palpation, retrograde urethro-cystography or transrectal ultrasonography.

No adverse reaction was observed during Cernilton therapy.

In conclusion, it is suggested that Cernilton may be effective and safe for the conservative treatment of patients with early stage prostatic hyperplasia of non-surgical indication.

Key words: Cernilton, Prostatic hyperplasia

緒　　言

セルニルトン®錠はスウェーデンの AB セルネレ社で製造された8種の植物の混合花粉エキスを主成分とする製剤で，前立腺炎や前立腺肥大症に有効であることが報告されている[1~4]．前立腺肥大症に対する薬物療法として最近抗男性ホルモン作用のある酢酸クロルマジノンやオキセンドロンといった薬物が開発され，投与される傾向にある[10,11]．しかし前立腺肥大症は元来良性疾患であり，長期投与による副作用に注意しなければならない．ことに前立腺肥大症を有する患者の多くは老人であり，心・循環器系に少なからず問題があり，これらに影響の少ない薬物の投与が望まれる．

われわれはセルニルトン®錠の副作用の少ないことに注目し，前立腺肥大症に対して臨床的検討をおこなったので報告する．

対象および方法

対象は排尿困難，残尿感などを訴え，当科を受診した患者で，直腸診，逆行性尿道・膀胱造影，経直腸的超音波検査などにより前立腺肥大症と診断した22症例である．年齢は57歳より82歳（平均67歳）で，尿道狭窄および膀胱頸部硬化のあるもの，尿路感染の強いもの，手術対象のもの，投与前1週間以内にほかの前立腺肥大症治療剤を使用していたもの，前立腺癌を合併

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するものなどを除外した．セルニルトン®錠の投与方法は1回2錠，1日3回経口投与とし，原則として4週間以上継続投与した．ほかの前立腺肥大症治療剤および消炎剤との併用はおこなわなかった．また合併症を有する症例では本疾患に影響がないと考えられる薬剤を投与した．

前立腺肥大症の病期分類としては Güyon 分類[7]を用いた．すなわち第Ⅰ期：刺激症状期（前駆期），第Ⅱ期：残尿発生期（不完全尿閉期），第Ⅲ期：慢性尿閉期（尿閉期）の3期に分類した．

観察項目および効果判定

自覚症状として夜間頻尿回数，遷延性排尿，再延性排尿，排尿時のいきみ，尿線の勢いの低下，残尿感などについてセルニルトン®錠の投与前後に問診をおこなった．夜間頻尿回数以外は3段階に分類し，それぞれの効果判定に用いた．なお自覚症状に対する全般的な効果判定として上記の6項目について(1)著明改善：悪化項目なく5項目以上が改善，(2)中等度改善：3～4項目改善，(3)軽度改善：1～2項目改善，(4)不変：6項目すべてに変化なし，(5)悪化：1～6項目悪化，の5段階評価をおこなった（Table 1）．

他覚的所見の検索としては直腸内触診所見，残尿量，尿流量測定（DISA ZIC 10 mictiometer 使用による），逆行性尿道・膀胱造影，経直腸的超音波断層法（アロカ USI-5l 型と ASU-8R 型の使用による）などをおこなった．そのほか一般検査として血液学検査（赤血球数，白血球数，血小板数，血色素量＝g/dl，ヘマトクリット値＝%），血清化学検査（GOT, GPT, alkaline phosphatase, acid phosphatase, BUN, クレアチニン，Na, K, Cl），尿検査（蛋白，糖の半定量および沈渣検鏡所見）などを検索した．他覚的所見に対する効果判定法としては上記の5項目のうち，1項目も悪化したものがなく，1項目以上改善されたものを改善，1項目でも悪化したものを悪化，改善および悪化項目がなかったものを不変と判定した．

Table 1. 効果判定法

夜間頻尿回数		
排尿困難	遷延性排尿	
	1. スムーズに出る	1
	2. やや時間がかかる	2
	3. 非常に時間がかかる	3
	再延性排尿	
	1. 若い時と同様ごく普通である	1
	2. やや時間がかかる	2
	3. 非常に時間がかかる	3
	排尿時のいきみ	
	1. 特に意識しなくても普通に排尿できる	1
	2. 時々意識して腹に力をいれねば排尿できない	2
	3. 排尿のあいだ中いつも力まないと尿がでない	3
	尿線の勢いの低下	
	1. 尿線の太さや弧を描く状態は若い時と変らない	1
	2. 勢がない時には弧を描かず途切れることがある	2
	3. 出はじめから滴状でやっと出る程度	3
残尿感	1. なし	1
	2. ややある	2
	3. ある	3
病歴期間	i) 1カ月未満　iv) 1年未満 ii) 3カ月未満　v) 2年未満 iii) 6カ月未満　vi) 2年以上（　年　月）	
効果判定	1. 著明改善　2. 中等度改善　3. 軽度改善 4. 不変　5. 悪化	

結果

自覚症状を中心とした22症例の治療結果を Table 2 にまとめた．Güyon の分類別ではⅠ期が12例，Ⅱ期が10例でⅢ期はなかった．病歴期間は比較的長期の症例が多く，22例中18例が6カ月以上であり，このうち2年以上の症例は11例（50%）を占め，最長は8年であった．自覚症状に対する改善率は非常に良く，排尿困難の各症状については85%以上の改善がみられた（Table 3）．全般的な症状判定では悪化した例がなく，中等度改善以上が18例（81.8%），軽度改善が2例（9.1%），不変2例（9.1%）という成績であった（Table 4）．これを Güyon 分類別にみてみると，Ⅰ期で有効であったものは12例中9例（75.0%），Ⅱ期では10例中9例（90.0%）であり，ややⅡ期の方が改善率が良かった（Table 5）．夜間頻尿については22例中16例（72.7%）が回数の減少をみた．とくに症例 No. 9, 16, 17 では著明に改善した．他覚的所見では直腸内触診所見，逆行性尿道・膀胱造影，経直腸的超音波断層法ではいずれも所見の変化したものはみられなかった．残尿量および尿流量測定などを施行し，変化のみられた4症例を Table 6, Fig. 1 にまとめた．残尿量は3例に改善がみられた．尿流量測定では症例 No. 10 以外の3例で改善がみられた．血液・生化学検査ではセルニルトン®錠の投与前後において著明な変動を認めなかった．また副作用は全例においてなんら認められなかった．

Table 2. 症例治療成績一覧

症例 No.	年令 (才)	Güyon 分類	主訴	病歴期間	効果判定までの投与期間(週)	自覚的症状 夜間頻尿 前	夜間頻尿 後	遷延性排尿 前	遷延性排尿 後	再延性排尿 前	再延性排尿 後	排尿時のいきみ 前	排尿時のいきみ 後	尿線の勢い 前	尿線の勢い 後	残尿感 前	残尿感 後	効果判定	副作用
1	63	I	頻尿	iv	2	2	0	1	1	2	1	1	1	1	1	1	1	3	
2	60	I	排尿困難	vi (5年)	4	2	1	2	1	2	2	2	1	2	1	2	1	1	
3	69	II	排尿困難	vi (5年)	12	5	5	2	2	3	2	3	2	3	2	2	1	2	
4	71	I	排尿困難	iii	6	1	1	2	1	2	1	1	1	1	1	1	1	3	
5	72	I	排尿困難	vi (3年)	8	3	2	2	1	2	1	2	1	2	1	2	1	1	
6	82	II	夜間頻尿	vi (6年)	4	6	3	3	1	3	2	3	1	2	1	3	1	1	全
7	69	I	排尿困難	ii	4	1	1	2	2	2	2	2	2	2	2	2	2	4	
8	57	I	排尿困難	iv	4	0	0	2	1	2	1	2	1	2	1	2	1	1	例
9	74	I	夜間頻尿	iv	6	5~6	2	2	1	2	1	2	1	2	1	3	1	1	
10	59	II	排尿困難	vi (5年)	20	5	2	2	1	2	1	2	1	2	1	2	1	1	に
11	58	I	排尿困難	iv	16	2	1	2	1	2	1	2	1	2	1	2	1	1	
12	67	I	夜間頻尿	iv	6	3	2	2	1	2	1	2	1	2	1	2	1	1	認
13	59	I	排尿困難	ii	2	1	0	2	1	2	1	2	1	2	1	1	1	1	
14	76	II	排尿困難	iv	8	7	3	3	1	3	2	3	1	2	2	3	1	1	め
15	67	II	排尿困難	vi (4年)	8	2	2	2	2	2	2	2	2	2	2	2	2	4	
16	73	II	排尿困難	vi (8年)	2	4	1	2	1	2	1	2	1	2	1	2	1	1	ら
17	67	I	排尿困難	vi (5-6年)	6	6	1	2	1	2	1	2	1	2	1	1	1	1	れ
18	59	II	排尿困難	iii	4	2	2	2	1	2	1	2	1	3	2	2	1	1	
19	69	II	排尿困難	vi (—)	2	1	0	2	1	2	1	2	1	2	1	2	1	1	ず
20	70	II	排尿困難	vi (—)	16	3	2	2	1	2	1	2	1	2	1	2	1	1	
21	66	I	排尿困難	iv	8	4	2	2	1	2	1	2	1	2	1	2	1	1	
22	67	II	排尿困難	vi (3年)	14	3	1	2	1	2	1	2	1	2	1	2	1	1	

Table 3. 自覚症状に対する効果

症状	※症例数	改善例	非改善例	悪化例	有効率(%)
遷延性排尿	21	18	3	0	85.7
再延性排尿	22	19	3	0	86.4
排尿時のいきみ	20	18	2	0	90.0
尿線の勢い	20	17	3	0	85.0
残尿感	18	16	2	0	88.9

※投与前，正常の症例は省く。

Table 4. 自覚症状に対する効果判定

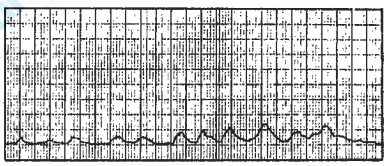
著明改善	中等度改善	軽度改善	不変	悪化
17 例 (77.3%)	1 例 (4.5%)	2 例 (9.1%)	2 例 (9.1%)	0 例 (0%)
18例 (81.8%)				

Table 5. Güyon 分類別効果判定

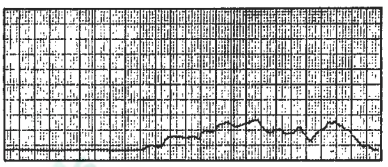
Güyon 分類	症例数	中等度改善以上の症例数(%)
I	12	9 (75.0%)
II	10	9 (90.0%)
III	0	0 (0 %)

Table 6. 残尿量，尿流量測定成績

症例 No.	残尿量(ml) 前	残尿量(ml) 後	排尿量(ml) 前	排尿量(ml) 後	平均排尿量(ml/sec.) 前	平均排尿量(ml/sec.) 後	最大排尿量(ml/sec.) 前	最大排尿量(ml/sec.) 後
10	0	0	325	573	8.5	7.9	13.2	12.5
11	10	0	211	441	2.0	5.8	6.6	10.5
15	5	0	196	382	4.9	6.3	9.7	11.3
20	50	0	58	68	1.8	4.5	3.5	7.4



Cernilton 投与前
voided volume：211 ml
MFR：6.6 ml/sec.
AFR：2.0 ml/sec.
voiding time：103 sec.



Cernilton 投与後
voided volume：441 ml
MFR：10.5 ml/sec.
AFR：5.8 ml/sec.
voiding time：75 sec.

Fig. 1　症例 No. 11 の UFM

考　　察

セルニルトン®錠はスウェーデン南部のスカニヤ地方で栽培された8種類の植物の花粉を抽出したセルニチンポーレンエキストラクト(pollen extract)である．本剤の薬理作用としては抗炎症作用，ラット前立腺重量増加抑制作用，排尿力増進効果などが報告されている[8,9]．またその副作用の少ないことも諸家によって報告されており[1~3]，それに注目し，今回臨床検討をおこなった．

前立腺肥大症は元来良性疾患であるために，その薬物療法をおこなう際には長期投与による副作用に注意する必要がある．最近前立腺肥大症に対して抗男性ホルモン薬が開発され，投与される傾向にあるが[10,11]手術適応のない初期の前立腺肥大症に対して第一次選択剤として投与されて良いものだろうか．これらの薬剤の副作用として性欲の低下，動悸などが報告されており[5,6]，心血管系の合併症を有する高齢者に投与する場合，留意すべきと考える．また剖検による前立腺潜在癌発見率は日本人では20.5%と高率に報告されており，またこのうち近い将来顕性癌となると考えられる浸潤性増殖型は8.8%になるといわれている[12]．前立腺肥大症に対して抗男性ホルモン療法をおこなう場合は，血清酸性ホスファターゼ値の測定，経直腸的超音波検査などで十分前立腺癌を否定しておき，投与すべきと考える．

今回のわれわれの対象とした22症例は病歴期間が比較的長期のものが多く，22例中18例が6カ月以上であり，2年以上のものは11例であった．病期分類(Güyon)ではすべてⅠ期とⅡ期ばかりであった．

大田黒は前立腺肥大症に対する治療方針として上部尿路への影響がなく，残尿も軽度で膀胱結石などの合併もなく，尿路感染症の反復もない例(肥大の大きさとは無関係)では薬物療法で経過観察するのみでよいと述べており，今回の22症例も手術適応がないものと判断された．このような症例に対してはまず副作用の少ない薬物療法が第一選択と考えられ，セルニルトン®錠を投与した．結果は他覚的所見では残尿量減少と尿流量測定の改善がみられたが，逆行性尿道・膀胱造影，直腸診，経直腸的超音波断層法などではいずれも前立腺の縮小変化がみられなかった．しかし自覚的所見の改善はいちじるしく，排尿困難の各症状については85%以上の改善がみられ，さらには全般的症状判定では悪化例がなく，自覚症状の改善率は22例中18例(81.8%)という成績がえられた．ほかの報告者による自覚症状改善率は，北野ら[1]で66.7%，古川ら[2]では78.6~92.9%，竹内ら[3]では64%であり，他覚的所見の改善率は北野らでは9.5%，竹内らでは36%という成績で，自覚的所見の改善は諸家の認めるところである．この作用機序としては竹内らが指摘しているように，肥大症にともなう同部の炎症性浮腫や前立腺管内の分泌物貯留の排除が考えられ，このことからも本剤の肥大した前立腺の縮小効果は弱いように思われる．

いっぽう副作用としては今回の22症例ではなんら認められなかった．前述した諸家の報告でも副作用はみられていない．

以上の成績よりセルニルトン®錠は手術適応のない初期の前立腺肥大症に有用であり，副作用がなんらみられなく，安心して投与できる薬剤であることが結論された．

結　　語

Güyon の病期分類Ⅰ期，Ⅱ期の前立腺肥大症22例に対してセルニルトン®錠を投与し，下記の成績をえ

た．

1)自覚症状に対する改善率は非常に良く，排尿困難の各症状については85%以上の改善率がえられた．全般的自覚症状改善率は22例中，中等度改善以上が18例（81.8%），軽度改善が2例（9.1%），不変2例（9.1%），悪化0例という成績であった．

2)他覚的所見では排尿量測定，残尿量などで3例に改善例がみられたが，直腸診，逆行性尿道・膀胱造影，経直腸的超音波断層法などでは前立腺の縮小変化が認められなかった．

3)副作用は全例になんらみられなかった．

以上よりセルニルトン®錠は手術適応のない初期の前立腺肥大症に有用であり，副作用がなんらみられないことより安心して投与できる薬剤と考えた．

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Clinical evaluation of Cernilton on benign prostatic hypertrophy – a multiple center double-blind study with Paraprost

Maekawa M, Kishimoto T, Yasumoto R, Wada S, Harada T, Ohara T, Okajima E, Hirao Y, Ohzono S, Shimada K, et al

A multiple center double blind study was performed to study the effectiveness of Cernilton (CN) on benign prostatic hypertrophy in comparison to Paraprost (PP). Among a total of 192 patients, overall effect was studied on 159 patients, overall safety rate on 178 patients and rate of effectiveness on 159 patients. There were no differences between the two groups in the selected patients, criteria for exclusion and drop out cases or background data of the patients. Impression of patients and overall effect by committee and physician judgment were slightly higher in the CN group compared to the PP group, but there was no significant difference between the two groups.

For the improvement in subjective symptoms, the rate of moderate improvement or more after 4 weeks by committee judgment was higher in the CN group compared to the PP group. The rate of improvement in protracted miction, which is an effective marker of urinary disturbance, was also higher in the CN group compared to the PP group. An analysis of objective symptoms showed a significant improvement in residual urinary volume, average flow rate, maximum flow rate and prostatic weight in the CN group. A significant improvement in the phased change of residual urinary volume was also seen in the CN group. No side effects or abnormalities in clinical test levels were noted in the CN group. By committee judgment, the rate of more than moderate effectiveness was 49.1% in the CN group compared to 41.2% in the PP group, but there was no significant difference between the two groups.

By physician's judgment, the rate of more than moderate effectiveness was 49.4% in the CN group compared to 46.3% in the PP group, but there was also no significant difference between the two groups. These results suggested that Cernilton was an effective drug for benign prostatic hypertrophy.

Publication Types:

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前立腺肥大症に対する Cernilton® の臨床評価

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CLINICAL EVALUATION OF CERNILTON® ON BENIGN PROSTATIC HYPERTROPHY

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From the Department of Urology, Yamaguchi University School of Medicine
(Director: Prof. J. Sakatoku)

Twenty patients with benign prostatic hypertrophy were treated with Cernilton®, 6 tablets a day for an average of 13.2 weeks.

Subjective effectiveness was observed in the improvement of sense of residual urine (92%), retardation (86%), night frequency (85%), strain on urination (56%), protraction (53%) and forceless urinary stream (53%). The overall subjective effectiveness was 80% of patients, and the overall objective effectiveness was 54% of patients. Night frequency, residual urine volume and tidal urine volume were improved significantly. The overall effectiveness was 80%. No side effects were observed.

Key words: Cernilton, Benign prostatic hypertrophy

緒　　言

前立腺肥大症は加齢とともに前立腺内腺が良性増殖し肥大結節組織を形成，それによる膀胱頸部および尿道の圧迫による排尿困難を主症状とする．その根治治療は結節の手術的療法による除去にあるが，本疾患は対象患者の老齢や循環器系，呼吸器系などの合併症をともなうことにより，手術不能例がしばしばみられる．また，完全尿閉をきたす症例や排尿障害に続発する腎障害例は手術的療法の適応となるが，刺激期，残尿期などの初期症例は保存的療法の期待されるところである．

薬物療法としては植物製剤，前立腺抽出物剤，アミノ酸製剤およびホルモン剤などがあるが，前立腺肥大症は老人性疾患であること，合併症の問題もあり，長期投与による副作用のないことが望まれる．

今回われわれは花粉抽出エキスである Cernilton® を，前立腺肥大症の手術的療法の適応にいたらない患者を対象としてその有効性と安全性を検討したので報告する．

対象および方法

1．対象症例

1983年8月より1984年8月までに山口大学医学部附属病院泌尿器科を受診した外来患者で，前立腺肥大症初期と診断された20例を対象とした．病期分類としては Güyon 分類（第Ⅰ期　刺激症状期〔前駆期〕，第Ⅱ期残尿発生期〔不完全尿閉期〕，第Ⅲ期　慢性尿閉期〔尿閉期〕）を用いた．ただし下記の症例は除外した．

1）試験開始前1週間以内に他の前立腺肥大症治療剤の投与を受けていたもの
2）ホルモン性前立腺肥大症治療剤の投与を最近6カ月以内に受けていたもの
3）尿道狭窄あるいは膀胱頸部硬化症のあるもの
4）尿路感染の高度なもの
5）前立腺癌を有するもの

2．投与方法および投与期間

Cernilton® 錠は1回2錠，1日3回経口投与とし，投与期間は原則として12週間以上連続投与とした．なお症状が改善し，薬剤投与の必要性がなくなった症例はその時点で投与を中止した．

3．併用薬剤

併用薬剤は原則として使用しないこととし，抗生物質はやむをえない場合にかぎり使用を可とした．合併症治療については本疾患に影響がないと判断される薬剤の使用は可とした．

4．調査項目および効果判定

1）自覚症状

遷延性排尿，再延性排尿，排尿時のいきみ，尿線の勢いおよび残尿感について Table 1 のような3段階の評価基準を設けた．また夜間排尿回数は実数を調査した．

2）他覚所見

残尿量，尿流量測定（排尿量，平均排尿量，最大排尿量）は実数で調査し，前立腺重量は Thumann 法[1] により推定し，直腸内触診，尿道膀胱造影（斜位像における尿道前立腺部延長，腺腫の膀胱内突出）は Table 1 のような5段階の評価基準を設けた．

他覚所見判定は前記項目を総合し，1：著明改善　2：中等度改善　3：軽度改善　4：不変　5：悪化の5段階で評価した．

3）総合効果

本剤の前立腺肥大症に対する効果は，自覚症状と他覚所見の改善度を総合的に判定し，1：著効　2：有効　3：やや有効　4：無効の4段階で評価した．

5．安全性に対する検討

1）副作用

副作用症状が発現した場合は，発現日，症状，程度，処置および経過を調査することとした．

2）臨床調査

投与前後に一般血液検査（赤血球数，白血球数，血小板数，血色素量，ヘマトクリット），血液生化

Table 1. 評　価　基　準

項目		評価基準
自覚症状	排尿困難 遷延性排尿	1.スムーズに出る
		2.やや時間がかかる
		3.非常に時間がかかる
	再延性排尿	1.若い時と同様ごく普通である
		2.やや時間がかかる
		3.非常に時間がかかる
	排尿時のいきみ	1.特に意識しなくても普通に排尿できる
		2.時々意識して腹に力をいれねば排尿できない
		3.排尿のあいだ中いつも力まないと尿が出ない
	尿線の勢い	1.尿線の太さや弧を描く状態は若い時と変わらない
		2.勢いがない時は弧を描かず途切れることがある
		3.出はじめから滴状でやっと出る程度
	残尿感	1.なし
		2.ややある
		3.ある
他覚所見	直腸内触診	1.鶏卵大(直径3.4cm以下)
		2.小鶏卵大(直径4.4cm以下)
		3.鶏卵大(直径5.4cm以下)
		4.超鶏卵大(直径6.4cm以下)
		5.鷲卵大(直径6.5cm以上)
	尿道膀胱造影	1.正常
		2.軽度変化
		3.中等度変化
		4.やや高度変化
		5.高度変化

Table 2. 症例治療成績一覧

症例 No.	年齢（歳）	Güyon の分類	既往歴	病歴期間	主訴	投与期間（週）	夜間排尿回数（回） 前	後	自覚症状 遷延性排尿 前	後	苒延性排尿 前	後	排尿困難時のいきみ 前	後	尿線の勢い 前	後	残尿感 前	後	自覚症状判定
1	70	I	初発	3年6カ月	頻尿・排尿困難	14	1～2	1～2	2	1	2	2	1	1	2	2	1	1	軽度改善
2	65	I	〃	5年	排尿困難	12	1～2	1～2	2	2	2	2	1	1	2	2	1	1	不変
3	59	I	〃	6カ月未満	排尿困難	10	1～2	0	2	1	2	1	1	1	2	1	1	1	著明改善
4	69	II	〃	1年未満	夜間頻尿	14	4	1	1	1	2	1	1	1	2	2	1	1	中等度改善
5	66	I	〃	4年	排尿困難	13	3	0	1	1	1	1	1	1	1	1	2	1	著明改善
6	71	II	〃	6カ月未満	頻尿	13	3	2	1	1	2	2	1	1	2	2	2	1	中等度改善
7	67	I	〃	3カ月未満	排尿困難	14	2	1～2	2	2	2	2	2	2	2	2	2	2	不変
8	61	II	〃	1年未満	頻尿	14	2～3	0	2	1	3	1	2	1	2	1	2	1	著明改善
9	73	I	再発	1カ月未満	排尿困難	5	3	2	2	1	2	1	2	1	2	1	1	1	著明改善
10	61	I	初発	1カ月未満	排尿困難	21	2	1	2	1	2	1	1	1	2	1	1	1	著明改善
11	75	I	〃	5年	夜間頻尿	14	3～4	2	2	1	2	1	1	1	2	1	2	1	著明改善
12	71	II	〃	1カ月未満	排尿困難	13	4	1	1	1	2	1	1	1	2	1	2	1	著明改善
13	72	II	〃	1カ月未満	残尿感	12	7	4	2	1	2	1	2	1	2	1	2	1	著明改善
14	76	I	〃	6カ月未満	夜間頻尿	19	5～6	3～4	1	1	2	2	1	1	2	2	3	2	軽度改善
15	64	II	〃	1カ月未満	排尿困難	15	3	1	2	1	2	1	2	2	2	1	2	1	著明改善
16	63	I	〃	6カ月未満	排尿時不快感	14	2～3	1～2	2	1	2	2	1	1	2	2	1	1	中等度改善
17	59	I	〃	3年	頻尿	10	3～4	2～3	2	1	2	2	2	2	2	2	2	1	中等度改善
18	64	I	〃	1年未満	頻尿・排尿困難	13	4	1	2	1	2	2	2	2	2	1	2	1	中等度改善
19	70	I	〃	10年	排尿困難	13	4	3	1	1	2	1	2	1	2	1	1	1	著明改善
20	67	I	〃	3カ月未満	排尿困難	11	1	1	2	1	2	2	2	1	2	2	3	1	中等度改善

学検査（GOT, GPT, Al-P, BUN, クレアチニン, Na, K, Cl, 血糖, Ac-P（総）, Ac-P（前立腺））, 尿検査（蛋白, 糖, 潜血反応, pH, 沈渣）を可及的に実施した.

成　績

1．症例の背景

対象となった20例の年齢は59歳から76歳（平均67.2歳）で1例を除き初発の外来患者で病期は第I期14例, 第II期6例で, 主訴は排尿困難12例（54.5%）, 頻尿5例（22.7%）, 夜間頻尿3例（13.6%）などであった.

20例の成績は一括して Table 2 に示した.

2．自覚症状に対する効果（Table 3, 4）

夜間排尿回数は20例中17例（85%）に改善が認められ, 3例（15%）は投与後夜間排尿が1回も認められなかった. またミッドレンジを用いた投与前後値は3.1回から1.6回に減少しており. 統計学的検討により有意差を認めた（$p<0.001$）.

遷延性排尿は14例中12例（85.7%）, 苒延性排尿は19例中10例（52.6%）, 排尿時のいきみは9例中5例（55.6%）, 尿線の勢いは19例中10例（52.6%）, 残尿感は12例中11例（91.7%）に改善が認められ, 全症状とも悪化したものはなかった.

医師の総合的な自覚症状の判定は20例中16例（80%）が中等度改善以上の効果を認めた（Table 5）.

3．他覚所見に対する効果（Table 4, 6）

残尿量は14例中13例（92.9%）に改善を認め, 前後値は 45 ml から 16 ml に減少しており統計学的な有意差を認めた（$p<0.05$）.

排尿量は13例中11例（84.6%）に増加を認め, 前後値は 199 ml から 284 ml に増加しており統計学的な有意差を認めた（$p<0.05$）.

平均排尿量は13例中9例（69.2%）に改善を認め, 前後値は 4.7 ml/sec から 6.5 ml/sec に増加していた.

最大排尿量は13例中10例（76.9%）に改善を認め, 前後値は 10 ml/sec から 13 ml/sec に増加していた.

前立腺重量は8例中5例（62.5%）に改善を認め, 投与前後の重量は 15 g から 13 g に減少していた.

尿道膀胱造影による斜位像は, 尿道前立腺部延長像では10例とも変化が認められず, 腺腫の膀胱内突出像では9例中2例（22.2%）に改善が認められ, 2例とも中等度変化から軽度変化に改善していた.

Table 2. 症例治療成績一覧（つづき）

症例 No.	他覚所見																他覚所見判定	副作用	総合判定
	直腸内触診		残尿量 (ml)		尿流測定 排尿量 (ml)		尿流測定 平均排尿量 (ml/sec)		尿流測定 最大排尿量 (ml/sec)		尿道膀胱造影 斜位像 尿道前立腺部延長		尿道膀胱造影 斜位像 腺腫の膀胱内突出		前立腺重量 (g)				
	前	後	前	後	前	後	前	後	前	後	前	後	前	後	前	後			
1	2	2	20	5	107	259	4.2	6.5	7.6	17.5	2	2	3	2	16.0	9.0	中等度改善	なし	有効
2	2	—	10	—	126	—	3.0	—	8.8	—	4	—	4	—	41.6	—	不明	〃	無効
3	2	—	—	—	—	—	—	—	—	—	2	—	2	—	—	—	不明	〃	有効
4	2	—	40	0	163	158	10.0	7.0	18.6	12.5	2	2	3	3	13.2	9.8	軽度改善	〃	有効
5	1	1	32	0	144	146	4.3	4.6	10.8	11.0	2	2	3	3	9.4	9.4	不変	〃	有効
6	2	2	110	60	217	276	2.5	4.8	6.7	10.6	3	—	2	—	11.7	—	中等度改善	〃	有効
7	2	2	10	5	601	645	8.5	8.0	20.5	18.0	2	2	2	2	16.6	16.6	不変	〃	無効
8	1	—	95	25	418	384	6.3	13.0	14.6	19.4	2	2	2	2	—	—	著明改善	〃	著効
9	2	—	10	—	355	—	8.8	—	11.4	—	2	—	2	—	11.2	—	不明	〃	有効
10	2	—	23	18	91	577	4.1	8.4	7.6	13.0	2	—	2	—	6.4	—	中等度改善	〃	有効
11	3	—	24	20	125	213	2.4	7.5	8.1	12.3	2	2	3	2	12.7	8.6	中等度改善	〃	著効
12	3	—	215	0	118	202	2.2	7.4	4.7	15.5	3	3	3	3	17.9	16.6	著明改善	〃	著効
13	2	2	100	75	21	62	0.7	0.8	2.3	2.6	2	—	2	—	10.7	—	軽度改善	〃	有効
14	2	—	9	8	136	150	4.5	4.5	9.1	11.3	3	3	3	3	22.8	22.0	軽度改善	〃	やや有効
15	2	—	110	—	220	—	2.3	—	6.3	—	3	—	3	—	18.5	—	不明	〃	有効
16	2	—	3	5	335	410	8.2	6.8	17.4	15.4	3	3	3	3	14.3	14.3	不変	〃	やや有効
17	2	—	5	—	38	—	1.6	—	4.8	—	2	—	2	—	2.3	—	不明	〃	有効
18	2	—	21	2	243	—	5.8	—	15.5	—	3	3	—	—	—	—	不明	〃	有効
19	3	2	13	1	107	205	2.6	5.4	6.0	10.6	2	—	3	—	16.6	—	著明改善	〃	著効
20	2	—	4	—	341	—	5.2	—	10.9	—	2	—	2	—	—	—	不明	〃	有効

Table 3. 自覚症状別効果

項　目	症例数*	改善	非改善	改善率(%)
夜間排尿回数	20	17	3	85.0
遷延性排尿	14	12	2	85.7
再延性排尿	19	10	9	52.6
排尿時のいきみ	9	5	4	55.6
尿線の勢い	19	10	9	52.6
残尿感	12	11	1	91.7

* 投与前、正常の症例は除く

直腸内触診は6例中1例（16.7%）のみに改善が認められ，鶏卵大から小鶏卵大への縮小であった．

他覚所見の効果は，投与後の測定値や造影像などのない7例を不明例と判定し集計から除いた．判定対象の13例中7例（53.8%）に中等度改善以上の効果を認めた（Table 7）．

4．総合効果判定（Table 8）

総合効果は著効4例（20%），有効12例（60%），やや有効2例（10%），無効2例（10%）で有効以上は

Table 4. 実数値の推移（前後値のある症例）

項　目	症例数	投与前の M±SD	投与後の M±SD	t－検定
夜間排尿回数（回）	20	3.1±1.4	1.6±1.1	$p<0.001$ ($t=6.44921$)
残尿量（ml）	14	51.1±57.2	16.0±22.6	$p<0.05$ ($t=2.35236$)
排尿量（ml）	13	198.7±154.2	283.6±167.1	$p<0.05$ ($t=2.34810$)
尿流測定　平均排尿量（ml/sec）	13	4.65±2.70	6.52±2.70	N.S.
最大排尿量（ml/sec）	13	10.31±5.48	13.05±4.16	N.S.
前立腺重量（g）	8	15.34±3.74	13.29±4.57	N.S.

Table 5. 自覚症状総合効果

著明改善	中等度改善	軽度改善	不変	悪化	計	中等度改善以上	軽度改善以上
10	6	2	2	0	20	16/20	18/20
(50%)	(30%)	(10%)	(10%)	(0%)		(80%)	(90%)

Table 6. 他覚所見別効果

項　目	症例数*	改善	非改善	改善率(%)
残尿量	14	13	1	92.9
尿流　排尿量	13	11	2	84.6
測定　平均排尿量	13	9	4	69.2
最大排尿量	13	10	3	76.9
尿道　前立腺重量	8	5	3	62.5
膀胱　斜位　尿道前立腺部延長	10	0	10	0
造影像　腺腫の膀胱内突出	9	2	7	22.2
直腸内触診	6	1	5	16.7

* 投与前後に検査を実施した症例数

Table 7. 他覚所見別効果*

著明改善	中等度改善	軽度改善	不変	悪化	計	中等度改善以上	軽度改善以上
3	4	3	3	0	13	7/13	10/13
(23.1%)	(30.7%)	(23.1%)	(23.1%)	(0%)		(53.8%)	(76.9%)

* 不明7例は除く

Table 8. 総合効果

著効	有効	やや有効	無効	計	有効以上	やや有効以上
4	12	2	2	20	16/20	18/20
(20%)	(60%)	(10%)	(10%)		(80%)	(90%)

Table 9. 層別効果

項目	内容	著効	有効	やや有効	無効	計	有効以上	やや有効以上
年齢	70才未満	1 (8.3)	8 (66.7)	1 (8.3)	2 (16.7)	12	9/12 (75.0)	10/12 (83.3)
	70才以上	3 (37.5)	4 (50.0)	1 (12.5)	0 (0)	8	7/8 (87.5)	8/8 (100)
Güyonの分類	第Ⅰ期	2 (14.3)	8 (57.1)	2 (14.3)	2 (14.3)	14	10/14 (71.4)	12/14 (85.7)
	第Ⅱ期	2 (33.3)	4 (66.7)	0 (0)	0 (0)	6	6/6 (100)	6/6 (100)
病歴期間	1年未満	2 (14.3)	9 (64.3)	2 (14.3)	1 (7.1)	14	11/14 (78.6)	13/14 (92.9)
	1年以上	2 (33.3)	3 (50.0)	0 (0)	1 (16.7)	6	5/6 (83.3)	5/6 (83.3)
残尿量	50ml以下	2 (14.3)	8 (57.1)	2 (14.3)	2 (14.3)	14	10/14 (71.5)	12/14 (85.7)
	51ml以上	2 (40.0)	3 (60.0)	0 (0)	0 (0)	5	5/5 (100)	5/5 (100)

(%)

80%であった.

5．安全性についての検討

副作用は対象患者が高齢であるにもかかわらず1例も認められず，最長21週間まで連続投与ができた.

臨床検査は，一般血液検査・血液生化学検査・尿検査のいずれの項目においても，本剤投与によると思われる検査値への影響は認められなかった.

考察

Cernilton® は南スウェーデンの8種類の花粉エキスであるセルニチンポーレンエキスを1錠中に 63 mg 含有する．その成分は水溶性の CernitinT-60 と油性の CernitinGBX が 20：1 の比で含まれている.

Cernilton® の薬理作用は抗炎症作用[2]，前立腺の発育抑制作用[3]および排尿促進作用[4]が報告されており，前立腺炎[5,6]や前立腺肥大症[7~9]の治療に使用されている.

今回われわれにおける前立腺肥大症の自覚症状効果は80%の改善率であり，これは諸家の報告（竹内ら[8]の64%，北野ら[9]の67%）より優っていた．効果判定基準の異なる成績を比較することは困難ではあるが，自覚症状について効果のあることは諸家も認めるところである．個々の症状では残尿感（92%），遷延性排尿（86%），夜間排尿回数（85%）などに好成績が得られた．また夜間排尿回数で統計学的な有意差を認めたことなどから，前立腺肥大の顕著でないものや手術をためらう患者の自覚症状の改善に本剤の効果が期待される.

他覚所見効果は54%の改善率であり，これは諸家の報告（北野ら[9]の9.5%，竹内ら[8]の36%）よりあきらかに優っていた．個々の項目では残尿量と排尿量に統計学的な有意差を認めた．前立腺肥大症では残尿があると二次的尿路感染をともないやすく，残尿に対して優れた効果を認めたことは特記すべきことと思われる．直腸内触診や前立腺重量測定であきらかな縮小効果や減少効果が認らめれなかったことは，Cernilton® 投与による前立腺組織の器質的な縮小効果はあまり期待できないと考えられる.

前立腺肥大症における臨床症状の強さは腺腫の増大に必ずしも比例するものでなく，このことが本疾患における薬物療法の効果の確認を複雑にしている.

Cernilton® の効果は稲田ら[7]の述べているごとく膀胱頸部や後部尿道の浮腫，うっ血に対する消褪や前立腺管内の内分泌物の除去などのいわゆる variable element の改善にあると考えられる.

総合効果は80%の有効以上の効果が得られ，この成績は他の非ホルモン療法の成績[10] 70~80% の効果と匹敵する.

総合効果を患者の年齢，病期，病歴期間，残尿量で層別して検討すると，Table 9 に示すごとく各項目ともより臨床像が進んでいると思われる症例にも効果が高かった．Cernilton® は軽症から中等症までの広い範囲の患者に使用できると思われる.

Cernilton® の安全性については，平均連続投与13週間におよぶ治療期間中になんらの随伴症状や臨床検査値の異常な変動がみられなかったことから，安全性

の高い薬剤であると思われる．前立腺肥大症は元来良性な腺腫であり治療は長期にわたり，患者の高齢などを考えて薬剤を選択投与する必要がある．

Cernilton® の明確な腺腫の縮小効果は望めないとしても，自覚症状の改善，とくに残尿に奏効を呈したことなどから前立腺肥大症の variable element の改善が期待できる．さらに長期投与でも安全性の高いことが確認されたことから，手術適応のない患者などに有用と考えられる．

結　　語

前立腺肥大症の20例に Cernilton® を1日6錠平均13.2週投与し，下記の結果を得た．

1．自覚症状の改善は残尿感92％，遷延性排尿86％，夜間排尿回数85％，排尿時のいきみ56％，再延性排尿53％，尿線の勢い53％であった．

2．自覚症状の総合効果は80％が中等度改善以上であった．

3．他覚所見の総合効果は54％が中等度改善以上であった．

4．夜間排尿回数，残尿量，排尿量に統計学的な有意差を認めた．

5．総合効果は80％が有効以上であった。

6．副作用は全く認められなかった．

以上の成績により Cernilton® は前立腺肥大症の自覚症状の改善が期待でき，長期連用に耐えうる薬剤と思われる．

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Clinical evaluation of long-term treatment using Cernitin pollen extract in patients with benign prostatic hyperplasia

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Abstract

Seventy-nine patients with benign prostatic hyperplasia (BPH) were treated with cernitin pollen extract. Patient ages ranged from 62 to 89 years (mean, 68 years). Mean baseline prostatic volume was 33.2 cm^3. Cernitin pollen extract was administered in a dosage of 126 mg (2 tablets, 63 mg each), three times a day, for more than 12 weeks. Symptom scores, based on a modified Boyarsky scoring scale, uroflowmetry, prostatic volume, residual urine volume, and urinalysis results were examined before and after administration of cernitin pollen extract. Symptom scores significantly decreased from baseline, and the favorable results continued during the treatment period. Urine maximum flow rate and average flow rate increased significantly from 9.3 mL/s to 11 mL/s and from 5.1 mL/s to 6 mL/s, respectively. Residual urine volume decreased significantly from 54.2 mL to less than 30 mL. There was no change in prostatic volume. However, 28 patients treated for more than 1 year showed a mean decrease of prostatic volume to 26.5 cm^3. No adverse reactions were observed. Clinical efficacy at 12 weeks was rated excellent, good, satisfactory, and poor in 11%, 39%, 35%, and 15% of patients, respectively. Overall clinical efficacy was 85%. In conclusion, cernitin pollen extract showed a mild beneficial effect on prostatic volume and urination variables in patients with symptomatic BPH.

Introduction

Because cernitin pollen extract has anti-inflammatory and anticongestive effects,[1] it is useful for the treatment of nonbacterial prostatitis and prostatodynia. Recent studies have demonstrated that cernitin pollen extract improved detrusor activity and decreased resistance of the prostatic urethra.[2,3] It therefore provides better efficacy in urination. It has also been reported to suppress prostatic cell growth.[4,5] For these reasons, cernitin pollen extract is thought to be useful in the treatment of patients with dysuria due to benign prostatic hyperplasia (BPH).

We report here the efficacy of cernitin pollen extract in patients with BPH

Patients and methods

Seventy-nine patients with mild or moderate symptomatic BPH, who did not require prostatectomy, were selected for this study. Patients provided informed consent to participating in the study. Ages ranged from 62 to 89 years (mean, 68 years). For the evaluation of BPH, serum prostatic specific antigen, digital examination, transrectal ultrasonography, roentgenographic examination was performed. No abnormal findings in any patient were recorded.

Subjective assessment was based on a modified Boyarsky scoring scale[7] for the symptoms of urgency and discomfort, dysuria, nocturia, incomplete emptying, prolonged voiding, delaying voiding, intermittency, and postvoid dribbling, with a score of 0 (normal) to 3 (severe) for each of these symptoms. The average baseline symptom score was 9.6. Sixty-six percent of the patients urinated more than three times during the night. Maximum flow rate, average flow rate, residual urine volume at baseline were 9.3 ± 5.0 mL/s, 5.1 ± 2.7 mL/s, and 54.2 ± 78.8 mL, respectively. Mean prostatic volume was 33.2 cm^3 on transrectal ultrasonography.

Cernitin pollen extract was administered orally in a dosage of 126 mg (2 tablets, 63 mg each), three times a day, for more than 12 weeks. For subjective and objective assessments, symptom score, uroflowmetry, prostatic volume, residual urine volume, and urinalysis results were examined before treatment. Blood pressure and laboratory values were recorded every 3 months. Clinical efficacy, based on symptoms and objective signs, was assessed as excellent, good, satisfactory, and poor.

Values of measured variables are given as mean ± SD. For statistical analysis, the chi-square test and paired *t* test were used. A *P* value of <0.05 was considered statistically significant.

Results

Mean improvement of subjective symptoms, irritative symptoms, and obstructive symptoms, compared with baseline, and are shown in Figure 1 for short-term treatment. Urgency or discomfort improved by 76.9 %; dysuria, by 71.45 %; nocturia, by 56.8 %; incomplete emptying, by 66.2 %; prolonged voiding, by 64.1 %; delayed voiding, by 62.2 %; intermittency, by 60.6 %; and postvoid dribbling, by 42.7 %. Figure 2 shows change of symptom score during treatment. Average symptom score decreased significantly from 9.6 to 6.0 after the first 4 weeks of treatment and decreased continually to 5.4 during the following 8 weeksResults of the objective assessment are shown in Figure 2; maximum flow rate and average flow rate increased significantly from 9.3 mL/s and 5.1 mL/s to 11 mL/s and 6 mL/s, respectively, after the first 12 weeks of treatment. Residual urine volume decreased from 54.2 mL to less than 30 mL. However, no changes in prostatic volume and urine volume were observed. In short-term follow-up, 11 % of patients had excellent results; 39 %, good; 35 %, satisfactory; and 15 %, poor. Overall clinical efficacy was 85 %. No adverse reactions, such as impotence or hypotension, and no abnormal laboratory findings were observed.

During long term follow-up, 28 patients who had good results after short-term treatment continued treatment with cernitin pollen extract for more than 1 year. A significant decrease in prostatic volume to 26.5 cm^3, a significant increase in maximum flow rate, and a significant decrease in symptom score and residual urine volume were observed (Figure 2). During the long term treatment, no abnormal hematologic or biochemical findings were observed.

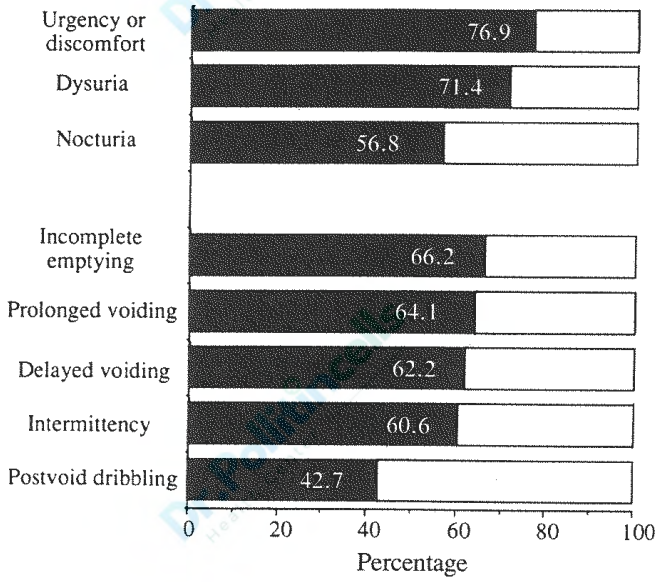

Figure 1. Mean improvement of subjective symptoms (%) of benign prostatic hyperplasia in 79 patients after 12 weeks of treatment with cernitin pollen extract.

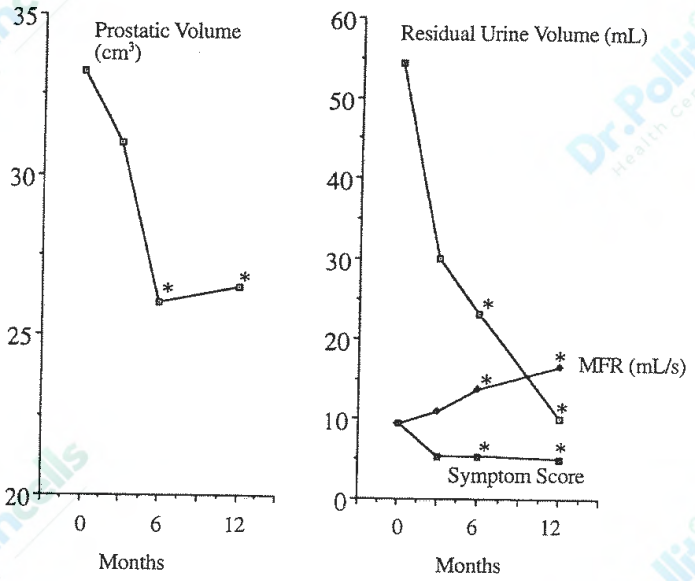

Figure 2. Change of symptom score and objective variables in patients with benign prostatic hyperplasia during treatment with cernitin pollen extract. A significant increase in flow rate and decrease in residual urine volume were noted in short-term follow-up (12 weeks, 79 patients), and a significant decrease in prostatic volume was also observed in long-term treatment (1 year, 28 patients). MFR = maximum flow rate. *$P < 0.05$ versus baseline.

Discussion and Conclusion

Transurethral resection of the prostate (TURP) is considered the gold standard for the treatment of BPH. Mortality and morbidity of TURP and quality of life of patients after TURP were studied in 1988,[8] and the results were not good. In one place of TURP, many modalities for the treatment of BPH (eg, hyperthermia or thermotherapy, urethral stent, urethral balloon dilation, and laser prostatectomy) have been developed and performed throughout the world.[9-11] However, the long-term results of these new modalities are controversial.

New medications,[12-14] such as antiandrogen drugs, alpha$_1$- blockade, and 5α-reductase inhibitors, have also been developed and used for treatment of patients with BPH. These drugs have excellent efficacy, but a few adverse reactions, including impotence[12] and hypotension,[13] have been reported.

Since 1970, many investigations on cernitin pollen extract have been done. As a result, it is well known that this extract improves detrusor activity, decreases resistance of the prostatic urethra, and suppresses prostatic cell growth[2-5] and thus has been used for the treatment of BPH patients. Buck and others[6] reported that cernitin pollen extract produced statistically significant improvement of 69 % in subjective symptoms compared with an improvement of 30 % with placebo. A significant decrease in residual urine volume and in the anterior-posterior diameter of the prostate was observed in patients treated with this drug. Our short-term results were satisfactory in 85 % of 79 patients with BPH, and long-term treatment reduced prostatic volume in 28 patients who continued treatment with Cernitin pollen extract. Compared with chlormadinone acetate,[12] prazosin,[13] and finasteride,[14] cernitin pollen extract has a slightly lower clinical efficacy. However, the advantage of cernitin pollen extract is the rare occurrence of side effects during long-term use.

Based on our results, we conclude that cernitin pollen extract has beneficial effects, especially a decrease in prostatic volume and an improvement in urination, in patients with symptomatic BPH.

Acknowledgement

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

In vitro Evaluation of the Pollen Extract, Cernitin T-60, in the Regulation of Prostate Cell Growth

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Summary—Nine human-derived cancer and non-cancer continuous cell lines were employed to evaluate the relative *in vitro* activity of the pollen extract, Cernitin T-60. Responses of the cell lines to the drug were assessed by measuring growth and cell survival as determined by cell count. The results demonstrated that of the 9 continuous cell lines tested, only those derived from the human prostate were growth inhibited by the pollen extract, whereas the non-prostate derived cells exhibited variable degrees of resistance to the T-60. The selectivity of the drug for the prostate cell lines was even more pronounced in the hormone- independent models, suggesting that there might be a place for the pollen extract in the control of abnormal growth in hormone-insensitive cells.

In spite of the considerable advances in our understanding of the processes leading to the growth and proliferation of the human prostate, the management of prostate diseases still remains a major clinical problem (Chisholm, 1989). Cancer of the prostate is the second most common cause of death due to cancer in males in the United Kingdom (Cancer Research Campaign, Factsheet 10.1, 1988) and the death rate is increasing. Clearly, the traditional forms of treatment such as surgery at the primary site, orchiectomy, hormone treatment and radiation are not as effective as Huggins might have originally perceived (Huggins and Hodges, 1941) and there is now every reason to find an alternative form of treatment.

Recently, there have been several reports suggesting that the pollen extract, Cernilton, is an effective agent in the treatment of prostate disease (Ito *et al*., 1986; *Buck et al.,* 1989). The pollen extract is a preparation produced by AB Cernelle in Sweden and is essentially a microbial digestion of a mixture of pollens which have been extracted first in water and subsequently with an organic solvent (Kimura *et al*., 1986).

In an attempt to assess the selectivity and specificity of these pollen extracts, we undertook a number of experiments to compare the *in vitro* activity of Cernilton towards a wide range of human-derived cancerous and non-cancerous continuous cell lines of prostate and non-prostate origin. We confined our experiments to the water soluble fraction T-60 component, which, accounts for approximately 60% of the pollen extract. In addition, we also undertook a few experiments on benign hyperplastic prostates to test the impact of the pollen extract on testosterone metabolism and the binding of androgens to their receptors.

Materials and Methods

Chemicals
Cernitin T-60 was a gift from AB Cernelle, Helisingborg, Sweden.

Tissues
Specimens of benign prostatic hyperplasia (BPH), obtained by transurethral resection, were transferred to the laboratory and either used immediately or snap frozen in liquid nitrogen and stored at -70° C.

Cell cultures
The epithelial and fibroblastic cell lines were all derived from human cancerous and non-cancerous tissue and details of their sources are given in Table 1. Of the 3 human prostate

cancer cell lines investigated, the LNCaP model is the only one which is hormonally responsive (Horosewicz *et al*., 1983), whereas the other 2 cell lines, the DU145 (Stone *et al.,* 1978) and the 1013L (Williams, 1980) were all hormone-insensitive. All cell lines were maintained at 37° C under a humidified atmosphere at 5% CO_2 and 95% air in 75cm^2 tissue culture flasks (Corning, New York, USA). The culture medium used was RPMI-1640 (Gibco, Paisley) supplemented with 10% (v/v) fetal calf serum, 20 mM HEPES, penicillin (100 units/ml), streptomycin (100 µg/ml) and 1% (v/v) L-glutamine. At each transplant, cells from the confluent monolayer were removed by trysinisation (trypsin 0.05%, EDTA 0.025%, Gibco) and suspended at 5x10^4 cells/ml in the growth medium.

Growth assays

Dose-response curves of Cernitin T-60 treatment were determined using the following method. Triplicate determinations for each treatment were performed in 24 well culture plates (Cell-Cult, Sterilin, Teddington). Each well was seeded with 5x10^4 cells and incubated overnight in the medium under incubation conditions as described above for routine cell culture. The following day, the T-60 stock solution was serially diluted in supplemented RPMI 1640 medium to yield concentrations of 1-4 mg/ml. Controlled cultures receive medium alone. For the dose-response curve studies, the cells were exposed to Cernitin T-60 for a total period of 4 days, with changes of freshly diluted T-60 in medium every 2 days. For the time course study, cells were treated in the presence and absence of T-60 for 1, 2, 3, or 4 days. Experiments were terminated by the removal of cells from the monolayer by 2 successive trypsinisations and the pellets of harvested cells were subsequently suspended in 0.5 ml of Dulbecco A Medium (Oxoid Ltd, Basingstoke). The counting of cells was achieved on a haemocytometer slide after a 1-2 dilution with trypsin/ glutamine.

Nuclear androgen receptors

Method used for the preparation of nuclear fractions and measurements of androgen receptors followed those previously published (Habib *et al*., 1986). For androgen receptor determinations, the competition binding assay was with 17α-methyl-^{3}H-methyltrienolone (R1881) in the presence of triamcinolone acetonide. Dissociation constants (Kd) and number of binding sites were determined by the Scatchard (1949) method.

Assay for 5a -reductase activity

5α-reductase was assayed at 37° C by following the conversion of (^{3}H) testosterone to (^{3}H) dihydrotestosterone and (^{3}H) 3α)β) androstanediol as previously detailed Habib *et al*., 1985).

Results

The effect of T-60 on cell growth

Proliferation curves of the hormone-sensitive and hormone-insensitive prostate cell lines in

Table 1 Details of Cell Lines

Cell line	*Tumour type*	*Source*	*Cell/well*	*Duration of drug exposure (days)*
HEP	Cancer of the larynx	Gifts from Dr Mary Norval, University Medical School, Edinburgh	5×10^4	1–4
CHANG	Cancer of the liver		5×10^4	1–4
HEF	Human embryo fibroblast		5×10^4	1–4
RT112	Cancer of the bladder	Dr J. R. W. Masters, Department of Pathology, St Paul's Hospital, London	5×10^4	1–4
SUZA	Cancer of the testis		5×10^4	1–4
DU145	Cancer of the prostate	Gifts from Dr D. Mickey, Department of Urologic Research, University of North Carolina, USA	5×10^4	1–4
1013L	Cancer of the prostate		5×10^4	1–4
LNCaP	Cancer of the prostate	Gift from Dr J. S. Horoszewicz, Department of Medical Virology and Oncology, Roswell Park Memorial Hospital, Buffalo, USA	5×10^4	1–4
MCF-7	Cancer of the breast	Gift from Dr W. R. Miller, Department of Clinical Surgery, University Medical School, Edinburgh	5×10^4	1–4

the absence and presence of increasing concentrations of T-60 for periods of up to 4 days are shown in Figure 1. Although the growth of each of these prostate cell lines was slowed following the addition of the pollen extract, the results show that the inhibition was much more marked in the case of the androgen-insensitive cell lines. Indeed, at 1mg/ml the pollen had no effect on the growth of the LNCaP cells, which exhibited an identical profile to that of the control, whereas the androgen-insensitive 1013L and DU145 cells demonstrated significant inhibition, particularly on day 4. By contrast, at the higher pollen concentrations (4mg/ml) the growth of all 3 prostate cell lines was arrested and the cell numbers were rapidly depleted with the time of exposure. After 4 days, cell counts had been reduced by an average of 94% compared with controls.

Parallel experiments on the non-prostate derived cell lines showed no response to pollen extract (1mg/ml) even after 4 days' exposure (Fig. 2). However, at the higher concentrations (4mg/ml) the pollen induced some inhibition with the HEF and RT112 cells ($P < 0.01$) following a 4-day incubation (Fig. 2), although this was not as marked as in the prostate cells. Significantly, none of the other non-prostate derived cells showed any significant response ($P > 0.5$).

The effect of T-60 on androgen metabolism and steroid receptors

We also tested the impact of increasing concentrations of Cernitin T-60 (0-10mg/ml) on the 5α-reductase activity of tissue obtained from 6 separate BPH patients. As demonstrated in Table 2, there was no change in the activity of the enzyme with increase in T-60 even at concentrations as high a 10mg/ml.

Table 2 Effect of T-60 Concentrations on 5α - Reductase Activity of the Human Benign Prostate

Patient no.	T-60 concentration (mg/ml) 0	0.75	2	10
1	1.44 ± 0.2*	1.34 ± 0.23	1.38 ± 0.12	1.25 ± 0.09
2	1.55 ± 0.18	2.08 ± 1.10	0.98 ± 0.12	1.58 ± 0.29
3	6.29	6.98 ± 2.72	8.46 ± 1.29	9.89 ± 0.89
4	2.21 ± 0.15	2.18 ± 0.19	—	2.23 ± 0.23
5	2.98 ± 0.52	3.18 ± 0.21	4.45 ± 0.56	—
6	2.58 ± 0.26	2.4 ± 0.24	2.32 ± 0.04	2.28 ± 0.65

* Values expressed in pmol/mg protein/min ± SD.

Table 3 Effect of Cernitin T-60 (4mg/ml) on Nuclear Androgen Receptor Measurements in 6 BPH Specimens

Treatment	K_d (nmol/l ± SD)	Binding site (fmol/g tissue ± SD)
Control	2.95 ± 0.60	84.4 ± 27.5
T-60 added	2.80 ± 0.57	78.8 ± 32.1

In addition, we undertook several experiments to measure nuclear androgen receptor levels in the absence and presence of the pollen extract at 4mg/ml. The results summarized in table 3

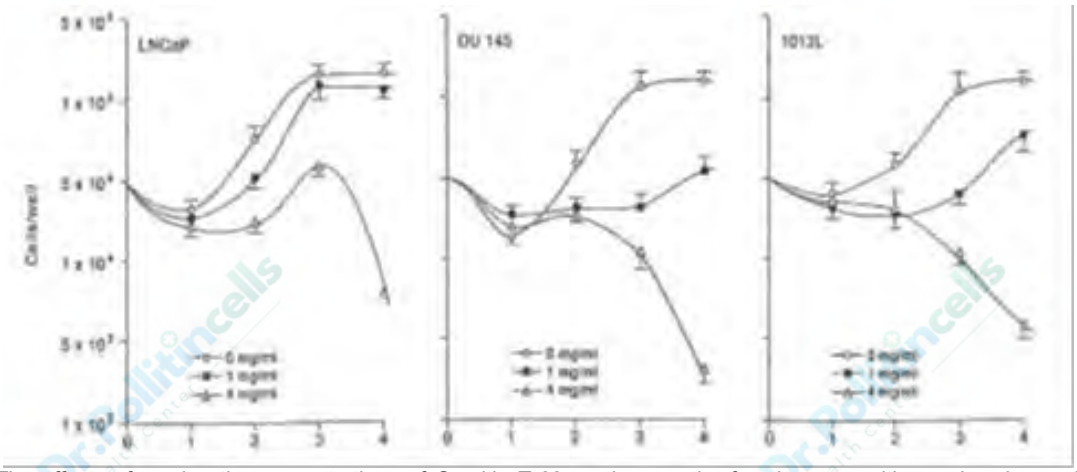

Fig 1. The effects of varying the concentrations of Cernitin T-60 on the growth of androgensensitive and androgen insensitive prostate cell lines. Each point represents the mean ± SD of 3 separate experiments each run 6 times.

indicate that there was no significant difference between the control and test groups with regard to the number of binding sites (P> 0.5) and dissociation constants (p> 0.5).

Discussion

These data represent the first report of the *in vitro* evaluation of the water-soluble fraction of the pollen extract, Cernitin T-60, using a panel of human prostate tumor-derived continuous cell lines. In addition, parallel in vitro experiments were also undertaken on 6 other cell lines derived from non-prostatic sources essentially to assess the specificity and efficacy of pollen extract.

Attempts to minimize variations between experiments were made by standardizing experimental conditions with regard to the same medium, fetal calf serum concentrations, and narrow range of cell passages. Furthermore, we observed a little variation in drug response with repeated experiments for each particular cell line. Nonetheless, the results of this study suggest that the responses induced were varied and these were predominantly a function of the cell lines: high in the case of the prostate, low or non-existent in the non-prostate derived cells. Of interest also is the heterogeneity in responses of the prostate cell lines to the agent. The hormone-insensitive cells demonstrated a greater sensitivity to the pollen extract than the androgen-dependent line and this was particularly evident at the lower pollen concentrations.

We are not yet sure of the mechanism of action of this drug but quite obviously it is not mediated via the androgen delivery system of the cell, since the pollen had no effect on either the 5α-reductase activity of the tissues or its steroid receptors. There have also been reports suggesting that Cernilton might be a potent inhibitor of the cyclo-oxygenase and lipoxygenase enzymes which are needed for leukotriene and prostaglandin synthesis (Loschen, personal communication) but these reports have not been extended to the prostate and will require verification.

However, it is gratifying to note that the selectivity of the pollen extract for the prostate, as demonstrated in the present study, was also supported by the work carried out by Ito *et al*. (1986). Following an intake of Cernilton over a period of 21 days, the rats in the latter study showed significant reductions in the weight of the ventral and dorsal prostate but there was no change in any of the other major organs.
Following these encouraging results, a double-blind trial was undertaken on a group of patients with BPH, the results of which are described by Buck *et al*. (1990).

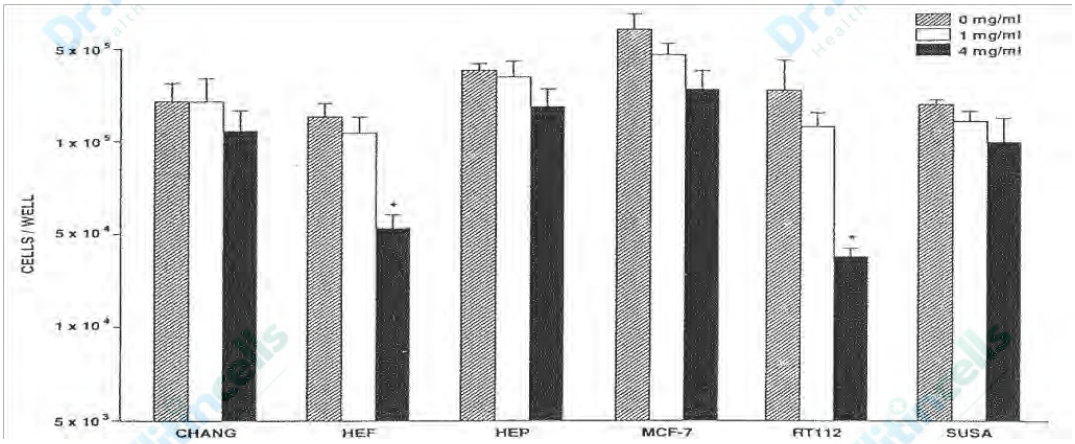

Fig. 2 The effect of Cernitin T-60 on the growth of 6 non-prostate derived cell lines after 4 days' exposure to the drug. Results are the mean ± SD of 3 separate experiments each run 6 times (P> 0.01).

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Clinical experience with Cernilton by means of double blind test

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Tokyo, Japan
March 25, 1968

Basing on the clinical results obtained, the author has previously reported that CERNILTON is effective in the treatment of prostatic hypertrophy. However, as the criteria of evaluation used then were primarily based on improvement in subjective symptoms, he thought psychosomatic factors might have played a substantial role. For this reason he performed, as reported here, a double blind test, using 4 cases which showed favorable response in the previous experiment and 10 new cases.

The details of each case are as shown in Table. Cases 1-5 were responsive to CERNILTON but were then given placebos in the course of treatment. Placebos and CERNILTON were identical in appearance, though slightly differing in smelling. None of the patients, however, noticed the difference.

In cases 2 and 3 there were noted no specific changes in symptoms after administration of placebos. This can mean one or the other: either that the effect of CERNILTON was continuing or that the effectiveness of CERNILTON had a suggestive effect on the patients. If in the former, it means placebos were ineffective and, if in the latter, psychosomatic factors played a part.

In cases 1 and 4 the subjective symptoms became exacerbated after administration of placebos, showing ineffectiveness of the placebos. In other words, the effectiveness of CERNILTON was proved. Subsequently, however, suprapubic prostatectomy was carried out in case 1 at the request of the patient.

Cases 6-14 visited the Outpatient Clinic with chief complaints of pollakisuria and dysuria and were all diagnosed as having prostatic hypertrophy. To avoid the influence the drug or psychic suggestions, placebos were given first, 4 tablets daily, or 2 tablets each in the morning and evening. As, however, there was obtained no improvement either in subjective or objective symptoms after 1-2 weeks' administration except in case 9, CERNILTON was given in place of placebos. In 2 weeks all the patients had good urination with marked improvement in subjective symptoms; residual urine decreased, too.

In case 9, with administration of placebos, the frequency of urination was decreased from 10 times to 5-6 times in the daytime and from 5-6 times to 1-2 times at night. Even after switching over to CERNILTON, the favorable clinical course continued.

In summary, while placebos exerted influence in 3 of 14 cases, no influence was noted at all in the other 11 cases. In other words, in 11 (78%) of 14 cases the effect was definitely due CERNILTON. It is obvious then that CERNILTON can be considerably effective in the treatment of dysuria associated with prostatic hypertrophy.

No.	Age	Chief Complaints	Residual urine	Clinical Course
1	60	Pollakisuria	100	Cernilton was given in doses of 4 tablets for 4 weeks. No residual urine. Then placebos were given for 2 weeks. The symptoms were exacerbated and prostatectomy was performed.
2	63	Pollakisuria	50	With Cernilton, residual urine was 10cc and urination decreased in frequency. With placebos, no specific changes were noted in subjective symptoms.
3	75	Nocturnal pollakisuria	80	With Cernilton, residual urine was 50cc. Placebos were given for two weeks but residual urine was not changed. Subjective symptoms were not exacerbated.
4	86	Dysuria	0	Urination improved with Cernilton. Placebos were given, but urination was again disturbed.
5	66	Anuria	600	Residual urine was 550cc after 7 days and 300cc after 14 days with Cernilton. Placebos were then given but the symptom was not improved.
6	74	Pollakisuria	50	Placebos were ineffective. Cernilton was given in doses of 4 tablets for two weeks. Frequency of urination decreased to 5—6 times in the daytime and one time at night. Residual urine was 20cc.
7	71	Imcomplete anuria	150	Placebos were given in doses of 4 tablets for 7 days after catheterization without effect. With Cernilton, sensation of urinary retention disappeared and residual urine was not found.
8	70	Dysuria	0	The patient voided 10 times in the daytime and 4 to 5 times at night had complained of marked sensation of urinary retention. Placebos had no effect at all. With Cernilton, good urination ensued.
9	55	Pollakisuria	10	The patient complained of dysuria and voided 4 to 5 times at night. Placebos were first given. In one week the frequency of urination decreased to 5—6 times in the daytime and 1—2 times at night. Cernilton was then given, but no changes vere noted.
10	75	Dysuria	130	The patient voided every one to two hours. With placebos, sensation of urinary retention became even worse. With Cernilton, the frequency of urination decreased to 4—5 times in the daytime and 1—2 times at night, and one month later urination was no longer disturbed.
11	74	Pollakisuria	30	The patient voided every 20 minutes in the daytime and had severe sensation of urinary retention. The symptoms were not changed at all with placebos. With Cernilton, sensation of retention disappeared and residual urine was 10cc.
12	75	Dysuria	50	No changes with placebo. After administration of Cernilton for two weeks, the frequency of urination was decreased from 4 times to 2 times at night.
13	63	Pollakisuria	0	The patient voided 8 times in the daytime and 3 times at night. Placebos were ineffective. Good urination with normal frequency was noted after administration of Cernilton.
14	71	Pollakisuria	100	The patient voided every 20 minutes in the daytime and 3 times at night. Placebos were ineffective. After administration of Cernilton, he voided every 3 hours and 2 times at night. Disturbance of urination was improved.

Conservative Treatment of Benign Prostatic Hyperplasia (BPH) with Cernilton N – Results of a placebo-controlled double-blind study

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Summary

The efficacy and tolerability of the pollen-extract preparation, Cernilton N*1, were investigated in a double-blind, placebo-controlled study carried out over a treatment period of 12 weeks in 6 urological practices, in a total of 103 patients suffering from benign prostatic hyperplasia (BPH) in Stages II and III. The investigational parameters were the disturbances of micturition classied according to the FDA recommendation, residual urine volume, palpation findings and uroflow index, as well as the global assessment of the therapy by the doctor and by the patient. Under the pollen-extract nocturia, the principal sign of BPH, improved in 68.8% of the cases, compared with 37.2% under the placebo medication (P<0.005). Notable differences were observed in day time frequency and in sensation of residual urine, which were statistically significant as regards absence of these symptoms after the treatment, between the treatment (AT) and placebo (Pl) (P = 0.010 and P = 0.016, respectively). Observation of the course of the symptoms after 6 weeks and 12 weeks showed higher rates of improvement under the active treatment, for all the individual symptoms. In case of the urodynamic study parameters similar changes were observed in the findings for all uroflow parameters, whereby the differences between the comparative groups were unremarkable.

At the control examination after 6 weeks a continuous increase in the maximum urine flow was observed, averaging 3.3 ml/sec under placebo (P = 0.060). The difference in the average decrease in the residual urine volume in the course of the treatment was statistically significant (AT/Pl: 24.3 ml/3.7 ml ; P = 0.006). The pollen-extract led to a continuous reduction, whereas in the placebo-group the residual urine after 12 weeks had increased in comparison with the value recorded after 6 weeks. Significant differences in the residual urine volumes before and after the treatment, in favour of the pollen-extract, were observed also in the patients in BPH Stage III (P = 0.042).

Prostate size and congestion showed higher response rates, in the sense of reduction in size and decongestion, as detected by palpation, under the active treatment, with a marked trend (AT/Pl : 88.5% / 69.0%; P = 0.155). Nausea was recorded under active treatment in one case. In accordance with their positive experiences with the treatment the investigating physicians and the patients assessed the therapeutic result under the pollen-extract as very good or good significantly more often than that obtained under placebo (P = 0.001). The results of the study prove the efficacy of the pollen-extract in patients with BPH in Stages II and III, in regard to the clinical symptomatology, urodynamics and the global assessment, and demonstate the good tolerability of the global assessment, and demonstrate the good tolerability of the drug, which permits long-term therapy with little risk of side effects.

Introduction

In view of the changing age structure and the rising average life expectancy of the male population the phytotherapeutic treatment of benign prostatic hyperplasia (BPH) will become increasingly more relevant. The justification and the need for such a drug therapy can be estimated on the basis of the available epidemiological data: the probability for a 40-year-old man to be operated for a BPH at the age of eighty is P = 0.292, and for him to develop the clinical symptoms of the disease it is P = 0.777 [4]. Consequently, for the treatment of BPH patients a symptomatically oriented medication

has priority. However, continuous observation of the course of the treatment must ensure that surgical measures are taken whenever they are indicated.

On the basis of our own positive experiences with the standardized pollen-extract preparation (trade-name Cernilton N) in the treatment of BPH, a placebo-controlled, double-blind study of the efficacy and tolerability of this drug was initiated and carried out in collaboration with six practicing urologists.

An effect on the congestion of the prostate and on the chronic inflammatory changes occurring in the framework of BPH is to be suggested as the pharmacodynamic mechanism of action for the symptomatic therapeutic effectiveness of pollen-extract preparation, as clinically a normalization of the pathological parameters of inflammation has been demonstrated in the EPS-expressed prostatic secretion (leucocytosis, raised pH value) [2].

Patients and Methods

For this randomized, placebo-controlled, double-blind study in BPH patients in Stages II and III according to Vahlensieck [12] a total of 103 patients could be include by six practicing urologists. Due to carcinoma in 1 case and antibiotic therapy for a concomitant urinary tract infection in 6 cases, a total of 96 patients were eligible for the statistical analysis.

Further specific criteria for exclusion form the study were: suspected carcinoma of the prostate, residual urine volume more than 150 ml, neurogenic disturbances of micturition, acute and/or chronic prostatitis/ prostatovesiculitis, malformation or post-operative status in the urogenital area with obstruction of the efferent urinary tract, bladder stones. Previously treated BPH patients were subjected to a four-weeks wash-out phase. All the patients received identical trial packs containing active drug or placebo capsules also of identical outward appearance. The treatment lasted 12 weeks, with control examinations of weeks 0, 6 and 12. The examination time 2 weeks after the start of the treatment, which was originally planned, proved to be impracticable. The dosage was 2 capsules t.i.d.

The control parameters investigated were: disturbances of micturition, nocturia, sensation of residual urine, dysuria, urge to urinate, discomfort in the inguinal, peritoneal and genital areas, palpation findings (enlargement, congestion of the prostate) uroflow index, residual urine volume determined by ultrasound, and the global assessment of the therapy by the doctor and by the patient.

In the laboratory examinations, SGOT, SGPT, PAP and creatinine in the serum were determined, as well as leucocytes, erythrocytes and germ count (if possible with identification of pathogens) in the sediment or in the urine culture. Besides descriptive-statistical methods the following analytical procedures were used: chi-square test (with Yates' correction for 2 x 2-field tables) for testing the homogeneity of qualitative parameters, comparison of the changes in the clinical symptoms at the end of the treatment versus the baseline findings, and for the comparison of the assessments of tolerability, the incidence of side effects and the global assessments by the doctor and by the patients, in both trial-groups; the t-test for
independent random tests in the homogeneity testing for age, height, body weight and urodynamic and quantitative laboratory parameters; the U-test in the homogeneity testing for the length of previous treatment of the BPH; variance analysis for the split-plot design for the evaluation of the course of the quantitative parameters. On account of
the findings, the different levels of attendance at the appointed examination times and the practicability of the study, parameter specific sample sizes were achieved which, in the evaluations of courses, are documented in the form of a reduced number of patients.

In accordance with the FDA recommendations, the disturbances of micturition were classified according to their intensity [1]. The statistical comparison was based on the changes observed under the treatment, which were recorded as ‘symptom-free’, ‘improved’, ‘unchanged’, or ‘worsened’. In patients with symptoms at the start of the study, response to the treatment is defined as a ‘symptom-free’ or ‘improved’ status of the therapy. Quantitative parameters were evaluated for the course and the pre-treatment/post-treatment comparison. The parallelism of the mean levels of intensity was also tested. The uroflow findings were

based on the secondary parameter, uroflow index (10).

Results

As regards medication and stage of the BPH, randomization gave a practically evenly distributed study population, with homogeneous baseline status in the two comparative groups. The age of the patients ranged from 42 to 85 years with a medium duration of the disease of 10 months; the BPH had been treated previously in 40.6 % of the cases (Table 1).

The initial clinical examination showed nocturia to be the leading symptom, occurring as a disturbance of micturition in 96.9 % of the patients (Figure 1). In the total study population examination by palpation showed enlargement of the prostate, with retained sulcus in 35.8 %, with obliterated sulcus in 55.8 % and with undefinable laterallobes in 8.4 % of the patients. On admission to the study, congestion of the prostate was palpable in 61.5 % of the cases, being classified as slight in 33.0 %, moderate in 17.5 % and severe in 11.0 %. The urodynamic status on admission to the study also showed homogeneous baseline data in the two comparative groups, whereby the uroflow parameters are presented also according to the uroflow index (Table 2).

Clinical symptomatology

As regards the clinical symptomatology, the pre-treatment/post-treatment comparison shows clear differences between the treatment groups: Under the pollen-extract the nocturia improved significantly, in 68.8% of the patients compared with 37.2% under the placebo medication. Freedom from the symptoms daytime frequency and sensation of residual urine is found significantly more frequently under the active treatment (table 3). For all the individual symptoms the examinations of the courses after 6 weeks and after 12 weeks of the study show higher rates of improvement or positive response course under the active treatment, with no change or deterioration under placebo. In the case of nocturia, day time frequency and sensation of residual urine these differences are particularly pronounced (Figure 2).

Enlargement and congestion of the prostate show higher response rates, in the sense of decrease in size and decongestion, under the active treatment (AT), whereby a striking trend is to be observed in comparison with placebo (PI) (Table 3). In contrast to the course in regard to the enlargement of the prostate, where the response rate remained constant in both groups, in the case of the congestion the improvement rate after 12 weeks, at 86.7%, was 20% higher than that recorded after 6 weeks' treatment, under the active preparation. In comparison, the response under placebo at these two examination times was 70.8% and 70.9%, respectively.

Urodynamics

Significant differences in favour of the pollen-extract are also to be seen in regard to the urodynamic test parameters. For all the uroflow parameters the changes in the findings were similar in both treatment groups, whereby the differences before and after the treatment are not statistically significant. Taking into account the examination after 6 weeks, a continuous increase of the initially pathological uroflow index is to be observed, by an average of 0.18, under the pollen-extract. In the placebo group ($\bar{x}$ = +0.10 after 12 weeks) the uroflow decreased in the second half of the study (Table 4, Figure 3).

The peak urine flow rate increase by an average of 3.3 ml/sec in the pollen extract group and by 0.9 ml / sec in the placebo group.

The difference in the reduction of the residual urine volume in the course of the study was statistically significant (AT 24.3 ml / PL 3.7 ml; $P = 0.006$). The pollen-extract leads to a continuous reduction, whereas in the placebo group there is a decrease after 6 weeks, compared with an increase in the residual urine volume after 12 weeks (Figure 3). When BPH stage III is considered separately there is an average decrease of 36.9 ml under the active treatment, compared with 7.2 ml under placebo, whereby an increase in the residual urine volume is to be observed in the second of the two 6-week study periods in the placebo group (Figure 4).

Global Assessment

The laboratory parameters show no noteworthy changes. Unwanted drug effects in the form of slight nausea are recorded in one case under the

active treatment. The good tolerability of the treatment is documented in 95.8% of the patients. With regard to the therapeutic efficacy, both investigator and patient assessed the result of the treatment as 'very good' or 'good' significantly more frequently under the pollen- extract (Figure 5). A statistically significant difference of the assessments by the investigator and by the patient was observed in the patients with an initially pathological uroflow index (Table 5).

Discussion

The results of this study demonstrate the good efficacy of the pollen-extract preparation in benign prostatic hyperplasia (BPH) in stages II and III. The superiority of the active therapy is documented in the symptomatology, the results of the urodynamic investigations and by the global evaluation of the therapy by both doctor and patient.

The course of the characteristic disturbances of micturition is an important parameter for the assessment of therapeutic efficacy. Under the pollen-extract the nocturia improved in the course of the 12-week study period in 68.8 % of the patients. In the placebo group, on the other hand, regression was observed in only 37.2 %. In the pre-treatment/post-treatment comparison this leading symptom of BPH showed a significant difference, which increased progressively in the course of the study, in favor of the active trial therapy. While under placebo the response rate remained practically constant, under the pollen-extract medication, regression of the symptoms was observed in a further 21.3% of the patients after the second 6-week period of the study. For the symptoms of daytime frequency and sensation of residual urine there are also clear differences in favour of the active treatment, whereby the differences as regards symptom-free status are statistically significant. For dysuria, urge to urinate and discomfort no statistically significant differences are recorded on account of the high placebo-response rates. The irritative symptoms, which are predominant in BPH, showed a particularly positive response to the active treatment. The obstructive components of the general disturbance of micturition were investigated on the basis of the urodynamic parameters, so that here an evaluation based on the symptoms themselves was not necessary.

As was to be expected, the size of the prostate, as determined by palpation, showed a low response rate, which remained constant in the course of the study.

Particularly striking is the change in the findings in regard to congestion of the prostate, which showed improvement in 69.0 % of the patients under placebo. Because of this high placebo-response rate, the response rate of 88.5 % under the active treatment is not statistically significant.

The differences in the response rates observed in the course of the study, between the active treatment and placebo, in the clinical symptomatology and in the congestion of the prostate demonstrate the sustained therapeutic effect of the pollen extract on the intensity of the disturbance of micturition.

Because of the relation of the peak urine flow on the volume voided (3,10), the uroflow index was chosen for the evaluation of these parameters. An increase in this index is to be observed in both comparative groups, whereby the difference is not statistically significant. In the assessment over the course of the study a continuous increase is seen in the active- treatment group, while under placebo the index decreases in the second half of the study.

The proportion of 35%, compared with 20% in the placebo group of initially pathological uroflow index values getting borderline or normal after treatment, is to be evaluated as a trend in favour of the active treatment. Clear differences are recorded in regard to the decrease in residual urine volume.

Under both trial preparations a reduction is to be observed in the first 6 weeks, which in the active treatment group becomes even more pronounced in the second half of the study, whereas under placebo there is a deterioration of the value recorded after the first 6 weeks.

As the separate evaluations according to the stage of the BPH demonstrate, the pollen extract leads to a more pronounced mean reduction in those cases with an initially high residual urine volume. The reduction in the residual urine volume in the patients with stage III BPH was 54.7 % under the active treatment and 12.5 % under placebo.

As a reflection of the therapeutic efficacy of the pollen-extract there are clear differences between the active treatment and placebo in the global assessments of the therapy by the doctors and by the patients. Particularly also in regard to the patient group with an initially pathological uroflow index, where the assessment of efficacy by the urologists as “poor” was documented in 41.9 % of the patients under placebo.

The fact that in 55.2 % of these patients the result of the treatment under the pollen extract was evaluated as “very good" or “good" is possibly an indication that the uroflow index is a relatively inaccurate parameter for detecting the more subtle urodynamic changes.

In order to obtain a representative patient population for the investigation of the efficacy of a drug therapy, this study was carried out in collaboration with six practicing urologists. The consistency of the data confirms our view that in the case of conservative therapeutic measures which are used mainly on an ambulant basis, the involvement of the preclinical aspects in the clinical research is both desirable and possible. However, the possible disadvantage that the number of patients attending the different control examinations can very has to be taken into account.

The mechanism of action of the pollen-extract can be suggestied as being its effect on the congestive and inflammatory changes occurring in BPH. Too little attention has been paid to the possible clinical relevance particularly of the chronic inflammatory changes (9, 11), the incidence of which, in BPH, is given as up to 98.1 % (5-8). In the long term, changes can develop in the connective tissue, which then become pathological in the form of fibrosis and sclerosis. The congestion of the prostate caused by stasis of secretions or the formation of interstitial edema also has to be considered as a pathophysiological substrate of the disturbances of micturition occurring in BPH. It is to be assumed that these concomitant changes lead to alterations in the nerve supply in the prostate and this influence the clinical symptomatology and urodynamice.

The documented normalization of the parameters of inflammation in the EPS with the pollen-extract in patients with chronic prostatitis (2), can explain the therapeutic efficacy of this preparation, in the sense of its antiedematous and anti-inflammatory action, also in patients with BPH. In view of the antisclerotic properties of the pollen-extract, with continuous application a long-term pharmacological effect on the clinical symptomatology and urodynamics is conceivable, so that surgical intervention, at least in certain cases, is not necessary (9).

Conclusion

The results of this study demonstrate the efficacy of the pollen-extract preparation in BPH patients in stages II and III, in regard to the clinical symptomatology, urodynamics, and global assessment. The pollen-extract preparation is well tolerated and makes long-term treatment possible with a low risk of side effects.The use of Cernilton N is recommended for the treatment of BPH stages II and III.

Acknowledgements

For their efforts in the realization of this study and for their excellent cooperation, our special thanks are due to our colleagues from Cologne, Dr. R.G. Kahrmann, Dr. J. Nuding, Dr. L. Pausch, Dr. G.-H. Rautenbach, Dr. J. Thissen and Dr. W.P. Winkler, and their assistants. We also thank Dr. J. Schnitker and his staff at the Institute for Applied Statistics, Bielefeld, for the biometric evaluation, Intramed GmbH, Hamburg, for production of the figures, and Mrs. U. Bumke, Hamburg, for the typing of the manuscript.

SYMPTOM	CLINICAL STATUS ON ADMISSION	% OF PATIENTS
Nocturia	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	96,9%
Daytime frequency	XXXXXXXXXXXXXXXXXXXXXXXXXXXX	89,1%
Urge to urinate	XXXXXXXXXXXXXXXXXXXXXXXX	87,9%
Sensation of residual urine	XXXXXXXXXXXXXXXXXX	66,3%
Discomfort	XXXXXXXXXXXXXXX	62,4%
Dysuria	XXXXXXXXXXXXX	47,3%

Figure 1: Clinical status on admission into the study: incidence of the different symptoms in the total study population (n = 96)

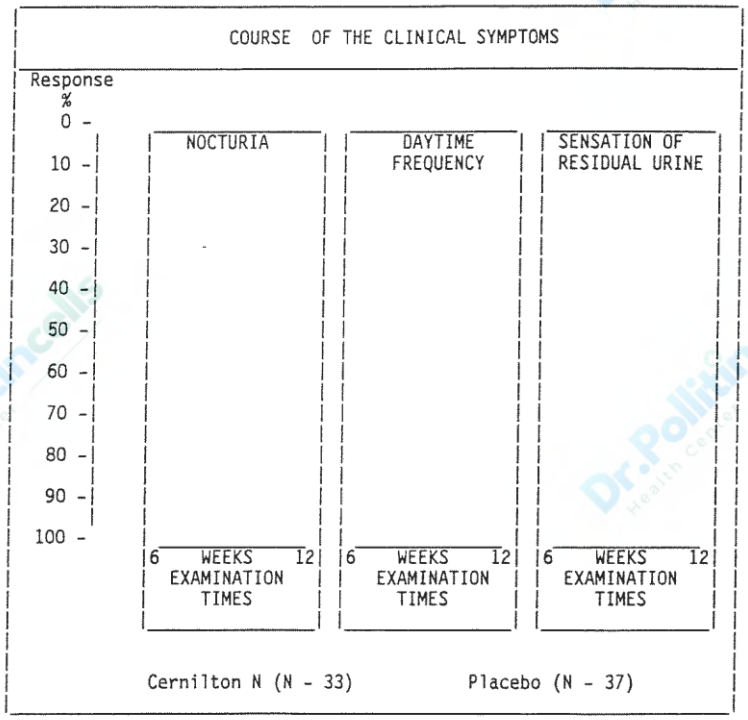

Figure 2: Response rate for the symptoms nocturia, daytime frequency and sensation of residual urine at the examinations after 6 weeks and 12 weeks, under the pollen-extract and placebo.

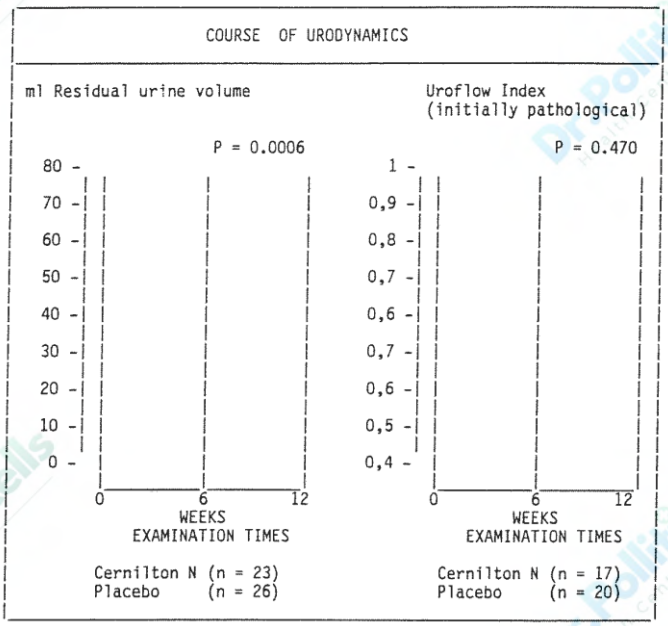

Figure 3: Course of the residual urine volume (ml) and the uroflow index (initially pathological) in the comparative groups. Continuous reduction resp. increase of the two parameters, under the pollen-extract.
Unfavourable response of both parameters after 6 weeks under placebo.

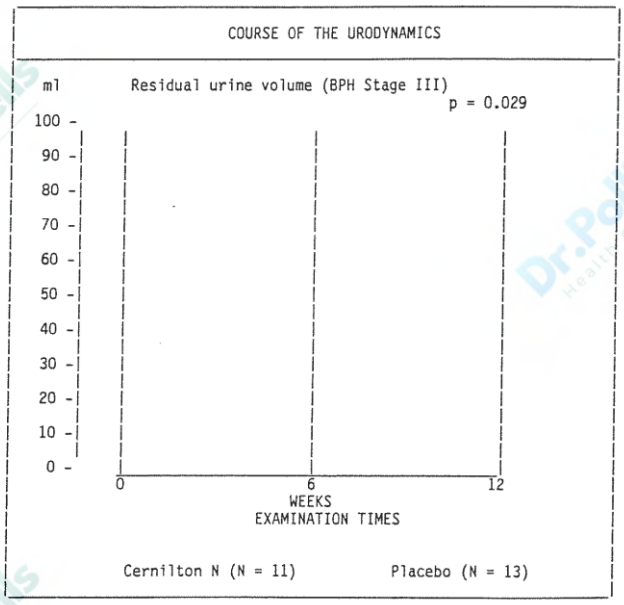

Figure 4: Course of the residual urine volume (ml) in BHP stage III. Significantly different and continuous reduction of the residual urine volume under the pollen-extract.
Increase of the residual urine volume in the second half of the study period under placebo.

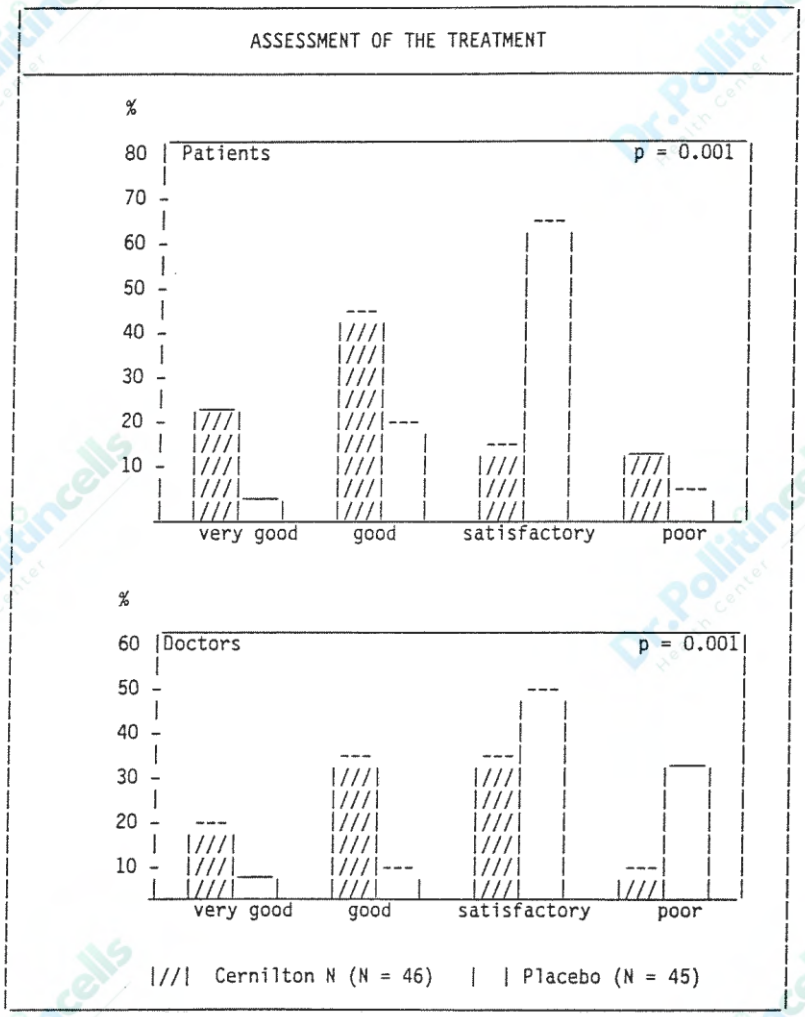

Figure 5: Significantly better assessment of the treatment by both doctors and patients in the pollen-extract group.

Table 1: Age distribution, BPH stage, duration of symptoms and previous treatment in the comparative groups. The BPH Stages are according to the classification of W. Vahlensieck.

Age Distribution and baseline status

Parameter	Value/Code	Cernilton N	Placebo
Age (years)	Minimum	42	45
	Maximum	83	85
	Median	65	67
	Mean value	66.0	67.1
	Standard deviation	9.7	10.1
BPH Stage	II	23	22
	III	25	26
Duration of Symptoms (months)	Minimum	1	1
	Maximum	48	48
	Median	11.4	8.3
	Missing data	4	3
Previous Treatment	No	29	28
	Yes	19	20

Table 2: Baseline urodynamid status: residual urine volume (ml) and uroflow index in the comparative groups. Homogeneous baseline status in both parameters (n = 96 and 86, respectively.

Urodynamic status at baseline

Parameter	Value/Code	Cernilton N	Placebo	Total	Homogeneity P-value
Residual urine volume (ml)	Minimum	0	0	0	
	Maximum	100	120	120	
	Mean value	45.6	47.8	46.7	0.735
	Standard deviation	30.6	31.5	31.5	
Uroflow Index	Minimum	0.21	0.27	0.21	
	Maximum	1.43	1.76	1.76	
	Mean value	0.73	0.71	0.72	0.843
	Standard deviation	0.26	0.33	0.29	

Table 3: Statistically significant differences in favour of the active treatment, in the symptoms nocturia , daytime frequency and sensation of residual volume. The congestion of the prostate improved significantly more frequently under the pollen-extract.

Pre-/Post-treatment comparison of clinical symptomatology

Symptom	Cernilton N	Placebo	Significance P-value
	Response		
Nocturia	68.8 %	37.2 %	0.005
Daytime frequency	65.8 %	43.9 %	0.076
Sensation of residual urine	71.4 %	48.1 %	0.109
	Freedom from symptoms		
Nocturia	25.0 %	16.3 %	0.445
Daytime frequency	48.8 %	19.5 %	0.010
Sensation of residual urine	37.1 %	7.7 %	0.016

Palpation	Cernilton N	Placebo	Significance P-value
Enlargement of the prostate	17.4 %	10.6 %	0.522
Congestion of the prostate	88.5 %	69.0 %	0.155

Table 4: Residual urine volume (ml) and uroflow index before and after treatment in the two comparative groups. Statistically significantly greater reduction of the residual urine volume under the pollen extract.

Pre-/Post-treatment comparison of the urodynamic findings

Parameter	Time of the control	Cernilton N		Placebo		Variance analysis P-value
		$\bar{x}$	s	$\bar{x}$	s	
Residual urine volume (ml)	n	48		48		
	Before treatment	45.6	30.4	47.8	32.8	
	After treatment	22.5	20.9	37.0	28.9	0.032
Uroflow Index	n	40		40		
	Before treatment	0.74	0.27	0.72	0.34	
	After treatment	0.86	0.25	0.82	0.31	0.747

Table 5: Significant better assessment of the treatment by Invti-gator in favour of pollen-extract in patients with initially pathological uroflow-index ($p < 0,001$)

ASSESSMENT OF TREATMENT (INVESTIGATOR) ON PATIENTS WITH INITIALLY PATHOLOGICAL UROFLOW-INDEX

	Cernilton N (n = 29)	Placebo (n = 31)
Very good	17,3 %	6,5 %
Good	37,9 %	6,5 %
Satisfactory	41,4 %	45,1 %
Poor	3,4 %	41,9 %

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Identification of a Prostate Inhibitory Substance in a Pollen Extract

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ABSTRACT: Recently, much attention has focused on the treatment of BPH with the pollen extract, Cernilton. The present investigation was designed to identify the active component in this agent which might be responsible for the symptomatic relief of BPH as previously reported [1,2]. Sequential purification of the active component present in the pollen extract was carried out by a combination of dialysis, gel filtration, and reverse phase chromatography. To monitor the biological activity of each of the purified fractions, a biological assay employing the human prostate cancer cell line DU145 was undertaken.

While we have identified a number of constituent components in the pollen extract, only one fraction designated V-7 (FV-7) maintained a strong inhibitory effect on the growth of DU145 cells. The inhibition was time- and dose-dependent, and the concentrations of FV-7 required to reduce the cell numbers by 50% (IC_{50}) after 2 days of exposure was 5 µg/ml. FV-7 was also inhibitory towards the primary culture of prostate stroma and epithelial cells, with the stroma/fibroblast showing greater sensitivity towards the HPLC-purified component. However, it should be noted that this inhibitory activity measured in the primary culture cells was only achieved at higher concentrations of FV-7. Preliminary characterization of the active ingredient identified FV-7 as DIBOA which is a cyclic hydroxamic acid. FV-7 and DIBOA induce similar inhibitory effects on the growth of DU145 cells.

KEY WORDS: BPH, primary culture, Cernilton, fraction V-7, DIBOA

INTRODUCTION

Attention has recently focues on an extract from rye pollen which was found to be most effective in the treatment of prostate diseases with no untoward side effects [1-3]. The pollen extract know as “Cernitin” is obtained by microbial digestion of the pollen followed by extraction with water and an organic solvent in a two-step process. Two fractions are consequently obtained: “T-60,” containing the water-soluble substances and accounting for more than 80% of the total extracted material and “GBX,” containing the fat-soluble substances. The two fraction T-60 and GBX are mixed in the final product designated “Cerniton” in a ration of 20:1 respectively.

Earlier studies on the water-soluble fraction, T-60, have shown that T-60 was inhibiting the growth of prostate cancer cell lines and primary cutlures from BPH specimens [4,5]. In the primary cultures, the inhibition was time- and concentraction-dependent, with the fibroblast stomal component showing greater sensitivity to the pollen extract than the epithelial cells derived from the same BPH tissue [5].

The results from the in vitro studies seem to be backed up by pharmacological and clinical data. Pharmacological investigations have demonstrated a significant reduction ($P<0.05$) in the ventral and dorsal lobes of rat prostates after Cernitin was administered orally for 21 days [6]. Furthermore, in a double-blind placebo-controlled study, there was a significant decrease in residual urine in patients with Cernilton ($P<0.025$) and in the antero-posterior and transverse diameters of the prostate on ultrasound ($P<0.025$) following 6 months’ treatment [2].

In an attempt to identify the growth inhibiting factor in T-60, fractionation was carried out

employing gel filtration and reverse phase chromatography. The eluted fractions were subsequently tested for their inhibiting effects on the prostate cancer cell line (DU145), and the active fractions singled out for further characterization and comparison with a known synthetic compound. Finally, the biological activity of the identified active substance was tested in primary cultures from BPH specimens.

MATERIALS AND METHODS

Chemicals and Purification Procedures

Cernitin T-60 was a gift from Cernitin SA, Lugano, Switzerland. The purification of the active compound present in T-60 was carried out by a combination of dialysis, gel filtration, and reverse phase chromatography steps. Details of the fractionation steps and of the chemical properties of the constituent product are the subject of a separate report [7; manuscript in preparation]. However, a brief summary of the strategy used is outlined in Figure 1. The synthesis of the active DIBOA compound was carried out by Professor U. Burger, Department of Organic Chemistry, University of Geneva, as detailed previously [8].

Cell Culture

To monitor and evaluate the biological activity of each of the purified fractions detailed in Figure 1, a biological assay employing the human prostate cancer cell line DU145 [9] was undertaken. This was based on the earlier experiments which demonstrated an inhibition in DU145 growth following exposure to the pollen extract [4]. The conditions employed for the growth of these cells have previously been described [4,10,11].

Primary Culture of Prostate Epithelial and Fibroblast Cells

Human BPH epithelial and fibroblast cells were cultured from prostate chips removed by transurethral resection. The epithelial and fibroblast cells were released from prostate tissue following overnight digestion in collagenase solution (600 IU/ml in 5% FCS RPMI 1640), and sub- and primary cultures were grown by plating onto plastic culture flasks and incubated at 37°C in a 95% air and 5% CO_2-humdified atmosphere. By using this system it was possible to establish and serially culture pure populations of both epithelial and fibroblast cells in well-defined media as detailed previously [5,12,13]. Verification of the cultures as prostatic fibroblast and epithelial cells has been confirmed by immunocytochemical staining employing a variety of antibodies, and also by phase contrast microscopy as described in our earlier work [5].

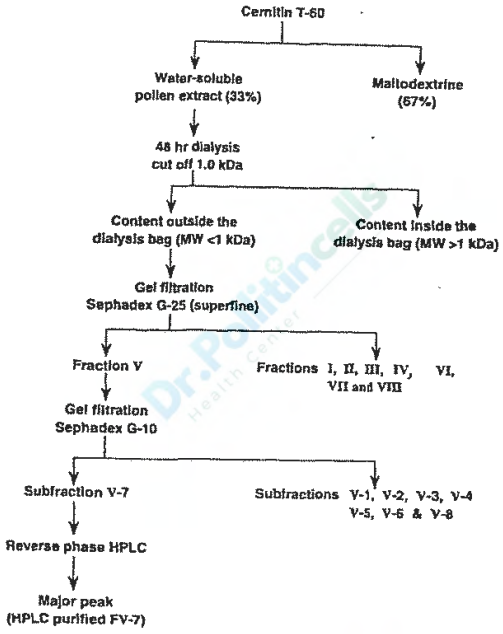


Fig. 1. Details of the fractionation steps and the strategy employed to isolate and purify the active ingredients in Cernitin T-60.

Cell Growth and Thymidine Incorporation

Cell growth was monitored using thymidine incorporation, backed up well cell counting using the trypan blue exclusion method. Confluent DU145 as well as stroma and epithelial cells from 75-cm^2 tissue culture flasks were harvested and plated at a density of 1.5 x 10^3 cells/well in 96-well plates. After plating the cells, the Cernitin fractions (1-100 µg/ml) were added for periods of up to 6 days, with media changes on day 3; control wells received no pollen extract fractions. Following the incubation, cells were plated with thymidine and harvested, and radioactivity was counted as published previously [5,10,11]. The patterns obtained were also confirmed by cell count using the trypan blue exclusion method. In parallel experiments, the activity of the synthetic DIBOA compound was tested for its effects on the growth of DU145 cells and compared to the activity of the natural component isolated from Cernitin T-60.

Statistical Analysis

Differences between control and test groups were examined for statistical significance by Student's *t* test.

RESULTS

Localization of the Active Ingredients in Cernitin T-60

At each step of the purification procedure (Fig. 1), aliquots of the fractionated substances were removed and tested for their DU145 inhibitory activity. Dialysis of the water-soluble component demonstrated that the activity was merely confined to the diffusate with an apparent molecular weight < 1 kD; the inert dialysate was therefore discarded. The diffusate was subsequently lyophilized and chromatographed one G-25 column yielding eight well-resolved fractions, of which only fraction V (FV) exhibited potent inhibitory activity (Fig. 2; Table 1). FV was, in turn, eluted on a G-10 chromatography column resulting in eight subfractions of which only subfraction 7 (FV-7) manifested a significant inhibitory activity towards the DU145 cells (Fig. 3; Table 1). Further purification of subfraction FV-7 was carried out on a reverse-phase high-performance chromatography column resulting in one major peak which was strongly inhibitory towards DU145 cells (Fig. 4). This peak accounted for approximately 90% of the material loaded on the HPLC column [7].

The biological potency of each of the active fractions was compared to the starting T-60 material, and the IC50 for each fraction was determined (Table 1). It is apparent from the data in Table 1 that the potency of the active substances increases markedly with each purification step, yielding a final product (FV-7) which is roughly 200 times more active than the starting T-60 product, and showing inhibitory activity at concentrations as low as 5 µg.ml (Table 1).

Effect of Fraction FV-7 on DU145

The results depicted in Figure 4 demonstrate the impact of increasing concentrations of FV-7 (Fig. 4a) and DIBOA (Fig, 4b.) on the growth of DU145 cells at different days of incubation. While both FV-7 and DIBOA at 1µg/ml demonstrated no effect on cell growth, increasing the concentration of either FV-7 or DIBOA to 10 µg/ml induced a strong inhibitory effect which was significantly different from control values ($P<0.001$) even after one day of exposure to either compound. However, the inhibitory activity of the natural product at 10 µg/ml appeared to be slightly more potent than that of the synthetic compound. Futher incubation of the cells for longer periods and/or with higher concentrations of the extract totally inhibited growth and depleted cell numbers.

Effects of Fraction FV-7 on Primary Culture of Prostate Epithelia and Fibroblast Cells

In addition to the studies on DU145, we have also examined the impact of the HPLC-purified FV-7 at various concentrations on the growth of primary culture of prostate epithelial and fibroblast cells obtained from patients with BPH. These studies were carried out over a period of 6 days.

The results depicted in Figure 5a,b demonstrate that FV-7 maintains a time- and concentration-dependent effect on both stroma and epithelial cells. At concentrations of 1 µg/ml, FV-7 stimulated DNA synthesis in the epithelial cells, including a 300% increase in thymidine incorporation ($P<0.001$) after 5 days' exposure. However, a dose-dependent decrease in DNA synthesis was also noted with concentrations >1 µg/ml. This was particularly evident in FV-7 at concentrations of 100 µg/ml, with the inhibition of the epithelial cells increasing with time of exposure and demonstrating an 80% inhibition following 4 days' treatment ($P<0.001$).

Experiments with primary culture of fibroblast cells yielded similar results to those described for the epithelium. Initially at a low concentration of FV-7 (1 µg/ml), the fibroblast cells were stimulated and thymidine incorporation increase by 90% after 5 days; treatment ($P<0.001$). However, at concentrations >10 µg/ml, FV-7 inhibited the growth of the fibroblast cells, with maximum inhibition being reached after 4 days' exposure.

DISCUSSION

The commercial preparation, Cernilton, contains a pollen extract of which the water-soluble fraction, designated Cernitin T-60, is exceeding heterogeneous and comprises mainly low

TABLE I. Identification of the Biologically Active Products in Cernitin T-60 Following Fractionation

Method for fractionation	Active fraction[a]	Weight of active fraction (% of T-60)	IC_{50}[b]
Initial product	T-60	100	1.0 mg/ml
Dialysis (cut off <1 kD)	Diffusate	60	0.8 mg/ml
Sephadex G-25	Fraction V	3.6	100 µg/ml
Sephadex G-10	Fraction V-7	0.3	10 µg/ml
Reverse phase HPLC	Fraction V-7 (HPLC-purified)	0.2	5 µg/ml

[a]As monitored by the DU145 cell proliferation test.
[b]Concentrations of active ingredient causing 50% growth inhibition of DU145 after two days of exposure.

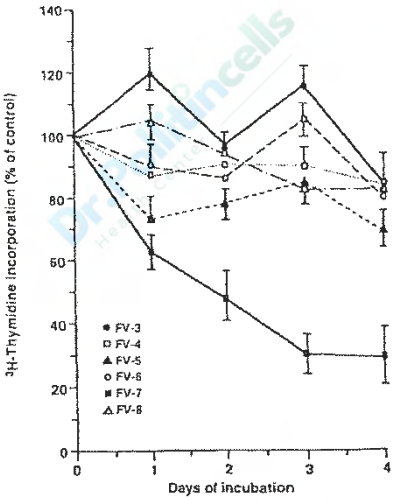


Fig. 3. Growth of the androgen-insensitive DU145 human prostate cell line following treatment with subfractions of FV (100 µg/ml). Experiments were carried for periods of up to four days, and the results are expressed as the percentage of ^3H thymidine incorporated relative to the untreated control. Each point is the mean of three separate experiments, each run eight times. Bars represent coefficient of variation.

molecular weight components, most of which have not yet been identified. All of the biological investigations to date have been conducted using the whole unfractionated Cernitin T-60 extract. This extract was recently reported to inhibit in vitro the growth of various prostatic cancer cell lines and primary cultures of fibroblast and epithelial cells [4-5]. The main objective of the present investigation was to extend those studies by identifying the active agent(s) present in the pollen extract, and to investigate the biological activity of the pure substance(s).

The strategy of combining the biological assays with the fractionation techniques enabled us to pinpoint the precise component responsible for inhibiting the prostate growth in vitro. The fraction designated FV-7 was shown to be inhibitory at a concentration as low as 5 µg/ml, and this is closely comparable to the concentrations of most other drugs used in in vitro assays. It was also of interest to note that FV-7 accounts for only 0.3% (w/w) of the total T-60 pollen extract, a value based on the combined material recovered from all fractions following the initial lyophilization. However, because of the losses incurred after every fractionation step, estimated at around 30% for each of the gel permeation chromatography and HPLC steps, it would be more realistic to assume that the concentration of FV-7 in the whole pollen extract may be close to 1% (w/w). Such a percentage is compatible with the growth inhibition data obtained with T-60 where inhibition >50% was recorded in the presence of 1 mg/ml of the original material [4].

The inhibitory effects of FV-7 on prostatic tumor cell growth appear to be dose- and time-dependent. After the initial exposure to FV-7, DU145 cells stop growing and dividing, an effect which can persist for at least nine days. Following reverse-phase HPLC, purified FV-7 at concentrations as low as 10 µg/ml induced significant inhibition of the DU145 cells, even after two days' exposure. The structure of FV-7 has been elucidated by mass spectrometry and nuclear magnetic resonance. The bulk of FV-7 (over 95%) was identified as DIBOA (2,4-dihyroxy-2H-1,4-benzoxazine-3(4H)-one; Fig. 6), a cyclic hydroxamic acid [7] which was originally found in most members of the Gramineae family of plants [14]. Up to now, the physiological properties of DIBOA had not been clearly elucidated, although its role as a phytotoxic agent has been suggested [15,16]. Furthermore, several laboratories have evaluated the antitumor activity of hydroxamic acid. It has

been shown that these may act as inhibitors of ribonucleotide reductase activity [17-19], but whether this is their mode of action in the human prostate still remains to be established. However, it was interesting to note that the inhibitory activities of FV-7 towards the prostate DU145 cells mimicked those of the synthetic DIBOA.

Although the usage of immortal cell lines has been most helpful in identifying the active inhibitory agent in the Cernitin T-60, their use is somewhat limited because of: a) the neoplastic nature of the continuous cells, while Cernilton is prescribed purely for BPH [3]; b) immortal cell lines are identical clones and do not therefore take account of the morphological heterogeneity of the prostate [20]; and c) continuous cell lines may undergo phenotypic changes and this might render them distinctive from the cells of origin [21]. In view of these limitations, we have decided to continue our work with the HPLC-purified Cernitin T-60 subfraction FV-7, employing the well-established primary cultures of epithelial and fibroblast cells form human hyperplastic prostates [5,12-13]. Those studies were facilitated by our abilities to establish and serially culture pure populations of epithelial and fibroblast cells in a well-defined serum-free medium [5].

The results outlines in this manuscript demonstrate that the HPLC-purified subfraction FV-7 acts on both epithelial and stromal cells in a dose-dependent fashion. At low concentrations, we have observed a stimulatory

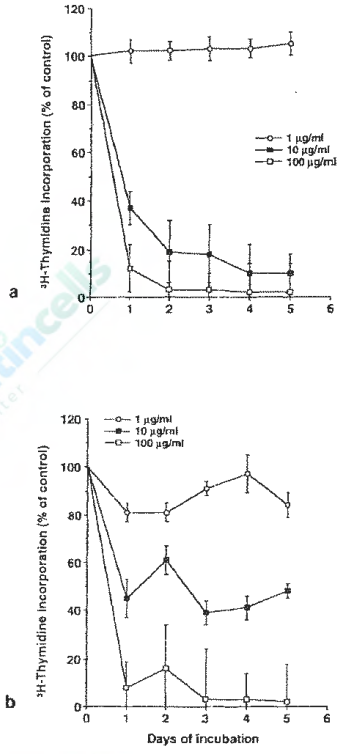


Fig. 4. The effect of time of exposure (1–6 days) to FV-7 (HPLC-purified, 1–100 µg/ml, **a**) and DIBOA (1–100 µg/ml, **b**) on DNA synthesis in the androgen-insensitive *DU145* prostate cell line. The data are expressed as percent of ^{3}H-thymidine incorporation relative to the untreated control. Each point represents the mean of three separate experiments, each run eight times. Bars represent coefficient of variation.

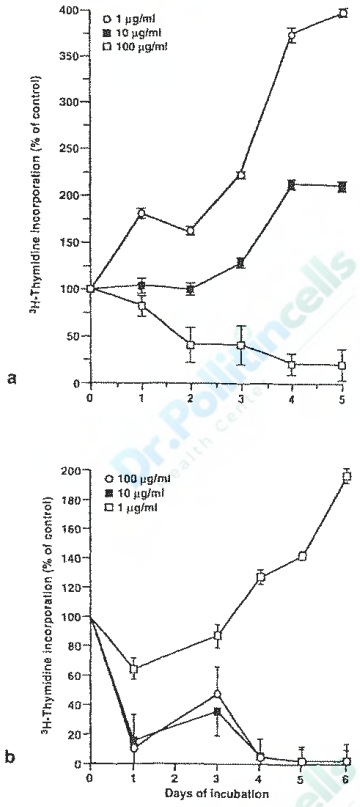
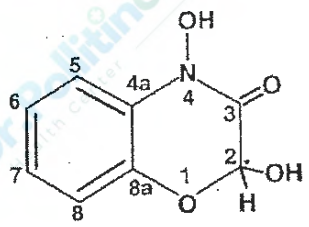


Fig. 5. The effect of HPLC-purified FV-7 at various concentrations on the cell growth of primary culture of epithelial **(a)** and fibroblast **(b)** cells. The data is normalized relative to the untreated control (100%), and each point represents the mean of three separate experiments, each run eight times. Bars represent coefficient of variation.



DIBOA

Fig. 6. The structure and formula of DIBOA (2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one).

effect, but this is totally reserved at higher concentrations when the active factor induces an inhibitory effect on both cell types. The reasons for the initial stimulation of DNA synthesis at the lower doses of FV-7 (<1 µg/ml) is not very clear, but it is significant that similar patterns have been observed with other herbal medicines [22] and may be related to an increase in cells in the A_0 or D_3 regions of the cell cycle [23] at the lower doses of FV-7. Additional studies are currently underway to elucidate the exact mechanism(s) responsible for this phenomenon. However, the stroma cells appear to be far more sensitive to exposure to this factor than the epithelium, which requires 10 times the concentrations of FV-7 to induce a comparable inhibitory effect. Since the human BPH is predominantly a stromal hyperplasia, the greater susceptibility of the stromal component to the Cernitin factor highlights the potential usefulness of this drug in the management of BPH. Efforts are now directed at identifying its mode of action and at the possibility that this is mediated via growth factors known to induce BPH pathogenesis [24].

ACKNOWLEDGEMENTS

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Diagnosis and Treatment of Chronic Prostatitis

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Introduction

Chronic prostatitis is one of genital disease frequently occurring in grown-up men, but its diagnosis is in many cases difficult, if it may seem easy at a glance. At present there is no proper therapy for chronic prostatitis, although marked results are now obtainable in acute cases thanks to the recent development in chemotherapeutics.

The present report concerns the author's experience with CERNILTON, a pollen preparation produced by AB Cernelle. Diagnosis and treatment of this disease are also dealt with.

Diagnosis

In chronic prostatitis complaints of patients are diverse. Thus, often the disease is erroneously diagnosed as chronic cystitis, prostatomegaly, neurogenic cystitis, etc. Leader describes that chronic prostatitis is a stagnant uninfectious lesion resulting from an inflammation in the past. However, in many cases organisms are not detectable or, if detected, cannot be precisely related to the disease. Moreover, there are patients who complain of various symptoms even though tests reveal no abnormal findings in urine, prostatitc secretion, etc., thus making the diagnosis more difficult.

In making a diagnosis of chronic prostatitis, it is first necessary to examine thoroughly the patient's anamnesis and present state of illness. As shown in Table 1, the symptoms of chronic prostatitis can be classified into 4 groups: symptoms of urethra, symptoms of rectum, symptoms of genital organs, and disturbance of sexual function. Various diseases are associated with these symptoms. According to Schnierstein, of the patients with these symptoms, 30% are suffering from true chronic prostatitis, 30% from rectal disturbance, and 30-40% from neurosis of genital organs.

Secondly, it is important to know the patient's sexual anamnesis, such as marital status, with or without children, ages of children, frequency of sexual intercourse, masturbation, nocturnal pollution, and disturbances in libido, erection, ejaculation, and orgasmus, though such questions difficult to make. If all these are considered, a fairly correct diagnosis can be made.

Of course, findings of palpation differ with state of inflammation of the prostate. Cases with comparatively new inflammations usually present a state in a) (Table 2), cases with old obsolete inflammations the state in b), and cases with localized inflammations in state in c). Thus, all inflammations are not necessarily associated with prostatic fluid or tenderness. Some cases are utterly free of fluid and tenderness and yet with a hard prostate. In such cases it may be necessary to suspect prostatic cancer.

Clinical examinations are also important. Urine test is an important means to find out where the lesion exists: urethra, prostate or urinary bladder. The best procedure employed is: first collect voided urine 10-20 cc, then take out urine in the bladder, and lastly collect voided urine after massaging prostate. Examination of semen is also necessary since chronic prostatitis is frequently associated with vesiculitis. Next important is x-ray examination. Chronic prostatitis often shows the same symptoms as

ureterolithiasis, prostatomegaly and urethral stricture. Therefore, it is necessary to take the x-ray of the urinary tract and then the ureterogram. If it is chronic prostatitis, Ask-Upmark says, there will be observed an infiltration of contrast media into the prostate, but, as he also says, the absence of the infiltration does not necessarily deny chronic prostatitis. The author has also tried ureterography on his cases. Indeed, as shown in Fig. 1, there were cases which showed infiltration of contrast media into the prostate, but it seems that such cases are rather rare. Finally, regarding cystoscopy, Schnierstein recommends that it be avoided in general. In some cases, however, cystoscopy is essential for distinction of the disease from others and thus cannot be uniformly forbidden. If all that have been said above are well taken into consideration, a reliable diagnosis of chronic prostatitis can perhaps be expected.

According to the author's experience in the past 4 years, as shown in Table 3, chronic prostatitis occurs most frequently in patients of the twenties and, when patients are old, prostatomegaly will come to be associated making the diagnosis more difficult and leaving only a few cases to be treated as true chronic prostatitis.

Subjective symptoms of chronic prostatitis are as shown in Table 4. Among them pollaksuria is most commonly observed, and it seems that a great number of patients are with complaints of urethral symptoms.

Table 5 shows palpation findings of the prostate. Patients with tenderness are noted in 42 cases, or 82%. It is believed that tenderness provides an important clue to the diagnosis of chronic prostatitis.

The urinary findings are given in the upper columns of Table 6. As may well be expected, WBC, RBC, and bacteria are more frequently revealed in those cases which received massage. The alterations of WBC, RBC, and bacteria after massage are shown in the lower columns of Table 6. While more cases showed increase after massage, decrease was also observed in a considerable number of cases. Thus, diagnosis cannot be made solely from urinary findings.

Treatment

Based chiefly on the theory of stagnant inflammation advocated by Leader, treatment of chronic prostatitis has hitherto consisted of massage and warming of the prostate, to which sulfonamides, antiphlogistic enzymes and antibiotics are added. Although in some cases this kind of treatment may take effect, in most cases the symptoms recur, with one symptom disappearing and a new one appearing. Therefore, complete cure is extremely difficult with this treatment.

The author has recently tried pollen preparation CERNILTON on 30 cases of patients diagnosed to be suffering from chronic prostatitis, the samples of which were supplied by Tobishi Pharmaceutical Co., Ltd.

CERNILTON has been employed as a tonic in patients of convalescent phase following treatment of infectious diseases or operation until 1960, when Ask-Upmark described it to be effective in chronic prostatitis. In 1961 Jonsson used it in 10 cases. Then, in 1962 Leander carried out a double blind test in a total of 179 cases. He said that about 90% of cases treated with CERNILTON showed disappearance or improvement of symptoms and about 50% of those treated with placebos showed improvement of symptoms. Considering, however, that all cases were given massage about once a week, he said the effective rate of CERNILTON would be roughly between 60 and 80%.

In the present experiment, other drugs were not combined in the cases treated with CERNILTON, and massage was given at intervals of 5-7 days merely for the purpose of urinary examination.

Improvements in subjective symptoms are shown in Table 8, with marked effects obtained in the CERNILTON-administration group. The palpation findings are given in Table 9, also showing marked improvement in the CERNILTON-administration group. The urinary findings are treated in Table 10 (only urine collected after massage was examined), with a slightly better

result obtained in the CERNILTON-administration group.

The criteria of evaluation were based on improvements in subjective and objective symptoms (urinary findings were not taken into consideration):

-Markedly effective: Cases where both subjective and objective symptoms nearly completely disappeared.

-Effective: Cases where symptoms were improved with one or more symptoms still persisting.

-Ineffective: Cases where no improvement was noted at all.

Results obtained according to these criteria are shown in Table 11. As may be noted therefrom, of all the cases treated with CERNILTON, only one case (dysuria) was utterly unresponsive. Symptoms were improved in 3 days in the earliest case, but on the average they were improved in about a week, which is significantly shorter than the length required in the control group. The dosage was uniformly 6 tablets per day in all cases. No side-effects were evidenced at all.

Concluding Remarks

Diagnosis of chronic prostatitis is extremely difficult. However, if the patient's anamnesis is accurately grasped, palpation of the prostate is properly made, and examinations of urine, semen, and x-ray are carried out systematically, it is believed an exact diagnosis can be made.

Hitherto, prolonged treatment has been instituted for this disease, yet repeated recurrence of symptoms has been quite common. With the pollen preparation CERNILTON, the author has been able to obtain improvement in a relatively short period of time, with an effective rate of over 80% as against 60-80% obtained by Leander.

Table 1. Symptoms of Chronic Prostatitis

1. Symptoms of urinary tract	:	Pollakisuria Dysuria Vesical tenesmus Discomfort on urination Pain on or after urination Feeling of residual urine
2. Symptoms of rectum	:	Rectal tenesmus Rectal oppression
3. Symptoms of genital organs	:	Sense of disturbance in genital organs, groin, sacrum and perineum Pubic pain Prostatorrhea Spermatorrhea Hemospermia Pyospermia
4. Disturbance of sexual function	:	Libido impediment Erection impediment

Table 2. Palpation findings of prostate

a) Size : Normal
Hardness : Elastic, soft
Surface : Uneven
Diffused or Localized tenderness
Tiny quantity of prostatic fluid
Increased WBC in prostatic fluid

b) Prostatic atrophy
Hardness : "Narbig" hard
Surface : Smooth or uneven
No prostatic fluid

c) Size : Normal or slightly swollen
Localized infiltration and tenderness

Table 3. Age

Under 20 years old	3 cases
20—29 years old	21 cases
30—39 years old	10 cases
40—49 years old	11 cases
Above 50 years old	6 cases

Table 4. Subjective Symptoms

Pollakisuria	26 cases
Pain after urination	14 cases
Feeling of residual urine	13 cases
Perineum pain	12 cases
Pain on urination	11 cases
Dysuria	9 cases
Abdominal pain	8 cases
Discomfort on urination	7 cases
Lumbago	4 cases
Bleeding after urination	3 cases
Bloody semen	3 cases
Pain on ejaculation	2 cases
Itching of urethra	2 cases
Urethral secretion	1 case
Anal pain	1 case

Table 5. Palpation Findings of Prostate

Tenderness	42 cases
Swelling	11 cases
Hardening	8 cases
Discharge of pus	1 case
Atrophy	1 case

Table 6. Urinary Findings

	Before Massage	After Massage
W.B.C.	39 cases	45 cases
R.B.C.	27 cases	31 cases
Microbes	9 cases	16 cases

Alterations after Massage

	Decreased	Increased
W.B.C.	11 cases	27 cases
R.B.C.	8 cases	25 cases
Microbes	5 cases	12 cases

Table 7. Composition of Cernilton

A. Kinds of Pollens

1.	Timothy	26 %
2.	Maize	26 %
3.	Rye	40 %
4.	Pine	5 %
5.	Orchard grass	2 %
6.	Alder	1 %

B. Contents in one tablet

1.	Cernitin GBX	3 mg
2.	Cernitin T 60	60 mg
3.	Calcium glyconicum	70 mg
4.	Saccharum lactis	70 mg
5.	Calcium phosphoricum dibasicum	140 mg
6.	Acidum alginicum	10 mg
7.	Potato starch	20 mg
8.	Pigmentum	3 mg
9.	Magnesium stearatum	4 mg
10.	Talcum	20 mg

Table 8. Improvement of Subjective Symptoms

	Cernilton + Massage			Other Drugs + Massage + Warming		
	Unchanged	Improved	Disappeared	Unchanged	Improved	Disappeared
Pollakisuria	0	4	14	0	3	5
Pain after urination	0	0	11	0	1	1
Feeling of residual urine	1	3	5	0	3	1
Perineum pain	1	2	7	0	1	1
Pain on urination	0	0	2	0	0	2
Dysuria	1	1	2	2	2	2
Abdominal pain	0	0	5	1	1	1
Discomfort on urination	0	0	7	0	0	0
Lumbago	0	1	1	1	0	1
Bleeding after urination	0	1	2	0	0	0
Bloody semen	0	0	0	0	3	0
Impotence	0	0	0	3	0	0
Pain on ejaculation	0	0	0	0	0	2
Itching of urethra	0	0	2	2	0	0
Urethral secretion	0	0	0	0	0	1
Anal pain	0	0	0	0	1	0

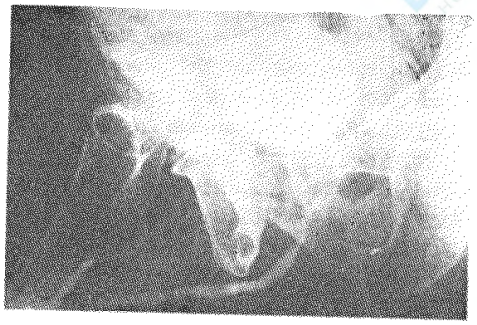
Table 9. Improvement of Objective Symptoms

	Cernilton + Massage			Other Drugs + Massage + Warming		
	Unchanged	Improved	Disappeared	Unchanged	Improved	Disappeared
Tenderness	3	6	14	5	6	7
Swelling	1	2	3	1	5	0
Hardening	3	2	1	0	1	0
Discharge of pus	0	0	1	0	0	0
Atrophy	1	0	0	0	0	0

Table 10. Urinary Findings

	Cernilton + Massage			Other Drugs + Massage + Warming		
	Unchanged	Decreased	Disappeared	Unchanged	Decreased	Disappeared
W.B.C.	9	10	9	2	9	4
R.B.C.	5	6	9	1	5	2
Microbes	2	0	7	0	1	1

Fig. 1. Urogram of Chronic Prostatitis



No.	Age	Length of adm. (days)	Subjective Symptoms	before adm.	after adm.	Objective Symptoms	before adm.	after adm.	Results
1	44	12	Lower abdominal pain Pain after urination Lumbago	+ + +	— — —	Prostate hardened	++	+	Effective
2	48	10	Pain after urination Pollakisuria Urethral bleeding	+ + +++	— — —	Prostate tender	+	±	Effective
3	28	19	Lower abdominal pain Pain on urination Dysuria	+ +++ +++	— — ±	Prostate tender	+	—	Effective
4	54	21	Pain after urination	+	—	Prostate swollen Prostate tender	+ ++	— +	Effective
5	25	7	Pollakisuria Pain of perineum	+ +	— —	Prostate tender	+	—	Markedly effective
6	17	5	Discomfort on urination Pain on urination Pain of perineum Feeling of residual urine	+ + + ++	— — — +	Prostate tender	+	+	Effective
7	27	14	Dysuria	+	+	No findings			Ineffective
8	30	36	Pain after urination Pollakisuria Pain of perineum Lower abdominal pain	+ ++ + +	— — — ±	Prostate tender	++	—	Markedly effective

No.	Age	Length of adm. (days)	Subjective Symptoms	before adm.	after adm.	Objective Symptoms	before adm.	after adm.	Results
9	41	11	Discomfort on urination Pain after urination Pollakisuria	+ ++ +++	— — ±	Prostate tender Prostate hardened	++ +	± ±	Markedly effective
10	32	9	Discomfort on urination Pain after urination Pollakisuria Pain of perineum	+ ++ ++ +	— — + +	Discharge of pus	+	—	Effective
11	33	7	Pain after urination Dysuria Lower abdominal pain	+ + +	— — —	No findings			Markedly effective
12	48	5	Pain on urination Pollakisuria Bleeding after urination	+ + +	— — —	Prostate tender	+	—	Markedly effective
13	26	12	Pollakisuria Bleeding after urination	++ ++	— +	Prostate tender Prostate swollen	+ +	+ —	Effective
14	25	21	Pain on urination Pollakisuria Feeling of residual urine	+ + ++	— — —	Prostate tender	+	—	Markedly effective
15	40	3	Discomfort on urination Pain after urination Feeling of residual urine	+ ++ +	— — —	No findings			Markedly effective
16	28	5	Discomfort on urination Pain on urination Pollakisuria Feeling of residual urine	++ + + +	— — ± +	Prostate tender	+	—	Effective

No.	Age	Length of adm. (days)	Subjective Symptoms	before adm.	after adm.	Objective Symptoms	before adm.	after adm.	Results
17	50	14	Pain on urination Pollakisuria	+ ++	— —	Prostate tender	+	—	Markedly effective
18	37	9	Discomfort on urination Pollakisuria Feeling of residual urine	+ ++ +	— — —	No findings			Markedly effective
19	24	7	Pain of perineum	+	—	Prostate tender			Markedly effective
20	54	9	Pain on urination Discomfort on urination Pollakisuria Feeling of residual urine	+ + ++ ++	— — — —	Prostate tender	+	—	Markedly effective
21	61	6	Pollakisuria	+++	—	Prostate hardened	+	+	Effective
22	23	11	Pain after urination Pain of perineum Pollakisuria	+ + +	— — —	Prostate tender Prostate swollen	+ +	± —	Markedly effective
23	21	7	Pollakisuria Pain of perineum	+ ++	— +	Prostate tender Prostate hardened	+ +	± +	Effective
24	40	15	Pain of perineum	+	±	Prostate tender Prostate swollen	+++ ++	+ +	Effective

No.	Age	Length of adm. (days)	Subjective Symptoms			Objective Symptoms		
				before adm.	after adm.		before adm.	after adm.
25	45	20	Lumbago Pain after urination	+ +	— —	Prostate tender Prostate atrophyed	+++ ++	— +
26	20	25	Pain on urination Itching of urethra Feeling of residual urine	+ + +	— — ±	Prostate tender Prostate swollen	++ ++	— —
27	52	5	Itching of urethra Pollakisuria Feeling of residual urine	+ ++ +++	+ +	Prostate tender Prostate hardened	+ +	+ +
28	29	5	Pain after urination Pollakisuria Pain of perineum	+ + +	— — —	Prostate tender Prostate swollen	+++ +	+ +
29	24	35	Lower abdominal pain Pain on urination Pain of perineum	+ + +	— — —	Prostate tender Prostate swollen	++ +	— —
30	17	20	Pollakisuria Dysuria Feeling of residual urine	+++ + +	— — —	Prostate tender	++	—

Effect of Cernitin on Rat Physiology

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Male rats, 8-day trial period

Comparative tests with Normal Feed, D Feed and C Feed.

Normal Feed:	Pellets used as rat food at the present laboratory.
D Feed:	Neutral feed pellets; do not contain Cernitin.
C Feed:	Cernitin D30 UK. Tablets containing 10% dehydrated extract.

The tests were performed on immature male rats (21 days old at commencement of tests). The rats were sacrificed after 8 days. The prostate, adrenals, pituitary, thyroid, thymus, the testes and the levator ani muscle were excised and weighed.

Supplements:

1. Weights of levator ani, prostate gland and testes of animals on all diets.
2. Weights of pituitary, thyroid, thymus and adrenal glands of animals on all diets.
3. The increase in body weight of the animals during the 8-day trial period, and the body weight at the end of experiment.

Suppl. 1

Lev. ani, testes and prostate weights

Normal Feed

	Lev. ani	*Prostate* mg				*Testes* mg
		V.L.	*D.L.*	*S.V.*	*Total*	
1.	27.8	78.9	34.4	23.3	136.6	895.4
2.	17.4	49.7	26.7	10.4	86.8	653.0
3.	34.6	47.3	30.3	14.7	92.3	809.9
4.	68.0	56.4	32.7	25.2	114.3	1104.9
5.	29.7	69.2	29.6	18.9	117.7	891.3
6.	43.8	61.6	47.8	20.0	129.4	1056.9
Mean:	36.9	60.5	33.6	18.8	112.9	901.9

D Feed:

Neutral, *no Cernitin* in the tablets

	Lev. ani	*Prostate* mg				*Testes* mg
		V.L.	*D.L.*	*S.V.*	*Total*	
1.	28.1	56.8	27.7	22.8	107.3	1029.4
2.	25.5	39.3	34.6	17.8	91.7	1007.3
3.	39.5	—	—	—	—	1022.4
4.	23.0	43.5	35.3	12.0	90.8	967.1
5.	28.6	50.5	29.0	16.6	96.1	1094.0
6.	29.0	34.1	30.6	15.6	80.3	752.4
Mean:	29.0	44.8	31.4	17.0	93.2	978.8

C Feed:

Including *Cernitin D30 UK*, respond. 10 % dehydrated extract in the tablets

	Lev. ani	*Prostate* mg				*Testes* mg
		V.L.	*D.L.*	*S.V.*	*Total*	
1.	17.7	50.0	38.4	15.5	103.9	911.9
2.	22.2	47.5	32.1	14.5	94.1	1021.0
3.	14.7	41.2	24.9	14.7	80.8	662.4
4.	25.7	55.6	30.3	13.3	99.2	603.4
5.	31.2	50.6	31.0	19.0	100.6	953.0
6.	56.3	50.1	32.0	17.9	100.0	872.5
7.	15.2	53.4	35.7	16.3	105.4	830.9
Mean:	20.3	49.8	32.1	15.9	97.7	836.4

Pituitary, thyroid, thymus and adrenals weights

Suppl. 2

Normal Feed

	Pituitary mg	*Thyroid* mg	*Thymus* mg	*Adrenals* mg
1.	4.2	8.2	373.4	21.8
2.	4.2	9.0	258.6	24.6
3.	5.0	6.6	234.4	24.7
4.	3.5	9.6	193.2	23.3
5.	5.0	6.6	235.4	24.2
6.	4.5	5.5	231.4	25.4
Mean:	4.4	7.6	254.4	24.0

D Feed:

Neutral, *no Cernitin* in the tablets

	Pituitary mg	*Thyroid* mg	*Thymus* mg	*Adrenals* mg
1.	3.2	7.0	305.1	21.0
2.	2.4	6.2	240.2	21.0
3.	3.2	6.8	282.7	19.1
4.	2.2	5.5	271.1	23.0
5.	4.0	7.0	216.2	20.8
6.	2.4	6.4	249.9	18.8
Mean:	2.9	6.5	260.9	20.6

C Feed:

Including *Cernitin D30 UK*, respond. 10 % dehydrated extract in the tablets

	Pituitary mg	*Thyroid* mg	*Thymus* mg	*Adrenals* mg
1.	3.5	7.5	265.7	20.6
2.	3.6	5.6	304.4	20.2
3.	5.0	10.9	295.2	17.1
4.	4.5	5.4	301.0	19.7
5.	4.8	7.0	287.0	21.6
6.	3.5	6.1	349.8	22.0
7.	2.0	5.4	329.7	21.3
Mean:	3.8	6.8	304.7	20.4

Suppl. 3

	Normal Feed (weight incr.	final weight)	*D Feed* (weight incr.	final weight)	*C Feed* (weight incr.	final weight)
1.	35.4	94.2	31.8	93.6	21.6	81.2
2.	25.0	78.4	26.4	87.8	26.9	86.4
3.	34.0	84.4	29.7	88.5	20.0	72.8
4.	35.4	93.2	28.4	89.6	18.8	75.0
5.	13.4	76.2	30.0	90.8	31.2	91.2
6.	35.8	95.8	20.7	79.5	24.2	80.2
7.	—	—	—	—	28.0	85.2
Mean:	29.8	87.0	27.8	88.3	24.4	81.7
Quantity:	472 g (78.7 g/rat)		750 g (125 g/rat)		465 g (66.3 g/rat)	

Final weight: weight on day of sacrifice
Weight increase: per 8 days.

3

Hypophysectomized male rats, 8-day trial period

Comparative Tests with Normal Feed, D Feed and C Feed.

Normal Feed: In this test = white bread, milk, oranges.
D Feed: Neutral food pellets, not containing Cernitin.
C Feed: Cernitin D30 UK. 10% dehydrated extract in the tablets.

The D and C diets were supplemented with milk.

The tests were performed on immature, hypophysectomized male rats. The animals were 21 days old when operated on and the tests commenced 4 days later. The rats were sacrificed after 8 days. The prostate, testes, adrenals, thyroid and thymus glands, and the levator ani were excised and weighed.

Supplements:

1. Weights of levator ani, prostate gland and testes.

   Abbreviations:
   V.L. = ventral prostate lobe
   D.L. = dorsal prostate lobe
   S.V. = seminal vesicles
   Total = total weight of accessory reproductive organs
   Lev. Ani = Levator ani.

2. Weights of thyroid, thymus and adrenal glands, weight of animals on day of sacrifice, and weight increase or weight decrease.

Suppl. 1

Normal Feed (white bread, milk, oranges)

	Lev. ani	*Prostate*			*Total*	*Testes*
		V.L.	*D.L.*	*S.V.*		
	mg		mg			mg
1.	8.7	4.8	11.9	4.6	21.3	138.2
2.	8.0	7.1	11.9	7.3	26.3	130.4
3.	6.0	4.2	8.5	6.3	19.0	117.2
4.	8.0	3.5	5.1	5.4	14.0	101.8
5.	12.0	5.9	12.0	4.6	22.5	140.9
6.	10.4	5.4	11.7	4.5	21.6	127.7
7.	9.2	4.2	11.0	4.0	19.2	124.7
Mean:	8.9	5.0	10.3	5.2	20.5	125.8

D Feed=Neutral diet, *no Cernitin* in the tablets

	Lev. ani	*Prostate*			*Total*	*Testes*
		V.L.	*D.L.*	*S.V.*		
	mg		mg			mg
1.	8.2	4.6	9.6	3.8	18.0	89.2
2.	8.4	6.0	11.5	5.5	23.0	94.4
3.	18.2	6.5	10.5	4.4	21.4	87.8
4.	9.6	4.7	12.7	4.7	22.1	118.2
5.	13.0	7.2	13.7	5.7	26.6	228.8
6.	8.4	2.3	11.9	5.2	19.4	87.7
7.	13.8	5.3	11.9	5.6	22.8	88.3
Mean:	11.4	5.2	11.7	5.0	21.9	113.5

C Feed=Cernitin D30UK. 10 % dehydrated extract in the tablets

	Lev. ani	*Prostate*			*Total*	*Testes*
		V.L.	*D.L.*	*S.V.*		
	mg		mg			mg
1.	14.4	—	15.8	6.7	—	114.5
2.	7.6	—	14.7	4.4	—	89.4
3.	11.9	5.1	12.7	5.5	23.3	105.8
4.	10.6	2.6	12.2	4.6	19.4	88.2
5.	12.6	4.3	12.5	4.8	21.6	103.2
6.	6.2	4.3	14.5	4.9	23.7	107.7
Mean:	10.6	4.1	13.7	5.1	22.0	101.5

Suppl. 2

Normal Feed (white bread, milk, oranges)

	Thyroid	*Thymus*	*Adrenals*	*Weight on day of sacrifice*	*Weight increase 8 days*
	mg	mg	mg	g	g
1.	5.2	142.8	4.6	47.4	+1.6
2.	5.0	147.2	7.0	48.2	+2.0
3.	3.4	132.8	5.0	47.3	+0.5
4.	4.2	142.8	7.8	51.8	+4.4
5.	5.5	138.2	8.5	51.6	+2.6
6.	4.0	60.3	8.2	42.9	+2.7
7.	4.5	121.3	8.0	45.0	+0.0
Mean:	4.5	126.5	7.0	47.7	

D Feed = Neutral diet, *no Cernitin* in the tablets

	Thyroid	*Thymus*	*Adrenals*	*Weight on day of sacrifice*	*Weight increase 8 days*
	mg	mg	mg	g	g
1.	5.0	79.3	8.0	46.0	+0.8
2.	12.5	86.7	9.0	43.4	—3.0
3.	7.3	100.4	13.8	45.2	+3.8
4.	5.8	63.2	8.4	46.5	—2.3
5.	4.8	105.2	10.2	50.4	—0.6
6.	6.5	99.7	7.0	45.6	+1.2
7.	4.8	53.6	7.6	43.0	—11.8
Mean:	6.7	84.0	9.1	45.7	

Food consumption for 7 animals during 8 days: 220 g.
Initial number of animals = 12. 5 deaths during the experiment.

C Feed = Cernitin D30 UK. 10 % dehydrated extract in the tablets

	Thyroid	*Thymus*	*Adrenals*	*Weight on day of sacrifice*	*Weight increase 8 days*
	mg	mg	mg	g	g
1.	4.0	56.0	8.2	45.2	—1.4
2.	4.5	92.4	6.6	44.8	—2.6
3.	6.8	72.0	8.0	44.0	—4.4
4.	6.2	42.8	6.0	42.0	—0.8
5.	5.5	74.6	6.5	41.5	—1.9
6.	3.4	40.0	6.8	41.0	—7.6
Mean:	5.1	63.0	7.0	43.1	

Food consumption per 8 days: 45 g (6 animals died during the experiment).

Female rats, 8-day trial period

Comparative Tests with Normal Feed, D Feed and C Feed.

Normal Feed =	Pellets as used in this laboratory
D Feed =	Neutral food pellets, no Cernitin in the tablets.
C Feed =	Cernitin D30 UK. 10% dehydrated extract in the tablets.

The tests were performed on immature female rats aged 21 days at the commencement. The rats were sacrificed after 8 days. The ovaries, uteri, pituitary, thyroid, thymus, and adrenal glands, were excised and weighed.

Vaginal smears were taken on the 6th, 7th, and 8th days.

Supplements

1. Weights of ovaries and uteri, results of vaginal smears, the weight increase and the final weight.

   Abbreviation: V-smear = vaginal smear.

2. Weights of pituitary, thyroid, thymus and adrenal glands.

Suppl. 1

Normal Feed

	Ovaries	*Uterus*	*V-smear*	*Weight increase*	*Final weight*
	mg	mg	(6th-8th day)	g	g
1.	18.0	25.9	negative	23.4	75.2
2.	23.1	33.6	negative	31.7	82.3
3.	19.8	21.6	negative	17.0	67.8
4.	28.2	35.4	negative	26.8	78.8
5.	25.7	45.2	negative	27.8	79.4
6.	20.9	31.8	negative	27.3	79.8
7.	23.3	36.6	negative	32.0	83.2
8.	22.2	27.2	negative	31.0	81.2
Mean:	22.7	32.2	—	27.2	78.5

Food consumed: 574 g (71.8 g/rat)

D Feed: Neutral diet, *no Cernitin* in the tablets

	Ovaries	*Uterus*	*V-smear*	*Weight increase*	*Final weight*
	mg	mg	(6th-8th day)	g	g
1.	18.7	28.8	negative	18.0	69.3
2.	21.3	33.3	negative	26.0	74.2
3.	21.1	27.3	negative	24.3	76.5
4.	18.6	41.7	negative	26.6	82.8
5.	17.0	25.7	negative	12.0	64.5
6.	17.8	26.3	negative	17.2	65.6
7.	22.6	23.4	negative	18.0	69.2
Mean:	19.6	28.4	—	20.3	71.7

Food consumed: 773 g (110.4 g/rat)

C Feed: Cernitin D30 UK, respond. 10 % dehydrated extract in the tablets

	Ovaries	*Uterus*	*V-smear*	*Weight increase*	*Final weight*
	mg	mg	(6th-8th day)	g	g
1.	22.8	24.0	negative	16.0	69.2
2.	27.0	—	negative	17.4	65.2
3.	18.2	39.7	negative	8.2	59.0
4.	18.5	26.1	negative	17.5	65.5
5.	23.5	49.5	negative	23.8	77.8
6.	22.4	32.7	negative	23.2	75.0
7.	20.3	38.2	negative	16.2	66.6
Mean:	21.8	35.0	—	17.4	68.3

Food consumed: 497 g (71 g/rat)

Suppl. 2

Normal Feed

	Pituitary mg	*Thyroid* mg	*Thymus* mg	*Adrenals* mg
1.	—	13.7	142.2	18.7
2.	4.0	10.4	332.0	23.2
3.	2.0	6.0	211.8	24.3
4.	3.8	6.8	232.6	26.9
5.	2.8	5.4	192.0	22.2
6.	4.0	9.4	227.6	25.1
7.	2.8	6.2	289.4	26.8
8.	4.1	5.4	282.2	23.2
Mean:	3.4	7.9	238.7	23.8

D Feed: Neutral diet, *no Cernitin* in the tablets

	Pituitary mg	*Thyroid* mg	*Thymus* mg	*Adrenals* mg
1.	3.3	8.5	199.2	27.2
2.	2.5	8.0	219.6	24.9
3.	2.6	8.8	223.8	22.7
4.	1.8	5.2	277.2	25.2
5.	2.2	4.6	132.9	20.7
6.	2.5	6.2	232.0	20.0
7.	2.5	5.2	166.8	17.2
Mean:	2.5	6.6	207.4	22.6

C Feed: with *Cernitin D30 UK*, respond. 10 % dehydrated extract in the tablets.

	Pituitary mg	*Thyroid* mg	*Thymus* mg	*Adrenals* mg
1.	3.2	5.8	262.4	23.8
2.	3.0	6.5	203.0	23.6
3.	2.8	6.8	209.8	22.4
4.	2.2	5.2	234.2	23.1
5.	3.2	5.6	336.4	22.8
6.	3.5	7.0	245.0	23.3
7.	3.2	5.3	259.6	24.0
Mean:	3.0	6.0	250.1	23.3

Immature male rats, 21-day trial period

Comparative tests with Normal Feed, D Feed and C Feed.

Normal Feed: Pellets as used in this laboratory
D Feed: Neutral food pellets, no Cernitin in the tablets.
C Feed: Cernitin D30 UK. 10% dehydrated extract in the tablets.

The tests were carried out on immature male rats (21 days old at the commencement). The rats were weighed twice weekly and sacrificed after 21 days. The prostate, adrenals, pituitary, thyroid and thymus glands, and the levator ani, were excised and weighed.

The tests were performed on litter-mate controlled animals, each animal in the same litter having the same number in the different diet tables. Each litter consisted of six animals, and three litters were used, the animals being numbered 1A, 1B, 2A, 2B, etc.

Supplements:

1 A, 1B = weights of organs of animals on normal diet.
2 A, 2B = weights of organs of animals on D Feed.
3 A, 3B = weights of organs of animals on C Feed.
4 = weight increase during 21-day period and food consumption.
5 = weight of animal on day of sacrifice.

Suppl. 1 A

Normal Feed

(Testes and Prostate weights)

Litter No.	*Prostate* mg				*Testes* mg
	V.L.	*D.L.*	*S.V.*	*Total*	
1. A	93.8	92.0	34.0	219.8	1.845.3
1. B	104.3	62.3	57.2	223.8	1.868.1
2. A	83.0	59.6	60.0	202.6	1.844.0
2. B	54.7	61.3	47.5	163.5	2.034.8
3. A	96.9	94.8	83.0	274.7	1.981.3
3. B	113.3	86.8	71.4	271.5	2.080.7
4.	104.9	89.5	80.2	274.6	2.025.0
5.	106.8	61.1	43.1	211.0	1.793.1
6.	128.6	94.6	88.8	312.0	1.786.1
7.	85.7	83.7	47.2	216.6	1.805.6
8.	86.8	98.4	82.1	267.3	1.905.6
9.	101.5	91.0	74.7	267.2	1.901.0
10.	85.7	97.0	55.1	237.8	1.956.0
11.	111.0	89.0	84.0	284.0	2.135.9
12.	61.4	89.3	65.2	215.9	1.706.4
Mean:	94.6	83.4	64.9	242.8	1.911.3

Abbreviations: V.L. = Ventral prostate lobe
D.L. = Dorsal prostate lobe
S.V. = Seminal Vesicles
Total = total weight of accessory reproductive organs (= V.L. + D.L. + S.V.)

Suppl. 1 B

Normal Feed

(Adrenals, pituitary, thyroid, thymus and levator ani weights)

Litter No.	*Adrenals* mg	*Pituitary* mg	*Thyroid* mg	*Thymus* mg	*Levator ani* mg
1. A	27.3	6.3	10.3	393.0	12.7
1. B	23.2	6.6	12.8	396.5	42.2
2. A	19.6	4.1	8.5	489.9	44.6
2. B	28.6	4.7	6.1	304.8	37.5
3. A	26.8	—	13.4	408.1	35.0
3. B	23.5	5.6	9.4	483.8	27.8
4.	26.2	5.1	12.8	380.3	44.9
5.	24.3	5.4	9.0	352.4	36.8
6.	19.2	5.6	7.5	375.2	38.4
7.	27.2	7.2	10.4	338.4	54.1
8.	28.0	6.8	10.0	384.4	51.1
9.	26.1	6.3	12.1	463.8	56.7
10.	22.3	4.4	10.5	334.7	42.5
11.	28.4	4.6	8.5	315.7	60.3
12.	24.3	4.6	8.0	273.9	43.6
Mean:	25.0	5.5	9.95	379.7	41.9

Suppl. 2 A

D Feed: Neutral diet, *no Cernitin* in the tablets

(Weights of testes and prostate)

Litter No.	*Prostate* mg				*Testes* mg
	V.L.	*D.L.*	*S.V.*	*Total*	
1. A	70.8	40.7	25.7	137.2	1.893.0
1. B	54.5	49.1	20.8	124.4	1.605.0
2. A	62.2	55.4	36.3	153.9	1.834.2
2. B	37.3	39.7	19.3	96.3	1.272.2
3. A	69.0	61.7	30.0	160.7	1.945.4
3. B	57.5	44.4	23.5	125.4	1.608.9
4.	32.6	34.6	12.8	80.0	1.120.7
5.	43.8	42.0	17.5	103.3	1.152.4
6.	36.6	39.1	10.2	85.9	1.225.7
7.	40.0	36.7	10.1	86.8	1.416.3
8.	49.6	46.8	22.2	118.6	1.543.0
9.	56.3	42.2	19.7	118.2	1.513.2
10.	43.5	40.1	16.9	100.5	1.484.0
11.	63.4	58.0	28.1	149.5	1.828.7
12.	—	—	—	—	1.407.0
Mean:	51.2	45.0	20.9	117.2	1.523.3

Suppl. 2 B

D Feed: Neutral diet, *no Cernitin* in the tablets

(Weights of adrenals, pituitary, thyroid and thymus glands and the levator ani.)

Litter No.	*Adrenals* mg	*Pituitary* mg	*Thyroid* mg	*Thymus* mg	*Levator ani* mg
1. A	23.4	3.9	11.1	348.3	30.8
1. B	24.1	3.0	8.7	228.2	27.1
2. A	22.0	4.5	8.2	260.1	26.5
2. B	24.3	3.0	7.5	121.5	22.7
3. A	26.9	3.2	10.2	305.4	41.5
3. B	20.0	3.5	7.6	226.8	24.4
4.	17.7	3.4	7.5	215.0	16.0
5.	23.1	3.0	6.0	173.5	23.7
6.	19.1	3.1	5.8	216.8	20.0
7.	18.5	3.6	9.9	188.2	35.0
8.	18.2	3.7	7.7	167.4	34.5
9.	19.8	3.1	7.9	186.3	34.3
10.	20.7	3.6	7.6	184.5	25.4
11.	21.7	4.0	5.8	210.4	41.5
12.	15.3	3.5	5.8	108.2	13.1
Mean:	21.0	3.5	8.0	209.4	27.8

Suppl. 3 A

C Feed: With *Cernitin D30 UK*, respond. 10 % dehydrated extract in the tablets.

(Weights of testes and prostate glands)

Litter No.	*Prostate* mg				*Testes* mg
	V.L.	*D.L.*	*S.V.*	*Total*	
1. A	81.3	45.6	80.6	207.5	1.882.7
1. B	52.1	37.9	24.8	114.8	1.257.7
2. A	67.7	76.1	36.4	180.2	1.401.2
2. B	29.3	41.9	20.8	92.0	1.221.7
3. A	71.0	73.6	50.0	194.6	1.991.1
3. B	45.6	49.1	22.5	117.2	1.157.5
4.	47.0	44.5	28.2	119.7	1.437.7
5.	43.9	41.8	21.1	106.8	1.163.1
6.	66.0	55.2	31.9	153.1	1.315.2
7.	28.7	38.6	16.4	83.7	803.5
8.	36.3	41.9	20.6	98.8	956.1
9.	67.9	54.2	28.7	150.8	1.528.0
10.	52.4	50.9	28.1	131.4	1.351.4
11.	73.0	58.3	30.0	161.3	1.530.9
12.	39.3	46.5	18.9	104.7	1.325.7
Mean:	54.4	50.4	30.6	134.4	1.354.9

Suppl. 3 B

C Feed: With *Cernitin D30 UK*, respond. 10 % dehydrated extract in the tablets.

(Weight extract of adrenals, pituitary, thyroid, thymus glands and levator ani.)

Litter No.	*Adrenals* mg	*Pituitary* mg	*Thyroid* mg	*Thymus* mg	*Lev. ani* mg
1. A	24.2	4.7	9.8	315.7	28.0
1. B	29.0	4.4	8.9	231.5	24.3
2. A	31.3	6.8	11.8	298.2	42.8
2. B	27.3	3.3	8.0	196.4	22.4
3. A	22.5	6.8	10.6	324.9	25.8
3. B	21.7	3.3	6.7	270.3	25.2
4.	25.7	4.3	6.9	257.8	26.4
5.	26.4	5.6	7.3	242.6	24.2
6.	19.8	4.9	8.4	234.5	26.7
7.	21.3	4.4	8.2	223.9	21.3
8.	23.3	4.5	8.8	217.2	19.2
9.	26.8	4.6	9.0	230.5	20.2
10.	20.8	3.7	4.9	232.8	25.4
11.	24.6	4.0	8.1	343.6	35.3
12.	22.5	3.4	6.9	210.0	26.7
Mean:	24.5	4.6	8.3	255.3	26.3

Suppl. 4

Weight Increase per 21-day period

Quantity consumed per 21 days. (12 animals)	*Normal Feed* 4.388 g (292.5 g/rat)	*D Feed* 3.758 g (250.5 g/rat)	*C Feed* 3.327 g (221.8 g/rat)
Litter No.	g	g	g
1. A	138.6	90.2	77.2
1. B	92.4	40.0	55.6
2. A	142.8	92.5	87.0
2. B	87.7	33.2	53.4
3. A	120.2	90.5	89.4
3. B	85.4	35.5	46.5
4.	108.0	37.5	53.2
5.	91.4	34.6	50.6
6.	94.5	34.0	59.1
7.	98.2	41.6	45.5
8.	89.5	42.0	51.2
9.	103.3	45.6	56.0
10.	84.2	36.6	49.8
11.	92.0	41.6	49.6
12.	86.2	21.0	37.0
Mean:	101.0	47.8	57.4

Suppl. 5

Weight of animals on day of sacrifice

Litter No.	*Normal Feed*	*D Feed*	*C Feed*
	g	g	g
1. A	200.0	148.0	138.0
1. B	155.0	99.0	112.0
2. A	200.0	148.0	152.0
2. B	144.0	87.0	115.0
3. A	180.0	149.0	148.0
3. B	144.0	95.0	95.0
4.	168.0	92.0	109.0
5.	150.0	92.0	108.0
6.	144.0	85.0	110.0
7.	154.0	96.0	97.0
8.	144.0	100.0	104.0
9.	152.0	98.0	112.0
10.	140.0	97.0	105.0
11.	154.0	110.0	114.0
12.	139.0	74.0	92.0

Feed C:

Including Cernitin D30 UK, corresponding to 10% dehydrated extract in the tablets.
Cernitin D 30 UK=90% Cernitin T60 + 10% Cernitin GBX.

Contents:

Cernitin D 30 UK		1.000 g
Pellets, ground (AB Fors, Helsingborg)		6.500 g
Dextrin-maltose		2.000 g
Talc		500 g
	Total	10.000 g

Corresponding to approx. 7.000 tablets a 1.4g/ tablet.

Feed D:

Neutral, no Cernitin in the tablets.

Contents:

Pellets ground (AB Fors, Helsingborg)		6.500 g
Dextrin-maltose		2.000 g
Modocoll E 600 FF, (Mo & Domsjo AB, Ornskoldsvik)		1.000 g
Talc		500 g
	Total	10.000 g

Corresponding to approx. 7,000 tablets a 1.4g/ tablet

Comments:

Dextrin-maltose:	hydrolyzed starch, heterogenous.
Modocoll E 600 FF:	aethyl-para-hydroxycellulose (= Tylose, cellugel, etc.).

Statistical Evaluation

In a study of immature male rats using litter-mate control, it was found that the addition of Cernitin to the diet increased the weight of various organs, the differences from controls being significant at the following P-values:

Prostate D.L.	+12 %	$0.05 > P > 0.01$
Prostate S.V.	+46 %	$0.01 > P > 0.001$
Total accessory repr. organs	+14 %	$0.05 > P > 0.01$
Adrenals	+17 %	$0.01 > P > 0.001$
Pituitary	+31 %	$0.01 > P > 0.001$
Thymus	+22 %	$0.01 > P > 0.001$
Body weight	+20 %	$0.001 > P > 0.0001$
Sacrificial weight	+15 %	$0.05 > P > 0.01$

The addition of Cernitin did not give any significant reduction of the mean value in any of the aspects observed.

A comparison between the C and D diets showed significant differences in three respects only:

Thymus weight in infant female rats
21% increase ($t = 6.50$; $P < 0.001$)

Body weight of infant male rats
7% decrease ($t = 3.73$; $0.01 > P > 0.001$)

Adrenals in hypophysectomized male rats
23% decrease ($t = 2.19$; $0.05 > P > 0.01$)

17.9.64
Rune Cederlof

Effect of Cernitin Pollen-Extract on Experimental Nonbacterial Prostatitis in Rats

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BACKGROUND. The treatment for chronic nonbacterial prostatitis (NBP) has not been established. Cernitin pollen-extract (CN-009) is reported to have therapeutic effects for NBP. The effects and mechanisms of CN-009 were investigated.
METHODS. Ten-month-old rats were used with administration of estradiol after castration, which were similar to human NBP histologically. Since CN-009 consists of T-60 and GBX, these drugs were administered, respectively. The prostate was evaluated histopathologically including glandular damage (epithelial score), stromal ratio and immunohistochemical assays for epithelial function (PAP), stromal evaluation (Vimentin), cell proliferation (PCNA) and apoptosis (deoxyuridine triphosphate biotin nick end-labeling (TUNEL)).
RESULTS. Controls revealed severe acinar gland atrophy and stromal proliferation. CN-009 showed diminished these damages. Epithelial score was better ($P<0.01$) and PAP positive materials were more abundant in CN-009 and GBX than in Controls. The stromal ratio was lower in CN-009 ($P<0.01$) and T-60 ($P<0.05$). There was no difference for PCNA positive cells in the epithelium and stroma, and TUNEL positive cells in epithelium. While, the number of TUNEL positive cells in the stroma of CN-009 and T-60 increase ($P<0.01$).
CONCLUSIONS. These findings suggest than CN-009 protects acinar epithelial cells mainly by GBX and also inhibits stromal proliferation in association with enhanced apoptosis mainly by T-60. Prostate 49: 122-131, 2001.

KEYWORDS: cernitin pollen-extract; apoptosis; chronic prostatitis; sex-hormone induced prostatitis

INTRODUCTION

The chronic prostatitis syndromes have been recognized; chronic bacterial prostatitis (CBP), chronic nonbacterial prostatitis (NBP) and prostatodynia. NBP is the most frequent disorder of 64% in these three diseases [1]. The etiology of NBP is unknown. A number of organisms or other factors have been reported to be the possible causes for NBP. They are *Trichomonas vaginalis, Chlamydia trachomatis,* genital mycoplasmas, staphylococci, coryneforms, genital viruses [2], biofilms [3], stagnation of prostatitc secretion, autoimmune disease, allergy, disorder of sex hormone and psychological effects [4,5]. For the treatment of CBP or NBP, antibiotics of new-quinolone or tetracycline have been administered. However, many cases resist these treatments [6].

CN-009 is a pollen extract, which contains 20:1 ratio of powdered aqueous and organic extract. It is essentially a microbial digest of a standardized mixture of eight plant species grown at the Scania area in southern Sweden. The active ingredients consist of water-soluble (T-60) and fat-soluble (GBX) fractions [7,8]. It was reported that CN-009 showed urine discharge action [9,10], anti-prostatic hypertrophic action [7] and anti-inflammatory effects to the prostate [11] in a preliminary study. Since Ask-Upmark [12] reported CN-009 showed an efficacy to prostatitis, it has been used for the treatment of chronic prostatitis with

high therapeutic effects. However, the mechanisms for these effects remain unknown.

To assess the mechanisms of the anti-prostatitis effect by CN-009, the present study was performed using a nonbacterial prostatitis rat model [13,14] induced by 17β-estradiol administration and castration.

MATERIALS AND METHODS

Sex Hormone-Induced Nonbacterial Prostatitis Model

Ten month-old Wistar aged male rats were purchased from Japan Slc Co. (Tokyo, Japan). The rats were housed in a climatised environment with a 12-hr light/ dark cycle, 40-70% humidity. Food and water were supplied ad libitum. The rats were castrated under ether anesthesia, and then 17 β-estradiol (Sigma, MI) 0.25 mg/ 2 ml/ kg diluted by sesame oil, as an inducer for prostatitis, was subcutaneously injected into the back of rats for 30 days from 1 day after castration [13,14].

Experimental Structure and Schedule

CN-009 was suspended for 630 or 1,260 mg/ 5 ml with 1% HCO-60 (Japan Surfactant, Tokyo, Japan). T-60 and GBX were similarly prepared for 1,200 and 60 mg/ 5 ml, respectively. Testosterone (TS) (Wako Chemicals, Tokyo, Japan), as a positive control, was diluted for 2.5 mg/ 2 ml with corn oil (Yuro Chemical, Tokyo, Japan).

The experimental structure is shown in Table I and the experimental schedule is illustrated in Figure 1. The rats were divided into seven groups consisting of Sham-operation (Sham-ope), Control, CN-009 630, CN-009 1260, T-60, GBX and TS with five or six animals in each group.

In the Sham-ope group, the rats were treated with only Sham-castration and without any drugs. In the Control group, the rats were injected subcutaneously with 17 β-estradiol for 30 days from the day following castration and administered orally with only 1% HCO-60 5 ml/ kg for 14 days from Day 17. In the CN-009 630, CN-009 1260, T-60 and GBX groups, similar protocols were performed with oral administration of CN-009 630, CN-009 1260, T-60 1200 and GBX 60 mg/ kg, respectively. Also in the TS group, the rats were injected subcutaneously with 17 β-estradiol for 30 days from the next day of castration. After 14 days, TS 2.5 mg/ kg was injected subcutaneously for 14 days. All studies were conducted in accordance with institutional guidelines of animal care and in accordance with Japanese Government Animal Protection and Management Law.

Prostate Weights and Histopathological Evaluation

The rats were sacrificed on the day following the final administration. The prostate was extirpated and weighed. Relative prostatic weight was calculated from body weight and absolute weight.

After fixation in 10% neutral buffered formalin, each prostate was cut into coronal blocks. The tissue samples were dehydrated and embedded in paraffin. Sections (3-4 μm thickness) were stained with Hematoxyline-Eosin (HE), Periodic acid Shiff (PAS) and Masson's tri-chrome. The specimens were evaluated histopathologically.

Immunohistochemistry

Immunohistochemistry studies were performed with anti-prostatic acid phosphatase (PAP), and Viementin. PAP staining was performed for the evaluation of glandular epithelial function. In

TABLE I. The Structure of the Experiment

Group	No. of animals	Inflammatory agent	Drug treatment
Sham-ope.	5	No-treatment	No-treatment
Control	6	17 β-estradiol 0.25 mg/kg (s.c.)	1% HCO-60 (p.o.)
CN-009 630	5	17 β-estradiol 0.25 mg/kg (s.c.)	CN-009 630 mg/kg (p.o.)
CN-009 1260	6	17 β-estradiol 0.25 mg/kg (s.c.)	CN-009 1260 mg/kg (p.o.)
T-60	5	17 β-estradiol 0.25 mg/kg (s.c.)	T-60 1200 mg/kg (p.o.)
GBX	6	17 β-estradiol 0.25 mg/kg (s.c.)	GBX 60 mg/kg (p.o.)
TS	5	17 β-estradiol 0.25 mg/kg (s.c.)	Testosterone 2.5 mg/kg (s.c.)

Each parenthesis represents the route of administration. s.c, subcutaneous injection; p.o., oral administration.

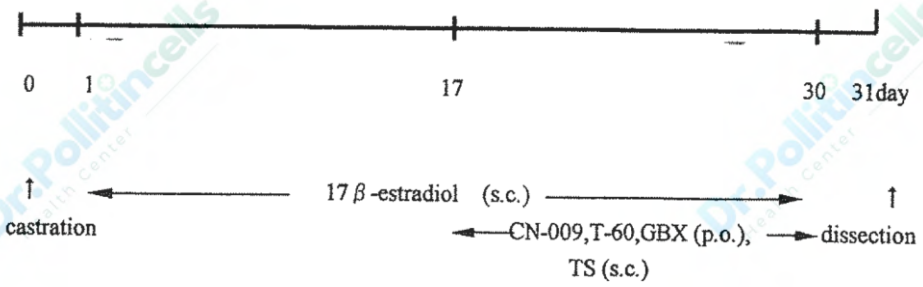

Fig. 1. The experimental schedule for this study.

PAP stained specimens, anti-PAP polyclonal antibody (Chemicon International, New York, NY) was diluted by PBS including 0.1% BSA of a 1:100 ratio, and incubated for 2 hr at 37° C. Biotinylated anti-rabbit IgG and the avidin-biotin peroxidase complex (ABC) method was performed. Unitect rabbit immunohistochemistry detection systems (Oncogene Science, New York, NY) were reacted by those methods. Vimentin staining was performed for the evaluation of stromal proliferation. An ImmunoCruz staining system (Santa Cruz BioTech., Santa Cruz, CA) for Vimentin staining was used according to the manufacturer's instructions.

Cell Proliferation and Apoptosis

Cell proliferation and apoptosis were investigated with proliferating cell nuclear antigen (PCNA) and terminal deoxynucleotidyl tranferase mediated deoxyuridine triphospate bitotin nick end-labeling (TUNEL), respectively. PCNA staining was performed with PCNA staining kit (ZYMED Laboratories, South San Francisco, CA). TUNEL method was performed with ApoTag Peroxidase In Situ Apoptosis Detection kit (Intervene, New York, NY). In PCNA and TUNEL specimen, 5,000 cells were counted under a microscope in glandular epithelial cells and stromal cells, respectively.

Acinar Epithelial Score and Stromal Area Ratio

To evaluate glandular damage, acinar epithelial cells were classified and scored, as follows; columnar (2 points), cuboidal (1 point), squamous-like (0 point) shape. Three different pathologists without any information judged the score. Using this scoring evaluation, 20 acinar glands of each specimen were investigated. To assess stromal proliferation, all areas of the specimen and the glandular area were measured using a digitizer (Graph Tech, Tokyo, Japan) with photomicrographs. Using these findings, the stromal ratio was calculated.

Statistical Analysis

All experiments were repeated at least twice. Each value was demonstrated as the mean±SD. Dunnett's test if in equal variance, or non-parametric Dunnett's test if in unequal variance between treatment groups and Control group was performed after 1-way ANOVA followed by Bartlett variance analysis test. Mann-Whitney U test was performed between the Sham-ope and Control groups.

RESULTS

Body and Prostate Weights (Fig. 2)

There was no significant difference in body weight among the CN-009 630, CN-009 1260, T-60, GBX and TS groups compared with the Control group. Absolute and relative prostate weights were significantly ($P<0.01$) decreased in the Control group compared with the Sham-ope group (Fig. 2) in the CN-009 630, CN-009 1260, T-60 and GBX 60 groups, there was no difference compared with the Control group. In the TS group, absolute and relative prostate weights were very close to the Sham-ope group and were significantly different ($P<0.01$) from other groups.

Histopathology and Immunohistochemistry (PAP and Vimentin Staining)

In the Sham-ope group, the prostate was larger than in other groups. Acinar glands were roundly shaped. The acinar lumen was filled with eosinophilic materials. Acinar epithelial cells were cylindrical with a normally situated nucleus and the supranuclear spaces of these cells

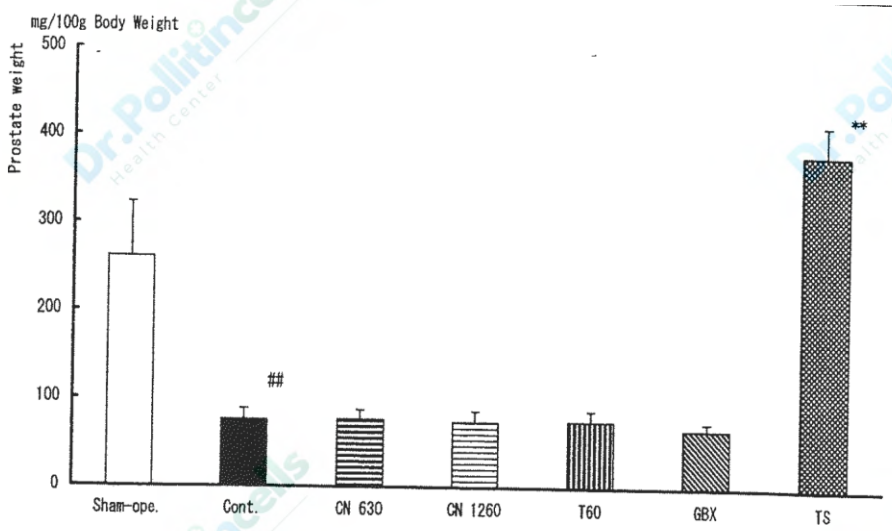

Fig. 2. Relative prostate weight. Each column represents the mean ± SD. ##Significantly different from the Sham-ope group at $P < 0.01$. **Significantly different from the Control group at $P < 0.01$

contained secretory materials, which were strongly stained with PAP antibody. A few fibrous tissues were found in the stroma (Figs. 3A and 4A). Vimentin positive cells were few, and the Vimentin positive area was small (data not shown).

In the control group, the prostate was atrophic. Acinar glands were irregularly shaped. The acinar lumen was poor with pale stained eosinophilic materials and filled with inflammatory cell infiltrations mainly characterized by neutrophils. Acinar epithelial cells were flattened similar to a squamous cell. A few secretory materials in the epithelial cells were poorly reacted with PAP antibody. The stroma showed severe proliferation with many lymphocyte and monocyte infiltrations and marked fibrosis with fibroblasts (Figs. 3B and 4B). The stroma was stained very strongly with Vimentin. The Vimentin positive area was significantly increased (data not shown). In the CN-009 630 group, the findings were basically identical with the Control group (data not shown).

In the CN-009 1260 group, acinar glands were more roundly shaped than in the Control group. Acinar epithelial cells were cuboidal, and the supranuclear spaces contained secretory materials stained with anti-PAP that were much more abundant than in the Control group. Inflammatory cell infiltrations into the acinar lumen were diminished. The stroma showed mild proliferation with a few lymphocytes, monocytes and mild fibrosis with fibroblasts (Figs. 3C and 4C). The Vimentin positive area was much less than that of the Control group (data not shown).

In the T-60 group, acinar epithelial cells were more roundly shaped than in the Control group. Although inflammatory cell infiltrations into the lumen were found, stromal cell infiltrations (Fig. 3D), the Vimentin positive cells were also less than that of the Control group (data not shown).

In the GBX group, acinar epithelial cells were more cuboidal than in the Control group. Epithelial cells contained secretory materials stained with anti-PAP, which was basically identical with the CN-009 1260 group. Diminished cell infiltration into the lumen was found (Fig. 3E). However, the stroma showed a proliferative condition with many lymphocyte and monocyte infiltrations and marked fibrosis with many fibroblasts. The stroma was stained strongly with Vimentin, and the positive area was markedly increased (data not shown).

In the TS group, acinar glands were roundly shaped. The acinar lumen was filled with eosinophilic materials with a few cell infiltrations. Acinar epithelial cells were cylindrical and the supranuclear spaces contained many secretory materials with reactive anti-PAP. However, the stroma was stained strongly with Vimentin and showed mild proliferation with fibroblasts (data not shown).

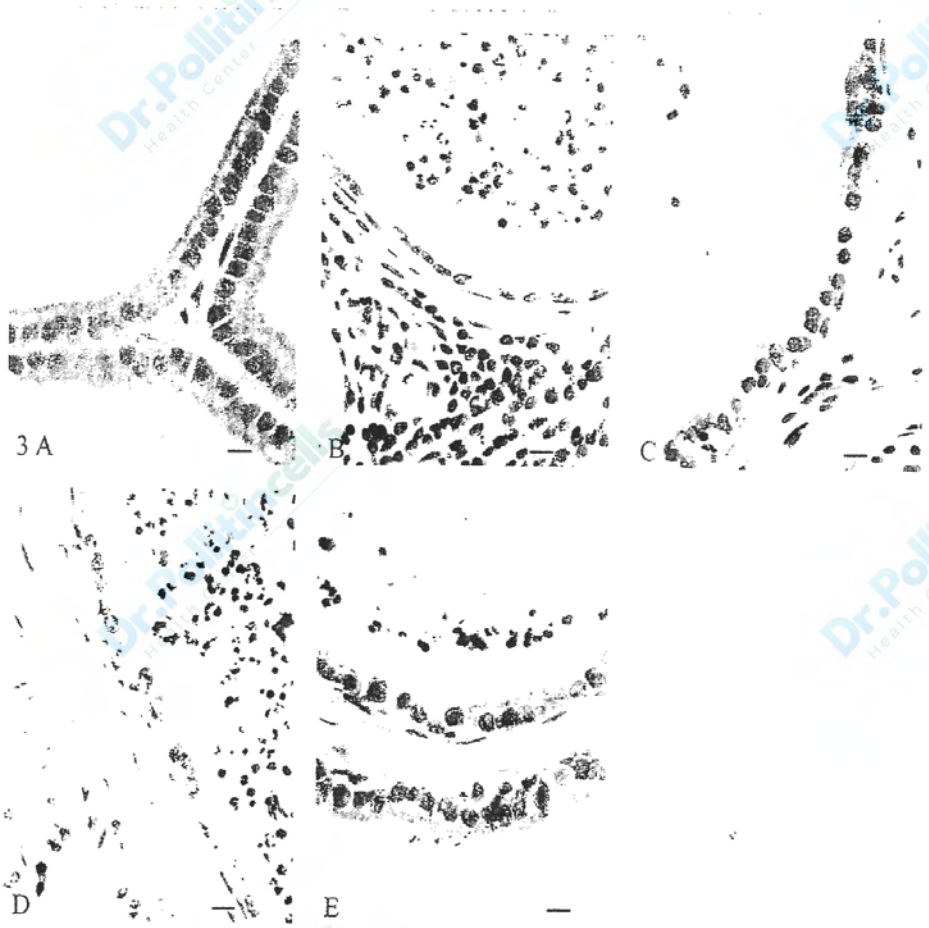

Fig. 3. HE staining of the prostate in experimental nonbacterial prostatitis rat. **(A)** Sham-ope group: The acinar lumen is filled with eosinophilic materials without any cells. Acinar epithelial cells are cylindrical. A few fibrous tissues are found in the stroma. **(B)** Control group: The acinar lumen is filled with induced inflammatory cells mainly characterised by neutrophils. Acinar epithelial cells are flattened similar to squamous cells. The stroma shows severe proliferation with many lymphocyte and monocyte infiltrations and remarkable fibrosis with fibroblasts. **(C)** CN- 009 1260 group: Acinar epithelial cells are cuboidal. Inflammatory cell infiltrations into the acinar lumen are diminished. The stroma shows mild proliferation with a few lymphocytes, monocytes and fibroblasts. **(D)** T- 60 group: Stromal proliferation is relatively mild without severe inflammatory cells. **(E)** GBX group: Acinar epithelial cells are cuboidal, and diminished inflammatory cell infiltrations are shown. 400 The bar indicates 10 μm

Cell Proliferation and Apoptosis (PCNA and TUNEL Positive Cell Counts (Fig. 5))

No significant differences among the groups were observed in the PCNA positive cell counts in epithelial cells (Fig. 6) or in stromal cells (Fig. 7). In the Sham-ope group, a few TUNEL positive cells were found (Fig. 5A). The findings of the Control group were basically identical with the Sham-ope group (Fig. 5B). In the CN-009 1260 group, TUNEL positive cells in the stroma were more abundant than in the Sham-ope and Control groups (Fig. 5C). In TUNEL positive cell counts, no significant differences were observed in acinar epithelial cells (Fig. 8). However, in the stroma, TUNEL positive cells were significantly ($P<0.05$) increased in the CN-009 1260 group or T60 group compared with the Control group (Fig. 9).

Acinar Epithelial Score (Fig. 10)

In the Control group, acinar epithelial score was significantly lower ($P<0.01$) than that of the Sham-ope group. In comparison with the Control group (Fig. 10), the acinar epithelial score was significantly higher ($P<0.01$) in the CN-009 1260, GBX, and TS groups.

Stromal Area Ratio (Fig. 11)

In the Control group, the stromal area ratio was significantly higher ($P<0.01$) than that of Sham-ope group in comparison with the Control group.

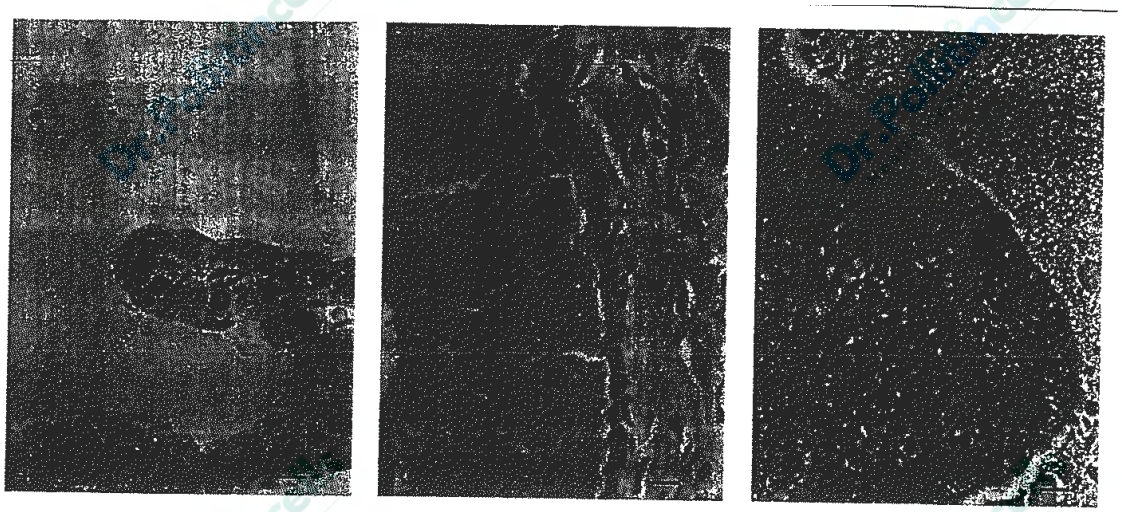

Fig. 4. Immunohistochemical findings (PAP staining) of the prostate in experimental nonbacterial prostatitis rats. **(A)** Sham-ope group: Supranuclear spaces of acinar epithelial cells contain secretory materials which are stained with anti-PAP. **(B)** Control group: Acinar epithelial cells are flattened similar to squamous cell. Secretory materials are poorly reactive with anti-PAP. **(C)** CN-009 1260 group: Supranuclear spaces contained secretory materials with PAP staining, which are significantly more abundant than in the Control group. × 400 The bar indicates 10 μm.

In comparison with the Control group (Fig. 11) the stromal area ratio of the CN-009 1260 was significantly ($P<0.01$) lower. The T-60 group was also significantly ($P<0.05$) lower than the Control group. However, there was no difference between other groups.

Discussion

Although chronic prostatitis is a common disease, it is very difficult to treat effectively.

Typical clinical findings are decreased potential, perineal or scrotal pain, urethral discharge and lower urinary tract irritative symptoms. The prostate gland is irregularly indurated and the numbers of leukocytes in expressed prostatic secretion are increased [15]. Pathological findings of this disease are chronic inflammation characterized by aggregates of lymphocytes in the stroma and

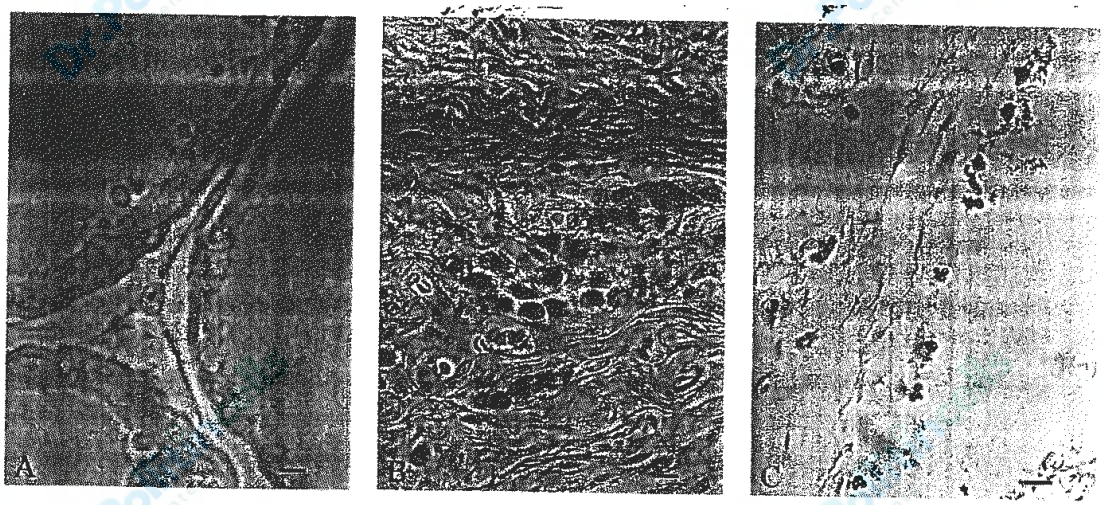

Fig. 5. Immunohistochemical findings (TUNEL) of the prostate in rats. **(A)** Sham-ope group: A few TUNEL positive cells are shown. **(B)** Control group: The findings are basically identical to these of the Sham-ope group. **(C)** CN-009 1260 group: TUNEL positive cells in the stroma are more abundant compared with the Sham-ope and Control groups. ×400. The bar indicates 10 μm.

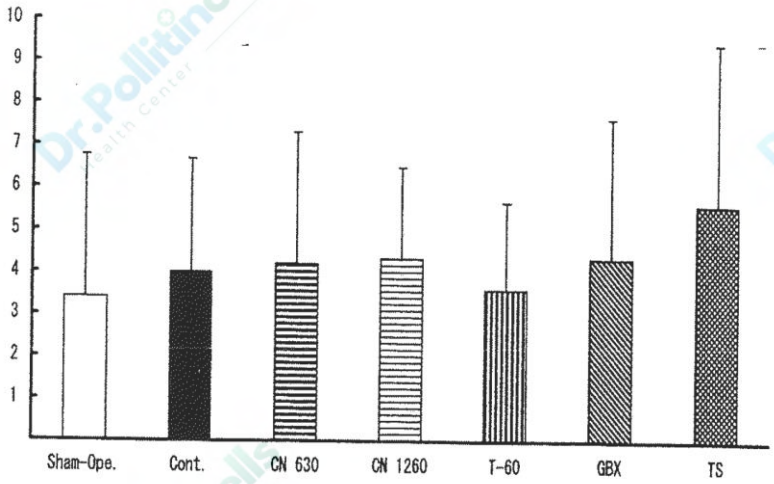

Fig. 6. Effects of CN-009 on acinar epitelial PCNA positive cell counts of the prostate. Each column represents the mean ± SD.

acute inflammation characterized by the presence of neutrophic polymorphonuclear leukocytes in the lumen of acinar glands [15-17]. Pathological definition of chronic prostatitis is different from clinical definition for the urologists. Clinical definition has been the combination of a clinical symptom and inflammatory cells in expressed prostatic secretion. The pathological inflammation of the prostate was reported to be not frequent in patients with symptoms of chronic prostatitis/ chronic pelvic pain syndrome [16].

In experimental animals, Lewis, Wistar and Copenhagen rats have a high incidence of spontaneous nonbacterial prostatitis [14]. Administration of exogenous 17 β-estradiol can induce 100% of the incidence on prostatitis in old Wistar rats [18] and castration also has a similar effect [13, 18]. Naslund et al. [13] reported that histopathological findings were very similar between spontaneous nonbacterial prostatitis and estradiol-induced prostatitis in rats [13]. These histopathological findings in rat spontaneous nonbacterial age-dependent prostatitis demonstrated several similarities to pathologically defined chronic prostatitis in human [19, 20]. These findings suggested that this rat model would be a useful model for the study of the treatment of human chronic prostatitis. Therefore, we decided to investigate the effects and mechanisms of CN-009 using a nonbacterial prostatitis rat model [13, 14] induced by 17 β-estradiol injection and castration.

No differences in the prostate weight were found in CN-009 630, CN-009 1260, T-60, and GBX

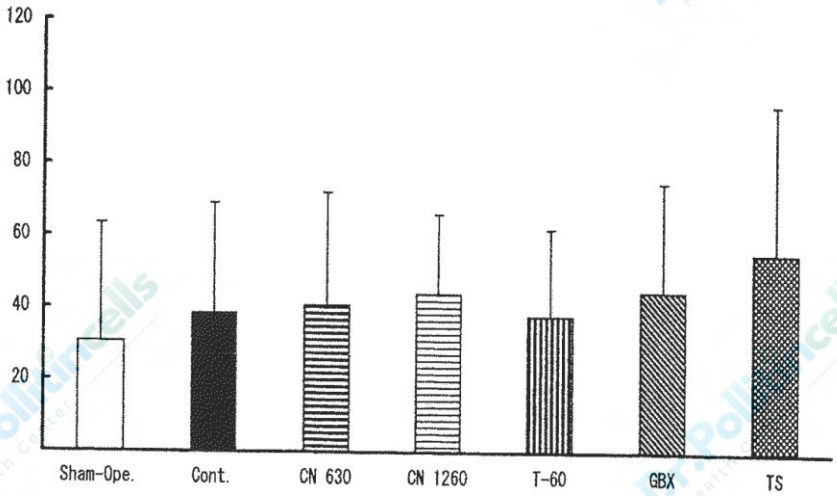

Fig. 7. Effects of CN-009 on stromal PCNA positive cell counts of the prostate. Each column represents the mean ± SD.

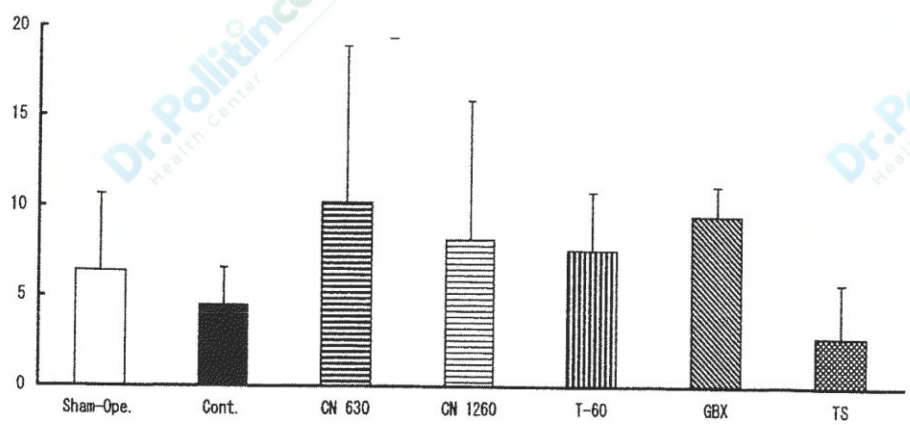

Fig. 8. Effects on CN-009 on acinar epithelial TUNEL positive cell counts of prostate. Each columun represents the mean ± SD.

groups compared with the Control group. Since the weight of the prostate is mostly determined by the amount of residual secretory fluid, these findings may indicate that CN-009 cannot prevent the reduction of secretory prostatic fluid.

In the CN-009 1260 group, we observed roundly shaped acinar glands, cuboidal acinar epithelial cells containing secretory materials with positive PAP staining and diminished cell infiltrations into the lumen compared with the Control group. The acinar epithelial score was significantly increased. CN-009 could protect acinar epithelial function and cell shape against nonbacterial inflammation. GBX had a similar effect to CN-009 in the acinar glands. T-60 was not effective in the acinar epithelial function of this rat model. Therefore, GBX may play a central role for the protection of epithelial damage in the NBP. The effect of GBX was similar to that of TS. However, GBX does not contain androgenic activity, because GBX has no effect on normal and hypertrophic prostate (unpublished data, 1968). Accordingly, this protective effect of GBX is discriminated from TS effect. In an in vitro study, GBX was reported to inhibit the cyclooxygenases and 5-lipoxygenases in the biosynthesis of the prostaglandins and leucotrienes [21]. Since prostaglandins and leucotriens enhance inflammatory cell infiltrations, GBX may protect against inflammation into the acinar lumen by inhibition of these enzymes. Furthermore, CN-009 showed an inhibition on the heat-induced hemolysis, which is correlated to lysosomal membrane stability [11]. CN-009 appears to

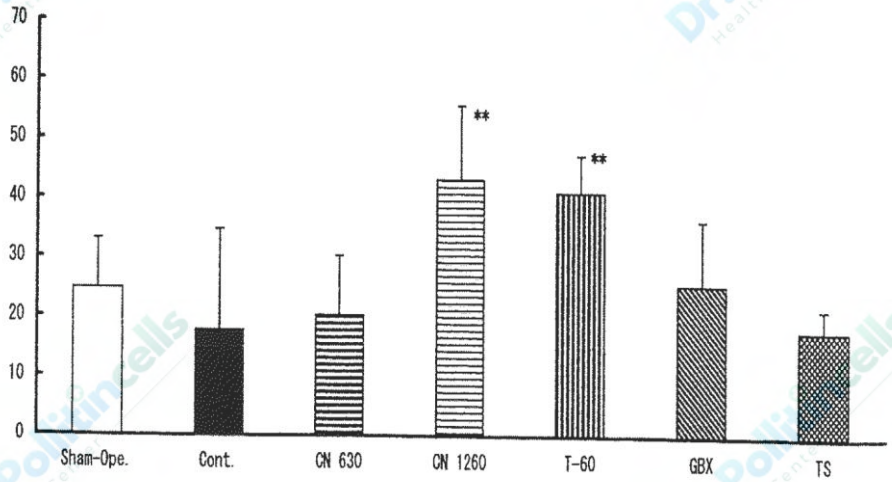

Fig. 9. Effects of CN-009 on stromal TUNEL positive cell counts of the prostate. Each columun represents the mean ± SD. **Significantly different from the Control group at $P < 0.01$.

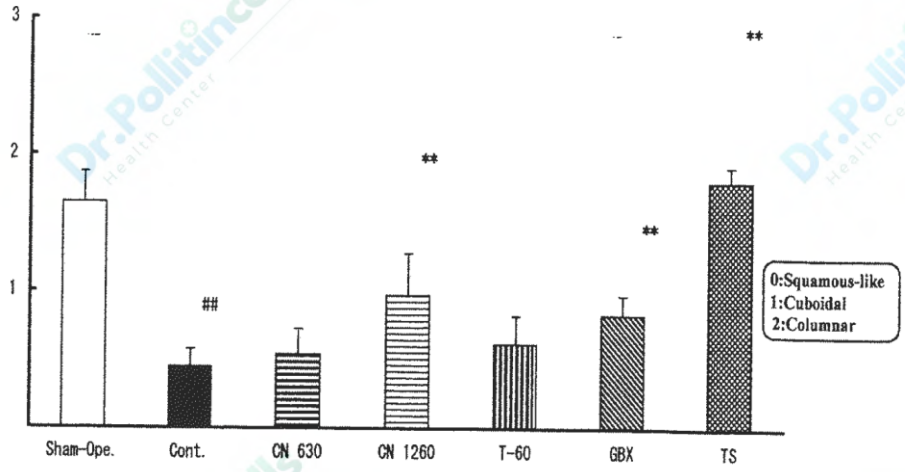

Fig. 10. Effects of CN-009 on acinar epithelial score of the prostate. Each column represents the mean ± SD. ##Significantly different from the Sham-ope group at $P < 0.01$. **Significantly different from the Control group at $P < 0.01$.

stabilize a lysosomal membrane, recover cell function and protect against degeneration of the acnar epithelium.

In addition, T-60 was shown to inhibit the growth of an immortal prostate cancer cell line in vitro [22]. However, their mechanisms are unknown. In the present study, the ratio of stromal area was significantly decreased in the CN-009 1260 and T-60 groups. Stromal TUNEL positive cell counts were increased in these groups. Therefore, CN-009 and T-60 may inhibit stromal cell proliferations by enhanced apoptosis. Although the exact mechanism of this process is unclear, several speculations are possible such as the direct effect by the apoptosis of fibroblast, and the indirect effect by the apoptosis of lymphocytes throught the the inhibition of several cytokines, such as several interleukins.

Further laboratory studies are necessary to elucidate the exact mechanisms of this compound.

Since no toxicological effects have been shown even in long-term administration, CN-009 is thought to be a safe drug [6, 23]. Here we reported the effects and mechanisms of CN-009 on rat experimental nonbacterial prostatitis model. CN-009 will also be a safe and effective against human nonbacterial chronic prostatitis.

In conclusion, CN-009 can work as a potent anti-inflammatory agent against chronic prostatitis. The present findings suggest that GBX, a fat soluble fraction of CN-009, protects the function and shape of acinar glandular epithelium and T-60, a water soluble fraction of CN-009, inhibits stromal cell proliferations in association with enhanced apoptosis.

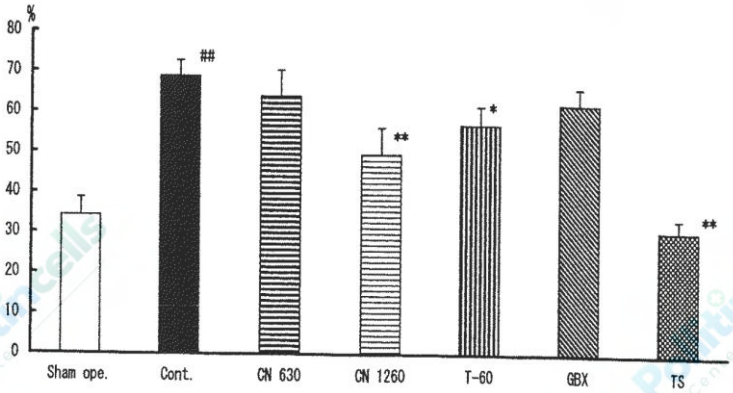

Fig. 11. Effects of CN-009 on stromal ratio in the prostate. Each column represents the mean ± SD. ##Significantly different from the Sham-ope. Group at $P < 0.01$. **Significantly different from the Control group at $P < 0.01$. *Significantly different from the Control group at $P < 0.05$.

Acknowledgements

We thank M. Komukai, M. Ishii, F. Kimura and E. Higaki for their technical assistance.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Findings on Prostatitis through the "Pollen Extract G63" of Graminex Company

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(Kanda New Medical Clinic)

Pollen, containing a rich source of nutrition (amino acids, minerals, and vitamins), represents the emergence of the next generation of plant substances with not yet fully understood hidden action that should not be overlooked. Pollen formulations have been used for the last 35 years in urology (enlargement of the prostate, prostatitis) treatment. This has been administered for a long time with peace of mind and without harmful effects as an alternative to pharmaceuticals for the improvement of both prostatitis and the associated indeterminate complaints. Moreover, this has seen as the welcome birth of supplements in improving associated symptoms. This time, we are reporting on study findings and the improvement effect obtained in the treatment of prostatitis with the supplement pollen extract.

Objective and Method

At this Clinic, 13 patients visiting the clinic for prostatitis treatment agreed to receive administration. The degree of improvement was determined based upon the IPSS score (International Prostate Symptom Score). The period of administration was from 1 month to three months. The pollen extract used in the trial was produced by Graminex Company in Ohio, USA from the pollen of raw materials such as rye, corn, and timothy hay (referred to as Phlegm pratense in Japan) which were cultivated without using agrochemicals or genetically modified varieties. However, a slight amount of pollen from timothy weeds (referred to as Phleum pratense in Japan) was also included. The pollen which has a double hull is not digested or absorbed even when ingested since it has strong resistance to acid and heat (cannot be destroyed even at 300°C).Graminex Company using a special technology is able to separately extract G60 (water soluble nutrition component) and GFX (lipid soluble component) and we received the product G63 which is a 20:1 combination of G60 and GFX. The dosage was _ tablets per day; three tablets each after breakfast and dinner. One _ _ 0 mg tablet contains 62.5 mg of pollen extract. (The daily quantity .... 375mg as pollen extract)

Results

The trial study was stopped for 2 subjects among the 13 participants (one subject was stopped because his PSA value had increased prior to the start of administration and one was stopped because he was taking Gaster for epigastric distress before administration started but symptoms did not improve), and one other subject was eliminated from the effect determination since the IPSS was not filled in after administration.

Graminex Prostatitis Therapy Trials ... Prostatitis

Name	Age	Progress	IPSS	Perineal pain	Erection Ejaculation Difficult	Pain during urination	Change
S. K	56	Before	25	None	None	None	
		After 1 month	24	None	None	None	Morning erections increased.
S. T	73	Before	17	None	None	None	

		After 1 month	13	None	None	None	
I. Y	74	Before	12	None	occasionally	occasionally	
		With PSA - Therapy Trial stopped No related cause					
O. T	65	Before	8				
		After 3 months	3				Painful urination improved, did not have to go to the toilet at night
N. K	57	Before	11	None	Always	None	
		After 1 month	11	None	at times	None	Nocturia (night urination) (3~4 times)
		After 2 months	6	None	None	None	Nocturia (night urination) (2~3 times)
		After 3 months	9	None	None	None	Daytime urination, urinate freely
I. T	62	Before	10	pain at times	occasionally difficult	None	
		After 1 month	8	pain at times	occasionally difficult	None	A little improvement of perineal pain
		After 3 months	8	pain at times Difficult	occasionally	None	No particular change In symptoms, Watching the drop of of PSA
M. T	73	Before	18	None	None	None	
		After 1 month	14	None	None	None	
		After 3 months	14	None	None	None	
S. I	68	Before	7	None	None	None	
		After 1 month	5	None	None	None	Urination
S. M	61	Before	27				
		After 1 month		No IPPS record			improved a little,
T. M	71	Before	17	None	No Erection	None	Concomitant administration of Gastar (20)
				Reverse flow			Related cause unknown
U. T	62	Before	_ _ _	None	None	None	
		After 1 month	14	at times painful, At times difficult		None	
M. H	74	Before	15	None	None	None	
		After 1 month	6	None	None	None	rather improved
S. T	71	Before	24	None	always difficult	pain at times	
		After 1 month	17	None	difficult at times	pain at times	Pain is improving

Conclusion

The Average subject age was 66.1 ± 5.7, and 9 out of 10 patients saw improvement with a drop in IPSS score. The average IPSS was 15 before and administration, dropping to an IPSS average of 11 after administration. Additionally, improved patients evidenced an improving trend in their symptoms of perineal pain, erection, ejaculation difficulty, and pain during urination.

Discussion

Reshaping of the inflamed portion becomes necessary in the case of bacterial and non-bacterial inflammation of the prostrate occurring. Pollen extract makes possible rapid recovery since it contains plentiful amino acids and co-enzymes that work with the vitamins and mineral which are required for the repair of cells. Additionally, it is can be considered that the prostrate function also recovers since the zinc and selenium which are necessary for the Prostrate are also included in the extract.

Safety

There was an example of the medical trial being stopped for 2 subjects. As previously mentioned, the trial was stopped because of the high PSA

value and treatment was changed to another method. And, the other case was stopped because Gaster was taken for epigastric distress before administration started but symptoms did not improve. Based upon examination by stomach camera, reflux esophagitis and erosive gastritis were evidenced and a causal relationship with pollen extract could not be recognized.

There were no other symptoms of particular note and this supplement can be administered long term with peace of mind.

7/29/2005

Effect of Cernitin pollen-extract on the Sex-hormone-induced Nonbacterial Prostatitis in Rats

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Cernitin pollen-extract (Cernilton®, CN-009) is a preparation made from eight kinds of pollen. The active components are water-soluble (T60) and fat-soluble (GBX) fractions. CN-009 has been used for the treatment of chronic prostatitis in Europe and Japan. To study the action of CN-009 on the prostatitis, we examined the effect of CN-009 on the sex-hormone-induced nonbacterial prostatitis in rats.

Aged Wistar rats (10 months old) were castrated and then injected 17*β*-estradiol (0.25 mg/kg, s.c.) for 30 days. These treatments reduced the weight of prostate and induced the inflammation and epithelial cell dysfunction of the lateral prostate lobe in the rats. Testosterone (2.5 mg/kg, s.c.) injected for the last 14 days of the treatment of 17*β*-estradiol to the rats restored markedly the estradiol-induced prostatitis. Those changes were similar to the findings reported by others. CN-009 was administered orally for the last 14 days of the treatment of 17*β*-estradiol to the rats. The administration of 378 mg/kg of CN-009 did not change in the prostatic histopathological findings, while 1260 mg/kg of CN-009 increased the number of intracellular secretory granules of epithelial cells and diminished weakly the invasion of inflammatory cells into the lumen or the stroma in the prostatic gland.

These results suggest that CN-009 may recover the prostatic epithelial cell dysfunction and have the mild anti-inflammatory properties.

Key Words: Cernitin pollen-extract, Cernilton, CN-009, Aged Wistar rat, Castration, Sex-hormone-induced nonbacterial prostatitis

Effects of pollen extract EA-10, P5 on chronic prostatitis or infertility with chronic prostatitis

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KEY WORDS: prostatitis; infertility; free radicals; pollen

ABSTRACT

AIM: To determine the drug action mechanism of pollen extract EA-10, P_5 on the treatment of chronic prostatitis (CP) or infertility with CP. **METHODS:** Malondiadehyde (MDA), super oxide dismutase (SOD), and nitrogen monoxide (NO) were measured by biochemical assay, and zinc content was assayed by atomical spectrophotography in the pre-treatment and post-treatment of CP or infertility with CP. **RESULTS:**Compared with control group, leukocytes in expressed prostatic secretion (LEPS), MDA, and NO were increased, and zinc content and SOD were decreased significantly in the pre-treatment of CP. After the treatment, LEPS was improved, and MDA and NO were reduced, while zinc content were increased apparently and the alteration of SOD was not evident *(*$P>0.05$). In the pre-treatment of infertility with CP, LEPS, MDA, NO, sperm viability, and seminal leukocytes were obviously higher and seminal plasma SOD, zinc content, and sperm motility were obviously lower than those in control group. After the treatment, LEPS, sperm motility, and sperm viability were improved, MDA, NO, and seminal leukocytes were decreased, SOD and zinc content were increased markedly. **CONCLUSION:** There was inter-correlation between oxygen free radicals (OFR) and occurrence, development, and recovery of CP; Change of OFR may be involved in the drug action mechanism of EA-10, P_5 in the treatment of CP or infertility with CP.

INTRODUCTION

Chronic prostatitis (CP) is one of the most common diseases in andrology. Its therapeutic efficacy is not very satisfactory. Recent studies showed that CP might defect semen quality. Thus, it is significant to make an investigation of pathogenesis and medication of CP.

Oxygen free radicals (OFR) which causes tissue damage by lipid peroxidation (LPO)[1], includes mainly superoxide anion (O_2), hydrogen peroxide (H_2O_2), hydroxy free radical (·OH), and nitrogen monoxide (NO). LPO has yielded several types of secondary free radicals and a large number of reactive compounds (including MDA), resulting in the destruction of cellular portion. Of course, cells are equipped with various antioxidants, such as vitamin E, vitamin C, glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and so on. These can scavenge supernumerary OFR and protect organism from cytotoxic effect of OFR[2,3]. In addition, there was apparent negative correlation between semen OFR level and semen quality, but with the increasing of semen OFR level and prolonging of contact time between OFR and sperm, sperm vital force would obviously decrease[4,5]. Studies also showed seminal MDA might be increased apparently in chronic bacterial prostatitis, resulting in the influence of sperm vitality and sperm motility[6,7]. These data indicated that OFR played an important role in pathogenesis of CP and infertility.

EA-10, P_5 is regarded as a satisfactory drug in the treatment of CP. At present, it is still unknown that whether OFR, antioxidase, and zinc content in semen will be regulated in the

treatment of CP or infertility with CP by EA-10, P_5. Therefore, we investigated whether EA-10, P_5 could inhibit LPO, and thus to obtain the primary conclusion about drug action mechanism of EA-10, P_5 in our treatment.

MATERIALS AND METHODS

Population

All 68 cases of CP (group I) and 63 cases of infertility with CP (group II) were divided into two groups, which were then subdivided into three treatment subgroups respectively (group A: EA-10, P_5 + Roxithromycin, group B: EA-10, P_5 alone, and group C: Roxithromycin alone). Twenty cases who were normal healthy donors of proven fertility were used as control group. The treatment period was four weeks. Group A received EA-10, P_5 (product from Sweden Pharmacia Allergon AB, 375 mg/pill) and roxithromycin (150 mg/pill) twice daily. Group B-C received respectively EA-10, P_5 and Roxithromycin twice daily. During the treatment, all 131 cases were treated with sitzing bath in hot water and controlled diet (wine and pungent diet prohibited).

Semen samples and treatment

Semen samples were obtained from all cases by masturbation after 3 d of abstinence. Samples were incubated for 20 min in 37 ºC warm bath box. Firstly, regular semen analysis and seminal MDA content were analyzed after semen has been liquefied completely; Secondly, liquefied semen was centrifuged at 1000×*g* for 10 min, and seminal plasma was used to determine the content of NO and SOD. Finally, surplus seminal plasma was frozen at -20 ºC until further use for zinc content assay.

Determination of seminal MDA content and SOD activity

Seminal MDA content was determined by thiobarbituric acid (TBA) method [8]. SOD activity was measured as the inhibition of nitroblue tetrazolium reduction due to superoxide anion generation by xanthine plus xanthineoxidase [9].

Zinc and NO content in seminal plasma assay

Zinc content was assayed by a method based on atomical spectrophotography [10]. The NO concentration was estimated by a method based on nitrite salt response with sulfanilamide to from diazole, which could appear purplish red color reacting with naphthalene ethylenediamine in the acid conditions. The absorbance of 530 nm was measured [11].

Semen parameters

All semen analysis adopt with color quality analysis system of WLJY-9000, which was devised by skill trade Company Weili Peking. All parameters were settled down to refer to standard of World Health Organization (WHO)[12].

Statistical

Date were expressed as mean ±SD and analyzed with *t*-test. Value of $P<0.05$ was considered to be statistically significant.

RESULTS

Changes in symptom and LEPS in CP or infertility with CP

After the treatment by EA-10, P_5 + Roxithromycin, EA-10, P_5 alone, and roxithromyc alone in CP or infertility with CP, remissive rate of symptom was 92 %, 66.67 %, 68.17 %, and 90 %, 61.91 %, 63.64 %, while

Tab 1. Changes in symptom and LEPS in different treated groups of CP. $^bP<0.05$ *vs* EA-10, P_5+Roxithromycin groups.

Treatment	Case	Symptom improved		LEPS improved	
		Efficiency	Percent/%	Efficiency	Percent/ %
EA-10, P_5+Roxithromycin	25	23	92	22	88
EA-10,P_5	21	14	66.67^b	12	57.14^b
Roxithromycin	22	15	68.17^b	13	59.09^b

Tab 2. Changes in the symptom and LEPS in different treated groups of infertility with CP. $^{b}P<0.05$ *vs* EA-10, P_5 +roxithromycin groups.

Treatment	Case	Symptom improved		LEPS improved	
		Efficiency	Percent/%	Efficiency	Percent/%
EA-10, P_5+roxithromycin	20	18	90	17	85
EA-10,P_5	21	13	61.91^{b}	11	52.38^{b}
Roxithromycin	22	14	63.64^{b}	12	54.55^{b}

effective rate of LEPS was 88 %, 57. 14 %, 59.09 %, and 85 %, 52. 38 %, 54. 55 %, respectively. Therapeutic efficacy in group A was significantly higher than that in group B or C *(*P<0. 01) (Tab 1, 2).

Changes in LEPS, MDA, SOD, Zinc content, and NO in CP

Compared with control group, LEPS, MDA, and NO were increased, while zinc content and SOD were decreased significantly in the pretreatment *(*P<0.01). After the treatment, LEPS and zinc content were improved, while MDA and NO were decreased apparently *vs.* pre-treatment *(*P<0.01), but there was no obvious alteration of SOD *(*P>0.05) (Tab 3).

Changes in LEPS, MDA, SOD, Zinc content, NO, and semen parameters in infertility with CP

In the pre-treatment, LEPS, MDA, NO, sperm viability, and seminal leukocytes were obviously higher and SOD, zinc content, and sperm motility were obviously lower than those in controlled group *(*P<0.01). After the treatment, LEPS, SOD, zinc content, sperm motility, and sperm viability were improved and MDA, NO, and seminal leukocytes were decreased significantly (P<0.01). Compared with the pre-treatment, MDA levels and seminal leukocytes were reduced significantly in group A than these in group B or C in the post-treatment *(*P<0.01) (Tab 4).

DISCUSSION

In this test, we have used EA-10, P_5 and roxithromycin to treat CP and infertility with CP. Roxithromycin has a good effect to chlamydia besides much of Gram-negative bacteria [13]. Therapeutic efficacy was lower in our works than that in literature. But our therapeutic efficacy was still satisfactory. We considered that the reason may be as follows: (1) Chronic bacterial prostatitis may be selected in all the chosen cases, which might influence therapeutic efficacy of EA-10, P_5. (2) The treatment period was shorter compared with that illustrated in literature. In addition, we have found that therapeutic efficacy in group A was better than

Tab 3. Changes in LEPS, MDA, SOD, Zn^{2+} content, and NO in different treated groups of CP. Mean±SD. $^{b}P<0.05$, $^{c}P<0.01$ *vs* control. $^{d}P>0.05$, $^{f}P<0.01$ *vs* pre-treatment at the same group. $^{b}P<0.05$ *vs* EA-10, P_5+Roxithromycin group.

	Control (n=20)	EA-10,P_5+Roxithromycin (n=25)		EA-10,P_5 (n=21)		Roxithromycin (n=22)	
		pre-treat	post-treat	pre-treat	post-treat	pre-treat	post-treat
LEPS /Hp	3.4±2.1	25±16^{b}	5.0±2.8^{f}	23±13^{b}	7±4^{f}	25±14^{b}	7±4^{f}
MDA/μmol·L^{-1}	4.1±1.1	8.3±1.9^{c}	4.3±1.4^{f}	8.3±1.7^{c}	5.4±1.6^{bfh}	8.4±1.8^{c}	5.2±1.2^{bfh}
Zn^{2+}/mmol·L^{-1}	2.3±0.6	1.2±0.4^{b}	1.8±0.5^{f}	1.2±0.5^{b}	1.6±0.5^{f}	1.2±0.4^{b}	1.6±0.5^{f}
SOD/kU·L^{-1}	920±119	850±118^{b}	851±122^{d}	838±110^{b}	840±113^{d}	829±120^{b}	831±123^{d}
NO/μmol·L^{-1}	4.6±1.6	63±20^{c}	39±16^{bf}	63±20^{c}	45±18^{bf}	63±21^{c}	47±18^{bf}

Tab 4. Changes in LEPS, MDA, SOD, Zinc content, NO, and Semen parameters in different treated groups of infertility with CP. Mean±SD. $^{a}P>0.05$, $^{b}P<0.05$, $^{c}P<0.01$ *vs* control. $^{d}P>0.05$, $^{e}P<0.05$, $^{f}P<0.01$ *vs* pre-treatment at the same group. $^{h}P<0.05$ *vs* EA-10, P_5+Roxithromycin groups.

	Control (n=20)	EA-10,P_5+Roxithromycin (n=25)		EA-10,P_5 (n=21)		Roxithromycin (n=22)	
		pre-treat	post-treat	pre-treat	post-treat	pre-treat	post-treat
LEPS/Hp	3.4±2.1	23±13^{e}	6±4^{f}	23±12^{e}	7±5^{f}	23±12^{e}	6±4^{f}
MDA/μmol·L^{-1}	4.1±1.1	9.2±1.6^{e}	5.5±2.1^{f}	9.1±1.9^{e}	7.5±2.4^{beh}	9.1±1.7^{e}	7.2±2.5^{beh}
Zn^{2+}/mmol·L^{-1}	2.3±0.6	1.1±0.4^{e}	1.6±0.4^{bf}	1.1±0.4^{e}	1.5±0.4^{bf}	1.1±0.3^{e}	1.4±0.4^{bf}
SOD/kU·L^{-1}	920±119	653±115^{e}	736±125^{bf}	663±91^{e}	727±104^{bf}	660±97^{e}	722±109^{bf}
NO/μmol·L^{-1}	4.6±1.6	78±20^{e}	55±18^{bf}	76±27^{e}	63±27^{bf}	77±25^{e}	61±21^{bf}
10^{9}×Sperm density/L^{-1}	76±24	82±49^{a}	79±46^{ad}	79±42^{a}	77±41^{ad}	80±41^{a}	79±40^{ad}
Sperm motility/%	75±12	37±14^{e}	46±14^{bf}	38±17^{e}	43±19^{bf}	37±16^{e}	43±18^{bf}
Sperm viability/%	14±8	36±14^{e}	24±10^{bf}	34±14^{e}	28±11^{bf}	34±13^{e}	28±11^{bf}
10^{9}×Seminal leukocytes/L^{-1}	0.5±0.3	1.6±0.9^{e}	0.7±0.4^{af}	1.6±0.8^{e}	0.9±0.4^{bf}	1.6±0.8^{e}	0.9±0.5^{bf}

in group B or C. This indicated that EA-10, P_5 should be used together with effective antibiotic in the treatment of CP.

Some studies have proved that OFR was related to occurrence and development of CP[3- 4,14]. In our studies, MDA was higher and SOD was lower significantly in the pre-treatment of CP than those in the control group, which suggested that there be an increase of OFR, a decrease of antioxidation, and reinforce a of LPO. But MDA was decreased after the treatment, indicated that OFR was scavenged massively and LPO was obviously inhibited.

Similarly, MDA was higher and SOD was lower significantly in pre-treatment of infertility with CP than those in the control group, which suggested that oxidation be increased and antioxidation be decreased in semen. At the same time, we discovered that sperm motility was declined and sperm viability was raised significantly. But after the treatment, MDA was decreased and SOD was increased significantly than those in the pre-treatment ($P<0.01$), accompanying with improvement of sperm motility and sperm viability apparently. This indicated that LPO was inhibited and antioxidation was reinforced. From the result above, we believed that EA-10, P_5 could reduce LPO and enhance antioxidation in the treatment of CP or infertility with CP.

In our treatment, antibiotic and EA-10, P_5 were used not only to cure CP but also to improve semen quality. We found that EA-10, P_5 had an effect on weakening oxidative stress and increasing antioxidation in protatic secret and semen. This suggested that change of OFR may be involved in the drug action mechanism of EA-10, P_5 in the treatment of CP or infertility with CP. At present, it is known that ferulic acid was an antioxidant containing phenolic hydroxy[15]; and P_5, one of valid portion in pollen extract EA-10, P_5, may have anti-oxidative effect owing to providing phenolic hydroxy too. Nevertheless this view still needs to be confirmed by more investigation.

It was reported that zinc content in prostatic secretion and semen was higher than in other organ and body fluid, which showed that zinc played an important role in keeping function of prostate and other accessory sex glands. Our studies showed that zinc content was increased accompanying with improvement of an illness state. EA-10, P_5 can enhance zinc content in seminal plasma, which may be related to improve local circumstance.

In summary, all these results could provide us with a possible therapeutics approach to treat infertility with CP. In order to improve therapeutic efficacy, anti-infection and anti-oxidation should be adopted in the treatment of CP or infertility with CP.

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Effects of Yanlieping Formula on Mice with Chronic Bacterial Prostatitis (Abstract)

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Objectives

To study the mechanism of Yanlieping Formula in treating chronic nonbacterial prostatitis.

Methods

Thirty-two C57BL/ 6 mice were divided into Chinese traditional Medicine group (Yanlieping group, 10 mice), treatment control group (Cernilton group, 10 mice), model group (6 mice) and normal group (6 mice). The animal model was created by using immunologic adjuvant, and Yanlieping (0.84 g per mouse), Cernilton (7.5 mg per mouse), distilled water (1.05 ml per mouse) and distilled water (0.5 ml per mouse) were respectively administered to the four groups every day for one month. The prostate weight, pathological changes, TNF-alpha and IL-2 in serum were observed.

Results

The prostate weight in Yanlieping group and Cernilton group became significantly lower than in the model group ($P<0.05$). Pathologic sign of chronic inflammation became better significantly (Yanlieping group showed more significant improvement). The expression of IL-2 in Yanlieping group and Cernilton group were down regulated significantly. And the expression of TNF-alpha in Yanlieping group was higher than that of the model group ($P<0.05$).

Conclusions

The mechanism of Yanlieping Formula in treating chronic prostatitis may lie in the max urethral close pressure reduction, anti-inflammation, local blood circulation improvement.

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Efficacy of Cernilton administration for infertile males associated with asymptomatic pyospermia

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Introduction

The cases, that white blood cell is significantly higher in semen, accounts for 16 ~ 17% of male infertility patients. Interestingly, it was common that no bacterial finding is presented in these cases, using standardized bacterial test, PCR methods for Chlamydia trachomatis (C. trachomatis), and semi-quantitative analysis for Ureaplasma urealyticum (U. urealyticum). Although these cases are classified in nonbacterial chronic prostatitis, it has been generally recognized to be associated with male infertility.

In present study, we reported that administration of Cernilton reduce PMN-elastase activity and to improve seminal findings in semen for 17 male infertility patients with no bacterial finding in semen.

Materials and Methods

17 male infertility patients associated with nonbacterial asymptomatic pyospermia were treated with Cernilton 6 tablets daily over 12 weeks, and then sperm density, progressively motile sperm ratio, sperm motility and PMN-elastase activity in semen were measured.

Results

In all patients, progressively motile sperm ratio, sperm motility and PMN-elastase activity in seminal fluid were improved.

Conclusion

Administration of Cernilton is seemed to be effective in the treatment of infertile males associated with nonbacterial asymptomatic pyospermia.

List of Patients

Number	Age	Sperm Density ($\times 10^6$/ml)	% progressively motile sperm	Sperm motility	PMN—elastase activity (μg/ml)
1	35	31 → 59	34 → 42	± → +	760 → 529
2	33	44 → 40	31 → 52	± → ++	1770 → 640
3	40	22 → 24	40 → 48	± → +	2080 → 610
4	32	10 → 10	30 → 54	± → +	7130 → 1860
5	36	38 → 27	42 → 55	± → +	610 → 240
6	34	32 → 35	40 → 52	± → +	890 → 290
7	35	28 → 31	44 → 67	± → ++	2270 → 114
8	36	67 → 49	41 → 62	± → ++	1710 → 380
9	41	100 → 64	15 → 55	± → +	1910 → 780
10	32	32 → 30	32 → 36	± → +	1510 → 1090
11	36	57 → 60	20 → 48	± → +	1800 → 1020
12	28	38 → 32	24 → 30	± → ++	2820 → 980
13	30	1.2 → 1.6	0 → 20	– → +	3970 → 1120
14	36	0.3 → 0.3	40 → 50	± → +	1710 → 940
15	32	0.6 → 0.5	21 → 34	± → +	5140 → 1200
16	34	38 → 30	0 → 23	– → +	4520 → 1070
17	41	0.7 → 0.5	34 → 38	± → ++	1060 → 720

The Treatment of Benign Prostatic Hyperplasia with Phytopharmata

A comparative study of Cernilton[R] vs. β-sitosterol

H. Bräuer

The conservative treatment of benign prostatic hyperplasia (BPH) has gained increasingly in significance in view of the increased life expectancy. In a controlled comparative study (n = 39) with Cernilton[R] and β- sitosterol the course of treatment was objectified by clinical-chemical findings. The results demonstrate the marked improvement of symptoms and signs, whereas the regression of complaints was more pronounced under Cernilton[R]. The significant decrease of PAP and PSA serum levels shows the reduction of cell lesions in BPH under the treatment with Cernilton[R]. A comparable effect of β-sitosterol could not be demonstrated. The relative lack of toxicity of both drugs can be confirmed by the biochemical data.

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In the second half of the normal life-span the physiological process of ageing leads to the appearance of an increasing number of diseases. One of these is benign prostatic hyperplasia (BPH), which sooner or later develops in practically all males. The data on the incidence of benign prostatic hyperplasia vary more than for almost any other condition.

Some authors assume that from the fourth decade of life almost 80%, and from the seventh decade almost 100% of all men show a more or less pronounced nodular hyperplasia of the prostate (2, 6). This means that the older a man becomes the more certain it is that he will be confronted with an alteration of his prostate and its consequences. The almost unbelievable increase in life expectancy which has been achieved through the diagnostic, therapeutic and prophylactic measures of modern medicine means that more and more men are reaching the critical age for prostate disease. In Sweden, the United Kingdom and Germany, for example more than 50% of the population is over the age of 65 years.

The figures published by the German Federal Statistics Office in Wiesbaden for 1983 show that 156,000 people in the Federal Republic were 90 years of age or over. Ten years earlier the corresponding figure was only 92,000. The trend is the same in all industrial countries and will continue. As a result, the incidence of the "old man's disease", prostatic hyperplasia, will also increase.

The aetiology and pathogenesis of benign prostatic hyperplasia are still unclear and are the subject of controversial discussion. Changes in enzyme activity in the prostate, shifts in various hormonal parameters (e.g. DHT) and, more recently, altered hormone-receptor conditions, are accepted as possible triggering factors (1, 2, 4, 6, 7). It is established that the endocrine system influences the development of a prostatic hyperplasia.

Rationale of Study

The fact that only relatively few men are not affected by benign prostatic hyperplasia makes it almost impossible to find a healthy control group in the same ate-range, in order to obtain comparative clinico-chemical data, for reference. This is probably also the reason for the sometimes contradictory results reported in many publications.

In our study two phytopharmaca, Cernilton[R] (Stroschein, Hamburg and β-sitosterol, were compared and the course of the treatment with each preparation objectified on the basis of clinico-chemical data.

Our Investigations

Selection of Patients

It was possible to carry out the study almost exclusively with trial subjects from a large old people's home, who always received food of the same type and composition, and to a certain extent the same amount. It was thus relatively easy to exclude changes attributable to nutritional factors in the parameters to be measured in the course of the study, in both groups.

With a predictable drop-out rate of 20%, 50 patients were taken into the study, in accordance with the defined criteria for exclusion and inclusion, in order to reach a total of at least 20 patients in each group, for the final evaluation. The patients were allocated to the two groups according to a strict randomization procedure. All the patients entered the study without any additional medication. In order to exclude possible uncheckable drug effects, a one-week wash-out period was included before the start of the treatment, in 4 cases. All the patients required treatment and had been receiving medical therapy for their prostatic symptomatology for more than 6 months. Because of unsatisfactory results of previous therapy they can be considered as a "simple negative" patient selection.

Two patients were excluded from the initial patient population because of extreme obesity and a further seven because of the results of diagnostic laboratory investigations (malignant tumors, sever alcoholic liver disease and extreme electrolyte imbalances). One patient had to discontinue the study for private reasons. At the final evaluation one patient of Group A with residual urine values of over 130 ml and who had to be operated for anuria before the end of the study period, was excluded. Table 1 shows the mean values for age, height, and weight in the two groups, A and B. Tables 2a and 2b provide information on concomitant diseases and the general condition of the patients of Groups A and B, respectively.

Methodology

The patients of Group A (trial preparation: a specially prepared pollen extract (3). Cernilton[R] [1)] received, as did the patients of Group B (control preparation: β-sitosterol [2)] , 2 tablets/capsules 3 times a day for the first week, and then 1 tablet/capsule 3 times a day[3)] from the 8th to the 42nd day.

The blood samples were taken in the morning, between 8:00 and 9:00 a.m., in the fasting state, by the Vacutainer system (Becton & Dickinson), centrifuged after maturation of the fibrin (1 hour at room temperature), separated by means of Seraclear filters and deep-frozen at -25º C and kept constantly at this temperature until the analytical processing. The clinico-chemical and hematological parameters were analyzed on a Type 12/60,6/60, 9/60 and 7A Auto-analyzer on a Type determinations of prostatic acid phosphatase (PAP) and prostate-specific antigens (PSA) were carried out by radioimmunoassay (RIA), as double-blind determinations which were repeated if the results exceeded the normal values by more than 600 counts. The counting was carried out with a Y-counter system (MR-1032-W+W) of the Kontron Co.

The enzyme activities were measured at the normal physiological temperature of 37ºC. The reproducibility for these values and for the hematology is ±3%, and for the other clinico-chemical parameters ±1%.

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1) One tablet contains: Stand. Extr. Pollin. sicc. (Cernitin T60) 60 mg; Stand. Extr. Pollin. dialys (Cernitin GBX) 3 mg.

2) One capsule contains: 10 mg β-sitosterol.

3) The manufacturer's recommendation of a dosage of 2 capsule 3 times a day was not followed, in order to be able to compare the therapeutic effects of the two preparations.

The data of the clinical investigations were classified according to symptoms and complaints and recorded according to the degree of change at each examination.

The residual urine was determined by catheterization, always performed by the same investigator. The bacterial examinations of the urine samples were performed by means of the classical culture methods.

All the data have been documented in accordance with GLP[4)] and processed according to standard biostatisical methods on an EDP unit (Olivetti L I M 40 ST).

Results

Changes in the clinical symptomatology

Subjective Complaints

Comparison of the initial findings with those at the end of the study shows improvement in the clinical symptoms with both preparations, which were clearly more pronounced with the pollen-extract preparation, according to both the investigating physician's impression and that of the patients themselves. This is true particularly for the patients with several concomitant symptoms. If the results are classified, then on the basis of the subjective findins of the patients and the observations of the treating physicians these data are supported, at least semi-quantitatively, by Table 3. This table shows a clinically relevant rate of improvement in the subjective symptoms, painful micturition, changes in the urinary stream and pollakisuria, for both preparations, with Cernilton^R proving better than β-sitosterol. For vesicle tenesmus, polyuria, urinary dribbling, as well as for pain and a feeling of pressure there is also a marked regression of the symptomatology in both groups.

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4) GLP = Good Laboratory Practice: recommendations of the German GLP committee, according to the guidelines of the Food and Drug Administration.

Determination of residual urine

In the β-sitosterol group the residual urine volume was 35 ± 22.5 ml and in the pollen-extract group 28 ± 16.6 ml. In both groups the mean values had fallen to under 15 ml at the end of the treatment.

Urine Examinations

Table 4 gives an overview of the changes in the cell-counts and the bacterial status during the treatment. With the improvement in the symptomatology the pathomorphological picture also improved.

Changes in biochemical parameters under the medication

The parameters indicating disturbances of renal function, namely creatinine and blood urea nitrogen, showed a clear decrease under both Cernilton^R and β-sitosterol. The urea nitrogen fell from 19.5 mg/100 ml to below 18.5 mg/ 100ml and from 21.0 mg/100 ml to 20.2 mg/100 ml under the two medications, respectively. The creatinine also showed a trend towards a slight decrease in the plasma concentration, which can be interpreted as not statistically significant tendency to improvement. The uric acid concentration was not influenced by either of the two preparations. The electrolytes remained largely within the ranges of the baseline values. Only in the case of chloride was there slight regression, by about 1 mmol/l. Neither preparation has any effect on blood pressure.

Impressive are those enzyme values which indicate cellular lesions. The γ-GT, generally known as a cholestase-indicating enzyme in alcohol abuse, had its highest intracellular value in the renal parenchymal cells. The fall in the primarily intrarenal γ-GT was not only statistically significant but also clinically relevant, and was more pronounced in the Cernilton^R group.

Although the alkaline phosphatase (AP) isoenzyme group is not particularly prostate-specific, an enzyme of this group is however to be found in a high concentration in the prostate tissue. During the course of the study there was a marked fall in the serum concentration of AP in both groups.

The PAP and PSA determinations in the serum show a clear difference in the effectiveness of the two preparations. Prostatic acid phosphatase (PAP) is a highly tissue-specific enzyme which is normally passed into the seminal fluid. All pathological changes of the prostate, whether carcinoma, benign hyperplasia or prostatitis, lead to an increase in the concentration of this enzyme in the peripheral blood. In Group A the PAP concentration fell, the decrease being not only clinically relevant but also statistically significant ($p < 0.05$), from 3.5 to 2.7 ng/ml, i.e. the serum concentration reached the normal range, the upper limit of which, measured by the RIA method , is 2.8 ng/ml. Group B, with a high baseline value, showed a similar initial fall from 4.4 to 3.7 ng/ml, which remained at this level until the end of the study, and thus did not reach the normal range (Fig. 1).

The prostate-specific antigen (PSA) originates from the epithelium of the excretory ducts of the

glandular complex and shows a maximum physiological concentration in the serum of 2.3 ng/ml. In benign prostatic hyperplasia concentrations of up to 12 ng/ml are reached. β-sitosterol lowered the serum concentration from the start to the end of the study by only 0.5 ng/ml (from 12.9 to 12.4 ng/ml). This value is not statistically significant and also there is no detectable trend. Statistically significant and also there is no detectable trend. Statistically significant ($p < 0.01$), and in our opinion clinically relevant, on the other hand, is the fall in the PSA value in the pollen-extract group. Here the value fell from 8.25 to 5.8 ng/ml, i.e. a decrease of 2.45 ng/ml was obtained (Fig. 2).

For the other clinico-chemical parameters, namely iron, total protein, albumin, calcium, anorganic phosphate, bilirubin, LDH, GPT (ALT), GOT (AST), triglycerides, cholesterol, cholinesterase, copper, magnesium and zinc, no significant changes were recorded, between the baseline and final values. Only in the values for leukocytes, erythrocytes, haematocrit, haemoglobin and CPK is there a trend towards a slight fall in both groups, so that on the basis of this spectrum of parameters the relative innocuity of both preparations can be confirmed.

Discussion

Prostatic acid phosphatase (PAP) is a glycoprotein with a relatively low carbohydrate content of only 6%. Under normal physiological conditions this enzyme is passed from the prostate to the seminal fluid in which, together with hyaluronidase, it influences the fluidity of the semen (8). Because of secretory obstruction a benign prostatic hyperplasia is always accompanied by raised internal pressure in the glandular complex. This raised pressure leads to compressive cellular lesions and cytolysis, as a result of which the PAP concentration in the peripheral blood increases. During the course of the study the mean value of the PAP concentration in Group A fell below the upper limit of the normal rage (Fig. 1), while in Group B there was an initial improvement, but then no further change in the mean value for the rest of the period of the study.

In healthy subjects the prostate-specific antigen (PSA) is to be found in high concentrations only in the semen. In the peripheral blood it is normally present only in a very low concentration (up to 2.3 ng/ml) (5), but increases markedly (up to 12 ng/ml) in the presence of cellular lesions of the excretory ducts resulting from a benign prostatic hyperplasia. Like the PAP concentration, that of the PSA also shows a marked fall under pollen extract therapy, from 8.25 ng/ml (Day 0) to 5.8 ng/ml (Day 42), while underβ sitosterol therapy the values fall only slightly (Fig. 2).

The fall in the serum concentrations of these two highly prostate-specific markers (PAP and PSA) permits the conclusion to be drawn that the cellular lesions of the glandular tissue resulting from prostatic changes show marked improvement under treatment with pollen extract. Presumably the internal pressure in the glandular complex due to the secretory obstruction also subsides. The concentrations of the mediators of inflammation, of the prostaglandin and leukotriene types, are certainly also reduced. In this way the vicious circle of a self-perpetuating inflammatory process can be broken, since the excessive secretion of prostaglandin is always set in motion by cellular lesions and persists for as long as these lesions are present. Thus with these values it can be confirmed that Cernilton^{R} exerts an anti-inflammatory effect.

On the basis of the measurement values presented here the use of Cernilton^{R} can be recommended for the indication, “benign prostatic hyperplasia in Stages I and II”, provided the residual urinary volume is still under 100 ml. Cernilton^{R} reduces the symptomatolofy of prostatic hyperplasia. The antiinflammatory and micturition-improving effects are confirmed by the various measurement data. We consider very important the fact that the preparation is extremely well tolerated.

The conservative drug therapy of benign prostatic hyperplasia is also of great significance, both in the hospital environment and in general practice, in view of the fact that the proportion of the general population over the age of 50 will in future be even greater than it is today.

Keywords: Prostatic hyperplasia, benign, Cernilton^{R}, β-sitosterol, Prostatic acid phosphatase, Prostate-specific antigen.

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Table 1: Statistical data (age, height, weight) in the two comparative groups (x±s)

Group	n	Age (years)	Height (cm)	Weight (kg)
A (Cernilton^{R})	19	68.9 ± 15.13	171.5 ± 8.28	76.3 ± 10.32
B (B-sitosterol)	20	73.0 ± 10.9	171.1 ± 6.8	73.9 ± 9.9

Table 2a: Concomitant diseases and general condition of the patients of Group A

Patient No.	Concomitant diseases	General Condition
5	Arteriosclerosis, cerebral sclerosis	Poor
9	Moderate hypertension, diabetes mellitus	Good
12	Moderate hypertension, diabetes mellitus, cholelithiasis, coronary sclerosis	Satisfactory
13	Osteoarthritis of the hip, arteriosclerosis, hypertension, coronary sclerosis	Satisfactory
15	Hypertension, coronary sclerosis	Good
18	-	Good
19	-	Satisfactory
21	Nephrolithiasis	Satisfactory
23	Spondylarthrosis, arteriosclerosis	Satisfactory
24	Coronary sclerosis, angina pectoris	Poor
27	-	Good
30	Generalized osteoarthritis, diabetes mellitus	Poor
31	Coronary sclerosis	Satisfactory
32	Moderate hypertension, coronary sclerosis	Poor
33	-	Satisfactory
36	Arteriosclerosis, coronary sclerosis	Good
37	Duodenal ulcer	Good
38	Glaucoma, bronchial asthma, coronary sclerosis	Satisfactory

Table 2b: Concomitant diseases and general condition of the patients of Group B

Patient No.	Concomitant disease	General condition
1	Slight hypertension	Satisfactory
2	Slight hypertension	Satisfactory
3	Nephrolithiasis, diabetes mellitus, angina pectoris	Poor
4	Slight hypertension, varicose veins	Poor
6	Slight hypertension	Satisfactory
7	Moderate hypertension, spondylosis	Satisfactory
8	Spondylosis, spondylarthropathy	Good
10	Moderate hypertension	Good
11	Slight hypertension, coronary sclerosis	Satisfactory
14	Arteriosclerosis, Parkinson's disease	Satisfactory
16	Cerebral sclerosis	Satisfactory
17	Cor pulmonale	Satisfactory
20	-	Good
22	Generalized osteoarthritis	Satisfactory
25	Angina pectoris	Poor
26	Cor pulmonale, arteriosclerosis, chronic obstructive bronchitis	Satisfactory
28	Slight hypertension, angina pectoris	Good
29	Slight hypertension, cerebral sclerosis, cerebral insufficiency, coronary sclerosis	Satisfactory
34	Angina pectoris, coronary sclerosis	Satisfactory
36		Satisfactory

Table 3: Baseline status and course of the subjective complaints
(A = Cernilton^{R} group, B=B-sitosterol group)

Complaints	Group	n	Day 0	Day 14			Day 42		
				No change	Reduced	Absent	No change	Reduced	Absent
Painful micturition	A B	19 20	13 14	7 10	6 4	0 0	1 1	7 9	5 4
Changes in urinary stream	A B	19 20	9 16	3 12	4 4	2 0	2 1	1 9	6 6
Pollakisuria	A B	19 20	15 13	10 10	5 2	0 1	1 2	6 5	8 6
Vesical tenesmus	A B	19 20	4 5	4 3	0 1	0 1	2 0	1 4	1 1
Polyuria	A B	19 20	1 3	1 2	0 1	0 0	0 0	1 3	0 0
Incontinence	A B	19 20	2 0	1 0	1 0	0 0	1 0	0 0	1 0
Urinary dribbling	A B	19 20	4 5	3 3	1 2	0 0	2 2	1 1	1 1
Pain or feeling of pressure	A B	19 20	7 4	5 1	2 3	0 0	0 0	5 3	2 1

Table 4: baseline status and course of the urinary findings (A = Cernilton^{R} , B = β-sitosterol group)

	Day 0		Day 14		Day 42	
	A n	**B n**	**A n**	**B n**	**A n**	**B n**
Erythrocytes						
None	15	14	17	14	18	13
Few	4	4	2	4	1	5
Moderately numerous	-	-	-	-	-	-
Numerous	-	-	-	-	-	-
Leukocytes						
None	3	1	3	2	5	4
Few	8	8	12	10	11	9
Moderately numerous	7	8	4	8	2	6
Numerous	1	3	-	-	1	1
Epithelial cells						
None						
Few	18	17	16	16	19	16
Moderately numerous	1	1	2	2	-	2
Numerous	-	-	-	-	-	-
	-	-	1	-	-	-
Bacteria						
None	13	12	15	12	16	13
Few	3	5	3	8	3	7
Moderately numerous	2	3	1	-	-	-
Numerous	1	-	-	-	-	-

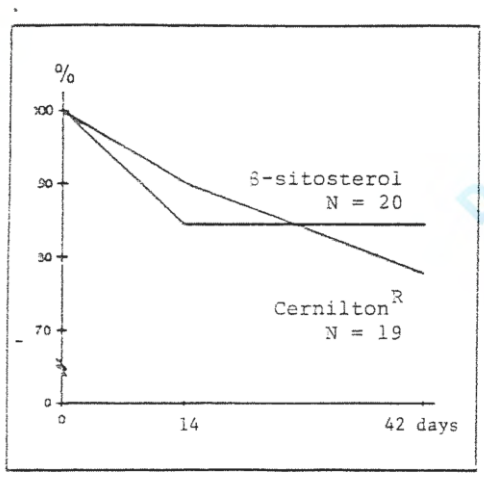

Fig. 1: Significant reduction ($p < 0.05$) of the serum PAP in %, after 6 weeks Cernilton^{R} therapy. A comparable effect with β-sitosterol cannot be demonstrated*.

*The absolute values before and after treatment are, in the Cernilton^{R} group 3.5 ± 1.67 ng/ml (Day 0) and 2.7 ± 1.11 ng/ml (Day 42), and in the β-sitosterol group 4.4 ± 5.68 ng/ml (Day 0) and 3.7 ± 4.42 ng/ml (Day 42). Normal serum PAP value, by radioimmunoassay (RIA) = ≥ 2.8 ng/ml.

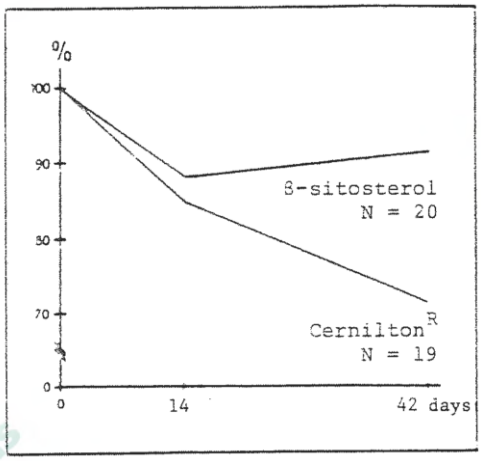

Fig. 2: Significant reduction ($p < 0.01$) of the serum PSA in %, after 6 weeks Cernilton^R therapy. A comparable effect with β-sitosterol cannot be demonstrated**.

**The absolute values before and after treatment are, in the Cernilton^R group 8.25 ± 10.77 ng/ml (Day 0) and 5.8 ± 6.56 ng/ml (Day 42), and in the β-sitosterol group 12.9 ± 14.55 ng/ml (Day 0) and 12.4 ± 13.57 ng/ml (Day 42). Normal serum PSA value, by radioimmunoassay (RIA) = ≥ 2.3 ng/ml.

Treatment of Chronic Prostatitis and Prostatodynia with Pollen Extract

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Summary— Chronic abacterial prostatitis and prostatodynia are notoriously difficult both to diagnose and to treat. These patients tend to have received several courses of antibiotics, anti-inflammatory agents or adrenergic blockade and various other therapeutic manoeuvres with little success. The pollen extract, Cernilton, is reported to be effective in the treatment of this condition and we present the results of an open trial with Cernilton in a group of 15 patients with chronic prostatitis and prostatodynia. In 13 patients there was either complete and lasting relief of symptoms or a marked improvement; 2 patients failed to respond.

Cernilton was found to be effective in the treatment of chronic prostatitis and prostatodynia. Its precise mode of action is not known, although experimental studies suggest that is has anti-inflammatory and anti-androgenic properties.

The treatment of chronic, relapsing non-bacterial prostatitis presents a formidable challenge to the clinician. It is also well recognized that other conditions, such as pelvic floor myalgia, prostatodynia, adductor muscle strain and chronic traumatic osteitis pubis, may give rise to symptoms of dysuria, perineal, groin, testicular and suprpubic pain that mimic inflammatory disease in the prostate (Segura et al., 1979; Osborn et al., 1981; Buck et al., 1982). It is, therefore, important to differentiate such conditions from chronic prostatic inflammation on the basis of objective morphological, biochemical, radiological, urodynamic and microbiological criteria.

To achieve a cure in these patients is extremely difficult. The response to antibiotics, α-adrenergic blockage, non-steroidal anti-inflammatory drugs and other empirical manoeuvres is either ineffective or, at best, variable (Meares and Barbalias, 1983; Meares, 1986). The pollen extract Cernilton (A. B. Cernelle, Sweden) has been used in the treatment of chronic prostatitis for nearly 30 years with favourable results (Ask-Upmark, 1963; Denis, 1966; Ebeling, 1986; Saito, 1967). The aim study was to evaluate the efficacy of Cernilton in the treatment of patients with chronic non-bacterial prostatitis and prostatodynia.

Patients and Methods

Fifteen patients, ranging in age from 23 to 63 years (mean 42.9±SD 11.1) and with a clinical diagnosis of chronic relapsing non-bacterial prostatitis or prostatodynia, were entered into an open trial to study the effect of Cernilton. Twelve patients had previously been treated with 1 or more courses of antibiotics for varying periods of time, 4 had been treated with an alpha-adrenergic blocker, 1 had undergone a transurethral resection of the prostate and 1 an epididymectomy without relief of symptoms. At the time that the patients were commenced on Cernilton they had suffered from their symptoms for periods ranging from 5 months to 7 years (mean 3.3±SD 2.2). Their clinical presentation was as follows: 13 complained of irritative urinary symptoms, mainly dysuria (13) and frequency (6). All complained of pain or discomfort, persistent or intermittent, localised to the testis (7), groin (4), perineum (5), suprapubic area (1) urethra / penis (3) or on ejaculation (2) (Table).

The diagnosis of chronic prostatitis or prostatodynia was made on the basis of the segmented urine sample method of Meares and Stamey (1968). No significant bacteriuria was present in any of the patients, nor were pathogenic organisms, including Chlamydia

Table Details of Patients

Name age (years)	Dur. of symptoms (years)	Urinary symptoms	Pain site/ occurrence	Previous therapy: Antibiotics	Previous therapy: Relaxants/ α adrenergic blockade	Previous surgery	Response to Cernilton
TW 36	7	Dysuria	L testis	Multiple		Epididymectomy	Complete
DD 61	5	Dysuria	Suprapubic	None	Yes	TURP	Partial
FM 49	0.5	Dysuria	Lumbosacral	None			Partial
GS 47	2	Dysuria	L. testis	Multiple			Partial
DB 33	1	Frequency	R. testis	Multiple			Complete
JG 46	2	Dysuria, frequency	Perineum, ejaculation	Multiple		Cystoscopy	None
MP 44	7	Dysuria	Groin	Multiple	Yes	Cystoscopy	Complete
RJ 29	1	Dysuria, frequency	Perineum, penis	Multiple		Cystoscopy	Complete
DP 51	4	Dysuria	Perineum, testes	Multiple			Partial
HG 63	2	Frequency	Penile, on intercourse	Single	Yes	Cystoscopy	None
SC* 36	2	Dysuria	L. testis, groin	Multiple			Complete
DH 40	7	Dysuria	Perineum, testes	Multiple			Partial
JM 35	3	Dysuria	Testes, urethra	None	Yes		Partial
RD* 23	3	Dysuria	Groins	Multiple			Complete
AP 51	3	Frequency	Groins, perineum	Multiple	Yes	Cystoscopy	Complete

* Patients SC and RD relapsed when treatment was stopped and responded again to further treatment.

trachomatis, cultured from the EPS (expressed prostatic secretion). In 5 patients the pH of the prostatic fluid was alkaline (pH 7.0-8.0) with >10 leucocytes and fat laden macrophages /high power field on microscopy. In 8 patients the characteristics of the EPS were normal (pH < 6.5; pus cells < 10 / HPF) and in 2 cases no fluid could be obtained by massage for examination. The patients were commenced on Cernilton 2 tablets twice daily and assessed clinically at monthly intervals.

Results

The duration of treatment with Cernilton varied from 1 to 18 months. Seven patients became symptom-free, 6 were significantly improved and continue to take Cernilton regularly, and 2 failed to respond. Most patients (11) did not begin to show any improvement in signs or symptoms until 3 months after starting treatment (Table).

Only 1 patient, with a 12-month history of right testicular pain and urinary frequency, who had received 3 courses of antibiotics, with sterile urine and an EPS pH of 6.8 with < 5 leucocytes/HPF, was completely relieved of symptoms after 1 month's treatment with Cernilton. A second patient with a 5-month history of dysuria, frequency, back ache and sterile urine, but an EPS pH of 8 and > 20 pus cells/ HPF, was partially relieved of symptoms at 2 months and the pH of the EPS fell to 7.8, < 10 pus cells / HPF.

Two patients had a recurrence of symptoms after cessation of treatment. A 36 year-old man had a 2-year history of intermittent dysuria, left groin and testicular discomfort and an EPS pH of 8 with masses of pus cells /HPF on microscopy; he had been treated with several courses of antibiotics (minocycline, doxycycline, trimethoprim) without relief of symptoms or a

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change in the alkalinity or leukocytosis of the EPS. After 3 months' treatment with Cernilton the symptoms were completely relieved and the pH of the EPS fell to 7.1 with < 5 pus cells / HPF. On discontinuing treatment the symptoms recurred, with a return to leukocytosis and an alkaline shift in the pH of the EPS. After recommencing Cernilton the signs and symptoms again reverted to normal.

Discussion

Cernilton is an extract of various pollens from different plants. The active ingredients are a water-soluble (T60) and fat-soluble (GBX) fraction. The water-soluble fraction attenuated the inflammatory response in experimental animals (Ito et al., 1984). The acetone-soluble fraction was found to consist of 3ß-sterols with a similarity on UV absorption spectra to oestrone and stigmasterol (Kvanta, 1968). More recently, in vitro studies have shown that GBX inhibits cyclo-oxygenase and lipoxygenase enzyme in the eicosanoid cascade, blocking both leukotriene and prostaglandin synthesis (Loschen, personal communication). Cernilton was shown to reduce significantly the size of the ventral and dorsal prostate in the rat and to inhibit testosterone-induced prostatic hypertrophy in the castrated animal (Ito et al., 1986). Kimura et al. (1986) observed that T60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle.

Although the precise mode of action of Cernilton on the inflammatory process in the prostate is not known, it has been shown to be effective in the treatment of chronic abacterial prostatitis (Ohkoshi et al., 1967; Ebeling, 1986). In this study, Cernilton was found to relieve completely the symptoms of prostatitis in 7/15 patients and a further 6 were markedly improved. All patients had previously received several courses of antibiotics, analgesics and muscle relaxants and some were given adrenergic blockade, without effective or lasting relief of symptoms. It is of interest that the effect of the pollen extract was mainly observed after 3 months or more of treatment. Most patients have opted to continue with treatment and no adverse side effects have been reported. The in vitro experiments suggest that it could be either a potent cyclo-oxygenase and lipoxygenase inhibitor or a smooth muscle relaxant. These actions could explain its anti-inflammatory effect in abacterial prostatitis and symptomatic relief in prostatodynia, a condition in which an increase in the maximum urethral closure pressure and spasm of the external sphincter mechanism has been observed in association with a diminished urine flow rate (Buck, 1975; Meares and Barbalias, 1983). Conversely, it may affect metabolic processes within the prostatic cell (Habib, personal communication). Further clinical and laboratory studies are necessary to elucidate the exact mode of action of this compound.

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Treatment of Outflow Tract Obstruction due To Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton ® *

A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Summary-Whilst prostatectomy remains the “gold standard” for the treatment of outflow tract obstruction due to benign prostatic hyperplasia, medical treatment-if only for symptomatic relief-appears to be an attractive alternative. Most of the pharmacological agents in use block the hormonal or sympathetic neurological pathways that influence prostate growth and function. All of these drugs are known to have side effects.

Sixty patients with outflow obstruction due to benign prostatic hyperplasia (BPH) were entered into a double-blind, placebo-controlled study to evaluate the effect of a 6-month course of the pollen extract, Cernilton. There was a statistically significant subjective improvement with Cernilton (69% of the patients) compared with placebo (30%). There was a significant decrease in residual urine in the patients treated with Cernilton and in the antero-posterior (A-P) diameter of the prostate on ultrasound. However, differences in respect to flow rate and voided volume were not statistically significant. It is concluded that Cernilton has a beneficial effect on BPH and may have a place in treatment of patients with mild or moderate symptoms of outflow obstruction.

From numerous experimental studies in animals and clinical studies in man there is unequivocal evidence for the role of androgens in the development of benign prostatic hyperplasia, but the precise hormonal interactions which initiate or, indeed, sustain these changes in the prostate gland are unknown (Wilson, 1980; *Habib* et al., 1981; *Stone* et al., 1986). The symptoms that ensue from BPH are variable and bear little relation to the size of the gland. They can be either obstructive or functional and irritative, owing to concomitant detrusor instability and alpha-adrenergic overactivity of the sympathetic innervation of the bladder neck and prostatic musculature. The medical approach to the treatment of symptomatic BPH has been both endocrine and neuropharmacological. More than 30,000 prostatectomies are performed in the UK every year and approximately 10 times that number in the USA. Because of the large number of patients with moderate or mild symptoms of prostatic outflow obstruction awaiting surgery and a clearer insight into the pathophysiology of "prostatism", interest has been rekindled in the medical management of BPH with either hormonal manipulation or adrenergic blockade *(Lancet,* 1988). Reports of the efficacy of the pollen extract, Cernilton, in the symptomatic relief of BPH *(Takeuchi* et al., 1981; *Becker* and *Ebeling,* 1988) prompted us to carry out a placebo-controlled, double-blind study to evaluate its effect in patients with outflow obstruction due to BPH.

Patients and Methods

Sixty patients awaiting operative treatment for outflow obstruction due to benign enlargement of the prostate were entered into a double-blind, placebo-controlled study. Their ages ranged from 56 to 89 years (mean 68.6 ± SD 7.7). The patients consented to enter the study and their family doctors were informed. Cernilton and a placebo were administered in a dose of 2 capsules *bd* over a 6-month period.

The objective criteria for the evaluation of outflow obstruction were (i) the urine flow rate (an accurate measurement of flow rate required a minimum voided volume of 150 ml. With volumes < 150 ml the flow rate was repeated twice with the sensation of a full bladder and the mean of 3 readings taken as representative of the flow rate); (ii) the voided volume; (iii) an ultrasound measurement of residual urine; (iv) ultrasound measurement of prostate size by transrectal ultrasound probe using the Kretz ultrasound equipment. The prostate was scanned from the level of the seminal vesicles at the base of the prostate to its apex. An image of the prostate at its largest dimension was frozen on the screen and the outline of the prostatic image was circumscribed and measured in mm; the antero-posterior and transverse diameters were recorded (Fig. 1).

Subjective assessment was based on a modified "Boyarsky" scoring scale, as recommended by the Food and Drug Administration, for the symptoms of frequency, hesitancy, urgency, intermittency, incomplete emptying, terminal dribbling and dysuria, with a score of 0-3 for each of these symptoms (0 being an absence of symptoms and 3 being the most severe; see Appendix) *(Boyar*sky et al., 1977).

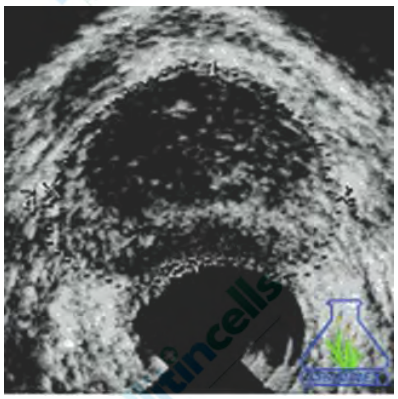

Fig. 1 Frame showing the prostate in its largest dimension

In addition, a full hematological and biochemical profile was performed, including liver function tests and serum cholesterol, triglycerides, high and low density lipo-proteins. All blood samples were obtained between 09.00 and 10.00h, following an overnight fast. The investigations were performed before the patients began treatment with either active compound or placebo, again at 3 months and finally at the conclusion of the study. The study was commenced and completed within a 7-month period, from October 1987 to April 1988. All urodynamic and ultrasound measurements were performed by one observer (A.C.B.) but the subjective evaluation was done by 2 clinicians independently.

Statistical Method and Analysis

The statistical analysis was divided into 5 sections dealing with (i) the homogeneity of demographic distribution and clinical presentation, (ii) the homogeneity of baseline findings, (iii) therapeutic measurements and trial course, (iv) assessment of efficacy and (v) assessment of safety and tolerance.

The tests for comparability of the trial groups were carried out by means of X^2 tests for categorical data, X^2 test with Yates' correction (4-fold tables) and Student's *t* test for continuous data. The comparison of trial groups with regard to symptoms was carried out by means of the X^2 test. The changes in urodynamic and ultrasound data, and in laboratory and clinical parameters in both groups, were compared using analysis of variance. All tests were performed using the 5% level of significance.

Results

Of the 60 patients entered into the study, 3 were excluded after the initial assessment: the first had an iron deficiency anemia caused by gastrointestinal bleeding that required further investigation and treatment; the second patient had undergone an abdominoperineal resection for carcinoma of the rectum which precluded objective evaluation of the prostate and the third patient decided against continuing in the study. Thus 57 patients took part. There were 31 patients in the Cernilton arm and 26 in the placebo arm. During the course of the study a further 4 patients were excluded: 2 in the placebo arm were admitted with acute retention of urine and underwent transurethral resection of the prostate (TURP); 1 patient in the Cernilton arm was admitted with acute epididymitis that was considered to be unrelated to the trial procedure and another patient was admitted with acute retention of urine and underwent a TURP. Fifty-three patients were fully evaluable at the end of 6 months, 29 in the Cernilton arm and 24 in the placebo arm.

With regard to the stratification of patients, the 2 groups were evenly matched with respect to demographic data, clinical presentation, symptoms, laboratory investigations and objective evaluation with the exception that the patients in the Cernilton arm had a higher mean body weight (P = 0.05).

Subjective Evaluation

There was no statistical difference in the symptoms of diurnal frequency between the 2 groups (P = 0.66), but 60 % of patients on Cernilton were improved or symptom-free as regards nocturia compared with 30 % of patients on placebo (P < 0.063). On Cernilton, 57% of patients showed improvement in bladder emptying compared with only 10 % in the placebo group (P < 0.004). There were no significant differences in hesitancy (P= 0.48), urgency (P=0.157), intermittency (P= 0.5), terminal dribbling (P = 0.9) or dysuria (P = 1.0). There was a statistically significant overall improvement in subjective symptoms in the Cernilton group (69 % of patients) compared with patients in the placebo group (29 %) (P < 0.009) (Table 1).

Table 1 Frequency of Symptom-free Findings following Cernilton and Placebo at 6 months

	Response Rate (%)		
Symptom	*Cernilton*	*Placebo*	*P value*
Frequency			
Daytime	37	47	0.664
Nocturia	60	30.4	0.063*
Hesitancy	47	29	0.480
Urgency	71	45	0.157
Intermittency	52	33	0.505
Incomplete emptying	57	10	0.004*
Terminal dribble	61	56	0.99
Dysuria	62	71	1.0

*Statiscally significant
Some test results remained non-significant because of the small number of positive findings before the start of the treatment.

Table 2 Results of Measurements before and after Treatment
*Statistically significant

Parameter	*Time of examination*	*Cernilton* $\bar{X}$	*Cernilton* SE	*Placebo* $\bar{X}$	*Placebo* SE	*Analysis of variance (P value)*
Peak flow rate (ml/s)		(n = 26)		(n = 24)		
	Before treatment	10.3	5.2	11.8	6.4	0.92
	After treatment	10.5	5.1	12.1	5.1	
Volume voided (ml)		(n = 29)		(n = 24)		
	Before treatment	241.5	144	235	96.8	0.11
	After treatment	203.4	90.3	257	106.6	
Residual urine (ml)		(n = 28)		(n = 24)		
	Before treatment	145.4	107.5	93.4	91.4	0.025*
	After treatment	101.9	87.3	113.4	87.3	

*Statistically significant.

Objective Evaluation

The results of peak urine flow rate, voided volume and residual urine in the 2 groups of patients before and after treatment are shown in Table 2. There was no significant change in peak urine flow rate (both groups showed a slight increase) or voided volume

The results of ultrasound measurement of the parameters for prostate volume are shown in Table3. The A-P diameter was found to be significantly reduced after treatment with Cernilton at 6 months (P<0.025) (Fig. 3).

There were no significant changes in the hematological or biochemical measurements in either group. No significant changes in serum cholesterol, triglyceride or lipoprotein values were observed with Cernilton and no adverse side effects were reported.

(slight decrease after Cernilton and a slight increase with placebo) before and after treatment in the 2 groups. However, residual urine volume decreased significantly in the patients receiving Cernilton compared with the placebo group, in whom it increased (P < 0.025) (Fig. 2).

Discussion

Transurethral resection or open prostatectomy undoubtedly remains the most effective treatment for BPH but is not without complications in both the short and longer term, whilst symptomatic improvement and patient satisfaction after the operation appears to be less in those who are only mildly or moderately symptomatic than in those with severe symptoms or retention *(Fowler* et al., 1988). Thus there may be a place for therapeutic compounds that are of proven benefit and free of side effects for the treatment of patients with mild or moderate symptoms who are awaiting operation or are unfit for surgery.

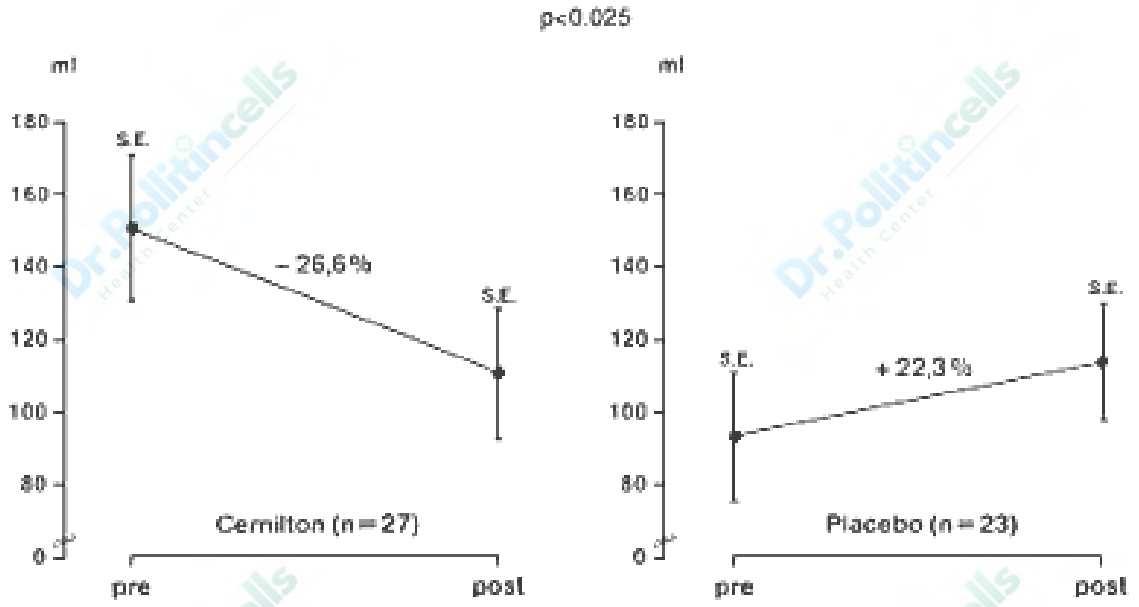

Fig. 2 Residual urine volume.

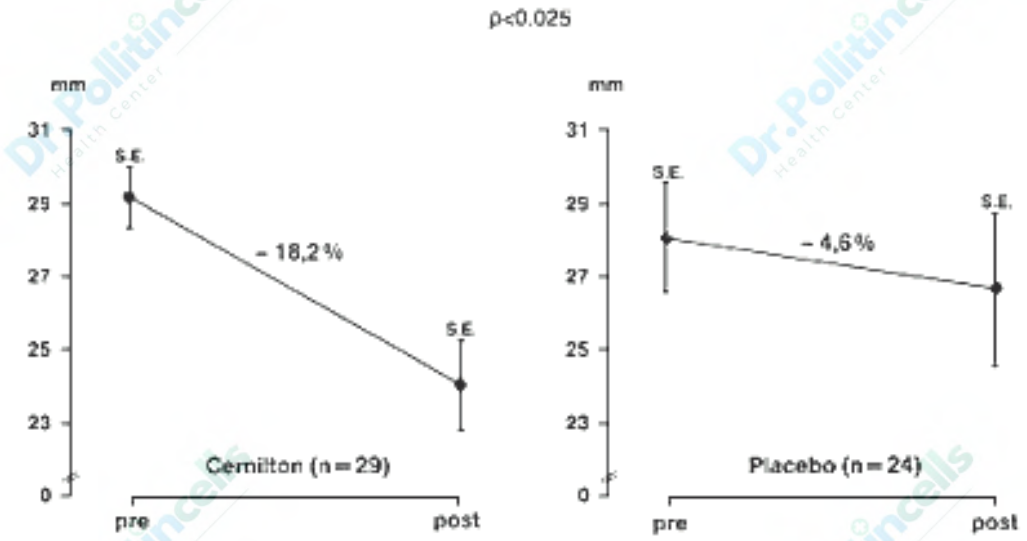

Fig. 3 Prostate volume.

Several studies aimed at achieving androgen deprivation in BPH have been reported. These have included castration *(Huggins* and *Stevens,* 1940), oestrogens *(Beacock* et al., 1985), progestogens *(Geller* et al., 1965; *Hald* and *From,* 1972), anti-androgens *(Caine* et al., 1975) and, more recently, LH-RH agonists *(Gabrilove* et al., 1987; *Peters* and *Walsh,* 1987). With the introduction of selective xl adrenergic blockers, there has been renewed interest in their use for symptomatic relief *(Caine,* 1986; *Kirby* et al., 1987). The discovery of high concentrations of cholesterol in BPH has led to the use of cholesterol-lowering drugs such as candicidin, with variable results *(Jensen* and *Madsen,* 1983). However, none of these compounds has proved to be consistently effective and most have significant untoward side effects.

An interesting empirical approach to the non-adrenergic, non-hormonal treatment of symptomatic BPH has been the use of pharmacological compounds derived from plants, *Donkervoort* et al. (1977) evaluated Tandenan, an extract of African prunes, in a double-blind study in 20 patients. Although the drug was harmless, it had no beneficial effect. An extract from the fruit of the American dwarf palm, Serenoa repens, reputed to have antiandrogenic activity, brought about a significant improvement in flow rate, residual urine and nocturia, although peak urine flow rates did not reach normal values in the large group of patients studied (5.35±SE 1.51 before and 8.05±SE 2.47 after treatment; n= 46) *(Champault* et al., 1984).

Table 3 Measurement of Prostate Volume

Prostate size	*Time of examination*	*Cernilton* $\bar{X}$	*SE*	*Placebo* $\bar{X}$	*SE*	*Analysis of variance (P value)*
Circumference (mm)		(n = 29)		(n = 17)		
	Before treatment	169.6	26.3	163.2	16.2	0.446
	After treatment	153.4	27.5	150.5	21.6	
Transverse diameter (mm)		(n = 29)		(n = 24)		
	Before treatment	56.4	8.3	53.8	8.1	0.753
	After treatment	52.2	9.7	50.3	8.1	
Anteroposterior diameter (mm)		(n = 29)		(n = 24)		
	Before treatment	29.1	5.3	28.3	7.4	0.025*
	After treatment	23.8	7.0	26.7	9.1	

*Statistically significant.

The pollen extract, Cernilton, known to be effective in the treatment of chronic abacterial prostatitis and prostatodynia *(Ohkoshi* et al., 1967; *Ebeling,* 1986; *Buck* et al., 1989), has also been shown to provide symptomatic relief in patients with benign prostatic hyperplasia *(Takeuchi* et al., 1981; *Becker* and *Ebeling,* 1988). Cernilton is an extract of pollen derived from several different plants in southern Sweden. It is rendered free of allergens and its 2 principal active constituents are a water soluble fraction, T-60, and an acetone soluble fraction, GBX. The acetone-soluble fraction was found to consist of 3 B-sterols with a similarity on UV absorption spectra to oestrone and Stigmasterol *(Kvanta,* 1968). Cernilton produced a significant decrease in the size of the ventral and dorsal lobes of the prostate gland accompanied by histological evidence of epithelial cell atrophy, a significant fall in total and prostatic acid phosphatase, with a significant increase in the zinc concentration in the dorsal lobe of the prostate and in blood in mature Wistar rats compared with the control animals *(Ito* et al., 1986). *Habib* et al. (1990) reported the inhibition of immortal human cell line growth in culture derived from prostate carcinoma in the presence of T-60. The hormone-stimulated growth of BPH tissue transplanted into nude mice is significantly inhibited by Cernilton extract but no histological differences were observed between the treated and untreated groups (Otto, etal., 1990). Despite the results of these experimental studies there have been no clinical studies to indicate that Cernilton has any influence on hormonal metabolism in man. In the present investigation the levels of LH, FSH, testosterone and DHT were unchanged, but the possibility that it acts on hormone-dependent target organs cannot be ruled out. The significant decrease in the A-P diameter of the prostate in patients treated with Cernilton suggests that prostate size was reduced with treatment, even within the short time of the trial period. Adenomatous hyperplasia takes several years to develop and a dramatic regression could be expected only with total androgen deprivation. In a placebo controlled study, Cernilton was reported to lower the levels of serum cholesterol and low density lipoprotein (LDL) *(0ckerman,* personal communication) but we were unable to show any difference in these lipid fractions between the 2 groups in this study, carried out under strict fasting conditions.

Kimura et al. (1986) observed that T-60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle in a concentration-dependent manner. These studies were confirmed by Nakase et al. (1988), using rat vesicourethral and external urethral muscle strips; they showed that T-60 and GBX inhibited the contraction of muscle induced by noradrenaline bitartrate, with evidence for competitive antagonism of noradrenalin at the site of adrenergic receptors. Thus the subjective improvement in symptoms of nocturia and bladder emptying could be due to the effect of Cernilton on the rich adrenergic innervation of the bladder neck and prostate.

The precise mode of action of Cernilton in BPH is not known and further studies to determine its pharmacological action are in progress. However, this double-blind placebo-controlled study has shown distinct subjective and objective improvement with a positive response in the Cernilton group. As with other studies to evaluate the effect of drugs in BPH, there was a 30% subjective improvement in patients in the placebo arm of the study, which highlights the need for placebo control. In addition, we studied all of the patients together within a 7-month period in order to synchronize the times of serial evaluation and thus to eliminate the marked effect that seasonal variation can have on the symptomatology of this condition. A longer duration of treatment or a larger dosage may produce a more pronounced benefit and Cernilton, which appears to have no untoward side effects, may prove to be a useful agent in alleviating the early symptoms of outflow tract obstruction due to BPH.

Acknowledgements

We thank *Mr. Golding* of Kretztechnik (UK) for his generous help in supplying the ultrasound equipment. Our thanks are also due to Dr. J. *Schnitker* and Dr. *H.-F. Koch,*

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Appendix

Daytime Frequency
0- 1 to 4 times daily
1- 5 to 7 times daily
2- 8 to 12 times daily
3-13 or > times daily

Nocturia
0 - absence of symptoms
1 - subject awakened once each night because of the need to urinate
2 - subject awakened 2 to 3 times each night
3 - subject awakened 4 or > times each night

Hesitancy
0 -occasional hesitancy (occurs in 20 % or fewer of subject's attempts to void)
1 - moderate hesitancy (occurs during 20 to 50 % of subject's attempts to void)
2 - frequent hesitancy (occurs more than 50 % of subject's attempts to void)
3 - symptoms always present, lasts for 1 minute or longer

Urgency
0 - absence of symptoms
1 - occasionally difficult for subject to postpone urination
2 - frequently difficult (--nore than 50 % of the time) to postpone urination and may rarely loose urine
3 - always difficult to postpone urination and subject sometimes loses urine.

Intermittency
0 - occasional intermittency (occurs in 20 % or fewer of subject's attempts to void)
1 - moderate intem-dttency (occurs during 20 to 50 % of subject's attempts to void)
2 - frequent intermittency (occurs more than 50 % of the time, but not always, and may last up to 1 n-dnute)
3 - symptoms always present, lasts for 1 minute or longer

Incomplete Emptying
0 - absence of symptoms
1 - occasional sensation of incomplete emptying of bladder after voiding
2 - frequent (more than 50 % of the time) sensation of incomplete voiding
3 - constant and urgent sensation and no relief upon voiding

Terminal Dribbling
0 - occasional terminal dribble (occurs in 20 % or less of the subject's attempts at voiding)
1 - moderate terminal dribble (occurs in 20 to 50 % of subject's voiding)
2 - frequent terminal dribble (occurs in more than 50 % of the time but not always)
3 - symptom always present, dribbling lasts for 1 minute or more, or wets clothes

Dysuria
0 - absence of symptoms
1 - occasional burning sensation during urination
2 - frequent (more than 50 % of the time) burning sensation during urination
3 - frequent and painful burning sensation during urination

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Use of Cernilton in Patients with Prostatic Hypertrophy

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Introduction

Today the only radical therapy for prostatic hypertrophy is prostatectomy or transurethral prostatectomy. Prostatic hypertrophy is a kind of geriatric disease in urology whose incidence in Japan is now increased as high as that in European countries. Frequently, this disease involves such aged patients as are not indicated for surgical manipulation in general surgery. Under this situation, conservative therapy would be considered as treatment of choice if it can indeed effect curing or improvement of the disease. Thus, various drugs, chiefly female hormones, have been developed and placed for clinical evaluation in recent years.

The present report concerns the authors' recent experience with CERNILTON, a pollen product, whose samples were supplied by Tobishi Pharmaceutical Co., Ltd. Results are reported below.

Composition of CERNILTON

CERNILTON, when initially introduced in 1952, was used as a prophylactic agent against infections chiefly in convalescent patients having undergone treatment of infectious diseases or surgical operations, and it was by Ask-Upmark later in 1960 that the effectiveness in prostatitis was reported.

According to the literature, it contains in one tablet:

- Cernitin GBX – 3 mg
- Cernitin T60 – 60 mg
- Calcium glyconicum – 70 mg
- Saccharum lactis – 70 mg
- Calcium phosphoricum dibasicum – 140 mg
- Acidum alginicum – 10 mg
- Potato starch – 20 mg
- Pigment – 3 mg
- Magnesium stearate – 4 mg
- Talcum – 20 mg

Of these components, Cernitin GBX and Cernitin T60 are extracts of a mixture of 8 different pollen strains, namely, timothy, maize, rye, hazel, sallow, aspen, oxeye daisy and pine, and their chemical structure, molecular formula and molecular weight are unknown. The drug is also reported to have bacteriostatic, tonic and desensitizing actions.

Materials and Methods

The subjects were 24 patients with prostatic hypertrophy seen at our Outpatient Clinic. The

drug was given in doses of 4 tablets once daily in the morning over periods ranging from 25 to 150 days. In general, other drugs were not employed. Of the 24 cases, complete follow-up study was made in 12 cases as to subjective symptoms and urinary retention before, during and after administration. The present report deals with these 12 cases.

Results

The results of the 12 cases where follow-up study was made are given in Table 1.

- Evaluation of effects was made on the basis of the follow criteria:
- Effective.. Subsidence of symptoms with marked improvement in urinary retention.
- Slightly Effective.. Slight subsidence of symptoms with little or slight improvement in urinary retention.
- Ineffective.. Symptoms and urinary retention unchanged or exacerbated.

Results according to these criteria were: “effective” 5 cases (41.7%), “slightly effective” 5 cases (41.7%), and “ineffective” 2 cases (16.7%). Two of the 5 “effective” cases underwent prostatectomy subsequently because of symptoms relapsed after withdrawal of the drug. It is to be noted that one case was already on the way toward spontaneous healing at the time of administration. One of the “slightly effective” cases also underwent prostatectomy markedly extended.

Clinical course: Urinary retention disappeared and relatively smooth urination was possible in one month. Anuresis, however, developed again one month after withdrawal of the drug and patient was thus readmitted for prostatectomy.

Case 5. H. Y. Age 83. No Occupation.

- First examination: April 18, 1966
- Chief Complaints: Anuresis, dysuria
- Past History: Nothing of note.
- Present Illness: Anuresis developed suddenly in May 1959. Diagnosed as having prostatic hypertrophy, patient was admitted in June and underwent transurethral prostatectomy. Subjective symptoms subsided and a favorable clinical course ensued. Dysuria developed again in September 1964. The symptom gradually progressed reaching a state of anuresis in April 1966, when he visited our Outpatient subsequently.

Side effects due to the medication were observed in none of the cases. Five representative cases will be discussed in detail below.

Case 1. T. Y. Age 69. No Occupation.

- First Examination: September 2, 1966
- Chief Complaints: Dysuria, anuresis
- Past History: No history of venereal diseases, tuberculosis or trauma.
- Present Illness: Dysuria developed 3-4 years ago and catheterization was performed each time. The present episode was anuresis which developed after drinking of alcoholic drinks.
- Palpation of Prostate: Third degree hypertrophy, smooth surface, elastic hardness, symmetry, regular margin.
- Laboratory Findings: Residual urine 420 cc. Micropyuria present. Urethrocystography revealed the prostate protruding greatly into the bladder and the posterior urethra Clinic again. Thereafter, a balloon catheter was retained in the bladder for urination. The catheter was removed on July 27 and administration of CERNILTON instituted.
- Palpation of Prostate: First degree hypertrophy, smooth surface, elastic hardness, symmetry, regular margin.
- Laboratory Findings: Residual urine 350 cc. Micropyuria present.
- Clinical Course: Relatively smooth urination was possible one month after administration of CERNILTON, though voiding force was still somewhat weak.

After 2 months, urination was almost normalized, but urinary retention was still noted. In 3 months dysuria disappeared totally with residual urine decreased to about 10 cc.

Case 7. K. S. Age 72. No Occupation.

- First examination: June 27, 1966
- Chief Complaints: Dysuria, pollakisuria.
- Past History: Nothing of note.
- Present Illness: Pollakisuria, retardation and protraction of urination, and sense of retention appeared about one year ago, associated with dull pain in the lower abdomen but not with such bladder symptoms as voiding pain and cloudiness of urine. Dysuria was particularly exacerbated lately.
- Palpation of Prostate: First degree hypertrophy, smooth surface, elastic hardness, symmetry regular margin.
- Laboratory Findings: Residual urine 20 cc. Urinary findings nearly normal. Urethrocystography revealed the posterior urethra slightly extended.
- Clinical Course: Subjectively, dysuria disappeared completely in one month. Pollakisuria, too, disappeared and frequency of urination became normal. Residual urine was decreased to about 10 cc.

Case 8. T.K. Age 68. Company Employee.

- First examination: April 25, 1966.
- Chief complaints: Dysuria, anuresis
- Past History: nothing of note
- Present Illness: patient was seen at this clinic in November 1963 with complaints of dysuria and pollakisuria. Operation was recommended under a diagnosis of prostatic hypertrophy but was ignored. Then, anuresis occurred in early April 1966 and catheterization was performed by some doctor. Anuresis developed further, eventually to a state where urination occurred only in drops.
- Palpation of Prostate: Second degree hypertrophy, smooth surface, elastic hardness, symmetry.
- Laboratory Findings: Residual urine 600 cc. Urinary findings nearly normal. Urethrocystrography revealed the prostate slightly protruding into the bladder and the posterior urethra slightly extended.
- Clinical Course: Dysuria was improved considerably after one month, together with pollakisuria. On palpation hypertrophy was somewhat improved. Two months later, dysuria disappeared subjectively and residual urine was decreased to about 20 cc.

Case 9. T.S. Age 63. No Occupation.

- First Examination: May 23, 1966.
- Chief Complaints: Dysuria, anuresis.
- Past History: Nothing of note.
- Present Illness: Dysuria developed in October 1964 and catheterization was performed. A diagnosis of prostatic hypertrophy was made and admission was recommended, but as the symptom somewhat subsided the recommendation was ignored. In early May 1966, anuresis occurred after drinking of alcoholic drinks and catheterization was again performed. Retardation and protraction of urination had since been exacerbated and sense of retention come to be associated.
- Palpation of Prostate: Third degree hypertrophy, smooth surface, elastic hardness, symmetry.
- Laboratory Findings: Residual urine 30 cc. Urinary findings normal. Urethrocystography revealed marked extension of the posterior urethra.
- Clinical Course: One month later, the urine stream became somewhat larger, sense of retention slightly decreased to 5 cc. Two months later, the urine stream became even larger and the retarded urination disappeared. Urethrocystrography revealed no

significant changes. Three months later, the urine stream remained almost unchanged from one month before. Anuresis occurred once during this period but favorable urination ensued with residual urine of about 10 cc. No changes were noted in the prostate on palpation. The patient, however, developed anuresis one month after withdrawal of the drug and eventually underwent prostatectomy two months later.

Discussion

From an absolute pathological point of view, formation of nodules in the urethral area of the prostate is an aging process seen in all males over the age of 70, and it is only part of them that actually develop clinical symptoms such as pollakisuria, dysuria and anuresis and receive treatment for prostatic hypertrophy. On the other hand, as urologists would often experience, these symptoms sometimes disappear or subside without any specific treatment, and there are even cases where patients with sudden development of anuresis are improved to their premorbid state by mere catheterization or chemotherapy. Experience shows, moreover, that clinical symptoms are not always correlated to prostatic adenoma.

Under the circumstances, it is extremely difficult to decide what criteria to be used for evaluation of effects. Review of clinical reports on other similar drugs shows that more or less the same problem is encountered by other authors. Their conclusions are essentially the same, i.e., drugs are usable for treatment of prostatic hypertrophy if they can improve subjective symptoms without side-effects and can be employed for long-term administration.

In the present study, too, we have been unable to set up definite criteria and thus based our evaluation on the changes of subjective symptoms and residual urine and the findings of the prostate on palpation. Results were, as already seen, “effective” 5 cases, “slightly effective” 5 cases, and “ineffective” 2 cases. While 10 out of 12 cases showed improvement in subjective symptoms, the objective improvement in residual urine was obtained in only 6 cases and there was no case which showed a marked diminution in the size of the prostate on palpation. Of the 10 cases which showed improvement in subjective symptoms, 3 cases were in the first degree of hypertrophy, 4 cases in the second degree, and 3 cases in the third degree, when judged by the findings of the prostate on palpation. All the patients in the third degree of hypertrophy subsequently underwent prostatectomy. From this point of view, it may be said that the drug improves only dysuria due to so-called “variable elements” such as hyperemia and congestion around the neck of the bladder and the posterior urethra and does not reduce the size of the prostatic adenoma itself. This means the drug is still far from being able to substitute for radical therapy. In other words, it is to be used only in cases where surgical management is contradicted or to improve clinical symptoms when the disease is still in its early phase. It should not be employed indiscriminately for long-term administration, for it may aggravate the renal function and thus increase the rink in surgical operations.

Conclusions

A. A pollen product, CERNILTON, was used in 12 cases of prostatic hypertrophy. Results were “effective” 5 cases, “slightly effective” 5 cases, and “ineffective” 2 cases. In the 2 of 5 “effective” cases the symptoms relapsed within one month after withdrawal of the drug and the patients eventually underwent prostatectomy. Both had the third degree of hypertrophy. Prostatectomy was also subsequently performed in one “slightly effective” case which also had the third degree of hypertrophy.
B. Side-effects were observed in none of the cases treated.

Table 1. Results of Treatment

Case	Age	Before Administration			Dosage Cernilt	After Administration					Remarks
		Symptoms	Findings of Prostate on Palpation	Residual urine		Symptoms	Findings of prostate on Palpation	Residual urine	Side-effect	Effect	
1	69	Dysuria, Anuresis	Third degree hypertrophy	cc 420	T. Day 4×25	Improved	Third degree hypertrophy	cc 0	—	Effective	Anuresis appeared one month after cessation of therapy and prostatectomy was carried out.
2	74	Dysuria	Second degree hypertrophy	45	4×25	Slightly improved	Second degree hypertrophy	25	—	Slightly effective	
3	67	Dysuria, Pollakisuria	First degree hypertrophy	130	4×25	Unchanged	First degree hypertrophy	40	—	Ineffective	
4	60	Dysuria, Sense of retention	First degree hypertrophy	100	4×150	Slightly improved	First degree hypertrophy	20	—	Slightly effective	
5	83	Anuresis, Dysuria	First degree hypertrophy	350	4×75	Improved	First degree hypertrophy	10	—	Effective	
6	79	Dysuria,	First degree hypertrophy	600	4×25	Unchanged	First degree hypertrophy	500	—	Ineffective	
7	72	Dysuria, Pollakisuria	First degree hypertrophy	20	4×25	Improved	First degree hypertrophy	10	—	Effective	
8	68	Dysuria, Anuresis	Second degree hypertrophy	600	4×50	Improved	First to second degree hypertrophy	20	—	Effective	
9	63	Dysuria, Anuresis	Third degree hypertrophy	30	4×75	Improved	Third degree hypertrophy	10	—	Effective	Anuresis appeared one month after cessation of therapy and prostatectomy was carried out two months later.
10	67	Dysuria, Pollakisuria, Sense of retention	Second degree hypertrophy	80	4×25	Slightly improved	Second degree hypertrophy	20	—	Slightly effective	
11	78	Dysuria Sense of retention	Second degree hypertrophy	400	4×100	Slightly improved	Second degree hypertrophy	200	—	Slightly effective	
12	78	Dysuria, Pollakisuria	Third degree hypertrophy	200	4×25	Slightly improved	Third degree hypertrophy	150	—	Slightly effective	Prostatectomy subsequently performed.

Table 2. Therapeutic effect and degree of hypertrophy on palpation

**N.B.: Indicates a case in which prostatectomy was performed later.*

Effect / Degree of hypertrophy	Good	Fair	None
First degree	2	1	2
Second degree	1	3	0
Third degree	2*	1*	0
Total	5	5	2

Usefulness of Cernilton in the treatment of benign prostatic hyperplasia

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A total of 89 patients with benign prostatic hyperplasia (BPH) were treated pharmacologically for 4 months: 51 received Cernilton and 38 Tadenan (controls). Significant subjective improvement was found in 78% of the patients in the Cernilton group compared to only 55% of the Tadenan treated patients. The obstructive and irritative symptoms responded best to the therapy. In the Cernilton-treated patients a significant improvement in the uroflow rate, decrease in residual urine and in prostate volume were found. This study shows that Cernilton is an effective therapy for patients with BPH.

Benign prostatic hyperplasia (BPH) is a major problem for the patient, the urologist, and health care systems. Pharmacologic treatment may be indicated for patients with moderate BPH-related symptoms. Although plant extracts may not effectively alter the natural history of clinical BPH, their use is favored in patients with mild symptoms in a number of countries. Plant extracts are inexpensive and have virtually no side effects [4, 6].

Among plant extracts Cernilton, the Graminaceae flower pollen extract, is an interesting product. Results of clinical studies with Cernilton demonstrate a marked reduction in residual urine, prostate volume, and substantial improvement in urinary flow rate in patients with BPH [2]. Enlargement and congestion of the prostatic gland are the principal factors responsible for the obstructive symptoms in BPH. The anticogestive effect of Cernilton leads to a marked reduction in prostate volume [10]. The anticongestive action of Cernilton is based on the inhibition of prostaglandin and leukotriene biosynthesis. The activities of both the 5-lypoxygenase and cyclo-oxygenase enzymes are substantially reduced and the arachidonic cascade is interrupted. The inhibition of the arachidonic acid cascade by Cernilton prevents intraprostatic tissue oedema and fibrosis and leads to a significant reduction in clinical symptoms [2, 9].

The aim of the study was to assess the effectiveness of Cernilton therapy of BPH.

Patients and methods

Studied were 89 patients with clinical stage I and II BPH, aged 50-68 years. For the first two weeks Cernilton was administered in doses of two tablets three times daily, followed by one tablet three times a day for up to a total of 4 months of treatment. The remaining 38 patients were given Tadenan, 2 tablets twice daily (control group). Subjective assessment was made by using our own symptom score system [4] and objective evaluation by physical examination, uroflowmetry and ultrasound examination of residual urine and prostate size. Additionally, biochemical blood and urine tests, including urine culture, were performed in all patients prior to and after therapy.

Qualified were patients with short history, i.e. with symptoms of no longer than a few weeks duration. No patient had complete urine retention. The results of blood tests did not differ significantly from the normal laboratory reference values. All urine cultures proved sterile but in 12 patients leukocyturia was found adequate antimicrobial therapy was instituted (Tarivid 2 tablets twice daily). The tests were done also after completion of the treatment and no significantly abnormal results were observed.

Results

The following tables show objective and subjective parameters measured before (I) and after (II) Cernilton (C) and Tadenan (T) therapy of BPH patients; peak flow rate (ml/s) – table 1; residual urine volume (ml) –

Table 2; prostate volume (cm3) – Table 3; obstructive symptom score – Table 4; irritative symptom score – table 5

The therapeutic response was positive in 40 (78%) and 21 (55%) patients in Cernilton and Tadenan groups, respectively. Both drugs were well tolerated and no adverse reactions were seen.

Table 1
Peak flow rate (ml/s) in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	12.49 13.54	15.6 15.9	8.0 8.5	3.0 3.2	- -	- -
II C (51) T (38)	15.51 15.18	19.0 17.2	11.2 9.0	4.3 4.5	+3.20 +1.67	19.5 10.8

Table 2
Residual volume (ml) in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	77 61	112 101	56 31	15.7 14.1	- -	- -
II C (51) T (38)	45 50	63 70	0 20	21.0 15.8	-32 -11	47.8 21.6

Table 3
Prostate volume (cm3) in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	53.83 51.12	61.2 59.1	41.0 39.0	6.6 5.9	- -	- -
II C (51) T (38)	48.58 50.67	58.0 59.0	32.0 39.0	4.4 5.8	-9.6 -0.9	5.15 0.45

Table 4
Obstructive symptom score in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	5.1 4.8	9 8	2 1	2.1 1.9	- -	- -
II C (51) T (38)	1.9 2.6	4 8	0 0	1.2 1.8	- -	62.75 45.80

Table 5
Irritative symptom score in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	3.8 3.5	7 8	1 0	1.9 2.0	- -	- -
II C (51) T (38)	1.2 2.1	6 8	0 0	2.1 2.8	- -	68.4 40.0

Discussion

BPH is a universal concomitant of male ageing but its epidemiology and natural history are incompletely understood [1]. The natural history of BPH can be divided into two phase when the patients develop symptomatic dysuria. Although macroscopic enlargement of the prostatic is necessary for the development of clinical BPH, it is not sufficient by itself for the progression to infract, tensile strength of the glandular capsule [7]. The clinical manifestations of BPH are often attributed to infravesical obstruction. Therefore, pharmacologic outlet resulting from the prostate enlargement and eliminate instable bladder [4, 8].

Medical treatment of BPH is presently dominated by a-adrenoceptor blockers but plant extracts are used extensively in a number of countries. Treatment with other drugs has also proven to be effective symptomatically, notably with finasteride (5a-reductase inhibitor). Some plant extracts are claimed to exert a-adrenergic blocking or 5-a-reductase inhibiting effects. A few controlled studies have shown that some of the preparations provide both subjective and objective improvement [6].

In BPH patients the decongestive effect of Cernilton leads to a lasting improvement of voiding difficulties. The residual urine volume decreases significantly.

In comparison to Pygeum africanum extract (brand name Tadenan), for 20 years in wide use in stage I BPH patients, Cernilton proved much more effective. Objective evaluation of maximal urethral flow, residual volume and prostate size gave almost twice better results with Cernilton. Similarly, the obstructive symptom score improved by 62.75% with Cernilton and by 45.8% with Tadenan, and the irritative symptom score by 68.4% and 40%, respectively.

Positive therapeutic responses totaled 78% and 55% with Cernilton and Tadenan, respectively. Although Tadenan is also characterized by decongestive activity, it decreases bladder instability, increases detrusor elasticity and probably inhibits fibroblast proliferation, and alleviated voiding problems in over 2000 cases [5]. In our study the benefit of Cernilton therapy proved to be far greater than that of Tadenan. During the 4 months of treatment none of the drugs produced side effects in the BPH patients; both Cernilton and Tadenan were well tolerated.

Conclusions

1. Cernilton markedly reduces residual urine and prostate volume in BPH patients. It also significantly improves the voiding difficulties.
2. In the therapy of BPH Cernilton proved to be effective, well tolerated and safe.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Conservative Treatment of Benign Prostatic Hyperplasia (BPH) with Cernilton N – Results of a placebo-controlled double-blind study

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Summary

The efficacy and tolerability of the pollen-extract preparation, Cernilton N*1, were investigated in a double-blind, placebo-controlled study carried out over a treatment period of 12 weeks in 6 urological practices, in a total of 103 patients suffering from benign prostatic hyperplasia (BPH) in Stages II and III. The investigational parameters were the disturbances of micturition classied according to the FDA recommendation, residual urine volume, palpation findings and uroflow index, as well as the global assessment of the therapy by the doctor and by the patient. Under the pollen-extract nocturia, the principal sign of BPH, improved in 68.8% of the cases, compared with 37.2% under the placebo medication (P<0.005). Notable differences were observed in day time frequency and in sensation of residual urine, which were statistically significant as regards absence of these symptoms after the treatment, between the treatment (AT) and placebo (Pl) (P = 0.010 and P = 0.016, respectively). Observation of the course of the symptoms after 6 weeks and 12 weeks showed higher rates of improvement under the active treatment, for all the individual symptoms. In case of the urodynamic study parameters similar changes were observed in the findings for all uroflow parameters, whereby the differences between the comparative groups were unremarkable.

At the control examination after 6 weeks a continuous increase in the maximum urine flow was observed, averaging 3.3 ml/sec under placebo (P = 0.060). The difference in the average decrease in the residual urine volume in the course of the treatment was statistically significant (AT/Pl: 24.3 ml/3.7 ml ; P = 0.006). The pollen-extract led to a continuous reduction, whereas in the placebo-group the residual urine after 12 weeks had increased in comparison with the value recorded after 6 weeks. Significant differences in the residual urine volumes before and after the treatment, in favour of the pollen-extract, were observed also in the patients in BPH Stage III (P = 0.042).

Prostate size and congestion showed higher response rates, in the sense of reduction in size and decongestion, as detected by palpation, under the active treatment, with a marked trend (AT/PI : 88.5% / 69.0%; P = 0.155). Nausea was recorded under active treatment in one case. In accordance with their positive experiences with the treatment the investigating physicians and the patients assessed the therapeutic result under the pollen-extract as very good or good significantly more often than that obtained under placebo (P = 0.001). The results of the study prove the efficacy of the pollen-extract in patients with BPH in Stages II and III, in regard to the clinical symptomatology, urodynamics and the global assessment, and demonstate the good tolerability of the global assessment, and demonstrate the good tolerability of the drug, which permits long-term therapy with little risk of side effects.

In view of the changing age structure and the rising average life expectancy of the male population the phytotherapeutic treatment of benign prostatic hyperplasia (BPH) will become increasingly more relevant. The justification and the need for such a drug therapy can be estimated on the basis of the available epidemiological data: the probability for a 40-

year-old man to be operated for a BPH at the age of eighty is P = 0.292, and for him to develop the clinical symptoms of the disease it is P = 0.777 [4]. Consequently, for the treatment of BPH patients a symptomatically oriented medication has priority. However, continuous observation of the course of the treatment must ensure that surgical measures are taken whenever they are indicated.

On the basis of our own positive experiences with the standardized pollen-extract preparation (trade-name Cernilton N) in the treatment of BPH, a placebo-controlled, double-blind study of the efficacy and tolerability of this drug was initiated and carried out in collaboration with six practicing urologists.

An effect on the congestion of the prostate and on the chronic inflammatory changes occurring in the framework of BPH is to be suggested as the pharmacodynamic mechanism of action for the symptomatic therapeutic effectiveness of pollen-extract preparation, as clinically a normalization of the pathological parameters of inflammation has been demonstrated in the EPS-expressed prostatic secretion (leucocytosis, raised pH value) [2].

Patients and Methods

For this randomized, placebo-controlled, double-blind study in BPH patients in Stages II and III according to Vahlensieck [12] a total of 103 patients could be include by six practicing urologists. Due to carcinoma in 1 case and antibiotic therapy for a concomitant urinary tract infection in 6 cases, a total of 96 patients were eligible for the statistical analysis.

Further specific criteria for exclusion form the study were: suspected carcinoma of the prostate, residual urine volume more than 150 ml, neurogenic disturbances of micturition, acute and/or chronic prostatitis/ prostatovesiculitis, malformation or post-operative status in the urogenital area with obstruction of the efferent urinary tract, bladder stones. Previously treated DPH patients were subjected to a four-weeks wash-out phase. All the patients received identical trial packs containing active drug or placebo capsules also of identical outward appearance. The treatment lasted 12 weeks, with control examinations of weeks 0, 6 and 12. The examination time 2 weeks after the start of the treatment, which was originally planned, proved to be impracticable. The dosage was 3 capsules t.i.d.

The control parameters investigated were: disturbances of micturition, nocturia, sensation of residual urine, dysuria, urge to urinate, discomfort in the inguinal, peritoneal and genital areas, palpation findings (enlargement, congestion of the prostate) uroflow index, residual urine volume determined by ultrasound, and the global assessment of the therapy by the doctor and by the patient.

In the laboratory examinations, SGOT, SGPT, PAP and creatinine in the serum were determined, as well as leucocytes, erythrocytes and germcount (if possible with identification of pathogens) in the sodiment or in the urine culture. Besides descriptive-statistical methods the following analytical procedures were used: chi-square test (with Yates' correction for 2 x 2-field tables) for testing the homogeneity of qualitative parameters, comparison of the changes in the clinical symptoms at the end of the treatment versus the baseline findings, and for the comparison of the assessments of tolerability, the incidence of side effects and the global assessments by the doctor and by the patients, in both trial-groups; the t-test for independent random tests in the homogeneity testing for age, height, body weight and urodynamic and quantitative laboratory parameters; the U-test in the homogeneity testing for the length of previous treatment of the BPH; variance analysis for the split-plot design for the evaluation of the course of the quantitative parameters. On account of the findings, the different levels of attendance at the appointed examination times and the practicability of the study, parameterspecific sample sizes were achieved which, in the evaluations of courses, are documented in the form of a reduced number of patients.

In accordance with the FAA recommendations, the disturbances of micturition were classified according to their intensity [1]. The statistical comparison was based on the changes observed under the treatment, which were recorded as ‘symptom-free’, ‘improved’, ‘unchanged’, or ‘worsened’. In patients with symptoms at the start of the study, response to the treatment is defined as a ‘symptom-free’ or ‘iroved’ status of the therapy. Quantitative

parameters were evaluated for the course and the pre-treatment/post-treatment comparison. The parallelism of the mean levels of intensity was also tested. The uroflow findings were based on the secondary parameter, uroflow index (10).

Results

As regards medication and stage of the BPH, randomization gave a practically evenly distributed study population, with homogeneous baseline status in the two comparative groups. The age of the patients ranged from 42 to 85 years with a medium duration of the disease of 10 months; the BPH had been treated previously in 40.6 % of the cases (Table 1).

The initial clinical examination showed nocturia to be the leading symptom, occurring as a disturbance of micturition in 96.9 % of the patients (Figure 1). In the total study population examination by palpation showed enlargement of the prostate, with retained sulcus in 35.8 %, with obliterated sulcus in 55.8 % and with undefinable laterallobes in 8.4 % of the patients. On admission to the study, congestion of the prostate was palpable in 61.5 % of the cases, being classified as slight in 33.0 %, moderate in 17.5 % and severe in 11.0 %. The urodynamic status on admission to the study also showed homogeneous baseline data in the two comparative groups, whereby the uroflow parameters are presented also according to the uroflow index (Table 2).

Clinical symptomatology

As regards the clinical symptomatology, the pre-treatment/post-treatment comparison shows clear differences between the treatment groups: Under the pollen-extract the nocturia improved significantly, in 68.8% of the patients compared with 37.2% under the placebo medication. Freedom from the symptoms daytime frequency and sensation of residual urine is found significantly more frequently under the active treatment (table 3). For all the individual symptoms the examinations of the courses after 6 weeks and after 12 weeks of the study show higher rates of improvement or positive response course under the active treatment, with no change or deterioration under placebo. In the case of nocturia, day time frequency and sensation of residual urine these differences are particularly pronounced (Figure 2).

Enlargement and congestion of the prostate show higher response rates, in the sense of decrease in size and decongestion, under the active treatment (AT), whereby a striking trend is to be observed in comparison with placebo (PI) (Table 3). In contrast to the course in regard to the enlargement of the prostate, where the response rate remained constant in both groups, in the case of the congestion the improvement rate after 12 weeks, at 86.7%, was 20% higher than that recorded after 6 weeks' treatment, under the active preparation. In comparison, the response under placebo at these two examination times was 70.8% and 70.9%, respectively.

Urodynamics

Significant differences in favour of the pollen-extract are also to be seen in regard to the urodynamic test parameters. For all the uroflow parameters the changes in the findings were similar in both treatment groups, whereby the differences before and after the treatment are not statistically significant. Taking into account the examination after 6 weeks, a continuous increase of the initially pathological uroflow index is to be observed, by an average of 0, 18, under the pollen-extract. In the placebo group (x = +0.10 after 12 weeks) the uroflow decreased in the second half of the study (Table 4, Figure 3).

The peak urine flow rate increase by an average of 3.3 ml/sec in the pollen extract group and by 0.9 ml / sec in the placebo group.

The difference in the reduction of the residual urine volume in the course of the study was statistically significant (AT 24.3 ml / PL 3.7 ml; P = 0.006). The pollen-extract leads to a continuous reduction, whereas in the placebo group there is a decrease after 6 weeks, compared with an increase in the residual urine volume after 12 weeks (Figure 3). When BPH stage III is considered separately there is an average decrease of 36.9 ml under the active treatment, compared with 7.2 ml under placebo, whereby an increase in the residual urine volume is to be observed in the second of the two 6-week study periods in the placebo group (Figure 4).

Global Assessment

The laboratory parameters show no noteworthy changes. Unwanted drug effects in the form of slight nausea are recorded in one case under the active treatment. The good tolerability of the treatment is documented in 95.8% of the patients. With regard to the therapeutic efficacy, both investigator and patient assessed the result of the treatment as 'very good' or 'good' significantly more frequently under the pollen-extract (Figure 5). A statistically significant difference of the assessments by the investigator and by the patient was observed in the patients with an initially pathological uroflow index (Table 5).

Discussion

The results of this study demonstrate the good efficacy of the pollen-extract preparation in benign prostatic hyperplasia (BPH) in stages II and III. The superiority of the active therapy is documented in the symptomatology, the results of the urodynamic investigations and by the global evaluation of the therapy by both doctor and patient.

The course of the characteristic disturbances of micronutrition is an important parameter for the assessment of therapeutic efficacy. Under the pollen-extract the nocturia improved in the course of the 12-week study period in 68.8 % of the patients. In the placebo group, on the other hand, regression was observed in only 37.2 %. In the pre-treatment/post-treatment comparison this leading symptom of BPH showed a significant difference, which increased progressively in the course of the study, in favour of the active trial therapy. While under placebo the response rate remained practically constant, under the pollen-extract medication, regression of the symptoms was observed in a further 21.3% of the patients after the second 6-week period of the study. For the symptoms of daytime frequency and sensation of residual urine there are also clear differences in favour of the active treatment, whereby the differences as regards symptom-free status are statistically significant. For dysuria, urge to urinate and discomfort no statistically significant differences are recorded on account of the high placebo-response rates. The irritative symptoms, which are predominant in BPH, showed a particularly positive response to the active treatment. The obstructive components of the general disturbance of micturition were investigated on the basis of the urodynamic parameters, so that here an evaluation based on the symptoms themselves was not necessary.

As was to be expected, the size of the prostate, as determined by palpation, showed a low response rate, which remained constant in the course of the study.

Particularly striking is the change in the findings in regard to congestion of the prostate, which showed improvement in 69.0 % of the patients under placebo. Because of this high placebo-response rate, the response rate of 88.5 % under the active treatment is not statistically significant.

The differences in the response rates observed in the course of the study, between the active treatment and placebo, in the clinical symptomatology and in the congestion of the prostate demonstrate the sustained therapeutic effect of the pollen extract on the intensity of the disturbance of micturition.

Because of the relation of the peak urine flow on the volume voided (3,10), the uroflow index was chosen for the evaluation of these parameters. An increase in this index is to be observed in both comparative groups, whereby the difference is not statistically significant. In the assessment over the course of the study a continuous increase is seen in the active-treatment group, while under placebo the index decreases in the second half of the study.

The proportion of 35%, compared with 20% in the placebo group of initially pathological uroflow index values getting borderline or normal after treatment, is to be evaluated as a trend in favour of the active treatment. Clear differences are recorded in regard to the decrease in residual urine volume.

Under both trial preparations a reduction is to be observed in the first 6 weeks, which in the active treatment group becomes even more pronounced in the second half of the study, whereas under placebo there is a deterioration of the value recorded after the first 6 weeks.

As the separate evaluations according to the stage of the BPH demonstrate, the pollen extract leads to a more pronounced mean reduction in those cases with an initially high residual urine volume. The reduction in the residual urine volume in the patients with stage III BPH was 54.7 % under the active treatment and 12.5 % under placebo.

As a reflection of the therapeutic efficacy of the pollen-extract there are clear differences between the active treatment and placebo in the global assessments of the therapy by the doctors and by the patients. Particularly also in regard to the patient group with an initially pathological uroflow index, where the assessment of efficacy by the urologists as bad 2 was documented in 41.9 % of the patients under placebo.

The fact that in 55.2 % of these patients the result of the treatment under the pollen extract was evaluated as “very good" or “good" is possibly an indication that the uroflow index is a relatively inaccurate parameter for detecting the more subtle urodynamic changes.

In order to obtain a representative patient population for the investigation of the efficacy of a drug therapy, this study was carried out in collaboration with six practicing urologists. The consistency of the data confirms our view that in the case of conservative therapeutic measures which are used mainly on an ambulant basis, the involvement of the preclinical aspects in the clinical research is both desirable and possible. However, the possible disadvantage that the number of patients attending the different control examinations can very has to be taken into account.

The mechanism of action of the pollen-extract can be suggestied as being its effect on the congestive and inflammatory changes occurring in BPH. Too little attention has been paid to the possible clinical relevance particularly of the chronic inflammatory changes (9, 11), the incidence of which, in BPH, is given as up to 98.1 % (5-8). In the long term, changes can develop in the connective tissue, which then become pathological in the form of fibrosis and sclerosis. The congestion of the prostate caused by stasis of secretions or the formation of interstitial oedema also has to be considered as a pathophysiological substrate of the disturbances of micturition occurring in BPH. It is to be assumed that these concomitant changes lead to alterations in the nerve supply in the prostate and this influence the clinical symptomatology and urodynamice.

The documented normalization of the parameters of inflammation in the EPS with the pollen-extract in patients with chronic prostatitis (2), can explain the therapeutic efficacy of this preparation, in the sense of its antiedematous and antiinflammatory action, also in patients with BPH. In view of the antisclerotic properties of the pollen-extract, with continuous application a long-term pharmacological effect on the clinical symptomatology and urodynamics is conceivable, so that surgical intervention, at least in certain cases, is not necessary (9).

Conclusion

The results of this study demonstrate the efficacy of the pollen-extract preparation in BPH patients in stages II and III, in regard to the clinical symptomatology, urodynamics, and global assessment. The pollen-extract preparation is well tolerated and makes long-term treatment possible with a low risk of side effects.The use of Cernilton N is recommended for the treatment of BPH stages II and III.

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SYMPTOM	CLINICAL STATUS ON ADMISSION	% OF PATIENTS
Nocturia	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	96,9%
Daytime frequency	XXXXXXXXXXXXXXXXXXXXXXXXXXXX	89,1%
Urge to urinate	XXXXXXXXXXXXXXXXXXXXXXXX	87,9%
Sensation of residual urine	XXXXXXXXXXXXXXXXX	66,3%
Discomfort	XXXXXXXXXXXXXXX	62,4%
Dysuria	XXXXXXXXXXXX	47,3%

Figure 1: Clinical status on admission into the study: incidence of the different symptoms in the total study population (n = 96)

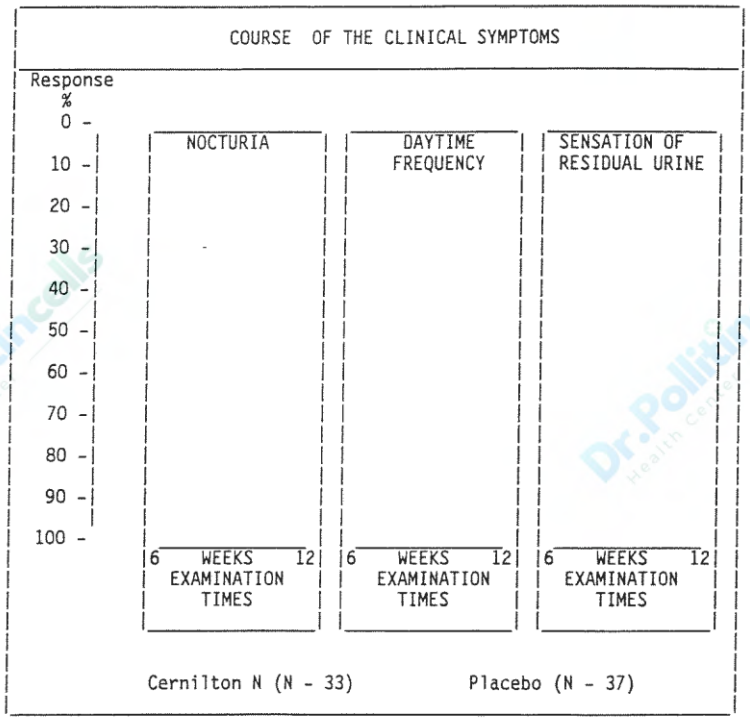

Figure 2: Response rate for the symptoms nocturia, daytime frequency and sensation of residual urine at the examinations after 6 weeks and 12 weeks, under the pollen-extract and placebo.

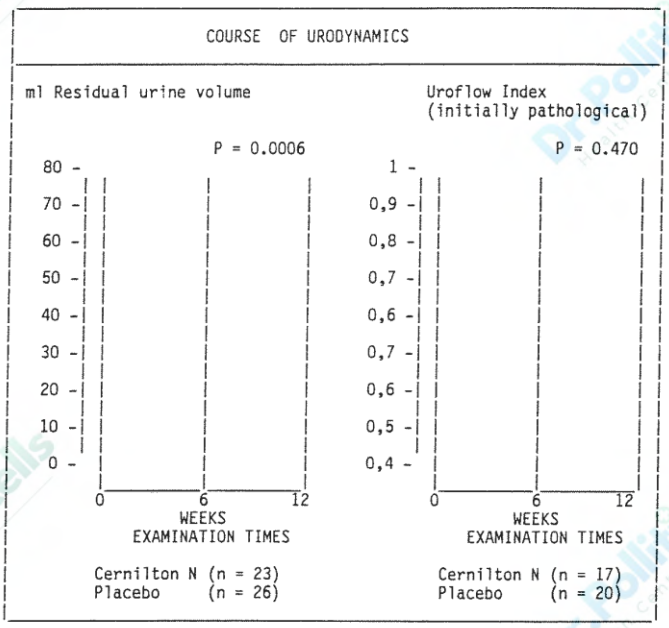

Figure 3: Course of the residual urine volume (ml) and the uroflow index (initially pathological) in the comparative groups. Continuous reduction resp. increase of the two parameters, under the pollen-extract.
Unfavourable response of both parameters after 6 weeks under placebo.

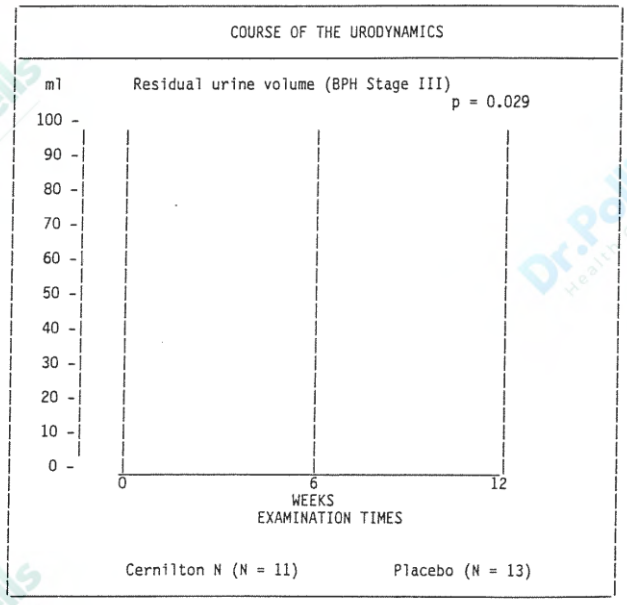

Figure 4: Course of the residual urine volume (ml) in BHP stage III. Significantly different and continuous reduction of the residual urine volume under the pollen-extract.
Increase of the residual urine volume in the second half of the study period under placebo.

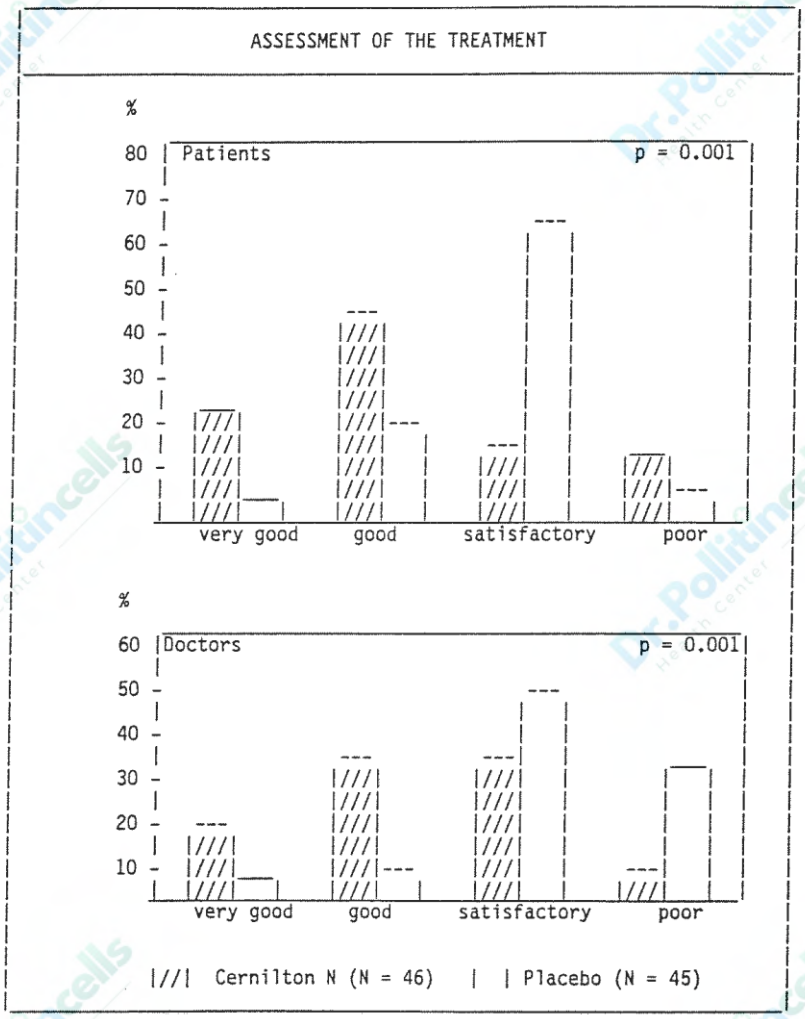

Figure 5: Significantly better assessment of the treatment by both doctors and patients in the pollen-extract group.

Table 1: Age distribution, BPH stage, duration of symptoms and previous treatment in the comparative groups. The BPH Stages are according to the classification of W. Vahlensieck.

Age Distribution and baseline status

Parameter	Value/Code	Cernilton N	Placebo
Age (years)	Minimum	42	45
	Maximum	83	85
	Median	65	67
	Mean value	66.0	67.1
	Standard deviation	9.7	10.1
BPH Stage	II	23	22
	III	25	26
Duration of Symptoms (months)	Minimum	1	1
	Maximum	48	48
	Median	11.4	8.3
	Missing data	4	3
Previous Treatment	No	29	28
	Yes	19	20

Table 2: Baseline urodynamid status: residual urine volume (ml) and uroflow index in the comparative groups. Homogeneous baseline status in both parameters (n = 96 and 86, respectively.

Urodynamic status at baseline

Parameter	Value/Code	Cernilton	N	Placebo	Total	Homogeneity P-value
Residual urine volume (ml)	Minimum	0		0	0	
	Maximum	100		120	120	
	Mean value	45.6		47.8	46.7	0.735
	Standard deviation	30.6		31.5	31.5	
Uroflow Index	Minimum	0.21		0.27	0.21	
	Maximum	1.43		1.76	1.76	
	Mean value	0.73		0.71	0.72	0.843
	Standard deviation	0.26		0.33	0.29	

Table 3: Statistically significant differences in favour of the active treatment, in the symptoms nocturia , daytime frequency and sensation of residual volume. The congestion of the prostate improved significantly more frequently under the pollen-extract.

Pre-/Post-treatment comparison of clinical symptomatology

Symptom	Cernilton N	Placebo	Significance P-value
	Response		
Nocturia	68.8 %	37.2 %	0.005
Daytime frequency	65.8 %	43.9 %	0.076
Sensation of residual urine	71.4 %	48.1 %	0.109
	Freedom from symptoms		
Nocturia	25.0 %	16.3 %	0.445
Daytime frequency	48.8 %	19.5 %	0.010
Sensation of residual urine	37.1 %	7.7 %	0.016

Palpation	Cernilton N	Placebo	Significance P-value
Enlargement of the prostate	17.4 %	10.6 %	0.522
Congestion of the prostate	88.5 %	69.0 %	0.155

Table 4: Residual urine volume (ml) and uroflow index before and after treatment in the two comparative groups. Statistically significantly greater reduction of the residual urine volume under the pollen extract.

Pre-/Post-treatment comparison of the urodynamic findings

Parameter	Time of the control	Cernilton N		Placebo		Variance analysis P-value
		$\bar{x}$	s	$\bar{x}$	s	
Residual urine volume (ml)	n	48		48		
	Before treatment	45.6	30.4	47.8	32.8	
	After treatment	22.5	20.9	37.0	28.9	0.032
Uroflow Index	n	40		40		
	Before treatment	0.74	0.27	0.72	0.34	
	After treatment	0.86	0.25	0.82	0.31	0.747

Table 5: Significant better assessment of the treatment by Invtigator in favour of pollen-extract in patients with initially pathological uroflow-index ($p < 0,001$)

ASSESSMENT OF TREATMENT (INVESTIGATOR) ON PATIENTS WITH INITIALLY PATHOLOGICAL UROFLOW-INDEX

	Cernilton N (n = 29)	Placebo (n = 31)
Very good	17,3 %	6,5 %
Good	37,9 %	6,5 %
Satisfactory	41,4 %	45,1 %
Poor	3,4 %	41,9 %

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A Critical Review of Cernitin™ for Symptomatic Relief of Lower Urinary Tract Symptoms (LUTS) in Men

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Objective

We reviewed published data concerning the ability of a defined flower pollen ex-tract derived from rye, corn, and timothy, commonly referred to as Cernitin to provide symptomatic relief in men suffering from lower urinary tract symptoms (LUTS). This same defined pollen extract has also been called Cernilton in other reports and is commercially available as Graminex Flower Pollen Extract. To maintain clarity, however, we will only use the term Cernitin to describe the defined pollen extract. In writing this review, our major goal is to present evidence concerning the therapeutic role of Cernitin in the management of mild to moderate LUTS. Nevertheless, we briefly describe prostatic perturbations in general and other natural therapeutic approaches to alleviate symptoms caused by them.

Introduction

It is estimated that 9-10 million men have lower urinary tract symptoms (LUTS) secondary to an enlarged prostate; and 400,000 surgeries are conducted each year in the U.S to alleviate such symptoms [1,2]. Although cancer might be a root cause, LUTS are more commonly found in men with non-cancerous conditions such as benign prostate hyperplasia (BPH), prostadynia, acute and chronic prostatitis caused by a bacterial infection, as well as chronic non-bacterial prostatitis. BPH, the most common cause of LUTS, does not distinguish between race and ethnic background, although African-American men are at a slightly greater risk [3]. It does not relate to sexual activity, since it can occur in celibate priests as well as the most sexually active of men [4]. Regardless of the etiology of the specific prostate-related disorders, health worries associated with prostatic enlargement are significant. Over $1 billion dollars are spent each year on treatment for prostatic enlargement, because LUTS can lead to more serious health problems if not treated properly [5].

The term LUTS describes men experiencing one or more symptoms listed on the International Prostate Symptom Score (IPSS) questionnaire. Among the mentioned urinary symptoms are daytime and night time (nocturia) frequency, urgency, hesitancy, intermittency, sensation of incomplete voiding, and decreased force of urinary stream [2]. An individual often becomes aware of the problem when urination occurs more frequently than usual. He may eventually become the person who rarely can sit through a movie or concert -- the one that requests the aisle seat on an airplane so as not to disturb his fellow passengers on his frequent sojourns to the restroom. At night, the trips to the bathroom caused by nocturia steadily increase, and there is a definite impingement on sleep. Suffice it to say, any experiencing of such frequency should lead to suspicion of the disorder.

What do we know about this troublesome gland? The prostate gland is associated with the male reproductive system. Its major function is to produce and discharge a viscous, alkaline liquid that provides a major portion of the seminal fluid. The prostate makes and stores fluid almost continuously. Because of the environment afforded by the presence of prostatic fluid, sperms are protected, at least to some extent, and can survive longer after ejaculation. In addition, the prostatic fluid contains prostaglandins, which are fatty acids that, similar to hormones, affect smooth muscle fibers and blood vessel walls. Although the prostate plays no direct role in the functioning of the male urinary system, its location near the bladder and urethra cause many urinary perturbations when it expands via growth or response to chronic inflammation [6-8].

At birth, the gland is the size of a pea and grows slowly until puberty. Under the influence of sex hormones, the prostate grows at a faster pace. During the 20's and 30's, the gland is characteristically the size of a walnut and weighs roughly one ounce. The gland, made up of muscular and glandular tissue, is located in front of the rectum and below the urinary bladder. Importantly, the gland surrounds the urethra, a tube that carries urine from the bladder to the tip of the penis for expulsion. Obviously, this setting has the potential to cause problems and unfortunately does. Around the age of 45, cells in the majority of prostates began to multiply again and the gland can reach up to 10 times the normal adult size [3].

The prostate can be divided into various lobes, with the major problems of BPH lying in the small transitional zone. The transitional zone that lies within the so-called middle lobe is the sole site of BPH [9]. Interestingly, the small transition zone comprises only two per cent of the entire prostatic mass before enlargement. Obviously, enlargement of this area does not in itself increase the size of the prostate greatly. Because of this, the degree of urethral obstruction may not directly relate to the overall size of the prostate gland but instead to the direction of growth enlargement. Some men with greatly enlarged prostates may have no signs of obstruction, while those with relatively small prostates may have severe obstruction.

While the exact mechanism behind age-related enlargement of the prostate is uncertain, a highly active form of the male hormone, testosterone, called dihydrotestosterone (DHT), is considered a major factor behind prostatic enlargement [4]. Excessive levels of DHT have been found in men with enlarged glands, and high concentrations of DHT are also associated with an increased risk of prostate cancer. To make matters worse, the concentration of DHT within the prostate increases with age. A major factor in the rise is that the enzyme responsible for the conversion of testosterone to DHT, 5-alpha reductase, becomes more active over the lifespan. Therefore, it is not too surprising that 5-alpha reductase is an important focal point in the medical treatment of prostate enlargement. Nevertheless, it is equally important to be aware that other prostatic enzymes, such a 3 oxidoreductase, deficiency of minerals such as zinc, and inflammation may also play a role in the enlargement process.

Background of Treatment

Bruskewitz points out that since serious complications from BPH and related non-cancerous conditions are rare, the primary aim of pharmacological treatment is to improve quality of life by relieving the vexing symptoms [10]. Studies conducted in the U.S. showed that urologists provided no specific treatment 77% of the time to men with mild symptoms. With moderate symptoms, however, prescription drugs were given 89% of the time; and surgery was conducted 1% of the time. The primary therapeutic treatment was use of alpha (1)-adrenoceptor antagonists such as terazosin hydrochloride (Hytrin®) that provide symptomatic relief but have not been shown to influence the incidence of surgery, acute urinary obstruction, or other complications of BPH [11]. In the past, treatment options for significant prostate enlargement focused on surgery. In a given year, approximately 400,000 men are driven to undergo a procedure called a transurethral resection of the prostate (TURP). Even now, transurethral resection is the standard treatment for BPH, i.e., the gold standard by which all other procedures are measured [12]. Unfortunately, while many symptoms of obstruction are ameliorated, post urination dripping may continue and may even result in severe incontinence. Even worse, the operation may be followed by a decline in sexual function. This may also occur with the use of the common pharmaceuticals as well [2]. Accordingly, a need exists for safe, effective products that can be used to treat mild

to moderate LUTS in lieu of or in addition to prescription drugs and major surgery. Natural products have been considered among the alternative therapies.

Natural Products to Treat LUTS

Saw Palmetto (Serenoa Repens)

Research carried out in Europe over the past 20 years shows that natural, fat-soluble extracts from specific plants effectively inhibit the function of 5-alpha-reductase, and block, at least in part, the formation of DHT [13-16]. The best-known and most extensively researched plant is saw palmetto. Saw palmetto is an extract of the pulp and seeds of a dwarf, scrubby palm tree native to the West Indies and the Atlantic coast of the United States. Saw palmetto works, for the most part, by the same mechanism as the pharmaceutical Proscar®, i.e., preventing the conversion of testosterone to DHT [16]. Additional benefits from plant extracts have also been found and may add to the good results found with their use. Some plant extracts not only lower the rate of DHT formation, but also block the ability of DHT to bind to cells, preventing the action of hormone [17,18]. In addition, they may prevent severe inflammatory responses. Saw palmetto, known to be popular in Europe, has recently become recognized in America. In one study using saw palmetto in 110 men, it decreased nighttime urination by 45 percent, increased urinary flow rate more than fifty percent, and reduced the amount of urine left in the bladder after urination by 42 per cent [19]. In other large trials, improvement in prostatic symptomatology was readily noted and saw palmetto even compared favorably with Hytrin and Proscar when they were compared head to head [20-24].

Pygeum Africanum

The powdered bark of the pygeum tree, a large tropical African evergreen, has been used for centuries to treat urinary disorders [25]. Pygeum contains phytosterols, which have been purported to have anti-inflammatory properties. In addition, much benefit has been attributed to their ability to decrease prostatic swelling, to reduce harmful prostaglandins that induce inflammation, and to diminish circulating prolactin that decreases the prostate uptake of testosterone. When 263 German men were tested with Pygeum africanum, urinary symptoms improved in 66% compared to 31% in the placebo group [26]. Occasional gastrointestinal upset seems to be the major adverse side effect.

S*tinging Nettle (Urtical dioica)*

Less research has been performed using the stinging nettle to ameliorate BPH. Laboratory studies have shown its ability to inhibit laboratory induced prostate growth in mice [27]. The results from one study suggest that the steroidal components of stinging nettle roots suppressed prostate cell growth [28].

Beta-sitosterol

Much attention has recently been focused on beta-sitosterol. In a randomized double blind study reported in the Lancet, 200 patients from eight private urological practices were treated for six months with either 20 mg of beta-sitosterol or placebo [29]. At the end of six months, modified Boyarsky scores decreased statistically in the beta-sitosterol treated group compared to placebo. The quality of life score improved, the peak urine flow increased, the mean voiding time and the urinary volume retention also improved from the initial scores in the verum group, whereas no changes were noted in the placebo group. Results were also positive in another randomized, double-blind and placebo-controlled study carried out in Germany [30].

Cernitin

Cernitin is a natural product recently introduced in the USA to be used to treat LUTS. However, it has actually been around a long time. In 1950, in a tiny Swedish village, a beekeeper found a way to collect pollen artificially [31]. Since it was good for bees, his hypothesis was that it would be good for humans. Initially, the flower pollen was used as a prophylactic agent against infections. Later the extraction process was modified so that the active pollen was released and was non allergenic. Found in the pollen are peptides, carbohydrates, fatty acids, vitamins, minerals, nucleic acids, and enzymes. Whatever the original hypothesis concerning overall health, the defined pollen extract called "Cernitin" proved specifically useful in treating BPH and other prostate conditions [2,32].

Cernitin is a standardized extract of rye pollen (*Secale cereale)*, corn pollen (*Zea mays),* and

timothy pollen (*Phleum pratense).* From these combined pollens, two important, therapeutic extracts are derived -- a water-soluble fraction and a lipid-soluble fraction with different physiological functions. *In vitro* and *in vivo* animal studies [33,34] have shown that both fractions have anti-inflammatory properties emanating from inhibition of prostaglandin and leukotriene synthesis. The water-soluble fraction has been shown to reduce the size of the ventral and dorsal prostate in the rat [35] and to inhibit testosterone-induced BPH in castrated animals [8]. The combined extracts were shown to inhibit growth of transplanted human BPH tissue in an athymic nude mouse model (36). Both fractions have been shown to relax the smooth muscle of the mouse and pig urethra, increase bladder muscle contractions [34], and reduce prostate size in mature Wistar rats [37].

Cernitin extracts are also sold as Graminex Flower Pollen Extract and are available in the marketplace in tablet and capsule forms, usually contain 63 mg of a 20:1 ratio of water-soluble to lipid-soluble fractions. Cernitin is contained in products regulated as drugs in Switzerland, Germany, Austria, Japan, South Korea and South Africa. In the U.S., the use of botanicals for LUTS is relatively less. No botanicals are approved as prescription or over-the-counter drugs for LUTS or BPH in the U.S. Accordingly, they are sold as dietary supplements and are labeled with non-specific information, e.g., "maintains prostate health." In a study conducted in Chicago in 1997-1998 with 738 men having LUTS and/or prostate disease, Bales et al [38] found that 13% of the group had used botanicals for their condition (59% in combination with prescription drugs), 37% were aware of botanicals as an option but had never used them, and 50% were unaware of this treatment option. Such information prompted our review of Cernitin.

Methods

Literature searches were conducted on Medline and the Cochrane Library. Sources such as review articles and monographs in botanical reference books and other books referring to Cernitin were included in the analysis. Open label and comparative trials were included in the assessment, although more weight was given to placebo-controlled, double-blind studies. Emphasis was placed on subject ratings of symptoms in light of the potential for self-medication of this extract.

Results

Reviews, Books, and Monographs

Four reviews [39-43] and a number of books/monographs [2,44-46] dealing largely with the clinical efficacy and safety of Cernitin have been published in recent years. Each used its own criteria to select studies considered to be valid. Because all reviews concluded that Cernitin is very safe with few or no side effects, the summaries described below are essentially limited to efficacy.

In the first, Commission E, an expert committee established by the German government to evaluate the safety and efficacy of over 300 botanical and botanical combinations sold in Germany, concluded in 1994 that combining extracts of rye, corn, and timothy pollen was useful in the treatment of "micturition difficulties associated with Alken stage I-II benign prostatic enlargement (BPH)" [39]. In the second, the Natural Medicines Comprehensive Database concluded that rye grass pollen extract (Cernitin) was "possibly effective" for the management of BPH symptoms, for shrinking prostate size, and for prostatitis and prostadynia based on the information it gathered [40]. In the third source, the same group published reviews in 1999 and 2000 based upon results from 4 double-blind studies (444 men in total, 2 studies with placebo; 2 with active controls) [41,42]. Results consistently showed a "modest" improvement in subjective symptoms and nocturia in the Cernitin groups compared to placebo, Paraprost (a mixture of the amino acids L-glutamic acid, L-alanine, glycine) and Tadenan (Pygeum africanum extract). The authors called for additional studies to evaluate long-term effects. In the final review, Shoskes concluded that there was credible clinical and scientific evidence that treatment with Cernitin pollen extract was efficacious for the majority of patients with non-bacterial prostatitis and prostadynia [43]. The books/monographs largely corroborate the conclusions of the reviews [2,44-46].

Research Papers

Again, Cernitin was well tolerated in all of the published studies from primary literature with minimal reported side effects. Therefore, the discussion will continue to focus on efficacy.

In the 1960's, Leander [47] published results of a carefully controlled trial. He compared placebo

with Cernitin pollen extract in 179 cases. Using pollen extract, Leander found a 60-80 per cent improvement over placebo in symptoms of obstruction, probably through elimination of inflammatory edema. Around the same time, much work was progressing in Japan. Inada et al [48] reported favorable effects in 12 patients suffering from prostatic hypertrophy. They reported that five cases had "effective" results; five showed "slightly effective" results and two reported "ineffective" results. In 1967, Ohkoshi, Kawamura and Nagakubo of Keio University, reported impressive results in 30 patients with prostatitis and/or urethritis [49]. Examining 14 patients receiving Cernitin, it was found that treatment was "successful" in 10, "slightly effective" in three, and "ineffective" in only one case. In 16 patients given placebo, seven found the treatment to be "effective" and nine reported "no change."

In 1981, Takeuchi [50] investigated both subjective and objective effects of Cernitin on 25 men with BPH. The efficiency rate for Cernitin was reported as 64%. There was a 50% improvement for nocturnal micturition. Horii et al [51] reported the results of 30 subjects with BPH who were given Cernitin 2 tablets, 3 times daily for at least 12 weeks. The overall clinical efficacy for subjective symptoms was rated at 80% and objective symptoms at 43%. Ueda et al [52] treated 22 patients with stage I and II BPH with Cernitin for over 4 weeks. Eighty-two percent of the patients were rated as moderately improved or better. Hayashi et al [53] treated 20 BPH patients with Cernitin, 6 tablets a day for an average of 13.2 weeks. They reported improvements in sense of residual urine (92%), retardation (86%), night frequency (85%), strain on urination (56%), protraction (53%), and forceless urinary stream (53%). Overall subjective effectiveness was 80% and overall objective effectiveness was 54%.

In 1986, a field study of 2,289 patients being treated by 170 urologists was undertaken [54]. They examined the effectiveness of Cernitin pollen extracts on chronic prostatitis and/or BPH. Improvement of symptoms was reported in 64 to 82%, in contrast to a low rate of adverse reaction found only in 2.9% of cases. In the same year [55], Brauer compared the effects of Cernitin and beta-sitosterol in 39 patients. A significant reduction in circulating levels of PSA with Cernitin therapy indicated a reduction of cell lesions in BPH. In contrast, no such change occurred with beta-sitosterol treatment. Although flower pollen extract proved superior to beta-sitosterol in many respects, the mean values for residual volume fell under 15 ml for both at the end of treatment. Jodai et al [56] reported the results of a study on 32 patients with chronic prostatitis given 6 tablets of Cernitin daily for an average of 12 weeks. Subjective symptoms improved in 74.2% of the subjects as compared to 65.6% for objective symptoms. The overall efficacy rate was 75.0%.

In a double-blind, placebo-controlled study, Becker et al [57] reported data for 96 subjects with BPH in stages II or III according to the Vahlensieck. Subjects received two Cernitin capsules or placebo three times daily for 12 weeks. The results showed significant improvement in nocturia (68.8% on Cernitin versus 37.2% on placebo, $p = 0.005$), daytime frequency (65.8% on Cernitin versus 43.9% on placebo, $p = 0.076$), freedom from daytime frequency (48.8% on Cernitin versus 19.5% on placebo, $p = 0.010$) and freedom from sensation of residual urine (37.1% on Cernitin versus 7.7% on placebo, $p = 0.016$). In addition there was significant improvement in global assessment scores of both the physicians ($p = 0.001$) and patients ($p = 0.01$). Physicians rated the overall response as very good or good for 68.1% of patients taking Cernitin versus 13.7% taking placebo group. 72.1% of patients taking Cernitin rated their overall response as very good or good versus 27.3% in the placebo group. However, there was no significant change in the size of the prostate as determined by palpation.

In an open study, Buck et al [58] studied the effect Cernitin, 2 tablets twice daily for up to 18 months on 15 patients with chronic, relapsing non-bacterial prostatitis and prostadynia. Seven patients became symptom-free, 6 patients were significantly improved, and 2 patients failed to show improvement in symptoms. Improvement in symptomatology occurred for most patients after 3 months of treatment.

In a double-blind, placebo-controlled study, Buck et al [59] reported data for 53 subjects awaiting operative treatment for outflow obstruction due to prostate enlargement. Patients were instructed to take 2 capsules of Cernitin or placebo twice a day over a 6-month period. The results showed 60% of the subjects receiving Cernitin had less nocturia compared to 30% receiving placebo ($p < 0.063$), and 57% showed improvement in bladder emptying with Cernitin compared to only 10% taking placebo ($p < 0.004$). There was a significant difference ($p < 0.009$) in overall

improvement in subjective symptoms in the Cernitin group (69%) versus placebo (29%). Despite no significant change in peak urinary flow rate or voided volume, residual urinary volume decreased significantly in the Cernitin group compared to placebo ($p < 0.025$).

In a double-blinded, active-control study, Maekawa et al [60] conducted a double-blind study comparing Cernitin, 2 capsules twice daily for 12 weeks, to Paraprost (a mixture of the amino acids L-glutamic acid, L-alanine, glycine) in 159 patients with BPH. The two botanical preparations were comparable in improving symptoms (IPSS) from baseline (55% for Cernitin and 62% for Paraprost). There was a significant improvement in residual urinary volume, average flow rate, maximum flow rate and prostatic weight in the Cernitin group versus Paraprost. Greater than moderate effectiveness rating was 49.1% for Cernitin and 41.2% for Paraprost.

Becker et al [61] continued the placebo-controlled study described above [57] with an open label study in which 92 subjects previously treated in the first phase of the study with Cernitin (n=45) or placebo (n=47) were continued or now treated with Cernitin for 12 weeks. Physicians were blinded in this second phase as to whether the subjects received Cernitin or placebo in the first phase. The results showed that the differences observed between the two groups in the first phase were eliminated in the 2nd phase. Subjects previously treated with placebo improved significantly when treated with Cernitin. Significant improvements were observed in nocturia ($p = 0.051$), frequency ($p = 0.039$), feeling of incomplete emptying ($p = 0.013$), palpable enlargement of the prostate ($p = 0.046$) and prostatic congestion ($p=0.03$).

Bach and Ebeling [62] reported the results from a large open-label trial in Germany involving 208 physicians and 1798 patients with BPH capable of being evaluated. The patients were treated for 24 weeks with Cernitin; 2 tablets 3 times daily. The patients were divided into 3 groups (stage 1, 2 and 3) for data analysis based on the severity of the BPH symptoms. Patients in stage 1 had the most improvement of the three groups in irritative symptoms whereas patients in stage 2 had significant improvement in both irritative and obstructive symptoms. Peak urinary flow rates increased significantly in all 3 groups. A continuing improvement in symptoms was noted when comparing the results after 12 and 24 weeks of treatment. Efficacy in stage 1 and 2 patients was judged to be satisfactory or better in 90% of the patients. Efficacy in stage 3 patients was judged to be satisfactory or better in 65% of the patients. The authors concluded that treatment with Cernitin is justified even for stage 3 patients until surgery is performed.

Rugendorff et al [63] reported the results of a study on 90 patients with non-bacterial prostadynia and chronic prostatitis. Subjects were given Cernitin, 1 tablet 3 times daily for 6 months. Seven-two patients were found to have complicating factors (such as bladder neck sclerosis, prostatic calculi or urethral stricture), while the remaining 18 possessed no complicating factors. Seventy-eight percent of the patients without complications responded to the treatment with 36% of these becoming asymptomatic. In contrast, only 6% of patients with complicating factors improved. Peak urine flow rate in the uncomplicated group increased significantly ($p < 0.001$) from 15.9 to 23.5 ml/s.

Braun and Peyer [64] in a 1993 double blind, placebo-controlled investigation on 44 patients with Grade I and II BPH assessed the validity of treatment with flower pollen extract on subjective and objective parameters. They found by using questionnaires, echography, and laboratory analysis of PSA that flower pollen extract had a clear benefit over placebo. In 25 patient receiving verum compared to 19 receiving placebo, there was a significant reduction in the mean number of both diurnal and nocturnal micturations with flower pollen extract ($p<0.05$). Using ultrasonic measures, the mean volume of the prostate decreased significantly more in the verum group (-29% vs. -8.8%, $p<0.05$). More reduction in residual urine volume and PSA levels were noted in the verum group.

Yasumoto and colleagues [65] conducted an open-label trial with 79 BPH patients. Patients were given 2 Cernitin tablets 3 times a day for at least 12 weeks. The results showed that symptom scores improved significantly from baseline. Overall clinical efficacy was rated 85%. Clinical efficacy at 12 weeks was rated satisfactory or better in 85% of the patients. Dutkiewicz [66] gave Cernitin to 51 patients with BPH -- 2 capsules three times daily for 2 weeks then 1 capsule 3 times daily for an additional 14 weeks. Thirty-eight subjects were given Tadenan (Pygeum africanum extract) for 4 months. Significant improvement in subjective symptoms was reported for both -- Cernitin group (78%) and the Tadenan group (55%). In a recently published

study, 24 patients with chronic prostatitis (NIH-category III) were treated with Cernitin for at least 6 weeks. The results showed a significant decrease in the symptom scores at 4 and 6 weeks [67].

Potential Role of Combination Therapy

Although published clinical trials support the efficacy of Cernitin in the relief of mild to moderate LUTS, a precedent exists to examine beneficial effects of combining Cernitin with other botanical products. A recently completed clinical study sponsored by the National Institutes of Health concluded that the combination of finasteride and doxazosin was more effective that either treatment alone in preventing progression of BPH [68]. This study demonstrates the therapeutic advantages of combining drugs with different mechanisms of action.

The precise mechanisms behind the therapeutic benefits of Cernitin are not fully understood, but it is generally accepted that anti-inflammatory and/or alpha adrenergic blocking effects are important. Therefore, combining Cernitin with a botanical and/or prescription drug with different mechanisms of action may provide additional symptomatic relief. Two recently published trials using combinations of agents with Cernitin support this theory.

Preuss et al [69] reported on a double-blind, placebo-controlled trial comparing a combination of Cernitin (378 mg); saw palmetto fruit standardized to 43% B-sitosterol (286mg) and vitamin E (100IU). Seventy subjects completed the combination therapy and 57 subjects completed the placebo over a 90-day period. There was a significant reduction in nocturia ($p < 0.001$), daytime frequency ($p < 0.04$) and overall symptomatology as measured by the American Urological Association Symptom Score. This combination therapy is logical, since saw palmetto may have different mechanisms of action than Cernitin. As an example, it is believed that saw palmetto compared to Cernitin prevents to a greater extent the conversion of testosterone to dihydroxytestoterone, a potent androgen that stimulates enlargement of the prostate [17,21,22].

Aoki et al [70] conducted an open label trial to study tamsulosin hydrochloride (Flomax®), an alpha1A adrenoceptor antagonist, Cernitin, and the combination in 243 patients with symptomatic BPH over a 12-week period. The results showed that whereas symptoms improved in each group, supporting the efficacy of Cernitin, the best results were obtained in the group that used the combination.

Discussion

A review of placebo-controlled trials, active-controlled and open-label studies indicate that Cernitin is a safe and effective therapy for the management of mild to moderate LUTS. By reducing bothersome symptoms, Cernitin improves quality of life. The placebo-controlled, double-blind studies with Cernitin alone [47,57,59,60] and combined with other natural products [69] especially provide evidence that Cernitin is effective in reducing nocturia, daytime frequency, and sensation of residual urine. The number of subjects in these studies was small relative to the studies conducted for prescription therapeutics such as Terazosin [11] (Hytrin, minimum of 430 subjects) and Doxazosin [71] (Cardura, minimum of 900 subjects), however the duration of the studies were comparable. Cernitin studies were generally conducted for 12 to 24 weeks, terazosin trials were conducted for 12 to 24 weeks, and doxazosin studies were also conducted over a 14 to 16 week period.

Since the number of subjects studied in placebo-controlled trials is small, it was necessary to review open-label and active control studies as supporting data. Concerning the use of Cernitin alone, we report on 15 open label studies and 4 double-blind, placebo-controlled studies that showed consistent reduction in subjective symptoms and overall effectiveness ratings of 75% and greater. In addition, 1 double-blind, active-controlled study, 1 open-label study on a combination, and 1 double-blind, placebo-controlled study on a combination strengthen the conclusions on the therapeutic merits of Cernitin.

Conclusions

Sufficient evidence exists in the primary and secondary literature to indicate that a standardized flower pollen extract commonly referred to as Cernitin is safe and effective for the treatment of mild to moderate LUTS. This dietary supplement composed of pollen extracts from rye, corn, and timothy has the potential to be used in combination with other dietary supplements or pharmaceuticals to provide relief of bothersome symptoms and improve quality of life for millions of men.

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A Critical Review of Graminex Flower pollen extract for Symptomatic Relief of Lower Urinary Tract Symptoms (LUTS) in Men

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Objective

To review published data concerning the ability of a Graminex's Flower Pollen Extract to provide symptomatic relief in men suffering from lower urinary tract symptoms (LUTS).

Introduction

The National Institutes of Health (NIH) estimates 9 million men suffer from symptoms related to an enlarged prostate and 400,000 surgeries are conducted each year in the U.S.[1] The term lower urinary tract symptoms (LUTS) is used to describe symptomatology in men who are experiencing one or more symptoms on the International Prostate Symptom Score (IPSS) questionnaire that includes urgency, daytime and nighttime urinary frequency, hesitancy, intermittency, sensation of incomplete voiding, and force of urine stream. [2] LUTS is used to describe urinary tract disorders in men with benign prostate hyperplasia (BPH), prostatodynia, acute and chronic prostatitis caused by a bacterial infection and acute and chronic abacterial prostatitis.

Bruskewitz stated the primary aim of pharmacological treatment is to improve quality of life by relieving bothersome symptoms since serious complications from BPH are rare[3]. However, he reported the results of a study conducted in the U.S. that showed Urologists gave no treatment 77% of the time to men with mild symptoms. Prescription drugs were given 89% of the time and surgery was conducted on 1% of the time for men with moderate symptoms. The primary therapeutic treatment was alpha(1)-adrenoceptor antagonists such as terazosin hydrochloride (Hytrin®) that provides symptomatic relief but has not be shown to provide long-term effects on the incidence of surgery, acute urinary obstruction or other complications of BPH[4]. The need exists for safe, effective products that can be used by men to treat mild to moderate LUTS in lieu of or in addition to prescription drugs. This review focuses on the potential for flower pollen extract, a dietary supplement, to fill this therapeutic void.

Graminex Flower Pollen Extract is a standardized extract of rye pollen (*Secale cereale)*, corn pollen (*Zea mays)* and timothy pollen (*Phleum pratense)*. The extract contains a blend of water-soluble and lipid-soluble fractions and is available around the world under other brand names such as Cernitin, and in capsule and tablet forms as Cernilton. In vitro[5] and animal model studies[6] have shown that both fractions have anti-inflammatory properties through inhibition of the prostaglandin and leukotrien synthesis. The water-soluble fraction has been shown to reduce the size of the ventral and dorsal prostate in the rat[7] and to inhibit

testosterone-induced BPH in castrated animals8. Both fractions have been shown to relax the smooth muscle of the mouse and pig urethra, increase bladder muscle contractions[8] and reduce prostate size in mature Wistar rats[9].

Methods

Literature searches were conducted on Medline and the Cochrane Library. Secondary sources such as review articles and monographs in botanical reference books were included in the analysis. Open label and comparative trials were included in the assessment, although more weight was placed on placebo-controlled, double-blind studies. Emphasis was placed on subject ratings of symptoms in light of the potential for self-medication of this extract.

Results

Secondary Literature

Four reviews of the clinical efficacy and safety of flower pollen extract have been published in the past 8 years. Although each used their own criteria in selecting valid studies they all concluded that flower pollen extract was very safe with few or no side effects so summaries below are limited to efficacy.

Commission E, an expert committee established by the German government to evaluate the safety and efficacy of over 300 botanical and botanical combinations sold in Germany, concluded in 1994 that the combination extract of rye, corn and timothy pollen was useful in the treatment of "micturition difficulties associated with Alken stage I-II benign prostatic enlargement (BPH)".[10]

The Natural Medicines Comprehensive Database concluded that rye grass pollen extract (Cernilton®) was "possibly effective" for the management of BPH symptoms, for shrinking prostate size and when used for prostatitis and prostatodynia.[11]

McDonald et al concluded in reviews published in 1999[12] and 2000[13] that results from 4 double-blind studies (444 men in total, 2 studies with placebo; 2 with active controls) consistently showed a "modest" improvement in subjective symptoms and nocturia in the flower pollen extract groups compared to placebo, and 2 control products, Paraprost and Tadernan, although the authors called for additional studies to evaluate long-term effects.

Shoskes concluded that there was credible clinical and scientific evidence that treatment with flower pollen extract was efficacious for the majority of patients with nonbacterial prostatitis and prostadynia.[14]

Primary Literature

Flower pollen extract was well tolerated in all of the published studies with minimal reported side effects therefore the discussion will be limited to efficacy considerations.

Double-Blind, Placebo-Control Studies

Two double-blind, placebo-controlled studies have been published with a total of 149 subjects. Becker et al[15] reported data for 96 subjects with BPH in stages II or III according to the Vahlensieck. Subjects received 2 Cernilton® capsules or placebo three times daily for 12 weeks. The results showed significant improvement in nocturia (68.8% on Cernilton® versus 37.2% on placebo), daytime frequency (65.8% on Cernilton® versus 43.9% on placebo), freedom from daytime frequency (48.8% on Cernilton® versus 19.5% on placebo) and freedom from sensation of residual urine (37.1% on Cernilton® versus 7.7% on placebo). In addition there was significant improvement in global assessment scores of both the physicians and patients. Physicians rated the overall response as very good or good for 68.1% on Cernilton® versus 13.7% on placebo. Patients rated the overall response as very good or good for 72.1% on Cernilton® versus 27.3% on placebo. There was no significant change in the size of the prostate as determined by palpitation.

Buck et al[16] reported data for 53 subjects awaiting operative treatment for outflow obstruction due to prostate enlargement. Patients were instructed to take 2 capsules of Cernilton® or placebo twice a day over a 6-month period. The results showed 60% of the subjects on Cernilton® had improve nocturia compared to 30% on placebo ($p < 0.063$), 57% showed improvement in bladder emptying compared to only 10% on placebo. There was a significant difference in overall improvement in subjective symptoms in the Cernilton® group (69%) versus placebo (29%). There was no significant change in peak urine flow rate or voided volume. Residual urine volume decreased significantly in the Cernilton® group compared to placebo.

Double-Blind, Active-Control Studies

Maekawa M., et al[17] conducted a double-blind study comparing Cernilton®, 2 capsules twice daily for 12 weeks to Paraprost (a mixture of the amino acids L-glutamic acid, L-alanine, glycine) in 159 patients with BPH. The two supplements were comparable in improving symptoms from baseline (55% for Cernilton® and 62% for Paraprost). There was a significant improvement in residual urinary volume, average flow rate, maximum flow rate and prostatic weight in the Cernilton® group versus Paraprost. Greater than moderate effectiveness rating was 49.1% for Cernilton® and 41.2% for Paraprost.

Open Label Studies

Eleven published open label studies with a total of 2291 subjects were reviewed. The results indicate significant beneficial effects in subjective LUTS when Cernilton® is used on average for 13.6 weeks.

Becker et al[18] continued the placebo-controlled study[15] described above with an open label study in which 92 subjects previously treated in the first phase of the study with Cernilton® (n=45) or placebo (n=47) were treated with Cernilton® for 12 weeks. Physicians were blinded as to whether the subjects received Cernilton® or placebo in the first phase. The results showed that the differences observed between the two groups in the first phase were eliminated in the 2nd phase. Subjects previously treated with placebo improved significantly when treated with Cernilton®. Significant improvements were observed in nocturia, frequency, feeling of incomplete emptying, palpable enlargement of the prostate and prostatic congestion.

Hayashi et al[19] treated 20 BPH patients with Cernilton®, 6 tablets a day for an average of 13.2 weeks. They reported improvements in sense of residual urine (92%), retardation (86%), night frequency (85%), strain on urination (56%), protraction (53%), and forceless urinary stream (53%). Overall subjective effectiveness was 80% and overall objective effectiveness was 54%. Overall effectiveness was rated 80%.

Yasumoto and colleagues[20] conducted an open label trial with 79 BPH patients. Patients were given 2 Cernilton® tablets 3 times a day for at least 12 weeks. The results showed that symptom scores improved significantly from baseline. Overall clinical efficacy was rated 85%. Clinical efficacy at 12 weeks was rated satisfactory or better in 85% of the patients.

Bach and Ebeling[21] reported the results from a large open label trial in Germany involving 208 physicians and 1798 evaluable patients with BPH. The patients were treated for 24 weeks with Cernilton®; 2 tablets 3 times daily. The patients were divided into 3 groups (stage 1, 2 and 3) for data analysis based on the severity of the BPH symptoms. Patients in stage 1 had the most improvement of the three groups in irritative symptoms whereas patients in stage 2 had significant improvement in both irritative and obstructive symptoms. Peak urine flow rate increased significantly in all 3 groups. A continuing improvement in symptoms was noted when comparing the results after 12 and 24 weeks of treatment. Efficacy in stage 1 and 2 patients was judged to be satisfactory or better in 90% of the patients. Efficacy in stage 3 patients was judged to be satisfactory or better in 65% of the patients. The authors concluded that treatment with Cernilton® is justified even for stage 3 patients until surgery is performed.

Dutkiewicz[22] reported on a study in 51 patients with BPH were given Cernilton®, 2 capsules three times daily for 2 weeks then 1 capsule 3 times daily for an additional 14 weeks. Thirty-eight subjects were given Tadenan (Pygeum africanum extract) for 4 months. Significant improvement in subjective symptoms was reported for the Cernilton® group (78%) versus the Tadenan group (55%).

Horii et al[23] reported the results of 30 subjects with BPH who were given Cernilton®; 2 tablets, 3 times daily for at least 12 weeks. The overall clinical efficacy for subjective symptoms was rated at 80% and objective symptoms at 43%.

Ueda et al[24] treated 22 patients with stage I and II BPH with Cernilton® for over 4 weeks. Eighty-two percent of the patients were rated as moderately improved or better.

In a recently published study 24 patients with chronic prostatitis (NIH-category III) were treated with Cernilton® for at least 6 weeks. The results showed a significant decrease in the symptom scores at 4 and 6 weeks.[25]

In another open study, Buck et al[26] studied the effect Cernilton®, 2 tablets twice daily for up to 18 months on 15 patients with chronic, relapsing abacterial prostatitis and prostodynia. Seven patients became symptom-free, 6 patients were significantly improved and 2 patients failed to show improvement in

symptoms. Improvement in symptomatology occurred for most patients after 3 months of treatment.

Jodai et al[27] reported the results of a study on 32 patients with chronic prostatitis given 6 tablets of Cernilton® daily for an average of 12 weeks. Subjective symptoms improved in 74.2% of the subjects and objective symptoms improved in 65.6%. The overall efficacy rate was 75%.

Rugendorff et al[28] reported the results of a study on 90 patients with abacterial prostadynia and chronic prostatitis. Subjects were given Cernilton®, 1 tablet 3 times daily for 6 months. Seven-two patients were identified as without complicating factors (such as bladder neck sclerosis, prostatic calculi or urethral stricture) and the remaining 18 with complicating factors. Seventy-eight percent of the patients without complications responded to the treatment with 36% of these becoming asymptomatic whereas only 6% of patients with complicating factors improved. Peak urine flow rate in the uncomplicated group increased significantly from 15.9 to 23.5 ml/s.

Discussion

A review of 2 placebo controlled trials and 11 open label studies indicate that flower pollen extract is a safe and effective therapy for the management of mild to moderate LUTS. The studies showed a consistent reduction in subjective symptoms and overall effectiveness ratings of 75% and greater. The extract reduces bothersome symptoms thereby improving quality of life. The two placebo-controlled, double-blind studies provide evidence that the extract is effective in reducing nocturia, daytime frequency and sensation of residual urine.

Potential Role of Combination Therapy

Although published clinical trials support the safety and efficacy of flower pollen extract in the relief of mild to moderate LUTS, a precedent exists to examine beneficial effects of combining flower pollen extract with other dietary supplement or pharmaceutical products. A recently completed clinical study sponsored by the National Institutes of Health concluded that the combination of 2 prescription drugs, finasteride and doxazosin were more effective that either treatment alone in preventing progression of BPH.[1] This study demonstrates the therapeutic advantages of combining pharmacologically active constituents with different mechanisms of action.

Although the mechanism of action of flower pollen extract is not fully understood, it appears to work via an anti-inflammatory effect, therefore a combination with a botanical or prescription drug that works via a different mechanism may provide additional symptomatic relief. Two recently published trials on combinations with flower pollen extract are very encouraging. Preuss et al[29] reported on a double-blind, placebo controlled trial comparing a combination of flower pollen extract (378 mg), saw palmetto fruit standardized to 43% B-sitosterol (286mg) and vitamin E (100 IU). Seventy subjects completed the combination therapy and 57 subjects completed the placebo over a 90-day period. There was a significant reduction in nocturia, daytime frequency and overall symptomatology as measured by the American Urological Association Symptom Score. This combination therapy is logical since saw palmetto may have a different mechanism of action that flower pollen extract. It is generally believed that Saw Palmetto prevents the conversion of testosterone to dihydroxytestoterone, a potent androgen that stimulates enlargement of the prostate[30].

Aoki et al[31] conducted an open label trial to study tamsulosin hydrochloride (Flomax®), an alpha1A adrenoceptor antagonist, flower pollen extract and their combination in 243 patients with symptomatic BPH over a 12 week period. The results showed that whereas symptoms improved in each group, supporting the efficacy of flower pollen extract, the best results were obtained in the group that used the combination product.

Conclusions

Sufficient evidence exists in the primary and secondary literature to indicate that Graminex's Flower Pollen Extract is safe and effective for the treatment of mild to moderate LUTS. This dietary supplement ingredient has the potential to be used in combination with other dietary supplements or pharmaceuticals to provide relief of bothersome symptoms and improve quality of life for millions of men with this common condition.

Table 1 – Summary Data
Symptom Scores

Patient	Age/Sex	Initial	1 mo.	2 mo.	% change *
K.S.	57 M	12	12	-	0
M.K.	77 M	7	-	2	71
T.S.	46 M	13	Dropout		
Y.N.	48 M	5	4	2	60
M.S.	51 M	6	Dropout		
K.N.	57 M	7	6	2	71
E.H.	43 F	7	5	-	29
H.Y.	30 M	10	10	-	0
T.O.	48 F	10	1	-	90

*Percent change in total symptom score from initial to last visit

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A long-term therapeutic experience with Cernilton in Chronic Prostatitis

Jodai A, Maruta N, Shimomae E, Sakuragi T, Shindo K, Saito Y

Thirty-two patients with chronic prostatitis were given 6 tablets of Cernilton daily for 12.6 weeks on the average. Improvement of subjective symptoms and objective findings was noted in 74.2% and 65.6% of the cases, respectively. The effective rate was 75.0%. No subjective symptoms or abnormal changes in laboratory data were observed in any case after Cernilton medication.

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A multicenter, Placebo-controlled Study on the Efficacy and Tolerability of Adenoprostal in Patients with Benign Prostatic Hyperplasia (BPH)

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Abstract

Prostatectomy is considered as the gold standard treatment for BPH and some 400,000 men undergo the procedure each year in the US alone. Several new pharmacological products for the treatment of BPH have been developed over the last few years but have given unconvincing results and a side effect profile which included impotence. Phytotherapeutic treatments are therefore of particular interest especially due to the low incidence of side effects.

Methods

A multicenter, double-blind, placebo-controlled study was carried out to evaluate the therapeutic activity and tolerability of Adenoprostal in the treatment of BPH. Patients suffering from benign prostatic hyperplasia with sporadic disturbances of micturition and residual urine < 100 ml (Grade I) or persistent disturbances of micturition and residual urine ≥ 100 ml (Grade II) were recruited into this study and randomly assigned to 2 treatment groups. Patients received 1 capsule of Adenoprostal (containing 189 mg pollen extracts) or placebo per day for 8 weeks. At the end of the treatment period there was an 8-week follow-up period; another examination was carried out at Week 24 to evaluate how long the improvement lasted after treatment was stopped.

Benign prostatic hyperplasia (BPH) of the periurethral prostate gland is commonly seen in men over 50 years of age and causes varying degrees of bladder outlet obstruction. The etiology of this disease is unknown but may involve alterations in hormonal balance associated with aging.

As life expectancy has risen significantly over the last decade more than 15% of the population is now over 60 years of age. About 50-60% of 60 year old males suffer from benign prostatic hyperplasia and these increases in men over 70 years of age.

Given the incidence of the disease and the resulting functional disturbances, treatment of BPH becomes more important in order to improve the quality of life of the affected patients and perhaps avoid prostatic surgery.

Prostatectomy is widely used for the treatment of BPH. Some 400,000 men undergo the procedure each year in the USA for an estimated expenditure of $3.5 billion.

Quality of life improves after surgery only for patients with severe symptoms. Yet most surgery is carried out in patients with mild or moderate symptoms which mean that for the majority of men this treatment will not have a great impact.

Several new products for the treatment of BPH have been introduced in the pharmaceutical market over the last few years. In a 1645-patient double-blind, placebo-controlled study, finasteride (Proscar, Merck Sharp, and Dohme), a 5-a reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone, which promotes prostate growth, gave unconvincing results. In addition, its side effects may include impotence, decrease libido and decrease ejaculate.

Hence phytotherapeutic treatments are of particular interest due to the low incidence of side effects.

*Adenoprostal is a novel phytotherapeutic treatment for benign prostatic hyperplasia. It contains selected rye pollen extracts which have been shown to be effective in the symptomatic treatment of BPH and the resultant functional disturbances.

Several studies have been published on the efficacy of pollen extract (Cernilton®) in the symptomatic treatment of BPH.
*Adenoprostal is marked by I.B.S.A., Lugano, Switzerland

Most of these studies used subjective parameters to assess efficacy and the evolution of BPH after treatment.

A more reliable objective marker that enables the diagnosis and evolution of the BPH to be assessed more accurately has recently been discovered. This marker, which is called prostate specific antigen (PSA), is a serine proteinase produced in the epithelial cells of the prostate. PSA levels are measurable in the serum of almost all men who have prostatic tissue present. While PSA is specific for prostatic tissue, its levels can be elevated in benign prostatic hyperplasia (BPH), adenocarcinoma of the prostate, prostatitis and after prostate biopsy or cytoscopy. Therefore, if patients with BPH only are selected, this parameter, together with echography, would enable the evolution of the disease to be assessed more accurately.

On this basis we carried out a multicenter, double-blind, placebo-controlled study to evaluate the therapeutic activity and tolerability of Adenoprostal in the treatment of BPH using both objective (PSA measurement and echography) and subjective parameters to assess efficacy.

Treatment

Patients received 1 capsule of Adenoprostal (containing 189 mg pollen extracts) or placebo per day for 8 weeks. At the end of the treatment period there was an 8-week follow-up period; another end point of this study was to evaluate how long the improvement lasted after treatment was stopped. Therefore a further examination was undertaken 16 weeks after the end of treatment (week 24).

Efficacy

The following were evaluated to assess treatment efficacy:

Symptoms

The parameters diurnal and nocturnal micturition, desire to urinate, difficulty or delay in initiating urination and prolonged micturition were individually assessed at baseline and 4, 8, and 24 weeks after the start of the study:

The parameters sensation of incomplete emptying, decreased force of the urinary stream, stranguria, terminal dribbling, incontinence, perineal disturbances, problems involving the testes were evaluated globally.

Ultrasonic examination

An echography of the prostate was carried out at baseline, after 8 weeks of treatment and at Week 24 as a post-treatment clinical control. This examination enables the width, height and length of the prostate to be measured to calculate the volume of the prostate. In addition, it also allowed the post-micturition residue to be measured on the basis of a normogram.

Prostate specific antigen

The prostate specific antigen was determined at baseline, after 8 weeks of treatment and at week 24. The PSA determination was carried out at an external laboratory (Anamedica SA, Giubiasco) using a RIA kit from Yang Laboratories INC, USA.

Global efficacy judgment

At week 8 and week 24, the doctors and patients expressed a global judgment on the efficacy of the treatments using a 4-point verbal scale (0=nil, 1=poor, 2=good, 3=excellent).

Secondary Effects

All secondary effects observed during the study were recorded in the individual patient case report forms including the type of effect, its duration and intensity.

Statistical methods

Parametric and non-parametric tests were used to analyze the date including the level of statistical significance within groups and

between groups. The following tests were used: Chi-square test, analysis of variance (ANOVA), paired t-test, Mann-Whitney test, and the two sample t-test.

Results

A total of 55 patients were recruited into this study and randomly divided into 2 treatment groups: the Adenoprostal group (32 patients) and the Placebo group (23 patients).

Of these, only 44 were assessable at the end of the study and their data were subjected to statistical analysis.

The characteristics of these 44 patients are reported in Table 1 below:

Table 1. Demographic characteristics of the patients

Patients' characteristics	Adenoprostal (N = 25)	Placebo (N = 19)
Average age ± S.D.	63.42 ± 7.407	62.11 ± 6.249
Age range	48 - 83 years	50 - 74 years
Height ± S.D.	169.60 ± 5.489	170.10 ± 5.089
Weight ± S.D.	76.84 ± 11.1	72.58 ± 8.79

The two groups were homogeneous for age, height and weight (two sample t-test: p = n.s.)

Eleven patients (7 from the Adenoprostal group and 4 from the Placebo group) were excluded from the analysis for the following reasons:

- Missing controls: 4 from Adenoprostal group, 1 from the placebo group.
- Death: 1 from the placebo group.
- Protocol violations: 3 patients from the Adenoprostal group and 2 from the placebo group: 2 patients from the Adenoprostal group were hospitalized for tumor removal and prostatectomy: 1 patient from the Adenoprostal group and 2 from the placebo group were excluded for use of diuretics.

The concomitant medications used were mostly psychoactive and cardioactive drugs. Three patients (2 from the Adenoprostal group and 1 from the placebo group), had taken non-steroidal anti-inflammatory drugs during the study.

Efficacy

Symptoms

Diurnal and nocturnal micturition:

Table 2 below shows that there was a reduction in the mean number of both diurnal and nocturnal micturitions in patients treated with Adenoprostal ($p<0.05$), two sample t-test).

Table 2. Diurnal and nocturnal micturition

	MICTURITION			
	DIURNAL		*NOCTURNAL*	
	START	COMPLETION	START	COMPLETION
Treatments				
ADENOPROSTAL (N = 25)	6	4	2	0
PLACEBO (N = 19)	6	6	2	2

Desire to urinate, difficult or delay in initiating urination, prolonged micturition

At the end of the study an improvement, even though at the limit of statistical significance, was observed in these symptoms only in the patients treated with Adenoprostal ($p<0.05$, Chi-squared test).

Global evaluation of the following symptoms which could not be assessed individually:

Sensation of incomplete emptying, decreased force of the urinary stream, stranguria, terminal dribbling, incontinence, perineal disturbances, and problems involving the testes.

The distribution of these judgments were very similar in the two treatment groups and were therefore non-significant (Chi-squared test, p=n.s.).

Ultrasonic examination

This test enabled the volume (ml) of the prostate to be assessed before (t = week 0) and at the end of the study (t = week 24).

The ecographic examinations were always carried out by the same investigator and the following formula was used to calculate the

volume of the prostate [23]: V(ml) = (4/3)π(axial value/2) (transversal value/2) (saggital value/2)

Table 3 reports the mean values for the volumes of the prostate in both treatment groups at baseline (t = week 0) and at week 24 (t = week 24). The mean volume of the prostate had decreased progressively in both treatment groups. However the reduction was significantly greater (p<0.05: two sample t-test) in the Adenoprostal group (-29%) than in the placebo group (-8.8%).

Table 3. Volume of the prostate (ML)

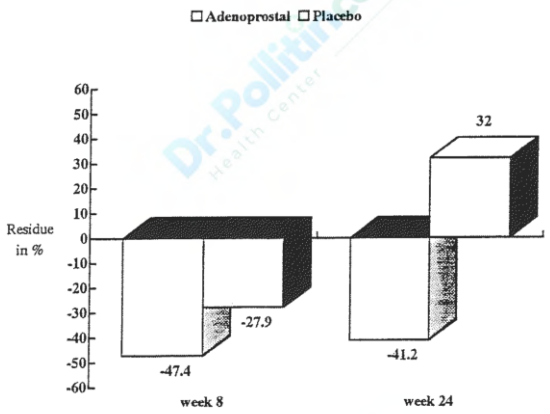
Treatments	t = 0 weeks	t = 24 weeks
ADENOPROSTAL		
(N = 21)	44.61 ± 23.25	31.66 ± 14.63 * (-29%)
PLACEBO		
(N = 17)	46.63 ± 42.50	42.50 ± 20.87 * (-8.8%)

difference between t = 24 / t = 0 (100) - 100

Measurement of post-micturition residue

The post-micturition residue in the patients treated with Adenoprostal decreased from 90.59 ml to 47.64 ml after 8 weeks of treatment (p<0.01: paired t-test) and increased to 53.27 ml at the Week 24 examination (p<0.01: paired t-test). In the placebo-treated patients, the decrease in post-micturition residue was not significant: the baseline value of 60.07 ml decreased to 43.94 ml after 8 weeks of treatment and increased to 80.4 ml at Week 24.

It is important to stress that if these results are expressed as a percent reduction of the post-micturition residue, a 47.4% reduction is observed after 8 weeks of treatment in the Adenoprostal group compared to a 27.9% reduction in the placebo group after the same period of treatment; at the end of the study (Week 24), the post-micturition residue remained at nearly the same levels (-41.2%) in the Adenoprostal group while it increased in the placebo group (+32%) compared to baseline values. The between-groups comparison was significant only at week 24 (p<0.01: two-sample t-test).



Determination of PSA

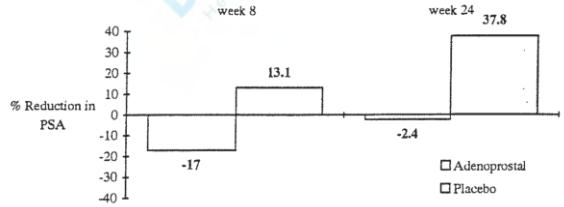
The serum levels* of the PSA in the two treatment groups were particularly interesting.

(*)PSA: normal up to 4 ng/ml

In the Adenoprostal group, the PSA levels decreased from baseline value of 5.5 ng/ml to 4.6 ng/ml after 8 weeks of treatment. This decrease was significant (p<0.05: paired t-test). At the week 24 control, the value increased to 5.4 ng/ml (p= n.s.: paired t-test).

On the other hand there was a constant increase in serum levels of PSA after 8 weeks of treatment and at the final control (Week 24). The baseline value of 5.2 ng/ml increased to 5.9 ng/ml at week 8 and to 7.2 ng/ml at week 24.

The difference between the groups was statistically significant in favor of Adenoprostal (p<0.05 at week 8 and at week 24: two-sample t-test).



Results

Adenoprostal significantly reduced the mean number of both nocturnal and diurnal micturitions (p<0.05) compared to placebo. The echography examination showed that both the volume of the prostate and the post-micturition residue decreased after treatment with Adenoprostal compared to placebo. Statistically, the prostatic specific antigen levels at the end of

the study showed a significant decrease, compared to baseline values, in patients treated with Adenoprostal. Tolerability was excellent in nearly all the patients.

Conclusions

Patients treated with Adenoprostal showed a greater overall benefit, compared to those treated with placebo, with a marked reduction in the intensity of symptoms at all the evaluation periods.

Key words: BPH – benign prostatic hyperplasia, phytotherapy, rye pollen extract, PSA – prostate specific antigen

Appendix

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Global judgements on Efficacy

The global judgments on the therapeutic activity of the two treatments were calculated on the basis of the judgments expressed by the investigators and the patients who used a verbal score (0=no efficacy, 1=poor, 2=good, 3=excellent).

The mean score in the group of patients treated with Adenoprostal was 1.4 at the week 4 control; this improved to 1.7 at week 8 and 1.8 at the end of the study (Week 24).

The analyses showed statistically significant differences from week 8 onwards ($p<0.05$: Wilcoxon test).

No statistically significant differences were seen in the scores from the placebo-treated group.

Even though a more favorable improvement was observed in the Adenoprostal group both at week 8 and at week 24, the analyses showed a statistically significant difference between treatments only at the end of the study (Mann-Whitney test: $p<0.05$).

Global judgments on Tolerability

The majority of the tolerability judgments were “excellent” or “good” in both study groups (95% in the placebo group and 96% in the Adenoprostal group) at week 4 and week 8 of treatment.

The incidence of secondary effects was low: one case of anxiety was reported at week 8 in the Adenoprostal group and another at week 4 in the placebo group; one patient in the placebo group presented orthostasis at week 4. These secondary effects were of slight severity, transient and did not require treatment suspension.

The laboratory parameters analyzed did not show any clinically important changes in the two treatment groups.

Table 4. Global efficacy judgements

VARIABLE	ADENOPROSTAL	PLACEBO
Excellent	4%	0%
Good	64%	56%
Poor	32%	17%
Nil	0%	27%

Discussion

Most of the clinical studies that have been performed to evaluate the efficacy and tolerability of phytotherapeutic treatment in benign prostatic hyperplasia (BPH) have used subjective assessment parameters.

The aim of this double-blind, placebo-controlled study was to assess the validity of treatment with Adenoprostal using both subjective and objective parameters. In addition to the questionnaire that the patients were supposed to complete, objective parameters such as echography and the laboratory evaluation of PSA have been used. These objective examinations enabled the evolution of BPH in patients under treatment with Adenoprostal or placebo to be followed.

The three methods used (questionnaire, echography and laboratory analysis of PSA) demonstrated the clear benefits of Adenoprostal compared to placebo.

Patients treated with Adenoprostal showed an overall benefit with a marked reduction in the intensity of symptoms at the pre-fixed evaluation periods. Of particular importance was the favorable improvement of the following symptoms: frequency of diurnal and nocturnal micturition, desire to urinate, difficulty or delay in initiating urination and prolonged micturition.

Nearly all investigators participating in this study had carried out the sonography examinations in a standardized manner using the suprapubic position [18] for the measurement of the prostate and for the calculation of the post-micturition residue. The post-micturition volume [19, 20, 21], showed a good correlation between the

result obtained using the formula (0.7 [x.y.z] = ml) and the result obtained with the normogram [21].

The echography examination demonstrated that Adenoprostal was effective in the treatment of benign prostatic hyperplasia. At the end of the study it was observed that both the volume of the prostate, measured echographically [22, 23, 24], and the post-micturition residue had shown a definite decrease following treatment with Adenoprostal compared to the results obtained in the patients treated with placebo. Although there was a significant disappearance of symptoms and a significant reduction in post-micturition residue, the fact that this was not accompanied by a striking reduction in prostate volume probably has a two-fold explanation. In our opinion, the first is due to the limitations of trans-abdominal sonography: the posterior parts of the prostate are often difficult to delimit and hence an exact measurement is rather difficult; in addition it is practically impossible to evaluate the exact prostatic volume when there are irregular protrusions inside the vesicle.

Finally, in the early stages, benign prostatic hyperplasia is often characterized by an increase in the central hypoechogenicity without significant alterations of the total diameter [25].

As a result, the measurement of post-micturition residue was shown to be the most reliable parameter for the evaluation of efficacy in our patients, compared to the measurement of the prostate volume which should be evaluation using more accurate instrumental parameters.

The laboratory parameters did not undergo any noteworthy variations. However, the prostatic antigen levels at the end of the study showed a significant decrease, compared to baseline values, in patients treated with Adenoprostal. This decrease was not seen in the placebo-treated patients. The difference between the groups was statistically significant in favor of Adenoprostal at week 8 and week 24 ($p<0.05$: two-sample t-test).

Tolerability was excellent in nearly all patients (95% favorable results in the Adenoprostal group; 96% favorable results in the placebo group). Secondary effects were seen only in three cases (one patient treated with Adenoprostal, two with placebo). However these were of slight severity and did not require treatment interruption.

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Pelvic Pain

A Pollen Extract (Cernilton) in Patients with Inflammatory Chronic Prostatitis–Chronic Pelvic Pain Syndrome: A Multicentre, Randomised, Prospective, Double-Blind, Placebo-Controlled Phase 3 Study

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Abstract

Background: National Institutes of Health (NIH) category III prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a prevalent condition for which no standardised treatment exists.
Objectives: To assess the safety and efficacy of a standardised pollen extract in men with inflammatory CP/CPPS.
Design, setting, and participants: We conducted a multicentre, prospective, randomised, double-blind, placebo-controlled phase 3 study comparing the pollen extract (Cernilton) to placebo in men with CP/CPPS (NIH IIIA) attending urologic centres.
Intervention: Participants were randomised to receive oral capsules of the pollen extract (two capsules q8 h) or placebo for 12 wk.
Measurements: The primary endpoint of the study was symptomatic improvement in the pain domain of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). Participants were evaluated using the NIH-CPSI individual domains and total score, the number of leukocytes in post–prostatic massage urine (VB3), the International Prostate Symptom Score (IPSS), and the sexuality domain of a life satisfaction questionnaire at baseline and after 6 and 12 wk.
Results and limitations: In the intention-to-treat analysis, 139 men were randomly allocated to the pollen extract ($n = 70$) or placebo ($n = 69$). The individual domains *pain* ($p = 0.0086$) and *quality of life* (QoL; $p = 0.0250$) as well as the total NIH-CPSI score ($p = 0.0126$) were significantly improved after 12 wk of treatment with pollen extract compared to placebo. Response, defined as a decrease of the NIH-CPSI total score by at least 25% or at least 6 points, was seen in the pollen extract versus placebo group in 70.6% and 50.0% ($p = 0.0141$), respectively. Adverse events were minor in all patients studied.
Conclusions: Compared to placebo, the pollen extract significantly improved total symptoms, pain, and QoL in patients with inflammatory CP/CPPS without severe side-effects.

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1. Introduction

Prostatitis syndrome is characterised by genitourinary pain and lower urinary tract symptoms (LUTS) [1]. The prevalence of symptoms suggestive of prostatitis ranges between 2.2% and 13.8% according to different studies [2]. National Institutes of Health (NIH) category III prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most frequent subtype, with a heterogeneous and mainly unknown aetiology. Classification of prostatitis syndrome is based on the clinical presentation of the patient, the presence or absence of white blood cells in the expressed prostatic secretion (EPS), post–prostatic massage urine (VB3) or seminal plasma, and the presence or absence of bacteria in the EPS or VB3 [1]. In the NIH classification bacterial prostatitis (acute and chronic) is distinguished from inflammatory and noninflammatory CP/CPPS [3].

Evidence-based treatment of CP/CPPS has been difficult because of the heterogeneous patient population in this syndrome. Even the seemingly proven use of α-blocker therapy in naïve patients [2] is now in dispute [4]. Phytotherapeutic agents such as pollen extract, quercetin, or saw palmetto are widely used with variable success [5,6] but have only rarely been evaluated in suitable clinical trials.

The pollen extract Cernilton contains 63 mg of the defined pollen extract fractions Cernitin T60 (water-soluble fraction) and Cernitin GBX (fat-soluble fraction). These fractions contain carbohydrates, fat, amino acids, vitamins, and minerals and have been used for treatment of benign prostatic hyperplasia [7] and prostatitis [5,8]. Experimental data in nonbacterial prostatitis in rats showed that Cernitin GBX protects mainly acinar epithelial cells and inhibits stromal proliferation in association with an enhanced apoptosis mediated by Cernitin T60 [9]. In a further study, a dose-dependent anti-inflammatory action in nonbacterial prostatitis in rats was noted, leading to decreased levels of interleukin-1β, interleukin-6, and tumour necrosis factor α, which decreases glandular inflammation and might be responsible for the decrease in proliferation and increase of apoptosis seen in the prostate [10]. A further in vitro study found an inhibition of the arachidonic acid cascade [11]; another possible effect on the prostate is via the androgen metabolism [12]. In three noncomparative clinical studies in 90, 24, and 15 patients with CP/CPPS treated with pollen extract, improvement of symptoms was noted in 78%, 63%, and 86%, respectively [5,8,13]. To our knowledge, however, no placebo-controlled study comparing pollen extract has been performed so far. This investigator-initiated (W.W.) study was designed to ascertain the safety and efficacy of pollen extract versus placebo in a clearly defined population of men diagnosed with inflammatory CP/CPPS.

2. Patients and methods

2.1. Study design

This double-blind, prospective, randomised, placebo-controlled, multicentre, clinical phase 3 study was conducted according to Good Clinical Practice (GCP) in 34 German urologic centres to ascertain the safety and efficacy of 12-wk pollen extract versus placebo in men diagnosed with inflammatory CP/CPPS. The study protocol was approved by the ethical committee of the Justus-Liebig-University, Giessen, Germany. The design of the study was in accordance with the guidelines for clinical trials in CP/CPPS described by the NIH Chronic Prostatitis Collaborative Research Network [14].

Inclusion criteria were (1) men between 18 and 65 yr of age with symptoms of pelvic pain for at least 3 mo during the 6 mo before study entry, (2) a score in the *pain* domain of the German-validated version of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) [15] of ≥7, and (3) leukocytes of ≥10 in VB3 (field of vision: ×400). Exclusion criteria were (1) urinary tract infection; (2) acute bacterial or chronic bacterial prostatitis at study entry (bacteriuria ≥104 colony-forming units (CFU)/ml in mid-stream urine (VB2) or ≥103 CFU/ml in VB3); (3) history of urethritis, with discharge 4 wk prior to study entry; (4) a history of epididymitis or sexually transmitted disease (STD); (5) residual urine volume >50 ml resulting from bladder outlet obstruction (BOO); (6) indication for or history of prostate surgery, including prostate biopsy; (7) history of urogenital cancer; (8) treatment with phytotherapeutic agents, α-blocker agents, or antimicrobial substances with prostatic penetration 4 wk prior to study entry; and (9) treatment with agents influencing intraprostatic hormone metabolism 6 mo prior to study entry. The above-listed substances were not allowed during the full study course, nor were any other accompanying treatments that could influence the study aims.

2.2. Study procedure

At the start of the 1-wk screening phase, after giving written informed consent, patients were evaluated using a detailed medical history, including German-validated versions of the NIH-CPSI [15], the International Prostate Symptom Score (IPSS) [16], and the *sexuality* domain of a life satisfaction questionnaire [17,18], as well as a physical examination, including prostate, external genitalia, vital parameters, routine laboratory tests, measurement of residual urine volume by ultrasound, and a standardised four-glass test localisation study [19]. Patients included in the screening phase were pretreated with azithromycin (250 mg q6h) for 1 d to eliminate atypical pathogens.

After 1 wk, the inclusion criteria were rechecked, and patients were included in the treatment phase when both conditions—*pain* domain of NIH-CPSI ≥7 and leukocytes ≥10 in VB3—were fulfilled. Patients were then allocated to receive either pollen extract (two capsules q8h, with the active substance consisting of 60 mg Cernitin T60 and 3 mg Cernitin GBX) or placebo (two capsules q8h, with identical capsulation and weight only containing the inactive substances in proportional doses as compared with the pollen extract) in a randomised order. Randomisation was carried out in blocks ($n = 4$) within the centre using a random number generator. The study medication was manufactured in accordance with the random scheme and Good Manufacturing Practice (GMP) and was labelled in accordance with regional law (AMG). The investigators were instructed to use the study drug in ascendant order of random numbers available in the respective trial centre.

NIH-CPSI (0–43) with its subscales (*pain* domain [0–21], *micturition* domain [0–10], and *quality of life* [QoL] domain [0–12]), IPSS (0–35), the *sexuality* domain of a life satisfaction questionnaire (0–42), a standard urologic examination, and the four-glass test were carried out at weeks 0 (before start of study drug), 6, and 12 (end of study drug). Residual urine was measured at weeks 0 and 12. At week 12 or at premature study end, a global assessment of the efficacy of treatment defined by five items (very good, good, moderate, bad, very bad) was collected from the patient and the corresponding physician.

Adverse events were documented during the whole course of study. Tolerability was assessed at study end by patient and physician using a scale with four items (very good, good, moderate, bad).

2.3. Statistical analysis and assessments

The primary target of the study was symptomatic improvement in the *pain* domain of the NIH-CPSI. This parameter had to be evaluated one sided in a statistical design according to Bauer and Köhne [20] with two sample size adaptive interim analyses. Secondary outcomes included symptomatic improvement of the NIH-CPSI total score and the *micturition* and *QoL* domains of the NIH-CPSI questionnaire as well as a decrease in the number of leukocytes in VB3. Further explorative outcome criteria were changes in the IPSS, the *sexuality* domain of the life satisfaction questionnaire, residual urine volume, and safety of the study drug. Additionally, qualitative efficacy parameters based on NIH-CPSI—namely, improvement of NIH-CPSI summary score by $\geq$ 25% and improvement of NIH-CPSI summary score by at least 6 points—were introduced as recommended by Nickel et al [21].

Usual methods of two-group comparisons were employed: student *t* test, Wilcoxon rank sum test, χ^2 test, and analysis of covariance with baseline values as covariates. The sample size estimation was based on a treatment difference of at least 3 $\pm$ 7 score points, a power of 1-β = 0.8, and a significance level of α = 0.025 one sided. At least 87 patients should be enrolled in each trial group. Using a three-stage adaptive procedure according to Bauer and Köhne [20], superiority of pollen extract versus placebo could be demonstrated with 70 (active) and 69 (placebo) patients.

3. Results

3.1. Disposition of patients

Thirty-seven of 176 screened patients were not included into the intention to treat (ITT) set of this trial (12 screening failures, 9 treatment failures [wrong allocation of trial drug], 4 GCP failures within one centre [cessation of the trial, no open access to study data], and 12 early drop-outs [no data postrandomisation] were identified). The analyses were carried out in the ITT (pollen extract: *n* = 70; placebo: *n* = 69) and in the per protocol (PP) population (pollen extract: *n* = 51; placebo: *n* = 60). Exclusions from the PP analysis were predominantly justified by bacterial infections at baseline, violations of the inclusion criteria regarding pain and leukocytes in VB3, and premature trial termination not due to efficacy reasons (Fig. 1).

3.2. Baseline characteristics

During the screening period between week −1 and week 0 (pretreatment with azithromycin), a slight improvement of

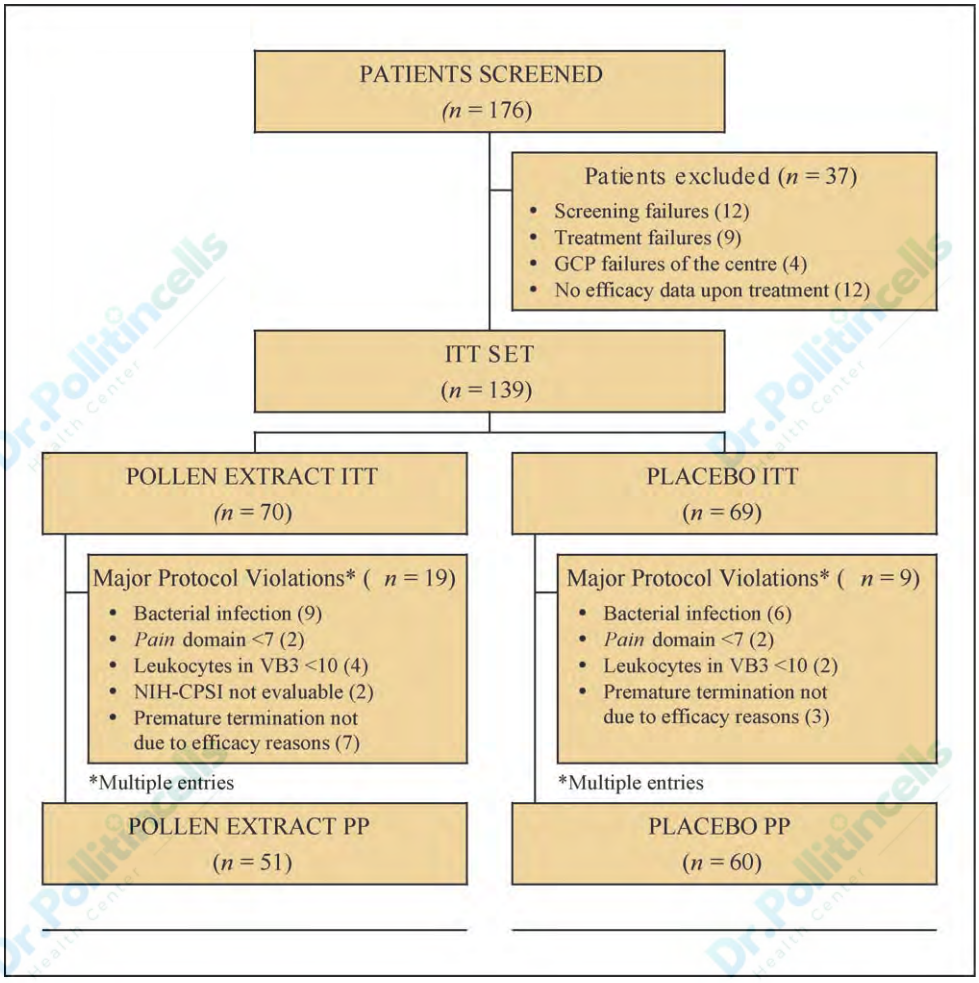

Fig. 1 – Disposition of patients.
GCP = Good Clinical Practice; ITT = intention to treat; VB3 = post–prostatic massage urine; NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index; PP = per protocol.

Table 1 – Baseline characteristics and clinical parameters at week 0*

Parameters	Pollen extract (*N* = 70)	Placebo (*N* = 69)	Overall (*N* = 139)
Patient age, yr (range)	39.7 ± 7.2 (20–54)	39.3 ± 9.1 (18–63)	39.5 ± 8.1 (18–63)
Height, cm	180 ± 8	178 ± 7	179 ± 7
Weight, kg	82.7 ± 12.2	81.2 ± 11.8	81.9 ± 12.0
Duration of disease, yr	4.4 ± 5.2	4.9 ± 6.2	4.6 ± 5.7
Duration of current symptoms, mo	7.6 ± 10.7	9.0 ± 16.0	8.3 ± 13.6
Prior medication† (%)	29 (41%)	32 (46%)	61 (44%)
NIH-CPSI	19.3 ± 5.1	20.3 ± 5.2	19.8 ± 5.2
Pain domain	10.0 ± 2.4	10.2 ± 2.6	10.1 ± 2.5
Micturition domain	2.8 ± 2.3	3.5 ± 2.5	3.2 ± 2.4
QoL domain	6.5 ± 2.5	6.7 ± 2.2	6.6 ± 2.4
IPSS	7.3 ± 5.3	8.5 ± 6.4	7.9 ± 5.9
Sexuality domain of life satisfaction questionnaire	2.2 ± 1.2	2.3 ± 1.1	2.3 ± 1.1
Leukocytes (field of vision: × 400) in VB3	17.7 ± 11.9	15.7 ± 6.4	16.7 ± 9.5
Residual urine volume, ml‡	11.9 ± 13.9	10.8 ± 12.3	11.4 ± 13.1

NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index; QoL = quality of life; IPSS = International Prostate Symptom Score; VB3 = post–prostatic massage urine; SD = standard deviation.

* Plus–minus values are means plus or minus SD. For NIH-CPSI, higher scores indicate more severe symptoms. The following score ranges are used: total score 0–43, *pain* score 0–21, *urinary* score 0–10, *QoL* score 0–12. For IPSS, higher scores indicate more severe symptoms on micturition; score range is 0–35. For the sexuality domain of the life satisfaction questionnaire, the score range is 1–7, and a lower score indicates less sexual satisfaction.

† Analgesics, antiphlogistics, antibiotics, anticholinergics, phytotherapeutics, α-blockers (median duration since last intake: 21 wk; minimum: 5 wk; maximum: 302 wk).

‡ Measurement at week −1.

the clinical signs was observed: The mean scores of NIH-CPSI decreased from 21.0 ± 5.0 to 19.8 ± 5.2, of IPSS from 8.5 ± 6.0 to 7.9 ± 5.9, of the *sexuality* domain of the life satisfaction questionnaire from 2.4 ± 1.2 to 2.3 ± 1.1, and of leukocytes in VB3 from 18.0 ± 9.8 to 16.7 ± 9.5. Baseline demographic characteristics and clinical parameters at week 0 are listed in Table 1. There were no significant differences between the two groups at the start of the double-blind treatment.

Localisation and circumstances of pain at baseline were indicated as (1) pain in the lower abdomen (71%); (2) pain in the perineum (64%); (3) pain in the testicles (55%); (4) pain in the tip of the penis (46%); (5) painful ejaculation (55%); (6) and painful micturition (46%).

3.3. Primary analysis

Using the preplanned primary outcome analysis procedure, a significant superiority of pollen extract versus placebo could be established at the third step ($p = 0.0080$). The rest of the results section show the overall findings in the total study population without consideration for the preplanned sequential construction analysis plan.

3.4. Changes from baseline in the National Institutes of Health Chronic Prostatitis Symptom Index

After 12 wk of treatment, the mean changes (plus or minus standard error [SE]) from baseline in the *pain* domain of the NIH-CPSI were −4.50 ± 0.42 in the pollen extract and −2.92 ± 0.42 in the placebo group. The higher improvement in the pollen extract group compared to placebo was statistically significant (ITT: −1.58 ± 0.59, $p = 0.0086$; Table 2). In the PP set, the treatment difference amounted to −2.14 ± 0.63 ($p = 0.0009$; Fig. 2).

The mean NIH-CPSI total score decreased from 19.18 to 11.72 in the pollen extract group and from 20.31 to 14.94 in the placebo group. There was a significantly higher baseline-adjusted improvement in the pollen extract group (−7.66 ± 0.70) compared to placebo (ITT: −5.16 ± 0.70, $p = 0.0126$; Table 2). In the PP set, the treatment difference was −3.95 ± 1.06 ($p = 0.0003$; Fig. 2). A definite improvement over baseline can be determined by a 25% decrease of the NIH-CPSI total score [21]. There was a significantly greater percentage of patients in the pollen extract group who demonstrated 25% improvement compared to the placebo group (ITT: 69.1% vs 48.5%, $p = 0.0147$; Table 2). Analysis of the percentage of patients who demonstrated a six-point decrease from baseline in the total score yielded a similar conclusion (ITT: 61.8% vs 42.6%, $p = 0.0256$; Table 2).

The *micturition* domain of the NIH-CPSI improved in both groups. A slightly higher improvement in the pollen extract group compared to placebo was not statistically significant (ITT: $p = 0.5469$; PP: $p = 0.1173$; Table 2).

The mean *QoL* domain of the NIH-CPSI decreased from 6.44 to 4.26 in the pollen extract group and from 6.68 to 5.28 in the placebo group. The baseline-adjusted improvement was significantly higher in the pollen extract group (−2.23 ± 0.27) compared to placebo (ITT: −1.35 ± 0.27, $p = 0.0250$; Table 2). In the PP set, the treatment difference was −1.50 ± 0.41 ($p = 0.0005$; Table 2).

3.5. Changes from baseline in International Prostate Symptom Score

The mean IPSS improved in both groups. A tendency in favour of pollen extract was statistically significant in the PP set only (ITT: $p = 0.0711$; PP: −1.53 ± 0.74, $p = 0.0418$; Table 2).

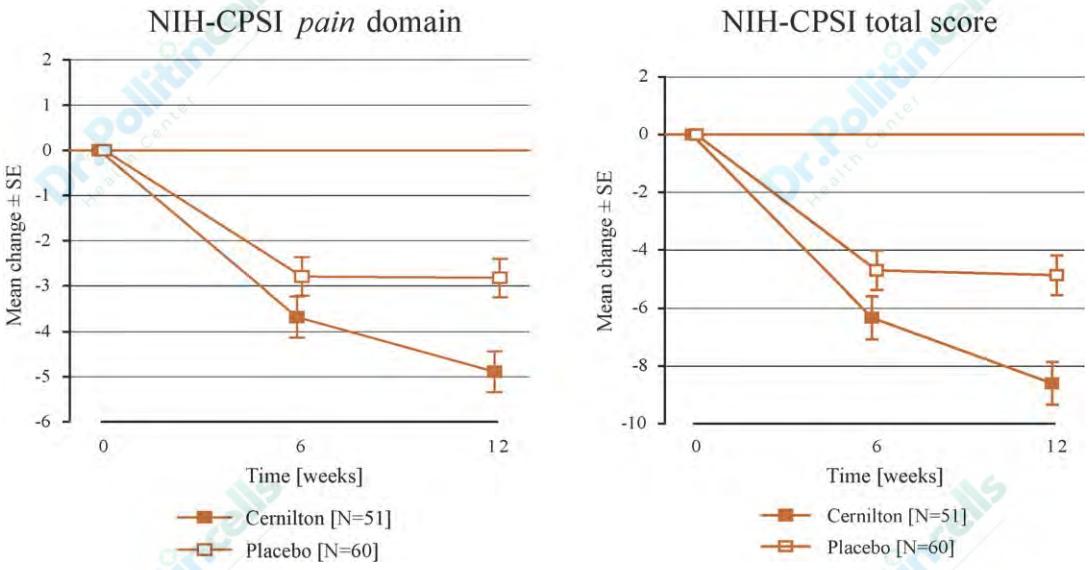

Fig. 2 – Mean change (plus or minus standard error [SE]) from baseline in the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) *pain* domain and in the NIH-CPSI total score after 6 and 12 wk of treatment with pollen extract (Cernilton group) or placebo (per-protocol group).

3.6. Changes from baseline in the sexuality domain of the life satisfaction questionnaire

The mean *sexuality* domain of the life satisfaction questionnaire decreased in both groups. A slightly higher improvement in the pollen extract group compared to placebo was not statistically significant (ITT: $p = 0.2964$; PP: $p = 0.4658$; Table 2).

3.7. Changes from baseline in leukocytes in post–prostatic massage urine

The mean changes from baseline in the number of leukocytes per field of vision were 5.0 in the pollen extract group and 3.0 in the placebo group. The Hodges–Lehmann estimate of the shift parameter from placebo to pollen extract was 2.0 (ITT: $p = 0.1243$; Table 2). In the PP set, the

Table 2 – Efficacy outcomes at week 12 in the intention to treat (ITT) and per protocol (PP) sets*

Parameter				Pollen extract		Placebo	Treatment difference	
NIH-CPSI	• *Pain* domain	ITT	68	−4.50 ± 0.42	69	−2.92 ± 0.42	−1.58 ± 0.59	$p = 0.0086$
	N, adj. mean ± SE	PP	51	−4.93 ± 0.46	60	−2.79 ± 0.43	−2.14 ± 0.63	$p = 0.0009$
	• *Micturition* domain	ITT	68	−1.02 ± 0.19	69	−0.86 ± 0.19	−0.17 ± 0.27	$p = 0.5469$
	N, adj. mean ± SE	PP	51	−1.27 ± 0.21	60	−0.82 ± 0.19	−0.46 ± 0.29	$p = 0.1173$
	• *QoL* domain	ITT	68	−2.23 ± 0.27	68	−1.35 ± 0.27	−0.88 ± 0.39	$p = 0.0250$
	N, adj. mean ± SE	PP	51	−2.62 ± 0.30	59	−1.12 ± 0.28	−1.50 ± 0.41	$p = 0.0005$
	• Total score	ITT	68	−7.66 ± 0.70	68	−5.16 ± 0.70	−2.49 ± 0.99	$p = 0.0126$
	N, adj. mean ± SEM	PP	51	−8.72 ± 0.77	59	−4.77 ± 0.72	−3.95 ± 1.06	$p = 0.0003$
	• 25% decrease in NIH-CPSI	ITT	68	69.1%	68	48.5%	–	$p = 0.0147$
	N, %	PP	51	76.5%	59	47.5%	–	$p = 0.0019$
	• Six-point decrease in NIH-CPSI	ITT	68	61.8%	68	42.6%		$p = 0.0256$
	N, %	PP	51	66.7%	59	40.7%	–	$p = 0.0065$
IPSS		ITT	69	−2.29 ± 0.44	69	−1.15 ± 0.44	−1.14 ± 0.63	$p = 0.0711$
N, adj. mean ± SE		PP	51	−2.52 ± 0.54	60	−0.99 ± 0.50	−1.53 ± 0.74	$p = 0.0418$
Sexuality domain of life satisfaction questionnaire		ITT	69	−0.30 ± 0.09	68	−0.17 ± 0.09	−0.13 ± 0.13	$p = 0.2964$
N, adj. mean ± SE		PP	51	−0.25 ± 0.10	59	−0.15 ± 0.09	−0.10 ± 0.14	$p = 0.4658$
Leukocytes in VB3		ITT	70	−5.0	69	−3.0	−2.0†	$p = 0.1243$‡
N, median		PP	51	−7.0	60	−4.5	−3.0†	$p = 0.0876$‡

NIH-CPSI = National Institutes of Health-Chronic Prostatitis Symptom Score; adj. = adjusted; SE = standard error; QoL = quality of life; IPSS = International Prostate Symptom Score; SEM = standard error of the mean; VB3 = post–prostatic massage urine.

* For the NIH-CPSI, higher scores indicate more severe symptoms; for the *QoL* domain, higher scores indicate a more negative effect; for the IPSS, higher scores indicate more severe symptoms; for the *sexuality* domain of the life satisfaction questionnaire, a lower score indicates less sexual satisfaction.

† Hodges–Lehmann estimate of shift parameters.

‡ Exact Mann-Whitney test.

Table 3 – Assessment of efficacy and tolerability

Set	Parameter		Pollen extract	Placebo
Efficacy				
ITT	Patient assessment, no. (%)	Good to very good	44 (62.9%)	28 (41.8%)
	($p = 0.0136$)	Very bad to moderate	26 (37.1%)	39 (58.2%)
		Missing values	–	2
	Investigator assessment, no. (%)	Good to very good	48 (69.6%)	39 (58.2%)
	($p = 0.1679$)	Very bad to moderate	21 (30.4%)	28 (41.8%)
		Missing values	1	2
PP	Patient assessment, no. (%)	Good to very good	35 (68.6%)	22 (36.7%)
	($p = 0.0008$)	Very bad to moderate	16 (31.4%)	38 (63.3%)
	Investigator assessment, no. (%)	Good to very good	38 (74.5%)	32 (53.3%)
	($p = 0.0212$)	Very bad to moderate	13 (25.5%)	28 (46.7%)
Tolerability				
ITT	Patient assessment, no. (%)	Very good	51 (72.9%)	49 (73.1%)
	($p = 0.7513$)	Good	15 (21.4%)	16 (23.9%)
		Moderate	3 (4.3%)	2 (3.0%)
		Bad	1 (1.4%)	–
		Missing values	–	2
ITT	Investigator assessment, no. (%)	Very good	52 (74.3%)	50 (74.6%)
	($p = 0.2122$)	Good	15 (21.4%)	17 (25.4%)
		Moderate	3 (4.3%)	–
		Bad	–	–
		Missing values	–	2

ITT = intention to treat; PP = per protocol.

shift amounted to −3.0 ($p = 0.0876$; Table 2); neither change was significant.

3.8. *Changes from baseline in residual urine volume*

Residual urine volume was ≤50 ml in all patients at any time measured, and there was no significant change from baseline or difference between groups.

3.9. *Assessment of efficacy*

The global assessment of efficacy by the patient showed significantly higher rates of *very good* or *good* results in the pollen extract group (ITT: 62.9%; PP: 68.6%) as compared to placebo (ITT: 41.8%; PP: 36.7%; Table 3). Regarding the global assessment of efficacy by the physician, a significant treatment difference was seen in the PP set only (pollen extract 74.5%; placebo: 53.3%; Table 3).

3.10. *Adverse events, physical examination, safety laboratory*

Adverse events were reported in 12.9% of patients for pollen extract and 14.5% of patients for placebo ($p = 0.7790$). No statistically significant differences were seen between groups on the level of MedDRA System Organ Class. No or an unlikely causal relationship with study medication was noted in the majority of events. In only two patients—both treated with pollen extract—adverse events possibly attributable to study drug were documented: mild gastrointestinal disorders that caused a short treatment interruption and moderate pain (not otherwise specified) that caused discontinuation of treatment. Serious adverse events were reported in three patients in the pollen extract group and in two patients in the placebo group. All serious adverse events were hospitalisations resulting from concomitant illnesses and not attributed to study drug administration. Physical examinations, including vital signs, and the laboratory examinations showed no relevant changes from baseline.

3.11. *Assessment of tolerability*

In both study groups, the tolerability was rated *very good* in >70% of patients (Table 3).

4. Discussion

Although antibiotic treatment is the standard treatment for chronic bacterial prostatitis [22], there is no standard treatment of CP/CPPS to date [23,24]. Even the evidence to recommend α-blocker therapies [2] is now in dispute [4]. Apart from that, a variety of other treatment options are reported, such as antibiotics, anti-inflammatory agents, phytotherapeutics, and various other modalities [5,8,21,25–29]. All treatment modalities, however, showed rather limited effects on the symptoms experienced in CP/CPPS, of which pain and dysfunctional voiding cause the greatest morbidity and a poor QoL [30]. Given the lack of proven efficacy of conventional therapies, alternative treatment options are urgently needed. Additionally, long-term treatment is usually conducted for CP/CPPS patients. Therefore, phytotherapeutics— amongst which are pollen extract, quercetin, saw palmetto, or terpenes—are an interesting option because of their generally low side-effects; however, few have been subjected to scientific scrutiny and prospective controlled clinical trials [8,26–28].

Cernilton, a standardised pollen extract mixture, has been used for treatment of CP/CPPS for almost 20 yr [8,13]. The exact mechanism of action is largely unknown; however, an anti-inflammatory potential associated with

cyclo-oxygenase and lipoxygenase inhibition is discussed and substantiated by in vitro experiments [9–11] and could be beneficial for patients with CP/CPPS [31].

This study is the first to compare pollen extract to placebo in a large, clearly defined patient cohort. The study focused on inflammatory CP/CPPS (NIH category IIIA), because elevated numbers of leukocytes in VB3 are indicative of an inflammatory prostatitis syndrome [32] and therefore defines a clear study cohort. To exclude possible contamination of this study cohort by infection with atypical pathogens, a 1-wk run-in phase, during which all patients were treated with azithromycin, was introduced before assessment of baseline and start of study drug medication. To exclude patients with LUTS resulting from BOO, patients with elevated residual urine (>50 ml) were also excluded.

Both study groups experienced progressive improvement in symptoms over 12 wk as measured by the NIH-CPSI total score and the subdomains *pain, micturition,* and *QoL*. However, the pollen extract group has significantly more improvement for the NIH-CPSI total score and the subdomains *pain* and *QoL* than did the placebo group. Interestingly, the differences between the two groups became significant after the sixth week (Fig. 2), suggesting that a long treatment period is required in this condition. Clinically significant improvement, as defined by a 25% (or six-point) improvement of the NIH-CPSI total score and a three-point improvement in the *pain* subdomain, was only seen in the pollen extract group, not in the placebo group (Table 2). The *micturition* subdomain of the NIH-CPSI did not reveal any significant difference concerning the improvement between the treatment groups, probably because symptoms in the *micturition* domain were generally low, which was also substantiated by the rather low symptoms in the IPSS (Table 2). The same holds true for the *sexuality* domain of the life satisfaction questionnaire. The global assessment on the efficacy of the treatment by the patient also exhibited a significantly better improvement for pollen extract compared to placebo.

Interestingly, the leukocytes in VB3 also showed a decrease in both arms. The meaning of cellular markers of inflammation in prostate secretions or VB3 in patients with CP/CPPS is still unclear, although the improvement of symptoms in this study was accompanied by a reduction of leukocytes in VB3. However, as there was no significant difference between the two groups, leukocytes cannot be correlated with clinical success in this study.

The pollen extract was generally well tolerated over the full study period.

5. Conclusions

This placebo-controlled study showed that 12 wk of pollen extract in men diagnosed with inflammatory CP/CPPS (NIH category IIIA) resulted in a significantly higher symptom improvement compared to placebo and was well tolerated. This symptom improvement was mainly the result of a significant response in the pain symptomatology, which consequently led to a significant improvement in the total NIH-CPSI score and the *QoL* subdomain but not in the *micturition* subdomain. Pollen extract can therefore be recommended for patients with CP/CPPS in the dosage and duration studied.

Author contributions: Florian M.E. Wagenlehner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wagenlehner, Weidner.
Acquisition of data: Wagenlehner, Ludwig, Schneider, Weidner.
Analysis and interpretation of data: Wagenlehner, Schnitker, Brähler.
Drafting of the manuscript: Wagenlehner.
Critical revision of the manuscript for important intellectual content: Wagenlehner, Weidner.
Statistical analysis: Schnitker.
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Administrative, technical, or material support: Brähler.
Supervision: Weidner.
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Trial registration: ClinicalTrials.gov, unique protocol ID: 4015497. The following 34 urologic centres in Germany participated in this study: Ludwig, Giessen; Weidenfeld, Wiesbaden; Randow and Henkert, Berlin; Geiges, Berlin; Warnack, Hagenow; Walter, Wismar; Rüssel, Borken; Himstedt, Schwerin; Henschel, Herzogenaurach; Rüdiger, Freiburg; Mahdi, Ansbach; Lux, Bamberg; Neubauer, Göttingen; Schaub, Bocholt; Kliesch and Pühse, Münster; Bohnenkamp, Köln; Fehrmann-Kumpe, Greifswald; Kreutzig, Freiburg; Radlmaier and Braig, Roth; Köttgen, Köln; Gleißner, Wuppertal; Hantelmann and Kemper, Berlin-Zehlendorf; Ruckdeschel, Neufahrn; Kochs, Berlin; Wiener, Kerpen; Tack, Paderborn; Baumgraß, Kleinmachnow; Siegmann, Berlin; Herzig, Berlin; Rühlmann, Düren; Sachse, Saar; Rose, Leipzig; Schneider, Sinzig; Boness, Lübeck.

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Clinical evaluation of the effect of tamsulosin hydrochloride and cernitin pollen extract on urinary disturbance associated with benign prostatic hyperplasia in a multicentered study

Aoki A, Naito K, Hashimoto O, Yamaguchi M, Hara Y, Baba Y, Wada T, Joko K, Nagao K, Yamakawa G, Suyama K, Nagata K, Matsuyama H, Hirao H, Shimizu Y, Hironaka H, Isoyama R, Takemoto M, Tuchida M, Shiraishi K, Kato M, Kamiryo Y, Harada H, Otsuka T, Mitsui H, Nasu T, Hayashida S, Jojima K, Sacho T, Koshido Y, Harada N.

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We evaluated the clinical efficacy and safety of tamsulosin hydrochloride and cernitin pollen extract in 243 patients with urinary disturbance associated with benign prostatic hyperplasia. They were assigned randomly to 3 groups, oral tamsulosin hydrochloride, cernitin pollen extract and their combination were administered for 12 weeks. The international prostate symptom score, post-voided residual urine and uroflowmetrogram were obtained before and after treatment. The international prostate symptom score improved in each group and then the maximum flow rate and average flow rate also increased significantly in the tamsulosin hydrochloride-administered groups. In conclusion, the administration of only tamsulosin hydrochloride and the combination of tamsulosin hydrochloride and cernitin pollen extract seemed more effective then the administration of only cernitin pollen extract in the treatment of urinary disturbance associated with benign prostatic hyperplasia.

Publication Types:

- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

PMID: 12094707 [PubMed - indexed for MEDLINE]

PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Clinical evaluation of long-term treatment using Cernitin pollen extract in patients with benign prostatic hyperplasia

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Abstract

Seventy-nine patients with benign prostatic hyperplasia (BPH) were treated with cernitin pollen extract. Patient ages ranged from 62 to 89 years (mean, 68 years). Mean baseline prostatic volume was 33.2 cm^3. Cernitin pollen extract was administered in a dosage of 126 mg (2 tablets, 63 mg each), three times a day, for more than 12 weeks. Symptom scores, based on a modified Boyarsky scoring scale, uroflowmetry, prostatic volume, residual urine volume, and urinalysis results were examined before and after administration of cernitin pollen extract. Symptom scores significantly decreased from baseline, and the favorable results continued during the treatment period. Urine maximum flow rate and average flow rate increased significantly from 9.3 mL/s to 11 mL/s and from 5.1 mL/s to 6 mL/s, respectively. Residual urine volume decreased significantly from 54.2 mL to less than 30 mL. There was no change in prostatic volume. However, 28 patients treated for more than 1 year showed a mean decrease of prostatic volume to 26.5 cm^3. No adverse reactions were observed. Clinical efficacy at 12 weeks was rated excellent, good, satisfactory, and poor in 11%, 39%, 35%, and 15% of patients, respectively. Overall clinical efficacy was 85%. In conclusion, cernitin pollen extract showed a mild beneficial effect on prostatic volume and urination variables in patients with symptomatic BPH.

Introduction

Because cernitin pollen extract has anti-inflammatory and anticongestive effects,[1] it is useful for the treatment of nonbacterial prostatitis and prostatodynia. Recent studies have demonstrated that cernitin pollen extract improved detrusor activity and decreased resistance of the prostatic urethra.[2,3] It therefore provides better efficacy in urination. It has also been reported to suppress prostatic cell growth.[4,5] For these reasons, cernitin pollen extract is thought to be useful in the treatment of patients with dysuria due to benign prostatic hyperplasia (BPH).

We report here the efficacy of cernitin pollen extract in patients with BPH

Patients and methods

Seventy-nine patients with mild or moderate symptomatic BPH, who did not require prostatectomy, were selected for this study. Patients provided informed consent to participating in the study. Ages ranged from 62 to 89 years (mean, 68 years). For the evaluation of BPH, serum prostatic specific antigen, digital examination, transrectal ultrasonography, roentgenographic examination was performed. No abnormal findings in any patient were recorded.

Subjective assessment was based on a modified Boyarsky scoring scale[7] for the symptoms of urgency and discomfort, dysuria, nocturia, incomplete emptying, prolonged voiding, delaying voiding, intermittency, and postvoid dribbling, with a score of 0 (normal) to 3 (severe) for each of these symptoms. The average baseline symptom score was 9.6. Sixty-six percent of the patients urinated more than three times during the night. Maximum flow rate, average flow rate, residual urine volume at

baseline were 9.3 ± 5.0 mL/s, 5.1 ± 2.7 mL/s, and 54.2 ± 78.8 mL, respectively. Mean prostatic volume was 33.2 cm^3 on transrectal ultrasonography.

Cernitin pollen extract was administered orally in a dosage of 126 mg (2 tablets, 63 mg each), three times a day, for more than 12 weeks. For subjective and objective assessments, symptom score, uroflowmetry, prostatic volume, residual urine volume, and urinalysis results were examined before treatment. Blood pressure and laboratory values were recorded every 3 months. Clinical efficacy, based on symptoms and objective signs, was assessed as excellent, good, satisfactory, and poor.

Values of measured variables are given as mean ± SD. For statistical analysis, the chi-square test and paired *t* test were used. A *P* value of <0.05 was considered statistically significant.

Results

Mean improvement of subjective symptoms, irritative symptoms, and obstructive symptoms, compared with baseline, and are shown in Figure 1 for short-term treatment. Urgency or discomfort improved by 76.9 %; dysuria, by 71.45 %; nocturia, by 56.8 %; incomplete emptying, by 66.2 %; prolonged voiding, by 64.1 %; delayed voiding, by 62.2 %; intermittency, by 60.6 %; and postvoid dribbling, by 42.7 %. Figure 2 shows change of symptom score during treatment. Average symptom score decreased significantly from 9.6 to 6.0 after the first 4 weeks of treatment and decreased continually to 5.4 during the following 8 weeksResults of the objective assessment are shown in Figure 2; maximum flow rate and average flow rate increased significantly from 9.3 mL/s and 5.1 mL/s to 11 mL/s and 6 mL/s, respectively, after the first 12 weeks of treatment. Residual urine volume decreased from 54.2 mL to less than 30 mL. However, no changes in prostatic volume and urine volume were observed. In short-term follow-up, 11 % of patients had excellent results; 39 %, good; 35 %, satisfactory; and 15 %, poor. Overall clinical efficacy was 85 %. No adverse reactions, such as impotence or hypotension, and no abnormal laboratory findings were observed.

During long term follow-up, 28 patients who had good results after short-term treatment continued treatment with cernitin pollen extract for more than 1 year. A significant decrease in prostatic volume to 26.5 cm^3, a significant increase in maximum flow rate, and a significant decrease in symptom score and residual urine volume were observed (Figure 2). During the long term treatment, no abnormal hematologic or biochemical findings were observed.

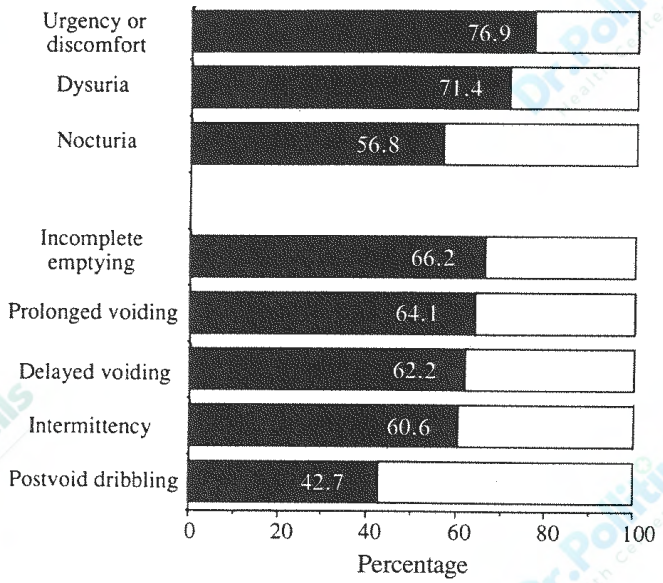

Figure 1. Mean improvement of subjective symptoms (%) of benign prostatic hyperplasia in 79 patients after 12 weeks of treatment with cernitin pollen extract.

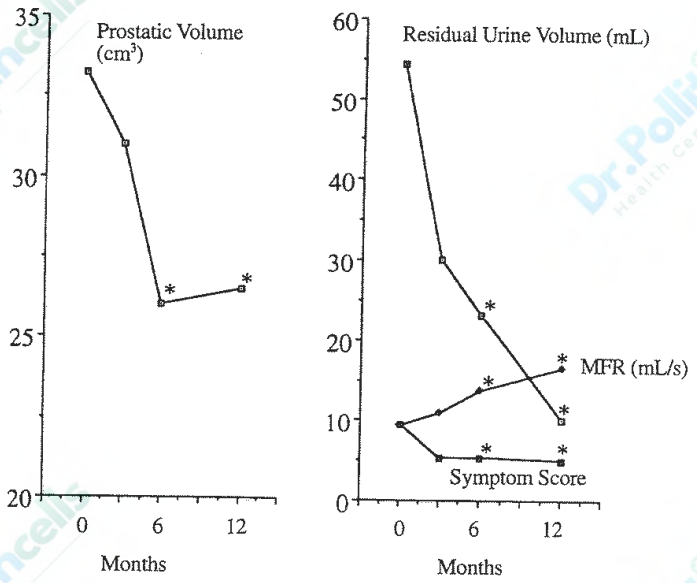

Figure 2. Change of symptom score and objective variables in patients with benign prostatic hyperplasia during treatment with cernitin pollen extract. A significant increase in flow rate and decrease in residual urine volume were noted in short-term follow-up (12 weeks, 79 patients), and a significant decrease in prostatic volume was also observed in long-term treatment (1 year, 28 patients). MFR = maximum flow rate. *$P < 0.05$ versus baseline.

Discussion and Conclusion

Transurethral resection of the prostate (TURP) is considered the gold standard for the treatment of BPH. Mortality and morbidity of TURP and quality of life of patients after TURP were studied in 1988,[8] and the results were not good. In one place of TURP, many modalities for the treatment of BPH (eg, hyperthermia or thermotherapy, urethral stent, urethral balloon dilation, and laser prostatectomy) have been developed and performed throughout the world.[9-11] However, the long-term results of these new modalities are controversial.

New medications,[12-14] such as antiandrogen drugs, alpha$_1$- blockade, and 5α-reductase inhibitors, have also been developed and used for treatment of patients with BPH. These drugs have excellent efficacy, but a few adverse reactions, including impotence[12] and hypotension,[13] have been reported.

Since 1970, many investigations on cernitin pollen extract have been done. As a result, it is well known that this extract improves detrusor activity, decreases resistance of the prostatic urethra, and suppresses prostatic cell growth[2-5] and thus has been used for the treatment of BPH patients. Buck and others[6] reported that cernitin pollen extract produced statistically significant improvement of 69 % in subjective symptoms compared with an improvement of 30 % with placebo. A significant decrease in residual urine volume and in the anterior-posterior diameter of the prostate was observed in patients treated with this drug. Our short-term results were satisfactory in 85 % of 79 patients with BPH, and long-term treatment reduced prostatic volume in 28 patients who continued treatment with Cernitin pollen extract. Compared with chlormadinone acetate,[12] prazosin,[13] and finasteride,[14] cernitin pollen extract has a slightly lower clinical efficacy. However, the advantage of cernitin pollen extract is the rare occurrence of side effects during long-term use.

Based on our results, we conclude that cernitin pollen extract has beneficial effects, especially a decrease in prostatic volume and an improvement in urination, in patients with symptomatic BPH.

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A preliminary investigation on the therapeutic effect of Cernilton in chronic prostatovesiculitis

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INTRODUCTION

It has been known for many years that chronic prostatovesiculitis is a very common disease. The highest incidence of cases reported in the literature on the subject is provided by Wiseman (1931). He accounted for 200 male patients selected at random, the majority of whom having sought medical advice on the grounds of extraurogenital symptoms. 54% percent of these cases were found to exhibit clinical signs of chronic prostatovesiculitis. Pelouze (1939) reported an incidence of 30-40% of all males over the age of 40 years, and Gartman (1960) gives a figure in excess of 40% in a material of 919 apparently healthy males aged between 17-40 years (routine military examination). Although Farman and McDonald (1961) do not state any incidence figures, they agree with Pelouze that this disease is probably the most prevalent chronic infection in men over 40 years of age.

The symptomatology of chronic prostatovesiculitis is extremely vague and, from his material, Gartman was able to record no less than 178 different symptoms (sic!). Because of the great variety of symptoms, and despite the fact that the symptoms occurring most frequently only constitute a fraction of the total number, diagnosis is seldom confirmed at an early stage. This delay leads both to a marked resistance to therapy and to a marked recidivism, two notable characteristics of the disease. The combination of these two characteristics often causes deviations from the normal in the psyche of the patients who may, for instance, become fixed in a sexual impotency that might otherwise have disappeared after a short time.

In spite of the fact that chronic prostatovesiculitis has been a well-known syndrome for so long therapeutic advances in this field have been negligible. Chemotherapeutics and antibiotics are of some value in the acute stage or during exacerbation periods, but they are worthless in the chronic course. The conservative treatment still consists of stripping and expulsions at regular intervals. The experienced urologist first handles the patient by stripping (to empty the gland and to diagnose the secretion) and follows up with massage (to eliminate adhesions and to stimulate the blood flow). Treatment given by an inexperienced person will, for the most part, only lead to negative results, and the patient will become disinclined to complete the treatment. This was illustrated by some American statistics which showed that only one-half of the patients persisted whereas the remaining number oscillated between different physicians only to find that the treatment recommended was practically identical and without any significant modification. In many cases, they gave up trying and only returned to the doctor when various sequalae became apparent (pelveospondylitis, uropolyarthritis, or sacral rhizopathy).

Cernilton was first mentioned as a possible therapeutic agent in chronic prostatovesiculitis in 1959 when Dr. Ask-Upmark, Sweden, published a short report on a typical case. The disease was so persistent that not even an antibiotic dose as large as 150 g chloromycin, administered over a two-month period, could prevent a relapse. The patient then began to take Cernilton on his own initiative. At that stage, the patient had been suffering from the disease for 5 years with practically continuous distress. He became symptom-free very rapidly and remained so, the last report being noted two years later. The only occasion upon which he experienced any distress during these two years was during a two-week trip when he did not have

access to the tablets. Owing to the rebellious nature of his particular case, the result naturally attracted attention. Later, Jönsson (1961) reported 10 cases who had received Cernilton for more than a year. As a result of his observations, Jönsson held the opinion that continued experimental therapy was motivated and emphasized the very great advantages which could be derived from a test series employing placebo tablets.

A preliminary Investigation

This investigation was based on a material consisting of 179 cases of chronic prostatovesiculitis selected from open urological praxis. The minimum observation period following the introduction of Cernilton was 4 months (14%) and the maximum period was 23 months (1 case). The mean observation period was 10 months. The entire investigation period dated from Dec. 1, 1959 to Oct. 31, 1961. Cases which had been under observation for less than 4 months by the terminal date, and those who came under observation afterwards, will be reported in a later article planned to cover a 3-year period and approximately 500 cases.

CERNILTON

The preparation was placed at the disposal of the author by the manufacturers, AB Cernelle, Vegeholm, Sweden. The raw material consists of an extraction taken from a given admixture of four types of pollen. The extraction is autolyzed and microbially digested before being spray dried. The purpose of this digestion is to break down any allergens which might be present. When the preparation is ready for use, it does not contain any precipitable protein and it is rich in certain B-vitamins. Tests have also been performed in order to determine whether the steroids present in the preparation contain the therapeutically active component. However, no results are available at the time of writing.

Patient material

The 179 cases were selected from about 400 cases available at the time in question. 80 cases were eliminated from the total when it was found that the placebo tablets given initially differed from the real Cernilton tablets both in colour and consistancy. Other cases were eliminated because they had undergone surgery or some other manipulation (apart from panendoscopes for diagnostic purposes), and, further, all cases suffering from serious diseases outside the urogenital tract. Cernilton treatment was not employed in cases of ascertained or suspected malignant degeneration of the gland although the material does include a few cases exhibiting a concurrent, but negligible, benign enlargement of the gland which, however, in no way affected the actual infection.

The age distribution of the material is given in Fig. 1. It should be noted that prostatovesiculitis can occur at any age; there are references in literature to new-born infants with the disease (Mann, Giannastasio).

Fig. 2 provides information concerning the duration of distress prior to the introduction of the therapy.

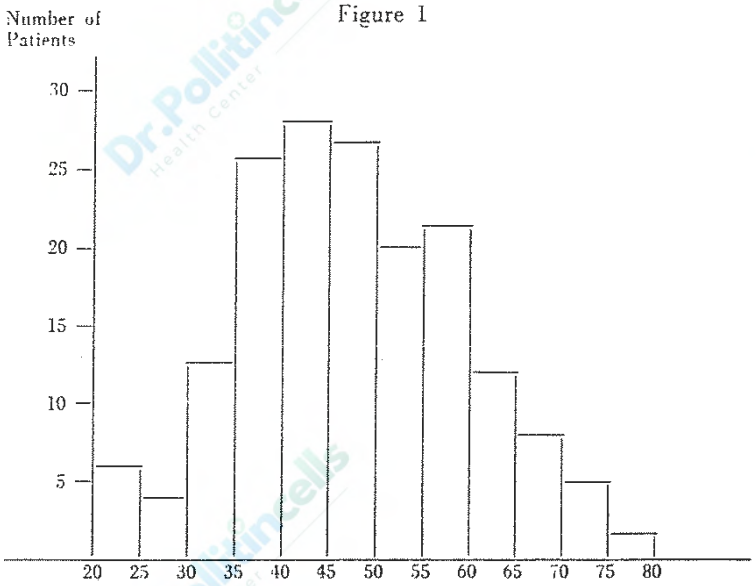
The patient material was not sufficiently large to permit the same age distribution in the different groups.

Method

The investigation was planned partly as a double-blind test and the material was divided into two groups for the treatment.

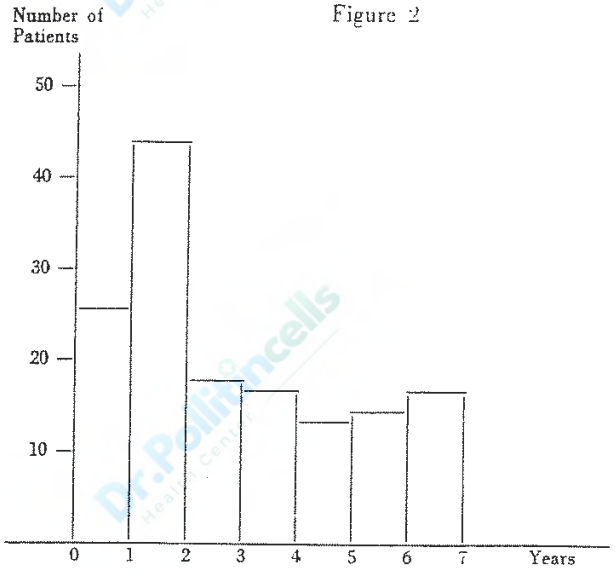
A. In this group, comprising 65% of the cases, the patients were supplied with Cernilton on prescription (druggist's Cernilton). The physician in charge was therefore fully aware of the nature of the preparations.

Figure 1



Age distribution of the patient material.

Figure 2



Duration of symptoms prior to combined Cernilton + conservative therapy.

B. In this group, comprising 35% of the cases, the patients received either placebo or the real tablets (code Cernilton). The physician in charge did not have access to the code and was therefore unaware of the nature of the preparation. The code number was noted in the journal and the results assessed objectively. This procedure made it possible to determine whether the physician exerted any influence over the patients (psychic supportation) when he knew the true composition of the tablets. Once the aforementioned eliminations had been made and the selection of patients completed, the tablets used all had exactly the same shape, size, smell, taste, and appearance.

All the patients underwent a complete urological examination including urography, urethrocystrography and, when necessary, panendoscopy. In connection with these examinations, the patients were given

chemotherapy for a few days but otherwise during the course of the treatment, both chemotherapeutics and antibiotics were to all intents and purposes banned.

Ataractics were administered when the patient exhibited an obvious psychogenic state. When impotence persisted even after the secretion had become normalized, hormone treatment was introduced (i.m. injections of hormone derivatives).

The conservative treatment — in 2/3rds of the cases in combination with druggist's Cernilton and in 1/3rd with code Cernilton —consisted of expulsion and subsequent massage performed initially once a week to once in 10 days. Concurrent to the normalizing of the secretion and to the reduction of the secretionary stasis in the gland, the interval between expulsions was extended to 2—3 up to 4 weeks, and even longer in some cases.

The dosage of both druggist's and code Cernilton was the same: 4 tablets each morning swallowed whole or chewed as preferred. More recently, a double dose has been given during the first 2—3 weeks, the patient being supplied with 4 tablets in the morning and another 4 at lunchtime.

Evaluation

Although the symptomatology of chronic prostatovesiculitis is very heterogeneous, the object of the therapy is quite definite: to achieve, as quickly and as effectively as possible, improved drainage of the gland and, simultaneously, to eliminate the prevailing stasis of the secretion which contains greater or lesser quantities of pus. When evaluating the results, two clinical findings have been most intensely investigated: the appearance of the secretion and urethrocystoscopy and microscopy, and the content of the prostate gland and the vesicles on rectal palpation. When an infection is in progress, the prostate and the vesicles have a doughy consistancy, they are tender when palpated and they contain a more or less pus-filled secretion. When therapy is successful, evacuation is improved and, consequently, the secretionary stasis is eliminated. This can be easily confirmed by palpation. Concurrently, the secretion reverts to normal and this too is easily confirmed by direct microscopy. A secretion containing a count of more than 10 white blood cells per field (enlargement x 240 diameters) is obviously pathological but even a secretion containing 4—6 cells per field should be considered pathological if these white blood cells form aggregations. A secretion is considered normal when the number of white blood cells does not exceed 6 and occur individually. A healed gland has a tough, indurated consistancy, is no longer tender when palpated and does not retain any secretion.

The therapy results were assessed as being positive when there was no more than one exacerbation in the course of six months and two exacerbation periods during a time of one year or longer. Most of these mild relapses were due to the fault of the patient who, since he became symptom-free at relatively early stage, became nonchalant in following up his treatment. However, these relapses were generally harmless and could be coped without difficulty. A temporary doubling of the Cernilton dose brought about a rapid improvement.

Results and Discussion

One the basis of the above, the results were assessed for three groups:

a) Tablet composition known to the physician in charge (Fig.3 (K)).
Total: 118 cases.

B) Real Cernilton tablets in the code group (Fig. 3 (R)).

C) Placebos (Fig. 3 (P)).
Total B) + C): 61 cases.

Figure 3

Cernilton effect on prostatovesiculitis.

Changes in stasis and secretion in per cent of patients in each group.

St = Stasis
Se = Secretion

It can be seen from Fig. 3 that the effect of the tablets in the K and R groups is practically identical. The number of symptom-free or considerably improved patients is about 90%. This also serves to show that the personal influence of the doctor is negligible and can be discounted entirely in the final results.

The improvement shown by the patients in the placebo group (P) is about 50%. Since the total material received absolutely uniform conservative treatment, the results of this preliminary investigation can be expressed as follows:

The results of the combination of conservative and Cernilton therapy were 60-30% better than those achieved with conservative treatment alone.

Taking into account the marked resistance of the disease to earlier therapeutic measures, its frequency, and, not least, the complications occurring later and leading to a high degree of invalidity if left untreated, this therapeutic result must be acknowledged with satisfaction.

It can further be seen from the figures that the pus content of the secretion and the secretionary stasis run a parallel course during changes in the state of the disease. The occurrence of a pus-containing secretion when the gland is indurated and free from secretion is highly exceptional. Apart from the two main symptoms mentioned, attention has been paid to only one other of the numerous symptoms reported, namely the sacral rhizopathies described by Bohm, Franksson and Peterson (1956). The author of the present paper felt this to be motivated since the connection between chronic prostatovesiculitis and sacral rhizopathy has not been elucidated and further, as the patient can nearly always give a clear picture of the area of pain, diagnosis of this particular syndrome is not difficult. However, so far the results of Cernilton therapy have not provided any statistically significant values in any direction.

A number of other observations have been made concerning miction frequency, elimination of residual urine, etc., but these symptoms have not been dealt with statistically.

Cernilton appears to have an antiphlogistic effect. The results obtained also indicate that the preparation improves or facilitates the drainage of the gland. The active component(s) of the substance has not been

isolated. A new and thorough double blind test with synthetic tablets containing exactly the same composition of vitamins and amino acids as Cernilton and with real Cernilton tablets will be commenced very shortly. Further, a test series is planned involving the use of only pollen steroids for the purpose of isolating and defining the active therapeutic component.

Complications

Cernilton treatment has not given rise to any serious complications. One case developed an obvious gynecomastia after two months of treatment. During this time, his prostatovesiculitis had improved considerably and the preparation could be discontinued, and he subsequently received only conservative therapy. The gynecomastia disappeared shortly afterwards. One other patient complained of a swelling sensation in the mammae although no changes in glandular substance could be confirmed. This symptom also disappeared rapidly when Cernilton was withdrawn. There were no other cases of similar side effects and it is obviously impossible to form any opinion of the hormonal effect on the basis of these two solitary cases (out of a material which, to date, consists of more than 500 cases).

A number of patients exhibiting clearly allergic reactions have been treated. The therapy has not caused any exacerbation although in a couple of cases it was found necessary to reduce the dose because of intestinal symptoms arising during therapy. As similar intestinal symptoms also occurred in a few isolated non-allergic patients, these symptoms can hardly be registered as allergic. Helander has, in fact, stated that the substance does not cause any allergic reactions when administered orally. However, in two cases included in a section of the primary material not included here, treatment had to be discontinued owing to nausea and pruritis. As soon as the drug was eliminated, the symptoms disappeared. When the substance is to be administered to patients who are highly allergic, the author suggests commencing the treatment with a small dose (e.g. 1 tablet each morning and, if not distress is experienced, gradually increasing to normal dose). In summarizing the complications, it can be stated without reservation that side effects were negligible and without any practical importance to the results as a whole.

Summary

A preliminary report is given of a current investigation on the effect of Cernilton in the treatment of chronic prostatovesiculitis. The investigation indicates the conservative treatment in combination with Cernilton gives results which are 60—80% better than those obtained with conservative treatment alone.

The author wishes to express this thanks to Dr. H. Palmstierna for his extremely valuable assistance in planning the investigation and in treating the results.

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A study on the effect of digested Pollen Extract* on the frequency of spontaneous lung infections in Rats

Introduction:

In a study carried out at the Norwegian Institute of Work Science, Department of Occupational Health, it was found that addition of a specially digested pollen extract to the food of rats, was preferred, when the test animals were given free choice between three different food mixtures. All of these food mixtures presumably being fully satisfactory combinations of necessary nutritious elements (protein, carbohydrates and fat, vitamins, minerals and trace elements) (1).

There was no change in the original three mixtures during the experimental except for the addition of 1% of Cernilton to one of the food mixtures. It is well-established that rats (as also many other animals) have a pronounced ability to choose a food mixture containing substances, which may prove necessary to them (2, 3). We found those results interesting and they gave a rational basis for further studies as to a possible effect of pollen extract in the form of Cernilton. If being a general roborating substance, it might be possible to explain at least to some degree the results reported on the good results obtained by giving Cernilton tablets to patients with chronic prostatitis and also to patients with infectious diseases e.g. in the upper respiratory tract.

Macroscopic pathological-anatomical lung infections.

In the same report there was by the macroscopical pathological-anatomical examination observed a marked difference as to the frequency of infected lungs in the control animals compared with those which had been given Cernilton in their food. An English edition of the above mentioned report were published in an almost identical form as the first mentioned report in Norwegian (4). Here the author is concluding: “in the tests carried out using self-selection cages, a tendency was detected, which might be interpreted to mean that the Cernitin diet may contain one or more substances that are useful to the living organism, although it is not possible to offer any explanation for the action mechanism of such an assumed effect”.

As to the pathological findings on autopsy of the lungs they were concentrated on the difference in the frequency of findings of gross macroscopical-pathological changes between the two groups: Controls and Cernilton-treated rats.

The following definitions were given as “marked pathological findings” (5):

a) Definite enlargement of the lungs with slow and uncomplete retraction. Muco-purulent excrete from the trachea either spontaneously or by slight pressure on the lung for further examination.

b) Distinct palpable nodules which by section contained large amounts of purulent secret, “infected bronchiectasis”.

c) Well-defined dark red or greyish-red atelectasis which by section contained purulent secretion.

These findings which according to many authors who have studied the lung pathology in rats (5, 6, 7, 8) are remarkably common, and they are of

decesive importance when using rats for studying experimentally, affections in their lungs.

Pathological-anatomical changes of the kind mentioned are very frequent when rats reach an age of 18-24 months or more. Mostly one will find such lung pathological changes in 50-75 percent when carefully examining the lungs by autopsy, even though these rats very seldom show obvious clinical symptoms or signs of advanced lung infection before being killed and subjected to autopsy.

By carefully standardizing of all controllable factors, the author has succeeded in keeping the number of such changes at a level at about 10 - 20 percent, when using rats in lung experiments. This has partly been obtained by using antibiotic treatment (given intraperitoneally once a week during the observation period).

In this first experiment the autopsy was carried out as a rutine and there had been no original intention to study especially the lung changes. The four groups of animals used in functional tests, studying the possible influence of Cernitin on spontaneous motoric activity were kept on the diet on 1% Cernilton for a total period of 6-7 months. In this Cernilton-treated group only one animal out of 12 (6 males and 6 females) showed a macroscopic lung change as defined above. In the control group one rat died before end of the experiment, nothing definite was mentioned by the physician, carrying out the routine autopsy, which thus did not indicate lung infection. Of the remainder 11 (5 males and 6 females) there was altogether 6 with macroscopical-pathological lung changes of the kind described above. Because of the often varying findings as to lung infections and the small number of animals in these tests, the author stated: “In the opinion of the author, it is not possible to present any definite conclusions on the basis of the above. These findings may possibly indicate a certain effect, but if a comparison is made with the often widely varying results obtained from otherwise untreated control animals in the same age group as the animals discussed above the results do not permit any definite conclusions to be drawn even though they may be interesting per se and can be considered to motivate continued investigations on the lines proposed here”.

In the above mentioned experiment the difference as to macroscopic lung infections between the control group and the Cernilton-treated group may be calculated statistically (Table 1).

Table 1

Effect on pathological lung changes in preliminary tests with 1 percent Cernilton in the food.

Treatment	Total Number of animals	No. of rats with macr. pathol. anat. lung changes		S.E. of the percentage
		No.	Percent	
Standard food without Cernitin	12	6	50	15.1
Standard food with Cernitin	12	1	8.3	8.2

Difference between Cernilton-treated and standard food-treated animals in percent:

41.3 ± 17.2
T = 2.42
0.05 > P > 0.0

This indicated a statistically, probable significance that the results might not have arisen by chance. If everything being equal except for the addition of Cernilton to the food, there is presumed to be less than 5 percent but more than 2 percent probability for an accidental result of this kind. Nevertheless the small number of animals and the somewhat lower frequency in the treated group than usual and, more important, the higher frequency in the control group, kept on our standard food, convinced the author that it was impossible to draw any other conclusions from these experiments than what was stated above.

Experimental conditions.

As a consequence of this first experiment it was therefore carried out two supplementary experiments, one during the winter 1968-69, and one during the winter 1969-70. These experiments were carried out in another animal stable, where the basic conditions were not so good and carefully controlled as in the animal stable in the first experiment. The first mentioned experiments were carried out where the functional tests took place. This makes it of primary importance to keep all controllable conditions as optimal and constant as possible.

The author holds the view that it might be of interest to find out whether the difference (if it should occur again) would be more or less pronounced when the conditions in the stable as draught, temperature, humidity, quality and care of cages etc. was not kept at the same optimal level as in the first experiment.

Two test series comprising originally altogether 40 animals in each group were carried out. Before starting the differentiation in food-supply (at about 4-5 months of age) there died two animals in the intended control-group and one in the intended Cernitin-group.

Cernitin (given as Cernilton) was added to the food in an amount of one percent. The experiment was started as mentioned above some time after dividing animals comparing each other as to sex and weight and as mentioned above at an age of 4-5 months and it was continued for 6 months.

Results:

During the 6 months of experiment there died 3 animals, all after more than three and a half months: one in the Cernitin-treated group and two in the control group. By autopsy of these rats that was marked lung infections in the one animal belonging to the Cernitin-treated group. One of them dying spontaneously in the control group had a big tumor, in the control group had distinct pathological infections in the lungs.

At the end of the experiment a careful macroscopical pathological-anatomical examination was carried out of all remaining animals, making at that time 38 rats in the Cernitin-treated group and 36 rats in the control group. All rats were of course presented with blind numbers to the examiner (the author). By this autopsy there was found 13 animals with lung changes of the kind defined above in the Cernitin-group, and 21 in the control group.

This may seem to indicate a probable statistical significance in favor of the group being given Cernilton-containing food compared with the standard food mixture. It may, however, be more conclusive when taking into consideration also the animals dying during the latter part of the experiment.

Table 2

Frequency of macroscopical pathological-anatomical lung infections at autopsy at the end of the experiment in Cernitin-treated and control rats.

Treatment	Number of rats at onset	Died spontaneously during experiment	Number of rats at end of experiment	Macr. pathol. anat. lung infections		
				No.	Percent	S.E.
Standard food	38	2	36	21	58.3	± 8.19
Standard food with Cernilton	39	1	38	13	34.2	± 7.91

Difference between controls and Cernitin-treated animals in percent:

23.9 ± 11.39
T = 2.098
0.05 P 0.02

Table 3

Frequency of pathological-anatomical lung infections in animals drying after more than three and a half months (14 weeks) of the experiments or at the autopsy at the end of the experiments (6 months).

Treatment	Number of animals at onset of experiment	Total number of rats with macr. pathol. anat. lung infections		
		No.	Percent	S.E.
Standard food	38	22	57.9	± 7.69
Standard food with Cernitin	39	14	35.9	± 8.01

Difference between controls and Cernitin-treated animals in percent:

22 ± 11.10
T = 1.982
P < 0.05

When making these animals into consideration there is hardly a 5 percent significance any longer.

Comments:

The results of these experiments may be of interest when compared with the first one (Table 1). The less pronounced favourable results in the last studied groups (Table 2 and 3) may indicate that an eventual effect of Cernilton, which most probably may be due to a general roborating effect of the preparation, are unable to prevent the deleterious effect of less satisfactory conditions. This seems according to the author's opinion to strengthen the view that there may possibly be a positive effect because of a general roborating influence e.g. due to the supply of a balanced combination of trace elements, vitamins, and a small amount of essential amino acids which may in itself give the type of effect which we in lack of a more precise expression are mentioning: general roborating effect. That there also is a certain streptolysin inhibitory effect of a hitherto not definitely defined substance in Cernitin is proved (9. 10) but whether this factor has any well-defined effect as to infections in the respiratory tract in rats is yet an open question.

Comparing the results obtained on the frequency of spontaneous lung infections in rats by adding Cernilton to the food, with observation reported as to the positive effect of Cernilton on infectious diseases in man, it also seems to suggest the view that the general roborating effect is the most probable explanation of a positive effect. The effect on chronic prostatitis (11, 12, 13, 14, 15, 16, 17, 18) and on infections in the upper respiratory tract (19, 20, 21, 22).

The statistical evaluation of the results seems to indicate a tendency in the direction that there may be a beneficial effect of Cernilton in these cases of infectious diseases, but the effect is seldom so pronounced that they are given a satisfactory statistical result by evaluation. This of course may be due to the mostly very small groups examined, but it may also be explained because of the very difficult deferential diagnostic problems in many of these infectious diseases.

It seems to the author that the general roborating effect yields a rational explanation for presuming an effect in cases where either the amount of or the balance between the substance which is unsatisfactory in the daily diet. In acute cases or cases where antibiotic—or chemotherapeutic treatment may be indicated, Cernilton is by no means an alternative and may be contraindicated when running the danger that it may be used not as a complement but as a substitute to well-defined indication for antibiotic and chemotherapeutic treatment. The effect of Cernilton may be to support the natural resources of the organism to counteract infections. This will mostly be actual for longterm treatment or as prophylaxis against exacerbations e.g. in chronic prostatitis or as prophylactic agent in very frequently recidiving infections in the upper respiratory tract.

Oslo, 21st January, 1971

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Jon Glømme, M.D.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Clinical evaluation of Cernilton on benign prostatic hypertrophy – a multiple center double-blind study with Paraprost

Maekawa M, Kishimoto T, Yasumoto R, Wada S, Harada T, Ohara T, Okajima E, Hirao Y, Ohzono S, Shimada K, et al

A multiple center double blind study was performed to study the effectiveness of Cernilton (CN) on benign prostatic hypertrophy in comparison to Paraprost (PP). Among a total of 192 patients, overall effect was studied on 159 patients, overall safety rate on 178 patients and rate of effectiveness on 159 patients. There were no differences between the two groups in the selected patients, criteria for exclusion and drop out cases or background data of the patients. Impression of patients and overall effect by committee and physician judgment were slightly higher in the CN group compared to the PP group, but there was no significant difference between the two groups.

For the improvement in subjective symptoms, the rate of moderate improvement or more after 4 weeks by committee judgment was higher in the CN group compared to the PP group. The rate of improvement in protracted miction, which is an effective marker of urinary disturbance, was also higher in the CN group compared to the PP group. An analysis of objective symptoms showed a significant improvement in residual urinary volume, average flow rate, maximum flow rate and prostatic weight in the CN group. A significant improvement in the phased change of residual urinary volume was also seen in the CN group. No side effects or abnormalities in clinical test levels were noted in the CN group. By committee judgment, the rate of more than moderate effectiveness was 49.1% in the CN group compared to 41.2% in the PP group, but there was no significant difference between the two groups.

By physician's judgment, the rate of more than moderate effectiveness was 49.4% in the CN group compared to 46.3% in the PP group, but there was also no significant difference between the two groups. These results suggested that Cernilton was an effective drug for benign prostatic hypertrophy.

Publication Types:

- Clinical Trial
- Controlled clinical trial
- Multicenter Study

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A systematic review of Cernilton for the treatment of benign prostatic hyperplasia

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Objective To systematically review the evidence for the clinical effects and safety of the rye-grass pollen extract (Cernilton) in men with symptomatic benign prostatic hyperplasia (BPH).

Methods Trials were identified by searching Medline, specialized databases (EMBASE, Cochrane Library, Phytodok), bibliographies, and contacting relevant trialists and manufacturers. Randomized or controlled clinical trials were included if: men with symptomatic BPH were treated with Cernilton; a control group received either placebo or pharmacological therapy; the treatment duration was ≥ 30 days; and clinical outcomes were reported.

Results In all, 444 men were enrolled in two placebo controlled and two comparative trials lasting 12- 24 weeks. Three studies used a double-blind method although the concealment of treatment allocation was unclear in all. Cernilton improved 'self-rated urinary symptoms' (the proportion reporting satisfactory or improving symptoms) vs placebo and another plant product, Tadenan. The weighted mean (95% confidence interval) risk ratio (RR) for self-rated improvement vs placebo was 2.40 (1.21-4.75) and the weighted RR vs Tadenan was 1.42 (1.21-4.75). Cernilton reduced nocturia compared with placebo or Paraprost (a mixture of amino acids); against placebo, the weighted RR was 2.05 (1.41-3.00), and against Paraprost the weighted mean difference for nocturia was -0.40 times per evening (-0.73 to 0.07). Cernilton did not improve urinary flow rates, residual volume or prostate size compared with placebo or the comparative study agents. Adverse events were rare and mild; the withdrawal rate for Cernilton was 4.8%, compared with 2.7% for placebo and 5.2% for Paraprost.

Conclusions The Cernilton trials analyzed were limited by their short duration, limited number of enrolees, omissions in reported outcomes, and the unknown quality of the preparations used. The comparative trials had no confirmed active control. The available evidence suggests that Cernilton is well tolerated and modestly improves overall urological symptoms, including nocturia. Additional randomized placebo and active-controlled trials are needed to evaluate the long-term clinical effectiveness and safety of Cernilton.

Key words: Cernilton, plant extracts, benign prostatic hyperplasia, BPH, efficacy

Introduction

The LUTS associated with BPH are common in ageing adult men [1]; in the USA, population studies show that the frequency of moderate to severe LUTS is 8-31% among men in their fifth decade and up to 44% among men in their seventh decade [2]. The cost of managing BPH is >$4 billion per year [3]. The primary aim of treatment in the vast majority of men is to relieve these bothersome obstructive and irritative symptoms.

Treatment options for symptomatic BPH include lifestyle change, medical, device or surgical therapy [4]. Phytotherapy, i.e. the use of plant extracts, is becoming widely used to manage BPH [5]; the use of phytotherapeutic agents is common in Europe and increasing in the Western hemisphere. In Germany, phytotherapy is the primary treatment for mild to moderate urinary obstructive symptoms and represents >90% of all drugs prescribed for treatment of BPH [6]. Phytotherapeutic agents are readily available in the USA as nonprescription dietary supplements and often recommended in 'natural health-food' stores or books for the self treatment of BPH symptoms [7].

Cernilton, prepared from the rye-grass pollen *Secale cereal*, is one of several phytotherapeutic agents available for the treatment of BPH. It is used by millions of men worldwide and is a registered pharmaceutical product throughout Western Europe, Japan, Korea and Argentina (data from the manufacturer, AB Cernelle, Engelholm, Sweden, 1999). In the USA, Cernilton is used as a nutritional supplement by ≈5000 men (D. Ruyan, Cernitin American, personal communication). One dose of Cernilton contains 60 mg of Cernitin T60, a water-soluble pollen extract fraction, and 3 mg of Cernitin GBX, an acetone-soluble pollen extract fraction (Cernelle AB). The acetone-soluble fraction contains β-sterols [8]. Several *in vitro* studies undertaken to investigate the mechanism of action suggest that Cernilton has antiandrogenic effects [9], may relax urethral smooth muscle tone and increase bladder muscle contraction [10], or may act on the a-adrenergic receptors and relax the internal and external sphincter muscles [11].

Despite many studies showing *in vitro* activity [9-11], the clinical effectiveness of Cernilton for the treatment of LUTS remains unclear. The objective of the present study was to systematically review the existing evidence for the clinical effectiveness and safety of Cernilton. Specifically, we assessed whether
Cernilton is more effective than placebo or as effective as other pharmacological therapies in improving the obstructive and irritative urinary symptoms associated with BPH.

Methods

Inclusion criteria and the identification of relevant trials

Randomized (RCTs) or controlled clinical trials (CCTs) were included if men had symptomatic BPH; the treatment intervention was Cernilton (Cernitin) or a preparation of *Secale cereale*; a control group received either placebo or pharmacological therapy for BPH; and the treatment duration was ≥30 days.

Medline (from 1966 to November 1998) was searched using a combination of the optimally sensitive search strategy for trials from the Cochrane Collaboration with the medical subject headings 'prostatic hyperplasia', 'phytosterols', 'plant extracts', 'pollen', 'sitosterols', *Secale cereale*, 'Cernilton.tw', and 'Cernitin.tw' including all subheadings [12]. EMBASE was searched from 1974 to 1997 (performed in July 1997) in a similar approach to the one used for Medline. The private database Phytodok (Munich, Germany) and the Cochrane Library, including the database of the Cochrane Prostate Group and the Cochrane Field for Complementary Medicine, were also searched similarly. The reference lists of all trials found were searched for additional trials. We attempted to solicit trialists identified, asking them to identify any further published or unpublished trials; there were no language restrictions.

Data extraction and study appraisal

Study characteristics, demographic information, enrolment criteria and outcomes were extracted independently by two reviewers. Authors or sponsors of the trials were petitioned for required missing or additional information. Extracted data were reviewed by the principal reviewer and discrepancies resolved by discussion. The number and age of enrolees, and dose and duration of treatment, were recorded. The main outcome was the efficacy of Cernilton vs placebo or control in improving urological symptom scores (e.g. the IPSS). The following secondary outcomes were also assessed: nocturia (times/evening); peak and mean urine flow; postvoid residual urine volume (PVR); and prostate size. One study used the Uroflow Index, a formula developed to examine urinary flow measurement based on maximum and mean flow [13]. The number of and reason for men withdrawing from the trial or being lost to follow-up were assessed, as were treatment-related side-effects.

The overall study quality was assessed according to the scale developed by Schulz *et al*. [14]. The

quality of the concealment of treatment allocation is assigned a score from 1 to 3, (1 for the poorest quality and 3 the best). Trials in which concealment was inadequate (e.g. alternation or reference to case-record numbers or to dates of birth) were given a score of 1. Trials in which the authors either did not report their approach to allocation concealment or reported an approach that did not fall into one of the other categories were given a score of 2. Trials deemed to have taken adequate measures to conceal allocation, e.g. central randomization, were scored as 3.

Statistical methods

Summary treatment effect sizes were determined for Cernilton vs placebo and vs pharmacological therapies. Weighted mean differences (WMDs) and their 95% CI were calculated [15]. Heterogeneity was assessed using a chi-squared test; if there was evidence of heterogeneity then a random-effects model was used. For continuous measurements, a difference between treatment means and its correlated se of the difference were calculated using the methods of Lau [16] and Laird [17]. To assess the percentage of patients having an improvement in urological symptoms a modified intention-to-treat analysis was conducted (i.e. men who withdrew or were lost to follow-up were considered to have had worsening symptoms) [18]. Chi-square tests were used to analyze bivariate comparisons.

Four studies met the inclusion criteria from a total of six [19-24] identified through the combined search strategy. Two trials were excluded because they had no control groups [23,24]. The concealment of treatment allocation was rated as unclear in the four studies reviewed, although two indicated randomization [19,22]. Three trials reported using a double-blind method [19,20,22]. Two studies were placebo-controlled [19,20] and two were 'active controlled' trials. The 'active-controlled' trials included Tadenan, a phytotherapeutic extract from the African plum plant, *Pygeum africanum* [21], and Paraprost (Nikken Kagakusha, Japan), a pharmacological treatment for BPH used primarily in Japan, and containing 265 mg of l-glutamic acid, 100 mg of lalanine and 45 mg of aminoacetic acid [22].

A total of 444 participants were enrolled in the four trials (163 in the placebo-controlled and 281 in the 'active controlled' trials). Table 1 describes the participants, intervention, follow-up period, number of participants randomized, number who withdrew or were lost to follow-up, double-blind method status, and adverse effects. The mean (range) age of the enrolees was 69 (42-89) years and the duration of the trials was 12-24 weeks. The overall mean (range) rate of reported withdrawals or losses to follow-up was 6.3 (0-11.7%) (n = 28).

Table 1 The description of the individual studies

	Study			
Characteristic	*[19]*	*[20]*	*[21]*	*[22]*
Participants	Symptomatic BPH Stage II–III (Vahlensieck)	Men with BOO from	Men with BPH; assessed	Men with BPH; global
BPH; modified Boyarsky	using authors' symptom	physician assessment;		
PVR >150 mL	scale; flow rate ⩾150 mL/s; US estimate of PVR and prostate size	score; uroflowmetry; US of PVR and prostate size	symptom score (graded 0–3 for nocturia, dysuria, hesitancy, etc.) peak flow 10 mL/s (> 150 mL); PVR <50 mL	
Mean (range) age (years)	66.6 (not reported)	68.6 (59–89)	? (50–68)	70 (54–68)
Intervention	1. Cernilton 2 caps × 3/day; 2. Placebo	1. Cernilton 2 caps × 2/day; 2. Placebo	1. Cernilton 2 caps × 3/day for 2 weeks then 1 cap × 3/day; 2. Tadenan 2 tabs × 2/day	1. Cernilton (63 mg) 2 caps × 2/day; Paraprost 6 g tab 2/day
Follow-up (weeks)	12	24	16	12
No. enrolled (withdrawals)	103 (7)	60 (7)	89 (0)	192 (14)*
Quality scale score†	2	2	2	2
Double-blind method	Yes	Yes	No	Yes
Adverse events	Mild nausea (1)	None	None	None

*Efficacy was studied in only 159 patients. †Bbased on Schulz *et al.* [14]. US, ultrasonography.

Results

Table 2 The summary of the outcome data

	Study							
	[19]		[20]		[21]		[22]	
Mean (SD) variable‡	Cernilton	Control	Cernilton	Control	Cernilton	Control	Cernilton	Control
Symptom score or rating								
Baseline	–	–	'Overall improvement'		+ve response		11.5 (3.5)	11.4 (4.0)
Follow-up	–	–					5.2 (2.5)	4.3 (2.7)
Difference	–	–	69%	29%†	78%	55%*	−6.3	−7.1
Nocturia (times/night)								
Baseline			Improved		–	–	3.7 (0.5)	4.0 (0.8)
Follow-up	'Improved' or symptom-free				–	–	2.8 (0.6)	3.2 (1.1)
Difference	69%	37%†	60%	30%	–	–	−0.9	−0.8
Peak urinary flow rate (mL/s)								
Baseline	0.74 (0.27)	0.72 (0.34)	10.3 (5.2)	11.8 (6.4)	12.59 (3.0)	13.54 (3.2)	9.29 (4.99)	9.34 (4.86)
Follow-up	0.86 (0.25)	0.82 (0.31)	10.5 (5.1)	12.1 (5.1)	15.51 (4.3)	15.18 (4.5)	10.94 (5.09)	10.57 (4.82)
Difference	0.12	0.10	0.2	0.3	3.02	1.64	1.65	1.23
PVR (mL)								
Baseline	45.6 (30.4)	47.8 (32.8)	145.4 (107.5)	93.4 (91.4)	77.0 (15.7)	61.0 (14.1)	54.2 (78.84)	33.1 (40.06)
Follow-up	22.5 (20.9)	37.0 (28.9)	101.9 (87.3)	113.4 (87.3)	45.0 (21.0)	50.0 (15.8)	25.2 (28.22)	23.8 (28.59)
Difference	−23.1	−10.8*	−43.5	20.0*	−32.0	−11.0	−29.0	−9.26

*$P < 0.05$; †$P < 0.01$, otherwise not significant. ‡Except for the values in [20], which are mean (sem).

Table 2 shows the summary of outcome data for urological symptoms scores, nocturia, peak urinary flow rate and PVR. Three studies reported symptom scores or measured the symptom improvement, nocturia was reported in three, peak urinary flow rate in four studies and four provided information related to PVR. Differences in the control agents and methods of reporting results did not permit all studies to be combined in a quantitative meta-analysis. However, the results from all studies were consistent with an improvement in symptoms and urinary flow measures, as described below.

Mean differences in outcomes

Cernilton was comparable with both Paraprost and Tadenan in improving urological symptoms based on the IPSS (Paraprost) and two undefined symptom scales evaluating obstructive or irritative symptoms. For the IPSS, the mean (95% CI) difference (MD) was 0.90 (-0.43 to 2.23), with a percentage improvement from baseline of 55% for Cernilton and 62% for Paraprost [22]. For the trial comparing Cernilton with Tadenan, the MD for the obstructive scale score was -0.70 (-1.78 to 0.40; % improvement from baseline, Cernilton 63%, Tadenan 46%) and for the irritative scale -0.90 (-2.26 to 0.46; % improvement from baseline, Cernilton 68%, Tadenan 40%) [21].

Table 3 A comparison of Cernilton and placebo for nocturia and PVR in the two RCTs

	Study		
Variable	[19]	[20]	Total
Reported improvement in nocturia			
Cernilton (n/N)	33/48	17/31	50/79
Placebo (n/N)	16/48	7/26	23/74
Weight (%)	67.8	32.2	100
Relative risk (95% CI fixed)	2.06 (1.32–3.21)	2.04 (1.00–4.14)	2.05 (1.41–3.99)
PVR (mL)			
Cernilton (n)	48	28	76
Mean (SD)	22.5 (42.08)	101.9 (134.46)	–
Placebo (n)	48	24	72
Mean (SD)	37.0 (41.08)	113.4 (124.48)	–
Weight (%)	94.8	5.2	100
WMD (95% CI fixed)	−14.5 (−30.94 to 1.94)	−11.5 (−81.93 to 58.93)	−14.35 (−30.35 to 1.66)

Cernilton was better than placebo, Paraprost and Tadenan in the self-reported improvement of symptoms. The mean (95% CI) risk ratio (RR) vs placebo was 2.40 (1.21-4.75) (percentage of men reporting improvement, Cernilton 69%, placebo 29%) [20]. The RR vs Tadenan for a positive overall therapeutic response was 1.42 (1.21-4.75; % of patients who reported improvement, Cernilton 78%, Tadenan 55%). Cernilton reduced nocturia compared with the controls (Table 3; 30.8% absolute improvement) [19,20] and against Paraprost, the MD was -0.40 times per evening (-0.73 to -0.07).

Urinary flow measures were not significantly different between men treated with Cernilton and the placebo or active controls. The mean (95% CI) differences for peak urinary flow and the Uroflow Index were 1.60 (-5.77 to 2.59) mL/s and 0.04 (-0.11 to 0.19) mL/s, respectively [19,20]. Against Paraprost, the MD was 0.37
(-1.90 to 2.64) mL/s for peak urinary flow rate (4.6% absolute improvement) and 0.39 (-0.80 to 1.58) mL/s for the mean flow rate [22]. Against Tadenan, the MD was 0.33 (-2.00 to 2.66) mL/s (8.7% absolute improvement) [21].

Cernilton modestly reduced the PVR in the two placebo controlled studies (Table 3; 36.5% absolute improvement vs placebo) [19,20]. Cernilton was comparable with the control agents; the MD was -5.00 (-14.98 to 4.98) mL vs Tadenan and 1.40 (-20.00 to 22.80) mL vs Paraprost [21,22]. No significant differences in prostate size were evident when compared with Tadenan, with a MD of -2.09 (-10.21 to 7.97) mL, and Paraprost, with a MD of -1.12 (-10.21 to 7.97) mL. One placebo-controlled study, reporting changes for three variables (circumference, transverse diameter and anteroposterior diameter) of the prostate, found a 'statistically significant reduction in the anteroposterior diameter' after treatment with Cernilton [20].

Adverse effects

In the short-term, Cernilton was well tolerated; the only reported adverse effect associated with the use of Cernilton was one case of mild nausea [20]. Withdrawal rates were Cernilton 4.8%, placebo 2.7% and Paraprost 5.2% (P = 0.26 for Cernilton vs placebo and P = 0.33 vs Paraprost).

Discussion

This is the first systematic review summarizing the evidence from RCTs or CCTs about the efficacy and safety of Cernilton; the results suggest that Cernilton improved subjective symptoms and nocturia compared with placebo, Paraprost and Tadenan. Cernilton produced a similar response to the comparative study agents in improving urinary symptoms when evaluated by symptom scores. Only one adverse effect was reported, indicating that
Cernilton was well tolerated; the withdrawal rate was <5%.

In contrast to the modest improvement in subjective symptom outcomes, Cernilton did not significantly improve objective measures such as peak and mean urinary flow rates when compared with placebo and the control study agents. Although Cernilton was analogous to Paraprost and Tadenan in improving peak flow rates and reducing PVR and prostate size, these results were limited by the lack of confirmed active controls to validate the comparisons.

Methodological issues

Although the results suggest that Cernilton provides modest benefit to men with BPH, the studies assessed for this review were limited by several factors. The concealment of treatment allocation was deemed unclear in all four trials and may be indicative of the questionable methodological quality of the studies meeting the inclusion criteria. Two of the studies reported random allocation with no detail of the method of concealment and three reported using a double-blind method. One trial did not report random allocation or a double-blind method [21].
Inadequate concealment of randomization and blinding are known to affect the sizes of the outcomes [25].

The treatment duration was short, with no studies lasting longer than 24 weeks. Cernilton dosages were not reported in three studies and whether a standardized preparation was used is also unknown. Additionally, fewer than 500 men were evaluated. Therefore, the long-term efficacy and safety of Cernilton, and its effectiveness in preventing complications of BPH such as acute urinary retention or the need for surgical interventions, is unknown. Only one study reported results from a standardized and validated urological symptom scale, the IPSS [22], although a modified Boyarsky Scale was used in one [20], the others reporting various outcome variables. Therefore, the effect sizes should be interpreted with caution until future RCTs are conducted [26].

Such RCTs should be of sufficient size and duration to detect important differences in outcome, including urological symptom scale scores (e.g. the IPSS), mean and peak urine flow, voided volume, prostate size, PVR, and the development of acute urinary retention or need for surgical intervention. Studies are needed to compare Cernilton, α-blockers, 5α-reductase inhibitors and other phytotherapeutic agents, e.g. extracts of *Serenoa repens* (saw palmetto) [5,27]. Studies should also use standardized doses of Cernilton products that have been analyzed for purity and potency by an independent laboratory to ensure the quality of the product.

Additionally, cost-effectiveness studies should be conducted to evaluate the long-term cumulative costs associated with plant extracts, including the potential need for surgical intervention. The cost of a 90-day supply of Cernilton (three tablets/day, suggested use 2-4 tablets daily) is ≈US $40.00. In comparison, the cost of a 90-day supply of finasteride or terazosin (5 mg/day) is ≈$200 and $120, respectively. Alpha-blockers appear to be the preferred medical therapy for improving urological symptoms and urinary flow [28]. However, the costs of the initial medication may not reflect the total charges incurred for the treatment of BPH-related conditions. Finasteride has been shown to reduce the need for surgical intervention in about 6% of men who have large prostates and moderate to severe symptoms [29]. The comparative total cumulative costs of medical or surgical management alone, and a combination of medicine and surgery caused by any failure of the initial medical management (mixed therapies), has been shown to depend on the age of the patient at onset of therapy and the avoidance of mixed therapies [30]. Medical management (including phytotherapeutic agents such as Cernilton) in younger patients appears to be costly over time unless it can also reduce urinary retention or the need for surgery. In men with mild to moderate symptoms of BPH that do not interfere with lifestyle watchful waiting remains a good initial option [31].

In conclusion, additional randomized placebo and active-controlled studies are needed to evaluate the clinical effectiveness of Cernilton. Until the results of such studies are available, the present systematic review provides the most complete assessment of the efficacy and safety of Cernilton in the treatment of mild to moderate BPH. The available evidence suggests that Cernilton is well tolerated and modestly improves subjective urological symptoms. Cernilton was not shown to improve urinary flow measures compared with placebo. The long-term effectiveness and safety of Cernilton, and its ability to prevent complications from BPH, are unknown.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Effect of Cernitin Pollen-Extract on Experimental Nonbacterial Prostatitis in Rats

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BACKGROUND. The treatment for chronic nonbacterial prostatitis (NBP) has not been established. Cernitin pollen-extract (CN-009) is reported to have therapeutic effects for NBP. The effects and mechanisms of CN-009 were investigated.
METHODS. Ten-month-old rats were used with administration of estradiol after castration, which were similar to human NBP histologically. Since CN-009 consists of T-60 and GBX, these drugs were administered, respectively. The prostate was evaluated histopathologically including glandular damage (epithelial score), stromal ratio and immunohistochemical assays for epithelial function (PAP), stromal evaluation (Vimentin), cell proliferation (PCNA) and apoptosis (deoxyuridine triphosphate biotin nick end-labeling (TUNEL)).
RESULTS. Controls revealed severe acinar gland atrophy and stromal proliferation. CN-009 showed diminished these damages. Epithelial score was better ($P<0.01$) and PAP positive materials were more abundant in CN-009 and GBX than in Controls. The stromal ratio was lower in CN-009 ($P<0.01$) and T-60 ($P<0.05$). There was no difference for PCNA positive cells in the epithelium and stroma, and TUNEL positive cells in epithelium. While, the number of TUNEL positive cells in the stroma of CN-009 and T-60 increase ($P<0.01$).
CONCLUSIONS. These findings suggest than CN-009 protects acinar epithelial cells mainly by GBX and also inhibits stromal proliferation in association with enhanced apoptosis mainly by T-60. Prostate 49: 122-131, 2001.

KEYWORDS: cernitin pollen-extract; apoptosis; chronic prostatitis; sex-hormone induced prostatitis

INTRODUCTION

The chronic prostatitis syndromes have been recognized; chronic bacterial prostatitis (CBP), chronic nonbacterial prostatitis (NBP) and prostatodynia. NBP is the most frequent disorder of 64% in these three diseases [1]. The etiology of NBP is unknown. A number of organisms or other factors have been reported to be the possible causes for NBP. They are *Trichomonas vaginalis, Chlamydia trachomatis,* genital mycoplasmas, staphylococci, coryneforms, genital viruses [2], biofilms [3], stagnation of prostatitc secretion, autoimmune disease, allergy, disorder of sex hormone and psychological effects [4,5]. For the treatment of CBP or NBP, antibiotics of new-quinolone or tetracycline have been administered. However, many cases resist these treatments [6].

CN-009 is a pollen extract, which contains 20:1 ratio of powdered aqueous and organic extract. It is essentially a microbial digest of a standardized mixture of eight plant species grown at the Scania area in southern Sweden. The active ingredients consist of water-soluble (T-60) and fat-soluble (GBX) fractions [7,8]. It was reported that CN-009 showed urine discharge action [9,10], anti-prostatic hypertrophic action [7] and anti-inflammatory effects to the prostate [11] in a preliminary study. Since Ask-Upmark [12] reported CN-009 showed an efficacy to prostatitis, it has been used for the treatment of chronic prostatitis with

high therapeutic effects. However, the mechanisms for these effects remain unknown.

To assess the mechanisms of the anti-prostatitis effect by CN-009, the present study was performed using a nonbacterial prostatitis rat model [13,14] induced by 17β-estradiol administration and castration.

MATERIALS AND METHODS

Sex Hormone-Induced Nonbacterial Prostatitis Model

Ten month-old Wistar aged male rats were purchased from Japan Slc Co. (Tokyo, Japan). The rats were housed in a climatised environment with a 12-hr light/ dark cycle, 40-70% humidity. Food and water were supplied ad libitum. The rats were castrated under ether anesthesia, and then 17 β-estradiol (Sigma, MI) 0.25 mg/ 2 ml/ kg diluted by sesame oil, as an inducer for prostatitis, was subcutaneously injected into the back of rats for 30 days from 1 day after castration [13,14].

Experimental Structure and Schedule

CN-009 was suspended for 630 or 1,260 mg/ 5 ml with 1% HCO-60 (Japan Surfactant, Tokyo, Japan). T-60 and GBX were similarly prepared for 1,200 and 60 mg/ 5 ml, respectively. Testosterone (TS) (Wako Chemicals, Tokyo, Japan), as a positive control, was diluted for 2.5 mg/ 2 ml with corn oil (Yuro Chemical, Tokyo, Japan).

The experimental structure is shown in Table I and the experimental schedule is illustrated in Figure 1. The rats were divided into seven groups consisting of Sham-operation (Sham-ope), Control, CN-009 630, CN-009 1260, T-60, GBX and TS with five or six animals in each group.

In the Sham-ope group, the rats were treated with only Sham-castration and without any drugs. In the Control group, the rats were injected subcutaneously with 17 β-estradiol for 30 days from the day following castration and administered orally with only 1% HCO-60 5 ml/ kg for 14 days from Day 17. In the CN-009 630, CN-009 1260, T-60 and GBX groups, similar protocols were performed with oral administration of CN-009 630, CN-009 1260, T-60 1200 and GBX 60 mg/ kg, respectively. Also in the TS group, the rats were injected subcutaneously with 17 β-estradiol for 30 days from the next day of castration. After 14 days, TS 2.5 mg/ kg was injected subcutaneously for 14 days. All studies were conducted in accordance with institutional guidelines of animal care and in accordance with Japanese Government Animal Protection and Management Law.

Prostate Weights and Histopathological Evaluation

The rats were sacrificed on the day following the final administration. The prostate was extirpated and weighed. Relative prostatic weight was calculated from body weight and absolute weight.

After fixation in 10% neutral buffered formalin, each prostate was cut into coronal blocks. The tissue samples were dehydrated and embedded in paraffin. Sections (3-4 μm thickness) were stained with Hematoxyline-Eosin (HE), Periodic acid Shiff (PAS) and Masson's tri-chrome. The specimens were evaluated histopathologically.

Immunohistochemistry

Immunohistochemistry studies were performed with anti-prostatic acid phosphatase (PAP), and Viementin. PAP staining was performed for the evaluation of glandular epithelial function. In

TABLE I. The Structure of the Experiment

Group	No. of animals	Inflammatory agent	Drug treatment
Sham-ope.	5	No-treatment	No-treatment
Control	6	17 β-estradiol 0.25 mg/kg (s.c.)	1% HCO-60 (p.o.)
CN-009 630	5	17 β-estradiol 0.25 mg/kg (s.c.)	CN-009 630 mg/kg (p.o.)
CN-009 1260	6	17 β-estradiol 0.25 mg/kg (s.c.)	CN-009 1260 mg/kg (p.o.)
T-60	5	17 β-estradiol 0.25 mg/kg (s.c.)	T-60 1200 mg/kg (p.o.)
GBX	6	17 β-estradiol 0.25 mg/kg (s.c.)	GBX 60 mg/kg (p.o.)
TS	5	17 β-estradiol 0.25 mg/kg (s.c.)	Testosterone 2.5 mg/kg (s.c.)

Each parenthesis represents the route of administration. s.c, subcutaneous injection; p.o., oral administration.

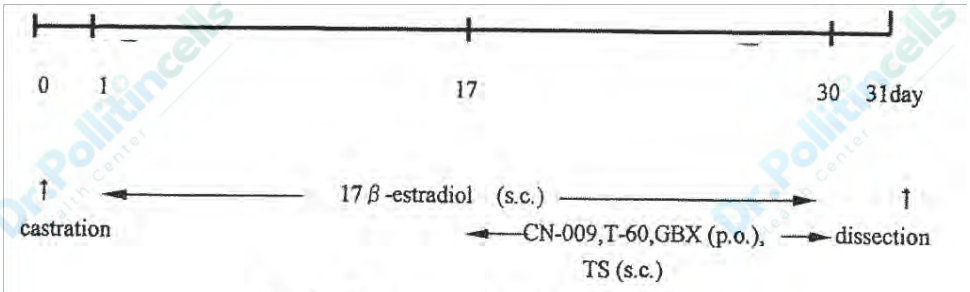

Fig. 1. The experimental schedule for this study.

PAP stained specimens, anti-PAP polyclonal antibody (Chemicon International, New York, NY) was diluted by PBS including 0.1% BSA of a 1:100 ratio, and incubated for 2 hr at 37° C. Biotinylated anti-rabbit IgG and the avidin-biotin peroxidase complex (ABC) method was performed. Unitect rabbit immunohistochemistry detection systems (Oncogene Science, New York, NY) were reacted by those methods. Vimentin staining was performed for the evaluation of stromal proliferation. An ImmunoCruz staining system (Santa Cruz BioTech., Santa Cruz, CA) for Vimentin staining was used according to the manufacturer's instructions.

Cell Proliferation and Apoptosis

Cell proliferation and apoptosis were investigated with proliferating cell nuclear antigen (PCNA) and terminal deoxynucleotidyl tranferase mediated deoxyuridine triphospate bitotin nick end-labeling (TUNEL), respectively. PCNA staining was performed with PCNA staining kit (ZYMED Laboratories, South San Francisco, CA). TUNEL method was performed with ApoTag Peroxidase In Situ Apoptosis Detection kit (Intervene, New York, NY). In PCNA and TUNEL specimen, 5,000 cells were counted under a microscope in glandular epithelial cells and stromal cells, respectively.

Acinar Epithelial Score and Stromal Area Ratio

To evaluate glandular damage, acinar epithelial cells were classified and scored, as follows; columnar (2 points), cuboidal (1 point), squamous-like (0 point) shape. Three different pathologists without any information judged the score. Using this scoring evaluation, 20 acinar glands of each specimen were investigated. To assess stromal proliferation, all areas of the specimen and the glandular area were measured using a digitizer (Graph Tech, Tokyo, Japan) with photomicrographs. Using these findings, the stromal ratio was calculated.

Statistical Analysis

All experiments were repeated at least twice. Each value was demonstrated as the mean±SD. Dunnett's test if in equal variance, or non-parametric Dunnett's test if in unequal variance between treatment groups and Control group was performed after 1-way ANOVA followed by Bartlett variance analysis test. Mann-Whitney U test was performed between the Sham-ope and Control groups.

RESULTS

Body and Prostate Weights (Fig. 2)

There was no significant difference in body weight among the CN-009 630, CN-009 1260, T-60, GBX and TS groups compared with the Control group. Absolute and relative prostate weights were significantly ($P<0.01$) decreased in the Control group compared with the Sham-ope group (Fig. 2) in the CN-009 630, CN-009 1260, T-60 and GBX 60 groups, there was no difference compared with the Control group. In the TS group, absolute and relative prostate weights were very close to the Sham-ope group and were significantly different ($P<0.01$) from other groups.

Histopathology and Immunohistochemistry (PAP and Vimentin Staining)

In the Sham-ope group, the prostate was larger than in other groups. Acinar glands were roundly shaped. The acinar lumen was filled with eosinophilic materials. Acinar epithelial cells were cylindrical with a normally situated nucleus and the supranuclear spaces of these cells

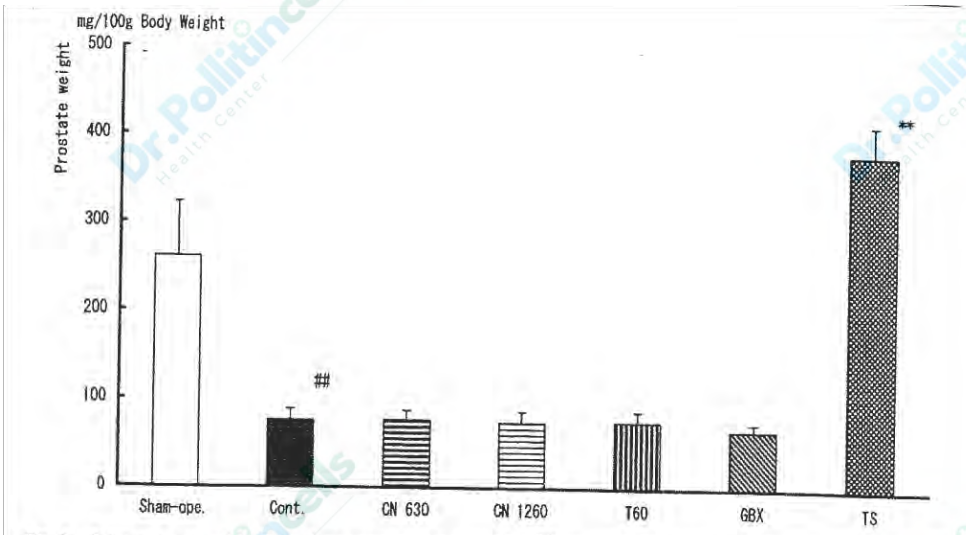

Fig. 2. Relative prostate weight. Each column represents the mean ± SD. ##Significantly different from the Sham-ope group at $P < 0.01$. **Significantly different from the Control group at $P < 0.01$.

contained secretory materials, which were strongly stained with PAP antibody. A few fibrous tissues were found in the stroma (Figs. 3A and 4A). Vimentin positive cells were few, and the Vimentin positive area was small (data not shown).

In the control group, the prostate was atrophic. Acinar glands were irregularly shaped. The acinar lumen was poor with pale stained eosinophilic materials and filled with inflammatory cell infiltrations mainly characterized by neutrophils. Acinar epithelial cells were flattened similar to a squamous cell. A few secretory materials in the epithelial cells were poorly reacted with PAP antibody. The stroma showed severe proliferation with many lymphocyte and monocyte infiltrations and marked fibrosis with fibroblasts (Figs. 3B and 4B). The stroma was stained very strongly with Vimentin. The Vimentin positive area was significantly increased (data not shown). In the CN-009 630 group, the findings were basically identical with the Control group (data not shown).

In the CN-009 1260 group, acinar glands were more roundly shaped than in the Control group. Acinar epithelial cells were cuboidal, and the supranuclear spaces contained secretory materials stained with anti-PAP that were much more abundant than in the Control group. Inflammatory cell infiltrations into the acinar lumen were diminished. The stroma showed mild proliferation with a few lymphocytes, monocytes and mild fibrosis with fibroblasts (Figs. 3C and 4C). The Vimentin positive area was much less than that of the Control group (data not shown).

In the T-60 group, acinar epithelial cells were more roundly shaped than in the Control group. Although inflammatory cell infiltrations into the lumen were found, stromal cell infiltrations (Fig. 3D), the Vimentin positive cells were also less than that of the Control group (data not shown).

In the GBX group, acinar epithelial cells were more cuboidal than in the Control group. Epithelial cells contained secretory materials stained with anti-PAP, which was basically identical with the CN-009 1260 group. Diminished cell infiltration into the lumen was found (Fig. 3E). However, the stroma showed a proliferative condition with many lymphocyte and monocyte infiltrations and marked fibrosis with many fibroblasts. The stroma was stained strongly with Vimentin, and the positive area was markedly increased (data not shown).

In the TS group, acinar glands were roundly shaped. The acinar lumen was filled with eosinophilic materials with a few cell infiltrations. Acinar epithelial cells were cylindrical and the supranuclear spaces contained many secretory materials with reactive anti-PAP. However, the stroma was stained strongly with Vimentin and showed mild proliferation with fibroblasts (data not shown).

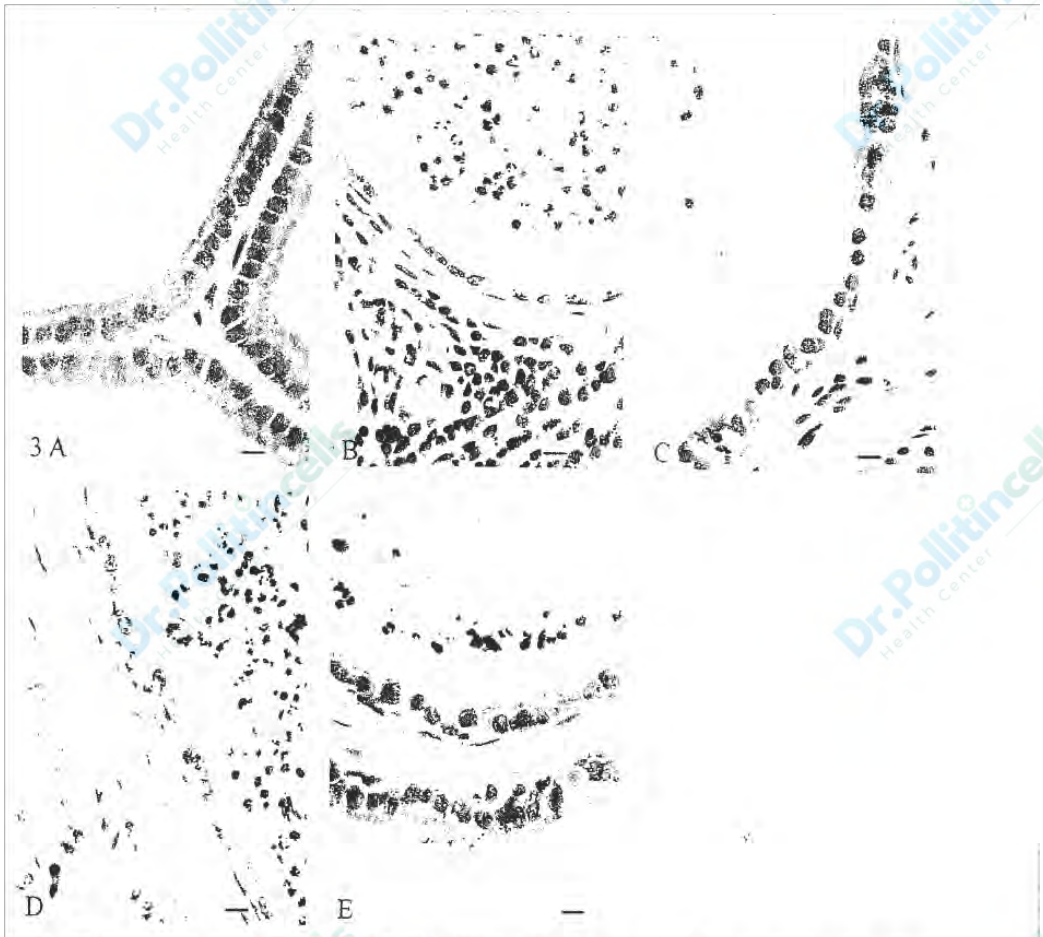

Fig. 3. HE staining of the prostate in experimental nonbacterial prostatitis rat. (**A**) Sham-ope group: The acinar lumen is filled with eosinophilic materials without any cells. Acinar epithelial cells are cylindrical. A few fibrous tissues are found in the stroma. (**B**) Control group: The acinar lumen is filled with induced inflammatory cells mainly characterised by neutrophils. Acinar epithelial cells are flattened similar to squamous cells. The stroma shows severe proliferation with many lymphocyte and monocyte infiltrations and remarkable fibrosis with fibroblasts. (**C**) CN-009 1260 group: Acinar epithelial cells are cuboidal. Inflammatory cell infiltrations into the acinar lumen are diminished. The stroma shows mild proliferation with a few lymphocytes, monocytes and fibroblasts. (**D**) T-60 group: Stromal proliferation is relatively mild without severe inflammatory cells. (**E**) GBX group: Acinar epithelial cells are cuboidal, and diminished inflammatory cell infiltrations are shown. 400. The bar indicates 10 μm.

Cell Proliferation and Apoptosis (PCNA and TUNEL Positive Cell Counts (Fig. 5))

No significant differences among the groups were observed in the PCNA positive cell counts in epithelial cells (Fig. 6) or in stromal cells (Fig. 7). In the Sham-ope group, a few TUNEL positive cells were found (Fig. 5A). The findings of the Control group were basically identical with the Sham-ope group (Fig. 5B). In the CN-009 1260 group, TUNEL positive cells in the stroma were more abundant than in the Sham-ope and Control groups (Fig. 5C). In TUNEL positive cell counts, no significant differences were observed in acinar epithelial cells (Fig. 8). However, in the stroma, TUNEL positive cells were significantly ($P<0.05$) increased in the CN-009 1260 group or T60 group compared with the Control group (Fig. 9).

Acinar Epithelial Score (Fig. 10)

In the Control group, acinar epithelial score was significantly lower ($P<0.01$) than that of the Sham-ope group. In comparison with the Control group (Fig. 10), the acinar epithelial score was significantly higher ($P<0.01$) in the CN-009 1260, GBX, and TS groups.

Stromal Area Ratio (Fig. 11)

In the Control group, the stromal area ratio was significantly higher ($P<0.01$) than that of Sham-ope group in comparison with the Control group.

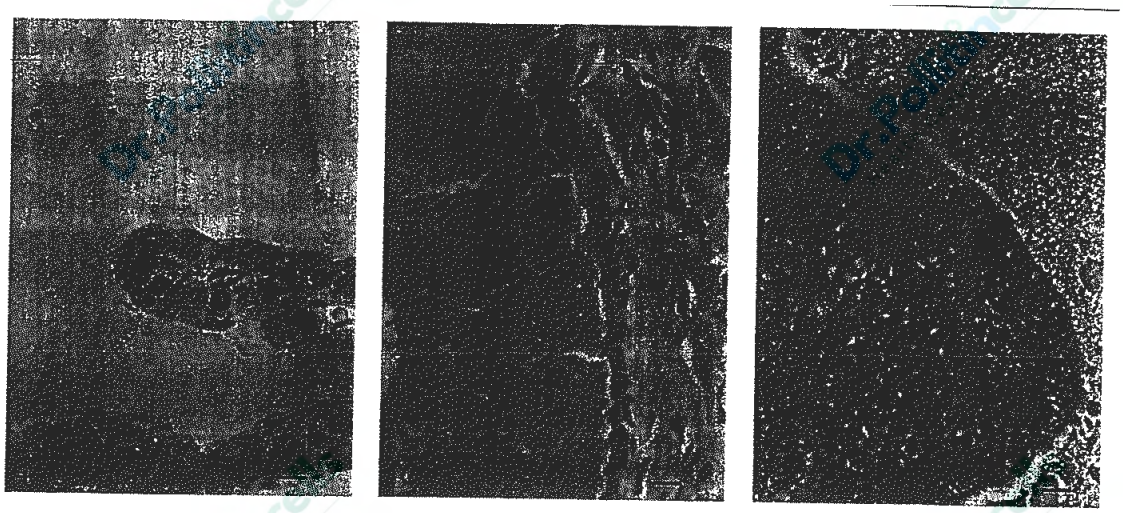

Fig. 4. Immunohistochemical findings (PAP staining) of the prostate in experimental nonbacterial prostatitis rats. **(A)** Sham-ope group: Supranuclear spaces of acinar epithelial cells contain secretory materials which are stained with anti-PAP. **(B)** Control group: Acinar epithelial cells are flattened similar to squamous cell. Secretory materials are poorly reactive with anti-PAP. **(C)** CN-009 1260 group: Supranuclear spaces contained secretory materials with PAP staining, which are significantly more abundant than in the Control group. ×400 The bar indicates 10 μm.

In comparison with the Control group (Fig. 11) the stromal area ratio of the CN-009 1260 was significantly ($P<0.01$) lower. The T-60 group was also significantly ($P<0.05$) lower than the Control group. However, there was no difference between other groups.

Discussion

Although chronic prostatitis is a common disease, it is very difficult to treat effectively.

Typical clinical findings are decreased potential, perineal or scrotal pain, urethral discharge and lower urinary tract irritative symptoms. The prostate gland is irregularly indurated and the numbers of leukocytes in expressed prostatic secretion are increased [15]. Pathological findings of this disease are chronic inflammation characterized by aggregates of lymphocytes in the stroma and

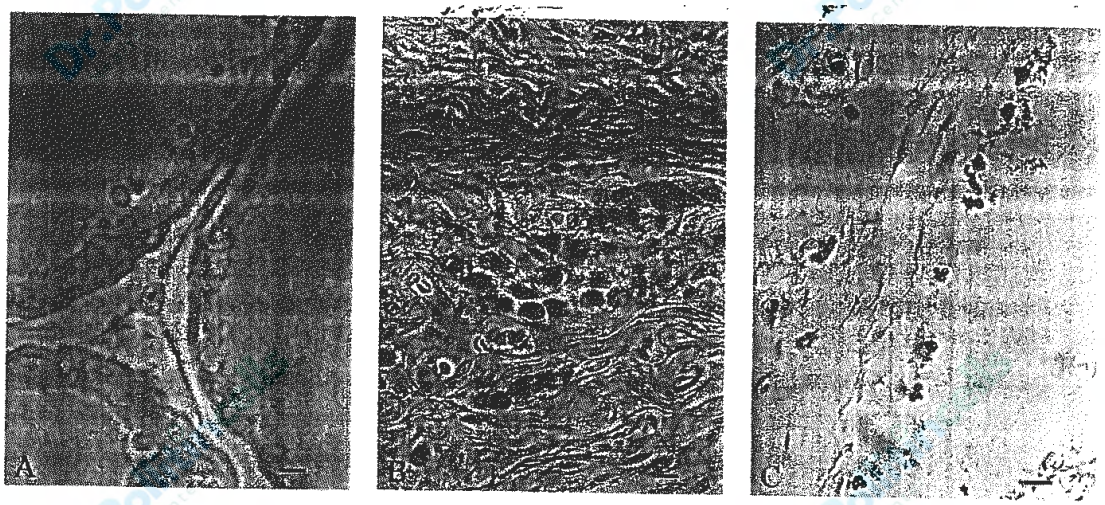

Fig. 5. Immunohistochemical findings (TUNEL) of the prostate in rats. **(A)** Sham-ope group: A few TUNEL positive cells are shown. **(B)** Control group: The findings are basically identical to these of the Sham-ope group. **(C)** CN-009 1260 group: TUNEL positive cells in the stroma are more abundant compared with the Sham-ope and Control groups. ×400. The bar indicates 10 μm.

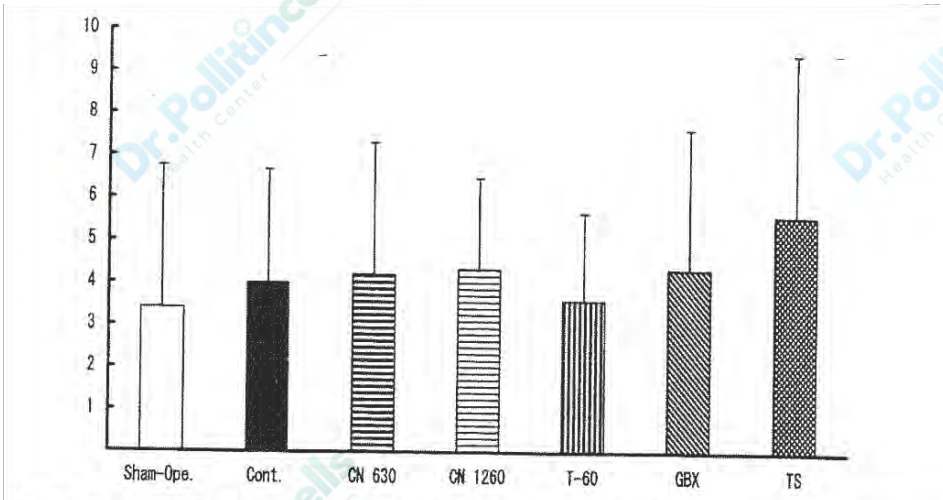

Fig. 6. Effects of CN-009 on acinar epitelial PCNA positive cell counts of the prostate. Each column represents the mean ± SD.

acute inflammation characterized by the presence of neutrophic polymorphonuclear leukocytes in the lumen of acinar glands [15-17]. Pathological definition of chronic prostatitis is different from clinical definition for the urologists. Clinical definition has been the combination of a clinical symptom and inflammatory cells in expressed prostatic secretion. The pathological inflammation of the prostate was reported to be not frequent in patients with symptoms of chronic prostatitis/ chronic pelvic pain syndrome [16].

In experimental animals, Lewis, Wistar and Copenhagen rats have a high incidence of spontaneous nonbacterial prostatitis [14]. Administration of exogenous 17 β-estradiol can induce 100% of the incidence on prostatitis in old Wistar rats [18] and castration also has a similar effect [13, 18]. Naslund et al. [13] reported that histopathological findings were very similar between spontaneous nonbacterial prostatitis and estradiol-induced prostatitis in rats [13]. These histopathological findings in rat spontaneous nonbacterial age-dependent prostatitis demonstrated several similarities to pathologically defined chronic prostatitis in human [19, 20]. These findings suggested that this rat model would be a useful model for the study of the treatment of human chronic prostatitis. Therefore, we decided to investigate the effects and mechanisms of CN-009 using a nonbacterial prostatitis rat model [13, 14] induced by 17 β-estradiol injection and castration.

No differences in the prostate weight were found in CN-009 630, CN-009 1260, T-60, and GBX

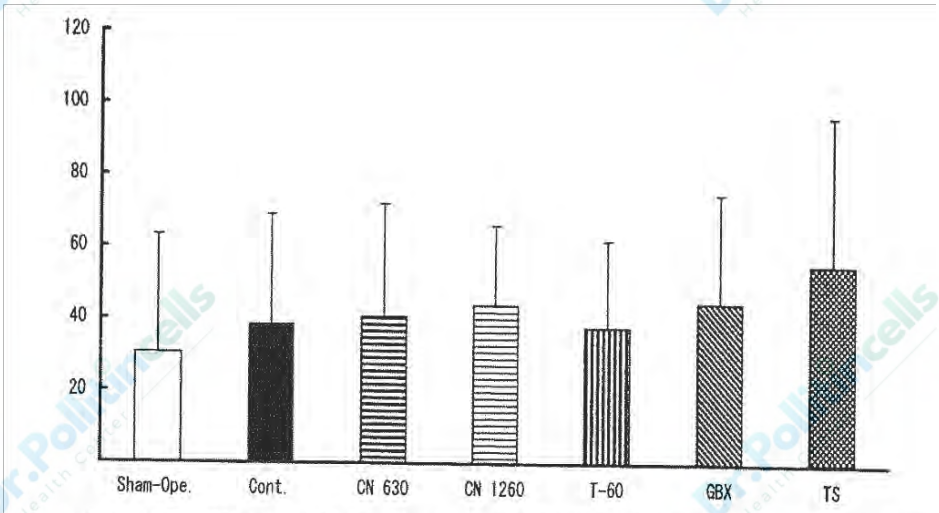

Fig. 7. Effects of CN-009 on stromal PCNA positive cell counts of the prostate. Each column represents the mean ± SD.

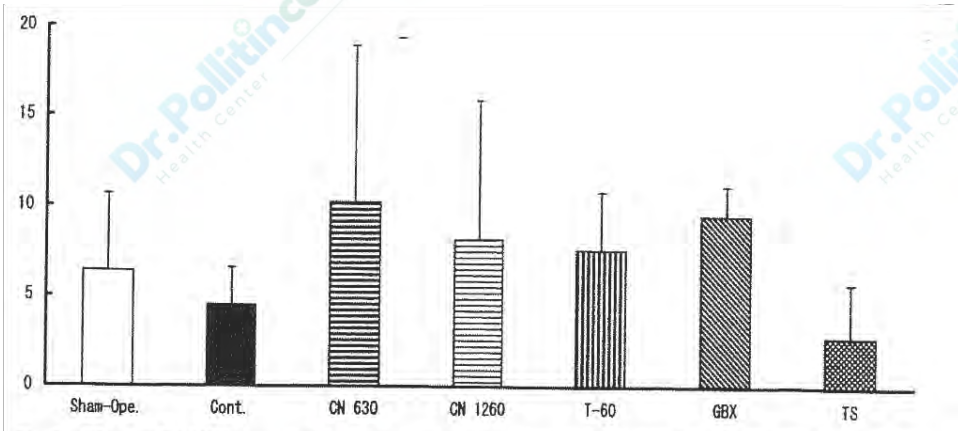

Fig. 8. Effects on CN-009 on acinar epithelial TUNEL positive cell counts of prostate. Each columun represents the mean ± SD.

groups compared with the Control group. Since the weight of the prostate is mostly determined by the amount of residual secretory fluid, these findings may indicate that CN-009 cannot prevent the reduction of secretory prostatic fluid.

In the CN-009 1260 group, we observed roundly shaped acinar glands, cuboidal acinar epithelial cells containing secretory materials with positive PAP staining and diminished cell infiltrations into the lumen compared with the Control group. The acinar epithelial score was significantly increased. CN-009 could protect acinar epithelial function and cell shape against nonbacterial inflammation. GBX had a similar effect to CN-009 in the acinar glands. T-60 was not effective in the acinar epithelial function of this rat model. Therefore, GBX may play a central role for the protection of epithelial damage in the NBP. The effect of GBX was similar to that of TS. However, GBX does not contain androgenic activity, because GBX has no effect on normal and hypertrophic prostate (unpublished data, 1968). Accordingly, this protective effect of GBX is discriminated from TS effect. In an in vitro study, GBX was reported to inhibit the cyclooxygenases and 5-lipoxygenases in the biosynthesis of the prostaglandins and leucotrienes [21]. Since prostaglandins and leucotriens enhance inflammatory cell infiltrations, GBX may protect against inflammation into the acinar lumen by inhibition of these enzymes. Furthermore, CN-009 showed an inhibition on the heat-induced hemolysis, which is correlated to lysosomal membrane stability [11]. CN-009 appears to

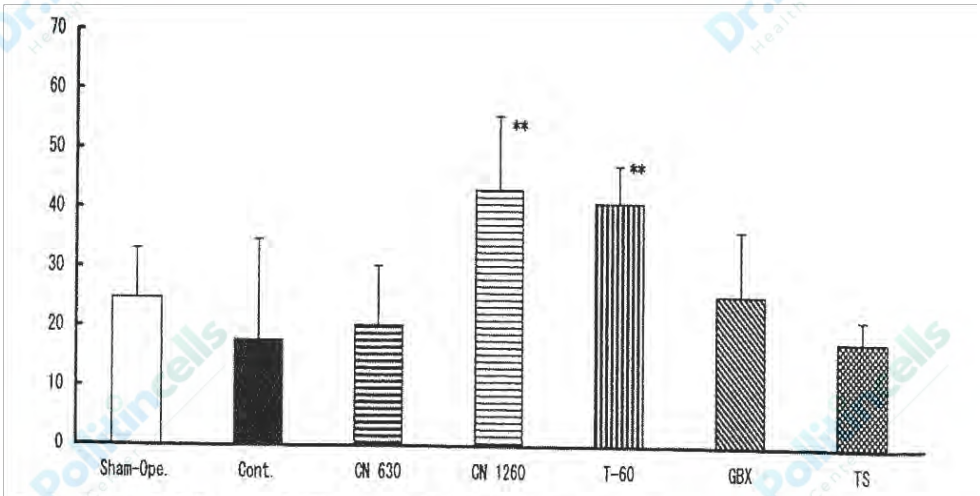

Fig. 9. Effects of CN-009 on stromal TUNEL positive cell counts of the prostate. Each columun represents the mean ± SD. **Significantly different from the Control group at $P < 0.01$.

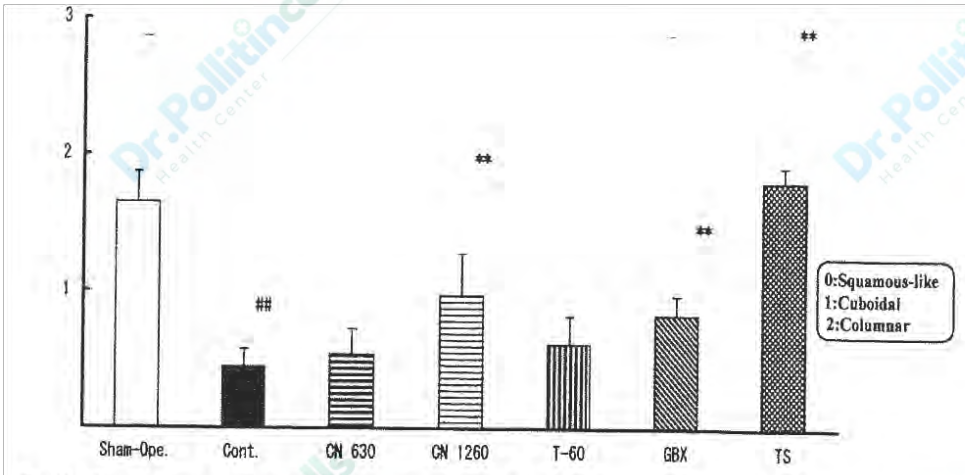

Fig. 10. Effects of CN-009 on acinar epithelial score of the prostate. Each column represents the mean ± SD. ##Significantly different from the Sham-ope group at $P < 0.01$. **Significantly different from the Control group at $P < 0.01$.

stabilize a lysosomal membrane, recover cell function and protect against degeneration of the acnar epithelium.

In addition, T-60 was shown to inhibit the growth of an immortal prostate cancer cell line in vitro [22]. However, their mechanisms are unknown. In the present study, the ratio of stromal area was significantly decreased in the CN-009 1260 and T-60 groups. Stromal TUNEL positive cell counts were increased in these groups. Therefore, CN-009 and T-60 may inhibit stromal cell proliferations by enhanced apoptosis. Although the exact mechanism of this process is unclear, several speculations are possible such as the direct effect by the apoptosis of fibroblast, and the indirect effect by the apoptosis of lymphocytes throught the the inhibition of several cytokines, such as several interleukins.

Further laboratory studies are necessary to elucidate the exact mechanisms of this compound.

Since no toxicological effects have been shown even in long-term administration, CN-009 is thought to be a safe drug [6, 23]. Here we reported the effects and mechanisms of CN-009 on rat experimental nonbacterial prostatitis model. CN-009 will also be a safe and effective against human nonbacterial chronic prostatitis.

In conclusion, CN-009 can work as a potent anti-inflammatory agent against chronic prostatitis. The present findings suggest that GBX, a fat soluble fraction of CN-009, protects the function and shape of acinar glandular epithelium and T-60, a water soluble fraction of CN-009, inhibits stromal cell proliferations in association with enhanced apoptosis.

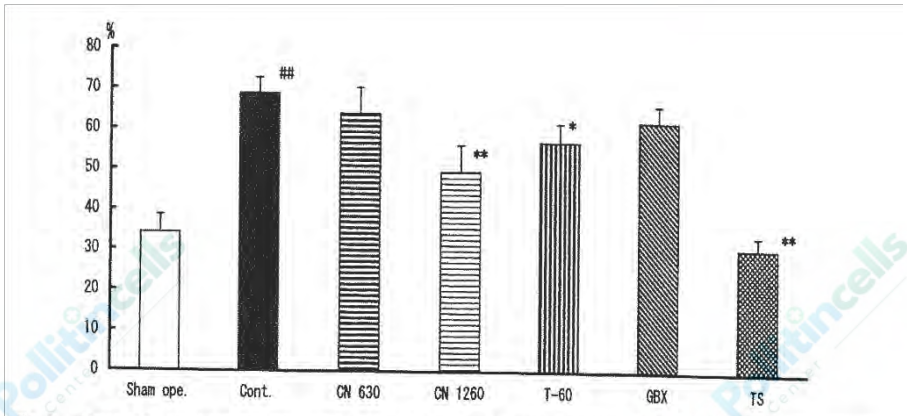

Fig. 11. Effects of CN-009 on stromal ratio in the prostate. Each column represents the mean ± SD. ##Significantly different from the Sham-ope. Group at $P < 0.01$. **Significantly different from the Control group at $P < 0.01$. *Significantly different from the Control group at $P < 0.05$.

Acknowledgements

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Alterations in the Intraprostatic Hormonal Metabolism by the Pollen Extract Cernilton®N

Sabine Tunn, M. Krieg

Introduction

A number of hypotheses have been implicated in the etiology of benign prostatic hyperplasia (BPH). The most important theories are: (1) an alteration of the androgen metabolism in BPH if compared to the normal prostate (NPR) leading to an accumulation of the biologically highly active androgen 5α-dihydrotestosterone (DHT) predominantly in the stroma; (2) a change in the androgen-estrogen ratio in favor of estrogens; (3) and an alteration in the intraprostatic interaction between stroma and epithelium [for an overview see (3)]. Such variable hypotheses do not allow a unified therapeutic concept for BPH.
For the medical treatment of BPH a variety of substances are utilized such as GnRH analogues, which reduce peripheral androgen and estrogen concentration (5,8), 5α-reductase inhibitors, which lower the intraprostatic DHT concentration (14), or aromatase inhibitors, which lower the peripheral estrogen concentration (12).

Besides these substances influencing the hormonal milieu, phytopharmaca are also utilized to treat patients with BPH who do not have indications for surgery. These drugs, such as the pollen extract Cernilton®N, lead to a subjective improvement in the patient's symptoms. The effect is supposedly based on an improvement in the inflammation or congestion of the prostate. To what extent these drugs influence the intraprostatic hormonal milieu is not known. We were interested in the question whether and to what degree phytopharmaca influence the intraprostatic androgen metabolism and may exert their effects by a change in the intraprostatic DHT content. To this end we characterized the main enzymes of the androgen metabolism (5α-reductase, 3α- and 3β-hydroxysteroid oxidoreductase) in the epithelium and stroma of the human prostate, and tested the in vitro influence of the phytopharmacon Cernilton®N on these enzymes.

Materials and Methods

The activity of DHT-metabolizing enzymes (5α-reductase, 3α-HSO_{red}, 3β-$HSOR_{red}$) was determined in mechanically separated epithelial and stromal fractions from 10 normal and 20 hyperplastic prostate glands. To this end aliquots of the tissue homogenates were incubated with at least 4 different concentrations of the individual substrates (either exclusively in ^{3}H-labelled or ^{3}H-labelled and unlabelled form: testosterone to measure the 5α-reductase in concentrations from 14 to 600 nM, DHT to measure 3α- and 3β-$HSOR_{red}$ in concentrations from 100 to 4860 nM). After addition of a co-factor NADPH-regenerating system (5 mM glucose-6-phosphate, 0.6 U glucose-6-phosphate dehydrogenase) the reaction was started with the co-factor NADPH (5α-reductase: 0.5 mM; 3α- and 3β-$HSOR_{red}$: 1.5 mM) and the mixture incubated for 15 min at 37° C. To determine the effect of the pollen extract, epithelial and stromal fractions of three of the hyperplastic prostates were incubated with various concentrations (49;246;493µg/ml) of the water-soluble (wPE) or fat-soluble (fPE) fractions of the extract, mixed well and then submitted to the same procedure as described above. After the reaction was stopped by the addition of either, and following extraction, the steroids were separated by HPLC (reversed phase, stationary phase: Lichrosorb RP 18, mobile phase: acetonitrile: H_20 = 50:50). Quantification was performed by measuring the radioactivity in the individual chromatographic fractions (substrate and various metabolites).

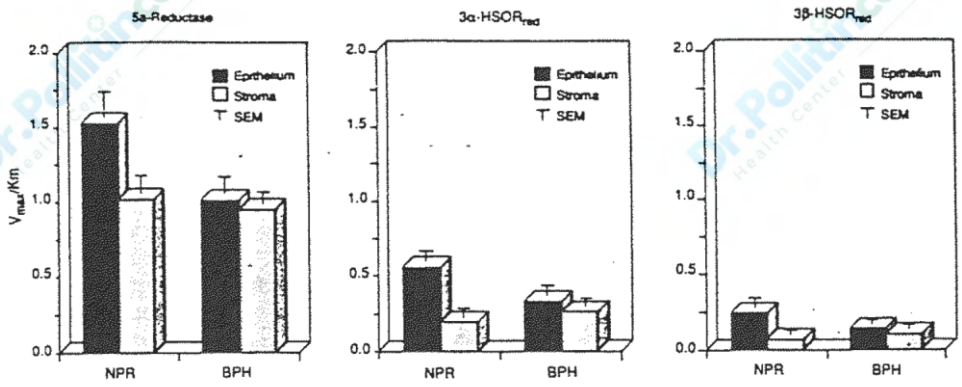

Fig. 1 Mean potential capacities (Vmax/Km) of 5α-reductase, 3α- and 3β-hydroxysteroid oxidoreductase (3α- and 3β-HSOR$_{red}$) in epithelium and stroma of 10 normal (NPR) and 20 hyperplastic (BPH) prostate glands.

The enzymatic activity was determined from the distribution of the radioactivity in these fractions. The specific activity of the labelled substrate, the ratio between labelled and unlabelled substrate, the incubation time, the protein concentration, and the blanks were utilized for the calculation. All assays were performed in duplicate.

Proteins were measured according to Lowry (6). The kinetic parameters Km and Vmax were calculated from the Lineweaver-Burk plot using regression analysis (least square method). The Student's t-test was utilized to determine significant differences between the means.
P <.05 was considered significant.

Results and Discussion

In the human prostate many androgen-metabolizing enzymes are present (see Fig. 1 in the chapter, ,,Hormone Metabolism in the Human Prostate"). The potential capacities of these enzymes vary greatly as our own published (10,11) and unpublished results show. The DHT-forming 5α-reductase and the DHT-removing 3α- and 3β-hydroxysteroid oxidoreductases (3α- and 3β-HSOR$_{red}$) have the highest potential capacity and therefore the greatest biological significance. It can therefore be assumed that these three enzymes are mainly responsible in the regulation of the intraprostatic DHT level.

Androgen Metabolism in the Normal and Hyperplastic Human Prostate

The potential capacity of an enzyme is expressed by the ratio Vmax / Km (10). In Fig. 1 the mean potential capacities for 5α-reductase, 3α-HSOR$_{red}$ and 3β-HSO$_{red}$ in epithelium and stroma of normal and hyperplastic prostates are shown. The 5α-reductase in the epithelium of normal prostate tissue has the highest potential capacity, where it is significantly higher than in the stroma, and also higher than in stroma or epithelium in hyperplastic prostate tissue. In the stroma there are no significant differences between NPR and BPH. The potential capacity of the 3α-HSOR$_{red}$ is significantly lower than that of the 5a-reductase, and the capacity of the 3β-HSOR$_{red}$ is again significantly lower than that of the 3α-HSOR$_{red}$. Both DHT- removing enzymes have significantly higher capacities in the epithelium of normal prostate tissue than in the stroma, and than in the epithelium and stroma of BPH tissue. The potential capacity of the 3α-HSOR$_{red}$ in NPR stroma is minimally lower, and that of the 3β-HSOR$_{red}$ even significantly lower than in BPH stroma.

A comparison of the potential capacities of the DHT-forming 5α-reductase and the DHT removing 3α-HSOR$_{red}$ and 3β-HSOR$_{red}$ allows the conclusion that there is no higher accumulation of DHT in BPH as compared to NPR. This conclusion is, however, only valid under the assumption of similar mean testosterone concentrations in men with normal and hyperplastic prostates. These results of the potential capacities therefore do not support the DHT accumulation hypothesis for BPH, but rather support the recently published data on DHT concentrations in normal prostate tissue (13,15) which demonstrated a higher concentration of DHT in normal prostate tissue removed immediately after death than in BPH tissue.

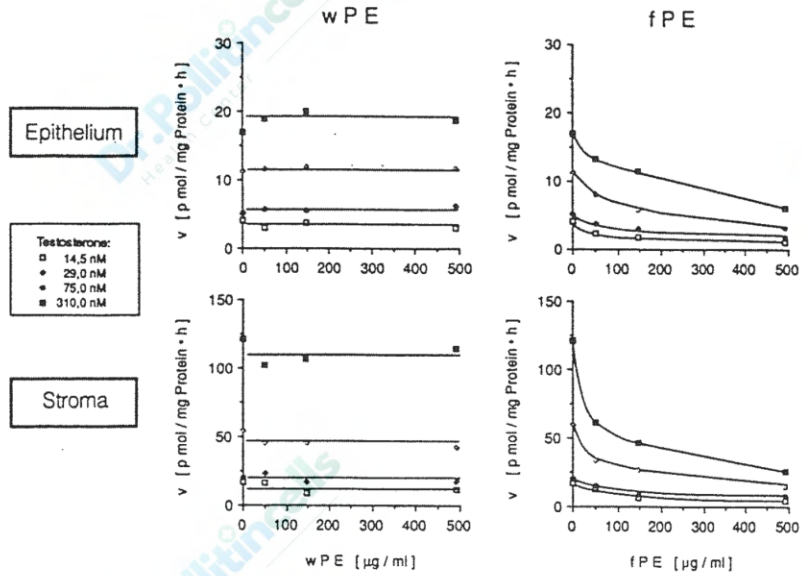

Fig. 2 Influence of the water-soluble fraction (wPE) of the pollen extract (left column) and the fat-soluble fraction (fPE) of the pollen extract (right column) on the enzyme activity (v). The activity of 5α-reductase in the epithelium (upper row) and stroma (lower row) is shown as an example. The enzyme activities were measured at different concentrations of the substrate testosterone (14.5–310 nM) and varying concentrations of wPE and fPE (49–493 µg/ml incubation mixture). All measurements were done in duplicate.

Alteration of the Intraprostatic Androgen Metabolism by the Pollen Extract Cernilton®N

To determine the effect of the pollen extract Cernilton®N on the enzymes of the intraprostatic androgen metabolism, the activities of the DHT-forming 5α-reductase and the DHT-metabolizing 3α-HSOR$_{red}$ and 3β-HSOR$_{red}$ were measured in epithelium and stroma of three hyperplastic prostates with varying concentrations of substrates as well as different concentrations of the water-soluble (wPE) and fat-soluble (fPE) fraction of the pollen extract. The activity of the 5α-reductase was not affected by wPE in a concentration range from 49 to 493 µg / ml incubation mixture in epithelium or stroma (Fig. 2). The activities of 3α-HSOR$_{red}$ and 3β- HSOR$_{red}$ were similarly not affected by this substance within the same concentration range (data not shown). However, fPE demonstrated in epithelium and stroma an inhibitory effect on the 5α-reductase (Fig. 2). The formation of DHT from testosterone is therefore significantly inhibited by the addition of fPE to the incubation mixture. Additionally, fPE also inhibited the activity of 3α-HSOR$_{red}$ and 3β-HSOR$_{red}$ in epithelium and stroma (data not shown). Therefore the metabolism of DHT to 5α-androstanediol is also diminished. The fat-soluble extract of another phytopharmacon (Serenoa repens B, Permixon®) was also found to inhibit the activity of 5α-reductase and 3α-HSOR$_{red}$ in human foreskin fibroblasts (9). This would indicate that nonspecific acting ingredients of such fat-soluble extracts are responsible for the inhibition of the enzymes.

To determine the kinetic mechanisms of the inhibitory effect of fPE, the enzyme activities were plotted for the different substrate and inhibitor concentrations in a double-logarithmic plot according to Lineweaver-Burk as shown exemplarily for the 3α-HSOR$_{red}$ in epithelium and stroma in Fig. 3. For all enzymes, 5α-reductase, 3α-HSOR$_{red}$ and 3β-HSOR$_{red}$, it was found in epithelium and stroma that the presence of fPE in the incubation mixture of the tissue homogenate did not change the Km, but that the Vmax changed corresponding to the concentration. Therefore the fPE acts as a non-competitive inhibitor of these enzymes, or in other words, the ingredients of the fat-soluble fraction do not bind at the active center for testosterone or DHT, but at another location, thereby altering the turnover number.

In Fig. 4 the mean potential capacities (ratio Vmax / Km) for the three enzymes in epithelium and stroma of the three hyperplastic prostates are depicted without (Fig. 4 A) and with (Fig. 4

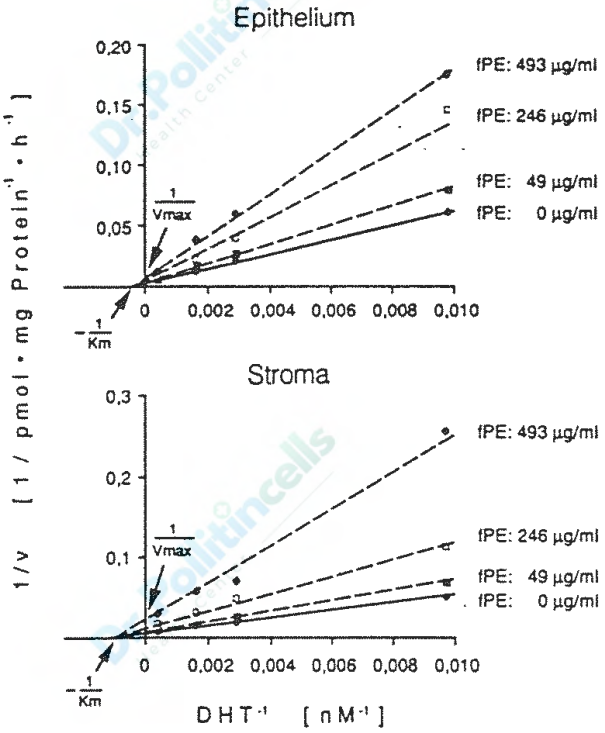

Fig. 3 Inhibition of the enzyme activity (v). The inhibition of the 3α-HSOR$_{red}$ by different concentrations (49–493 µg/ml incubation mixture) of the fat-soluble fraction (fPE) of the pollen extract as a function of the concentration of the substrate DHT in epithelium and stroma of a hyperplastic prostate is shown as an example (double logarithmic plot according to Lineweaver-Burk).

B) additional fPE (493 µg / ml incubation mixture). It is easily seen that the potential capacities of the 5α-reductase as well as the 3α- and 3β- HSOR$_{red}$ in epithelium and stroma are drastically reduced, but that the inhibitory effect of the fPE on the three enzymes is different. The mean potential capacity of the 3α-HSOR$_{red}$ is more inhibited in both compartments than that of both 5α-reductase and 3β-HSOR$_{red}$.

To estimate the expected changes in DHT content after in vitro incubation with fPE, the mean potential capacities of the three enzymes without additional fPE were assumed to be 1.0, and the percent activity after addition of the highest concentration of fPE (493 µg / ml incubation mixture) was calculated. The mean percentage activity of 5α-reductase after addition of fPE is shown next to the mean percentage activity of the DHT metabolizing enzymes 3α- and 3β-HSOR$_{red}$ (Fig. 5). It can be seen that the activity of the 3α-HSOR$_{red}$ in particular in the stroma, but also in the epithelium is more inhibited than that of the 5α-reductase, while the inhibition of the 3β- HSOR^{red} is similar to that of the 5α-reductase. The different reaction of the enzymes may be explained by the different intracellular localization. The 3α-HSOR$_{red}$ is equally distributed between cytosol and cytosolic membranes, while the 3β-HSOR$_{red}$ is mainly membrane-bound (1). The 5α-reductase is exclusively found in the perinuclear and microsomal membranes (2,4,7). Although our studies were conducted in a cell-free milieu, the membrane-bound enzymes are probably surrounded by membrane particles and should be only minimally influenced by fat-soluble extract.

Since these in vitro studies showed a stronger inhibition of the DHT catabolism compared to the DHT formation by the fat-soluble fraction of the phytopharmacon Cernilton®N, a lowering of the intraprostatic DHT level in tissue homogenates after fPE administration cannot be expected. On the contrary, an accumulation of DHT results, which should be similar to that in the normal prostate, however, at a generally lower activity level. This comparison is only valid under the condition that similar amounts of the fat-soluble extract are incorporated in the epithelial and stromal cells without being metabolized, and that these extracts reach the enzymes 5α-reductase, 3α- and 3β-HSOR$_{red}$ - which are located in different subcellular compartments - in similar concentrations. To make statements about the capacity of the

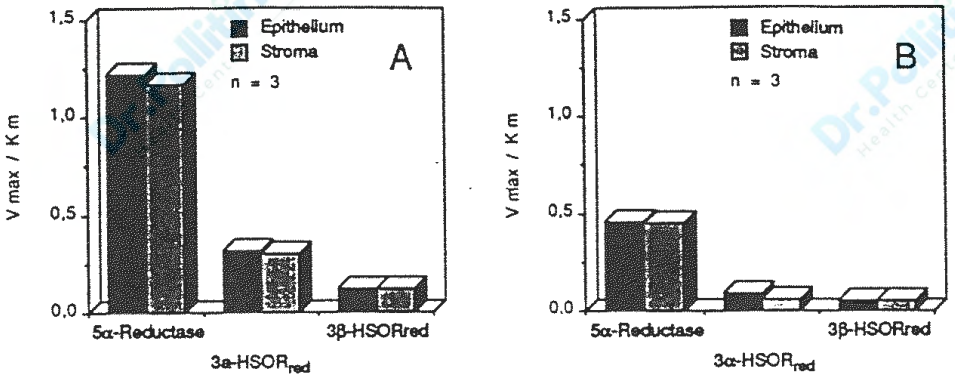

Fig. 4 Mean potential capacity (Vmax/Km) of 5α-reductase, 3α- and 3β-$HSOR_{red}$ in epithelium and stroma of three hyperplastic prostates without addition of fat-soluble fraction (fPE) of the pollen extract (A) and after addition of 493 µg fPE per ml of incubation mixture (B). All Vmax and Km values determined by Lineweaver-Burk plots.

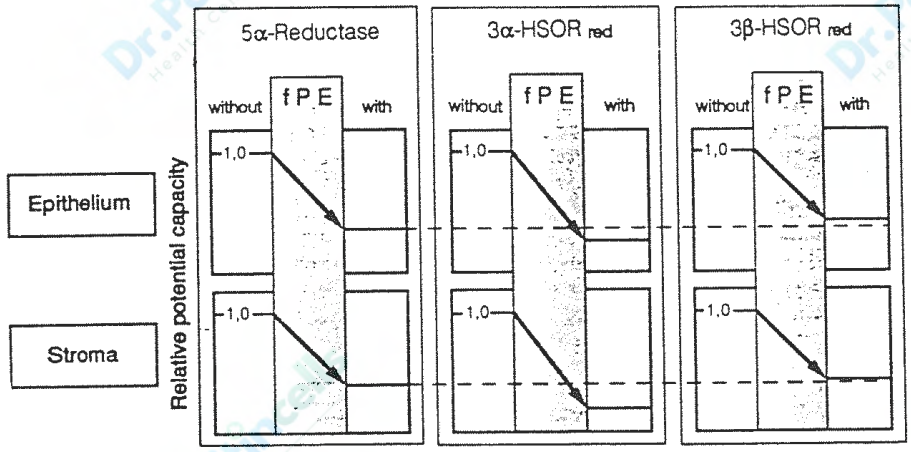

Fig. 5 Mean potential capacity (5a-reductase, 3α-$HSOR_{red}$ and 3β-$HSOR_{red}$) without (left columns) and after addition (right columns) of fat-soluble fraction (fPE) of the pollen extract in epithelium (upper row) and stroma (lower row) of three hyperplastic prostates. The potential capacities without additional fPE were assumed as 1.0, and the percentage remaining potential capacity after addition of fPE was calculated. The dotted lines indicate the relative potential capacities of the 5a-reductase in epithelium and stroma after addition of fPE.

pollen extract to influence androgen metabolism in vivo, further studies of androgen metabolism have to be conducted in prostate glands of patients who have been treated for a defined period of time with the pollen extract.

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Alternative medications for benign prostatic hyperplasia available on the Internet: a review of the evidence for their use

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Introduction

The number of people seeking alternative medications to treat disease is increasing; indeed, this was the subject of study conducted by Eisenberg *et al* in 1993 [1] who reported that there were 425 million visits to providers of alternative treatment during 1992 in the USA. This number has probably increased since then. These alternative therapies are sold as nutritional supplements for numerous illnesses, ranging from treatments for the common cold to those for depression. As with other specialties, there is now an abundance of alternative therapies for urological conditions. It is estimated that in the USA 30-90% of patients seen by urologists for putative BPH may be taking some form of alternative therapy for the condition [2-4]. Access to these agents has become easier with the increased use of the internet by these patients.

An internet search using the words 'alternative treatments for BPH' as a search term revealed >1000 sites offering help and advice about BPH. On reviewing these sites there were several available alternative therapies, available via the Internet, for treating BPH:

- *Serenoa repens (Saw Palmetto berry extract);*
- *Hypoxis rooperi (South African star grass);*
- *Pygeum africanum (African plum);*
- *Cucurbita pepo (pumpkin seeds);*
- *Urtica dioica (Stinging nettle);*
- *Secale cerale (Rye pollen);*
- *Flaxseed oil;*
- *Lycopene;*
- *zinc;*
- *β-sitosterol;*
- *selenium.*

Each of these substances can be bought singly but much more common are the various combined 'prostate health' products. Some combination products list numerous ingredients, but the amount of each ingredient varies among products, and therefore if a combination product is selected the patient is required to undertake much painstaking reading of the labels.

Despite the increased use of these products both in Europe and the USA, most urologists have little understanding or knowledge of them. There is also limited evidence of their efficacy [4]. In this article we review the evidence which supports their widespread use by current urological patients.

Serenoa repens (Saw palmetto berry extract)

This agent is derived from the olive-sized berries of the saw palmetto tree and is the most popular phytotherapeutic agent used in the treatment of BPH. The exact mechanism of its action has not been confirmed, although numerous mechanisms have been proposed. These include an anti-inflammatory effect, anti-androgenic activity, inhibitory effect on type 1 and 2 isoenzymes of 5α reductase, and inhibition of prolactin and growth factor-induced cell proliferation. The *in vitro* studies to determine its mechanism of action mainly used supraphysiological dosages, leaving the

significance of these studies open to debate [4-6].

Lowe *et al.* [7] conducted a meta-analysis which set out to review all placebo-controlled trials using the 'Permixon' brand of saw palmetto. There were seven such studies, each short duration, i.e. <3 months, reporting an improvement in symptoms, although the only symptom common to all of the studies was nocturia. There was also an improvement in urine flow when compared with placebo, although this was apparently limited.

The most widely quoted study of 'Permixon' saw palmetto was a comparison with finasteride, a 5α reductase inhibitor, and involved 1098 patients in a 6-month double-blind, randomized controlled study. Both symptom scores and urinary peak flow rate were improved to a similar extent in both groups. The differences were significant when compared with baseline for both drugs. However, there was no placebo group in this trial and therefore the improvements reported might simply have been the result of a placebo effect.

***Pygeum africanum* (African plum)**

In traditional African medicine a tea made from the powdered bark of this tall evergreen tree is drunk to control urinary disorders in men. Today, this supplement is commonly used in France, known more commonly under its trade name of Tadenan. It is frequently sold in combination with saw palmetto and other agents as part of pills for 'male health'.

Tadenan has been shown to have several effects, including inhibition of fibrolast growth factors, antioestrogenic effects, inhibition of chemotactic leukotrienes and other 5 lipo-oxygenase metabolites [4,8].

Breza *et al* [9] evaluated this agent in a recent 2-month open-label trial using a daily dosage of 100 mg. Using the IPSS they reported a 40% reduction in scores and an improvement in mean peak urinary flow rates (10.97 mL/s at baseline to 13.07 mL/s at the end of the study). This was an uncontrolled study, only suggesting a benefit from Tadenan, and obviously no other conclusions can be made. Unfortunately, there are no recent placebo-controlled clinical studies using Tadenan.

***Hypoxis rooperi* (South African star grass)**

This agent contains mainly β-sitosterol, which is thought to be the major active component, with other sterols being detected in lesser amounts [4,5]. The extract of star grass is marketed as Harzol. *In vitro* studies with Harzol show that it enhances the production and secretion of plasminogen activators in isolated epithelial cells. In prostate stromal cell cultures there are also increased levels of TGF-β1 when conditioned with β-sitosterol. TGF-β1 is a differentiation factor and induces apoptosis. These *in vitro* studies have not been verified *in vivo* and they have not been shown to be clinically relevant [4].

This drug has been studied in a double-blind placebo-controlled trial [10]; 200 patients were randomized to receive a placebo or a preparation of phytosterol. In both groups there were symptomatic improvements over baseline measurements and the difference was greater in the phytosterols group. These authors also reported a larger improvement (by 4.1 mL/s) in peak urinary flow rate in those treated with Harzol than in the placebo group. At the 18-month follow-up the group initially given the placebo were given Harzol; they then had improvements which were comparable with the group initially treated with Harzol. Interestingly, the beneficial effect of Harzol continued over the next 12 months regardless of whether the patient stopped Harzol or was given the placebo [11].

***Urtica dioica* (stinging nettle)**

There are at least 16 different preparations of this extract taken from the roots of the stinging nettle. The roots contain a mixture of lectins, phenols, sterols and lignins. Despite its widespread use in Germany for treating BPH there are limited clinical data about its efficacy for this condition. Two double-blind placebo-controlled studies were conducted >10 years ago, but with few patients and in trials <3 months, the data produced were of little value.

***Secale cerale* (rye pollen)**

The commercial preparation 'Cernilton' is pollen prepared from several plants found growing in countries such as Sweden and Switzerland. This drug is available across Europe and is manufactured by microbial digestion of the pollen. As with many alternative medications the mechanism of action remains unclear. Several mechanisms have been proposed, including an improvement in detrusor activity, inhibition of 5α

reductase activity, and an influence on androgen metabolism in the prostate [5].

A study reported in 1996 [4] compared Cernilton with Tadenan over a 4-month period; there was no placebo group in the study. No conclusions can be drawn from this study as the efficacy of Tadenan has, as yet, not been confirmed. Despite this, the authors [4] reported a better response, in terms of symptom scores, residual volumes and peak flow rates, with Cernilton. Clearly, a double-blind placebo-controlled trial is required.

Soy

Environmental factors such as diet are thought to influence the causes of BPH. The underlying rationale for this comes from epidemiological data showing that the incidence of BPH is much lower in the Orient than in the Western world. This difference is not solely caused by genetic differences, as the incidence of BPH increases in those who migrate from the Orient to the USA [12]. When Western and Oriental diets are compared a major difference is the high intake of soybean products in the latter. Genistein is derived from soybean and is a major ingredient of tofu; it is also an active oestrogen, with a high affinity for the oestrogen receptor. Geller et al. [13] studied the effects of genistein on human BPH tissue *in vitro*, showing a dose-dependent decrease in the growth of this tissue. These promising results support a possible role for soy products in managing BPH, although further study is required.

Trace elements

Trace elements such as zinc and selenium are often marketed for their beneficial effects in management of BPH. Although there is no evidence to support the efficacy of such trace elements they are still widely taken by patients.

Combination pills

Many of the above extracts are sold as combination pills. One such combination is 'Prostagutt forte', which is a combination of *Serenoa repens* and *Urtica dioica*; it is widely used although there are no data to support increased efficacy with combination products. This combination pill was compared with finasteride in 489 randomized patients in a 48-week trial; there were no statistically significant differences in the IPSS and peak urinary flow rates between the groups. Unfortunately, because there was no placebo group, no valid conclusions can be made from this study.

Combination pills remain popular, although in many the amount of saw palmetto varies considerably, with some actually containing very little. Despite the lack of evidence for them, there is still widespread use of these products.

What advice should be given to patients?

Lowe et al. [4] reported that should a patient wish to try an alternative medication for BPH, then their advice would be for the patient to select the least expensive one available and trial it for 1 month. If the agent 'does not work', then they should try another brand for a month, even trying a third. Lowe et al. felt that if there was no change after 3 months then the patient would be best advised to take conventional medication. We concur with this advice and also suggest that the patient should be made aware that the alternative medications that they might be taking have not been subjected to the same rigorous clinical trials that 'conventional' drugs are, and that several of these alternative drugs remain 'unknown quantities'.

In summary, patients are now resorting to alternative medications for BPH with increasing frequency. One of the main reasons for this is the increasing public awareness of these previously 'unknown' products, through the expansion of health-food shops but particularly through the increasing use of the Internet by patients.

From this review it is apparent that although the use of these medications is increasing, understanding about them and the mechanisms of action are not increasing at the same rate. Although some of the studies cited here have shown promising results, randomized controlled trials containing many patients followed for long periods are needed. This will allow the initial results reported with these alternative medications to be validated or refuted. Only then will urologists be able to confidently and safely recommend these products to patients.

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Effects of pollen extract EA-10, P_5 on chronic prostatitis or infertility with chronic prostatitis

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KEY WORDS: prostatitis; infertility; free radicals; pollen

ABSTRACT

AIM: To determine the drug action mechanism of pollen extract EA-10, P_5 on the treatment of chronic prostatitis (CP) or infertility with CP. **METHODS:** Malondiadehyde (MDA), super oxide dismutase (SOD), and nitrogen monoxide (NO) were measured by biochemical assay, and zinc content was assayed by atomical spectrophotography in the pre-treatment and post-treatment of CP or infertility with CP. **RESULTS:** Compared with control group, leukocytes in expressed prostatic secretion (LEPS), MDA, and NO were increased, and zinc content and SOD were decreased significantly in the pre-treatment of CP. After the treatment, LEPS was improved, and MDA and NO were reduced, while zinc content were increased apparently and the alteration of SOD was not evident *(*$P>0.05$). In the pre-treatment of infertility with CP, LEPS, MDA, NO, sperm viability, and seminal leukocytes were obviously higher and seminal plasma SOD, zinc content, and sperm motility were obviously lower than those in control group. After the treatment, LEPS, sperm motility, and sperm viability were improved, MDA, NO, and seminal leukocytes were decreased, SOD and zinc content were increased markedly. **CONCLUSION:** There was inter-correlation between oxygen free radicals (OFR) and occurrence, development, and recovery of CP; Change of OFR may be involved in the drug action mechanism of EA-10, P_5 in the treatment of CP or infertility with CP.

Introduction

Chronic prostatitis (CP) is one of the most common diseases in andrology. Its therapeutic efficacy is not very satisfactory. Recent studies showed that CP might defect semen quality. Thus, it is significant to make an investigation of pathogenesis and medication of CP.

Oxygen free radicals (OFR) which causes tissue damage by lipid peroxidation (LPO)[1], includes mainly super oxide anion (O_2), hydrogen peroxide (H_2O_2), hydroxyl free radical (·OH), and nitrogen monoxide (NO). LPO has yielded several types of secondary free radicals and a large number of reactive compounds (including MDA), resulting in the destruction of cellular portion. Of course, cells are equipped with various antioxidant, such as vitamin E, vitamin C, glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and so on. These can scavenge supernumerary OFR and protect organism from cytotoxic effect of OFR[2,3]. In addition, there was apparent negative correlation between semen OFR level and semen quality, but with the increasing of semen OFR level and prolonging of contact time between OFR and sperm, sperm vital force would obviously decrease [4,5]. Studies also showed seminal MDA might be increased apparently in chronic bacterial prostatitis, resulting in the influence of sperm vitality and sperm motility [6,7]. These data indicated that OFR played an important role in pathogenesis of CP and infertility.

EA-10, P_5 is regarded as a satisfactory drug in the treatment of CP. At present, it is still unknown that whether OFR, antioxidase, and zinc content in semen will be regulated in the treatment of CP or infertility with CP by EA-10, P_5. Therefore, we investigated whether EA-10, P_5 could inhibit LPO, and thus to obtain the primary conclusion about drug action mechanism of EA-10, P_5 in our treatment.

MATERIALS AND METHODS

Population. All 68 cases of CP (group I) and 63 cases of infertility with CP (group II) were divided into two groups, which were then subdivided into three treatment subgroups respectively (group A: EA-10, P_5 + Roxithromycin, group B: EA-10, P_5 alone, and group C: Roxithromycin alone). Twenty cases who were normal healthy donors of proven fertility were used as control group. The treatment period was four weeks. Group A received EA-10, P_5 (product from Sweden Pharmacia Allergon AB, 375 mg/pill) and roxithromycin (150 mg/pill) twice daily. Group B-C received respectively EA-10, P_5 and Roxithromycin twice daily. During the treatment, all 131 cases were treated with sitzing bath in hot water and controlled diet (wine and pungent diet prohibited).

Semen samples and treatment. Semen samples were obtained from all cases by masturbation after 3 d of abstinence. Samples were incubated for 20 min in 37 ºC warm bath box. Firstly, regular semen analysis and seminal MDA content were analyzed after semen has been liquefied completely; Secondly, liquefied semen was centrifuged at 1000×*g* for 10 min, and seminal plasma was used to determine the content of NO and SOD. Finally, surplus seminal plasma was frozen at -20 ºC until further use for zinc content assay.

Determination of seminal MDA content and SOD activity. Seminal MDA content was determined by thiobarbituric acid (TBA) method[8]. SOD activity was measured as the inhibition of nitroblue tetrazolium reduction due to superoxide anion generation by xanthine plus xanthine oxidase[9].

Zinc and NO content in seminal plasma assay. Zinc content was assayed by a method based on atomical spectrophotography[10]. The NO concentration was estimated by a method based on nitrite salt response with sulfanilamide to from diazole, which could appear purplish red color reacting with naphthalene ethylenediamine in the acid conditions. The absorbance of 530 nm was measured[11].

Semen parameters. All semen analysis adopt with color quality analysis system of WLJY-9000, which was devised by skill-trade Company Weili Peking. All parameters were settled down to refer to standard of World Health Organization (WHO)[12].

Statistical. Date were expressed as mean ±SD and analyzed with *t*-test. Value of $P<0.05$ was considered to be statistically significant.

RESULTS

Changes in symptom and LEPS in CP or infertility with CP. After the treatment by EA-10, P_5 +Roxithromycin, EA-10, P_5 alone, and roxithromyc alone in CP or infertility with CP, remissive rate of symptom was 92 %, 66.67 %, 68.17 %, and 90 %, 61.91 %, 63.64 %, while effective rate of LEPS was 88 %, 57. 14 %, 59.09 %, and 85 %, 52. 38 %, 54. 55 %, respectively. Therapeutic efficacy in group A was significantly higher than that in group B or C (P<0. 01) (Tab 1, 2).

Tab 1. Changes in symptom and LEPS in different treated groups of CP. $^bP<0.05$ vs EA-10, P_5+Roxithromycin groups.

Treatment	Case	Symptom improved		LEPS improved	
		Efficiency	Percent/%	Efficiency	Percent/ %
EA-10, P_5+Roxithromycin	25	23	92	22	88
EA-10,P_5	21	14	66.67^b	12	57.14^b
Roxithromycin	22	15	68.17^b	13	59.09^b

Tab 2. Changes in the symptom and LEPS in different treated groups of infertility with CP. $^{b}P<0.05$ *vs* EA-10, P_5 +roxithromycin groups.

Treatment	Case	Symptom improved		LEPS improved	
		Efficiency	Percent/%	Efficiency	Percent/%
EA-10, P_5+roxithromycin	20	18	90	17	85
EA-10,P_5	21	13	61.91^{b}	11	52.38^{b}
Roxithromycin	22	14	63.64^{b}	12	54.55^{b}

Changes in LEPS, MDA, SOD, Zinc content, and NO in CP. Compared with control group, LEPS, MDA, and NO were increased, while zinc content and SOD were decreased significantly in the pre-treatment *(*P<0.01). After the treatment, LEPS and zinc content were improved, while MDA and NO were decreased apparently *vs* pre-treatment *(*P<0.01), but there was no obvious alteration of SOD *(*P>0.05) (Tab 3).

Changes in LEPS, MDA, SOD, Zinc content, NO, and semen parameters in infertility with CP. In the pre-treatment, LEPS, MDA, NO, sperm viability, and seminal leukocytes were obviously higher and SOD, zinc content, and sperm motility were obviously lower than those in controlled group *(*P<0.01). After the treatment, LEPS, SOD, zinc content, sperm motility, and sperm viability were improved and MDA, NO, and seminal leukocytes were decreased significantly (P<0.01). Compared with the pre-treatment, MDA levels and seminal leukocytes were reduced significantly in group A than these in group B or C in the post-treatment *(*P<0.01) (Tab 4).

DISCUSSION

In this test, we have used EA-10, P_5 and roxithromycin to treat CP and infertility with CP. Roxithromycin has a good effect to chlamydia besides much of Gram-negative bacteria [13].

Therapeutic efficacy was lower in our works than that in literature. But our therapeutic efficacy was still satisfactory. We considered that the reason may be as follows: (1) Chronic bacterial prostatitis may be selected in all the chosen cases, which might influence therapeutic efficacy of EA-10, P_5. (2) The treatment period was shorter compared with that illustrated in literature. In addition, we have found that therapeutic efficacy in group A was better than in group B or C. This indicated that EA-10, P_5 should be used together with effective antibiotic in the treatment of CP.

Some studies have proved that OFR was related to occurrence and development of CP[3- 4,14]. In our studies, MDA was higher and SOD was lower significantly in the pre-treatment of CP than those in the control group, which suggested that there be an increase of OFR, a decrease of antioxidation, and reinforce a of LPO. But MDA was decreased after the treatment, indicated that OFR was scavenged massively and LPO was obviously inhibited.

Similarly, MDA was higher and SOD was lower significantly in pre-treatment of infertility with CP than those in the control group, which suggested that oxidation be increased and antioxidation be decreased in semen. At the same time, we discovered that sperm motility was declined and sperm viability was raised significantly.

Tab 3. Changes in LEPS, MDA, SOD, Zn^{2+} content, and NO in different treated groups of CP. Mean±SD. $^{b}P<0.05$, $^{c}P<0.01$ *vs* control. $^{d}P>0.05$, $^{f}P<0.01$ *vs* pre-treatment at the same group. $^{h}P<0.05$ *vs* EA-10, P_5+Roxithromycin group.

	Control (n=20)	EA-10,P_5+Roxithromycin (n=25)		EA-10,P_5 (n=21)		Roxithromycin (n=22)	
		pre-treat	post-treat	pre-treat	post-treat	pre-treat	post-treat
LEPS /Hp	3.4±2.1	25±16^{b}	5.0±2.8^{f}	23±13^{b}	7±4^{f}	25±14^{b}	7±4^{f}
MDA/μmol·L^{-1}	4.1±1.1	8.3±1.9^{c}	4.3±1.4^{f}	8.3±1.7^{c}	5.4±1.6^{bfh}	8.4±1.8^{c}	5.2±1.2^{bfh}
Zn^{2+}/mmol·L^{-1}	2.3±0.6	1.2±0.4^{b}	1.8±0.5^{f}	1.2±0.5^{b}	1.6±0.5^{f}	1.2±0.4^{b}	1.6±0.5^{f}
SOD/kU·L^{d}	920±119	850±118^{b}	851±122^{d}	838±110^{b}	840±113^{d}	829±120^{b}	831±123^{d}
NO/μmol·L^{-1}	4.6±1.6	63±20^{c}	39±16^{bf}	63±20^{c}	45±18^{bf}	63±21^{c}	47±18^{bf}

Tab 4. Changes in LEPS, MDA, SOD, Zinc content, NO, and Semen parameters in different treated groups of infertility with CP. Mean±SD. $^{a}P>0.05$, $^{b}P<0.05$, $^{c}P<0.01$ *vs* control. $^{d}P>0.05$, $^{e}P<0.05$, $^{f}P<0.01$ *vs* pre-treatment at the same group. $^{h}P<0.05$ *vs* EA-10, P_5+Roxithromycin groups.

	Control (n=20)	EA-10,P_5+Roxithromycin (n=25)		EA-10,P_5 (n=21)		Roxithromycin (n=22)	
		pre-treat	post-treat	pre-treat	post-treat	pre-treat	post-treat
LEPS/Hp	3.4±2.1	23±13^{e}	6±4^{f}	23±12^{e}	7±5^{f}	23±12^{e}	6±4^{f}
MDA/μmol·L^{-1}	4.1±1.1	9.2±1.6^{e}	5.5±2.1^{f}	9.1±1.9^{e}	7.5±2.4^{bch}	9.1±1.7^{e}	7.2±2.5^{bch}
Zn^{2+}/mmol·L^{-1}	2.3±0.6	1.1±0.4^{e}	1.6±0.4^{bf}	1.1±0.4^{e}	1.5±0.4^{bf}	1.1±0.3^{e}	1.4±0.4^{bf}
SOD/kU·L^{-1}	920±119	653±115^{e}	736±125^{bf}	663±91^{e}	727±104^{bf}	660±97^{e}	722±109^{bf}
NO/μmol·L^{-1}	4.6±1.6	78±20^{e}	55±18^{bf}	76±27^{e}	63±27^{bf}	77±25^{e}	61±21^{bf}
10^{-9}×Sperm density/L^{-1}	76±24	82±49^{a}	79±46^{ad}	79±42^{a}	77±41^{ad}	80±41^{a}	79±40^{ad}
Sperm motility/%	75±12	37±14^{e}	46±14^{bf}	38±17^{e}	43±19^{bf}	37±16^{e}	43±18^{bf}
Sperm viability/%	14±8	36±14^{e}	24±10^{bf}	34±14^{e}	28±11^{bf}	34±13^{e}	28±11^{bf}
10^{-9}×Seminal leukocytes/L^{-1}	0.5±0.3	1.6±0.9^{e}	0.7±0.4^{af}	1.6±0.8^{e}	0.9±0.4^{bf}	1.6±0.8^{e}	0.9±0.5^{bf}

But after the treatment, MDA was decreased and SOD was increased significantly than those in the pre-treatment *(*P<0.01), accompanying with improvement of sperm motility and sperm viability apparently. This indicated that LPO was inhibited and antioxidation was reinforced. From the result above, we believed that EA-10, P_5 could reduce LPO and enhance antioxidation in the treatment of CP or infertility with CP.

In our treatment, antibiotic and EA-10, P_5 were used not only to cure CP but also to improve semen quality. We found that EA-10, P_5 had an effect on weakening oxidative stress and increasing antioxidation in prostatic secretion and semen. This suggested that change of OFR may be involved in the drug action mechanism of EA-10, P_5 in the treatment of CP or infertility with CP. At present, it is known that ferulic acid was an antioxidant containing phenolic hydroxyl[15]; and P_5, one of valid portion in pollen extract EA-10, P_5, may have anti-oxidative effect owing to providing phenolic hydroxy too. Nevertheless this view still needs to be confirmed by more investigation.

It was reported that zinc content in prostatic secretion and semen was higher than in other organ and body fluid, which showed that zinc played an important role in keeping function of prostate and other accessory sex glands. Our studies showed that zinc content was increased accompanying with improvement of an illness state. EA-10, P_5 can enhance zinc content in seminal plasma, which may be related to improve local circumstance.

In summary, all these results could provide us with a possible therapeutics approach to treat infertility with CP. In order to improve therapeutic efficacy, anti-infection and anti-oxidation should be adopted in the treatment of CP or infertility with CP.

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Alternative Therapies for Benign Prostatic Hyperplasia

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Benign prostatic hyperplasia (BPH) is a non-cancerous increase in the tissue mass of the prostate, the muscular gland that produces seminal fluid. BPH is one of the most common medical conditions affecting older men. It may be diagnosed because of urinary symptoms, or identified when a large prostate is found during a routine screening rectal exam. Many men simply have a slow worsening of symptoms throughout their lifetimes, usually beginning in their 50's. Subclinical disease is very common: Approximately 80% of men older than age 60 will have histological changes indicative of BPH upon biopsy; by age 85, this percentage rises to 90%.[1] Some of these patients have severe disease progression, which can lead to incontinence, formation of calculi, frequent urinary tract infection, or permanent urinary tract damage.

Despite the possibility of progression and the bothersome symptoms, many men – perhaps half of those with the condition – never seek medical advice or treatment for BPH symptoms even when those symptoms are severe enough to warrant surgical intervention.[2] Patients may believe that urinary symptoms are part of the normal aging process, that nothing that can be done, or that the available treatments have unacceptable side effects.

Etiology/ Pathophysiology

BPH is related to age-associated changes in the body's hormone levels.[3] Although the clinical ramifications of these hormone changes are not completely characterized, it is known that the levels of serum testosterone decrease while dihydrotestosterone (DHT), the principle androgen responsible for prostatic growth,[4,5] accumulates. Until recently, it was believed that estradiol, converted from testosterone via the aromatase pathway, was implicated in initiating hyperplasia in the stroma and epithelium of the prostate.[4] That now seems unlikely.[6]

Factors that may accelerate disease progression are not well enumerated. Diet is one factor that has been implicated in the development of BPH. A Western diet characterized by high fat intake appears to be linked to earlier onset of BPH.[7,8] One study indicated that low intake of vegetables is positively associated with BPH risk,[9] whereas another drew a correlation between alcohol consumption (more than 25 ounces/ month) and BPH risk.[10] However, each of these studies had limitations and did not demonstrate a clear, direct correlation. Symptoms may be worsened by various factors such as evening intake of liquids, decongestant use, or caffeine, alcohol, or spicy food intake.

Symptoms

Urinary symptoms experienced by patients with BPH can be classified as obstructive or irritative (see Table 1). Obstructive symptoms, sometimes referred to as "voiding symptoms," include a decrease in the force of the urinary stream, difficulty in maintaining or initiating the stream, "dribbling" after ending the stream, or the inability to completely void the bladder. Although some obstructive symptoms can be directly correlated with restriction of urethral flow, others seem to be caused by a decrease in strength of the detrusor muscle or an increase in the excitability of the bladder muscle. Irritative symptoms of BPH also are referred to as "storage symptoms" and include dysuria, urge incontinence, urgency, nocturia, and increased frequency of urination during the day. These seem to be related to irritation of the epithelium of urethral and bladder structures.[3,4]

The International Prostate Symptoms Score (IPSS) is a validated instrument that is widely

accepted for staging the severity of the disease via scoring of subjective symptoms. It also is known as the American Urological Association Urinary Symptoms Index for Prostatism (AUA Index) and is a patient-completed instrument.[4] (See table 2). Score ranges equate to "mild" (0-7), "moderate" (8-19), and "severe" (20-35) symptoms. The Boyarsky Index and the Madsen-Iversen Score are additional instruments that are physician-completed.[11] Other instruments include the BPH Impact Index (BII), and various health-related quality of life (QOL) measurements. Interestingly, the severity of the symptoms experienced does not always correlate directly with the measured extent of glandular enlargement or with the objective measurements utilized to monitor disease progression.

Objective measurements include uroflowmetry, such as the maximum flow rate (MFR) in millimeters of urine passed per second (also termed peak urine flow rate) and post-void residual urine (PVR). Prostate volume usually is measured by transrectal ultrasonography.[3,4] Normal MFR ranges decrease with age. Generally, rates of less than 15 mL/s are considered to be diagnostic of a urinary flow problem; however, because of lower rates often found in older men, MFR rates alone do not indicate the need for therapy. They must be correlated with other physical findings and symptoms.[11]

Conventional Disease Management/ Treatment

"Usual" disease management can differ significantly based on the stage of the disease and the impact of symptoms on the patient's lifestyle. The emphasis of BPH treatment has changed over the last several years from surgical intervention to medical intervention.[2,11] The first medical approach usually is "watchful waiting" – a recognition that the problem exists. Initiation of pharmacological treatment is delayed until symptoms become more bothersome to the patient. The next step generally involves α-1 blockers (doxazosin, tamulosin, or terazosin). These agents relax muscles of the prostate and bladder neck, thus providing symptomatic relief. They are associated with side effects including hypotenstion, dizziness, fatigue, and changes in sleep patterns. Another drug treatment choice is finasteride (a 5-α reductase inhibitor), which decreases the conversion of testosterone to the more active DHT. This agent has been associated with an increased incidence of sexual dysfunction.

A final choice for treatment is surgical intervention, which generally achieves the greatest degree of efficacy. Surgical options include: localized cryotherapy or thermal therapy, transurethral incision of the prostate (TUIP), transurethral resection of the prostate (TURP), electrovaporization (modified TURP), laser surgery, or open prostatectomy. These procedures are costly and confer an increased risk of complications, such as bleeding, infection, incontinence, and sexual dysfunction.[3,4,11,12] All of the above treatment options, with the exception of watchful waiting, are associated with adverse effects and significant cost. For these and other reasons, patients and clinicians are beginning to consider the use of alternative therapies to treat BPH.

All of the treatments that will be discussed here are phytomedicinal in nature and are either whole extracts from botanical sources, or single extracted or manufactured constituents originally from botanical sources. Several of these treatments have been used in other parts of the world for many years. In fact, phytomedicinals are the initial treatments of choice in countries such as France and Germany. Many treatments show significant placebo effects in clinical trials; an examination of multiple BPH treatment trials provided estimates of this effect that ranged from 30% to 40%.[2] The maximal placebo effect usually is seen in the first 4-6 months of therapy.[2]

Pumpkin Seed

The use of pumpkin seed (*Cucurbitae peponis*) for treatment of symptoms associated with BPH has been approved by the Commission E, the German regulatory body responsible for phytomedicinals.

Pumpkin seed is theorized to act by displacing DHT from androgen receptors on human fibroblasts[13] or by antiandrogenic/anti-inflammatory effects.[14] Pumpkin seeds contain phytosterols and, therefore, may bind to androgen receptors. However, there are no human studies to support these proposed mechanisms. In addition, there have been a very limited number of clinical trials evaluating its efficacy, none of which are published in English.

Friedrich et al evaluated the efficacy of 1-2 capsules of Prosta Fink Forte, a brand-name standardized extract, in the treatment of 2,245 patients who were classified as "Alken stage I or II" (this scale has not been equated to other standardized scales).[15] The trial abstract reports that the results demonstrated a decrease in IPSS and quality of life improvement.

The average daily dose is 10 grams of the ground seeds in either single or divided doses.[14,16,17] No adverse reactions or interactions with other drugs have been reported with the use of pumpkin seeds.[14-17]

β-Sitosterol

β-Sitosterol is a dietary supplement used for cholesterol level modification as well as for the treatment of BPH. It is one of the principal phytosterols in pygeum, another supplement used to treat BPH symptoms.

Table 1
Symptoms of benign prostatic hyperplasia

Obstructive
Decreased force of urine stream
Hesitancy or difficulty in initiating stream
Straining to urinate
Dribbling after urination
Incomplete emptying of bladder
Urinary retention
Irritative
Increased urination frequency
Nocturia
Dysuria
Urgency
Urge incontinence

The mechanism of action of the sitosterols is not well understood. Multiple mechanisms have been proposed and include antiandrogenic and antiestrogenic effects, inhibition of prostaglandin synthesis, and anti-inflammatory action.[12,16]

A limited number of trials have evaluated the efficacy of β-Sitosterol. The β-sitosterol study group examined 200 patients and evaluated the efficacy of Harzol® brand β-sitosterol (extracted from African star grass [*Hypoxis rooperi*]) 20 mg three times per day for six months to treat the symptoms of BPH.[18] The researchers noted a significant decrease in modified Boyarsky score (6.7 in the treatment group vs. 2.1 in the placebo group) after four weeks of intervention. The study also showed statistically significant improvement in all of the following parameters in the treatment and placebo groups, respectively: IPSS (7.4 point vs. 2.1 point reduction), QOL (1.4 vs. 0.2 reduction), MFR (5.2 mL/s vs. 1.1 mL/s increase), median flow rate (3.0 mL/s vs. 0.3 mL/s increase), voiding time (15.5 s reduction vs. 2.8 s increase), and RUV (35.4 mL vs. 11.6 mL reduction). Those participants who continued in the β-sitosterol treatment group maintained the improvement in all parameters, but did not demonstrate further improvement during an 18-month follow-up to the study.[19]

A separate trial compared the efficacy of Azuprostat® 130 mg daily and placebo over a six-month period in 177 patients with symptomatic BPH.[20] The treatment group showed a statistically significant decrease in IPSS scores in favor of the treatment group compared to placebo, 8.2 vs. 2.8, as well as marked changes occurred during the first month of therapy, and then additional improvements were demonstrated more slowly throughout the course of treatment.

Very few adverse effects have been reported; the most common side effect is GI disturbance. Two incidents of sexual dysfunction have been reported.[18] The daily dose range is 60-130 mg of

β-sitosterol. Theoretically, interactions could include an additive effect with antihyperlipidemics. For that reason, firm adherence to scheduled cholesterol monitoring is recommended for patients on lipid-lowering medications.

Rye Grass

Rye grass pollen extract is supplement traditionally used for the relief of BPH symptoms. It is believed to work by multiple mechanisms that include antiandrogenic effects, increased bladder muscle control, relaxation of urethral smooth muscle,[21] and inhibition of prostaglandin and leukotriene synthesis.[22]

Several studies have evaluated the efficacy of a particular brand of extract called Cernilton®. One randomized, double blind, clinical trial evaluated Cernilton 126 mg twice daily for six month vs. placebo in 60 patients awaiting operative treatment for outflow obstruction.[23] The results indicated statistically significant improvement in symptoms of nocturia and incomplete emptying. The study also showed a statistically significant decrease in anteroposterior diameter (18.2% in the Cernilton group vs. 4.6% in the placebo group) and a decrease in residual urine volume (101.9 ± 87.3 mL vs. 113.4 ± 87.3 mL). The authors also reported no adverse effects in the treatment group.

One study in 159 patients compared Cernilton to Paraprost®, another product used for BPH symptoms that is a mixture of the amino acid L-glutamine, L-ariginine, and glycine.[24] The study noted significant improvements in the Cernilton group in respect to RUV, MFR, and prostate weight. The investigators determined that the intervention was “moderately effective” in 49.1% of the Cernilton patients as compared to 41.2% in Paraprost group. There were no adverse effects or clinical abnormalities noted.

Another study evaluating Cernilton 126 mg twice daily for 12 weeks in 79 men with mild-to-moderate symptomatic BPH concluded that the rye grass pollen extract caused improvement from baseline in all subjective symptoms measured as well as in flow rate and residual urine volume.[25] The symptoms examined were urgency/discomfort, dysuria, nocturia, incomplete emptying, prolonged voiding, delayed voiding, intermittency, and post-void dribbling. One major limitation to the validity of the study was the lack of a control group.

A more recent study evaluated the efficacy of Cernilton compared to Tadenan® in 89 patients (ages 50-68 years) with Stage I BPH.[22] Tadenan is *Pygeum africanum* extract standardized to 14% triterpenes and 0.5% n-docosanol. The results indicated that both products provided increased flow rate and decreased urine volume.

Table 2

American Urological Association (AUA) Urinary Symptom Index for Prostatism

Symptom	Score: Not at All	< 1 in 5 Times	< ½ the Time	= ½ the Time	> ½ the Time	Almost Always
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month or so, how often have you found you stopped and started several times when you urinated?	0	1	2	3	4	5
4. Over the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the past month or so, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 times	1 time	2 times	3 times	4 times	5 times

Interpretation of AUA Symptom IndexAUA Symptom Score = Sum of Questions 1-7 = _____

Mild prostatism ≤ 7

Moderate prostatism 8-18

Severe prostatism > 18

Highest possible score = 35

Adapted from: Barry M, et al. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol* 1992;148:1549-1557.

In addition, both treatment groups noted an improvement in subjective symptom scores. However, methodological limitations of the study limit its usefulness in clinical decision-making.

Additional studies evaluating the efficacy of Cernilton in the treatment of BPH have reported significant improvements in objective as well as subjective parameters; however, these studies have not been published in English and, therefore, the quality of methodology could not be evaluated.[26,27]

Clinical trials have reported no adverse effects associated with rye grass pollen extract therapy.[24-27] The typical dose of extract studied in trials is 126 mg twice or three times daily for 3-6 months. There are no known interactions with prescription medications. Recommended monitoring is limited to that associated with the disease state.

Stinging Nettle Root

The root of the stinging nettle (*Urtica dioca*) contains polysaccharides which are believed to be responsible for its anti-inflammatory effects. Unidentified components present in certain aqueous, but not lipophilic, extracts reduce the binding of sex hormone binding globulin (SHBG) to prostatic membrane receptors[28] and inhibit 5-α-reductase and prostatic aromatase.[13]

Although four double-blind, placebo-controlled studies have been performed, the quality of the evidence could not be analyzed for this review, because none of the trials have been published in English. Tertiary sources have summarized the results of the trials, which included a total of 210 patients. The most recent trial reported a significantly larger decrease in the IPSS for the nettle root group, but differences in MFR, PVR and QOL score were not significant. Other trials reported an improvement in symptoms, as well as significant improvements in urinary output and MFR and a reduction of SHBG.[13]

An observation study of 67 patients with BPH, ages 53-87 years, was conducted using an aqueous alcohol extract of *Urtica dioica* and *Urtica urens* (dog nettle) roots for six months.[29] The investigatiors documented clinically

Table 3

Clinical trials of alternative therapies for benign prostatic hyperplasia

Supplement	Dose	Urodynamics	Symptoms	Prostate Size	PSA	Nocturia	Side Effects	Efficacy Evidence
Pygeum (14% triterpenes and 0.5% n-docosanol)	75-200 mg/d	+	+	—	U	+	GI discomfort constipation, nausea, diarrhea	Good
Saw Palmetto (> 85% fatty acids and sterol)	160 mg bid	+	+	—	—	+	GI discomfort headache, dizziness, impotence (with high doses)	Good
Stinging Nettle (hydroalcoholic root extract)	600-1,200 mg/d	+	+	—	U	+	GI distress, skin reactions, hyperhidrosis	Fair
Rye Grass Pollen Cernilton®	126 mg bid or tid	+	+	+	U	+	None reported	Fair
β-Sitosterol	60-130 mg QD	+	+	—	U	U	GI upset, nausea, diarrhea	Fair
Pumpkin Seed	10 g/d ground seed	U	+	U	U	U	None reported	Poor

Legend: + = positive effect; — = no effect; U = unknown effect

Efficacy Evidence

Excellent: Several well-designed, controlled human trials with minimal limitations
Good: Controlled human trials, with moderate design limitations
Fair: Controlled human trials, with major design limitations or very small populations
Poor: Few uncontrolled human studies

significant reductions from baseline in episodes of nocturia and corresponding decreases in post-void bladder volume. Prostate volume, as measured by ultrasound, was unchanged.

Stinging nettle root is well tolerated. A six-month study in 4,087 patients were reported very few adverse events. These were GI distress, allergic skin reactions, and hyperhidrosis. There are no known drug interactions with stinging nettle root, although there is a theoretical interaction with finasteride, based on the possibility of a clinically significant level of 5-α-reductase inhibition. Until more is known, concomitant use with finasteride should be avoided or carefully monitored.

Doses of stinging nettle root used in majority of clinical trial ranged from 600 to 1,200 mg/d of hydroalcoholic root extract. Patients who choose to use stinging nettle need to be aware that products are available that use the leaves and other above ground parts of the plant; these products have different chemical components and indications and cannot be used interchangeably.[14]

Pygeum africanum

The lipid-soluble constituents within the bark of the pygeum tree are the most pharmacologically active. The bark contains approximately 14% triterpenes; ferulic acid esters, such as n-docosanol and n-tetracosanol; and several phytosterols.[13,30,31] The anti-inflammatory activity associated with pygeum is due primarily to the action of the triterpenes, which inhibit enzymes implicated in connective tissue deterioration.[13,32] Prostaglandin formation within the prostate also is inhibited.[33] The phytosterols components inhibit prostaglandin synthesis and compete with precursors of androgens.[13] N- docosanol, specifically, has been demonstrated to decrease levels of testosterone, luteinizing hormone (LH), and prolactin in animal studies,[31] although one human study examining testosterone, follicle-stimulating hormone, LH, and estrogens did not find significant changes.[34] Pygeum also has an effect on glandular epithelium, causing "normalization" of histological changes. Inhibition of fibroblasts proliferation and increase in prostatic secretions have been noted, as well as estrogenic and antiestrogenic activity.[35] The slight

decrease in prolactic (which stimulates intraprostatic DHT synthesis and testosterone uptake) and possibly in testosterone; a decrease in proliferation of fibroblasts within the gland;[36,37] and a reduction in the excitability of the detrusor muscle[37] all contribute to alleviation of obstructive symptoms. Irritative symptoms may be relieved more by the increase in prostatic secretions. Although pygeum does inhibit 5-α-reductase, as well as the androgen receptors' binding of DHT, these actions are so minimal they probably are clinically insignificant.[34]

Although 46 investigations of pygeum extract have been conducted to date, only 11 have been placebo-controlled trials. A review of available trials, completed in 1995, concluded that pygeum extract did provide some benefit for both objective and subjective BPH symptoms and should be investigated further in comparison to standard pharmacological treatments.[37] The 43 trials covered in the analysis included a total of 2,262 patients.

Of the placebo-controlled studies, the largest to date (n=263) was published in German by Barlet et al in 1990.[38] A moderately detailed description of the trial was based on an English translation was published in 2000.[39] Results of this trial showed statistically significant improvement compared to placebo for symptoms of daytime and nighttime micturations, residual urine volume (24.5% and 3.5% reduction, respectively), urine volume (12% and 3.2% increase, respectively) and MFR (17.2 and 4.3% increase, respectively), with no change in the prostate volume.

A more recent meta-analysis of pygeum trials was published in 2000.[40] Eighteen trials met the inclusion criteria for the meta-analysis and presented the experiences of 1,562 patients. Thirteen trials were placebo-controlled and five were compared to other treatments such as NSAIDS or other herbal products. No comparisons to finasteride or α-blockers have been conducted. Twelve of the 13 placebo-controlled trials reported more improvement in outcome measures for pygeum groups and one did not find any difference in outcomes. Based on the effect size calculated for each of the trials, an overall effect size was estimated using six trials, an overall effect size was estimated using six trials of pygeum (n=474) that were judged by the authors to be sufficient for result pooling. The overall summary effect size of -0.8 (95% CI, -1.4 to -0.3) calculated by the authors is equivalent to an improvement that is both large and statistically significant. A summary effect size for improvement in nocturia was calculated separately and also was -0.8 (95% CI of -1.4 to -0.1), a moderate to large effect. The authors concluded that overall results of the analysis support improvements in urinary symptoms, peak urine flow, and nocturia that are moderate and statistically significant and that *Pygeum africanum* extracts may be an effective short-term treatment option for patients with BPH symptoms.

Pygeum is well tolerated. Adverse effects reported in studies are mild and include nausea, constipation, diarrhea, and gastrointestinal discomfort.[37,38,40] No interactions with any pharmaceutical agents have been identified or reported, although the possibility of additive hormonal effects should be kept in mind.

Doses used in clinical trials have ranged from 75 to 200 mg/d. One trial compared a 100 mg/d dosage given once daily or in two divided doses and found no difference in outcome.[41] The extract should be standardized to contain 14% triterpenes and 0.5% n-docosanol.

Saw Palmetto

The lipophilic extract of *Serenoa repens* (also known as *Sabal serrulata*) inhibits 5-α-reductase activity, theoretically decreasing the amount of DHT produced from testosterone. Although finasteride more specifically inhibits type two 5-α-reductase, *Serenoa repens* (saw palmetto) inhibits both types one and two.[42] The extent and significance of this activity in vivo is not completely understood, and measurements of the reductase activity are not always significantly decreased.[43] In addition, saw palmetto may decrease prolactic and have anti-inflammatory activity, as well as inhibit fibroblast and epidermal growth factors. Although antiestrogenic effects

may exist, this action has not been well described.

Saw palmetto is the most investigated of all natural product therapies used for treatment of BPH. A systematic review of saw palmetto trials was published in 1998.[44] The investigators analyzed 18 of the 24 trials located in an exhaustive literature search. Analysis revealed 24-28% improvements in nocturia, MFR, mean urine flow, and "urinary tract symptoms" compared to placebo. Improvements were similar when compared to finasteride. The authors concluded that saw palmetto extracts do improve BPH symptoms and that improvements are similar to those experienced with finasteride treatments; however, fewer adverse effects were reported in the saw palmetto groups.

One of the placebo-controlled studies is of particular interest because of the investigators' attempt to reduce the influence of the placebo effect (i.e., BPH symptoms are known to be associated with placebo response rates of 30-40% or more clinical trials[2]). Descotes et al designed a trial in which all patients with a 30% or greater improvement in symptom scores during a 30-day placebo run-in period were excluded from the study population. The remaining patients (n=176) were randomized to receive placebo or a standardized saw palmetto extract 160 mg (Permixon®) twice daily for 30 days. Results included a significantly greater increase in MFR in the Permixon group (28.9% vs. 8.5% for Permixon and placebo, respectively). There also was a significant difference between groups in the decrease of nocturnal urinations (-32.5% vs. -17.7% for Permixon and placebo, respectively). Despite the differences in these more objective parameters, however, the patient-based and physician-based global assessments of efficacy did not reveal significant differences, although they did favor Permixon. The investigators concluded that the overall clinical significance of Permixon treatment probably was less than what might be indicated by the statistically significant differences between treatment groups.[45]

A three-year observational study of the IDS 89 extract of saw palmetto in 435 patients noted an increase in MFR of 6.1 mL/s (13.4 mL/s to 19.5 mL/s) and a 50% reduction in RUV (64 ± 41 mL to 32 ± 36 mL). Nocturia resolved or improved in 73.3% of patients. According to the Boyarsky scale, 53-80% of patients were classified as symptom-free or improved. The investigators noted that the deterioration rate at three years for the 315 patients who completed the study was significantly lower than would be expected in BPH patients not receiving pharmacological or surgical treatment.[46]

Additionally, the standardized saw palmetto lipophilic extract, Permixon, has been compared to the 5-α-reductase inhibitor finasteride.[47] Patients (n=1,098) were randomized to receive Permixon 160 mg twice daily or finasteride 5 mg once daily for 26 weeks. The primary outcome measure was improvement in the IPSS. Assessments of QOL, sexual function, prostate-specific antigen (PSA), urodynamics, and prostate volume were also performed. The IPSS decreased by 37% and 39% and MFR increased by 25% and 30% in the Permixon and finasteride groups, respectively. QOL improved approximately 40% in both groups. Differences were noted between the Permixon and finasteride groups for prostate volume, which decreased 6% vs. 18% respectively, and for PSA, which was unaffected by Permixon, but decreased 41% in the finasteride group. Adverse event reports indicated that sexual function was less affected by Permixon than by finasteride.

Saw palmetto generally is well tolerated. A few reports include adverse events of nausea, headache, dizziness, dysuria, and GI discomfort. A three-year study in 435 patients reported mild adverse events in 34 patients.[13] High doses have been associated with impotence and decreased libido. Although no interactions with pharmaceutical agents have been specifically identified, recommendations to avoid use in conjunction with hormonal or antihormonal therapies seem sound, based on the known pharmacological actions.

Saw palmetto products should be standardized to contain 85% or more fatty acids and sterols. The dose is 160 mg twice daily and may be taken with meals if GI upset occurs.

Conclusions

The most important contradiction to any alternative or complementary therapy is lack of a medical diagnosis. As with any BPH therapy, the possibility of prostate cancer must be eliminated before patients begin any symptomatic treatment.

Monitoring of patients taking any of the alternative treatments discussed should be the same as for any BPH patient: digital rectal exam to observe for increase in prostate size, a scored symptom questionnaire, and a regular serum PSA. An increase in or exacerbation of symptoms may indicate the necessity for uroflowmetry studies, urine culture, or biopsy. In addition, an inquiry into any possible side effects should be a part of any regular clinic visit.

Because BPH usually is a long-term, slowly processing disease state whose standard treatment often includes “watchful waiting,” the use alternative therapies for symptom reduction can be very appropriate. Unfortunately, those products tested in BPH clinical trials are not widely accessible in the United States. Therefore, successful treatment requires products standardized to the same component percentages as the tested products, good patient education to ensure safety, and reasonable patient and physician expectations.

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Biometric Analysis of a Retrospective Documentation Study of Cernilton®N in the Treatment of Patients with Chronic Symptomatic Prostatitis

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Summary

A retrospective documentation study of the efficacy and tolerability of Cernilton®N in the treatment of chronic bacterial prostatitis was conducted by Dr.Dr.med. Erwin W. Rugendorff (Study Director), Giessen, Germany, between January and October 1988. The study included 40 patients between 23 and 69 years of age who were started on treatment with Cernilton®N between January and April 1988. The following parameters were determined before the start and at the end of Cernilton N therapy:

Clinical Features

- Discomfort
- Pain
- Nocturia
- Pollakiuria
- Dysuria

Uroflometry

- Micturition volume
- Peak urine flow
- Mean urine flow
- Flow time
- Micturition time
- Flow rise time
- Uroflow index

Findings on palpation

- Size of the prostate
- Consistency of the prostate
- Tenderness
- Tenderness of the prostate

Leukocyturia

- Leukocytes in midstream urine
- Leukocytes in post-massage urine

Bacteriuria

Ejaculate findings:

- C_{3c}/ ceruloplasmin
- IgG
- Antichlamydia IgA

Adverse drug reactions

Reasons for premature discontinuation of therapy

Assessment of tolerability and efficacy

Results

1. History

   - Acute bacterial infection: *n* = 32
   - TUR-P: *n* = 3
   - Prostatectomy: *n* = 0
   - Previous therapy in the preceeding 3 month: *n* = 15
   - Complicating factors: *n* = 14
     [1. Urethrostenosis: *n* = 4]
     [2. Prostatic calculi: *n* = 3]
     [3. Sclerosis of the bladder neck: *n* = 7]
   - Concomitant diseases: *n* = 8

2. Clinical features and laboratory parameters on admission:

   The patients complained of mild-to-moderate symptoms on admission. Uroflometry detected abnormalities (mean uroflow index = 0.91); the white cell count in the postmassage urine was significantly increased (range 45-610, median 128 WBC/ml); and the C_{3c}/ ceruloplasmin and IgG concentrations in the ejaculate were elevated.

3. Complicating factors:

   The clinical features were, to a large extent, influenced by the presence of complicating factors. While the incidence of manifest symptoms was lower before treatment, the impairment of urine flow was more pronounced.

4. Cernilton®N therapy:
   Cernilton®N therapy was provided on a fixed dosing regimen: 1 tablet t.i.d. The duration of therapy varied between 25 and 196 days; the median duration was 146 days. Treatment was discontinued prematurely in 24 cases for the following reasons:

   - Freedom from symptoms: *n* = 3
   - Marked improvement: *n* = 6

- Ineffectiveness: *n* = 1
- Exacerbation: *n* = 13
- Dropout for personal reasons: *n* = 1

Early dropout reasons are primarily ineffectiveness of therapy/ exacerbation of the disease, while the majority of the patients who discontinued therapy prematurely in the second quarter of the study had achieved either freedom from or a marked improvement in their complaints.

5. Changes in clinical features on Cernilton® N therapy:

In the absence of complicating factors, the following percentages achieved freedom from the following complaints on Cernilton® N therapy:

- Discomfort: 89.5%
- Pain: 83.3%
- Nocturia: 53.8%
- Pollakiuria: 56.0%
- Dysuria: 86.4%

In the presence of complicating factors, however, the response rates to Cernilton® N therapy was significantly lower.

6. Uroflometry:

In the absence of complicating factors, the urine flow parameters showed the following average improvements

- Micturition volume: - 6.1 ml
- Peak urine flow: + 3.0 ml/sec
- Mean urine flow: + 2.7 ml/sec
- Flow time: - 7.1 sec
- Micturition time: - 7.3 sec
- Flow rise time: - 3.0 sec
- Uroflow index: + 0.22

In the presence of complicating factors, uroflometry showed a slight tendency for deterioration. The between-subset (without vs. with complicating factors) differences proved to be significant for peak urine flow, mean urine flow, and uroflow index.

Thus, an increase in the uroflow index was reported for 92.0 percent of patients without complicating factors, while as few as 36.4 percent of those with complications achieved such an improvement.

7. Findings on palpation:
The subset of patients without complicating factors experienced marked improvements in the findings on palpation. Thus, 75.0 percent had nontender prostates after Cernilton® N therapy, while as few as 33 percent of the complicated cases were asymptomatic in this respect.

8. Leukocyturia:

Lower white cell counts in the urine were recorded for the following percentages of patients:

Midstream urine:

- Without complicating factors: 73.1%
- With complicating factors: 28.6%

Post-massage urine:

- Without complicating factors: 80.8%
- With complicating factors: 28.6%

9. Bacteriuria:

Bacteria were again found in the urine in the following percentages of patients:

- Without complicating factors: 15.4%
- With complicating factors: 49.9%

10. Ejaculate findings:

Reductions in the C_{3c}/ ceruloplasmin concentrations were determined for the following percentages of patients:

- Without complicating factors: 80.8%
- With complicating factors: 28.6%

IgG was elevated in

- 7.7% of the patients without complications
- 50.0% of the patients with complications

The majority of patients without complicating factors were either unchanged or achieved improvement.

12 . Antichlamydial IgA:

No change.

13. Adverse drug reactions:

There was no report of an adverse drug reaction.

14. Assessment of tolerability:

Tolerability was rated as good in 35 patients and as fair in 5.

15. Assessment of efficacy:

Efficacy was judged as follows:

Judgment	Without complications	With complications
Normalization	3 (11.5 %)	1 (7.1 %)
Improvement	18 (69.2 %)	3 (21.4 %)
No improvement	5 (19.2 %	10 (71.4 %)
Comparison	p = 0.005 (chi-square test)	

The response was

- 80.8% without complicating factors
- 28.6% with complicating factors

Table of Contents

1. Study Objective

A retrospective documentation study of the efficacy and tolerability of Cernilton® N in the treatment of chronic bacterial prostatitis was conducted.

The present exposé reports about the biometric analysis of the clinical data.

2. Methods

The present retrospective documentation study includes patients with chronic bacterial prostatitis started on Cernilton® N therapy between January and April 1988. The study parameters were determined at baseline (before the start of the study) and at the end of therapy. The study period was > = 6 months for non-dropouts.

Enclosed CRF shows the scope of the clinical and laboratory workup done in the individual patients.

Outcome is assessed by comparing the results obtained for the study parameters before and after treatment. In addition, a comparison is made between

- The patients without complicating factors
  and
- Those with complicating factors (urethrostenosis, prostatic calculi, sclerosis of the bladder neck).

These two subsets are compared by

- The chi-square test for frequency distributions;
- Student's t-test for baseline means and mean pre-post differences (parametric test); and
- The U-test for baseline medians and median pre-post differences (non-parametric test).

The nonparametric statistic is used for testing the white cell count per ml urine.

Both documented parameters and selected derived parameters are included in the statistical analysis.

- *Normal range of peak urine flow:*

  The reference value + -20% range is used as the normal range. The micturition volume-dependent reference values are as follows:

Micturition volume	Reference value
"200 ml" = < 250 ml	22.5 ml/sec
"300 ml" = 250 - < 350 ml	26 ml/sec
"400 ml" = 350 - < 450 ml	28 ml/sec
"500 ml" = > = 450 ml	30 ml/sec

- *Normal range of mean urine flow:*

  The reference value + -20% range is used as the normal range. The micturition volume-dependent reference values are as follows:

Micturition volume	Reference value
"200 ml" = < 250 ml	15 ml/sec
"300 ml" = 250 - < 350 ml	17 ml/sec
"400 ml" = 350 - < 450 ml	20 ml/sec
"500 ml" = > = 450 ml	23 ml/sec

- *Assessment of uroflow index:*

Normal:	> = 1.2
Reduced:	0.8 - < 1.2
Markedly reduced:	< 0.8

The uroflow index I is calculated from the following formula:

$$I = \frac{\text{peak urine flow + Mean urine flow}}{[(\text{micturition volume}/400) + 0.75] * 20}$$

- *Normal range of white cells in the urine:*

Normal:	< = 20 ml urine*
Elevated:	> 20 ml urine

*Urine: Midstream urine
Postmassage urine

- *Ejaculate IgG determination:*

Normal:	0 mg/dl
Elevated:	1 - 20 mg/dl
Markedly elevated:	> 20 mg/dl

3. Patients

The retrospective documentation study included 40 patients with chronic bacterial prostatitis. Their age ranged between 23 and 69 years (median 42 yrs); their mean height was 176 cm, and their mean weight, 75.4 kg (Table 1). Three patients with concomitant BPH, whom we did not exclude from analysis, will be dealt with specifically in Section 6. Prominent history features include (Table 1):

- Acute bacterial infection: *n* = 32
  [bacterial prostatitis: *n* = 32; bacterial urethritis: *n* = 14]
- Previous therapy in the preceding 3 months: *n* = 15
- Complicating factors: *n* = 14
  [1. Urethrostenosis: *n* = 4]
  [2. Prostatic calculi: *n* = 3]
  [3. Sclerosis of the bladder neck: *n* = 7]
- Concomitant diseases: *n* = 8

The patients typically complained of mild-to-moderate symptoms on admission (Table 2). The following mean values were obtained for the uroflow parameters*:

- Micturition volume: 277 ml
- Peak urine flow: 17.7 ml/sec
- Mean urine flow: 9.5 ml/sec
- Flow time: 31.7 sec
- Micturition time: 33.2 sec
- Flow rise time: 10.2 sec
- Uroflow index: 0.91

The prostate was enlarged in 52.5 percent and tender in 85.0 percent of patients. Merely one patient showed a WBC count > 20/ml in the midstream urine. However, all patients had elevated WBC counts in postmassage urine (range: 45-610/ml; median: 128/ml). The C_{3c}/ ceruloplasmin and IgG concentrations in the ejaculate were elevated in all patients; 25.0 percent tested positive for antichlamydial IgA (Table 2).

Documented patients with complicating factors differed markedly from those without complications

- By a reduced incidence of the cardinal clinical features.
- By a more pronounced impairment of urine flow.
  (Table 3)

4. Cernilton® N Therapy

Cernilton® N was prescribed at a dosage of 1 tablet t.i.d. None of the patients included in this retrospective documentation study had his dose modified or his therapy suspended.

The treatment was continued for 25-196 days (median 146 days). Twenty-nine patients discontinued therapy prematurely (< 180 days). Five patients who had almost completed the “180-day minimum” (duration of therapy: 144, 158, 162, 163, 177 days) and another 4 patients who had achieved improvement in their signs and symptoms were obviously not classified as *dropouts*.

Early discontinuation of therapy was primarily due to exacerbation of the disease/ ineffectiveness of treatment (Table 4). Premature termination as a consequence of improvement occurred no earlier than after 3 months’ treatment in the present study cohort.

Treatment was discontinued prematurely in 24 cases for the following reasons:

- Freedom from symptoms: n = 3
- Marked improvement: n = 6
- Ineffectiveness: n = 1
- Exacerbation of the disease: n = 13
- Dropout for personal reasons: n = 1

5. Results

5.1 **Clinical Features**

The percentages of patients with the various clinical features before and after Cernilton® N therapy are shown in Table 5 and Figures 1 through 5:

- Discomfort (Figure 1)
- Pain (Figure 2)
- Nocturia (Figure 3)
- Pollakiuria (Figure 4)
- Dysuria (Figure 5)

The patients of the subset without complicating factors experienced marked improvements. The following percentages of patients achieved freedom from complaints:

- Discomfort 89.5%
- Pain 83.3%
- Nocturia 53.8%
- Pollakiuria 56.0%
- Dysuria 86.4%

The presence of complicating factors results in lower response rates (cf. Figure 6); in particular, there is a comparatively elevated incidence of deterioration. Estimative chi-square tests revealed parallel differences between the subsets “without” and “with” risk factors for the five cardinal features, the differences being marginal, as emerges from the p-values.

5.2 Uroflometry

Table 6 shows the distribution of the uroflometry parameters. The pre-post difference in micturition volume is small. Also, the difference between patients without and those with complicating factors is a minor one. Differences are, however, noted for the following parameters:

Peak urine flow (p = 0.020):
- Without complicating factors: +3.0 ml/sec
- With complicating factors: -1.7 ml/sec

Mean urine flow (p = 0.004):
- Without complicating factors: +2.7 ml/sec
- With complicating factors: -0.8 ml/sec

Flow time (p = 0.013):
- Without complicating factors: -7.1 sec
- With complicating factors: +1.3 sec

Uroflow index (p = 0.006):
- Without complicating factors: +0.22
- With complicating factors: -0.03

For the latter parameter, the overall change results from an average increase from 0.97 to 1.20 for uncomplicated patients and an essentially unchanged result for “high risk” patients (mean change from 0.77 to 0.75). While consistent influences of complicating factors emerge for the other parameters, these fail to attain the level of statistical significance also for high-risk patients, although there is a tendency for improvement. Figures 7 through 13 visualize the average values of the uroflometry parameters before and after Cernilton® N therapy:

- Micturition volume (Figure 7)
- Peak urine flow (Figure 8)
- Mean urine flow (Figure 9)
- Flow time (Figure 10)
- Micturition time (Figure 11)
- Flow rise time (Figure 12)
- Uroflow index (Figure 13)

The tables that follow complement the quantitative analysis of uroflometry by providing a qualitative pre-post comparison of urine flow and uroflow index:

Pre-post comparison of **peak urine flow** (qualitative)						
Post / Pre	Without complications			Complications		
	Below normal	Normal	Above normal	Below normal	Normal	Above normal
Below normal	12	2	1	11	-	-
Normal	-	6	3	2	1	-
Above normal	-	1	-	-	-	-

Pre-post comparison of **mean urine flow** (qualitative)						
Post / Pre	Without complications			Complications		
	Below normal	Normal	Above normal	Below normal	Normal	Above normal
Below normal	16	5	1	12	-	-
Normal	1	2	-	2	-	-
Above normal	-	-	-	-	-	-

Pre-post comparison of **uroflow index** (qualitative)						
Post / Pre	Without complications			Complications		
	< 0.8	0.8 to <1.2	> =1.2	< 0.8	0.8 to <1.2	> =1.2
<0.8	2	2	2	6	1	-
0.8 to <1.2	-	8	6	1	2	-
> =1.2	-	-	5	-	-	1

Marked gradual effects on the uroflow index emerged for the subset without complicating factors. These are particularly prominent for the individual tendency of the uroflow index:

Change	Without complications		Complications	
Increase	23	(92.0 %)	4	(36.4 %)
No change	--	(0.0 %)	1	(2.8 %)
Decrease	2	(8.0 %)	6	(54.5 %)

The differences between the subsets without and with complications are statistically significant (p = 0.002). The trend in the uncomplicated subset (23:2) is quite obvious (p < 0.001 in the signed rank test).

5.3 Findings on Palpation

Normalization of the enlarged prostate at baseline is achieved in 6/12 uncomplicated patients but in none of those with complicating factors. In fact, two patients of the latter group experienced deterioration (Table 7). As regards the consistency of the prostate, 16/26 patients without complications showed improvement while merely 2/14 of those with complications did so (Table 7). Similar results are obtained for tenderness (2 consistently negative cases of both subsets are not included).

Change	Complications NO	YES
Deteriorated	3	8
Unchanged	2	-
Improved	1	-
Asymptomatic	18	4
% asymptomatic	75.0	33.3
Comparison	p = 0.016 (chi-square test)	

The presence of complicating factors also proved to be a limiting factor for the response of the parameter tenderness of the prostate.

For graphic representations of tenderness please refer to Figures 14 and 15:

- Intensity of tenderness (Figure 14)
- Change in tenderness (Figure 15)

5.4 Leukocyturia

While the majority of the patients of the uncomplicated subset showed reductions in their white cell counts in the midstream urine in the course of therapy, the high-risk patients predominantly had higher WBC counts (Table 8; p < .001 for the between-subset comparison of the median change in white cell count). The within-patient pre-post comparison demonstrates reductions in the WBC count

- In 73.1% of the subset without complications, and
- In 28.6% of the subset with complications

(p = 0.005 for the between-subset comparison of the within-patient pre-post change).

Change	Without complications		Complications	
Decrease	19	(73.1 %)	4	(28.6 %)
No change	2	(7.7 %)	-	(0.0 %)
Increase	5	(19.2 %)	10	(71.4 %)

The 19:5 trend (decrease:increase) for uncomplicated cases attains the level of statistical significance (p = 0.007) in the signed rank test.

The increase in the white cell count was beyond the upper limit of normal

- In *n* = 1 patient in the subset without complications, and
- In *n* = 5 patients in the subset with complications

Pre-post comparison of **midstream urine WBC count** (qualitative)				
Post / Pre	Without complications		Complications	
	< = 20	> 20	< = 20	> 20
< = 20	24	1	9	5
> 20	1	-	-	-

The white cell count in postmassage urine decreased in the majority of patients without complications, but tended to increase in most of the high-risk patients (Table 8; p = 0.002 for the U-test subset comparison). The whitin-patient pre-post comparison demonstrates reductions in the WBC count.

- In 80.8% of the subset without complications, and
- In 28.6% of the subset with complications

(p = 0.001 for the between-subset comparison of the within-patient pre-post change).

Change	Without complications		Complications	
Decrease	21	(80.8 %)	4	(28.6 %)
Increase	5	(19.2 %)	10	(71.4 %)

The 21:5 trend (decrease/increase) for uncomplicated cases attains the level of statistical significance (p = 0.002) in the signed rank test.

The reductions in the white cell count was tantamount to normalization

- In *n* = 3 patients of the subset without complications, and
- In *n* = 1 patient of the subset with complications.

Pre-post comparison of postmassage urine WBC count (qualitative)				
Post / Pre	Without complications		Complications	
	< = 20	> 20	< = 20	> 20
< = 20	-	-	-	-
> 20	3	23	1	13

Figure 16 visualizes the leukocyturia findings.

5.5 Bacteriuria

Ten patients again had bacteria detected in their urine in the course of CERNILTON® N therapy, namely

- 4/26 (15.4%) of the patients without complications, and
- 6/14 (49.9%) of the high-risk patients.

5.6 Ejaculate Findings

The pre-post comparison of the ejaculate findings yields the following results (Table 9):

C3c/ceruloplasmin		
Change	Without complications	Complications
Improvement	21 (80.8 %)	4 (28.6 %)
No change	1 (3.8 %)	1 (7.1 %)
Deterioration	4 (15.4 %)	9 (64.3 %)
Comparison	*p* = 0.004 (chi-square test)	

IgG		
Change	Without complications	Complications
Improvement	8 (30.8 %)	3 (21.4 %)
No change	16 (61.5 %)	4 (28.6 %)
Deterioration	2 (7.7 %)	7 (50.0 %)
Comparison	*p* = 0.009 (chi-square test)	

The tendencies for improvement in the subset of uncomplicated cases are quantified by p = 0.001 (21:4) and p = 0.109 (8:2), respectively.

Figure 17 visualizes the ejaculate findings.

5.7 Antichlamydial IgA

No changes were seen on CERNILTON® N therapy.

5.8 Adverse Drug Reactions

There were no adverse drug reactions.

5.9 Assessment of Tolerability and Efficacy

Tolerability was rated as good in 35 patients and as fair in 5 (Table 10). The judgment of efficacy was significantly affected by the presence of complicating factors (urethrostenosis, prostatic calculi, sclerosis of the bladder neck; Table 10). The response rate was

- 80.8% in the subset without complicating factors, and
- 28.6% in the subset with complicating factors.

6. Specific Cases

6.1 Concomitant BPH

Three patients with existing prostatic hyperplasia (BPH) were included in the retrospective documentation study. The following therapeutic responses were obtained:

Pat #1 (absence of complicating factors):

- Improvement in all clinical symptoms;
- Increase in peak and mean urine flow;
- Reduction in flow time, micturition time, and flow rise time;
- Increase in uroflow index from 0.63 to 0.74;
- Normalization of the consistency of the prostate;
- Decrease in tenderness;
- Reduction in white cell count in the urine;
- Decrease in C_{3c}/ ceruloplasmin levels;
- Judgment of efficacy: Improvement.

Pat #12 (sclerosis of the bladder neck):

- No change in clinical features;
- No improvement in urine flow; decrease in uroflow index from 1.07 to 0.94;
- Palpation findings unchaged ;
- Increase in WBC count in postmassage urine;
- Ejaculate unchanged;
- Judgment of efficacy: No improvement.

Pat #14 (sclerosis of the bladder neck):

- Improvement in all clinical symptoms other than dysuria;
- No improvement in urine flow; uroflow index unchaged (0.66);
- Tenderness on palpation improved;
- Decrease in WBC count in post-massage urine from 312 to 92/ ml;
- Decrease in C_{3c}/ ceruloplasmin levels;
- Decrease in IgG;
- Judgment of efficacy: Improvement.

Given the impact of complicating factors on therapeutic effects, the presence of BPH does not cause an additional impairment.

6.2 Patient #26 (absence of complicating factors)

Patient #26 had been admitted to the study with a significantly elevated micturition volume.

- Improvement in all clinical symptoms;
- Normalization of urine flow;
- Tenderness on palpation improved;
- Decrease in WBC count in postmassage urine from 315 to 52/ ml;
- Decrease in C_{3c}/ ceruloplasmin levels;
- Judgment of efficacy: Improvement.

Given the overall consistent pattern of changes in the clinical features on Cernilton® N therapy, exclusion of patient #26 from analysis should be limited to the uroflometry parameters.

7. Data Listings

The individual data are collated in 4 lists:

- Demographics & History (List 1)
- Concomitant diseases/ therapy/ comedications (List 2)
- Clinical features & lab tests (List 3)
- ADR/ dropouts/ judgments (List 4)

Appendices

1 CRF	(6 pages)
10 tablets	(18 pages)
17 figures	(17 pages)
4 data listings	(21 pages)

Cernilton for Benign Prostatic Hyperplasia

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Background

Benign prostatic hyperplasia (BPH), nonmalignant enlargement of the prostate, can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH has been growing steadily. Cernilton, prepared from the rye-grass pollen Secale cereale, is one of the several phytotherapeutic agents available for the treatment of BPH.

Objectives

This systematic review aims to assess the effects of Cernilton on urinary symptoms and flow measures in men with benign prostatic hyperplasia (BPH).

Search Strategy

Trials were searched in computerized general and specialized databases (MEDLINE, EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting manufacturers and researchers.

Selection Criteria

Trials were eligible if they were: (1) randomized controlled trials or controlled clinical trials comparing Cernilton with placebo or other BPH medications in men with BPH; and (2) included clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements.

Data collection and analysis

Information on patients, interventions, and outcomes was extracted by at least two independent reviewers using a standard form. Main outcome measure for comparing the effects of Cernilton with placebo and standard BPH medications were the change in urologic symptoms scales. Secondary outcomes included changes in nocturia as well as urodynamic measures (peak and mean urine flow, residual volume, prostate size). Main outcome measure for side effects was the number of men reporting side effects. MAIN RESULTS: 444 men were enrolled in 2 placebo-controlled and 2 comparative trials lasting from 12 to 24 weeks. Three studies used a double-blind method although treatment allocation concealment was unclear in all. Cernilton improved "self rated urinary symptoms" (percent reporting satisfactory or improving symptoms) versus placebo and Tadenan. The weighted risk ratio (RR) for self-rated improvement versus placebo was 2.40 [95% CI = 1.21, 4.75], and the weighted RR versus Tadenan was 1.42 [95% CI = 1.21, 4.75]. Cernilton reduced nocturia compared with placebo and Paraprost. Versus placebo, the weighted RR was 2.05 [95% CI = 1.41, 3.00], and versus Paraprost, the WMD was -0.40 times per evening [95% CI = -0. 73, -0.07]. Cernilton did not improve urinary flow rates, residual volume or prostate size compared to placebo or the comparative study agents. Adverse events were rare and mild. The withdrawal rate for Cernilton was 4.8% compared to 2.7% for placebo and 5.2% for Paraprost.

Reviewer's Conclusions

The Cernilton trials analyzed were limited by short duration, limited number of enrollees, gaps in reported outcomes, and unknown quality of the preparations utilized. The comparative trials lacked a proven active control. The available evidence suggests Cernilton is well tolerated and

modestly improves overall urologic symptoms including nocturia. Additional randomized placebo and active-controlled trials are needed to evaluate the long-term clinical effectiveness and safety of Cernilton.

• Review
• Review, Academic
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Publication Types:

The National Institutes of Health chronic prostatitis symptom index (NIH-CPSI，日本語版・岡山大学案）の有用性と同案を用いた慢性非細菌性前立腺炎に対するセルニチンポーレンエキスの臨床評価

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安東　栄一　　公文　裕巳

A JAPANESE VERSION OF THE NATIONAL INSTITUTES OF HEALTH CHRONIC PROSTATITIS SYMPTOM INDEX (NIH-CPSI, OKAYAMA VERSION) AND THE CLINICAL EVALUATION OF CERNITIN POLLEN EXTRACT FOR CHRONIC NON-BACTERIAL PROSTATITIS

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(Purpose) The chronic prostatitis syndromes are common disorders in urologic practice and present various clinical symptoms. The development of a chronic prostatitis symptom index appropriate for judgment of therapeutic effects is awaited since the pathophysiology and appropriate treatment are not well defined so far. We developed a Japanese version of the National Institutes of Health Chronic Prostatitis Symptoms Index (NIH-CPSI, Okayama version), and examined its usefulness. In addition, we evaluated clinical effects of Cernilton® for chronic nonbacterial prostatitis using this symptom index.

(Subjects and methods) A total of 87 patients including 34 patients with NIH chronic prostatitis category III, 35 patients with BPH and 18 patients for control group who visited the Department of Urology at Okayama University Medical School filled in the questionnaire of our Japanese version of the NIH-CPSI to compare the NIH-CPSI scores among three groups. Twenty-four patients with NIH chronic prostatitis category III (IIIa 16, IIIb 8) were treated with Cernilton® and the NIH-CPSI scores were examined before and after its administration.

(Results) The pain/discomfort domain score was 9.79 (mean) in the chronic prostatitis group, 1.66 in the BPH group and 0.39 in the control group ; that of the urinary symptom domain was 3.82, 3.29 and 0.72, respectively ; and that of the quality of life (QOL) was 8.21, 4.17 and 1.39, respectively. The pain/discomfort domain score was significantly higher in the chronic prostatitis group than in the other groups ; the QOL domain score was higher in the order of the chronic prostatitis group, the BPH group and the control group. In the chronic prostatitis group, there was a significant, positive correlation between the pain/discomfort domain score and that of the QOL, and between the urinary symptom domain score and that of the QOL. These results suggested the usefulness of our Japanese version of the NIH-CPSI as a parameter of the severity of chronic prostatitis. Examination of changes in the NIH-CPSI scores revealed that scores of the items in all domains were significantly lower 4 to 6 weeks after the start of administration of Cernilton® than those obtained before the drug administra-

tion in patients with chronic prostatitis.

(Conclusions) A Japanese version of NIH-CPSI (Okayama version) accurately reflects clinical symptoms and the QOL in patients with chronic prostatitis. It seemed to be a useful and appropriate system for scoring symptoms of chronic prostatitis, indicating further studies on translation, adaptation and validation of the NIH-CPSI in Japan.

Key words: Chronic prostatitis, NIH-CPSI, Cernilton®

要旨：(目的) NIH-CPSI の日本語版(岡山大学案)を作成し，その有用性について検討した．この symptom index を用いて慢性非細菌性前立腺炎に対するセルニルトン®の臨床効果を評価した．

(対象・方法) 対象は慢性前立腺炎群 34 例，BPH 群 35 例，コントロール群 18 例とし，我々が作成した NIH-CPSI・日本語版 (岡山大学案) のスコアを比較検討した．慢性非細菌性前立腺炎 24 例にセルニルトン®を投与し，投与開始前後の NIH-CPSI スコアを比較検討した．

(結果) 各疾患群のスコアは，痛み・不快感 [慢性前立腺炎群：9.79 (平均値)，BPH 群：1.66，コントロール群：0.39]，排尿刺激症状 [3.82, 3.29, 0.72]，QOL [8.21, 4.17, 1.39] であった．痛み・不快感に関する領域は慢性前立腺炎群が他群と比べ有意に高く，QOL に関する領域は，慢性前立腺炎群，BPH 群，コントロール群の順に高い結果であった．慢性前立腺炎群では痛み・不快感，排尿刺激症状と QOL のスコアに統計学的にそれぞれ順相関が認められ前立腺炎の重症度の指標として有用であることが示唆された．セルニルトン®投与後の各領域のスコアは投与前と比較して有意に低下していた．

(結論) NIH-CPSI・日本語版 (岡山大学案) は，慢性前立腺炎の臨床症状および QOL を的確に反映しており，有用であった．今後さらに，翻訳の質，妥当性および信頼性など検討するに値する症状スコアと考えられた．

キーワード：慢性前立腺炎，症状スコア，セルニルトン®

緒　言

前立腺炎は成人男性に発症する性器疾患の一つで，比較的頻度の高い泌尿器科疾患である．従来，その病型は急性細菌性，慢性細菌性，慢性非細菌性ならびに前立腺痛 (prostatodynia) に分類されてきたが[1]，1995 年には NIH から新しい病型分類が提唱された[2]．それによるとⅠ型が急性細菌性，Ⅱ型が慢性細菌性となり，慢性非細菌性と前立腺痛はⅢ型 (慢性非細菌性/Chronic pelvic pain syndrome) として一括され，それぞれⅢA (炎症性)，ⅢB (非炎症性) に分類された．また新にⅣ型として無症候性・炎症性前立腺炎が加わっている．

このⅢ型前立腺炎は，現在においてもその病因が解明されておらず，各種治療に抵抗性を示し難治性であることから臨床的に課題の多い疾患である．また，Ⅲ型前立腺炎は多彩な臨床症状を呈する病態群であり，その病因の究明，治療効果の判定のために適切な症状スコアの作成が望まれている．1999 年には NIH より慢性前立腺炎での重症度と治療効果判定のための the National Institutes of Health chronic prostatitis symptom index (NIH-CPSI) が公表され[3]，北米を中心にこの NIH-CPSI を用いた研究がいくつか報告されている[4~8]．今回，我々はこの NIH-CPSI の日本語版 (岡山大学案) を作成し，その有用性について検討するとともに，この symptom index を用いて慢性非細菌性前立腺炎/Chronic pelvic pain syndrome (ⅢA 型およびⅢB 型前立腺炎) に対するセルニチンポーレンエキス (セルニルトン®，扶桑薬品) の臨床効果を評価したので報告する．

対象・方法

2000 年 3 月から 2001 年 2 月の期間に岡山大学泌尿器科外来を受診した慢性非細菌性前立腺炎患者 34 例 (ⅢA 型：24 例，ⅢB 型：10 例)，前立腺肥大症 (BPH) 患者 35 例，コントロール患者 18 例を対象とした．患者の年齢は，慢性非細菌性前立腺炎患者では 20～76 歳 (平均±標準偏差：45.0±16.5 歳)，BPH 患者では 51～85 歳 (69.3±6.3 歳)，コントロール患者では 33～82 歳 (53.1±13.9 歳) であった．前立腺炎の診断は尿路感染症臨床試験ガイドライン[9]を参考に，臨床症状と前立腺圧出液所見 (EPS) より行った．EPS 中の細菌数が 10^3CFU/ml 未満 (ただしグラム陽性球菌では 10^1CFU/ml 未満) かつ白血球数が 10WBCs/HPF 以上を ⅢA

型前立腺炎，白血球数が10WBCs/HPF未満をIIIB型前立腺炎と診断した．コントロール患者は疼痛，不快感，排尿症状以外の症状で当科外来を受診した男性患者とした．コントロール患者の疾患の内訳は高尿酸血症4例，PSA高値の精査3例，尿路結石3例，腎嚢胞2例，顕微鏡的血尿2例，その他4例であった．NIH-CPSI・日本語版（岡山大学案）（図1）の作成手順は，まず2名の泌尿器科専門医（著者のうち2名）がNIH-CPSI原本を和訳し，その和訳の内容が原本と比較して相違，矛盾のないことを2名の日本在住米国人（英会話講師と中学校英語講師）に確認した．NIH-CPSIの質問は大きく3領域に分類され，それぞれ痛み・不快感に関する4項目（項目1～4，合計スコア：0～21点），排尿刺激症状に関する2項目（項目5～6，合計スコア：0～10点），QOLに関する3項目（項目7～9，合計スコア：0～12点）の合計9項目から構成されている．今回，我々が作成したNIH-CPSI・日本語版（岡山大学案）に加えthe international prostate symptom score（IPSS）のアンケートを，対象となった患者自身に記載していただき各疾患群でスコアを比較検討した．また，慢性非細菌性前立腺炎患者群では痛み・不快感ならびに排尿刺激症状に関するスコアとQOLに関するスコアの相関関係についても検討した．

慢性非細菌性前立腺炎患者34例のうちセルニルトン[R]（1回2錠，1日3回経口投与）を投与した24例（IIIA型：16例，IIIB型：8例）を対象として，投与開

図1　NIH CHRONIC PROSTATITIS SYMPTOM INDEX（NIH-CPSI）・日本語版（岡山大学案）

痛みあるいは不快感について

1．最近1週間，あなたはどの部位に痛みあるいは不快感を感じましたか？

	はい	いいえ
a．陰嚢と肛門のあいだ（会陰部）	□1	□0
b．精巣（こうがん）	□1	□0
c．ペニスの先（排尿と関係しないもの）	□1	□0
d．下腹部，恥骨部ないし膀胱部	□1	□0

2．最近1週間，以下のことを感じましたか？

	はい	いいえ
a．排尿中の痛みないし灼熱感	□1	□0
b．射精時あるいはその後の痛みないしは不快感	□1	□0

3．最近1週間，これらの痛みあるいは不快感はどの程度の頻度でありましたか？

□0　全くない
□1　まれに
□2　ときどき
□3　しばしば
□4　だいたいいつも
□5　常に

4．最近1週間，あなたの痛みあるいは不快感の程度を平均するとどのくらいですか？

□ □ □ □ □ □ □ □ □ □ □
0　1　2　3　4　5　6　7　8　9　10
全くない　これ以上の痛みはない

排尿について

5．最近1週間，どの程度の頻度で，排尿後に尿が膀胱のなかに残っていると感じましたか？

□0　全くない
□1　5回に1回以下
□2　2回に1回よりはすくない
□3　だいたい2回に1回
□4　2回に1回以上
□5　ほとんど毎回

6．最近1週間，どの程度の頻度で，排尿後、2時間以内にもう一度行くことがありましたか？

□0　全くない
□1　5回に1回以下
□2　2回に1回よりはすくない
□3　だいたい2回に1回
□4　2回に1回以上
□5　ほとんど毎回

症状の影響

7．最近1週間，あなたの症状はあなたが日常おこなっていることにどの程度妨げになりましたか？

□0　全くない
□1　すこし
□2　あるていど
□3　すごく

8．最近1週間，どの程度症状のことが気になりましたか？

□0　全くない
□1　すこし
□2　あるていど
□3　すごく

Quality of life

9．最近1週間の状態が，今後も続くとしたらどう感じますか。

□0　非常に満足
□1　満足
□2　ほぼ満足
□3　満足、不満どちらでもない
□4　やや不満
□5　不満
□6　全く我慢できない

各領域でのスコア一化

・痛み：項目1a, 1b, 1c, 1d, , 2a, 2b, 3および4の総計　点
・排尿症状：項目5と6の総計　点
・QOL：項目7, 8および9の総計　点

始前と投与開始後4～6週目のNIH-CPSI・日本語版（岡山大学案）のスコアを比較し，セルニルトン®の臨床効果を評価した．セルニルトン®の投与期間は4～36週間（平均11.8週間，中央値10週間）であった．なお，セルニルトン®投与開始前1カ月以内に慢性前立腺炎に対して何らかの治療が施行された症例は除外した．

有意差の検定にはWilcoxon signed rank testを用い，相関係数の計算には，正規性を仮定しないノンパラメトリックなSpearmanの相関係数を用いた．

結　果

図2に各疾患群におけるNIH-CPSIの成績を示す．痛み・不快感に関する領域では，慢性前立腺炎群のスコアはBPH群およびコントロール群に比べ有意に高値であった．BPH群とコントロール群では有意差を認めなかった．排尿刺激症状に関する領域では，慢性前立腺炎群とBPH群はコントロール群に比べ有意に高値であった．慢性前立腺炎群とBPH群では有意差を認めなかった．QOLに関する領域では，慢性前立腺炎群，BPH群，コントロール群の順に高値を示し，各疾患群間でそれぞれ有意差を認めた．なお，IIIA型とIIIB型前立腺炎では，各領域のスコアはほぼ同様の傾向を示し，両者間で有意差を認めなかった．NIH-CPSIの公表時に報告された北米における多数例による成績[3]と我々の施設における成績を比較すると，各疾患群でほぼ同様の傾向を示し各領域のスコアの平均値も類似していた（表1）．

慢性前立腺炎群における疼痛・不快感とQOLスコア間の相関係数は0.662（$p<0.0001$），排尿刺激症状とQOLスコア間では0.531（$p=0.0023$）であり，それぞれ統計学的に順相関が認められた（図3）．

IPSSの成績を図4に示す．IPSSは，BPH群，慢性前立腺炎群，コントロール群の順に高値を示し，各疾患群の間でそれぞれ有意差を認めた．IPSSに関するQOLスコア（QOL-IPSS）は，慢性前立腺炎群とBPH群はコントロール群に比べ有意に高値であり，慢性前立腺炎群とBPH群の間では有意差を認めなかった．

III型前立腺炎におけるセルニルトン®投与開始前後のNIH-CPSIのスコアの推移を検討すると，セルニルトン®投与開始前と比較して投与開始4～6週後のスコアはすべての領域で統計学上有意に低下していた（図5）．また，項目9の満足度に関する質問では，やや不満，不満，全く我慢できないとした患者は，投与開始前では91.7%（22/24）であったが，投与開始後には33.3%（8/24）に減少した．ほぼ満足，満足，非常に満足とした患者は，投与開始前には1例も認めなかったが，投与開始後には50%（12/24）に増加した（図6）．各領域のスコアの総合計スコア（0～43点）が投与後に投与前の50%以下に低下した症例は62.5%（15/24），項目9の満足度が投与前より2段階以下に低下した症例は62.5%（15/24）であり，どちらかいずれかを満足した症例は66.7%（16/24）であった．なお，IIIA型とIIIB型前立腺炎における投与前後のスコアの推移はほぼ同様の傾向を示し，2つの病態間でセルニルトン®の有効性に差を認めなかった．

考　察

NIH-CPSIはNIHの強力なサポートにより，北米の

図2　3疾患群におけるNIH-CPSIの成績

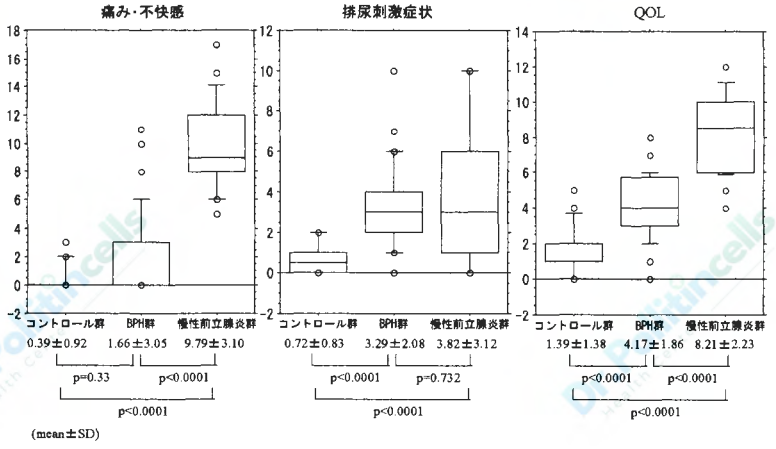
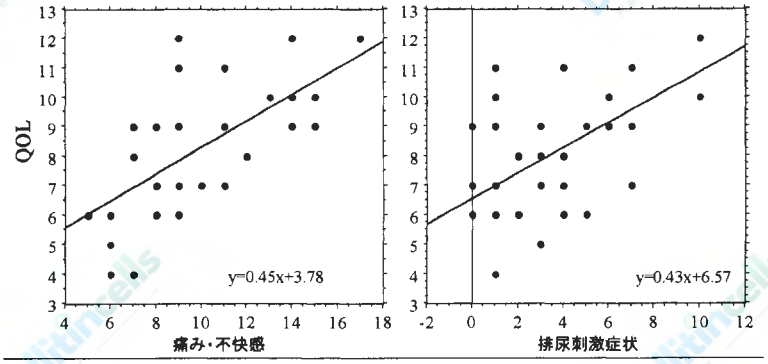


表1　岡山大学泌尿器科泌尿器科と NIH-CPSI 公表時に報告された北米における NIH-CPSI の成績[3]

疾患名(スコアレンジ)	岡山大学泌尿器科	北米(NIH-CPSI 公表時)
慢性前立腺炎		
痛み・不快感(0—21)	9.8±3.1	8.7±5.7
排尿症状(0—10)	3.8±3.1	4.1±3.1
QOL(0—21)	8.2±2.2	6.7±3.6
BPH		
痛み・不快感	1.7±3.0	1.7±2.7
排尿症状	3.3±2.1	3.6±2.5
QOL	4.2±1.9	2.2±2.6
コントロール		
痛み・不快感	0.4±0.9	0.4±1.3
排尿症状	0.7±0.8	1.0±1.3
QOL	1.4±1.4	0.6±1.5

(平均±標準偏差)

図3　III 型前立腺炎における痛み・不快感および排尿刺激症状と QOL スコアの関係



	痛み・不快感	排尿刺激症状
相関係数:	0.662	0.531
P value:	<0.0001	0.0023

多施設共同で作成された慢性前立腺炎に対する新しい症状スコアである．NIH-CPSI では，前立腺炎様症状や QOL に関する多数の質問項目の中から，Cognitive test，Validation test を経て健常者や BPH 患者との鑑別に有用とされ，さらに test-retest reliability の高かった9項目が最終的に採択されている[3]．すでに北米を中心とした多数の施設では，この NIH-CPSI を前立腺炎症状スコアとして採用し，臨床試験の効果判定[15]や慢性前立腺炎の疫学調査[6][7]を報告しいている．一方，本邦では統一された前立腺炎症状スコアはなく，慢性前立腺炎の臨床試験に関する報告では治療効果の判定方法も様々であり，それぞれの結果を比較検討することは困難である．したがって，本邦においても慢性前立腺炎症状スコアの確立が必要であり，今後の国際的 Bridging study も視野に入れると NIH-CPSI を活用するのが妥当と考えられる．

今回，我々の施設でこの NIH-CPSI の日本語版(岡山大学案)を作成し，慢性前立腺炎，BPH ならびにコントロール症例の3疾患群を対象にアンケートを実施し比較検討した．その結果，慢性前立腺炎群では痛み・不快感に関するスコアは他の2疾患群に比べ有意に高値を示し，痛み・不快感が慢性前立腺炎の主症状であることが再確認された．QOL に関するスコアも同様に慢性前立腺炎群が他の2疾患群に比べ有意に高値を示

し，慢性前立腺炎群のQOLが高度に障害されていることがうかがわれた．米国では慢性前立腺炎患者のQOLにあたえる影響は心筋梗塞，不安定狭心症，活動性のクローン病とほぼ同程度と報告されているが[10]，本邦においても慢性前立腺炎患者のQOLは，米国と比べ大差はないものと思われた．また，慢性前立腺炎群の排尿刺激症状に関するスコアはBPH群とほぼ同等であり，慢性前立腺炎患者はBPH患者と同程度の排尿刺激症状を自覚していることが判明した．我々の成績と米国を中心とした北米での成績[3]を比較すると3群間における各領域のスコアは極めて類似していた．以上の成績からも慢性前立腺炎患者の臨床症状および生活に与える影響は日本と米国で同程度であることが示唆されるとともに，NIH-CPSI・日本語版（岡山大学案）の内容はオリジナル版と比較して臨床症状の把握という観点からも大きな差異はないものと考える．さらに，III型前立腺炎では，QOLスコアと痛み・不快感および排尿刺激症状に関するスコアは，それぞれ統計学上順相関を認め，特に痛み・不快感はより強い相関を示したことから，NIH-CPSIの項目にある臨床症状は的確にQOLに反映しており，慢性前立腺炎の重症度の指標として有用であることが示唆された．

しかし，NIH-CPSI・日本語版（岡山大学案）では，今後解決すべき課題も残されている．NIH-CPSIの日本語版を確立するためには，QOL調査票のひとつであるSF-36において，International Quality of Life Assessment Project（IQOLA）が設けたガイドライン[11]に沿って日本語版の開発[12][13]がなされたように国際的基準に合致した翻訳の質，尺度の妥当性および信頼性に関する解析が必須であろう．現在，国島ら[14]の札幌医科大学泌尿器科を中心としたグループもNIH-CPSI・日本語版を作成し，これらの解析を行なっている．今回，岡山大学案として作成したNIH-CPSI・日本語版も，その有用性が示唆されたことから，尺度の妥当性および信頼性など更に詳細な検討を進めるに値するものと考えられた．泌尿器科領域では，国際勃起機能スコアの日本語版が作成され，その妥当性については詳細に検討がなされている[15]．しかし，そのスコアは，一般に使用される段階で日本語訳の内容がわかりにくいとの批判が多く，現在再検討がなされている[16]．NIH-CPSI・日本語版の開発においても注意を要する点であり，日本の患者に理解し易い症状スコアの作成を目指す必

図4　3疾患群におけるIPSSの成績

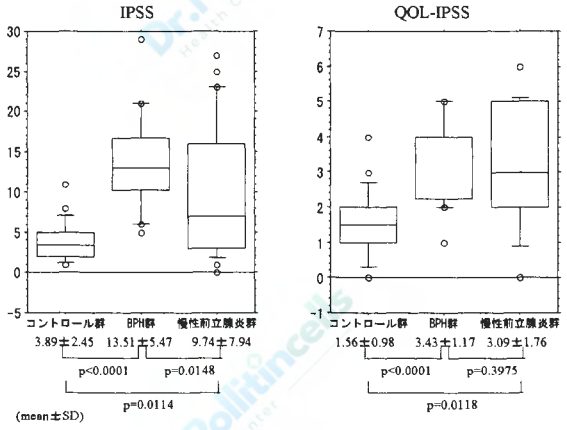


図5　III型前立腺炎におけるセルニルトン投与前後のNIH-CPSIの推移

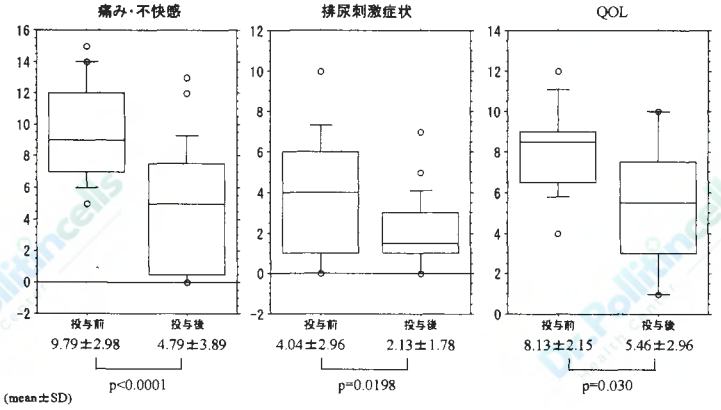
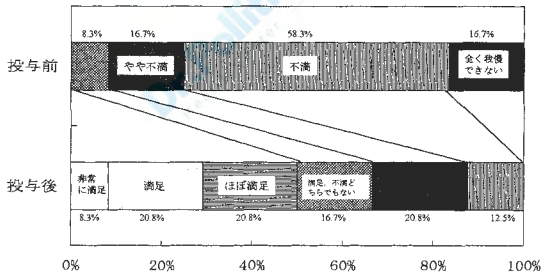


図6 III型前立腺炎におけるセルニルトン投与前後の満足度（NIH-CPSI項目9）の推移



要がある．また，日本の前立腺炎患者の症状をより的確に反映すると考えられる質問項目についても検討を加え，その結果によっては新たな尺度の作成も視野に入れる必要があろう．今後，国内でも多施設による慢性前立腺炎の臨床研究が企画されることが予想され，前立腺炎の症状スコアの作成は重要課題である．今後，NIH-CPSIを中心に検討を進め，必要であれば日本の前立腺炎患者に適した独自の症状スコアの確立も考慮すべきであろう．

慢性非細菌性前立腺炎は多彩な臨床症状を示し，その多くは難治性である．消炎酵素薬をはじめα-ブロッカーや抗菌薬，精神安定薬などの各種薬物治療，前立腺温熱治療，前立腺マッサージなど様々な治療法が試みられているが必ずしも十分な効果を得られていないのが現状である．慢性前立腺炎の病因として，排尿機能障害，前立腺腺管への逆流，通常では検出されない微生物，自己免疫の関与，化学物質，交感神経反射の異常などが考えられているが[17][18]いまだに十分解明されたとは言い難い．また，同時に複数の病因の関与も予測され，難治性の理由の一つと考えられる．植物エキス製剤であるセルニルトン®は慢性前立腺炎に適応のある数少ない薬物の一つである．1960年Ask-Upmarkにより初めて慢性前立腺炎に使用され[19]，その後，セルニルトン®の臨床効果についてはいくつかの検討がなされており，その有効率は75～88%と報告されている[20]～[23]．今回我々は，慢性非細菌性前立腺炎症例（IIIA型：16例，IIIB型：8例）に対するセルニルトン®の有効性について，NIH-CPSI・日本語版（岡山大学案）を用いて再評価した．その結果，セルニルトン®投与開始後4～6週目の評価では，NIH-CPSIの各領域の合計スコアは投与開始前に比べ有意に低下しており，セルニルトン®の有効性が確認された．特に，痛み・不快感に関するスコアの低下は顕著であった．それに伴いQOLスコアも有意に低下していた．項目9の満足度に関する質問では，やや不満，不満，全く我慢できないとした患者は投与前後で91.7%から33.3%に減少し，半数の患者が投与開始後にはほぼ満足，満足，非常に満足と答えており，セルニルトン®の投与により高い満足度が得られていた．各領域のスコアの合計が投与前の50%以下に低下した症例ないしは項目9の満足度が投与前より2段階以下に低下した症例を有効症例とすると，今回の検討における有効率は66.7%であった．

今回，セルニルトン®の臨床効果を投与開始後4～6週目の比較的短期の成績で評価したが，慢性前立腺炎の多くは長期の臨床経過をとり，再発，再燃を繰り返す症例が少なくない．セルニルトン®投与期間中ならびに投与終了後の症状の推移を長期的かつ客観的に解析することが重要であり，そのことからもNIH-CPSIの有用性は高いと考えられる．こうした解析を基に適切な治療（薬剤投与）期間を設定することが今後の課題の一つと考える．また，セルニルトン®の効果を最終的に確認するためにはprospectiveな比較試験が必要不可欠であり，国際的な多施設共同臨床試験の実施が望まれる．

結　語

1）NIH-CPSIの日本語版（岡山大学案）を作成し，その有用性を検討した．同案は，慢性前立腺炎の臨床症状およびQOLを的確に反映しており，有用であった．今後さらに，翻訳の質，妥当性および信頼性など検討するに値する症状スコアと考えられた．

2）NIH-CPSI・日本語版（岡山大学案）を用いてセルニルトン®の臨床効果を検討し，セルニルトン®の慢性前立腺炎に対する有効性が確認された．

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日本泌尿器科学会学術委員長コメント

Response criteria としての symptom score や健康関連 QOL（HQOL）は，近年臨床の現場や種々の臨床疫学研究において盛んに活用されるようになってきた．代表的な健康関連 QOL 尺度の一つである MOS Short-form 36-Item Health Survey (SF-36) は，IQOLA

(International Quality of Life Assesment) によって，現在 25 カ国以上の言語に翻訳され，検討されている．欧米文化のもとで開発された symptom score や QOL 尺度の内容が，言語的に，また文化的に日本人に理解しうるものか，あるいは価値観に適合するものであるか，これらの問題を解決するためには，多段階にわたる翻訳，逆翻訳，翻訳の質的検討，さらに信頼性と妥当性の検討が必要である．このような検討を経た日本語版 SF-36[1]は様々な疾病に臨床応用されている．また，同様に泌尿器系悪性腫瘍に特異的な QOL 評価としては，膀胱癌の FACT-BI，前立腺 FACT-P がこのような検討をへて確立されている[2]．国際前立腺症状スコア (I-PSS) についても，日本泌尿器科学会の ad hoc committee による翻訳の後に，現在 validation study が進行中である．今回岡山大学案として紹介された NIH-CPSI については，同様なステップを踏んで正式の日本語版が作成され，真に臨床に有意義な症状スコアとして今後定着・活用されることが期待される．

赤座　英之
日本泌尿器科学会学術委員長

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ORIGINAL PAPER

Efficacy of pollen extract in association with group B vitamins for pain relief in chronic prostatitis/chronic pelvic pain syndrome: A survey of urologists' knowledge about its clinical application

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Summary

Introduction and aim of the study: *Chronic prostatitis/chronic pelvic pain syndrome (CP/CPSS) is a pathology of high prevalence in Italian male population, difficult to diagnose and to treat and with poor response to conventional therapy.*
Aim of this study was to review the evidence of the literature about the therapeutic effects of a plant product containing flower pollen extracts and group B vitamins on symptoms resolution and amelioration of CP/CPPS patients' quality of life and to investigate the knowledge among practicing urologists about the clinical application of this product.
Materials and methods: *A group of 38 urologists was submitted to an investigational survey of the knowledge of the clinical applications of a plant product containing flower pollen extracts and group B vitamins*
Results: *71% of the urologists interviewed prescribed the plant product for CBP and CP/CPPS at least one time in a month and 11% prescribed it more than 5 times; 67% had evidence of clear ameliorations in pain relief and on patient's quality of life and 47% reported that the effectiveness is comparable to NSAIDs; 39% also reported a significant effect for the improvement of the urinary symptoms of patients. No gastric or general side effects have been noticed during the administration period of this plant product. Finally, the cost of the product has always reported to be sustainable for the patients.*
Conclusions: *From the results of this investigational survey, we can state that the plant product containing flower pollen extracts and group B vitamins is well-known and demonstrated beneficial effects on symptoms resolution and amelioration of quality of life in patients with chronic prostatitis/chronic pelvic pain syndrome.*

KEY WORDS: *Chronic prostatitis; Chronic pelvic pain syndrome; Prostatic benign diseases; Inflammation; Pollen extracts; Group B vitamins.*

Submitted 20 January 2017; Accepted 15 March 2017

INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) has a very high prevalence in Italian population, estimated by a recent multicenter observational study to affect about 13.8% of the male population with an age between 25 and 50 years old.
Several studies in Literature evaluate the prevalence of CP/CPPS in male population. This disorder, difficult to treat, has multiple consequences on lifestyle and on sexual life.
Furthermore, CP/CPPS is a chronic disease, with unsatisfactory results from conventional therapy. Among the multiple therapeutic approaches, long term administration of pollen extracts has been demonstrated to have a precise role in the limitation of flogistic process.
Bacterial and non-infectious chronic prostatitis could represent inciting factors leading to tissue hyper-proliferation and chronic inflammation, probably by an immuno-modulation mediated by prostatic stromal cells, enabling them to induce and sustain intra-glandular immune responses. Group B vitamins have been demonstrated to be capable to interfere with this mechanism, reducing the inflammatory component of CP/CPPS.
Finally, folic acid is well known for its anti-oxidant properties, who join a central role in the reduction of the Intracellular reactive oxygen species (ROS). Several recent studies reported the active role of this vitamin in reducing this component. This factor has a role in the IPB/ Inflammatory pathogenesis.
Commonly CP/CPPS requires a prolonged treatment with anti-infiammatory drugs like corticosteroid or non-steroidal anti-inflammatory drugs (FANS) in combination with antibiotics that can lead to gastrolesive and nephrotoxic side effects. About that aspect, really relevant for clinicians who face this pathology, phytotherapeutics are hopeful options of treatment due to their generally minimal side effects. Many studies in literature have shown that pollen extract and B vitamins induced a significantly and durable reduction of symptoms in patients with CP/CPPS with a relevant improvement in quality of life.
The aim of this paper is to review the actual state of art for clinical application of *Deprox 500®* (flower pollen extracts and group B vitamins) in the treatment of CP/CPPS. Furthermore, we realized an internal survey in our department to investigate the actual knowledge and application of this supplement in current clinical practice in an area of Italy.

No conflict of interest declared.

Materials and methods

Deprox 500® is a phytotherapeutic composed of flower pollen extract (1000 mg), B1 vitamin (1.4 mg), B2 vitamin (1.6 mg), B6 vitamin (2.0 mg), B12 vitamin (1.0 µg), folic acid (300 µg), PP vitamin (18 mg). It can be used for treatment of prostate chronic inflammatory processes often cause of irritative and obstructive symptoms: bacterial prostatitis, abacterial prostatitis, prostatodynia. Its posology is two tablets in a single dose daily and it can be administered for prolonged time for it generally minimal side-effects. Clinical use of this phytoterapeutic is based of molecular effect of its components and their synergic effects.

In order to understand how this dietary supplement is prescribed, in which patients and with which symptoms, we drafted a rapid and concise survey (Table 1). We administered this questionnaire to 10 residents in urology at the *University of Modena and Reggio Emilia* and to 28 urologists working in the provinces of *Modena and Reggio Emilia*.

The questionnaire was answered by mail or through direct compilation, anonymously. The sample was limited, but representative of the two provinces of Modena and Reggio Emilia, who have a population of about 1.3 million of citizens.

Results

Investigational survey on Deprox®

All the 38 physicians completed the questionnaire in all its parts demonstrating that *Deprox 500®* is a known product in this area, with a wide diffusion between young and senior urologists.

By the results (Table 2), it is evident that CBP and CP/CPPS are common pathological conditions. The 58% of physicians have diagnosed those pathologies in 3-6 patients during a month, and 13% of them in more than 6 patients during the same period of time.

11% of physicians surveyed did not believe in the use of dietary supplements for the treatment of any medical condition and consequently refused the use of *Deprox 500®* whereas 71% prescribed *Deprox 500®* at least one time in a month and 11% prescribed it more than 5 times.

The clear majority of physicians who utilized *Deprox 500®* prescribed it correctly for CBP and CP/CPPS.

9% of physicians who prescribe *Deprox 500®* haven't noticed a significant improvement in pain relief and on patient's quality of life suffering from CBP or CP/CPPS, while the 67% had evidence of clear ameliorations and 47% reported that the effectiveness is comparable to NSAIDs. Furthermore 39% also reported a significant effect for the improvement of the urinary symptoms of patients.

No gastric or general side effects have been noticed during the administration period of *Deprox 500®*. Finally, the cost of the integrator has always reported to be sustainable for the patients.

Table 1.
Investigational Survey on Deprox®.

- How many times have you diagnosed Chronic Bacterial Prostatitis (CBP) or Chronic pelvic pain syndrome/chronic prostatitis (CP/CPPS) during the last month?
  - 0-3 times
  - 4-6 times
  - > 6 times
- Do you trust in alimentary supplement (non pharmacological therapy) for the treatment of urological disorders?
  - yes
  - no
- How many times have you prescribed Deprox® during the last month?
  - 0 times
  - 1-5 times
  - > 5 times
- For which urological diseases have you prescribed Deprox® ?
  - none
  - Chronic Bacterial Prostatitis (CBP) in combination with antibiotic therapy chronic prostatitis or Chronic pelvic pain syndrome/chronic prostatitis (CP/CPPS)
  - others urologic diseases (specify)
- Have you noticed an improvement in the quality of life of patients affected of Chronic Bacterial Prostatitis (CBP) or Chronic pelvic pain syndrome/chronic prostatitis (CP/CPPS) with combination of Deprox® + antibiotic therapy?
  - I do not use Deprox®
  - yes
  - no
- Have you noticed an improvement in pain symptoms?
  - I do not use Deprox®
  - yes
  - no
- Have you noticed ameliorations comparable with the results obtained with Fans?
  - I do not use Deprox®
  - yes
  - no
- Have you noticed an improvement in urinary symptoms?
  - I do not use Deprox®
  - yes
  - no
- Have patients reported occurrence of gastric side effects after assumption of Deprox®?
  - I do not use Deprox®
  - yes
  - no
- Have patients reported occurrence of other side effects after assumption of Deprox®?
  - I do not use Deprox®
  - Yes (specify)
  - no
- Is the cost of Deprox® affordable for the majority of patients?
  - I do not use Deprox®
  - yes
  - no

Table 2.
Survey results.

	a n (%)	*b n (%)*	*C n (%)*
• How many times have you diagnosed Chronic Bacterial Prostatitis (CBP) or Chronic pelvic pain syndrome/chronic prostatitis (CP/CPPS) during the last month?	11 (29%)	22 (58%)	5 (13%)
• Do you trust in alimentary supplements (non pharmacological therapy) for the treatment of urological disorders?	34 (89%)	4 (11%)	
• How many times have you prescribed Deprox® during the last month?	7 (18%)	27 (71%)	4 (11%)
• For which urological diseases have you prescribed Deprox® ?	9 (24%)	28 (73%)	1 (3%)
• Have you noticed an improvement in the quality of life of patients affected of Chronic Bacterial Prostatitis (CBP) or Chronic pelvic pain syndrome/chronic prostatitis (CP/CPPS) with combination of Deprox® + antibiotic therapy?	9 (24%)	26 (67%)	3 (9%)
• Have you noticed an improvement in pain symptoms?	9 (24%)	26 (67%)	3 (9%)
• Have you noticed ameliorations comparable with the results obtained with Fans?	9 (24%)	18 (47%)	11 (29%)
• Have you noticed an improvement in urinary symptoms?	9 (24%)	15 (39%)	14 (37%)
• Have patients reported occurrence of gastric side effects after assumption of Deprox® ?	9 (24%)	0 (0%)	29 (76%)
• Have patients reported occurrence of other side effects after assumption of Deprox® ?	9 (24%)	0 (0%)	29 (76%)
• Is the cost of Deprox® affordable for the majority of patients?	9 (24%)	29 (76%)	0 (0%)

Discussion

From the investigational survey on *Deprox 500®*, it can be assumed that it is a dietary supplement widely used by the urologists in our area. The absence of side effects makes it easily and safely administrable for long periods, especially when compared to NSAIDs, which for many physicians are not considered superior for long-term pain control and expose patients to the risk to of gastric or renal side effects. The number of physicians surveyed is limited, but the data reported on the amount of prescriptions and on patient feedback to their physicians indicate that the product has a positive impact on long-lasting diseases as CBP or CP/CPPS.

Flower pollen extracts contained in *Deprox 500®* have an antioxidative action that presents an important role in treatment of many prostate inflammatory diseases.

The product is similar to *Cernilton* that was used by *Rugendorff et al.* in their study to evaluate the effect of treatment with pollen extract in chronic prostatitis and prostatodynia. In this research, 56 of 90 (78%) treated patients had a favorable response, in particular 26 (36%) recovered from their symptoms and 30 (42%) showed a functional improvement, with an increase in flow rate and a decrease of microbiological and physical infection related markers in urine and ejaculate (1).

Another interesting study realized by *Kamijo T et al.* shows the effect of cernitin pollen extracts on experimental sex-hormone induced nonbacterial prostatitis in rats. Cernitin pollen extract consist in a preparation composed by eight different pollens, of a water soluble fraction (T-60) and of a fat soluble fraction (GBX).

These fractions were administered separately. They observed that pollen extracts protect acinar epithelial cells mainly by GBX and inhibits stromal proliferation in association with enhanced apoptosis mainly by T-60 (2).

Wagenlehner et al. conducted in 2009 a multicenter, prospective, randomized, double-blind, placebo-controlled phase 3 study comparing the pollen extract (*Cernilton*) to placebo in patients affected by CP/CPPS. They demonstrated that, compared to placebo, the pollen extract significantly improved total symptoms, pain, and QoL in men with inflammatory CP/CPPS without any relevant side-effect. A 12-week administration of pollen extracts resulted in a significantly symptom improvement compared to control group, without any kind of side-effects.

The effects of *Cernilton* were also assessed for the treatment of benign prostate hyperplasia, that is a condition often related to chronic prostatitis with a systematic review by *Macdonald et al.* who pointed out that *Cernilton* is well tolerated and modestly improves urological symptoms associated with prostate hyperplasia (3).

Many studies in literature show an important role of group B vitamins in chronic pain molecular path-ways. Mader et al evaluated the vitamin status of inpatients with chronic cephalgia and dysfunction pain syndrome and demonstrated the benefic effects of a vitamin supplementation. They demonstrated that 65% of the patients involved into the study had a subclinical vitamin deficiency and they divided them in two groups treated respectively with a vitamin supplementation and with a placebo. A clear reduction in pain was presented in the active-treatment group and a deterioration of pain was more frequently observed in the placebo group (4).

Wang et al. investigated the analgesic role of the B vitamins thiamine (B1), pyridoxine (B6) and cyanocobalamin (B12) in rats with neuropathic pain. They assessed that these vitamins at high doses can effectively reduce

pain and thermal hyperalgesia caused by peripheral sensory neuron injury. Repetitive administration of B vitamins produces a long-term inhibition in both severity and duration of pain and thermal hyperalgesia. This study suggests the clinical utility of the B vitamins in treatment of neuropathic pain due to injury, degeneration or other disorders in the nervous systems (5).

Deprox 500®, due to its composition, can potentially induce the benefic effects of both components: flower pollen extract and B group vitamins.

Cai et al. realized a meaningful study to evaluate the efficacy of pollen extract in association with vitamins (*Deprox 500®*) for pain relief in order to improve the quality of life of young patients affected by chronic prostatitis type IIIb (CP/CPPS). In this study, 20 young men with clinical and instrumental diagnosis of CP/CPPS underwent a treatment consisting of 2 tablets of *Deprox 500®* in a single daily dose for 30 days. The main outcome assessment was the improvement of quality of life evaluated by questionnaires about the symptomatology.

The treatment significantly improved total symptoms, pain and QoL in patients, without relevant side effects. The association with vitamins seemed to improve the antioxidant activity of the pollen extract and the protective effect on the nerves against chronic hyperalgesia (6). The absence of severe side effects is relevant, because CP/CPPS requires a prolonged treatment and common antinfiammatory drugs like FANS can result in relevant side effects.

About that, *Cai et al.* realized a randomized controlled phase III study, including 87 young patients treated with *Deprox 500®* or ibuprofen to evaluate the effect of pollen extract in associations with vitamins treatment in order to early pain relief in patients affected by chronic prostatitis/chronic pelvic pain syndrome. Of the 87 enrolled patients 41 received *Deprox 500®* and 46 received 600 mg ibuprofen. *Deprox 500®* significantly ameliorated the total symptoms, pain and quality of life compared with ibuprofen without severe side effects (4). These results are encouraging and justify the clinical application of *Deprox 500®* in these pathological conditions.

Conclusions

Many studies in Literature have shown that pollen extract and B vitamins induced a significantly and durable reduction of symptoms in patients with CP/CPPS with a relevant improvement in quality of life. Moreover, the absence of several side effects during prolonged treatment is really considerable. Our investigational survey about the use of *Deprox 500®* by physicians has showed that the product is recognized and has a proved beneficial effect.

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RESEARCH ARTICLE Open Access

Eviprostat has an identical effect compared to pollen extract (Cernilton) in patients with chronic prostatitis/chronic pelvic pain syndrome: a randomized, prospective study

Hiromichi Iwamura, Takuya Koie*, Osamu Soma, Teppei Matsumoto, Atsushi Imai, Shingo Hatakeyama, Takahiro Yoneyama, Yasuhiro Hashimoto and Chikara Ohyama

Abstract

Background: Previously reported results of a prospective, randomized placebo-controlled study showed that the pollen extract (Cernilton) significantly improved total symptoms, pain, and quality of life in patients with inflammatory prostatitis/chronic pelvic pain syndrome (CP/CPPS) without severe side effects. A phytotherapeutic agent, Eviprostat, is reportedly effective in a rat model of nonbacterial prostatitis. The aim of the present study was to compare the efficacy and safety of Eviprostat to that of the pollen extract in the management of CP/CPPS.

Methods: The patients with category III CP/CPPS were randomized to receive either oral capsules of Eviprostat (two capsules, q 8 h) or the pollen extract (two capsules, q 8 h) for 8 weeks. The primary endpoint of the study was symptomatic improvement in the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). Participants were evaluated using the NIH-CPSI and the International Prostate Symptom Score (IPSS) at baseline and after 4 and 8 weeks.

Results: In the intention-to-treat analysis, 100 men were randomly allocated to Eviprostat ($n = 50$) or the pollen extract ($n = 50$). Response (defined as a decrease in the NIH-CPSI total score by at least 25 %) in the Eviprostat group and the pollen extract group was 88.2 and 78.1 %, respectively. There was no significant difference in the total, pain, urinary, and quality of life (QOL) scores of the NIH-CPSI between the two groups at 8 weeks. This was also the case with the total, voiding, and storage symptoms of the IPSS. There were no severe adverse events observed in any patients in this study.

Conclusion: Both the pollen extract and Eviprostat significantly reduced the symptoms of category III CP/CPPS without any adverse events. Eviprostat may have an identical effect on category III CP/CPPS compared the pollen extract.

Trial registration: The study was registered with the University Hospital Medical Information Network Clinical Trials Registry in Japan (UMIN000019618); registration date: 3 November 2015.

Keywords: Chronic prostatitis/chronic pelvic pain syndrome, Eviprostat, Pollen extract

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Background

Prostatitis is a relatively common urological disease that occurs in adult men [1]. The U.S. National Institutes of Health (NIH) Advisory Committees divided prostatitis into four categories [2, 3]. Of these, the incidence of category III disease, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is believed to be very high [1]. Category III prostatitis is subdivided into the inflammatory type (IIIA; similar to nonbacterial CP) and non-inflammatory type (IIIB; similar to prostatodynia) based on the presence (IIIA) or absence (IIIB) of leukocytes in prostatic secretions or seminal plasma [2, 3].

While the cause of CP/CPPS is presently unknown, it is a disease that has many clinical issues because it is often resistant to various treatments [4–6]. To date, CP/CPPS has been treated using alpha-blockers, antibacterial agents, anti-inflammatory agents, and phytotherapeutic agents with varying outcomes [4–12]. Phytotherapeutic agents that have been used include pollen extract, quercetin, and saw palmetto. Several years ago, Wagenlehner FM et al. announced the results of a prospective, randomized placebo-controlled study, which indicated that the pollen extract (Cernilton) significantly improved the total symptoms, pain, and quality of life in patients with inflammatory prostatitis/chronic pelvic pain syndrome (CP/CPPS) without any severe adverse effects [6].

Eviprostat is a phytotherapeutic agent widely used in the treatment of prostatic hypertrophy and has been used in Japan and Germany for more than 40 years [13–15]. Eviprostat consists of five components: four are extracted from the umbellate wintergreen Chimaphila umbellata, the aspen Populus tremula, the small pasque flower Pulsatilla pratensis, and the field horsetail Equisetum arvense, and the fifth is germ oil from wheat (Tritium aestivum) [13–15].

Oka et al. administered Eviprostat treatment in a rat model of nonbacterial prostatitis and reported that oxidative stress and proinflammatory cytokines in the enlarged prostate were considerably suppressed, and that Eviprostat may be useful in the clinical treatment of CP/CPPS [13–15]. Here we conducted a randomized prospective study to determine the effectiveness and safety of Eviprostat to treat CP/CPPS in comparison with pollen extract.

Methods

Study design

This double-blind, prospective, randomized and multicentre clinical phase 3 study was conducted in 8 Japan urologic centers to ascertain the safety and efficacy of 8-weeks Eviprostat in men diagnosed with inflammatory CP/CPPS.

The design of the study was in accordance with the guidelines for clinical trials in CP/CPPS described by the NIH Chronic Prostatitis Collaborative Research Network [16].

Inclusion criteria were [1] men between 20 and 80 year of age with symptoms of pelvic pain for 3 months or more before study [2]. Patients with a total National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score ≥15 point [3]. Patients diagnosed with NIH category IIIA and IIIB using the PPMT (pre- and post-massage test) . Category IIIA refers to the presence of white blood cells (WBC) after a prostate massage urine specimen (VB3) (WBC in VB3 > 10/hps). Category IIIB refers to patients with pelvic pain with no evidence of inflammation on VB3.

Exclusion criteria were [1] documented urinary tract infection (midstream urine culture with at least 100,000 colony-forming units per milliliter), [2] history of urethritis, epididymitis or sexually transmitted disease (STD) [3] history of prostate surgery [4] history of urogenital cancer [5] treatment with phytotherapeutic agents, a-blocker agents, or antimicrobials. [6] residual urine volume >50 ml resulting from bladder outlet obstruction (BOO).

The study protocol was approved by the ethical committee of Hirosaki University School of Medicine, Aomori, Japan. Written informed consent was obtained from all patients to participation in this study. This study was registered with the Hirosaki University Hospital Clinical Trials Registry in Japan (2009-013) on 24 May 2009 and was registered with the University Hospital Medical Information Network Clinical Trials Registry in Japan (UMIN000019618) on 3 November 2015.

Study procedure

We included in our study patients with urinary symptoms who met our inclusion criteria from among patients who had been diagnosed with clinically chronic prostatitis in medical interviews. The significance, objectives, and methods of this clinical study were fully explained to the patients, and their voluntary written informed consent was obtained. The patients' subjective symptoms were evaluated using NIH-CPSI (Japanese version) and International Prostate Symptom Score (IPSS) (Japanese version) [17, 18].

We checked patients 1 week after initiating drug therapy to ascertain whether they met the inclusion criteria. Patients were then allocated to receive either Eviprostat [two capsules q8h, with the active substance consisting of the umbellate wintergreen Chimaphila umbellate extract 0.5 mg, the aspen Populus tremula extract 0.5 mg, the small pasque flower Pulsatilla pratensis extract 0.5 mg, the field horsetail Equisetum arvense extract 1.5 mg and germ oil from wheat (Tritium aestivum) 15.0 mg.] or pollen extract (two capsules q8h, with the active substance consisting of 60 mg Cernitin T60 and 3 mg Cernitin GBX) The allocation

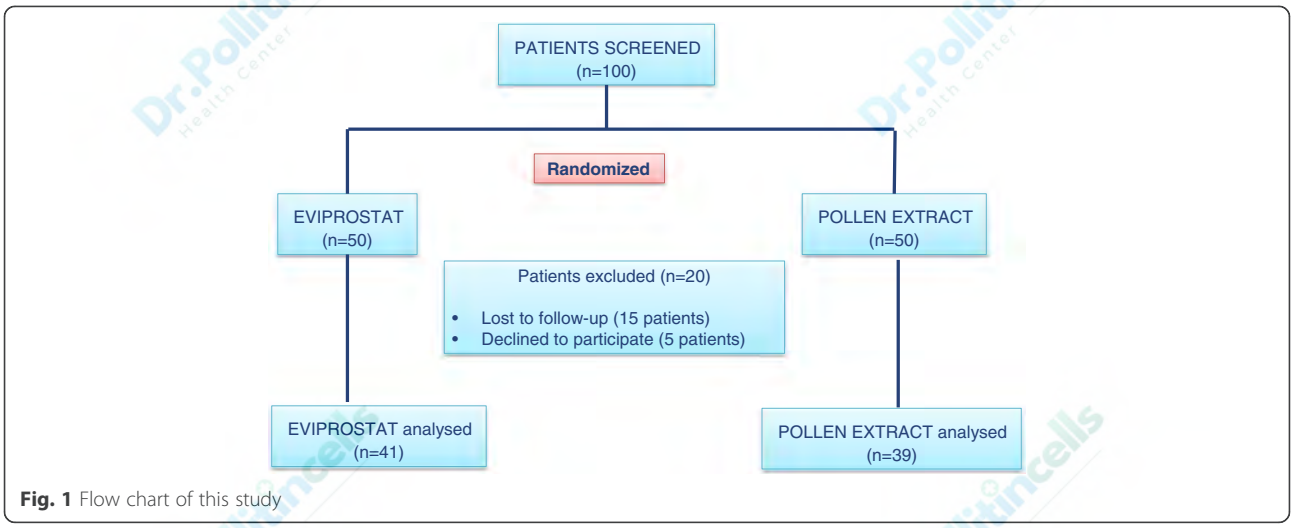

Fig. 1 Flow chart of this study

manager randomly determined which of the 2 drugs would be administered to each patient. Cards detailing the drug to be used were sealed in numbered envelopes and distributed to patients from the smallest number to the largest. The drug to be used was decided on the basis of the card.

Statistical analysis

We used the SPSS 21.0 software package (SPSS, Chicago, IL) for statistical analyses. Intergroup differences were analyzed by the Student's *t*-test. Intragroup differences were analyzed by a paired *t*-test. A value of $P < 0.05$ was considered statistically significant.

Results

We randomized 100 patients diagnosed Category III A/III B prostatitis. 80 patients completed 12 weeks of follow-up and had primary and secondary outcomes ascertained. Flow chart of this study was presented in Fig. 1. In Eviprostat group, 7 patients were lost to follow-up and 2 patients declined to participate the study. In pollen extract group, 8 patients were lost to follow up and 3 patients declined to participate the study.

In Eviprostat group, there were 26 category IIIA patients and 15 category IIIB patients. In pollen extract group, there were 20 category IIIA patients and 19 category IIIB patients. There were no differences from baseline in the number of leukocytes in the prostatic secretion between the two groups.

The baseline characteristics of each study group are presented in Table 1. In the Quality of Life (QOL) domain of NIH-CPSI, there were significant differences between two groups. ($p = 0.014$) Except for QOL domain, there were no significant differences between the two groups at the start of this study.

Response (defined as a decrease in the NIH-CPSI total score by at least 25 %) in the Eviprostat group and the pollen extract group at 4 week was 68.3 and 61.5 %, respectively. Response in the Eviprostat group and the pollen extract group was 88.2 and 78.1 %, respectively. There were no severe adverse events observed in any patients in this study (Table 2). There was no significant difference in the total, pain, urinary, and the QOL scores of the NIH-CPSI between the two groups at 4 weeks and 8 weeks (Fig. 2). There were no significant differences about the total, voiding, and storage symptoms of the IPSS between two groups (Fig. 3). There were no severe adverse events observed in any patients in this study.

Discussion

Antibiotics administration is the standard treatment for chronic bacterial prostatitis [19], however, the standard treatment for CP/CPPS has not yet been established [20].

Table 1 Patients background

	Eviprostat	Pollen extract	p value
Number	41	39	n.s.
Age	50.1 ± 13.7	53.0 ± 14.6	n.s.
CategoryIIIA/IIIB	26/15	20/19	n.s.
Duration of current symptoms (months)	8.2 ± 10.6	9.5 ± 11.2	n.s.
IPSS	10.8 ± 7.5	11.6 ± 7.3	n.s.
NIH-CPSI			
Total score	22.3 ± 4.7	20.3 ± 5.8	n.s.
Pain domain	9.4 ± 4.2	9.2 ± 4.0	n.s.
Urinary domain	4.6 ± 2.8	3.8 ± 2.7	n.s.
QoL domain	8.3 ± 1.6	7.3 ± 2.0	0.014

Table 2 25% response rates for NIH-CPSI

	Eviprostat		Pollen extract	
	4 weeks	8 weeks	4 weeks	8 weeks
Total variation	-8.9	-11.1	-7.8	-10.5
Adverse event (%)	1.7	2.3	2.3	4.7
25 % response rates (%)	68.3	88.2	61.5	78.1

To date, various treatments for CP/CPPS have been reported, including α-blockers, antibiotics, anti-inflammatory agents, phytotherapeutics, and various other modalities [4–12]. However it is believed that these treatments have little effect on major symptoms, such as pain and urinary disturbance, experienced in CP/CPPS that reduce the QOL [21].

In general, patients with CP/CPPS undergo long-term treatment, and therefore, phytotherapeutics such as pollen extract, quercetin, Saw palmetto, or terpenes may be useful because they have few side effects [5]. However, there is no scientific evidence supporting these agents, and only few prospective controlled clinical trials have been conducted.

Since a long time, Cernilton has been used for the treatment of prostatitis [6]. Wagenlehner et al. conducted a prospective, randomized, double-blind, placebo-controlled study to study the effect of Cernilton in patients with CP/CPPS (NIH IIIA). They reported that compared with a placebo, Certilton improved total symptom, pain, and QOL without any side effects [6].

Eviprostat is a phytotherapeutic agent commonly used to treat prostatic hypertrophy in Japan [13–15]. An experiment using nonbacterial prostatitis model suggested that Evoprostat is potentially effective for the treatment of CP/CPPS. Oka et al previously reported that by using a model of non-bacterial prostatitis (NBP) induced in castrated aging rats by the injection of 17b-estradiol, they showed that the increased production of oxidativestress marker malondialdehyde (MDA) and the proinflammatory cytokines TNF-a, IL-6, and IL-8 in prostate tissue homogenates from NBP rats. Eviprostat treatment significantly suppressed oxidative stress and proinflammatory cytokines in the NBP rats [13]. Sugimoto et al reported that chemokines, including CCL2/MCP-1 and CXCL1/CINC-1, were elevated in the prostate and urine of NBP rats, and Eviprostat potently suppressed the increases in CCL2/MCP-1 and CXCL1/CINC-1 [14].

The aim of the present study was to compare the efficacy and safety of Eviprostat to that of the pollen extract in the management of CP/CPPS.

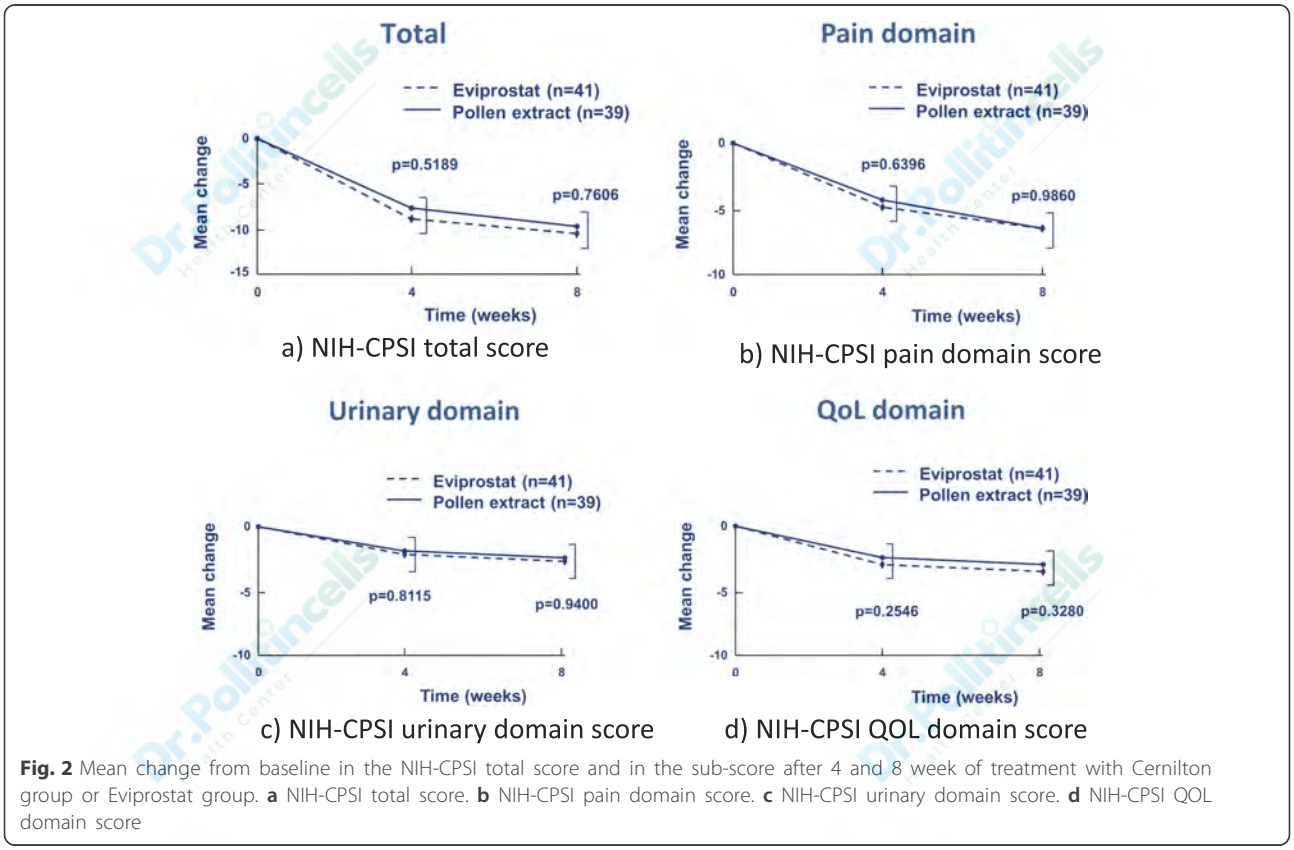

Fig. 2 Mean change from baseline in the NIH-CPSI total score and in the sub-score after 4 and 8 week of treatment with Cernilton group or Eviprostat group. **a** NIH-CPSI total score. **b** NIH-CPSI pain domain score. **c** NIH-CPSI urinary domain score. **d** NIH-CPSI QOL domain score

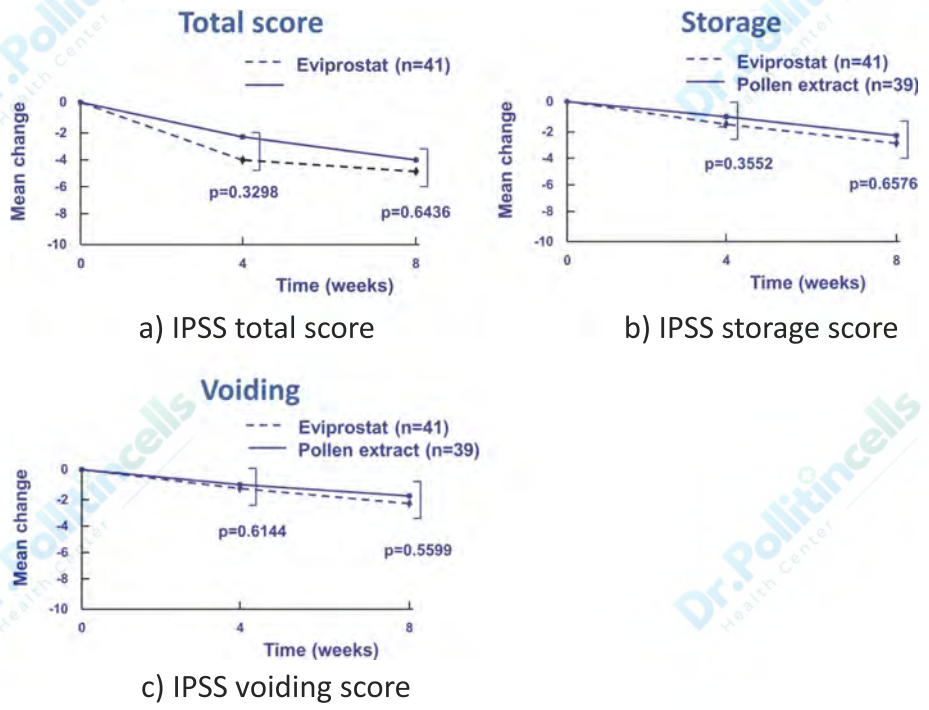

Fig. 3 Mean change from baseline in the IPSS total score and in the sub-score after 4 and 8 week of treatment with Cernilton group or Eviprostat group. **a** IPSS total score. **b** IPSS storage score. **c** IPSS voiding score

In the intention-to-treat analysis, 100 Category III CP/CPPS patients were randomly allocated to Eviprostat (n = 50) or the pollen extract (n = 50). Response (defined as a decrease in the NIH-CPSI total score by at least 25 %) in the Eviprostat group and the pollen extract group was 88.2 and 78.1 %, respectively. There was no significant difference in the total, pain, urinary, and QOL scores of the NIH-CPSI between the two groups at 8 weeks.

This study has several limitations. Study samples were very small, it is necessary to examine the therapeutic effects of Eviprostat with a placebo control and this study was conducted in only Japanese populations.

In the present study, we conducted a prospective, randomized trial to compare the therapeutic effects of Eviprostat and Certilton, the standard treatment for CP/CPPS in Japan, and found that both agents improved CP/CPPS without any side-effects. We believe that Eviprostat is a very promising phytotherapeutic agent for the treatment of CP/CPPS in the future.

Conclusion

Both the pollen extract and Eviprostat significantly reduced the symptoms of category III CP/CPPS without any adverse events. Eviprostat may have an identical effect on category III CP/CPPS compared the pollen extract.

Abbreviations

CP: chronic prostatitis; CPPS: chronic pelvic pain syndrome; hps: high-power field; IPSS: International Prostate Symptom Index; MDA: malondialdehyde; NBP: non-bacterial prostatitis; NIH: National Institutes of Health; NIH-CPSI: NIH-Chronic Prostatitis Symptom Index; PPMT: pre and post massage test; QOL: quality of life; STD: sexually transmitted disease; VB3: prostate massage urine specimen; WBC: white blood cells.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CO made study conception and design. HI, TK, OS, TM, AI, SH, TY, YH and CO participated in the patient's medical treatment. HI collected data and AI performed statistical analysis. HI drafted the first version of the manuscript and TK and CO helped to draft the revised manuscript. All authors have read and approved of this submission.

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Introduction

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The tumor size was assessed by measuring the diameters and calculating the volume according to the following formula: length x width^2 / 2 (7).

After 6 weeks the animals were sacrificed and the tissue removed for histology. A semiquantitative determination of the human LDH isoenzymes (electrophoresis) was planned 6 weeks after transplantation to determine the human origin of the tissue.

Statisical calculations were done to proof the experimental model, to test for homogeneity and for treatment effects. The t-test was used to compare mean values in two treatment groups, a one-way analysis of variance to compare mean values between all three groups, and an analysis of variance for the repeated measurement design. When all volume measurements were considered, the correlation between the two tissue pieces in each mouse showed a very strong correlation. Therefore the side related measurements were not considered an independent variable but interpreted as double measurements.

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The BPH tissue 6 weeks after transplantation is in all cases histologically vital and shows no sign of necrosis or rejection.

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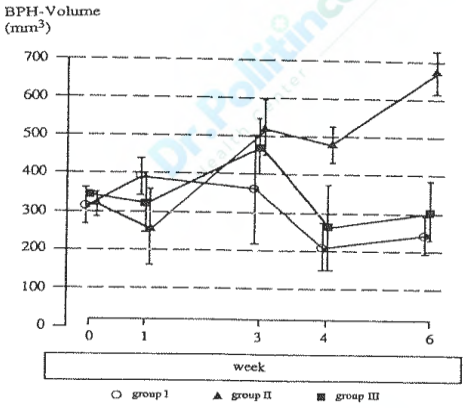

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In group III (hormonal stimulation with DHT and E_2 and treatment with pollen extract) a slight decrease in volume in comparison to the starting volume is noted after 6 weeks, which is significantly different from the mean volume at week 6 in group II (control treated animals) (p = .003) (Table 2). At no time there are any significant differences between group III (Cernilton®N-treated and hormonally induced) and the control group I (Table 3). Analysis of variance reveals a significany difference of the mean at all four measurement points between the two hormonally treated groups (p = .007) demonstrating a growth inhibition of the pollen extract treated animals (group III).

All examined specimens show histologically an epidermoid metaplasia (Fig.3). There is no histological difference between the two treatment groups.

Discussion

The results of this study demonstrate a significant growth-inhibiting effect of orally administered Cernilton®N on heterotransplanted human BPH tissue in nude mice after 6 weeks of treatment under conditions of hormonal stimulation by DHT and E_2. The model was validated and it can therefore be concluded that for the first time a growth-inhibiting effect of a phytopharmacon on human BPH tissue is demonstrated experimentally.

To what extent these results have clinical relevance as a therapeutic principal in patients

Tab. 1 Volume differences ($\bar{x} \pm s$) of the human BPH transplants (nude mouse model) in comparison with the starting volume in the groups without stimulation (I) and with hormonal stimulation (II). Statistical analysis demonstrated the effectiveness of the animal model (for details, see "Materials and Methods").

Time point of control	Group I $\bar{x}$	s	Group II $\bar{x}$	s	Validation of animal model p-value
1. week	74.5	95.3	–62.3	67.1	0.076
3. week	47.3	103.0	203.8	50.4	0.046
4. week	–102.1	106.1	161.5	57.2	0.008
6. week	–69.6	71.6	345.7	69.5	0.001

Tab. 2 Volumes ($\bar{x} \pm s$) of the human BPH transplants (nude mouse model) in the groups with hormonal stimulation (II) and with hormonal stimulation and Cernilton®N treatment (III). Statistical analysis revealed a significant difference after 6 weeks in a time-related comparison between the two groups (for details, see "Materials und Methods").

Time point of control	Group II $\bar{x}$	s	Group III $\bar{x}$	s	Group III vs. Group II
before treatment	318.3	32.7	343.0	6.1	p-value
1. week	256.0	99.5	324.8	78.1	0.516
3. week	522.2	75.0	473.5	72.8	0.208
4. week	479.8	48.0	262.8	112.5	0.047
6. week	673.0	58.4	307.0	79.3	0.003

with BPH cannot be answered definitely. Both stimulating hormores DHT and E_2 are given in relatively high doses, and the amount of pollen extract given exceedes that usually given to patients by a factor of 50. While this is done to allow the effect to take place in the relative short time span of 6 weeks, extrapolation of the data obtained to other experimental or therapeutic *in vivo* situations is not possible.

The pollen exrtact group starts to show a significant difference from the also hormonally treated control group II after about 4 weeks. The clinically observed effects on voiding symptoms residual urine and prostate volume (2,3) indicate positive changes within the first 6 weeks, and therefore there is no discrepancy between the human and the experimental data.

The mechanism of action cannot be determined from our observations since no histological differences were found between the treated groups. Since DHT and E_2 were supplied, the growth inhibition cannot be the result of an inhibition of the 5α-reductase or aromatase, which are target enzymes of innovative drug treatments for BPH (1). It is possible that the prostaglandin- and leukotrienbiosynthesis in the prostate is influenced by the pollen extract (6).

Investigations in rats (10) and dogs (14) have contributed greatly to our understanding of the hormonal mechanisms involved in the etiology of BPH. However, it must be remembered that the rat does not develop spontaneous BPH and that dog BPH differes greatly in its histological characteristic from human BPH. Since in the nude mice model human BPH tissue retrieved at the open prostatectomy is utilized, the observed effect caused by Cernilton®N may resemble the situation in humans more closely.

In summary, the nude mice model described here appears to be useful in experimental studies of the etiology of BPH as well as the mechanisms of effect of drug treatments for BPH. Futher investigations utilizing the pollen extract in this model could serve to elucidate better its pharmacody-namic mechanism of action.

Summary

The mechanism by which human BPH is induced is unresolved. As a result there is currently no established conservative treatment option available for patients with BPH. Up to stage III according to *Vahlensieck* phytotherapy is commoly used as conservative treatment.

Tab. 3 Volumes ($\bar{x} \pm s$) of the human BPH transplants (nude mouse model) in the groups without stimulation (I) and with hormonal stimulation and Cernilton®N treatment (III). Statistical analysis revealed no signifiant differences after 6 weeks in a time-related comparison between the two groups (for details, see "Materials and Methods").

Time point of control	Group I $\bar{x}$	s	Group III $\bar{x}$	s	Group III vs. Group I
before treatment	315.9	48.7	343.0	6.1	p-value
1. week	390.4	50.8	324.8	78.1	0.231
3. week	363.1	141.9	473.5	72.8	0.255
4. week	213.8	63.7	262.8	112.5	0.809
6. week	246.3	54.0	307.0	79.3	0.595

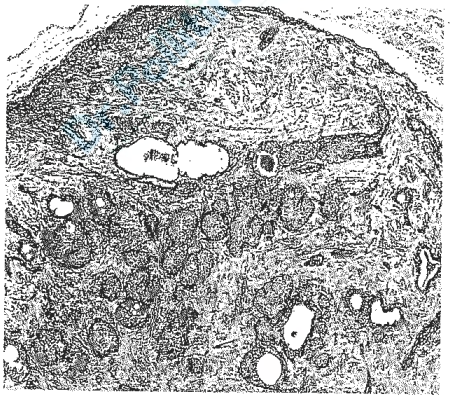

Fig. 3 BPH tissue 6 weeks after transplantation into the nude mouse and hormonal stimulation with DHT and E_2 (for details, see "Materials and Methods") (HE × 250).

We established the heterotransplantation of human BPH tissue in athymic nude mice (NMRI nu/nu mice) as a model to investigate the etiology of BPH as well as the possible mechanisms of therapeutic approaches. The study presented here was designed to test whether the phytophramacon Cernilton®N has a measurable effect on the volume of the transplanted BPH tissue in the model.

Human BPH tissue was grafted on NMRI nu/nu mice. The mice were stimulated by means of silicon implants containing dihydrostestosterone (DHT) and estradiol (E_2). In comparison with the non-stimulated controls, a significant increase in volume was noted ($p = .001$). Cernilton®N was tested in this model and induced a significant growth inhibition of the BPH tissue in comparison to the hormonally stimulated control group ($p = .007$). There were no histological differences noted. In all cases the tissue was vital 6 weeks after transplantation.

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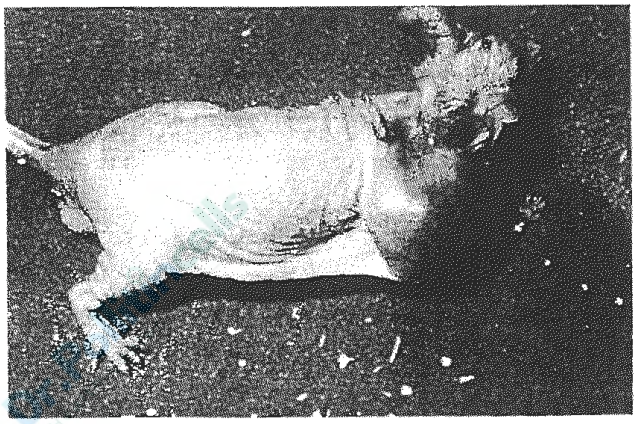

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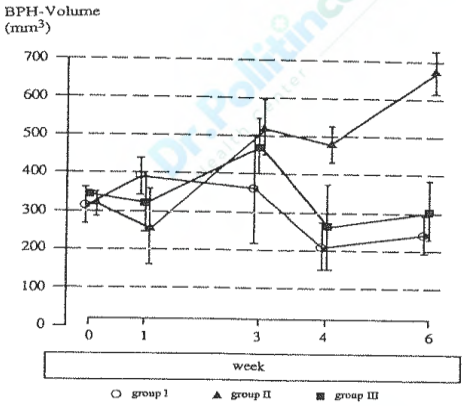

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4. week	479.8	48.0	262.8	112.5	0.047
6. week	673.0	58.4	307.0	79.3	0.003

with BPH cannot be answered definitely. Both stimulating hormores DHT and E_2 are given in relatively high doses, and the amount of pollen extract given exceedes that usually given to patients by a factor of 50. While this is done to allow the effect to take place in the relative short time span of 6 weeks, extrapolation of the data obtained to other experimental or therapeutic *in vivo* situations is not possible.

The pollen exrtact group starts to show a significant difference from the also hormonally treated control group II after about 4 weeks. The clinically observed effects on voiding symptoms residual urine and prostate volume (2,3) indicate positive changes within the first 6 weeks, and therefore there is no discrepancy between the human and the experimental data.

The mechanism of action cannot be determined from our observations since no histological differences were found between the treated groups. Since DHT and E_2 were supplied, the growth inhibition cannot be the result of an inhibition of the 5α-reductase or aromatase, which are target enzymes of innovative drug treatments for BPH (1). It is possible that the prostaglandin- and leukotrienbiosynthesis in the prostate is influenced by the pollen extract (6).

Investigations in rats (10) and dogs (14) have contributed greatly to our understanding of the hormonal mechanisms involved in the etiology of BPH. However, it must be remembered that the rat does not develop spontaneous BPH and that dog BPH differes greatly in its histological characteristic from human BPH. Since in the nude mice model human BPH tissue retrieved at the open prostatectomy is utilized, the observed effect caused by Cernilton®N may resemble the situation in humans more closely.

In summary, the nude mice model described here appears to be useful in experimental studies of the etiology of BPH as well as the mechanisms of effect of drug treatments for BPH. Futher investigations utilizing the pollen extract in this model could serve to elucidate better its pharmacody-namic mechanism of action.

Summary

The mechanism by which human BPH is induced is unresolved. As a result there is currently no established conservative treatment option available for patients with BPH. Up to stage III according to *Vahlensieck* phytotherapy is commoly used as conservative treatment.

Tab. 3 Volumes ($\bar{x} \pm s$) of the human BPH transplants (nude mouse model) in the groups without stimulation (I) and with hormonal stimulation and Cernilton®N treatment (III). Statistical analysis revealed no signifiant differences after 6 weeks in a time-related comparison between the two groups (for details, see "Materials and Methods").

Time point of control	Group I		Group III		Group III vs. Group I
	$\bar{x}$	s	$\bar{x}$	s	
before treatment	315.9	48.7	343.0	6.1	p-value
1. week	390.4	50.8	324.8	78.1	0.231
3. week	363.1	141.9	473.5	72.8	0.255
4. week	213.8	63.7	262.8	112.5	0.809
6. week	246.3	54.0	307.0	79.3	0.595

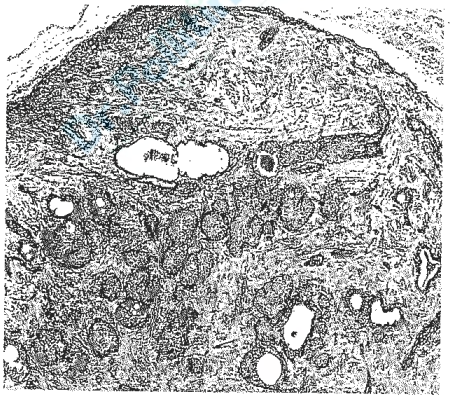

Fig. 3 BPH tissue 6 weeks after transplantation into the nude mouse and hormonal stimulation with DHT and E_2 (for details, see "Materials and Methods") (HE × 250).

We established the heterotransplantation of human BPH tissue in athymic nude mice (NMRI nu/nu mice) as a model to investigate the etiology of BPH as well as the possible mechanisms of therapeutic approaches. The study presented here was designed to test whether the phytophramacon Cernilton®N has a measurable effect on the volume of the transplanted BPH tissue in the model.

Human BPH tissue was grafted on NMRI nu/nu mice. The mice were stimulated by means of silicon implants containing dihydrostestosterone (DHT) and estradiol (E_2). In comparison with the non-stimulated controls, a significant increase in volume was noted ($p = .001$). Cernilton®N was tested in this model and induced a significant growth inhibition of the BPH tissue in comparison to the hormonally stimulated control group ($p = .007$). There were no histological differences noted. In all cases the tissue was vital 6 weeks after transplantation.

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Pollen extract in association with vitamins provides early pain relief in patients affected by chronic prostatitis/chronic pelvic pain syndrome

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Abstract. The therapeutic efficacy for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is currently unsatisfactory. The aim of the present study was to assess the safety and efficacy of pollen extract in association with vitamins (DEPROX 500®) in males with CP/CPPS. All patients with a diagnosis of CP/CPPS attending the same urologic centre between March and October 2012 were enrolled in this randomised controlled phase III study. Participants were randomised to receive oral capsules of DEPROX 500® (two capsules every 24 h) or ibuprofen (600 mg, one tablet three times a day) for four weeks. The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), International Prostate Symptom Score and Quality of Well-Being (QoL) questionnaires were used. In the intention-to-treat analysis, 87 males (25 class IIIa and 62 class IIIb) with a mean age of 33.6±5.9 years were randomly allocated to the DEPROX 500® (n=41) or ibuprofen (n=46) treatment groups. At the follow-up examination (following one month of treatment), in the DEPROX 500® group, 31/41 patients (75.6%) reported an improvement in quality of life, defined as a reduction of the NIH-CPSI total score by ≥25%, compared with 19/46 (41.3%) in the control group (P=0.002). The greater improvement in the DEPROX 500® group compared with the ibuprofen group was statistically significant (treatment difference in the NIH-CPSI pain domain, -2.14±0.51, P<0.001; QoL scores, P=0.002). All patients were negative at the Meares-Stamey test evaluation. Adverse events were less frequent in the DEPROX 500® group than in the ibuprofen group. The DEPROX 500® treatment significantly improved total symptoms, pain and quality of life compared with ibuprofen in patients with CP/CPPS, without severe side-effects.

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Key words: chronic pelvic pain syndrome, pollen extract, chronic prostatitis symptom index, quality of life, prostatitis syndrome

Introduction

Chronic prostatitis (CP) has been described as one of the most common illnesses in males aged <50 years (1), and exhibits different clinical presentations (2). According to the classification of the National Institutes of Health (NIH) (3), class III CP/chronic pelvic pain syndrome (CP/CPPS) is the most frequent category (4), in which either genitourinary symptoms or pain are usually found and the impact on quality of life is considerable (5). The efficacies of current therapies for CP/CPPS are unsatisfactory (6). Phytotherapeutics are a noteworthy option due to their generally minimal side-effects; however, few have been subjected to scientific scrutiny and prospective controlled clinical trials (7,8). In previous years, a number of studies have shown that pollen extract preparations are able to yield a durable and marked reduction of symptoms in young males with CP/CPPS, with an improvement in semen quality and a significant reduction in the NIH-Chronic Prostatitis Symptom Index (CPSI) score (9-11). Previously, Wagenlehner *et al* demonstrated that a standardized pollen extract significantly improved the total symptoms, pain and Quality of Well-Being (QoL) scores in patients with inflammatory CP/CPPS without severe side-effects, highlighting the role of the anti-inflammatory activity of pollen extract (12). In the last year, Cai *et al* demonstrated that pollen extract in association with vitamins significantly improved the total symptoms, pain and QoL scores in patients with non-inflammatory CP/CPPS without severe side-effects in a phase II study (10). Furthermore, the association with vitamins is likely to improve the antioxidant activity of the pollen extract as well as the protective effect on nerves and also reduce the pain in patients with inflammatory or non-inflammatory CP/CPPS (10). The aim of the present study was to assess the safety and efficacy of pollen extract in association with vitamins in comparison with ibuprofen in order to improve the quality of life of patients affected by CP/CPPS by the relief of pain.

Materials and methods

Study design. In order to assess the safety and efficacy of pollen extract in association with vitamins (DEPROX 500®) in males with CP/CPPS, all consecutive patients with a clinical and instrumental diagnosis of CP/CPPS (class IIIa or b), attending the same urologic centre (Santa Chiara Regional Hospital, Trento, Italy) between March and October 2012 were screened for this prospective randomised controlled phase III study. The design of the study was in accordance with the guidelines for clinical trials in CP/CPPS described by the NIH Chronic Prostatitis Collaborative Research Network (13). No placebo arm was included. The possible biases caused by the lack of placebo arm were considered in the results analysis. No placebo run-in period was considered necessary due to the fact that all enrolled patients were not blinded. The main outcome measure was the improvement of quality of life at the end of the whole study period, defined as the symptomatic improvement in the pain domain of the NIH-CPSI. Clinical failure was defined as the persistence of low quality of life following the treatment (failure to obtain a reduction of the NIH-CPSI total score by ≥25%), or the suspension of therapy for significant reported adverse effects (12). In addition, spontaneously reported adverse events, or those noted by the investigator, were recorded during the whole study period. The study was conducted in line with Good Clinical Practice guidelines, with the ethical principles laid down in the latest version of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to treatment. Furthermore, this study was conducted in line with the Consolidated Standards of Reporting Trials statement (The Ottawa Hospital Research Institute, Ottawa, ON, Canada).

Study schedule. On arrival at the center, all eligible individuals provided their written informed consent and underwent baseline questionnaires, urological examination and the Meares-Stamey test that was performed by the same urologist in accordance with the procedure described in the European Association of Urology (EAU) guidelines (14). All patients who met the inclusion criteria undertook oral administration of DEPROX 500® (two capsules every 24 h) or ibuprofen (600 mg, one tablet three times a day) for four weeks. Ibuprofen was selected in accordance with the results obtained by Lee *et al* (15). Proton-pump inhibitors (PPIs) were not routinely used due to the fact that all patients with gastrointestinal bleeding or a history of duodenal or gastric ulcers were excluded. Enrolled patients were not blinded to the preventative treatment. All patients were assigned to the two groups (DEPROX 500® and ibuprofen) according to a 1:1 randomization (Fig. 1). All patients were contacted by telephone on day 14 of the therapy to ensure correct timing and dose of treatment. Each subject was scheduled for a follow-up examination at 30 days from starting therapy, with a urological and microbiological examination and questionnaire collection.

Inclusion and exclusion criteria. Inclusion criteria were the presence of symptoms of pelvic pain for at least three months during the six months before study entry, according to the EAU guidelines, a score in the pain domain of the NIH-CPSI (14) of >7 and a negative four-glass result in the Meares-Stamey test (12). Subjects <18 and >65 years of age, affected by major concomitant diseases, with known anatomical abnormalities of the urinary tract or with evidence of other urological diseases, and with residual urine volume >50 ml resulting from bladder outlet obstruction were excluded. Males with a reported allergy to pollen extract, who had recently (<4 weeks) undergone oral or parental treatment or who were currently using prophylactic antibiotic drugs were also excluded. Additionally, all patients with a history of gastrointestinal bleeding or duodenal or gastric ulcers were excluded. All patients positive to tests for *Chlamydia trachomatis* (Ct), *Ureaplasma urealyticum*, *Neisseria gonorrhoeae*, herpes viruses (HSV 1/2) and human papillomavirus (HPV) were also excluded.

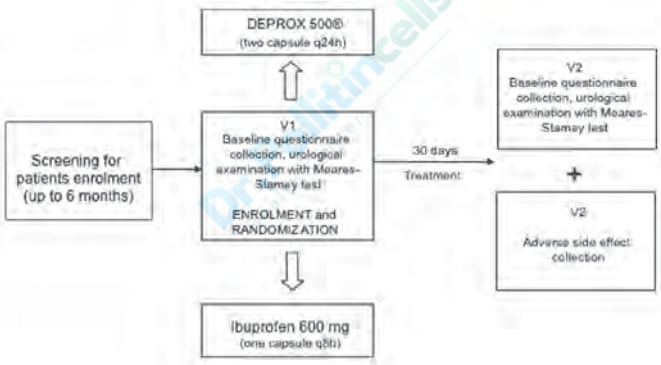

Figure 1. Study schedule. V1 = baseline, V2 = follow-up visit at 30 days. q, every.

Composition and characterization of the extracts used. All patients who were randomized to the DEPROX 500® group underwent oral administration of two tablets of DEPROX 500® in a single dose daily in the evening, in line with our previous study (10) and with the manufacturer's instructions (IDI Integratori Dietetici Italiani S.r.l, Sicily, Italy). Each administration contained 1 g pollen extract (500 mg per tablet), and vitamins B1, B2, B6, B9, B12 and PP. All compound analyses were carried out in accordance with the procedures described by Fiamegos *et al* (16). All patients randomized to the ibuprofen group received ibuprofen (600 mg) three times per day.

Questionnaires and urological examinations. The validated Italian versions of the NIH-CPSI (17) and the International Prostate Symptom Score (IPSS) (18) questionnaires were administered to each patient. The questionnaires were self-administered when the patient arrived at the urologic centre. Furthermore, patient quality of life was measured by using an Italian version of the QoL scale, a validated, multi-attribute health scale (19). This scale was selected because it has been successfully applied to acute illnesses, whereas other quality of life scales, including the Short Form-36 (SF-36) Health Survey, are more suitable in chronic cases (20). Higher scores on the QoL scale reflect a higher quality of life. In accordance with the study by Nickel *et al* (21), prostatitis-like symptoms were considered significant at a pain

score of ≥4. The NIH-CPSI was also used in determining clinical therapy efficacy (21).

Sample collection and laboratory procedures. All samples were collected during the urological examination and immediately taken to the laboratory, under refrigerated conditions, analysed for cultures and aliquoted for DNA extraction and polymerase chain reaction for Ct, *Neisseria gonorrhoeae*, HSV 1/2 and HPV detection. All subjects included in the study underwent urinary culture for common bacteria, yeasts and urogenital mycoplasma. Microbiological culture was carried out in accordance with the methods described by Mazzoli *et al* (22). DNA extraction and purification from urine were performed using the EZ1 DNA Tissue kit (Qiagen SpA, Milan, Italy), as described in our previous study (22).

Statistical analysis. The primary target of the study was the symptomatic improvement in the pain domain of the NIH-CPSI. In order to analyse the homogeneity of the two groups, the baseline characteristics were compared using the Student's t-test and Mann-Whitney U test for continuous variables and by the χ^2 test for categorical variables. The normal distribution of the variables was assessed using the Kolmogorov-Smirnov test. Data were analysed based on the intention-to-treat (ITT) approach. General characteristics of the study participants were expressed using descriptive statistics (means, standard deviations and ranges). The required sample size for the present study was calculated under the following conditions: Difference between the groups, 2±1 score points in the NIH-CPSI pain domain; α error level, 0.05 two-sided; statistical power, 80%; and anticipated effect size, Cohen's d=0.5. The calculation yielded 2x39 individuals per group. Randomization based on a single sequence of random assignments (simple randomization) was performed using a pseudo-random number generator software (Research Randomizer Version 4.0, Social Psychology Network, Wesleyan University, Middletown, CT, USA). Analysis of variance (ANOVA) was used for comparing the means. The Bonferroni adjustment test was also used at the second stage of the ANOVA. The effect size between the means (Cohen's d) was also calculated. The differences between the groups regarding the NIH-CPSI results were obtained using an ANOVA test. Statistical significance was achieved when P<0.05. All reported P-values were two-sided. Statistical analyses were performed using SPSS software, version 11.0 (SPSS, Inc., Chicago, IL, USA) for Apple-Macintosh.

Results

Patients. From the 115 patients attending the center for prostatitis-like symptoms during the study period, 94 were eventually enrolled and randomised. Out of the 21 patients excluded from the study, eight refused to be enrolled, six reported adverse effects to nonsteroidal anti-inflammatory drugs, two reported a clinical history of gastrointestinal ulcers and five elected to be treated in other centres. Additionally, seven patients were lost subsequent to randomisation and 87 males were finally enrolled (Fig. 2). The baseline questionnaire mean scores were 25.9±2.1, 8.0±3.6 and 0.55±0.15 for NIH-CPSI, IPSS and QoL, respectively. Historical medical information and clinical data at enrolment are described in Table I. No statistically significant differences between the groups were identified.

Randomisation. Of the 87 enrolled patients (mean age 33.6±5.9 years), 41 received DEPROX 500® (group A), and 46 received 600 mg ibuprofen (group B). The treatment arms were comparable for all variables at the enrolment and randomisation visits.

Compliance with treatment schedule and adverse effects. In group A, 1/41 patients (2.4%) had mild adverse effects that did not require additional treatment (nausea), while in group B, 7/46 patients (15.2%) reported nausea and epigastric pain. In group A, 40 patients (97.5%) were analysed subsequent to one being lost in follow-up. In group B, 38 patients (82.6%) were analysed subsequent to two being lost to follow-up and four discontinuing therapy due to gastrointestinal adverse effects. The DEPROX 500® treatment was well tolerated in all the patients analysed, and no significant drug-related side-effects were identified. The analyses were carried out in the ITT (pollen extract, n=41; ibuprofen, n=46) and per protocol (PP) populations (pollen extract, n=40; ibuprofen, n=40) (Fig. 2).

Clinical and laboratory results at follow-up (after one month of treatment). At the follow-up examination, in the ITT set and DEPROX 500® group, 31/41 patients (75.6%) reported an improvement of quality of life, defined as a reduction of the NIH-CPSI total score by ≥25%, compared with 19/46 (41.3%) in the control group (P=0.002). In the PP set and DEPROX 500® group, 31/40 patients (77.5%) reported an improvement of quality of life, compared with 20/40 (50.0%) in the control group (P=0.019). The questionnaire results at one month after treatment were as follows: NIH-CPSI, 12.8±2.20; IPSS, 7.6±1.58; and QoL, 0.69±0.10 in the DEPROX 500® group. By contrast the results in the control group were: NIH-CPSI, 19.5±2.10; IPSS, 8.00±2.81; and QoL, 0.59±0.18. The higher improvement in the DEPROX 500® group compared with the ibuprofen group was statistically significant (treatment difference in NIH-CPSI pain domain: ITT, -2.14±0.51, P<0.001; PP, -1.76±0.22, P<0.001). Statistically significant differences were also reported in the NIH-CPSI (P<0.001), and QoL (P=0.002) scores between the two visits in the DEPROX 500® group and between the two groups (Figs. 3 and 4). No statistically significant differences were identified in the IPSS scores (P=0.43). All patients were negative at the Meares-Stamey test evaluation. All questionnaire results at the follow-up visit are presented in Table II. The results of the physical examinations, including vital signs, and laboratory examinations showed no relevant changes from the baseline.

Sub-analysis on the basis of CP/CPPS type. Of the 87 patients, 25 (28.7%) showed inflammatory CP/CPPS (type IIIa), while 62 (71.3%) exhibited type IIIb. A statistically significant difference was identified between the two groups in terms of pain relief and QoL improvement when stratified by CP/CPPS type. In fact, in the DEPROX 500® group, patients affected by type IIIb CP/CPPS showed higher QoL results and a lower pain level following treatment (the NIH-CPSI score was

Table I. Baseline characteristics and clinical parameters at enrolment.

Parameter	DEPROX 500® group	Ibuprofen group
Patients, n	41	46
Age, years[a]	33.8±6.78	33.7±5.44
Marital status, n (%)		
Married	19 (46.3)	18 (39.1)
Unmarried	22 (53.7)	28 (60.8)
Educational qualification, n (%)		
Primary school	5 (12.2)	7 (15.2)
High school	29 (70.7)	27 (58.6)
University	7 (17.1)	12 (26.2)
Smoker status, n (%)		
Yes	11 (26.8)	13 (28.2)
No	30 (73.2)	33 (71.8)
Sexually active in the past month, n (%)	39 (95.1)	41 (89.1)
Sexual behaviour, n (%)		
1 partner	33 (80.4)	37 (80.4)
>1 partners	8 (19.6)	9 (19.6)
Contraceptive use, n (%)		
Condom	29 (70.3)	34 (73.9)
Coitus interruptus	12 (29.7)	12 (26.1)
Start of CP history (months)[a]	18.7±4.28	19.1±3.99
Symptoms score at baseline[a]		
NIH-CPSI	24.9±2.1	25.5±3.0
IPSS	8.3±3.6	8.0±2.5
QoL	0.57±0.17	0.55±0.15
Clinical presentation, n (%)		
Dysuria	12 (29.2)	14 (30.4)
Urgency	4 (9.7)	5 (10.8)
Dysuria + frequency	6 (14.6)	5 (10.8)
Burning	7 (17.0)	9 (19.5)
Pain, n (%)		
Perineal	19 (46.4)	21 (45.6)
Scrotal	4 (9.7)	4 (8.7)
Suprapubic	8 (19.6)	9 (19.6)
Lower abdominal	10 (24.3)	12 (26.1)
Pain frequency, n (%)		
Daily	33 (80.4)	36 (78.2)
Weekly	8 (19.6)	10 (21.8)
Sexual Symptoms, n (%)		
ED	12 (29.2)	13 (28.2)
PE	7 (17.0)	6 (13.0)
ED + EP	4 (9.7)	4 (8.6)
CP/CPPS type, n (%)		
Type a	12 (29.2)	13 (28.2)
Type b	29 (70.8)	33 (71.8)

[a]Data are presented as the mean ± standard deviation. CP, chronic prostatitis; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; IPSS, International Prostate Symptom Score; QoL, Quality of Well-Being; CPPS, chronic pelvic pain syndrome; ED, erectile dysfunction; PE, premature ejaculation.

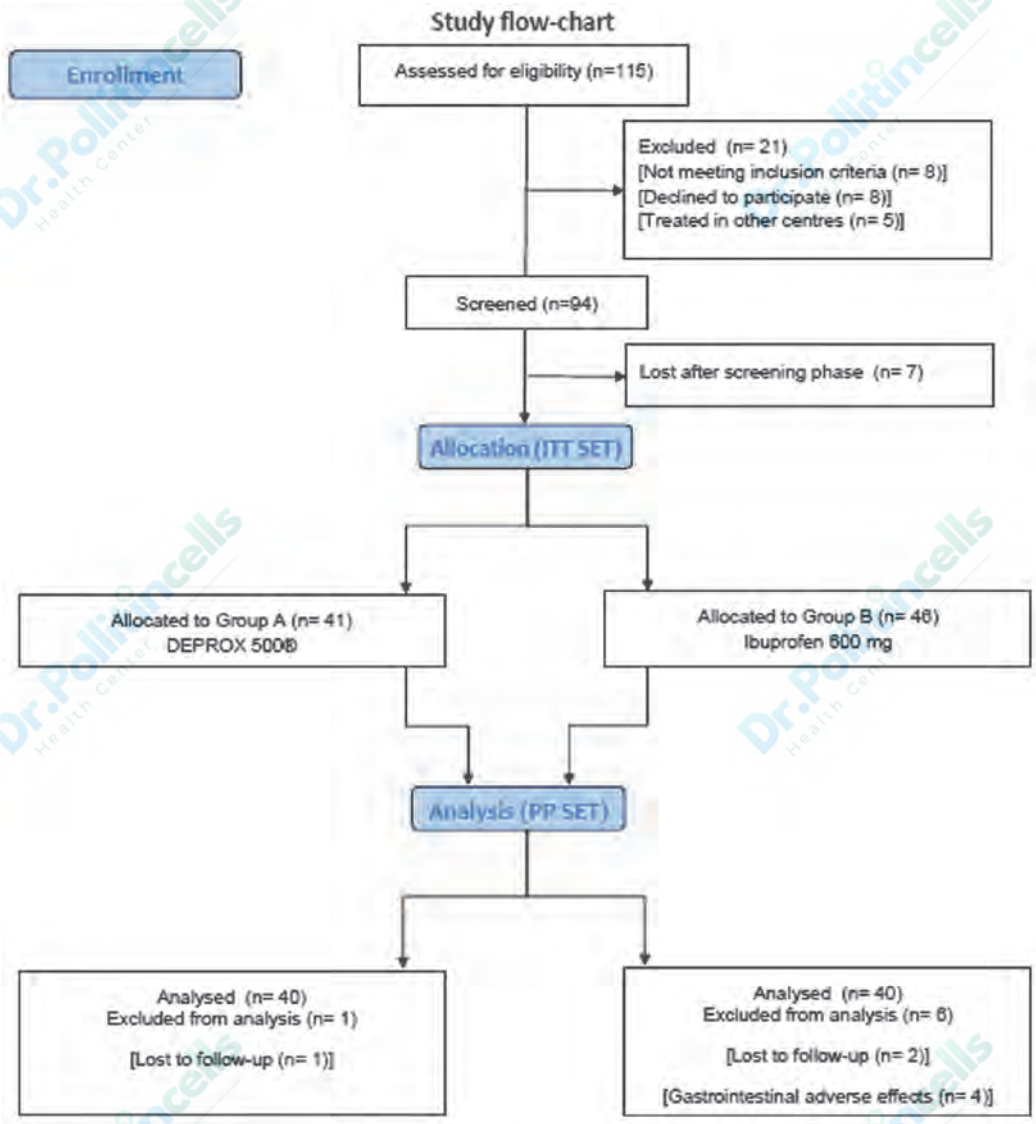

Figure 2. Study flow-chart according to the Consolidated Standards of Reporting Trials statement. ITT, intention-to-treat; PP, per protocol analysis.

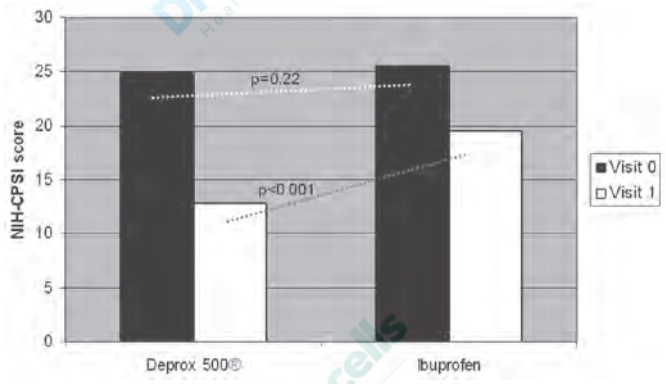

Figure 3. Statistically significant differences between the two visits in terms of the NIH-CPSI scores (P<0.001) between the two groups. NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index.

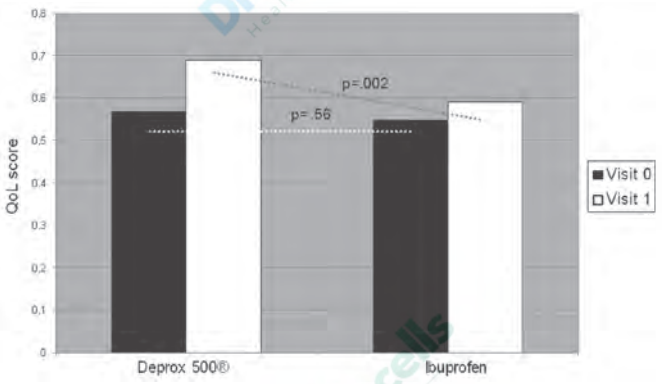

Figure 4. Statistically significant differences between the two visits in terms of the QoL scores (P=0.002) between the two groups. QoL, Quality of Well-Being.

24.8±1.8 at the enrolment versus 11.7±1.7 at the follow-up visit; P<0.001) when compared with type IIIa CP/CPPS patients (Table III). No differences were reported between the ITT or PP sets.

Discussion

The major finding of the present study was that DEPROX 500® is able to provide early pain relief and improve the quality of

Table II. Questionnaire results at the follow-up visit.

Variable	DEPROX 500® group	Ibuprofen group
NIH-CPSI (P<0.001)[a]	12.8±2.20	19.5±2.10
IPSS (P=0.87)[a]	7.6±1.58	8.00±2.81
QoL (P=0.002)[a]	0.69±0.10	0.59±0.18
Reduction in NIH-CPSI pain domain[b], n (%)	31 (77.5)	19 (47.5)
Efficacy outcomes (NIH-CPSI pain domain)[a,c]	-4.36±0.51	-2.22±0.53
Efficacy outcomes (NIH-CPSI pain domain)[a,d]	-3.86±0.21	-2.10±0.20

[a]Data are presented as the mean ± standard deviation; [b]pain, P<0.003; [c]intention-to-treat analysis, treatment difference -2.41±0.51, P<0.001; [d]per protocol analysis, treatment difference -1.76±0.22, P<0.001. NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; IPSS, International Prostate Symptom Score; QoL, Quality of Well-Being.

Table III. Results of the sub-analysis on the basis of CP/CPPS type a or b.

Variable	DEPROX 500® group	Ibuprofen group
Patients, n	40	40
Type a, n (%)	14 (35)	11 (27.5)
Type b, n (%)	29 (65)	32 (72.5)
NIH-CPSI[a]		
Type a	13.1±1.8	20.2±1.9
Type b	11.7±1.7	19.1±2.7
IPSS[a]		
Type a	7.9±0.9	7.9±3.1
Type b	7.4±1.5	8.0±2.2
QoL[a]		
Type a	0.61±0.3	0.57±0.2
Type b	0.70±0.1	0.60±0.1

[a]Data are presented as the mean ± standard deviation. NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; IPSS, International Prostate Symptom Score; QoL, Quality of Well-Being; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome.

life in patients with CP/CPPS without severe side-effects, when compared with ibuprofen. Furthermore, it was revealed that patients affected by type IIIb CP/CPPS may obtain greater advantages from this therapy. These findings lead to several points of discussion. Firstly, the early pain relief. In 2006, Elist (23), using a double-blind study with random distribution versus placebo, demonstrated the superiority of pollen extract versus placebo in terms of improvement in pain score and the filling and emptying symptoms from the start to the end of the treatment after six months of therapy. Additionally, in 2009, Wagenlehner *et al* (12) showed that pollen extract improved symptoms, pain and quality of life after 12 weeks of treatment in patients with this condition, with differences in favour of pollen extract at six weeks of treatment compared with the placebo, and the treatment being well tolerated. These two studies treated the patients for at least six weeks (12,23). Consistent with our previous study (10), 30 days of treatment with DEPROX 500® in the present study was able to provide significant results in terms of pain reduction when compared with ibuprofen. This effect is possibly due to the association between the pollen extract and vitamins B6 and B12 that improve the antioxidant activity of pollen extract with the protective effect on nerves. B vitamins including thiamine (B1), pyridoxine (B6) and cyanocobalamin (B12) are capable of anti-nociception in experimental animals with acute and chronic pain evoked by electrical, chemical and thermal stimulation, primary neuronal injury and diabetes (24,25). Notably, several studies have demonstrated that certain B vitamins, particularly B6 and B12, are able to protect neurons from certain injuries (26,27). The B vitamins, B1, B6 and B12, are clinically useful in the treatment of certain painful conditions including lumbago, sciatica, trigeminal neuralgia and chronic pain associated with diabetic polyneuropathy (28). Finally, we hypothesized that the early improvement on pain relief is due to the protective effect on nerves, and the following improvement in quality of life could be due to the antioxidant activity of pollen extract. Indeed, previous studies in which only pollen extract was administered demonstrated an improvement in quality of life and pain relief after ≥6 weeks of treatment. Furthermore, on the basis of the sub-analysis, the patients that best obtained the important advantages from this therapy were those with non-inflammatory CP/CPPS. Contrasting with previous studies, the present study revealed that patients with non-inflammatory CP/CPPS showed improved results compared with those with inflammatory CP/CPPS. This is possibly due to the fact that the protective effect on nerves of B vitamins occurs earlier than the anti-inflammatory effect of pollen extract. In this sense, DEPROX 500® is able to provide improved results in terms of early pain reduction in patients with non-inflammatory CP/CPPS. DEPROX 500® was generally well tolerated over the full study period.

The present study had a few limitations that should be taken into account: The small number of enrolled patients, a short follow-up period, a selected patient population, the lack of control group and that this was not a blinded study. Given the lack of prove efficacy of conventional therapies, alternative treatment options are urgently required and pollen extract in association with vitamins should be an noteworthy option due to its generally low side-effects and promising results in terms of quality of life improvement.

In conclusion, given the aforementioned limitations, DEPROX 500® significantly improved the total symptoms, pain, and quality of life compared with ibuprofen in patients with CP/CPPS, without severe side-effects.

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Regulation of Prostate Growth in Culture with the Pollen Extract, Cernilton T-60, and the Impact of the Drug on the EGF Tissue Profiles

F.K. Habib

Introduction

A major difference between the prostate and other accessory reproductive glands is the susceptibility of the prostate to hyperplasia in again men. Indeed, benign hyperplasia of the prostate (BPH) affects most males over 60 years of age and causes enlargement of the inner gland. When the urethra becomes constricted, treatment is required to relieve the kidney and circulation system of the damaging effects of back pressure.

Surgery in the form of transurethral resection still remains the “gold standard” for the treatment of outflow tract obstruction (1) but recently attention has also focused on alternative forms of therapy, namely hormonal (2, 16), 5α-reeducates inhibitors (11), and α-adrenergic blockers (5). However, the long-term prognosis for medical treatment has been poor and many of the endocrine and pharmacological agents presently in use have side effects (4). This has prompted the medical and scientific community to consider new lines of treatment of BPH. One recent development was sudden and unexpected interest in phytotherapy, which was in part instigated by the encouraging results and the undoubted beneficial effects of the pollen extract, Cernilton, in the symptomatic relief of BPH (1).

The mechanism by which the pollen induces its effect on the hyperplastic prostate is not yet clear even though extensive experimentation has been undertaken by many workers (8, 9, 10). Notably however, the bulk of the earlier research was focussed on experiements with animal tissue, which constitutes an unsatisfactory model for the human gland. Additionally, the few studies on the human prostate were carried out either on whole organ homogenates or on prostate epithelical cell lines (8), both of which ignore the potential heterogeneity of the cellular activity within the gland and the importance of stroma / epithelial interactions. Futhermore, the immortal cell lines represent a highly selective cell population which might have undergone phenotypic changes and may therefore be distinctive from the cells of orgin.

In attempt to overcome these earlier limitations, efforts in our laboratory have been directed towards developing primary culture of the human prostate and the serial culture of epithelial and fibroblast cells from BPH employing defined media. Initially, progress was slow and attempts to find the optimal concentration of ingredient to permit the growth of the cells and increase their plating efficieny were repeatedly frustrated. However, thanks to our collaboration with Dr. D. *Chaproniere,* to whom much of the credit for the earlier work goes (3), combined with the perseverance of the chief tissue culturist, Mrs. *Margaret Ross,* we managed to overcome many of the initial obstacles and finally establish a reliable technique for the serial culture of both prostate stroma and epithelial cells in serum-free medium (manuscript in preparation). This model was subsequently adapted to our Cernilton studies in which the experiements were confirned to the water-soluble Cernitin T-60 fraction; this fraction accounts for approximately 60% of the pollen extract. Detail of the procedures followed and summary of our findings on the characterization of the cultured cells along with the impact of the Cernitin T-60 are described within.

This chapter also includes some preliminary data on growth factor profiles in prostate tissue specimen and in expressed prostate secretions (EPS) obtained from a group of BPH patients

receiving the pollen extract. The relevance of growth factors peptides and particularly epidermal growth factor (EGF) to the prostate stems from their ability to maintain and regulate prostat growth either by acting in tandem with androgens or possbiliy even by by-passing the steroid hormomes and imprinting their own characteristics on the gland (7, 12). Recent reports on the preferential accumulation of EGF in BPH when compared to normal prostate tissue (6, 14) supports the belief that this peptide might be implicated in the pathogenesis of this condition. Since the action of Cernilton in the prostate has been found not to be mediated via the androgen delivery system of the cell (8), we are now looking at the possibility of an association between the expression of some of these growth factors and their response to Cernilton in patients receiving the drug.

Serial Culture of Prostate Epithelial and Fibroblast Cells

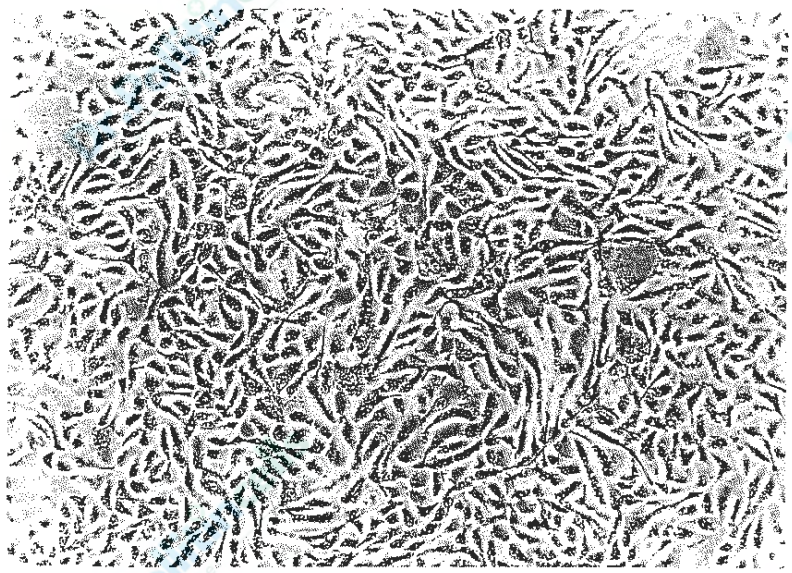
BPH specimens obtained by transurethral resection were transported under sterile conditions to the laboratory in transport medium. Acini and fibroblast cells were released from prostate tissue by collagenase digestion and primary and sub-cultures were grown by plating onto plastic culture flasks and incubating at 37°C in a 95% air-5% CO_2 humidified atmosphere. By using this sytem it was possible to establish and serially culture pure populations of both epithelial (Fig **1a**) and fibroblasts (Fib **1b**) cells in well-defined media. For epithelial cells the WAJC404 medium (3) was serum free and was supplemented with insuling (2.5µg / ml), EGF (10 ng / ml), dexamethasone (1µM), and choleratoxin (10µg / ml); this medium selects against the growth of the fibroblast cells. Four days after inculation of the epithelial cells onton T-75 flasks, the acini demonstrated good spread, and confluence was usually reached by day five. Fibroblast cells were maintained in RPMI1640 supplemented with fetal calf serum (10%) and penicillin and streptomycin (10µg / ml each). Fibroblast cells were initially slow in growing and confluence was reach usually after ten days.

Verification of the culture as prostatic fibroblast and epithelial cells is accomplished by immunocytochemical staining employing a variety of antiobodies including those for vimentin, desmin, prostatic-specific antigen (PSA), prostatic acid phosphatase (PAP), and cytokeratin. Assessment of the staining patterns and their intensities was always undertaken by an independent pathologist. A typlical pattern of the staining profiles obtained is illustrated in Table **1**.

In addition to the immunostaining (Table **1**), the cells were also examined by phase contrast microscopy. Analysis of the photomicrographs (Figs. **1a** and **1b**) suggest that the resultant epithelial monolayers contain very little or no contaminants – any residual fibroblasts will be totally destroying by the epithelial growth medium. Futhermore, the bulk of the epithelial cells appear to be of a secretory nature since PAP and PSA are strongly expressed (Table **1**). The epithelial cells also stain uniformly for cytokeratin and recognize the antibody for the epidermal growth factor receptor. This confirms our earlier findings on the presence of EGF-receptors in epithelial cells of human prostate tissue (14).

In contrast, the fibroblast cells failed to stain for PAP and PSA but were positively labeled by antibodies for vimentin and desmin. Somewhat surpisingly, the fibroblast cells were also outlined by the antibodies for cytokeratin and for Human Milk Fat Globulin (HMFG), which are exclusively epithelial in nature. This raises the possilbity that the fibroblast cells might contain small contaminats of a secondary cell. Closer examination of those fibroblastic cells by microscopy highlights the presence of small numbers of epithelial-like cells amongst the stromal monolayers. The secondary cells could be either non-secretory epithelial or endothelial cells which maintain an ,,epithelioid”-like appearance, but this needs to be confirmed. The presence of the fibroblast contaminants was also confirmed by flow cytometry and we are at present attempting to segregate the two cell populations employing a cell sorter. Interestingly, however, the “epithelioid”-like material appears not to multiply but remains constant throughout each passage and might merely act as a supportive matrix for the fibroblast.

a



b

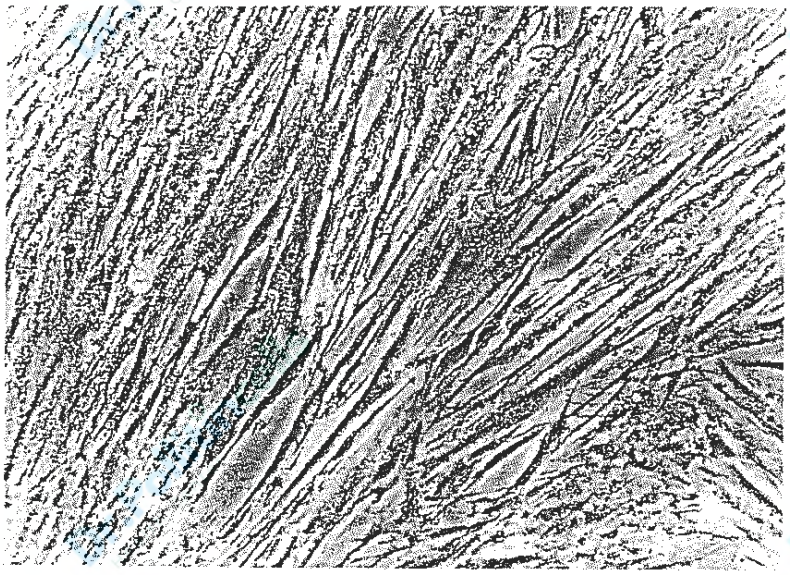


Fig. 1 Phase-contrast micrograph of a primary culture of epithelium (1 a; × 100) and a serial culture of fibroblast (1 b; × 200) from a patient with benign prostatic hyperplasia.

Markers used	Fibroblast cells	Epithelial cells
Prostatic acid phosphatase	–	++
Prostatic specific antigen	–	++
Epidermal growth factor receptor	–/+	++
Cytokeratin	–/+	++
Vimentin	++	–/+
Desmin	+	–
HMFG (Human Milk Fat Globulin)	–/+	++

Intensity of staining: (++) strongly positive; (+) moderately positive; (–/+) patchy; (–) negative.

Tab. 1 Immunocytochemical Staining of Epithelial and Fibroblast Cells in Culture.

The Effect of T-60 on Epithelial and Stromal Cell Growth in vitro

Dose response curves of Cernitin T-60 treatment were determined using the following method: triplicate determinations for each treatment were performed in 96 well culture plates; each well was seeded with 2.5 x 10^4 cells and incubated overnight at 37°C in the medium under defined incubation conditions. The following day, the Cernitin T-60 stock solution was serially diluted in the defined medium to yield a concentration varying from 0.05-1mg / ml. Controlled cultures received culture medium alone. For the dose response curve studies, the cells were exposed to Cernitin T-60 for a total period up to 4 days with changes of freshly diluted T-60 in medium every 2 days. For the time course study, cells were treated in the presence and absence of T-60 a total period of 7 days. After the incubation periods, the cells were pulse-labelled with radiolabelled thymidine whilst remaining in the defined medium for a further 24 hours.

For the determination of the rate of the DNA synthesis the cells were trypsinized and 10% ice cold tricholoacetic acid was added for 2 hours. The cells were subsequently harvested onto filter mats, dried at 60°C for 30 minutes and each disc of filter paper containing the precipitable material was then counted in scintillation fluid. The results illustrated in Fig **2** (fibroblast cells) and Fig. **3** (epithelial cells) are expressed as the percentage of ^{3}H-thymidine incorporated relative to the untreated control. These demonstrate that the effect of Cernitin T-60 on stroma and epithelial cells is biphasic: initially and at the low concentrations of T-60 (up to approximately 0.1 mg / ml) we detect significant stimulation, particularly in the fibroblast cells which show after 2 days of exposure an increase of appromately 75% in DNA synthesis. However, exposure to higher concentrations of the T-60 inhibits the uptake of thymidine and after 3-4 days exposure we do find that the concentrations of T-60 (P > 0.25 mg / ml) almost totally inhibit the fibroblast growth.

Although the epithelial cells do also show an inhibition in cell growth which is time-and concentration-dependent, it appears that the epithelial cells are slightly more resistant to the pollen extract than the fibroblast cells. Though there is initially a minute stimulation in the DNA synthesis of up to 25% after 2 days of exposure (results not shown), this is rapidly reserved, and inhibition is observed at approximately the same concentrations of T-60 as those required to induce the same effect with the fibroblast but following longer periods of response to the Cernitin T-60 (Fig. **3**).

EGF Concentrations in Prostate Tissue and Prostate Secretions following Cernitin Treatment

Prostate tissue was obtained at the time of transurethral resection from 19 patients with the BPH; the patients had been enterend into a Cernilton double-blind placebo-controlled study over a six-month period. The tissue was transported immediately to the laboratory in iced saline, dry blotted, snap-frozen in liquid nitrogen and stored at -70°C until analysis. Matching expressed prostatic secretions (EPS) were collected by transrectal massage before the commencement of the trial and at approximatelty three-month intervals with the last specimen obtained immediately prior to transurethral resection whilst the patient was under either regional or general anesthesia. The fluid was collected into 1-ml insulin syringes, frozen without delay, and stored at -70°C until needed.

Studies on EPS Specimens

Pre- and post-treatment samples of EPS were obtained from 8 patients in the Cernilton treatment group and 5 patients in the placebo group; the mean length of treatment with Cernilton was 147 ± 42 days. A comparison of EGF concentrations in both group before commencement of treatment revealed to significant difference (P > 0.5; Fig. **4**). Similarly, comparison of the EGF concentrations in samples before and after treatment also showed no significant difference (P > 0.5); these data are illustrated in Fig. **4**. In addition we have also examined the changes in EGF concentrations of consecutive samples of EPS from individual participants in the double-blind placebo-controlled study; the patterns obtained are illustrated in Fig. **5**. Clearly, there are no consistent patterns of change which could be of use for monitoring response to treatment.

Studies on Prostate Tissue

In addition to the measurements undertaken on EPS, we have also measured the ECG

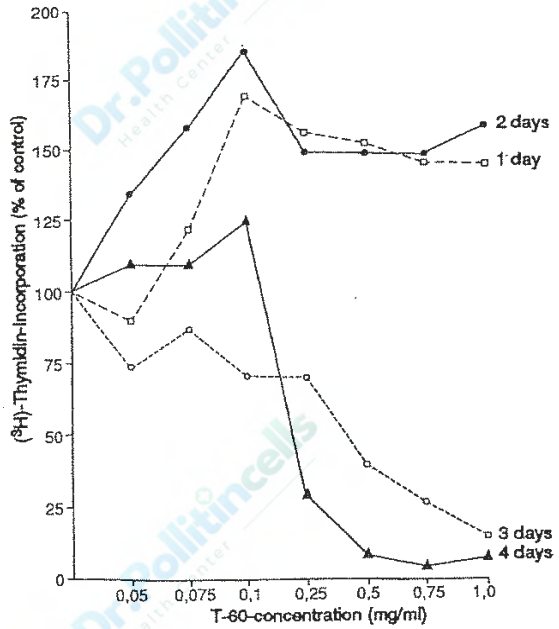


Fig. 2 Effect of T-60 concentration on fibroblast cell survival. Fibroblast cells (2.5×10^4 cells/well) were plated overnight in 96 well plates. Increasing concentrations of T-60 were added for varying times. (^{3}H)-thymidine was then added for 24 hours and the cells were trypsinized in 10 % TCA. The cells were then harvested onto filter mats, dried and counted in scintillation fluid. The data is normalized relative to the untreated control (100 %).

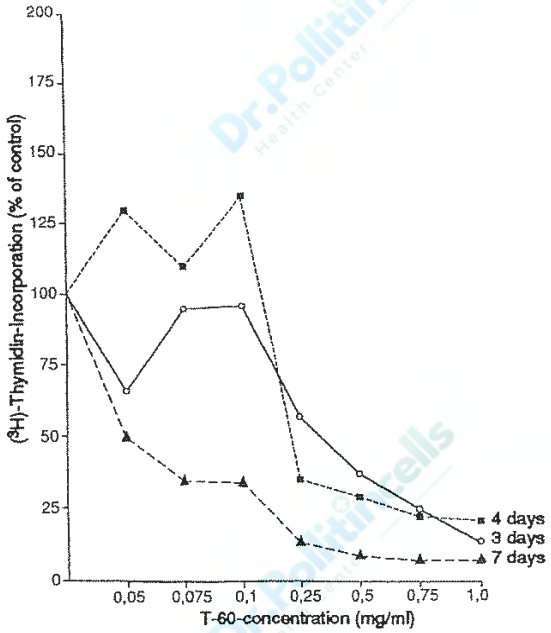


Fig. 3 Effect of T-60 concentration on epithelial cell survival. Details were identical to those followed for the fibroblast cells as detailed in legend to Fig. **2**.

concentrations in prostate tissue obtained from 15 BPH patients undergoing prostatectomy. These were compared to the concentrations found in a parallel group of 7 patients who were taking Cernilton as part of the double-blind placebo-controlled study. The data was expressed as ng EGF / mg protein in the tissue and the results obtained for the individual patients are outlined in Table **2**. Although the levels of EGF in the treated group appeard to be considerably lower than those measured in the controlled group, the difference is not statistically different. However, it should be noted that the population receiving the Cernilton tablet is comparatively small and the results obtained might have been slightly biased by the fact that 2 out of 7 patients showed relatively high concentrations of EGF whereas the remainder of the population had levels considerably lower than those measured in any of the other individuals in the controlled group. We are at present extending this study to incorporate a further 20 patients on the drug in the hope that this might show some light no the mechanism of action of Cernilton and whether the differences between the control and test groups are genuine and reflect actual changes in the metabolic pathways of the gland following treatment with the pollen extract.

Conclusion

The precise mode of action of Cernilton in BPH is not clearly understood even though many studies have been undertaken to elucidate the mechanism by with this pollen extract promotes

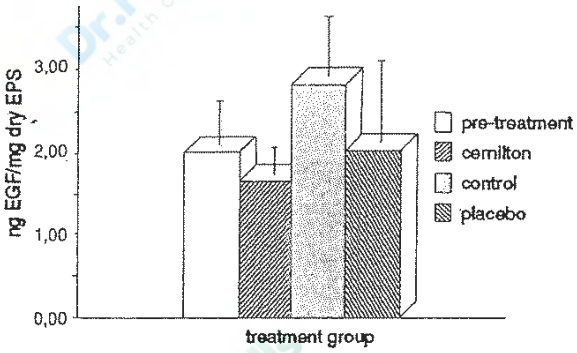


Fig. 4 EGF concentrations in expressed prostate fluid (EPS). Aliquots of EPS were taken from a group of patients who had entered the double-blind placebo trial of Cernilton, and EGF was measured in samples taken at the start and towards the end of the trial. The concentrations in the treated group were compared to those on placebo. Results are expressed as mean ± SEM for 8 patients in the treated group and 5 patients on placebo. Bars show SEM.

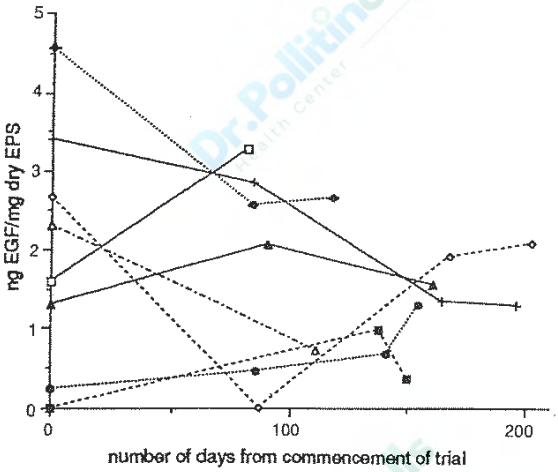


Fig. 5 EGF concentrations in consecutive EPS specimens taken from patients receiving Cernilton. For each patient EPS specimens were obtained before commencement of treatment and then at approximately 3 and 6 months into the trial.

symptomatic relief in patients with BPH. The earlier studies concentrated mainly on animal models and as reported by *Ito* et al. (9), Cernilton produced in mature Wistar rats a significant reduction in the size of the prostate as well as in PAP concentrations whilst also inducing a parallel increase in blood and tissue zinc concentrations. Additionally, Cernitin T-60 produced relaxtion of the smooth muscle of the mouse and increased the contraction of the bladder muscle in a concentration-dependent manner (10).

In view, however, of the specie differences in prostate anatomy and function, a fundamental distinction must be made between animal studies and experiements on human tissue. The attentions of this laboratory were therefore focused initially on the immortal human prostate cell lines which demonstrated an inhibitory response following treatment with Cernitin T-60 (7). Interestingly, the inhibitory effect was far more marked in the hormone unresponsice cell line when compared to the androgren-sensitive human prostate cells. Human prostate cell lines derived from non-prostatic tissue failed to exhibit a similar sensitivity to the pollen-extract (7).

Although the usage of immortal cell lines in our earlier studies was most helpful in dentifying the specificity and selectivity of the drug, their use is somewhat limited because of: (a) the cancer nature of the continuous cells whilst Cernilton is prescribed purely for BPH; (b) immortal cells are identical clones and do not therefore take account of the morphological heterogeneity of the prostate; and (c) continuous cell lines may undergo phenotypic changes and this might render them distinctive from the cells of origin. In view of these limitations we have decided to continue our work on Cerntin T-60 employing the well-established cultures of epithelial and fibroblast cells from human hyperplastic prostats (3, 15). Those studies were facilitated by our ability to establish and serially culture pure populations of epithelial and fibroblast cells in a well-defined serum-free medium. By using this system the specifc characteristics of Cernitin T-60 could be assessed in a cohesive and systematic fashion.

Clearly, the data outlined in this report indicates that Cernitin T-60 is a powerful mitogenic inhibitor of fibroblastic and epithelial

Control group	EGF concentration	Cernilton Group	EGF concentration
J. W.	1.50	W. F.	3.45
J. G.	1.35	C. F.	2.43
J. N.	2.09	C. S.	1.51
D. D.	1.61	K. B.	0.45
G. T.	2.07	A. S.	0.31
H. H.	1.20	T. S.	1.10
R. H.	2.84	R. H.	0.89
A. C.	3.98		
W. T.	3.67		
W. B.	4.38		
W. H.	1.50		
K. H.	3.40		
H. J.	2.57		
K. N.	3.00		
T. S.	1.76		
hEGF-Concentrations (µg EGF/mg Protein)			
Mean± S.D.	2.39 ± 0.85		1.45 ± 1.31

proliferation. Although the mechanism involved is not as yet understood, we have evidence derived from our earlier studies (8) to indicate that these responses are not medicated via the androgenic pathways. We have therefore decieded to look at the impact of Cernitin T-60 on the expression of growth factors which have been implicated in the growth of the prostate cells. Though the results on the prostate fluid indicate little difference in EGF concentrations between the control and test groups, the evidence derived in this report suggests that there might be some impact on the epidermal growth factor concentration of the tissue.

EGF is a well-established secretory product of the prostate and is retained in large concentrations by BPH when compared to the normal gland (6). This retention might be associated with the high concentrations of the EGF receptors found BPH which must sequester the growth factor for internal use (14). We are not too clear on the mechanism responsible for this build-up of EGF receptors and whether it is a causal factor or merely a result of the development of hyperplasia. We are also not cerntain whether there is an association between these abnormal growth factor concentrations and the dihydrotestosterone levels which have previously been linked to the growth of the gland (17). Significantly however, our most recent studies reveal no correlation between EGF recpetors and the endocrine status of the gland, suggesting that androgens do not modulate EGF-receptor expression in the prostate (13). Since the action of Cernilton on the prostate seems also to be independent of the endocrine functions of the gland, the impact of the pollen exract on the tissue EGF concentrations might be of significant importance, not only in controlling the abnormal growth of the gland but also in pinpointing new pathways relating to the pathogenesis of BPH.

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Original Article

The Clinical Efficacy of Pollen Extract and Vitamins on Chronic Prostatitis/Chronic Pelvic Pain Syndrome Is Linked to a Decrease in the Pro-Inflammatory Cytokine Interleukin-8

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Purpose: We aim to evaluate the efficacy of pollen extract in association with vitamins in patients affected by chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and to evaluate the level of the pro-inflammatory mediators interleukin (IL)-6, IL-8, and IL-10.

Materials and Methods: Patients diagnosed with CP/CPPS between January and December 2015 were enrolled in this study. Participants were randomly assigned to receive oral capsules of pollen extract and vitamins (group A) or bromelain (group B) for 3 months. At the enrolment time and 3 months after enrolment, all patients completed questionnaires (the National Institutes of Health Chronic Prostatitis Symptom Index [NIH-CPSI] and the Short Form-36 and underwent urological examinations and microbiological evaluation. Levels of IL-6, IL-8, and IL-10 were evaluated in seminal plasma.

Results: Sixty-five male patients (mean age of 32.7 ± 4.7 years) were analysed (group A, $n = 32$; group B, $n = 33$). At the follow-up examination, 24 of the 32 patients in group A showed a significant reduction in the NIH-CPSI total score compared with 8 of the 33 patients in the bromelain group ($p < 0.001$). Moreover, the mean level of IL-8 was significantly lower in the pollen extract and vitamins group when compared with the bromelain group (298 pg/mL *vs*. 736 pg/mL, respectively; $p < 0.001$). In group A we found a statistically significant reduction in the levels of IL-8 between enrolment and the follow-up visit (878 pg/mL *vs*. 298 pg/mL, respectively; $p < 0.001$).

Conclusions: Treatment with pollen extract and vitamins improved the quality of life in CP/CPPS patients by reducing the levels of pro-inflammatory IL-8.

Key Words: Interleukin-8; Pelvic pain; Pollen; Prostatitis

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INTRODUCTION

Chronic prostatitis (CP) is considered to be one of the most common illnesses in men aged over 50 years, with various clinical presentations [1]. According to the classification scheme of the United States National Institutes of Health (NIH), class III CP/chronic pelvic pain syndrome (CP/CPPS) is the most frequently diagnosed category of this illness [2]. Symptoms such as pelvic pain, painful voiding and ejaculation, and disturbed sexual function are common, often resulting in a significant impact on quality of life [3]. The therapeutic efficacy of current treatments for CP/CPPS has not been considered satisfactory, which introduces a number of aspects for consideration and analysis [4]. The use of antibiotics remains controversial, especially considering the fact that no bacteria have ever been isolated from the urogenital samples of CP/CPPS patients [5]. However, even if anti-inflammatory medications, can decrease pain, their high prevalence of drug-related adverse effects mean that these should be taken for a limited period of time only. Therefore, the standard treatment for CP/CPPS has not yet been definitively established. Given this situation, phytotherapeutics may present a viable option; however, few compounds have been subjected to scientific scrutiny and prospective controlled clinical trials [6,7]. Over the past few years, there has been increased interest in the use of flower pollen extract for the management of CP/CPPS [8]. Several studies have shown that flower pollen extract preparations may contribute to a lasting and marked symptom reduction in young men with CP/CPPS, with improvement in semen quality and a significant decrease in the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score [8-11]. Several studies have found that patients with CP/CPPS showed higher levels of pro-inflammatory cytokines, such as interleukin (IL)-1b, IL-6, tumour necrosis factor a, and IL-8 [12,13] compared to controls. Moreover, IL-8 could be considered a useful biomarker in the management of CP/CPPS and could potentially be applicable to disease diagnosis, prognosis, and treatment [12]. Herein, we aim to evaluate the efficacy of pollen extract in association with vitamins (Deprox 500®; IDI Integratori Dietetici Italiani S.r.l, Sicily, Italy) in patients affected by CP/CPPS and to perform a detailed evaluation of pro-inflammatory mediators IL-6, IL-8, IL-10 in order to establish the mechanism of action for this treatment.

MATERIALS AND METHODS

1. Study design

This study was a prospective, randomized, unblinded, controlled phase III clinical trial aimed at evaluating the efficacy of pollen extract and vitamins in patients affected by CP/CPPS and their levels of pro-inflammatory mediators. All consecutive patients with a clinical and instrumental diagnosis of inflammatory CP/CPPS (NIH class IIIa-inflammatory CP/CPPS) attending the same urologic centre between January and December 2015 were screened for enrolment in the study. The treatment group received pollen extract with vitamins (Deprox 500®), while the control group received bromelain. The choice of bromelain as control group treatment was due to the lack of a gold-standard treatment for CP/CPPS [5,7]. Bromelain was also chosen primarily for the fact that it is a phytotherapeutic compound with an anti-inflammatory effect, considered safe as a long-term therapy, with high patient compliance [14].

2. Outcome measures

The main outcome measures of our study were as follows: an improvement in quality of life, defined as an improvement in the NIH-CPSI score (*i.e.*, a reduction of the NIH-CPSI total score by ≥25%) and a decrease in pro-inflammatory mediators (*i.e.*, a reduction of at least 65% from the baseline) by the end of the complete study period.

3. Inclusion and exclusion criteria

The inclusion criteria were the presence of pelvic pain symptoms for at least 3 months during the 6 months before study enrolment in accordance with the European Association of Urology guidelines, a score in the pain domain of the NIH-CPSI of >4 and a negative result for the Meares-Stamey 4-glass test [11,15,16]. We excluded all patients with the following characteristics: subjects <18 and >65 years of age affected by major concomitant diseases with known anatomical abnormalities of the urinary tract or with evidence of other urological diseases with re-

sidual urine volume >50 mL resulting from bladder outlet obstruction, subjects with a reported allergy to pollen extract who had recently (within <4 weeks) undergone oral or parental treatment or who were currently using prophylactic antibiotic drugs, and all patients who tested positive for *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Neisseria gonorrhoeae*, herpesviruses (HSV 1/2), and human papillomavirus (HPV).

4. Study schedule

Upon arrival at our centre, all eligible individuals provided their written informed consent, completed baseline questionnaires, underwent a urological examination with the Meares-Stamey test, and provided a seminal sample on site [15,16]. All seminal plasma samples were used in the pro-inflammatory cytokine evaluation. All patients who met the inclusion criteria were randomized to either the treatment or control group by using a computer-generated allocation sequence. All patients were assigned to 1 of the 2 groups (group A: pollen extract in association with vitamins; and group B: bromelain) according to a 1:1 randomization. Those patients assigned to group A ingested a daily oral administration of 2 tablets of pollen extract and vitamins in a single dose in the evening. All patients assigned to group B underwent daily oral administration of 2 tablets of 40 mg of bromelain in a single daily dose in the evening. Neither the physicians nor the patients were blinded to the treatment type. All patients were contacted by telephone on day 30 of the therapy to ensure that they were correctly administering the drug, in order to ensure uniform treatment interval and dosage. A follow-up visit was scheduled at 3 months from the start of therapy, with urological and microbiological examinations, questionnaire collection, and pro-inflammatory cytokines evaluation. Fig. 1 shows the study schedule.

5. Composition and characterization of the extracts used

1) Pollen extract in association with vitamins (Deprox 500®)

Each administration contained 1 g of pollen extract (500 mg per tablet, GRAMINEX; IDI Integratori Dietetici Italiani S.r.l) and vitamins B1, B2, B6, B9, B12, and PP, as described in the manufacturer's instructions.

2) Bromelain

All patients in the control group received 80 mg of bromelain per day. Bromelain is a crude, aqueous extract obtained from both the stem and fruit of the pineapple plant, which contains a number of proteolytic enzymes and has shown potentially beneficial effects due to its anti-inflammatory and analgesic properties [17].

6. Questionnaires and urological examinations

The validated Italian versions of the NIH-CPSI [18] and Short Form-36 (SF-36) questionnaires were self-administered to all patients [19].

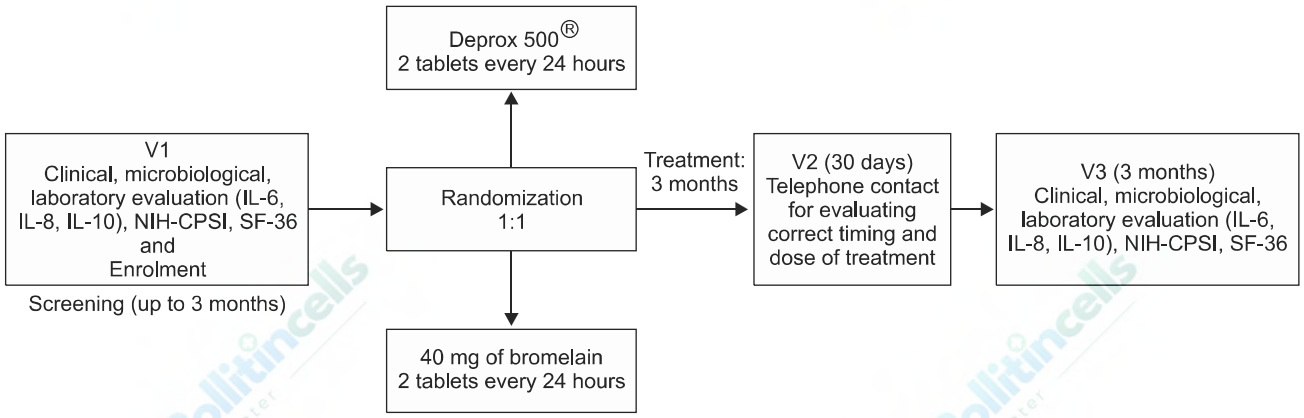

Fig. 1. The study schedule. V1: visit 1, IL: interleukin, NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index, SF-36: Short Form-36, V2: visit 2, V3: visit 3.

7. Microbiological considerations, sample collection, and laboratory procedures.

All samples from the Meares-Stamey test and seminal plasma were collected at the time of the urological visit and immediately taken to the laboratory under refrigerated conditions, analysed for cultures, and aliquoted for DNA extraction and polymerase chain reaction for *C. trachomatis*, *U. urealyticum*, *N. gonorrhoeae*, HSV 1/2 and HPV detection [20]. All microbiological evaluations and DNA extraction and purification were carried out in accordance with the methods described by Mazzoli et al [20]. In addition, natural human-produced IL-6, IL-8, and IL-10 concentrations were identified in the seminal samples of all patients and controls with the solid-phase enzyme-linked immunosorbent assay Quantikine IL-6, IL-8, and IL-10 Immunoassay (R&D Systems, Minneapolis, MN, USA) [20]. All samples were tested in duplicate by using independent analysis in accordance with the manufacturer's recommendations and in order to avoid errors. The medium minimal detectable doses of the IL-6, IL-8, and IL-10 assays were 0.70 pg/mL, 3.5 pg/mL, and 3.9 pg/mL, respectively [20].

8. Ethical and statistical considerations

The study was conducted in line with Good Clinical Practice guidelines, in compliance with the ethical principles published in the latest version of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to treatment. Furthermore, this study was conducted in line with the Consolidated Standards of Reporting Trials statement (URO-TN-2015). The homogeneity of the 2 groups at the baseline evaluation was carried out by using the Student t-test and Mann-Whitney U-test for continuous variables and by the chi-square test for categorical variables. General characteristics of the study participants were expressed using descriptive statistics (means, standard deviations, or ranges). Randomization based on a single sequence of random assignments (simple randomization) was performed using a pseudo-random number generator program (Research Randomizer ver. 4.0; Social Psychology Network,

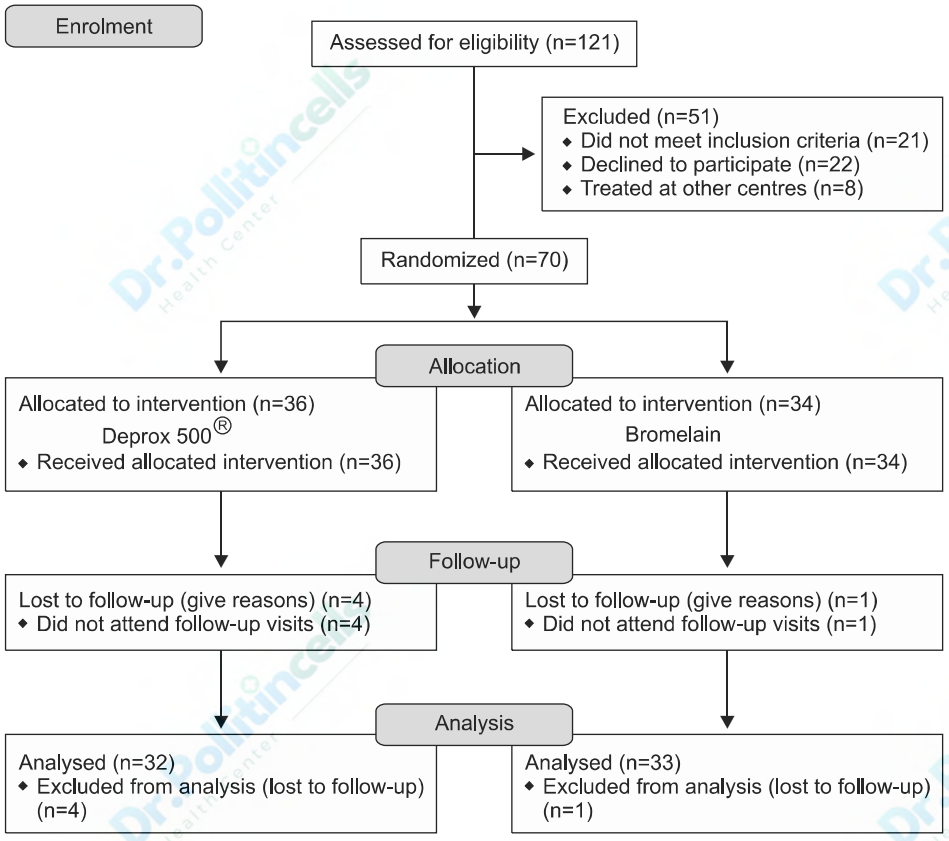

Fig. 2. The flowchart for the study according to the Consolidated Standards of Reporting Trials 2010 flow diagram.

Wesleyan University, Middletown, CT, USA). ANOVA was used for comparing the means. The Bonferroni adjustment test was also used at the second stage of the ANOVA. The differences between the groups regarding the NIH-CPSI results and mean concentration of pro-inflammatory cytokines were obtained using an ANOVA test. The calculation of the sample size needed for enrolment was based on the first outcome measure (improvement of quality of life), due to the fact that we had no data on the effects of pollen extract in association with

Table 1. Demographic and clinical data of the patients at the time of enrolment

Variable	Group A	Group B	p-value
Patient	32	33	
Age (yr)	32.4±4.3	32.8±4.9	0.72
Education level			
Primary school	2 (6.3)	2 (6.1)	0.79
High school	20 (62.5)	19 (57.6)	
University	10 (31.3)	12 (36.4)	
Smoking			
Yes	5 (15.6)	4 (12.1)	0.73
No	27 (84.4)	29 (87.9)	
Sexual behaviour			
1 partner	29 (90.6)	30 (90.9)	1.0
>1 partner	3 (9.4)	3 (9.1)	
Contraceptive use			
Condom	18 (56.3)	16 (48.5)	0.62
Coitus interruptus	14 (43.7)	17 (51.5)	
Start of CP/CPPS history (mo)	19.3±5.3	19.7±6.1	0.77
Symptoms score at baseline			
NIH-CPSI	25.1±2.1	25.6±2.9	0.43
SF-36	93.5±1.1	93.8±1.5	0.36
Clinical presentation			
Dysuria	15 (46.9)	16 (48.5)	0.85
Urgency	1 (3.1)	2 (6.1)	
Dysuria+frequency	7 (21.9)	7 (21.2)	
Burning	9 (28.1)	8 (24.2)	
Pain			
Perineal	15 (46.9)	16 (48.5)	0.82
Scrotal	3 (9.4)	3 (9.1)	
Suprapubic	8 (25.0)	9 (27.3)	
Lower abdominal	6 (18.8)	5 (15.2)	
Pain frequency			
Daily	29 (90.6)	29 (87.9)	0.97
Weekly	3 (9.4)	4 (12.1)	
Sexual symptoms			
Erectile dysfunction	7 (21.9)	8 (24.2)	0.61
Premature ejaculation	9 (28.1)	6 (18.2)	
ED+PE	3 (9.4)	2 (6.1)	
None	13 (40.6)	17 (51.5)	

Values are presented as number only, mean±standard deviation, or number (%). The sum of the percentages does not equal 100% because of rounding.
Group A: received pollen extract with vitamins (Deprox 500®); treatment group, Group B: received bromelain; control group, CP/CPPS: chronic prostatitis/chronic pelvic pain syndrome, NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index, SF-36: Short Form-36, ED: erectile dysfunction, PE: premature ejaculation.

vitamins on pro-inflammatory cytokines. In this sense and in line with the literature results, the required sample size was calculated under the following conditions: difference between the groups, 35% of patients who reach a reduction in 25% of the NIH-CPSI total score; α error level = 0.05, 2-sided; statistical power, 80%; and anticipated effect size, Cohen d = 0.5. Our calculation indicated that 32 individuals would be needed in each of 2 groups. Statistical significance was achieved when $p < 0.05$. All reported p-values were 2-sided. Statistical analyses were performed using SPSS software ver. 11.0 (SPSS Inc., Chicago, IL, USA) for Macintosh (Apple, Cupertino, CA, USA).

RESULTS

From a group of 121 patients attending our centre during the enrolment period, 70 met the inclusion criteria and were randomly allocated as follows: 36 to group A and 34 to group B. Five patients were excluded and a final total of 65 patients were analysed (Fig. 2). No statistically significant differences between the groups were identified. All clinical and laboratory data at enrolment are described in Table 1.

1. Clinical results at follow-up evaluation

At the end of the treatment period, 24 of 32 patients (75.0%) in the pollen extract and vitamins group reported an improvement in quality of life, as did 8 of 33 patients (24.2%) in the bromelain group ($p < 0.001$). The SF-36 questionnaires confirmed these results (mean SF-36 value in the treatment group: 98.6 ± 2.1; mean SF-36 value in the control group: 94.9 ± 2.9; $p < 0.001$). All questionnaire results at 3 months after treatment are listed in Table 2. The greater improvement in the treatment group compared with the control group was statistically significant (treatment difference in the NIH-CPSI pain domain: −4.8 ± 0.3 *vs.* −2.1 ± 0.7; $p < 0.001$).

2. Laboratory and microbiological results at follow-up evaluation

The mean levels of pro-inflammatory cytokines at the follow-up evaluation are detailed in Table 3. No statistically significant differences were identified between the 2 groups in terms of IL-6 and IL-10 levels ($p = 0.81$ and $p = 0.41$, respectively). The mean post-treatment level of IL-8 was significantly lower in group A compared with group B (IL-8, 298 pg/mL *vs.* IL-8, 736 pg/mL; $p < 0.001$). In group A we found a statistically significant reduction of IL-8 levels between the enrolment period and the follow-up visit (IL-8, 878 pg/mL *vs.* IL-8, 298 pg/mL; $p < 0.001$) (Table 3). A good correlation between the reduction of IL-8 (at least 65% from the pre-treatment value) and quality of life im-

Table 2. Questionnaire results at the 3-month follow-up visit

Variable	Group A	Group B	p-value
NIH-CPSI			
Before treatment	25.1 ± 2.1	25.6 ± 2.9	0.43
After treatment	11.7 ± 3.2	22.5 ± 3.7	< 0.001
p-value	< 0.001	0.0003	
NIH-CPSI pain domain			
Before treatment	11.3 ± 2.1	10.7 ± 2.5	0.29
After treatment	6.7 ± 1.9	8.1 ± 2.3	0.009
p-value	< 0.001	< 0.001	
Reduction in the NIH-CPSI pain domain	−4.8 ± 0.3	−2.1 ± 0.7	< 0.001
SF-36			
Before treatment	93.5 ± 1.1	93.8 ± 1.5	0.36
After treatment	98.6 ± 2.1	94.9 ± 2.9	< 0.001
p-value	< 0.001	0.08	

Values are presented as mean ± standard deviation.
Group A: received pollen extract with vitamins (Deprox 500®); treatment group, Group B: received bromelain; control group, NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index, SF-36: Short Form-36.

Table 3. Pro-inflammatory cytokine evaluation at enrolment and at the 3-month follow-up visit

Variable	Group A	Group B	p-value
IL-6 (pg/mL)			
Before treatment	38,126 (19,000～44,800)	39,060 (19,000～44,800)	0.43
After treatment	34,040 (19,000～44,800)	35,146 (19,000～44,800)	0.81
p-value	0.78	0.52	
IL-8 (pg/mL)			
Before treatment	878 (346～12,000)	912 (418～12,000)	0.09
After treatment	298 (100～3,460)	736 (346～12,000)	＜0.001
p-value	＜0.001	0.07	
IL-10 (pg/mL)			
Before treatment	64 (34～96)	66 (34～96)	0.38
After treatment	48 (34～96)	52 (34～96)	0.41
p-value	0.56	0.79	

Values are presented as median (range).
Group A: received pollen extract with vitamins; treatment group, Group B: received bromelain; control group, IL: interleukin.

provement (receiver operating characteristic, area under curve＝0.83; p＝0.001) was found. All patients tested negative at the Meares-Stamey evaluation.

3. Adverse effects

One patient out of 32 patients (3.1%) in group A and 2 of 33 patients (6.1%) in group B had mild adverse effects (nausea).

DISCUSSION

1. Major finding

Herein, we have demonstrated the clinical efficacy of pollen extract in association with vitamins for managing patients affected by CP/CPPS, and the results of our study revealed a relationship between the reduction of IL-8 and clinical efficacy. Another important aspect that came to light is that that the reduction of IL-8 (65%) could be considered a good marker for the response to treatment for CP/CPPS and improvement of patient quality of life.

2. Results in comparison with other studies

The efficacy of pollen extract in the treatment of patients affected by CP/CPPS has been demonstrated by several clinical studies [8-11,16,21-24]. All authors agree that pollen extracts significantly improved total symptoms, pain, and quality of life in patients with inflammatory CP/CPPS without severe side effects [8-11,16,21-24]. In particular, Cai et al [9] in a non-randomized clinical study reported a clinical response rate of 90%, demonstrating that pollen extract in association with vitamins significantly improved total symptoms, pain, and quality of life in patients with non-inflammatory CP/CPPS without severe side effects. Moreover, 3 studies by Japanese researchers demonstrated a high clinical response rate to pollen extract treatments in patients with both class IIIa and class IIIb CP/CPPS [24-26]. In a randomized control trial involving 139 patients affected by inflammatory CP/CPPS and treated for 12 weeks with flower pollen extract, Wagenlehner et al [11] demonstrated a clinical response rate of 70.6%. In addition, in a cohort of patients randomized to pollen extract or ibuprofen treatment groups, Cai et al [16] reported a response rate of 75.6% in the flower pollen extract group with a low prevalence of adverse effects. All authors hypothesized that the clinical effect of pollen extract was due to an anti-inflammatory anti-proliferative effect on the basis of pre-clinical studies [21]. Up to the present, no clinical study has yet demonstrated the effect of pollen extract on pro-inflammatory cytokines. The only available data come from an animal experiment on a dose-dependent anti-inflammatory action of pollen extract in comparison with aspirin in nonbacterial prostatitis in rats. The study findings showed an approximately 10× greater decrease in the levels of IL-1b, IL-6, and tumour necrosis factor in the pollen extract treatment group [21]. Herein, we have demonstrated for the first time that the clinical ef-

fect of pollen extract in association with vitamins is associated with a reduction in IL-8 levels. A few years ago, Penna et al [12] demonstrated that, among all the cytokines and chemokines analysed, IL-8 appears to be the most reliable and predictive surrogate marker for diagnosing prostate inflammatory conditions, such as CP/CPPS and benign prostatic hyperplasia. This aspect is very important, because in CP/CPPS patients no biological or molecular markers exist that may be used to evaluate the response to treatment [21]. In fact, Wagenlehner et al [11] found a decrease of leukocytes in post-prostate massage urine samples in both patients and controls; however, they did not find a significant difference between the 2 groups in terms of leukocyte numbers and, for this reason, they concluded that leukocytes cannot be correlated with clinical success [11]. This aspect supports the hypothesis that the presence of inflammatory cells in the post-prostate massage urine sample is not a laboratory characteristic adequately able to predict the response to the treatment. In this sense, our study highlights the feasible role of IL-8 evaluation in predicting the response to treatment in CP/CPPS patients. However, no statistically significant difference in terms of IL-6 or IL-10 levels was observed in our patient population. A few experiments have demonstrated the possible diagnostic role of IL-6 and/or IL-10 evaluation in patients affected by asymptomatic prostatitis (class IV) or benign prostate hyperplasia [27,28]. In particular, Miller et al [29] found that IL-10 levels correlated directly to measures of life interference and pain severity, thus highlighting their diagnostic role. However, no studies have ever evaluated changes to levels of IL-6 and/or IL-10 during therapy in CP/CPPS patients. As far as we are aware, ours is the first study to evaluate the changes in levels of IL-6 and IL-10 during treatment. On the basis of these considerations, the efficacy of pollen extract in association with vitamins in CP/CPPS patients is probably due to the anti-inflammatory effects of pollen extract and the neuroprotective role of B vitamins. The superiority of pollen extract in association with vitamins in comparison with bromelain is probably due to the additional role of B vitamins, because bromelain also shows an anti-inflammatory effect [30]. However, the neuroprotective role of B vitamins should be confirmed by future studies.

3. Strengths and limitations of the present study

The present paper reveals important factors that should be taken into account in CP/CPPS treatment: the evaluation of the pro-inflammatory cytokines level and the correlation between these and clinical results. However, some limitations of our study also need to be taken into account, including the small number of enrolled patients, the short follow-up period, the selected patient population, and the non-blinded nature of the study.

CONCLUSIONS

Treatment with pollen extract and vitamins improved the quality of life of patients affected by CP/CPPS, and its clinical efficacy was associated with a decrease in pro-inflammatory cytokine IL-8. Moreover, the reduction in IL-8 (65%) could be considered a good marker for response to the treatment.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Possibilities and Limitations of Phytotherapy for Benign Prostatic Hyperplasia (BPH)

Results of Treatment with Cernilton® N for Stages 1-3 according to Alken (or II-IV according to Vahlensieck)

D. Bach, L. Ebeling

Introduction

Surgical treatment (transurethral resection or open surgical enucleation of the adenoma) of benign prostatic hyperplasia (BPH) is still the only curative therapy and therefore the "gold standard" for the treatment of BPH. Other treatment modalities have to be judged according to this standard. Despite all improvements in surgical technique and modern anesthesiology, a perioperative mortality rate of 0.2% and an increased delayed mortality due to cardiovascular diseases remains a significant risk factor (19). Furthermore, other possible complications of surgery such as urinary incontinence, erectile impotence, or retrograde ejaculation are not acceptable to some patients.

Despite extensive investigation into the endocrinological control of the growth of the prostate, the etiology of the pathological enlargement of this gland has not yet been definitely resolved. As a target organ for male steroid hormones, the prostate is under the influence of dihydrotestosterone and 17ß-estradiol, which act in particular synergistically on the growth of the fibromuscular stroma. This explains why antiandrogens may be useful in the treatment of BPH (4,20). Because of the adverse effects of antiandrogens such as disturbances of libido and erectile function as well as gynecomastia, this therapeutic principle has thus far not been utilized widely, and is only used for certain patients such as those at prohibitive surgical risk. Other treatment attempts such as the inhibition of the enzyme 5alpha-Reductase require further studies concerning efficacy and adverse effects (14).

The importance of phytotherapeutic drugs with a low side effect profile has consequently increased in regard to the conservative treatment of BPH, which at least in Germany is mainly the responsibility of nonhospital-affiliated physicians. In recent years a standardized pollen extract (Cernilton ®N[1]) has been investigated (5,6,9) and utilized. This pollen extract has also been utilized to treat prostatic congestion and/or prostatodynia and non-bacterial prostatitis without proven pathogens (8). The anticongestive effect of the pollen extract in the treatment of BPH should be considered as a clinically relevant therapeutic principle.

To examine the value of treatment of BPH with phytotherapeutic drugs in clinical practice, a study was conducted in BPH patients to determine efficacy and tolerance of the pollen extract in the various stages of disease.

Patients and Methods

Patients

Over the course of one year, 208 practicing physicians documented their treatment experiences using Cernilton® N in 1,933 patients with BPH. Because of missing follow-up examinations or premature termination of either treatment or documentation not related to the treatment with Cernilton®, data on only 1,894 patients were available for analysis. An additional 96 cases which were not classified in regard to the stage of the disease were also excluded from the analysis. In seven of these patients treatment was terminated after the 12th week.

The patient material included therefore 1,798 patients with consecutive treatment over 24 weeks (2 tablets orally 3 times daily). In 1,661 patients pretreatment evaluations and evaluations after 12 and 24 weeks of treatment were available, while in 29 patients data were available for the pretreatment evaluation and after 24 weeks of treatment with Cernilton® N. In 51 patients the treatment was terminated because of symptomatic improvement (N = 11), lack of efficacy (N = 7), surgery (N = 27), untoward side effects (N = 4) or urinary tract infections (N = 2). In 57 cases treatment was terminated without a specified reason. Overall, therefore, 108/ 1,798 (6%) of the patients terminated treatment prematurely in the study population, as opposed to 115 / 1,894 (6.1 %) in the entire patient population.

The patients were staged according to *Alken*. Nine hundred and ten patients (50.6 %) were in stage 1, 770 patient (42.8 %) in stage 2, and 118 patients (6.6 %) in stage 3. The average age for these three groups was 60.0, 67.6, and 71.6 years, respectively. Overall, 59.1 % of patients had been pretreated, usually with other phytotherapeutic drugs used in BPH over an average duration of 21.2 (stage 1), 32.5 (stage 2), and 46.8 months (stage 3). This pretreatment was judged as "successful" in 52.0 % of stage 1 patients, 42.6 % of stage 2 patients and 30.4 % of stage 3 patients. Concomitant diseases existed in 812 (45.2 %) of the patients. Cardiovascular diseases (57.4%), endocrine and metabolic diseases (22.8%), and urological diseases (11.0 %) were most common. Among the urological diseases, prostatitis and bladder cancer were the most common.

To further describe the voiding disturbances, data such as age at the first manifestation, specific symptoms (irritative versus obstructive), intensity of the symptoms over time (constant versus variable, either increasing or decreasing), and incidence of episodes of acute urinary retention were documented.

Methods

Clinical evaluation was conducted prior to initiation of therapy as well as after 12 and 24 weeks of treatment. Irritative and obstructive symptoms (nocturia, frequency, feeling of incomplete emptying, urgency, delayed voiding, prolonged voiding time, weak urinary stream, and post-void dribbling) were classified as either mild, moderate, or severe.

Size and congestion of the prostate were evaluated by digital rectal examination (DRE). Residual urine volume was determined by ultrasonography. The documentation of residual urine was optional, and flow rate parameters were not documented at all since several of the participating physicians were family physicians and general practitioners who often did not have the means to perform residual urine or, in particular, flow rate measurements.

According to the design of the study, a statistical analysis was conducted using minimum, maximum, median, and mean values, standard deviation (STD), and frequency distributions. To compare frequency distribution across the various stages of BPH, the X^2 test was used. For the comparison of means, a simple analysis of variance was employed, and for the comparison of mean time effectiveness profiles, split plot variance analysis was utilized.

Results

Voiding Disturbances and Findings on DRE

The distribution of obstructive and irritative voiding symptoms at the time of entry into the study is tabularized in Table **1**. Data concerning age at first manifestation and type of voiding symptoms as well as their course are listed in Table **2**. While in stage 1 BPH nocturia and frequency are the dominating symptoms, prolonged voiding time and a weak urinary stream are most common in stage 2, and in particular in stage 3 BPH. Post-void dribbling was of particular importance in patients with stage 3 BPH. Prostatic congestion increased significantly with increasing stages. As expected, a more pronounced enlargement of the prostate was found in patients with stages 2 and 3.

Parameter	BPH 1 (N = 910)	BPH 2 (N = 770)	BPH 3 (N = 118)
Nocturia	43.6%	65.2%	79.8%
Frequency	53.8%	60.3%	77.9%
Feeling of incomplete emptying	20.9%	45.2%	69.8%
Urgency	26.4%	30.3%	49.5%
Delayed voiding	31.1%	62.3%	85.3%
Prolonged voiding	34.2%	70.1%	90.5%
Weak stream	38.7%	74.3%	88.8%
Postvoid dribbling	26.3%	44.0%	74.6%
Prostate enlargement	32.1%	86.1%	89.5%
Prostate congestion	28.1%	43.2%	63.0%

Tab. 1 Moderate to severe intensity of voiding symptoms and findings at digital rectal examination (DRE) in 1,798 patients with BPH. [The frequency of symptoms and DRE findings differ significantly between the three stages. (p<0.001).]

Of interest was the significantly different average age at the first manifestation of the voiding symptoms. In patients with stage 1, it was eight years earlier than in stage 3. If one takes the average age of the patient into account, symptoms have been present prior to treatment for 3.5 years in stage 1 patients, for 5.7 years in stage 2 patients, and for 7.1 years in stage 3 patients. If one excludes the possibility that the data obtained from older patients become relatively imprecise, these results can only be explained by an age-dependent dynamic course of progression of the disease process of BPH.

Irritative symptoms dominated in patients with stage 1, while in stages 2 and 3 obstructive symptoms were more common. However, in the advanced stages, often both irritative and obstructive symptoms were found equally common. Fluctuation of the intensity of the symptoms was particularly characteristic for patients with stage 1 BPH, while in patients with stages 2 and 3 a progression of the symptoms and a higher incidence of episodes of acute urinary retention was evident.

In regard to the findings on DRE and the voiding symptoms, the treatment with Cernilton ® N did not yield a significant difference in the response rates (range from 68% - 83%) between stages 1 and 2 (Table **3**). However, if one compares the therapeutic efficacy in stages 1 and 2 with respect to the symptom-free status concerning nocturia and the obstructive voiding symptoms as well as the DRE concerning the prostatic size, a significant difference in favor of stage 1 was found (Table **3**). For patients with stage 3 BPH, a response rate between 28% and 63% was found, while a symptom-free status was found in 0 - 15% of patients (Table **3**).

Unchanged positive symptoms and/or prostatic congestions (Non-responder) were found between 16.8% and 28.7% for patients with stage 1, 19.8% and 31.2% for patients with stage 2, and between 33.3% and 52.7% for patients with stage 3 BPH. Unchanged positive symptoms were found more commonly in the obstructive symptom category. Considering these findings, the comparison between the different stages yielded significant differences ($p < 0.001$) for all parameters, with a weaker effect in particular for stage 3 patients and in comparing stage 1 with stage 2. Worsening of the status in up to 6.4% of the patients was found particularly in patients with stage 3 BPH.

An analysis of the time course showed for all parameters - with the exception of the size of the prostate - an increase in the rate of patients with a symptom-free status in regard to voiding symptoms and prostatic congestions at 24-week evaluation in comparison with the 12-week evaluation. The incremental rate of improvement between 12 and 24 weeks of treatment was 13 % to 24 % for stage 1, 10 % to. 25 % for stage 2, and 1 % to 17 % for stage 3. There was no principle difference detected between stages 1 and 2. Fig. **1** illustrates the time course of one of the symptoms (nocturia) for the different stages of the disease throughout the treatment period. The mean severity index for this symptom is shown.

Tab. 2 Characteristic of voiding symptoms in the three stages of BPH.

Parameter		BPH 1	BPH 2	BPH 3	Comparison of Stages
Age at first manifestation (years)	$\bar{x}$	56.5	61.9	64.5	$p < 0.001$
	SD	10.2	8.7	8.0	
o not available		35	26	4	
Type of complaints					
o Mainly irritative		58.5%	29.7%	14.8%	
o Mainly obstructive		29.4%	42.5%	55.7%	
o Irritative and obstructive		11.8%	27.1%	28.7%	$p < 0.001$
o not available		8	10	3	
Clinical course (multiple listings)					
o Sometimes more, sometimes less		51.0%	32.5%	23.7%	$p < 0.001$
o Variable symptoms		47.8%	37.9%	22.0%	$p < 0.001$
o Increasing symptoms		31.9%	54.3%	73.7%	$p < 0.001$
o Episodes of retention		4.1%	9.9%	38.1%	$p < 0.001$
o not available		10	7	2	

Tab. 3 Overall treatment response rates (R) and symptom-free or negative DRE status (S) after treatment with Cernilton® N in percent (rounded) of patients who initially had symptoms or findings on DRE.

Parameter	Patients (N) Stage 1/2/3	BPH 1 R (%)	BPH 1 S (%)	BPH 2 R (%)	BPH 2 S (%)	BPH 3 R (%)	BPH 3 S (%)
Nocturia	727/719/111	76	43	73	21	57	5
Frequency	746/693/108	82	48	89	34	63	12
Feeling of incomplete emptying	469/605/101	83	64	79	47	56	15
Urgency	449/454/ 83	79	60	79	56	59	33
Delayed voiding	645/701/111	72	46	73	27	54	5
Prolonged voiding	629/711/113	72	40	70	20	47	2
Weak stream	736/737/112	71	37	70	17	46	4
Postvoid dribbling	592/651/109	72	49	68	37	55	15
Prostatic enlargement	802/746/111	29	13	33	3	28	–
Prostatic congestion	504/495/ 74	75	55	68	38	51	16

Residual Urine

Significant improvements in the amount of residual urine were noted under treatment with Cernilton® N in patients with stages 1 and 2. A comparison between pre-treatment and post-treatment values in patients who had initially at least 20 ml of residual urine revealed a mean decrease of 32.7ml (51 %) for stage 1, 43.1 ml (45 %) for stage 2, and 18.5 ml (13 %) for stage 3.

A time-course analysis in these patients showed for stages 1 and 2 a continuing decrease of the amount of residual urine under treatment. However, in patients with stage 3 BPH a worsening was noted at 24 weeks after an initial improvement (Fig.**2**). Analysis of variance revealed a significant difference when comparing the different stages of the disease (p=0.016). In patients with stage 2 BPH in comparison with stage 1, a more significant decrease of the residual urine volume was achieved after 24 weeks of treatment. In stage 1, 39.6 % of the patients with an initial residual urine volume of >20 ml had a residual urine volume of ≤20 ml at 24 weeks, while 25.0 % of patients with stage 2 achieved the same result. In patients with stage 3 BPH the residual urine volume was at the end of the treatment still significantly elevated. The degree of obstruction in this stage apparently does not allow a significant quantitative change of residual urine volume during treatment.

Adverse Effects

Adverse effects were noted in 15 patients for an incidence of 0.8 %. Except for two cases without specific documentation, the adverse effects were mainly gastrointestinal symptoms (stomach pain, pressure sensation, nausea, diarrhea, and indigestion). Treatment was terminated because of adverse effects after 12 weeks in four patients.

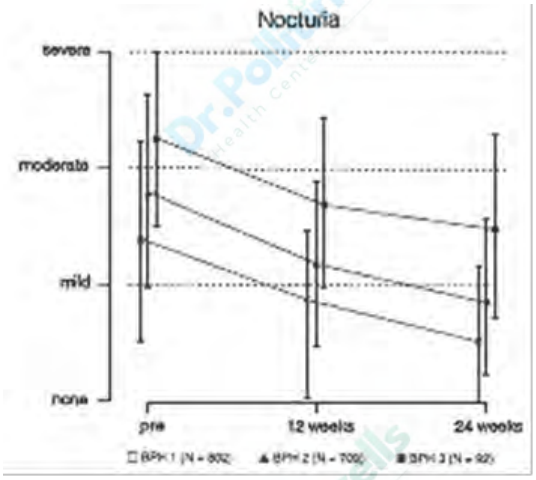

Fig.1 Nocturia (average intensity, ± SA) during 24 weeks of treatment in patients with stages 1, 2 and 3 BPH with Cernilton® N. The intensity of the symptom decreases throughout the treatment in all three stages.

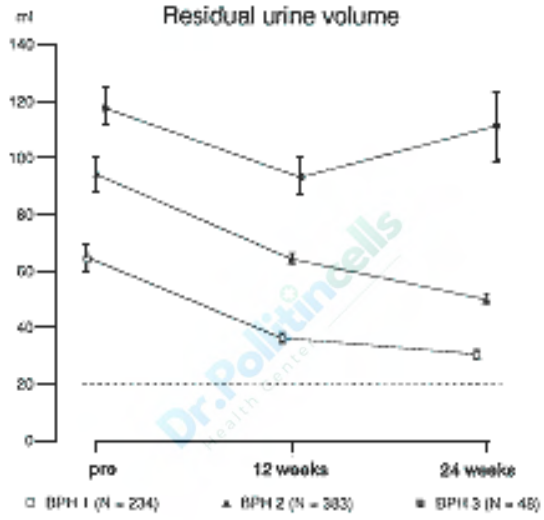

Fig.2 Residual urine volume (±SEM) during 24 weeks of treatment in patients with stages 1, 2, and 3 BPH with Cernilton® N. Continuing decrease of residual urine volume in stages 1 and 2, and a worsening after initial improvement during the first 12 weeks in stage 3 patients are observed.

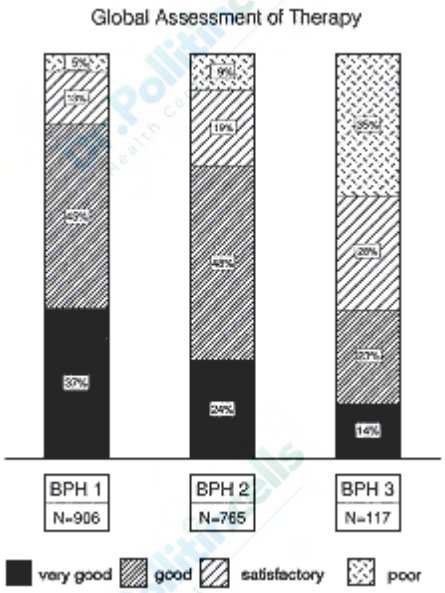

Fig. 3 Overall assessment of the efficacy of Cernilton® N in 1,788 patients with BPH by physicians stratified by stage.

Global Assessment of Efficacy and Tolerance

Independent of the stage of the disease, tolerance was judged to be good in over 99 % of patients. There were statistically significant differences in the judgment of the treating physicians concerning the efficacy across the three stages (Fig. **3**). The subjective assessment of the patients showed in principal a similar distribution of the results, but was overall somewhat more favorable when compared to the physicians' judgment. While the treatment result in patients with stages 1 and 2 BPH was judged as positive in over 90 %, it was judged as poor in 35 % of patients with stage 3. The main reasons for the treatment failure were advanced stage of the disease, need for surgery, psychogenic problems, bacterial prostatitis, and non-compliance of the patient.

Discussion

Reports in the urological literature document that several so-called conservative treatment options for BPH compete for both physicians and patients with BPH. Results following balloon dilation of the prostate, insertion of urethral spirals or stents made of surgical steel mesh in the prostatic urethra, thermotherapy, and drug treatment have been reported. Balloon dilation (15), insertion of spirals (11,18), or stents, (24), improved micturition only temporarily. Thermotherapy has apparently not yet reached practical applicability in the treatment of BPH (7,13,16,21).

If all these methods fail, oftentimes transurethral or suprapubic catheterization is a method of last resort. However, patients usually do not tolerate a permanent catheter over a long duration. This leaves the different drug treatments amongst which the low-risk phytotherapeutic drugs have a permanent place (2).

The use of these drugs is justified by good treatment results documented in case reports, open-label clinical studies, or prospective placebo-controlled double-blind studies. Criticism has been raised stating that the number of placebo-controlled studies is too low to prove the efficacy of the treatment (10). The placebo effect, which has to be taken into account with all drug treatments, is superimposed over the actual drug effect, and therefore no clear determination as to the efficacy of these drugs can be made.

However, concerning , the pollen extract preparation, Cernilton ® N, experimental *in vitro* and *in vivo* data, and clinical documentation of effectiveness are available. An inhibition of the prostaglandin and leukotriene synthesis (17), an inhibition of the enzymes 5alpha-Reductase, 3alpha- and 3ß-Hydroxysteroid-dihydroxygenase (22), an anti-proliferative effect on BPH cells (12), as well as on BPH heterotransplants (23), and a significantly better efficacy of verum as compared to placebo in regard to nocturia, residual urine, and the global assessment of the treatment results have been reported (5,9). The following discussion therefore aims at the question of the clinical relevance and the indication for the use of phytopharmaca in the treatment of BPH.

The present report details the observation made by 208 practicing physicians during the treatment of 1,933 BPH patients with Cernilton ® N. Under the conditions of routine clinical practice, it can be shown that

irritative and obstructive voiding symptoms, prostatic congestion, and the residual urine volume are significantly improved, depending on the stage of the disease.

When comparing the results with those of controlled clinical trials, the response rates and the percentage of patients who achieve a symptom-free status or whose clinical findings become negative are higher in the present report. This may be explainable by the patient selection necessary for clinical studies. However, except for the symptom of frequency, which may be judged differently because of inconsistencies in its definition, there are no principal differences and therefore the data of the present study remain valid.

Concerning the symptoms, it is noted that the irritative symptoms show the largest margin of improvement, and patients with stage 1 BPH obtain the most benefit. Since irritative and obstructive symptoms are often equally common in patients with stage 2 BPH, these subjective voiding symptoms also improve significantly in patients with stage 2 BPH.

The clinical course of the voiding symptoms indicates that with the progression of the disease, obstructive symptoms increase and become more important in comparison to irritative symptoms. In regard to the therapeutic effect, this results in a lower percentage of patients achieving a symptom-free status in those men with stage 2 disease. In this group, prostatic congestion is also usually more pronounced.

In contrast to this, the residual urine volume decreases both absolutely and relatively more in patients with stage 2 disease than in patients with stage 1 disease. This may explain the relatively small differences in the global assessment of the therapeutic results stratified by these stages of the disease. The course over 24 weeks of treatment indicates that the residual urine decreases in particular in patients with stage 2 BPH between week 12 and 24. The percentage of patients with improved or symptom-free status further increases during the second half of the treatment course. These results document therefore a relatively better efficacy of the treatment in stages 1 and 2 BPH during long-term therapy.

The clinical relevance of a therapeutic strategy is significantly impacted by the improvement of the quality of life as defined by the patient. The improvement of the voiding dysfunction is reflected in the overall global subjective assessment of the therapeutic result by the patient. If curative surgery is not medically indicated - this has to be decided for each individual patient - and an immediate surgical intervention independent of the stage of the disease is not necessary given the availability of continued monitoring of the patient (3), the results of the present study indicate that patients with stage 1 and 2 BPH according to *Alken* or stage II or III according to *Vahlensieck* represent a classical target group for the treatment with phytotherapeutic drugs. The impact of the treatment on prostatic congestion and associated inflammation is thereby the main focus of this treatment regimen (1).

The treatment of BPH with phytotherapeutic drugs is well tolerated and represents a treatment option with few risks. Therefore, a treatment trial may be justified even in patients with stage 3 BPH until the time of definite surgical treatment. In more than one-half of these patients some improvement in symptoms and a minor decrease in the amount of residual urine can be achieved. Phytotherapeutic drugs are not suitable for long-term treatment of patients at prohibitive surgical risk.

Summary

To examine the possibilities and limitations of phytotherapy for benign prostatic hyperplasia (BPH) a 24-week treatment trial using the pollen extract preparation Cernilton® Nwas conducted. Based on 1,798 cases a significant improvement in voiding symptoms, palpable prostatic congestion, and residual urine could be documented in stages 1 and 2. In patients with stage 3, the improvement in voiding symptoms was rather limited, as expected. When comparing the results after 12 and 24 weeks of treatment, a continuing improvement of all parameters during the second 12 weeks of treatment was noted.

The drug was tolerated well in over 99% of patients. The efficacy in stages 1 and 2 was judged to be satisfactory, good or very good by over 90% of the patients. Because of the lack of conservative treatment alternatives for patients with BPH, treatment with phytotherapeutic drugs with their associated minimal risks is recommended as one of the prime treatment modalities for patients with BPH who are under continued medical care and monitoring. Until surgery, a treatment trial is also justified in patients with stage 3.

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Therapeutic Results of Defined Pollen-Extract in Patients with Chronic Prostatitis or BPH Accompanied by Chronic Prostatitis

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Introduction

Depending mainly upon analysis of prostatic fluid and angloamerican classification divides the benign painful diseases of the prostate into four categories: Acute bacterial prostatitis, chronic bacterial prostatitis, non-bacterial prostatitis, and prostatodynia (1).

According to findings of *Weidner* (2) the largest group, the prostatodynia (vegetative urogenital syndrome), covers 52.4%. Besides clinical symptoms and normal laboratory findings the following urodynamics changes are characteristic: Elevation of the maximum urethral closure and reduced peak urine flow rates (3,4,5).

In approximately 40% of non-bacterial prostatitis the microbiological examination is negative (2) whereas by definition leucocytosis in the prostatic fluid can be demonstrated. The prostatic congestion, pathomorphologically considered as congestion of secretion and edemas in the prostate (6) can appear in every form of prostatism (7).

This demonstrates that antibiotics are indicated for a small number of patients only. Predominantly an anti inflammatory resp. symptomatic therapy is required.

The use of the pollen-extract in the treatment of benign prostatic diseases as BPH and prostatitis has already been described since 1960 and leads to clinical improvement of symptoms and positive changes by objective parameters.

In a double-blind study with 61 patients and a simultaneously carried out open examination with 118 patients *Leadner* (9) stated in the verum-group a normalization of initially pathological palpation findings and leucocytosis of prostatic fluid in 94% of patients with chronic prostatitis who were treated with pollen-extract. 6% of the patients showed unchanged results, aggravations were not observed. In the placebo-group 48% showed normalization, 34% demonstrated an unchanged status and in 18% of the patients the findings were deteriorated. The results of treatment in the open trial revealed only small differences in comparison to therapeutic effects in the verum-group which can be rated as accidental. *Takeuchi* (10) demonstrated in a clinical study with 25 BPH-patients in stage 1 or 2 under treatment with pollen-extract besides the elevation of peak urine flow rate a significant ($p < 0.05$) decrease of maximum urethral closure pressure with a corresponding diminished resistance of the prostatic part of the urethra.

Pharmacologically the pollen-extract is characterized by antiinflammatory and prostate cell selective growth inhibiting properties. Furthermore a specific affinity to the prostate could be demonstrated (11,12).

The aim of this field study was to control the acceptance and effectiveness of this drug on a large number of patients with chronic prostatic complaints, i.e. symptoms of chronic prostatitis or BPH, and to evaluate the possible role of the pollen-extract in their conservative treatment.

Methods

2,289 patients were divided according to the diagnoses given by 170 urologists based on clinical symptoms, palpation and laboratory findings as well as residual urine volume resp. uroflow measurements into three groups: 583 (25,4%) cases of chronic prostatitis (P), 590 (25,8%) cases of BPH accompanied by prostatitis (BP) and 1116 (48,8%) cases of BPH (B). The BP- and B-group was subdivided into stage 1, 2, and 3 (14).

The treatment with pollen-extract was in 84% of the cases in a dosage of 3 x 2 tablets/ day in the first week and continued in 78.5% with 3 x 2 tablets/ day up to twelve weeks.

Typical symptoms and palpation findings classified as light, medium or severe were recorded and evaluated before, during, and after therapy up to twelve weeks.

The residual urine volume determined by sonography, X-ray or catheterization, uroflow measurements as peak urine flow rate, urine volume voided and flow time, laboratory parameters as leukocytes in urine sediment or expressed prostatic secretions were controlled before and during treatment.

The courses of clinical signs and symptoms and the change of the objective parameters were documented. A further assessment was carried out by comparing the data before and after treatment.

Side effects, statements regarding the tolerance and a general assessment about the treatment with pollen-extract were investigated. Statistical analysis was performed as chi-square tests, variance analysis, split-plot variance analysis and factor analysis.

Results

[1] 1 tabl. Contains: Extr Pollin. sicc. (Cernitin T60) 60mg, Extr. Pollin. dialys. (Cernitin GBX) 3mg.

The age distribution showed a prevalence of the chronic prostatitis in the 4th and 5th decade whereas the BPH with prostatitis was diagnosed mainly in 60-70 years old men. The B-group represented the oldest patient-group (table 1).

Typical for patients with chronic prostatitis are also symptoms other than difficulties on micturition. These complaints reappeared in the BP-group in a less extensive form but compared to the B-group the significant difference is obviously (figure 1a). The correspondence between the P- and BP-group was similar regarding the leukocytes in prostatic expressate (figure 1b) and the >>painful prostate<< on palpation (figure 1c).

Depending on the respective complaints improvement or absence of symptoms were stated in 64% to 82%.

The palpated size of the prostate diminished more markedly in the BP-group compared to the B-group. A significant reduction in the P-group was found in 55.9% of the patients with initially enlarged prostate (n=169, n=302). The changes regarding the >>painful prostate<< on palpation are demonstrated by table II. The microscopic estimates of leucocytes in the prostatic expressate after therapy revealed for all diagnostic groups a decreased number of leucocytes ≤ 10/ HPF in 59% of the cases with initial findings >10 leucocytes/ HPF (n=291, n=493).

The residual urine volume diminished significantly ($p < 0.001$) in all stages (figure 2a) and showed a continuous decrease with the length of therapy (table III).

The peak urine flow rate increased in all groups significantly ($p < 0.001$) about 3 to 4 ml/sec comparing the pre/post-values (figure 2b and table IV). Concomitantly the urine volume voided increased and the flow time was reduced.

The general assessment of the therapy with pollen-extract by physician and patient was very good or good in 72.2% resp. 75%. Side effects (i.e. slight and temporary GIT disturbances)

were described in 66 cases (2.9%), in 1.2% the treatment was discontinued.

Table I. Age distribution in the diagnostic groups (P = chronic prostatitis, B = BPH, BP = BPH with prostatitis).

Parameter	Age range/Statistic	P	B	BP
Patients		583	1.116	590
Age, years	minimum	17	21	22
	maximum	85	97	94
	median	40.3	67.0	60.3
	mean	40.6	66.6	60.3
	standard deviation	12.0	9.3	11.7
	≤ 30	126	2	6
	31–40	170	4	22
	41–50	184	48	87
	51–60	61	210	182
	61–70	26	440	160
	71–80	12	328	113
	> 80	1	67	17
	negative	3	17	3
Stage of BPH	1		324	259
	2		598	244
	3		109	40
	negative		85	47

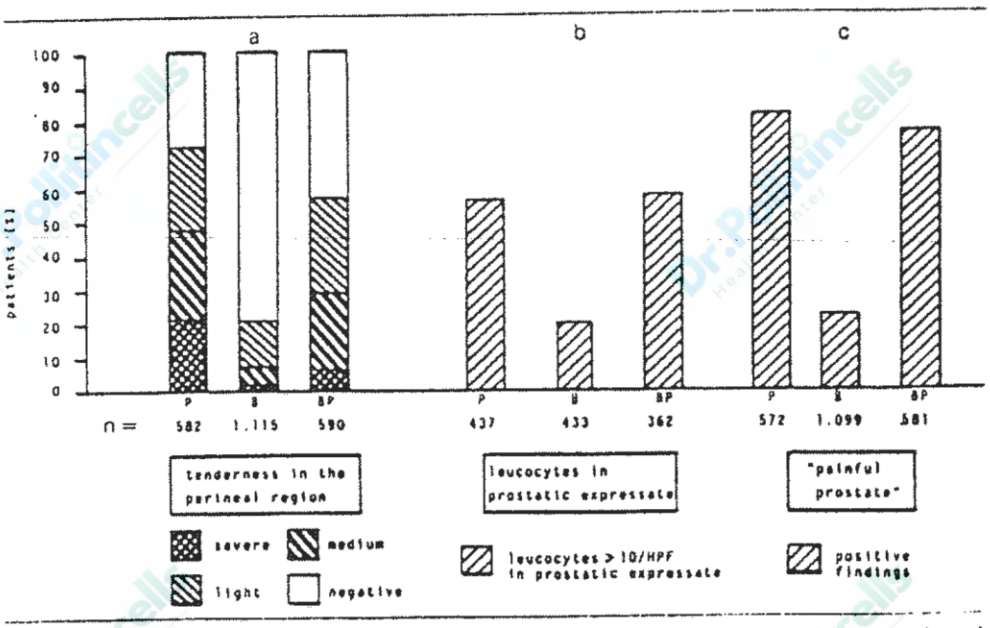

Figure 1a–c. Differences between the diagnostic groups regarding clinical symptoms (a), laboratory (b) and palpation findings (c) before therapy (P = chronic prostatitis, B = BPH, BP = BPH with prostatitis).

Table II. »Painful prostate« on palpation. Comparison of the pre/post-data. Significant ($p < 0.001$) differences in the findings before and after treatment with pollen-extract.

Intensity, scores	Chronic prostatitis		BPH		BPH with prostatitis	
	pre, n	post, n	pre, n	post, n	pre, n	post, n
Severe	96	4	12	–	56	3
Medium	196	26	62	5	186	22
Light	164	159	174	68	194	128
Negative	95	362	812	987	124	407
% negative	17.2	65.7	76.6	93.1	22.1	72.7

Course under therapy	Chronic prostatitis		BPH		BPH with prostatitis	
	n	%	n	%	n	%
Unchanged (all)	93		811		123	
Aggravated	4	0.9	1	0.4	3	0.7
Unchanged positive	50	10.9	41	16.5	47	10.8
Improved	135	29.5	31	12.4	103	23.6
Asymptomatic	269	58.7	176	70.7	284	65.0

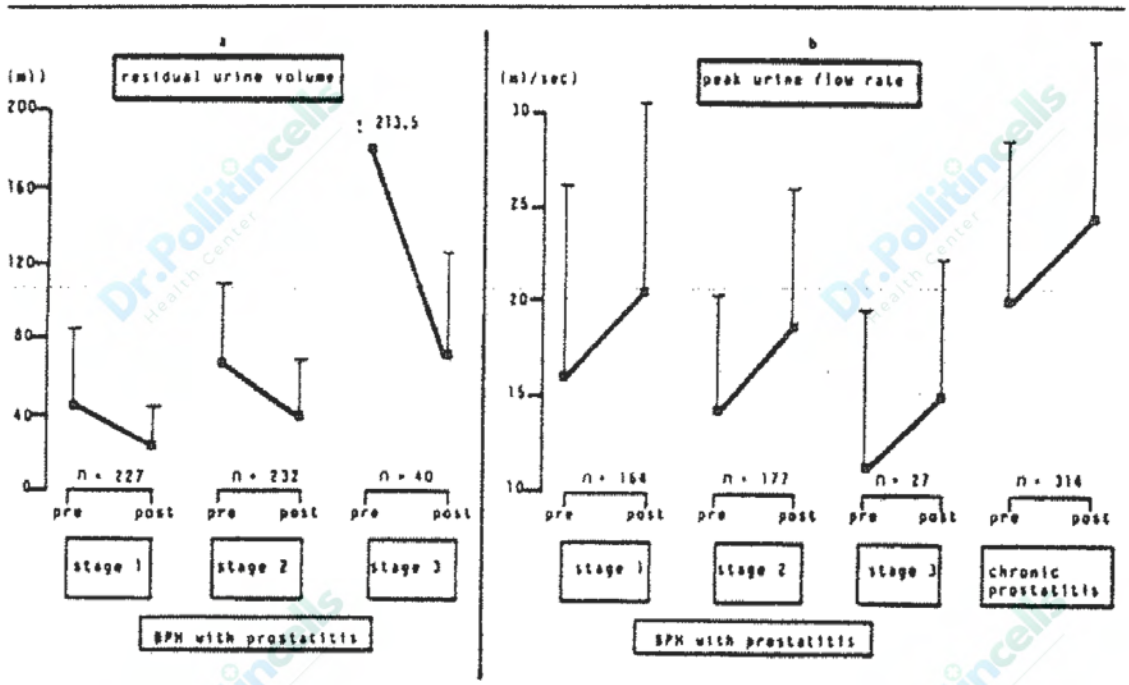

Figure 2a–b. Comparison of pre/post-findings regarding residual urine volume (a) and peak urine flow rate (b). Significant ($p < 0.001$) decrease of residual urine volume in BPH (stage 1–3) with prostatitis, significant ($p < 0.001$) increase of peak urine flow rate in patients with chronic prostatitis or BPH (stage 1–3) with prostatitis under the treatment with pollen-extract.

Table III. Residual urine volume (ml) under treatment with pollen-extract. Continuous decrease with the length of therapy. Significant ($p < 0.001$) differences in the findings before and after treatment.

	Time of control	BPH with prostatitis	
		x̄	s
Treatment over 12 weeks (n = 175)			
	pre	67.3	73.6
	2 weeks	50.0	46.2
	6 weeks	41.7	42.0
	12 weeks	32.0	35.7
Pre/post-comparison (n = 542)			
	pre	62.9	76.6
	post	34.2	34.2
	difference	−28.7	

Table IV. Peak urine flow rate (ml/sec) under treatment with pollen-extract. Continuous increase with the length of therapy. Significant ($p < 0.001$) differences in the findings before and after treatment.

	Time of control	Chronic prostatitis		BPH with prostatitis	
		x̄	s	x̄	s
Treatment over 12 weeks		n = 95		n = 119	
	pre	20.7	9.6	14.6	7.9
	2 weeks	22.6	8.8	16.3	7.5
	6 weeks	24.2	8.8	18.8	9.2
	12 weeks	26.1	8.8	20.0	9.3
Pre/post-comparison		n = 314		n = 403	
	pre	19.8	8.5	15.0	8.2
	post	24.1	8.9	19.3	8.9
	difference	+4.3		+4.3	

Discussion

The objective criteria for therapeutic effectiveness as residual urine volume, peak urine flow rate, urine volume voided, flow time and leucocytes findings show in their course and by comparison the status before and after therapy significant changes which are accompanied by improved palpation findings and a continuous decline of symptom-scores indicating the subjective relief in patients.

Under differential therapeutic aspects the conservative treatment of benign and chronic prostatic diseases is to consider as a predominantly antiinflammatory resp. symptomatic one. The findings of *Weidner* (2) regarding the various forms of chronic >>prostatitis<< confirm that at least in 68.3% of patients an antibiotic therapy is not primarily indicated.

The pre/post-comparison of leucocyte findings in the prostatic expressate reveals a decrease on ≤ 10 leucocytes/ HPF in 59% of all cases with initial values > 10/ HPF.

These results confirm previous findings by *Leander* (9). The differences regarding the percentage of improvement resp. normalization

are explainable by his definition of the pathological value as ≥ 10 leucocytes/ field (x 240).

Therefore it can be concluded that the pharmacologically demonstrated antiinflammatory property leads to clinical effects in human too.

The etiology of the prostatodynia remains uncertain. Whereas *Vahlensieck* (6) distinguishes between the static, vegetative and sexual dependent causes of prostatic congestion, a primary abnormality involving the pelvic sympathetic nervous system in most patients or tension myalgia of the pelvic floor is suggested by *Meares* et al. (4, 5).

The urodynamic findings in this study, i.e. significant ($p < 0.001$) increase about 3 to 4 ml/ sec of peak urine flow rate with concomitantly higher values of urine volume voided and reduced flow time, are investigated in the P- and BP-group, suggesting a homogenous effect of the pollen-extract on the bladder outflow obstruction.

Under treatment with pollen-extract a significant ($p < 0.05$) decrease of maximum urethral closure pressure with decreased resistance of the prostatic part of the urethra was demonstrated in BPH-patients (10).

These findings, due to the antiinflammatory and decongestive effects of this drug, give evidence for the therapeutic benefit of the pollen-extract in patients with non-bacterial prostatitis or prostatodynia since improvement of clinical symptoms and palpation findings occurs concomitantly.

The investigated parameter, evaluated before, during and after treatment with pollen extract, show in the B- and BP-group a reduction of residual urine volumes, elevated peak urine flow rates and voided urine volumes at simultaneously reduced flow times with improvement of both obstructive and irritative symptoms as well as laboratory and palpation findings.

Comparing the course of kinetics between the two hyperplasia-groups B and BP in regard of clinical symptoms, residual urine volume, uroflow and palpation findings it demonstrated even in different before findings a parallel development. This allows the conclusion, that within the BPH frame besides hyperplastic obstruction edematous resp. inflammatory as well as congestive changes in the prostatic tissue reach clinical effectiveness.

These results indicate an applicability of the pollen-extract in patients with BPH (with or without concomitant prostatitis) and suggest in addition therapeutic effects on the so-called non-pathogen post TURP-prostatitis, which is pathohistologically demonstrated in over 50% of patients after prostatectomy (8).

Due to the large number of substances in pollen the identification of (the) active substance(s) of the pollen-extract is difficult and not yet succeeded, but the demonstration of 5 different phytosteroles and of a biological active peptide looks promising as it is known that both peptides and sterols can influence the intracellular metabolism in biological systems (13).

In summary, the results of the multi-center study suggest a rationality for application of the pollen-extract in patients with non-pathogen dependent chronic prostatitis, prostatodynia, prostatic congestion, BPH with and without concomitant prostatitis and TURP-prostatitis.

The positive tolerance of the pollen-extract meets the requirement for a satisfying compliance in chronic and benign prostatic diseases and in thus indicated long-term treatment.

Further investigations with double-blind test design have to establish these encouraging results also to evaluate the degree of spontaneous improvement and placebo-effect.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Phytotherapy in Chronic Prostatitis

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Abstract

Chronic prostatitis is a very common condition that is poorly understood and has a significant impact on quality of life. Given the lack of proven efficacy of conventional therapies, such as antibiotics, it is not surprising that patients have turned with increasing frequency to phytotherapy and other alternative treatments. Although alternative therapies are plentiful, few have been subjected to scientific scrutiny and prospective controlled clinical trials. This review will cover phytotherapies commonly used in prostatitis patients and focus in detail on those with published data. These treatments include zinc, cernilton (flower pollen), quercetin, and saw palmetto. Although many of these therapies appear promising in small preliminary studies, phytotherapy requires the same scientific criteria for validation and acceptance as do conventional medical therapies.

Article Outline

All prostatitis researchers can agree that patient and physician dissatisfaction over the management of this disease is high. It is not surprising, therefore, that patients often seek alternative forms of therapy. Phytotherapy, the use of plant-derived or "herbal" products, is gaining popularity in North America and is already the treatment of choice for many chronic conditions in Europe and Asia. Advantages of phytotherapy include (1) unique mechanisms of action, (2) typically low side-effect profiles, (3) low cost, and (4) a high level of acceptance by patients. A large disadvantage of phytotherapy in the United States is lack of US Food and Drug Administration (FDA) oversight, and indeed, consumer watchdog groups have found that many herbal preparations do not contain what is claimed on the label. Other disadvantages include (1) unknown drug interactions (sometimes leading to catastrophic results[1]), (2) no side-effect data collection, and (3) meaningless labels (to circumvent FDA regulations), such as "supports prostate health" or "promotes normal bladder function."

Alternative herbal-based therapies are prevalent and popular in urologic disease in general and prostatic disorders in particular. Typical herbal therapies recommended for benign prostatic hypertrophy (BPH) with some clinical evidence of efficacy include saw palmetto (*Serenoa repens*), stinging nettle (*Urtica dioica*), and *Pygeum africanum*.[2] Flower pollen extract (Cernilton) has also been used with less evidence of efficacy for BPH. [3] Given the overlap of lower urinary tract symptoms between BPH and chronic prostatitis, these agents, either alone or in combination in "prostatic health" formulations, have also been recommended for men with prostatitis.

In patients with documented recurrent bacterial prostatic infection (category II), prolonged antibiotics remain the mainstay of therapy. Prolonged antibiotic use can alter intestinal flora, and use of probiotics (live beneficial bacteria) may reduce the incidence of gastrointestinal side effects.[4] Many men with category II prostatitis have recurrent urinary tract infections, and there is considerable interest in cranberry juice to treat cystitis in women, although randomized placebo-controlled data are lacking.

[5] Cranberry juice may reduce *Escherichia coli* adherence and biofilm load in uroepithelial cells.[6] There are no published data on the efficacy of cranberry juice in prostatic infections, however, and it is possible that the acidity of the product could actually exacerbate symptoms. Zinc was one of the first factors with an antimicrobial effect to be identified in seminal plasma. [7] The initial discovery that many men with chronic bacterial prostatitis have low levels of zinc in the semen has led to the long-standing recommendation for zinc supplements in men with all forms of prostatitis. Unfortunately, oral intake of zinc does not appear to increase zinc levels in semen. [8] There are no published clinical trials that demonstrate the efficacy of zinc supplements for either treating or preventing prostatitis.

Category III (chronic pelvic pain syndrome [CPPS]) is the most common and enigmatic prostatitis syndrome. In the absence of infection, there is evidence for an inflammatory or autoimmune component to CPPS in some patients. Even in the absence of visible white blood cells, expressed prostatic secretions and semen of men with CPPS have elevated levels of inflammatory cytokines and oxidative stress.[9, 10, 11 and 12] Phytotherapy has been used most commonly in this category of prostatitis, and evidence for efficacy is actually more compelling than for other standard therapies.

Cernilton, an extract of flower pollen, has been used in prostatic conditions for its presumed anti-inflammatory and antiandrogenic effects. In a small open-label study, 13 of 15 patients reported symptomatic improvement.[13] In a larger more recent open-label study, 90 patients received 1 tablet of cernilton N 3 times daily for 6 months. [14] Patients with complicating factors (prostatic calculi, urethral stricture, bladder neck sclerosis) had minimal response, with only 1 of 18 showing improvement. In the "uncomplicated" patients, however, 36% were cured of their symptoms and 42% improved. Symptomatic improvement was typically associated with improved uroflow parameters, reduced inflammation, and a decrease in complement C3/coeruloplasmin in the ejaculate. Side effects in studies of cernilton for BPH and prostatitis have been negligible.

Quercetin is a polyphenolic bioflavonoid commonly found in red wine, green tea, and onions.[15] It has documented antioxidant and anti-inflammatory properties and inhibits inflammatory cytokines implicated in the pathogenesis of CPPS, such as interleukin-8. [16] In a preliminary small open-label study, quercetin at 500 mg 2 times daily gave significant symptomatic improvement to most patients, particularly those with negative expressed prostatic secretions cultures. [17] This was followed by a prospective, double-blind, placebo-controlled trial of quercetin 500 mg 2 times daily for 4 weeks using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) as the primary endpoint. [18] Patients taking placebo had a mean improvement in NIH-CPSI from 20.2 to 18.8, and those taking quercetin had a mean improvement from 21.0 to 13.1 (P = 0.003). In all, 20% of patients taking placebo and 67% of patients taking the bioflavonoid had an improvement in symptoms of ≥25%. A third group of patients received Prosta-Q (Farr Cabs, Santa Monica, CA), a commercial formulation containing quercetin with bromelain and papain, digestive enzymes known to increase the intestinal absorption of quercetin. In this group, 82% had a significant improvement in symptoms.

Saw palmetto is the most commonly used phytochemical for lower urinary tract symptoms and BPH, and indeed, some of the clinical studies with entry criteria based on symptoms likely included patients with CPPS. There have been no published studies of saw palmetto use in CPPS. A poster presented at the 2001 American Urological Association meeting compared therapy with saw palmetto or finasteride in CPPS patients for 1 year.[19] Although there was some improvement seen in the finasteride group, there was no improvement in the saw palmetto group.

Traditional Chinese medicinal therapies typically use acupuncture and herbal preparations. There are some publications with English abstracts that suggest significant improvement with this approach, although it is difficult to interpret formulation composition, entry criteria, and endpoint measures.[20]

In summary, phytotherapy shows much promise for prostatitis patients. In category II, probiotics can reduce the gastrointestinal side

effects of prolonged antibiotic use. In category III, cernilton and quercetin have documented effects in both patient-reported improvement and improvement in biochemical markers of inflammation. Zinc, saw palmetto, and other agents used in BPH, such as stinging nettle and *Pygeum africanum*, do not have evidence for efficacy in CPPS. It is important that these phytotherapeutic approaches, and others, such as traditional Chinese medicine, be evaluated in prospective, randomized placebo-controlled trials with defined entry criteria and validated endpoints.

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Phytotherapy for benign prostatic hyperplasia

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Abstract

Objective

To systematically review the existing evidence regarding the efficacy and safety of phytotherapeutic compounds used to treat men with symptomatic benign prostatic hyperplasia (BPH).

Design

Randomized trials were identified searching MEDLINE (1966±1997), EMBASE Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. The studies were included if men had symptomatic benign prostatic hyperplasia, the intervention was a phytotherapeutic reparational one or combined, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Key data were extracted independently by two investigators.

Results

A total of 44 studies of six phytotherapeutic agents (Serenoa repens, Hypoxis rooperi, Secale cereale, Pygeum africanum, Urtica dioica, Curcubita pepo) met inclusion criteria and were reviewed. Many studies did not report results in a method allowing meta-analysis. Serenoa repens, extracted from the saw palmetto, is the most widely used phytotherapeutic agent for BPH. A total of 18 trials involving 2939 men were reviewed. Compared with men receiving placebo, men taking Serenoa repens reported greater improvement of urinary tract symptoms and flow measures. Serenoa repens decreased nocturia (weighted mean difference .WMD. 20:76 times per evening; 95% CI . 21:22 to 20.32; n . 10 studies) and improved peak urine flow.WMD . 1:93 ml s21; 95% CI . 0:72 to 3.14, n . 8 studies). Men treated with Serenoa repens rated greater improvement of their urinary tract symptoms versus men taking placebo (risk ratio of improvement. 1:72; 95% CI . 1:21 to 2.44, n . 8 studies). Improvement in symptoms of BPH was comparable to men receiving the finasteride. Hypoxis rooperi (n . 4 studies, 519 men) was also demonstrated to be effective in improving symptom scores and flow measures compared with placebo. For the two studies reporting the International Prostate Symptom Score, the WMD was 24.9 IPSS points (95% CI . 26:3 to 23.5, n . 2 studies) and the WMD for peak urine flow was 3.91 ml s21 (95% CI . 0:91 to 6.90, n . 4 studies). Secale cereale (n . 4 studies, 444 men) was found to modestly improve overall urological symptoms. Pygeum africanum (n . 17 studies, 900 men) may be a useful treatment option for BPH. However, review of the literature has found inadequate reporting of outcomes which currently limit the ability to estimate its safety and efficacy. The studies involving Urtica dioica and Curcubita pepo are limited although these agents may be effective combined with other plant extracts such as Serenoa and Pygeum. Adverse events due to phytotherapies were reported to be generally mild and infrequent.

Conclusions

Randomized studies of Serenoa repens, alone or in combination with other plant extracts, have provided the strongest evidence for efficacy and tolerability in treatment of BPH in comparison with other phytotherapies. Serenoa repens appears to be a useful option for improving lower urinary tract symptoms

and flow measures. Hypoxis rooperi and Secale cereal also appear to improve BPH symptoms although the evidence is less strong for these products. Pygeum africanum has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no convincing evidence supporting the use of Urtica dioica or Curcubita pepo alone for treatment of BPH. Overall, phytotherapies are less costly, well tolerated and adverse events are generally mild and infrequent. Future randomized controlled trials using standardized preparations of phytotherapeutic agents with longer study durations are needed to determine their long-term effectiveness in the treatment of BPH.

Keywords: Phytotherapy, Benign prostatic hyperplasia, Randomized controlled trials, Systematic reviews, Meta-analysis, Public health nutrition: 3(4a), 459±472 459

Phytotherapy or the use of plant extracts for treatment of lower urinary tract symptoms (LUTS) consistent with benign prostatic hyperplasia (BPH) was first described in Egypt in the 15th century BC1. Phytotherapy is common in Europe and is increasing in the Western Hemisphere. In 1998, the sale of botanical medications in the United States was $1.5 billion per year and the use of phytotherapeutic compounds increased nearly 70% among US adults 2,3. About 30 phytotherapeutic compounds are used for the treatment of BPH (Table 1). Phytotherapeutic agents represent nearly half the medications dispensed for treatment of BPH in Italy, compared with 5% for alpha-blockers and 5% for 5a-reductase inhibitors 4. In Germany and Austria, phytotherapy is the first-line treatment for mild to moderate lower urinary tract symptoms and represents more than 90% of drugs prescribed for treatment of BPH. In the United States, phytotherapies for BPH are available as nonprescription dietary supplements. Nearly a quarter of men attending a United States urology clinic who had previously treated BPH indicated they had used phytotherapeutic agents for self-treatment of urinary tract symptoms 5.

Phytotherapies are often promoted to ‘maintain a healthy prostate’ and as natural and harmless treatment of BPH symptoms. Despite their popularity with the public there has been reluctance among many practitioners to routinely recommend these products. This is because of uncertainty regarding their efficacy and safety 6,7. Most phytotherapeutic compounds are unlicensed and do not require evidence of efficacy, safety or purity. There have been over 40 published randomized controlled trials evaluating the efficacy of phytotherapy for symptomatic BPH in approximately 5000 men. Many more trials are in progress and should provide needed evidence regarding the role of phytotherapeutic products.

Systematic reviews of the existing literature provide a systematic assembly of the results of primary investigations using strategies that limit bias and random error 8. Systematic reviews efficiently integrate unmanageable amounts of information and provide results that allow for rational decision making. They can establish whether findings are consistent and generalized or whether findings vary by subsets. If clinically and statistically appropriate, a quantitative summary (meta-analysis) can be performed resulting in statistical pooling of results and enhancement of the estimates of therapeutic effects and risk estimates. This is especially helpful when a large number of small trials have been conducted or when results from comparable studies provide differing results. Systematic reviews also identify gaps in existing evidence and make recommendations for future research to close these scientific and clinical gaps. Phytotherapeutic compounds Serenoa repens (saw palmetto) background the most widely used phytotherapeutic agent for BPH is the extract of the dried ripe fruit from the American dwarf palm plant, saw palmetto, Serenoa repens (also known by its botanical name as Sabal serrulata). Serenoa repens has been approved in France and Germany for treatment of BPH. Berries from saw palmetto were first used by the American Indians in the southeast United States in the early 1700s to treat testicular atrophy, erectile dysfunction, and prostate gland swelling or inflammation 1. The medicinal value of Serenoa repens for relief of prostate gland swelling has been reported since the 1800s. The mechanism of action of Serenoa repens has been investigated in several in vitro or indirect in vivo studies and has not been definitively defined. The mechanism may include alteration of cholesterol metabolism, antioestrogenic, anti-androgenic (including 5a-reductase inhibitor activity), anti-inflammatory

effects, and a decrease in available sex hormone binding globulin 9±12.

Results of studies a systematic review and meta-analysis of randomized trials assessed the existing evidence regarding efficacy and safety of Serenoa repens in men with symptomatic BPH 13. Studies were identified through a search of MEDLINE (1966±1997), EMBASE, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. Randomized trials were included if participants had symptomatic BPH, the intervention was a preparation of Serenoa repens alone or in combination with other phytotherapeutic agents, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Two investigators independently extracted key data on design features, subject characteristics, therapy allocation and outcomes of the studies. A total of 18 studies involving almost 3000 men were identified and analysed 14±31 (Tables 2±5). Many studies did not report results in a method that permitted quantitative meta-analysis. Sixteen trials were double blinded, 14 were placebo controlled and four involved Serenoa repens in combination with other phytotherapeutic agents. The average study duration was 9 weeks (range 4±48 weeks) and the average age of enrollees was 65 years.
Baseline characteristics regarding prostate volume, urine flow rates and symptom scale scores were comparable with previous trials evaluating pharmacologic management of BPH. The available data indicate that Serenoa repens (alone or in combination with other phytotherapeutic agents) improves urinary symptoms and flow measures (Figs 1±3). Compared with placebo, saw palmetto improved urinary symptom scores by 28% and nocturia by 25% (the weighted mean difference .WMD.20:76 times per evening; 95% CI . 21:22 to 20.32; n . 10 studies). Peak urine flow was improved by 24% (WMD . 1:93 ml s21; 95% CI . 0:72 to 3.14, n . 8 studies), mean urine flow by 28% (2.22 ml s21; data not shown), and residual urine volume by 43% (222.05 ml; data not shown). Men taking Serenoa repens were more likely to report improvement in urinary symptoms than men taking placebo (73.6% vs. 50.9%; risk ratio . 1:76). Adverse effects were generally mild and comparable with placebo. Compared with finasteride17,30, saw palmetto provided similar responses in urologic symptom scores (0.37 International Prostate Symptom Score (IPSS) points), nocturia (20.20 times per evening) and flow measures. Saw palmetto was associated with a lower rate of erectile dysfunction than finasteride (1.1% vs. 4.9%; P , 0:001) and reduced neither prostate size nor prostate specific antigen (PSA) levels. Critics have stated that comparing saw palmetto with finasteride might be showing equivalency to placebo. However, previous trials and meta-analyses have demonstrated that finasteride provides symptomatic improvement in men with prostate glands .40 g, a size comparable to those enrolled in this study 32,33.

The treatment effect sizes noted with saw palmetto were comparable to effects reported with other pharmacologic agents, such as finasteride. However, the results should be viewed cautiously. Studies utilized different doses and preparations of Serenoa repens (including combination preparations). The most extensively investigated preparation of Serenoa repens is manufactured in France and sold as Permixon. The most commonly reported dosage was 160 mg twice per day. Many studies did not report outcome data in a consistent fashion. Only three studies reported validated urologic symptom scales. Trials were of short duration with only two studies having follow-up of at least phytotherapy for benign prostatic hyperplasia 463 6 months' duration. Therefore, it is not known whether Serenoa repens prevents long-term complications of BPH such as acute urinary retention or the need for surgical intervention. The only trial comparing Serenoa repens with alpha-blockers lasted less than 3 weeks, making a comparison impossible. Finally, it is possible that study results were not reported if there were no improvements in symptoms or flow measures (publication bias). There are two placebo-controlled studies involving 298 men that were scheduled for completion in 1998. However, their results have not yet been reported. Summary Extracts from the saw palmetto plant, Serenoa repens, provide modest improvement in urinary symptoms and flow measures. Compared with finasteride Serenoa repens produces similar improvements in symptoms and flow measures, has fewer adverse treatment effects and costs less. The long-term safety and efficacy of Serenoa repens and its ability to prevent complications from BPH are not known. Standardized preparations are often not available. Publication of ongoing trials is

encouraged and initiation of long term studies compared with alpha-blockers would be useful. Hypoxis rooperi (South African star grass, bsitosterol) Background Phytosterol extracts derived from the South African star grass, Hypoxis rooperi, are popular. The resumed active constituent is b-sitosterol. Beta-sitosterol contains a mixture of phytosterols, with smaller amounts of other sterols, bonded with glucosides 1. Additionally, the quantity of bsitosterol- bD-glucoside is often reported. The product is sold under the trade names Harzol or Azuprostat. Although the mechanism of action of b-sitosterols is not known it may be related to cholesterol metabolism or anti-inflammatory effects (via interference with prostaglandin metabolism) 1.

Results of studies for randomized controlled trials evaluated b-sitosterol in 519 men with symptomatic BPH34±37 (Table 3). All were 464 TJ Wilt et al. double-blinded and lasted between 4 and 26 weeks. Three trials used non-glucosidic b-sitosterols in doses ranging from 30 mg to greater than 120 mg per day 34,35,37. The other trial utilized a preparation that contained 100% bsitosteryl- b-D-glucoside (0.15 mg twice a day) 36. The average age of participants was 65 years. Men had moderately severe BPH (mean baseline IPSS score . 15:2; peak urine flow . 10:2ml s21; prostate size . 49 cc.: Beta-sitosterol provided statistically significant improvements in urinary symptom scores and flow measures (Figs 4 and 5). In the two studies reporting the IPSS score, the WMD compared with placebo was 24.9 points (95% CI . 26:3 to 23.5, n . 2 studies) (35% improvement). The WMD for peak urine flow was 3.91 ml s21 (45% improvement) and for residual volume the WMD . 228:62 ml (95% CI . 0:91±6:90; n . 4 studies) (29% improvement). Betasitosterol did not reduce prostate size and the trial using 100% b-sitosteryl- b-D-glucoside (WA184) did not show improvement in urinary flow rates. Adverse events were infrequent and mild. Withdrawal rates were less than 10% and did not differ from placebo.

An extract from South African star grass, b-sitosterol, improved urologic symptoms and flow measures. However, the existing evidence is limited to trials of short duration, relatively few patients studied and lack of standardized b-sitosterol preparations. Their long term effectiveness, safety and ability to prevent BPH complications are not known. Secale cereale (rye-grass pollen) Background Rye pollen extract is prepared from the rye-grass, Secale cereale. It is used by millions of men worldwide and is a registered pharmaceutical throughout Western Europe, Japan, Korea and Argentina 38. In the United States, Cernilton is used as a nutritional supplement by approximately 5000 men 39. One dose contains 60 mg of Cernitin T60, a water-soluble pollen extract fraction, and 3 mg of Cernitin GBX, an acetone soluble pollen extract fraction 38. The acetone-soluble fraction was found to contain b-sterols 40. In vitro studies suggest that Cernilton may have anti-androgenic effects, relax urethral smooth muscle tone and increase bladder muscle contraction, or may act on the alpha-adrenergic receptors and relax the internal and external sphincter muscles 41±43.

Phytotherapy for benign prostatic hyperplasia 467 Results of studies A total of 444 men have been enrolled in two placebo-controlled .n . 163. and two comparative trials lasting from 12 to 24 weeks 44±47 (Table 4). Three studies were double-blinded 44,45,47. The mean age of participants was 69 years. Differences in the control agents and methods of reporting results did not permit all studies to be combined in a meta-analysis. However, three studies reported symptom scores or measured symptom Improvement 45±47. Nocturia was reported in three studies 44,45,47 and all studies reported peak urine flow and residual urine volume. Data from all studies were consistent with improvement in symptoms and urinary flow. Cernilton improved ‘self-rated urinary symptoms’ versus placebo and Tadenan, an extract from Pygeum africanum 46. Almost 70% men taking Cernilton reported symptom improvement compared with 29% taking placebo. Obstructive and irritative symptom scores improved from baseline by 60% in men taking Cernilton compared with 40% with Tadenan. Cernilton reduced nocturia compared with placebo and Paraprost, a pharmacologic treatment used primarily in Japan containing 265 mg of L-glutamic acid, 100 mg of Lalanine and 45 mg of aminoacetic acid 47. Versus placebo, there was a two-fold improvement in the percentage of men reporting improvement in nocturia (63% vs. 31%) 44,45.

Compared with Paraprost, Cernilton reduced nocturia by 0.40 times per evening. The only adverse event reported was mild nausea. Although the results suggest that Cernilton

provided modest benefit there are limitations to the evidence. The longest treatment duration was 24 weeks. Only one study reported results from a standardized and validated urologic symptom scale. While the manufacturer suggests two to four tablets or capsules daily, the dosages and standardization of preparation were not usually reported. The most frequently reported amount was two Cernilton capsules three times per day.

Summary

The evidence suggests that an extract from rye-grass pollen, Cernilton, is well tolerated and modestly improves urologic symptoms. However, trials were of short duration, enrolled relatively few patients, and lacked standard product preparation. Additionally, there was infrequent use of validated symptom scale scores. It does not improve urinary flow measures and the long-term safety and effectiveness is not known.

Pygeum africanum (African plum)

Background

Traditionally, the bark of the African plum tree (Pygeum africanum) was collected and powdered, then drunk as a tea to improve genito-urinary symptoms. Purified bark extracts have been used throughout Europe for the past 30 years. The postulated active components include phytosterols, especially b-sitosterols, pentacyclic triterpenoids and esters of long-chain fatty alcohols. Pygeum africanum extract may suppress LUTS by reducing bladder hyperreactivity, decreasing inflammation, and protecting against abnormal prostate growth 48. A 1995 review identified 12 double-blind, placebo controlled studies involving 717 men with BPH 46, 49±63 (Table 5). Most studies used a Pygeum extract under the trade name Tadenan with doses ranging from 75 to 200 mg day 21. All studies were at least 16 weeks in duration. More than half the studies measured peak urinary flow and all but one measured urinary frequency. Standardized and validated symptom scores were not utilized and there was no pooled estimate of treatment effect size or adverse events. The majority of studies noted an improvement in nocturia compared with placebo.

An ongoing double-blind placebo-controlled study is evaluating Tadenan (100 mg and 400 mg) in 750 men with symptomatic BPH. The primary endpoint is a mean reduction in the IPSS score between baseline and 6 months. However, the results have not been reported. In five small-scale studies involving 183 men, P. africanum was compared with active drug or therapy 50,57,63. Two studies involved plant extracts (sitosterin and extract of Radix urticae urtae) 50. The results Fig. 5 Effect of b-sitosterol on peak urine flow vs. placebo 468 TJ Wilt et al. indicate that Pygeum reduced nocturia more than comparators in the 3 studies reporting this endpoint. However, in two of these studies there were no statistical comparisons. Since the publication of this review there have been two additional trials utilizing Pygeum. One was a study utilizing a combination of Pygeum with Urtica and is discussed in the section on Urtica 59. The other trial demonstrated that Pygeum was less effective than Cernilton in improving 'self-rated urinary symptoms' 46. Obstructive and irritative symptom scores improved from baseline by 60% in men taking Cernilton compared with 40% in men taking Tadenan.

Summary

Extracts from the African plum tree, Pygeum africanum may be a useful treatment option for BPH. However, inadequacies in the reporting of outcomes limit the ability to estimate its safety and efficacy. An ongoing trial should provide much needed information on the short-term effectiveness and tolerability of Pygeum africanum.

Urtica dioica (stinging nettle)

Background

Extracts from roots of the stinging nettle are often used in Germany for the treatment of BPH. The extracts contain a mixture of water- and alcohol-soluble compounds with extraction procedures varying from company to company. Proposed mechanisms of action include inhibition of prostatic growth factor including blocking the conversion of testosterone to dihydrostersterone 1. Results of studies There have been five randomized trials evaluating stinging nettle. Three of these involved combinations with other phytotherapeutic agents (Pygeum and Sabal), making it difficult to evaluate the efficacy of stinging nettle alone 26,30,59. Furthermore, one of these studies merely compared two different doses of a

combined extract of Urtica and Pygeum59. The report by Sokeland compared a combination of Sabal and Urtica (PRO 160/120) extract with finasteride and placebo30. This trial lasted 12 weeks and evaluated 543 men. Compared with finasteride there were no differences in IPSS scores (24.8 vs. 25.8 IPSS points), peak urine flow or residual urine volume. More adverse events were associated with finasteride, including more cases of erectile dysfunction, diminished ejaculation volume, and headaches. Compared with placebo, the combination of Sabal±Urtica (Prostagutt) improved IPSS scores by 17% (23.5 IPSS points) 26. One placebo-controlled study lasting 3 months compared a liquid preparation of stinging nettle with placebo in 41 men with BPH64. An improvement in IPSS scores was noted in men taking stinging nettle. However, because of unacceptable taste this preparation has been removed from the market. Another placebo-controlled trial examined the effectiveness of Urticae extract capsules65. Although improvements in peak urine flow and total voided volume were reported, there was no difference in urologic symptoms. Additionally, 24% of men (6/25) taking Urticae withdrew from the study; half of them due to unspecified side effects.

Summary

Evidence from randomized trials suggests combination preparations of Urticae appear to provide some benefit for treatment of lower urinary tract symptoms, although stinging nettle extracts alone do not appear to be beneficial. Additional randomized controlled trials need to be conducted before Urticae can be recommended as an effective option for the treatment of LUTS.

Curcubita pepo (pumpkin seed)

Results of studies

There has been only one small-scale randomized trial of short duration that has evaluated the efficacy of pumpkin seed extracts16. This study evaluated 55 men, lasted for 12 weeks and utilized a preparation that included pumpkin seed, Curcubita pepo, and Sabal serrulata (Curbicin 160 mg three times a day). Compared with placebo, Curbicin improved self-rating of urinary symptoms (85% noted improvement vs. 11% taking placebo) and nocturia. Residual urine volume was reduced by 31% (42.5 cc) compared with only 6.5% (7.6 cc) with placebo. Because the study utilized a combination preparation the reported improvement in urologic symptoms and flow measures cannot be clearly attributed to pumpkin seeds.

Summary

There is no convincing evidence that extracts of pumpkin seed alone improve urologic symptoms or flow measures. They may provide improvement in urinary symptoms and flow measures when used in combination with Sabal serrulata. Randomized controlled trials need to be conducted. Recommendations and conclusions Should physicians recommend plant extracts for treatment of BPH? Despite their popularity and the existence of over 40 randomized controlled trials involving nearly 5000 men, the available data do not yet provide clear evidence of efficacy for most phytotherapeutic products. Extracts of saw palmetto (Serenoa repens) (alone or in combination with other phytotherapeutic products) have the strongest evidence for efficacy and tolerability. They appear to be a useful option for improving lower urinary tract symptoms and flow measures. Rye-grass pollen (Secale cereale) and South African star grass (Hypoxis rooperi, b-sitosterol) also appear to improve symptoms and are well tolerated. However, the evidence is Phytotherapy for benign prostatic hyperplasia 469 less strong for these products. African plum tree bark (Pygeum africanum) has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no convincing evidence supporting the use of pumpkin seed (Curcubita pepo) or stinging nettle (Urtica dioica) extracts alone for treatment of BPH. They may be effective in combination with other phytotherapeutic products. The widespread use of phytotherapy attests to the popularity of plant extracts for treatment of BPH symptoms. They cost less and are better tolerated, at least in the shortterm, than either alpha-blockers or finasteride. However, if the primary goal is to reduce symptoms, alpha-blockers such as doxazosin, tamsulosin, alfuzosin or terazosin seem to be a better choice than finasteride and probably phytotherapy. Additionally, plant extracts have not yet been demonstrated to reduce complications from BPH or the need for surgical intervention in comparison with interventions such as

finasteride33. The Committee on Other Medical Therapies of the Fourth International Consultation on BPH concluded that: most plant extract preparations have different components; it is not known what mechanisms of action demonstrated in vitro might be responsible for clinical effects; short-term randomized studies suggest clinical efficacy for some preparations; and studies were usually inadequate due to the methodology utilized, small numbers and short duration of study. Of greatest importance is the completion of additional high quality studies of long duration to fully evaluate the efficacy and safety of phytotherapeutic products for treatment of BPH6. Until completion of these studies and/or regulation of these products the lack of universal definitions, practices, and standards within the supplement industry place the onus on the physician to judge product quality and efficacy. Manufacturers/companies of plant extracts often use different extraction processes. There is no evidence that the extract from one manufacturer is equivalent to that of another.

Additionally, since the active ingredient(s) are not known, it is possible that one product might have clinical efficacy while another does not. Each company's product must be tested to evaluate clinical efficacy and bioactivity. The following recommendations have been made for assessing quality measures (these do not directly address clinical efficacy or safety) in selecting high-quality and reliable preparations of phytotherapeutic products manufactured in the United States66. 1. The manufacturer tests raw ingredients for purity and potency prior to inclusion in a product. 2. The product is manufactured in a pharmaceutically licensed facility registered with the Food and Drug Administration. 3. The product's ingredients meet the applicable United States Pharmacopoeia (USP) standards. 4. All finished products are analyzed for purity and potency following production by an independent laboratory using established methods to ensure that the product meets label claims and is of good quality. In some cases, this information can be found on product labeling. All reputable manufacturers will keep certificates of laboratory results for each finished batch of product on file. These should be available to physicians and pharmacists on request.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Phytotherapeutic Agents in the Treatment of Benign Prostatic Hyperplasia

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Curr Urol Rep. 2000 Aug;1(2):103-9.

The rationale and efficacy of phytotherapeutic agents in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) are continuously debated. While plant extracts are prescribed and reimbursable treatment options in Europe, they are officially classified merely as dietary supplements in the United States. The most commonly used preparations originate from the species Serenoa repens, Pygeum africanum, hypoxis rooperi, pinus, picea, urtica dioica, and secale cereale (rye pollen). Combination extracts derived from two or more plants are also used. Various components have been suggested to be active, and different mechanisms of action are being supposed. Open trials and some short-term randomized studies, suggesting safety and efficacy have been reported. However, if stringent criteria of evidence-based medicine are applied, the data are inconclusive. Therefore, the 4th International Consultation on BPH and the recent German guidelines have not (yet) recommended phytotherapy for the management of symptomatic BPH.

Publication Types:
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• Review, Tutorial
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A long-term therapeutic experience with Cernilton in Chronic Prostatitis

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Thirty-two patients with chronic prostatitis were given 6 tablets of Cernilton daily for 12.6 weeks on the average. Improvement of subjective symptoms and objective findings was noted in 74.2% and 65.6% of the cases, respectively. The effective rate was 75.0%. No subjective symptoms or abnormal changes in laboratory data were observed in any case after Cernilton medication.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Usefulness of Cernilton in the treatment of benign prostatic hyperplasia

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A total of 89 patients with benign prostatic hyperplasia (BPH) were treated pharmacologically for 4 months: 51 received Cernilton and 38 Tadenan (controls). Significant subjective improvement was found in 78% of the patients in the Cernilton group compared to only 55% of the Tadenan treated patients. The obstructive and irritative symptoms responded best to the therapy. In the Cernilton-treated patients a significant improvement in the uroflow rate, decrease in residual urine and in prostate volume were found. This study shows that Cernilton is an effective therapy for patients with BPH.

Benign prostatic hyperplasia (BPH) is a major problem for the patient, the urologist, and health care systems. Pharmacologic treatment may be indicated for patients with moderate BPH-related symptoms. Although plant extracts may not effectively alter the natural history of clinical BPH, their use is favored in patients with mild symptoms in a number of countries. Plant extracts are inexpensive and have virtually no side effects [4, 6].

Among plant extracts Cernilton, the Graminaceae flower pollen extract, is an interesting product. Results of clinical studies with Cernilton demonstrate a marked reduction in residual urine, prostate volume, and substantial improvement in urinary flow rate in patients with BPH [2]. Enlargement and congestion of the prostatic gland are the principal factors responsible for the obstructive symptoms in BPH. The anticogestive effect of Cernilton leads to a marked reduction in prostate volume [10]. The anticongestive action of Cernilton is based on the inhibition of prostaglandin and leukotriene biosynthesis. The activities of both the 5-lypoxygenase and cyclo-oxygenase enzymes are substantially reduced and the arachidonic cascade is interrupted. The inhibition of the arachidonic acid cascade by Cernilton prevents intraprostatic tissue oedema and fibrosis and leads to a significant reduction in clinical symptoms [2, 9].

The aim of the study was to assess the effectiveness of Cernilton therapy of BPH.

Patients and methods

Studied were 89 patients with clinical stage I and II BPH, aged 50-68 years. For the first two weeks Cernilton was administered in doses of two tablets three times daily, followed by one tablet three times a day for up to a total of 4 months of treatment. The remaining 38 patients were given Tadenan, 2 tablets twice daily (control group). Subjective assessment was made by using our own symptom score system [4] and objective evaluation by physical examination, uroflowmetry and ultrasound examination of residual urine and prostate size. Additionally, biochemical blood and urine tests, including urine culture, were performed in all patients prior to and after therapy.

Qualified were patients with short history, i.e. with symptoms of no longer than a few weeks duration. No patient had complete urine retention. The results of blood tests did not differ significantly from the normal laboratory reference values. All urine cultures proved sterile but in 12 patients leukocyturia was found adequate antimicrobial therapy was instituted (Tarivid 2 tablets twice daily). The tests were done also after completion of the treatment and no significantly abnormal results were observed.

Results

The following tables show objective and subjective parameters measured before (I) and after (II) Cernilton (C) and Tadenan (T) therapy of BPH patients; peak flow rate (ml/s) – table 1; residual urine volume (ml) –

Table 2; prostate volume (cm3) – Table 3; obstructive symptom score – Table 4; irritative symptom score – table 5

The therapeutic response was positive in 40 (78%) and 21 (55%) patients in Cernilton and Tadenan groups, respectively. Both drugs were well tolerated and no adverse reactions were seen.

Table 1
Peak flow rate (ml/s) in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	12.49 13.54	15.6 15.9	8.0 8.5	3.0 3.2	- -	- -
II C (51) T (38)	15.51 15.18	19.0 17.2	11.2 9.0	4.3 4.5	+3.20 +1.67	19.5 10.8

Table 2
Residual volume (ml) in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	77 61	112 101	56 31	15.7 14.1	- -	- -
II C (51) T (38)	45 50	63 70	0 20	21.0 15.8	-32 -11	47.8 21.6

Table 3
Prostate volume (cm3) in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	53.83 51.12	61.2 59.1	41.0 39.0	6.6 5.9	- -	- -
II C (51) T (38)	48.58 50.67	58.0 59.0	32.0 39.0	4.4 5.8	-9.6 -0.9	5.15 0.45

Table 4
Obstructive symptom score in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	5.1 4.8	9 8	2 1	2.1 1.9	- -	- -
II C (51) T (38)	1.9 2.6	4 8	0 0	1.2 1.8	- -	62.75 45.80

Table 5
Irritative symptom score in BPH patients before (I) and after (II) therapy with Cernilton (C) and Tadenan (T)

Drug (# of patients)	Mean	Max	Min	SD	Mean Change	% improvement
I C (51) T (38)	3.8 3.5	7 8	1 0	1.9 2.0	- -	- -
II C (51) T (38)	1.2 2.1	6 8	0 0	2.1 2.8	- -	68.4 40.0

Discussion

BPH is a universal concomitant of male ageing but its epidemiology and natural history are incompletely understood [1]. The natural history of BPH can be divided into two phase when the patients develop symptomatic dysuria. Although macroscopic enlargement of the prostatic is necessary for the development of clinical BPH, it is not sufficient by itself for the progression to infract, tensile strength of the glandular capsule [7]. The clinical manifestations of BPH are often attributed to infravesical obstruction. Therefore, pharmacologic outlet resulting from the prostate enlargement and eliminate instable bladder [4, 8].

Medical treatment of BPH is presently dominated by a-adrenoceptor blockers but plant extracts are used extensively in a number of countries. Treatment with other drugs has also proven to be effective symptomatically, notably with finasteride (5a-reductase inhibitor). Some plant extracts are claimed to exert a-adrenergic blocking or 5-a-reductase inhibiting effects. A few controlled studies have shown that some of the preparations provide both subjective and objective improvement [6].

In BPH patients the decongestive effect of Cernilton leads to a lasting improvement of voiding difficulties. The residual urine volume decreases significantly.

In comparison to Pygeum africanum extract (brand name Tadenan), for 20 years in wide use in stage I BPH patients, Cernilton proved much more effective. Objective evaluation of maximal urethral flow, residual volume and prostate size gave almost twice better results with Cernilton. Similarly, the obstructive symptom score improved by 62.75% with Cernilton and by 45.8% with Tadenan, and the irritative symptom score by 68.4% and 40%, respectively.

Positive therapeutic responses totaled 78% and 55% with Cernilton and Tadenan, respectively. Although Tadenan is also characterized by decongestive activity, it decreases bladder instability, increases detrusor elasticity and probably inhibits fibroblast proliferation, and alleviated voiding problems in over 2000 cases [5]. In our study the benefit of Cernilton therapy proved to be far greater than that of Tadenan. During the 4 months of treatment none of the drugs produced side effects in the BPH patients; both Cernilton and Tadenan were well tolerated.

Conclusions

1. Cernilton markedly reduces residual urine and prostate volume in BPH patients. It also significantly improves the voiding difficulties.
2. In the therapy of BPH Cernilton proved to be effective, well tolerated and safe.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Use of Cernilton in Patients with Prostatic Hypertrophy

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Introduction

Today the only radical therapy for prostatic hypertrophy is prostatectomy or transurethral prostatectomy. Prostatic hypertrophy is a kind of geriatric disease in urology whose incidence in Japan is now increased as high as that in European countries. Frequently, this disease involves such aged patients as are not indicated for surgical manipulation in general surgery. Under this situation, conservative therapy would be considered as treatment of choice if it can indeed effect curing or improvement of the disease. Thus, various drugs, chiefly female hormones, have been developed and placed for clinical evaluation in recent years.

The present report concerns the authors' recent experience with CERNILTON, a pollen product, whose samples were supplied by Tobishi Pharmaceutical Co., Ltd. Results are reported below.

Composition of CERNILTON

CERNILTON, when initially introduced in 1952, was used as a prophylactic agent against infections chiefly in convalescent patients having undergone treatment of infectious diseases or surgical operations, and it was by Ask-Upmark later in 1960 that the effectiveness in prostatitis was reported.

According to the literature, it contains in one tablet:

- Cernitin GBX – 3 mg
- Cernitin T60 – 60 mg
- Calcium glyconicum – 70 mg
- Saccharum lactis – 70 mg
- Calcium phosphoricum dibasicum – 140 mg
- Acidum alginicum – 10 mg
- Potato starch – 20 mg
- Pigment – 3 mg
- Magnesium stearate – 4 mg
- Talcum – 20 mg

Of these components, Cernitin GBX and Cernitin T60 are extracts of a mixture of 8 different pollen strains, namely, timothy, maize, rye, hazel, sallow, aspen, oxeye daisy and pine, and their chemical structure, molecular formula and molecular weight are unknown. The drug is also reported to have bacteriostatic, tonic and desensitizing actions.

Materials and Methods

The subjects were 24 patients with prostatic hypertrophy seen at our Outpatient Clinic. The

drug was given in doses of 4 tablets once daily in the morning over periods ranging from 25 to 150 days. In general, other drugs were not employed. Of the 24 cases, complete follow-up study was made in 12 cases as to subjective symptoms and urinary retention before, during and after administration. The present report deals with these 12 cases.

Results

The results of the 12 cases where follow-up study was made are given in Table 1.

- Evaluation of effects was made on the basis of the follow criteria:
- Effective.. Subsidence of symptoms with marked improvement in urinary retention.
- Slightly Effective.. Slight subsidence of symptoms with little or slight improvement in urinary retention.
- Ineffective.. Symptoms and urinary retention unchanged or exacerbated.

Results according to these criteria were: “effective” 5 cases (41.7%), “slightly effective” 5 cases (41.7%), and “ineffective” 2 cases (16.7%). Two of the 5 “effective” cases underwent prostatectomy subsequently because of symptoms relapsed after withdrawal of the drug. It is to be noted that one case was already on the way toward spontaneous healing at the time of administration. One of the “slightly effective” cases also underwent prostatectomy markedly extended.

Clinical course: Urinary retention disappeared and relatively smooth urination was possible in one month. Anuresis, however, developed again one month after withdrawal of the drug and patient was thus readmitted for prostatectomy.

Case 5. H. Y. Age 83. No Occupation.

- First examination: April 18, 1966
- Chief Complaints: Anuresis, dysuria
- Past History: Nothing of note.
- Present Illness: Anuresis developed suddenly in May 1959. Diagnosed as having prostatic hypertrophy, patient was admitted in June and underwent transurethral prostatectomy. Subjective symptoms subsided and a favorable clinical course ensued. Dysuria developed again in September 1964. The symptom gradually progressed reaching a state of anuresis in April 1966, when he visited our Outpatient subsequently.

Side effects due to the medication were observed in none of the cases. Five representative cases will be discussed in detail below.

Case 1. T. Y. Age 69. No Occupation.

- First Examination: September 2, 1966
- Chief Complaints: Dysuria, anuresis
- Past History: No history of venereal diseases, tuberculosis or trauma.
- Present Illness: Dysuria developed 3-4 years ago and catheterization was performed each time. The present episode was anuresis which developed after drinking of alcoholic drinks.
- Palpation of Prostate: Third degree hypertrophy, smooth surface, elastic hardness, symmetry, regular margin.
- Laboratory Findings: Residual urine 420 cc. Micropyuria present. Urethrocystography revealed the prostate protruding greatly into the bladder and the posterior urethra Clinic again. Thereafter, a balloon catheter was retained in the bladder for urination. The catheter was removed on July 27 and administration of CERNILTON instituted.
- Palpation of Prostate: First degree hypertrophy, smooth surface, elastic hardness, symmetry, regular margin.
- Laboratory Findings: Residual urine 350 cc. Micropyuria present.
- Clinical Course: Relatively smooth urination was possible one month after administration of CERNILTON, though voiding force was still somewhat weak.

After 2 months, urination was almost normalized, but urinary retention was still noted. In 3 months dysuria disappeared totally with residual urine decreased to about 10 cc.

Case 7. K. S. Age 72. No Occupation.

- First examination: June 27, 1966
- Chief Complaints: Dysuria, pollakisuria.
- Past History: Nothing of note.
- Present Illness: Pollakisuria, retardation and protraction of urination, and sense of retention appeared about one year ago, associated with dull pain in the lower abdomen but not with such bladder symptoms as voiding pain and cloudiness of urine. Dysuria was particularly exacerbated lately.
- Palpation of Prostate: First degree hypertrophy, smooth surface, elastic hardness, symmetry regular margin.
- Laboratory Findings: Residual urine 20 cc. Urinary findings nearly normal. Urethrocystography revealed the posterior urethra slightly extended.
- Clinical Course: Subjectively, dysuria disappeared completely in one month. Pollakisuria, too, disappeared and frequency of urination became normal. Residual urine was decreased to about 10 cc.

Case 8. T.K. Age 68. Company Employee.

- First examination: April 25, 1966.
- Chief complaints: Dysuria, anuresis
- Past History: nothing of note
- Present Illness: patient was seen at this clinic in November 1963 with complaints of dysuria and pollakisuria. Operation was recommended under a diagnosis of prostatic hypertrophy but was ignored. Then, anuresis occurred in early April 1966 and catheterization was performed by some doctor. Anuresis developed further, eventually to a state where urination occurred only in drops.
- Palpation of Prostate: Second degree hypertrophy, smooth surface, elastic hardness, symmetry.
- Laboratory Findings: Residual urine 600 cc. Urinary findings nearly normal. Urethrocystrography revealed the prostate slightly protruding into the bladder and the posterior urethra slightly extended.
- Clinical Course: Dysuria was improved considerably after one month, together with pollakisuria. On palpation hypertrophy was somewhat improved. Two months later, dysuria disappeared subjectively and residual urine was decreased to about 20 cc.

Case 9. T.S. Age 63. No Occupation.

- First Examination: May 23, 1966.
- Chief Complaints: Dysuria, anuresis.
- Past History: Nothing of note.
- Present Illness: Dysuria developed in October 1964 and catheterization was performed. A diagnosis of prostatic hypertrophy was made and admission was recommended, but as the symptom somewhat subsided the recommendation was ignored. In early May 1966, anuresis occurred after drinking of alcoholic drinks and catheterization was again performed. Retardation and protraction of urination had since been exacerbated and sense of retention come to be associated.
- Palpation of Prostate: Third degree hypertrophy, smooth surface, elastic hardness, symmetry.
- Laboratory Findings: Residual urine 30 cc. Urinary findings normal. Urethrocystography revealed marked extension of the posterior urethra.
- Clinical Course: One month later, the urine stream became somewhat larger, sense of retention slightly decreased to 5 cc. Two months later, the urine stream became even larger and the retarded urination disappeared. Urethrocystrography revealed no

significant changes. Three months later, the urine stream remained almost unchanged from one month before. Anuresis occurred once during this period but favorable urination ensued with residual urine of about 10 cc. No changes were noted in the prostate on palpation. The patient, however, developed anuresis one month after withdrawal of the drug and eventually underwent prostatectomy two months later.

Discussion

From an absolute pathological point of view, formation of nodules in the urethral area of the prostate is an aging process seen in all males over the age of 70, and it is only part of them that actually develop clinical symptoms such as pollakisuria, dysuria and anuresis and receive treatment for prostatic hypertrophy. On the other hand, as urologists would often experience, these symptoms sometimes disappear or subside without any specific treatment, and there are even cases where patients with sudden development of anuresis are improved to their premorbid state by mere catheterization or chemotherapy. Experience shows, moreover, that clinical symptoms are not always correlated to prostatic adenoma.

Under the circumstances, it is extremely difficult to decide what criteria to be used for evaluation of effects. Review of clinical reports on other similar drugs shows that more or less the same problem is encountered by other authors. Their conclusions are essentially the same, i.e., drugs are usable for treatment of prostatic hypertrophy if they can improve subjective symptoms without side-effects and can be employed for long-term administration.

In the present study, too, we have been unable to set up definite criteria and thus based our evaluation on the changes of subjective symptoms and residual urine and the findings of the prostate on palpation. Results were, as already seen, “effective” 5 cases, “slightly effective” 5 cases, and “ineffective” 2 cases. While 10 out of 12 cases showed improvement in subjective symptoms, the objective improvement in residual urine was obtained in only 6 cases and there was no case which showed a marked diminution in the size of the prostate on palpation. Of the 10 cases which showed improvement in subjective symptoms, 3 cases were in the first degree of hypertrophy, 4 cases in the second degree, and 3 cases in the third degree, when judged by the findings of the prostate on palpation. All the patients in the third degree of hypertrophy subsequently underwent prostatectomy. From this point of view, it may be said that the drug improves only dysuria due to so-called “variable elements” such as hyperemia and congestion around the neck of the bladder and the posterior urethra and does not reduce the size of the prostatic adenoma itself. This means the drug is still far from being able to substitute for radical therapy. In other words, it is to be used only in cases where surgical management is contradicted or to improve clinical symptoms when the disease is still in its early phase. It should not be employed indiscriminately for long-term administration, for it may aggravate the renal function and thus increase the rink in surgical operations.

Conclusions

A. A pollen product, CERNILTON, was used in 12 cases of prostatic hypertrophy. Results were “effective” 5 cases, “slightly effective” 5 cases, and “ineffective” 2 cases. In the 2 of 5 “effective” cases the symptoms relapsed within one month after withdrawal of the drug and the patients eventually underwent prostatectomy. Both had the third degree of hypertrophy. Prostatectomy was also subsequently performed in one “slightly effective” case which also had the third degree of hypertrophy.
B. Side-effects were observed in none of the cases treated.

Table 1. Results of Treatment

Case	Age	Before Administration			Dosage Cernilt	After Administration					Remarks
		Symptoms	Findings of Prostate on Palpation	Residual urine		Symptoms	Findings of prostate on Palpation	Residual urine	Side-effect	Effect	
1	69	Dysuria, Anuresis	Third degree hypertrophy	cc 420	T. Day 4×25	Improved	Third degree hypertrophy	cc 0	—	Effective	Anuresis appeared one month after cessation of therapy and prostatectomy was carried out.
2	74	Dysuria	Second degree hypertrophy	45	4×25	Slightly improved	Second degree hypertrophy	25	—	Slightly effective	
3	67	Dysuria, Pollakisuria	First degree hypertrophy	130	4×25	Unchanged	First degree hypertrophy	40	—	Ineffective	
4	60	Dysuria, Sense of retention	First degree hypertrophy	100	4×150	Slightly improved	First degree hypertrophy	20	—	Slightly effective	
5	83	Anuresis, Dysuria	First degree hypertrophy	350	4×75	Improved	First degree hypertrophy	10	—	Effective	
6	79	Dysuria,	First degree hypertrophy	600	4×25	Unchanged	First degree hypertrophy	500	—	Ineffective	
7	72	Dysuria, Pollakisuria	First degree hypertrophy	20	4×25	Improved	First degree hypertrophy	10	—	Effective	
8	68	Dysuria, Anuresis	Second degree hypertrophy	600	4×50	Improved	First to second degree hypertrophy	20	—	Effective	
9	63	Dysuria, Anuresis	Third degree hypertrophy	30	4×75	Improved	Third degree hypertrophy	10	—	Effective	Anuresis appeared one month after cessation of therapy and prostatectomy was carried out two months later.
10	67	Dysuria, Pollakisuria, Sense of retention	Second degree hypertrophy	80	4×25	Slightly improved	Second degree hypertrophy	20	—	Slightly effective	
11	78	Dysuria Sense of retention	Second degree hypertrophy	400	4×100	Slightly improved	Second degree hypertrophy	200	—	Slightly effective	
12	78	Dysuria, Pollakisuria	Third degree hypertrophy	200	4×25	Slightly improved	Third degree hypertrophy	150	—	Slightly effective	Prostatectomy subsequently performed.

Table 2. Therapeutic effect and degree of hypertrophy on palpation

**N.B.: Indicates a case in which prostatectomy was performed later.*

Effect / Degree of hypertrophy	Good	Fair	None
First degree	2	1	2
Second degree	1	3	0
Third degree	2*	1*	0
Total	5	5	2

Treatment of Outflow Tract Obstruction due To Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton ® *

A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Summary-Whilst prostatectomy remains the "gold standard" for the treatment of outflow tract obstruction due to benign prostatic hyperplasia, medical treatment-if only for symptomatic relief-appears to be an attractive alternative. Most of the pharmacological agents in use block the hormonal or sympathetic neurological pathways that influence prostate growth and function. All of these drugs are known to have side effects.

Sixty patients with outflow obstruction due to benign prostatic hyperplasia (BPH) were entered into a double-blind, placebo-controlled study to evaluate the effect of a 6-month course of the pollen extract, Cernilton. There was a statistically significant subjective improvement with Cernilton (69% of the patients) compared with placebo (30%). There was a significant decrease in residual urine in the patients treated with Cernilton and in the antero-posterior (A-P) diameter of the prostate on ultrasound. However, differences in respect to flow rate and voided volume were not statistically significant. It is concluded that Cernilton has a beneficial effect on BPH and may have a place in treatment of patients with mild or moderate symptoms of outflow obstruction.

From numerous experimental studies in animals and clinical studies in man there is unequivocal evidence for the role of androgens in the development of benign prostatic hyperplasia, but the precise hormonal interactions which initiate or, indeed, sustain these changes in the prostate gland are unknown (Wilson, 1980; *Habib* et al., 1981; *Stone* et al., 1986). The symptoms that ensue from BPH are variable and bear little relation to the size of the gland. They can be either obstructive or functional and irritative, owing to concomitant detrusor instability and alpha-adrenergic overactivity of the sympathetic innervation of the bladder neck and prostatic musculature. The medical approach to the treatment of symptomatic BPH has been both endocrine and neuropharmacological. More than 30,000 prostatectomies are performed in the UK every year and approximately 10 times that number in the USA. Because of the large number of patients with moderate or mild symptoms of prostatic outflow obstruction awaiting surgery and a clearer insight into the pathophysiology of "prostatism", interest has been rekindled in the medical management of BPH with either hormonal manipulation or adrenergic blockade *(Lancet,* 1988). Reports of the efficacy of the pollen extract, Cernilton, in the symptomatic relief of BPH *(Takeuchi* et al., 1981; *Becker* and *Ebeling,* 1988) prompted us to carry out a placebo-controlled, double-blind study to evaluate its effect in patients with outflow obstruction due to BPH.

Patients and Methods

Sixty patients awaiting operative treatment for outflow obstruction due to benign enlargement of the prostate were entered into a double-blind, placebo-controlled study. Their ages ranged from 56 to 89 years (mean 68.6 ± SD 7.7). The patients consented to enter the study and their family doctors were informed. Cernilton and a placebo were administered in a dose of 2 capsules *bd* over a 6-month period.

The objective criteria for the evaluation of outflow obstruction were (i) the urine flow rate (an accurate measurement of flow rate required a minimum voided volume of 150 ml. With volumes < 150 ml the flow rate was repeated twice with the sensation of a full bladder and the mean of 3 readings taken as representative of the flow rate); (ii) the voided volume; (iii) an ultrasound measurement of residual urine; (iv) ultrasound measurement of prostate size by transrectal ultrasound probe using the Kretz ultrasound equipment. The prostate was scanned from the level of the seminal vesicles at the base of the prostate to its apex. An image of the prostate at its largest dimension was frozen on the screen and the outline of the prostatic image was circumscribed and measured in mm; the antero-posterior and transverse diameters were recorded (Fig. 1).

Subjective assessment was based on a modified "Boyarsky" scoring scale, as

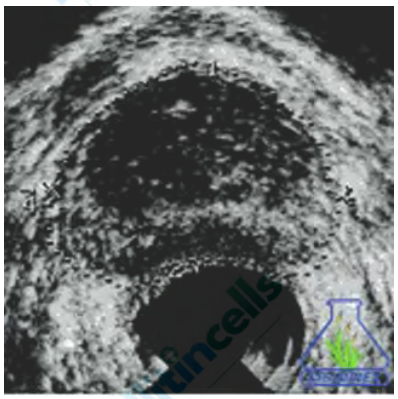

Fig. 1 Frame showing the prostate in its largest dimension

recommended by the Food and Drug Administration, for the symptoms of frequency, hesitancy, urgency, intermittency, incomplete emptying, terminal dribbling and dysuria, with a score of 0-3 for each of these symptoms (0 being an absence of symptoms and 3 being the most severe; see Appendix) *(Boyar*sky et al., 1977).

In addition, a full hematological and biochemical profile was performed, including liver function tests and serum cholesterol, triglycerides, high and low density lipo-proteins. All blood samples were obtained between 09.00 and 10.00h, following an overnight fast. The investigations were performed before the patients began treatment with either active compound or placebo, again at 3 months and finally at the conclusion of the study. The study was commenced and completed within a 7-month period, from October 1987 to April 1988. All urodynamic and ultrasound measurements were performed by one observer (A.C.B.) but the subjective evaluation was done by 2 clinicians independently.

Statistical Method and Analysis

The statistical analysis was divided into 5 sections dealing with (i) the homogeneity of demographic distribution and clinical presentation, (ii) the homogeneity of baseline findings, (iii) therapeutic measurements and trial course, (iv) assessment of efficacy and (v) assessment of safety and tolerance.

The tests for comparability of the trial groups were carried out by means of X^2 tests for categorical data, X^2 test with Yates' correction (4-fold tables) and Student's *t* test for continuous data. The comparison of trial groups with regard to symptoms was carried out by means of the X^2 test. The changes in urodynamic and ultrasound data, and in laboratory and clinical parameters in both groups, were compared using analysis of variance. All tests were performed using the 5% level of significance.

Results

Of the 60 patients entered into the study, 3 were excluded after the initial assessment: the first had an iron deficiency anemia caused by gastrointestinal bleeding that required further investigation and treatment; the second patient had undergone an abdominoperineal resection for carcinoma of the rectum which precluded objective evaluation of the prostate and the third patient decided against continuing in the study. Thus 57 patients took part. There were 31 patients in the Cernilton arm and 26 in the placebo arm. During the course of the study a further 4 patients were excluded: 2 in the placebo arm were admitted with acute retention of urine and underwent transurethral resection of the prostate (TURP); 1 patient in the Cernilton arm was admitted with acute epididymitis that was considered to be unrelated to the trial procedure and another patient was admitted with acute retention of urine and underwent a TURP. Fifty-three patients were fully evaluable at the end of 6 months, 29 in the Cernilton arm and 24 in the placebo arm.

With regard to the stratification of patients, the 2 groups were evenly matched with respect to demographic data, clinical presentation, symptoms, laboratory investigations and objective evaluation with the exception that the patients in the Cernilton arm had a higher mean body weight (P = 0.05).

Subjective Evaluation

There was no statistical difference in the symptoms of diurnal frequency between the 2 groups (P = 0.66), but 60 % of patients on Cernilton were improved or symptom-free as regards nocturia compared with 30 % of patients on placebo (P < 0.063). On Cernilton, 57% of patients showed improvement in bladder emptying compared with only 10 % in the placebo group (P < 0.004). There were no significant differences in hesitancy (P= 0.48), urgency (P=0.157), intermittency (P= 0.5), terminal dribbling (P = 0.9) or dysuria (P = 1.0). There was a statistically significant overall improvement in subjective symptoms in the Cernilton group (69 % of patients) compared with patients in the placebo group (29 %) (P < 0.009) (Table 1).

Table 1 Frequency of Symptom-free Findings following Cernilton and Placebo at 6 months

	Response Rate (%)		
Symptom	*Cernilton*	*Placebo*	*P value*
Frequency			
Daytime	37	47	0.664
Nocturia	60	30.4	0.063*
Hesitancy	47	29	0.480
Urgency	71	45	0.157
Intermittency	52	33	0.505
Incomplete emptying	57	10	0.004*
Terminal dribble	61	56	0.99
Dysuria	62	71	1.0

*Statiscally significant
Some test results remained non-significant because of the small number of positive findings before the start of the treatment.

Table 2 Results of Measurements before and after Treatment
*Statistically significant

Parameter	*Time of examination*	*Cernilton* $\bar{X}$	*Cernilton* SE	*Placebo* $\bar{X}$	*Placebo* SE	*Analysis of variance (P value)*
Peak flow rate (ml/s)		(n = 26)		(n = 24)		
	Before treatment	10.3	5.2	11.8	6.4	0.92
	After treatment	10.5	5.1	12.1	5.1	
Volume voided (ml)		(n = 29)		(n = 24)		
	Before treatment	241.5	144	235	96.8	0.11
	After treatment	203.4	90.3	257	106.6	
Residual urine (ml)		(n = 28)		(n = 24)		
	Before treatment	145.4	107.5	93.4	91.4	0.025*
	After treatment	101.9	87.3	113.4	87.3	

*Statistically significant.

Objective Evaluation

The results of peak urine flow rate, voided volume and residual urine in the 2 groups of patients before and after treatment are shown in Table 2. There was no significant change in peak urine flow rate (both groups showed a slight increase) or voided volume

The results of ultrasound measurement of the parameters for prostate volume are shown in Table3. The A-P diameter was found to be significantly reduced after treatment with Cernilton at 6 months (P<0.025) (Fig. 3).

There were no significant changes in the hematological or biochemical measurements in either group. No significant changes in serum cholesterol, triglyceride or lipoprotein values were observed with Cernilton and no adverse side effects were reported.

(slight decrease after Cernilton and a slight increase with placebo) before and after treatment in the 2 groups. However, residual urine volume decreased significantly in the patients receiving Cernilton compared with the placebo group, in whom it increased (P < 0.025) (Fig. 2).

Discussion

Transurethral resection or open prostatectomy undoubtedly remains the most effective treatment for BPH but is not without complications in both the short and longer term, whilst symptomatic improvement and patient satisfaction after the operation appears to be less in those who are only mildly or moderately symptomatic than in those with severe symptoms or retention *(Fowler* et al., 1988). Thus there may be a place for therapeutic compounds that are of proven benefit and free of side effects for the treatment of patients with mild or moderate symptoms who are awaiting operation or are unfit for surgery.

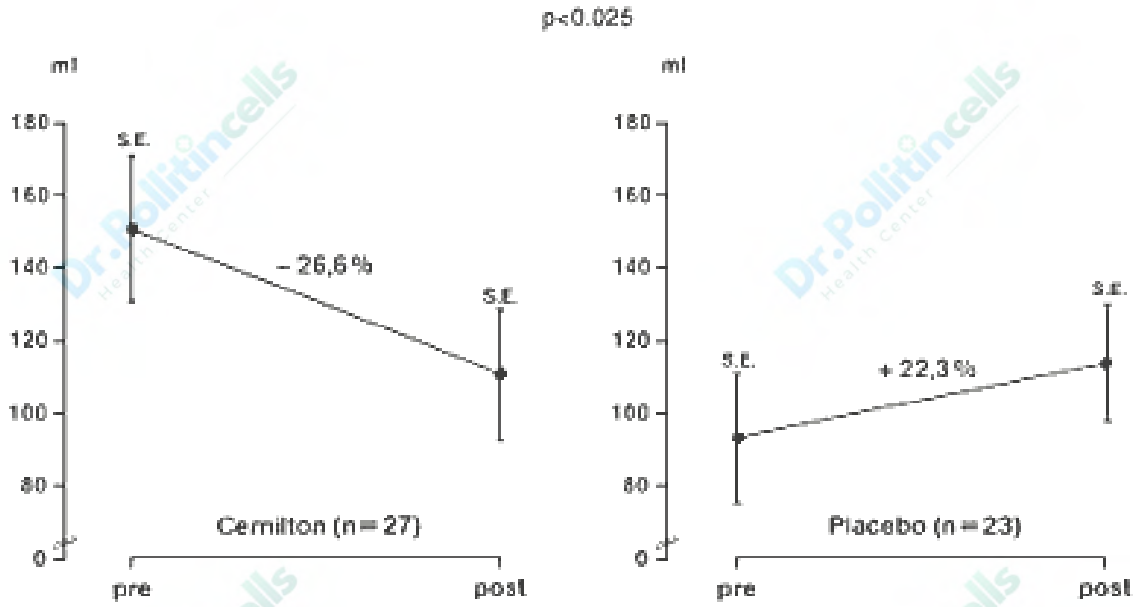

Fig. 2 Residual urine volume.

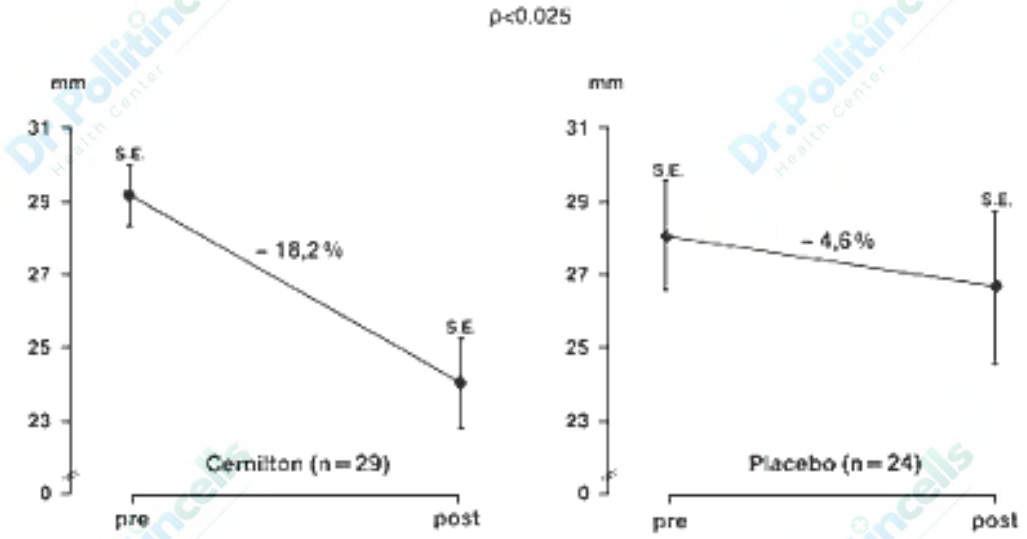

Fig. 3 Prostate volume.

Several studies aimed at achieving androgen deprivation in BPH have been reported. These have included castration *(Huggins* and *Stevens,* 1940), oestrogens *(Beacock* et al., 1985), progestogens *(Geller* et al., 1965; *Hald* and *From,* 1972), anti-androgens *(Caine* et al., 1975) and, more recently, LH-RH agonists *(Gabrilove* et al., 1987; *Peters* and *Walsh,* 1987). With the introduction of selective xl adrenergic blockers, there has been renewed interest in their use for symptomatic relief *(Caine,* 1986; *Kirby* et al., 1987). The discovery of high concentrations of cholesterol in BPH has led to the use of cholesterol-lowering drugs such as candicidin, with variable results *(Jensen* and *Madsen,* 1983). However, none of these compounds has proved to be consistently effective and most have significant untoward side effects.

An interesting empirical approach to the non-adrenergic, non-hormonal treatment of symptomatic BPH has been the use of pharmacological compounds derived from plants, *Donkervoort* et al. (1977) evaluated Tandenan, an extract of African prunes, in a double-blind study in 20 patients. Although the drug was harmless, it had no beneficial effect. An extract from the fruit of the American dwarf palm, Serenoa repens, reputed to have antiandrogenic activity, brought about a significant improvement in flow rate, residual urine and nocturia, although peak urine flow rates did not reach normal values in the large group of patients studied (5.35±SE 1.51 before and 8.05±SE 2.47 after treatment; n= 46) *(Champault* et al., 1984).

Table 3 Measurement of Prostate Volume

Prostate size	*Time of examination*	*Cernilton* $\bar{X}$	*SE*	*Placebo* $\bar{X}$	*SE*	*Analysis of variance (P value)*
Circumference (mm)		(n = 29)		(n = 17)		
	Before treatment	169.6	26.3	163.2	16.2	0.446
	After treatment	153.4	27.5	150.5	21.6	
Transverse diameter (mm)		(n = 29)		(n = 24)		
	Before treatment	56.4	8.3	53.8	8.1	0.753
	After treatment	52.2	9.7	50.3	8.1	
Anteroposterior diameter (mm)		(n = 29)		(n = 24)		
	Before treatment	29.1	5.3	28.3	7.4	0.025*
	After treatment	23.8	7.0	26.7	9.1	

*Statistically significant.

The pollen extract, Cernilton, known to be effective in the treatment of chronic abacterial prostatitis and prostatodynia *(Ohkoshi* et al., 1967; *Ebeling,* 1986; *Buck* et al., 1989), has also been shown to provide symptomatic relief in patients with benign prostatic hyperplasia *(Takeuchi* et al., 1981; *Becker* and *Ebeling,* 1988). Cernilton is an extract of pollen derived from several different plants in southern Sweden. It is rendered free of allergens and its 2 principal active constituents are a water soluble fraction, T-60, and an acetone soluble fraction, GBX. The acetone-soluble fraction was found to consist of 3 B-sterols with a similarity on UV absorption spectra to oestrone and Stigmasterol *(Kvanta,* 1968). Cernilton produced a significant decrease in the size of the ventral and dorsal lobes of the prostate gland accompanied by histological evidence of epithelial cell atrophy, a significant fall in total and prostatic acid phosphatase, with a significant increase in the zinc concentration in the dorsal lobe of the prostate and in blood in mature Wistar rats compared with the control animals *(Ito* et al., 1986). *Habib* et al. (1990) reported the inhibition of immortal human cell line growth in culture derived from prostate carcinoma in the presence of T-60. The hormone-stimulated growth of BPH tissue transplanted into nude mice is significantly inhibited by Cernilton extract but no histological differences were observed between the treated and untreated groups (Otto, etal., 1990). Despite the results of these experimental studies there have been no clinical studies to indicate that Cernilton has any influence on hormonal metabolism in man. In the present investigation the levels of LH, FSH, testosterone and DHT were unchanged, but the possibility that it acts on hormone-dependent target organs cannot be ruled out. The significant decrease in the A-P diameter of the prostate in patients treated with Cernilton suggests that prostate size was reduced with treatment, even within the short time of the trial period. Adenomatous hyperplasia takes several years to develop and a dramatic regression could be expected only with total androgen deprivation. In a placebo controlled study, Cernilton was reported to lower the levels of serum cholesterol and low density lipoprotein (LDL) *(0ckerman,* personal communication) but we were unable to show any difference in these lipid fractions between the 2 groups in this study, carried out under strict fasting conditions.

Kimura et al. (1986) observed that T-60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle in a concentration-dependent manner. These studies were confirmed by Nakase et al. (1988), using rat vesicourethral and external urethral muscle strips; they showed that T-60 and GBX inhibited the contraction of muscle induced by noradrenaline bitartrate, with evidence for competitive antagonism of noradrenalin at the site of adrenergic receptors. Thus the subjective improvement in symptoms of nocturia and bladder emptying could be due to the effect of Cernilton on the rich adrenergic innervation of the bladder neck and prostate.

The precise mode of action of Cernilton in BPH is not known and further studies to determine its pharmacological action are in progress. However, this double-blind placebo-controlled study has shown distinct subjective and objective improvement with a positive response in the Cernilton group. As with other studies to evaluate the effect of drugs in BPH, there was a 30% subjective improvement in patients in the placebo arm of the study, which highlights the need for placebo control. In addition, we studied all of the patients together within a 7-month period in order to synchronize the times of serial evaluation and thus to eliminate the marked effect that seasonal variation can have on the symptomatology of this condition. A longer duration of treatment or a larger dosage may produce a more pronounced benefit and Cernilton, which appears to have no untoward side effects, may prove to be a useful agent in alleviating the early symptoms of outflow tract obstruction due to BPH.

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Appendix

Daytime Frequency
0- 1 to 4 times daily
1- 5 to 7 times daily
2- 8 to 12 times daily
3-13 or > times daily

Nocturia
0 - absence of symptoms
1 - subject awakened once each night because of the need to urinate
2 - subject awakened 2 to 3 times each night
3 - subject awakened 4 or > times each night

Hesitancy
0 -occasional hesitancy (occurs in 20 % or fewer of subject's attempts to void)
1 - moderate hesitancy (occurs during 20 to 50 % of subject's attempts to void)
2 - frequent hesitancy (occurs more than 50 % of subject's attempts to void)
3 - symptoms always present, lasts for 1 minute or longer

Urgency
0 - absence of symptoms
1 - occasionally difficult for subject to postpone urination
2 - frequently difficult (--nore than 50 % of the time) to postpone urination and may rarely loose urine
3 - always difficult to postpone urination and subject sometimes loses urine.

Intermittency
0 - occasional intermittency (occurs in 20 % or fewer of subject's attempts to void)
1 - moderate intem-dttency (occurs during 20 to 50 % of subject's attempts to void)
2 - frequent intermittency (occurs more than 50 % of the time, but not always, and may last up to 1 n-dnute)
3 - symptoms always present, lasts for 1 minute or longer

Incomplete Emptying
0 - absence of symptoms
1 - occasional sensation of incomplete emptying of bladder after voiding
2 - frequent (more than 50 % of the time) sensation of incomplete voiding
3 - constant and urgent sensation and no relief upon voiding

Terminal Dribbling
0 - occasional terminal dribble (occurs in 20 % or less of the subject's attempts at voiding)
1 - moderate terminal dribble (occurs in 20 to 50 % of subject's voiding)
2 - frequent terminal dribble (occurs in more than 50 % of the time but not always)
3 - symptom always present, dribbling lasts for 1 minute or more, or wets clothes

Dysuria
0 - absence of symptoms
1 - occasional burning sensation during urination
2 - frequent (more than 50 % of the time) burning sensation during urination
3 - frequent and painful burning sensation during urination

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Treatment of Chronic Prostatitis and Prostatodynia with Pollen Extract

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The treatment of chronic, relapsing nonbacterial prostatitis presents a formidable challenge to the clinician. It is also well recognized that other conditions, such as pelvic floor myalgia, prostatodynia, adductor muscle strain and chronic traumatic osteitis pubis, may give rise to symptoms of dysuria, perineal, groin, testicular and suprapubic pain that mimic inflammatory disease in the prostate (3,13,15). It is, therefore, important to differentiate such conditions from chronic prostatic inflammation on the basis of objective morphological, biochemical, radiological, urodynamic and microbiological criteria.

To achieve a cure in these patients is extremely difficult. The response to antibiotics, a-adrenergic blockage, non-steroidal anti-inflammatory drugs and other empirical manoeuvres is either ineffective or, at best, variable (10, 11). The pollen extract Cernilton (A. B. Cernelle, Sweden) has been used in the treatment of chronic prostatitis for nearly 30 years with favourable results (1,4,5,14). The aim of this study was to evaluate the efficacy of Cernilton in the treatment of patients with chronic non-bacterial prostatitis and prostatodynia.

Patients and Methods

Fifteen patients, ranging in age from 23 to 63 years (mean 42.9±SD 11.1) and with a clinical diagnosis of chronic relapsing non-bacterial prostatitis or prostatodynia, were entered into an open trial to study the effect of Cernilton. Twelve patients had previously been treated with 1 or more courses of antibiotics for varying periods of time, 4 had been treated with an alpha-adrenergic blocker, 1 had undergone a transurethral resection of the prostate and 1 an epididymectomy without relief of symptoms. At the time that the patients were commenced on Cernilton they had suffered from their symptoms for periods ranging from 5 months to 7 years (mean 3.3±SD 2.2). Their clinical presentation was as follows: 13 complained of irritative urinary symptoms, mainly dysuria (13) and frequency (6). All complained of pain or discomfort, either persistent or intermittent, localized to the testis (7), groin (4), perineum (5), suprapubic area (1) urethra / penis (3) or on ejaculation (2) (Table 1).

The diagnosis of chronic prostatitis or prostatodynia was made on the basis of the segmented urine sample method of Meares and Stamey (1968). No significant bacteriuria was present in any of the patients, nor were pathogenic organisms, including Chlamydia trachomatis, cultured from the EPS (expressed prostatic secretion). In 5 patients the pH of the prostatic fluid was alkaline (pH 7.0-8.0) with >10 leucocytes and fat laden macrophages /high power field on microscopy. In 8 patients the characteristics of the EPS were normal (pH < 6.5; pus cells < 10 / HPF) and in 2 cases no fluid could be obtained by massage for examination. The patients were commenced on Cernilton 2 tablets twice daily and assessed clinically at monthly intervals.

Results

The duration of treatment with Cernilton varied from 1 to 18 months. Seven patients became symptom-free, 6 were significantly improved and continue to take Cernilton regularly, and 2 failed to respond. Most patients (11) did not begin to show any improvement in signs or symptoms until 3 months after starting treatment (See Table 1 below). Only 1 patient, with a 12-month history of right testicular pain and urinary frequency, who had received 3 courses of antibiotics, with sterile urine and an EPS pH of 6.8 with < 5 leucocytes/HPF, was completely relieved of symptoms after 1 month's treatment with Cernilton. A second patient with a 5-month history of dysuria, frequency, back ache and sterile urine, but an EPS pH of 8 and > 20 pus cells/ HPF, was partially relieved of symptoms at 2 months and the pH of the EPS fell to 7.8, < 10 pus cells / HPF.

Two patients had a recurrence of symptoms after cessation of treatment. A 36 year old man had a 2-year history of intermittent dysuria, left groin and testicular discomfort and an EPS pH of 8 with masses of pus cells /HPF on microscopy; he had been treated with several courses of antibiotics (minocycline, doxycycline, trimethoprim) without relief of symptoms or a change in the alkalinity or leucocytosis of the EPS. After 3 months' treatment with Cernilton the symptoms were completely relieved and the pH of the EPS fell to 7.1 with < 5 pus cells / HPF. On discontinuing treatment the symptoms recurred, with a return to leucocytosis and an alkaline shift in the pH of the EPS. After recommencing Cernilton the signs and symptoms again reverted to normal.

Tab. 1 Details of Patients.

				Previous Therapy			
Name age (years)	Dur. of Symptoms (years)	Urinary symptoms	Pain site/ occurrence	Antibiotics	Relaxants/ aadrenergic blockade	Previous surgery	Response to Cernilton
TW 36	7	Dysuria	L. testis	Multiple		Epididymecytomy	Complete
DD 61	5	Dysuria	Suprapubic	None	Yes	TURP	Partial
FM 49	.05	Dysuria	Lumbosacral	None			Partial
GS 47	2	Dysuria	L. testis	Multiple			Partial
DB 33	1	Frequency	R. testis	Multiple			Complete

JG 46	2	Dysuria, frequency	Perineum, ejaculation	Multiple		Cystoscopy	None
MP 44	7	Dysuria	Groin	Multiple	Yes	Cystoscopy	Complete
PJ 29	1	Dysuria, Frequency	Perineum, penis	Multiple		Cystoscopy	Complete
DP 51	4	Dysuria	Perineum, testes	Multiple			Partial
HG 63	2	Frequency	Penile, on intercourse	Single	Yes	Cystoscopy	None
SC136	2	Dysuria	L. testis, groin	Multiple			Complete
DH 40	7	Dysuria	Perineum, testes	Multiple			Partial
JM 35	3	Dysuria	Testes, urethra	Single	Yes		Partial
RD123	3	Dysuria	Groins	Yes			Complete
AP 51	3	Frequency	Groins, perineum	Yes	Yes	Cystoscopy	Complete

1 Patients SC and RD relapsed when treatment was stopped and responded again to further treatment.

Discussion

Cernilton is an extract of various pollens from different plants. The active ingredients are a water-soluble (T/60) and fat-soluble (GBX) fraction. The water-soluble fraction attenuated the inflammatory response in experimental animals (7). The acetone-soluble fraction was found to consist of 3ß-sterols with a similarity on UV absorption spectra to oestrone and stigmasterol (9). More recently, in vitro studies have shown that GBX inhibits cyclo-oxygenase and lipoxygenase enzyme in the eicosanoid cascade, blocking both leukotriene and prostaglandin synthesis (Loschen, personal communication). Cernilton was shown to reduce significantly the size of the ventral and dorsal prostate in the rat and to inhibit testosterone-induced prostatic hypertrophy in the castrated animal (7). Kimura et al. (1986) observed that T60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle.

Although the precise mode of action of Cernilton on the inflammatory process in the prostate is not known, it has been shown to be effective in the treatment of chronic abacterial prostatitis

(5,12). In this study, Cernilton was found to relieve completely the symptoms of prostatitis in 7/15 patients and a further 6 were markedly improved. All patients had previously received several courses of antibiotics, analgesics and muscle relaxants and some were given adrenergic blockade, without effective or lasting relief of symptoms. It is of interest that the effect of the pollen extract was mainly observed after 3 months or more of treatment. Most patients have opted to continue with treatment and no adverse side effects have been reported. The in vitro experiments suggest that it could be either a potent cyclo-oxygenase and lipoxygenase inhibitor or a smooth muscle relaxant. These actions could explain its anti-inflammatory effect in abacterial prostatitis and symptomatic relief in prostatodynia, a condition in which an increase in the maximum urethral closure pressure and spasm of the external sphincter mechanism has been observed in association with a diminished urine flow rate (2,10). Conversely, it may affect metabolic processes within the prostatic cell (Habib, personal communication). Further clinical and laboratory studies are necessary to elucidate the exact mode of action of this compound.

Summary

Chronic abacterial prostatitis and prostatodynia are notoriously difficult both to diagnose and to treat. These patients tend to have received several courses of antibiotics, anti-inflammatory agents or adrenergic blockade and various other therapeutic manoeuvres with little success. The pollen extract, Cernilton, is reported to be effective in the treatment of this condition and we present the results of an open trial with Cernilton in a group of 15 patients with chronic prostatitis and prostatodynia. In 13 patients there was either complete and lasting relief of symptoms or a marked improvement; 2 patients failed to respond.

Cernilton was found to be effective in the treatment of chronic prostatitis and prostatodynia. Its precise mode of action is not known, although experimental studies suggest that it has anti-inflammatory and antiandrogenic properties.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Treatment of Chronic Prostatitis and Prostatodynia with Pollen Extract

A.C. Buck, R.W.M. Rees and L. Ebeling
Departments of Urology, Leighton Hospital, Crewe, and University Hospital of Wales, Cardiff

Summary— Chronic abacterial prostatitis and prostatodynia are notoriously difficult both to diagnose and to treat. These patients tend to have received several courses of antibiotics, anti-inflammatory agents or adrenergic blockade and various other therapeutic manoeuvres with little success. The pollen extract, Cernilton, is reported to be effective in the treatment of this condition and we present the results of an open trial with Cernilton in a group of 15 patients with chronic prostatitis and prostatodynia. In 13 patients there was either complete and lasting relief of symptoms or a marked improvement; 2 patients failed to respond.

Cernilton was found to be effective in the treatment of chronic prostatitis and prostatodynia. Its precise mode of action is not known, although experimental studies suggest that is has anti-inflammatory and anti-androgenic properties.

The treatment of chronic, relapsing non-bacterial prostatitis presents a formidable challenge to the clinician. It is also well recognized that other conditions, such as pelvic floor myalgia, prostatodynia, adductor muscle strain and chronic traumatic osteitis pubis, may give rise to symptoms of dysuria, perineal, groin, testicular and suprpubic pain that mimic inflammatory disease in the prostate (Segura et al., 1979; Osborn et al., 1981; Buck et al., 1982). It is, therefore, important to differentiate such conditions from chronic prostatic inflammation on the basis of objective morphological, biochemical, radiological, urodynamic and microbiological criteria.

To achieve a cure in these patients is extremely difficult. The response to antibiotics, α-adrenergic blockage, non-steroidal anti-inflammatory drugs and other empirical manoeuvres is either ineffective or, at best, variable (Meares and Barbalias, 1983; Meares, 1986). The pollen extract Cernilton (A. B. Cernelle, Sweden) has been used in the treatment of chronic prostatitis for nearly 30 years with favourable results (Ask-Upmark, 1963; Denis, 1966; Ebeling, 1986; Saito, 1967). The aim study was to evaluate the efficacy of Cernilton in the treatment of patients with chronic non-bacterial prostatitis and prostatodynia.

Patients and Methods

Fifteen patients, ranging in age from 23 to 63 years (mean 42.9±SD 11.1) and with a clinical diagnosis of chronic relapsing non-bacterial prostatitis or prostatodynia, were entered into an open trial to study the effect of Cernilton. Twelve patients had previously been treated with 1 or more courses of antibiotics for varying periods of time, 4 had been treated with an alpha-adrenergic blocker, 1 had undergone a transurethral resection of the prostate and 1 an epididymectomy without relief of symptoms. At the time that the patients were commenced on Cernilton they had suffered from their symptoms for periods ranging from 5 months to 7 years (mean 3.3±SD 2.2). Their clinical presentation was as follows: 13 complained of irritative urinary symptoms, mainly dysuria (13) and frequency (6). All complained of pain or discomfort, persistent or intermittent, localised to the testis (7), groin (4), perineum (5), suprapubic area (1) urethra / penis (3) or on ejaculation (2) (Table).

The diagnosis of chronic prostatitis or prostatodynia was made on the basis of the segmented urine sample method of Meares and Stamey (1968). No significant bacteriuria was present in any of the patients, nor were pathogenic organisms, including Chlamydia

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* Patients SC and RD relapsed when treatment was stopped and responded again to further treatment.

trachomatis, cultured from the EPS (expressed prostatic secretion). In 5 patients the pH of the prostatic fluid was alkaline (pH 7.0-8.0) with >10 leucocytes and fat laden macrophages /high power field on microscopy. In 8 patients the characteristics of the EPS were normal (pH < 6.5; pus cells < 10 / HPF) and in 2 cases no fluid could be obtained by massage for examination. The patients were commenced on Cernilton 2 tablets twice daily and assessed clinically at monthly intervals.

Results

The duration of treatment with Cernilton varied from 1 to 18 months. Seven patients became symptom-free, 6 were significantly improved and continue to take Cernilton regularly, and 2 failed to respond. Most patients (11) did not begin to show any improvement in signs or symptoms until 3 months after starting treatment (Table).

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Two patients had a recurrence of symptoms after cessation of treatment. A 36 year-old man had a 2-year history of intermittent dysuria, left groin and testicular discomfort and an EPS pH of 8 with masses of pus cells /HPF on microscopy; he had been treated with several courses of antibiotics (minocycline, doxycycline, trimethoprim) without relief of symptoms or a

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change in the alkalinity or leukocytosis of the EPS. After 3 months' treatment with Cernilton the symptoms were completely relieved and the pH of the EPS fell to 7.1 with < 5 pus cells / HPF. On discontinuing treatment the symptoms recurred, with a return to leukocytosis and an alkaline shift in the pH of the EPS. After recommencing Cernilton the signs and symptoms again reverted to normal.

Discussion

Cernilton is an extract of various pollens from different plants. The active ingredients are a water-soluble (T60) and fat-soluble (GBX) fraction. The water-soluble fraction attenuated the inflammatory response in experimental animals (Ito et al., 1984). The acetone-soluble fraction was found to consist of 3ß-sterols with a similarity on UV absorption spectra to oestrone and stigmasterol (Kvanta, 1968). More recently, in vitro studies have shown that GBX inhibits cyclo-oxygenase and lipoxygenase enzyme in the eicosanoid cascade, blocking both leukotriene and prostaglandin synthesis (Loschen, personal communication). Cernilton was shown to reduce significantly the size of the ventral and dorsal prostate in the rat and to inhibit testosterone-induced prostatic hypertrophy in the castrated animal (Ito et al., 1986). Kimura et al. (1986) observed that T60 and GBX produced relaxation of the smooth muscle of the mouse and pig urethra and increased the contraction of the bladder muscle.

Although the precise mode of action of Cernilton on the inflammatory process in the prostate is not known, it has been shown to be effective in the treatment of chronic abacterial prostatitis (Ohkoshi et al., 1967; Ebeling, 1986). In this study, Cernilton was found to relieve completely the symptoms of prostatitis in 7/15 patients and a further 6 were markedly improved. All patients had previously received several courses of antibiotics, analgesics and muscle relaxants and some were given adrenergic blockade, without effective or lasting relief of symptoms. It is of interest that the effect of the pollen extract was mainly observed after 3 months or more of treatment. Most patients have opted to continue with treatment and no adverse side effects have been reported. The in vitro experiments suggest that it could be either a potent cyclo-oxygenase and lipoxygenase inhibitor or a smooth muscle relaxant. These actions could explain its anti-inflammatory effect in abacterial prostatitis and symptomatic relief in prostatodynia, a condition in which an increase in the maximum urethral closure pressure and spasm of the external sphincter mechanism has been observed in association with a diminished urine flow rate (Buck, 1975; Meares and Barbalias, 1983). Conversely, it may affect metabolic processes within the prostatic cell (Habib, personal communication). Further clinical and laboratory studies are necessary to elucidate the exact mode of action of this compound.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

The Treatment of Benign Prostatic Hyperplasia with Phytopharmata

A comparative study of Cernilton[R] vs. β-sitosterol

H. Bräuer

The conservative treatment of benign prostatic hyperplasia (BPH) has gained increasingly in significance in view of the increased life expectancy. In a controlled comparative study (n = 39) with Cernilton[R] and β- sitosterol the course of treatment was objectified by clinical-chemical findings. The results demonstrate the marked improvement of symptoms and signs, whereas the regression of complaints was more pronounced under Cernilton[R]. The significant decrease of PAP and PSA serum levels shows the reduction of cell lesions in BPH under the treatment with Cernilton[R]. A comparable effect of β-sitosterol could not be demonstrated. The relative lack of toxicity of both drugs can be confirmed by the biochemical data.

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In the second half of the normal life-span the physiological process of ageing leads to the appearance of an increasing number of diseases. One of these is benign prostatic hyperplasia (BPH), which sooner or later develops in practically all males. The data on the incidence of benign prostatic hyperplasia vary more than for almost any other condition.

Some authors assume that from the fourth decade of life almost 80%, and from the seventh decade almost 100% of all men show a more or less pronounced nodular hyperplasia of the prostate (2, 6). This means that the older a man becomes the more certain it is that he will be confronted with an alteration of his prostate and its consequences. The almost unbelievable increase in life expectancy which has been achieved through the diagnostic, therapeutic and prophylactic measures of modern medicine means that more and more men are reaching the critical age for prostate disease. In Sweden, the United Kingdom and Germany, for example more than 50% of the population is over the age of 65 years.

The figures published by the German Federal Statistics Office in Wiesbaden for 1983 show that 156,000 people in the Federal Republic were 90 years of age or over. Ten years earlier the corresponding figure was only 92,000. The trend is the same in all industrial countries and will continue. As a result, the incidence of the "old man's disease", prostatic hyperplasia, will also increase.

The aetiology and pathogenesis of benign prostatic hyperplasia are still unclear and are the subject of controversial discussion. Changes in enzyme activity in the prostate, shifts in various hormonal parameters (e.g. DHT) and, more recently, altered hormone-receptor conditions, are accepted as possible triggering factors (1, 2, 4, 6, 7). It is established that the endocrine system influences the development of a prostatic hyperplasia.

Rationale of Study

The fact that only relatively few men are not affected by benign prostatic hyperplasia makes it almost impossible to find a healthy control group in the same ate-range, in order to obtain comparative clinico-chemical data, for reference. This is probably also the reason for the sometimes contradictory results reported in many publications.

In our study two phytopharmaca, Cernilton[R] (Stroschein, Hamburg and β-sitosterol, were compared and the course of the treatment with each preparation objectified on the basis of clinico-chemical data.

Our Investigations

Selection of Patients

It was possible to carry out the study almost exclusively with trial subjects from a large old people's home, who always received food of the same type and composition, and to a certain extent the same amount. It was thus relatively easy to exclude changes attributable to nutritional factors in the parameters to be measured in the course of the study, in both groups.

With a predictable drop-out rate of 20%, 50 patients were taken into the study, in accordance with the defined criteria for exclusion and inclusion, in order to reach a total of at least 20 patients in each group, for the final evaluation. The patients were allocated to the two groups according to a strict randomization procedure. All the patients entered the study without any additional medication. In order to exclude possible uncheckable drug effects, a one-week wash-out period was included before the start of the treatment, in 4 cases. All the patients required treatment and had been receiving medical therapy for their prostatic symptomatology for more than 6 months. Because of unsatisfactory results of previous therapy they can be considered as a "simple negative" patient selection.

Two patients were excluded from the initial patient population because of extreme obesity and a further seven because of the results of diagnostic laboratory investigations (malignant tumors, sever alcoholic liver disease and extreme electrolyte imbalances). One patient had to discontinue the study for private reasons. At the final evaluation one patient of Group A with residual urine values of over 130 ml and who had to be operated for anuria before the end of the study period, was excluded. Table 1 shows the mean values for age, height, and weight in the two groups, A and B. Tables 2a and 2b provide information on concomitant diseases and the general condition of the patients of Groups A and B, respectively.

Methodology

The patients of Group A (trial preparation: a specially prepared pollen extract (3). Cernilton[R] [1)] received, as did the patients of Group B (control preparation: β-sitosterol [2)] , 2 tablets/capsules 3 times a day for the first week, and then 1 tablet/capsule 3 times a day[3)] from the 8th to the 42nd day.

The blood samples were taken in the morning, between 8:00 and 9:00 a.m., in the fasting state, by the Vacutainer system (Becton & Dickinson), centrifuged after maturation of the fibrin (1 hour at room temperature), separated by means of Seraclear filters and deep-frozen at -25º C and kept constantly at this temperature until the analytical processing. The clinico-chemical and hematological parameters were analyzed on a Type 12/60,6/60, 9/60 and 7A Auto-analyzer on a Type determinations of prostatic acid phosphatase (PAP) and prostate-specific antigens (PSA) were carried out by radioimmunoassay (RIA), as double-blind determinations which were repeated if the results exceeded the normal values by more than 600 counts. The counting was carried out with a Y-counter system (MR-1032-W+W) of the Kontron Co.

The enzyme activities were measured at the normal physiological temperature of 37ºC. The reproducibility for these values and for the hematology is ±3%, and for the other clinico-chemical parameters ±1%.

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1) One tablet contains: Stand. Extr. Pollin. sicc. (Cernitin T60) 60 mg; Stand. Extr. Pollin. dialys (Cernitin GBX) 3 mg.

2) One capsule contains: 10 mg β-sitosterol.

3) The manufacturer's recommendation of a dosage of 2 capsule 3 times a day was not followed, in order to be able to compare the therapeutic effects of the two preparations.

The data of the clinical investigations were classified according to symptoms and complaints and recorded according to the degree of change at each examination.

The residual urine was determined by catheterization, always performed by the same investigator. The bacterial examinations of the urine samples were performed by means of the classical culture methods.

All the data have been documented in accordance with GLP[4)] and processed according to standard biostatisical methods on an EDP unit (Olivetti L I M 40 ST).

Results

Changes in the clinical symptomatology

Subjective Complaints

Comparison of the initial findings with those at the end of the study shows improvement in the clinical symptoms with both preparations, which were clearly more pronounced with the pollen-extract preparation, according to both the investigating physician's impression and that of the patients themselves. This is true particularly for the patients with several concomitant symptoms. If the results are classified, then on the basis of the subjective findins of the patients and the observations of the treating physicians these data are supported, at least semi-quantitatively, by Table 3. This table shows a clinically relevant rate of improvement in the subjective symptoms, painful micturition, changes in the urinary stream and pollakisuria, for both preparations, with Cernilton[R] proving better than β-sitosterol. For vesicle tenesmus, polyuria, urinary dribbling, as well as for pain and a feeling of pressure there is also a marked regression of the symptomatology in both groups.

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4) GLP = Good Laboratory Practice: recommendations of the German GLP committee, according to the guidelines of the Food and Drug Administration.

Determination of residual urine

In the β-sitosterol group the residual urine volume was 35 ± 22.5 ml and in the pollen-extract group 28 ± 16.6 ml. In both groups the mean values had fallen to under 15 ml at the end of the treatment.

Urine Examinations

Table 4 gives an overview of the changes in the cell-counts and the bacterial status during the treatment. With the improvement in the symptomatology the pathomorphological picture also improved.

Changes in biochemical parameters under the medication

The parameters indicating disturbances of renal function, namely creatinine and blood urea nitrogen, showed a clear decrease under both Cernilton[R] and β-sitosterol. The urea nitrogen fell from 19.5 mg/100 ml to below 18.5 mg/ 100ml and from 21.0 mg/100 ml to 20.2 mg/100 ml under the two medications, respectively. The creatinine also showed a trend towards a slight decrease in the plasma concentration, which can be interpreted as not statistically significant tendency to improvement. The uric acid concentration was not influenced by either of the two preparations. The electrolytes remained largely within the ranges of the baseline values. Only in the case of chloride was there slight regression, by about 1 mmol/l. Neither preparation has any effect on blood pressure.

Impressive are those enzyme values which indicate cellular lesions. The γ-GT, generally known as a cholestase-indicating enzyme in alcohol abuse, had its highest intracellular value in the renal parenchymal cells. The fall in the primarily intrarenal γ-GT was not only statistically significant but also clinically relevant, and was more pronounced in the Cernilton[R] group.

Although the alkaline phosphatase (AP) isoenzyme group is not particularly prostate-specific, an enzyme of this group is however to be found in a high concentration in the prostate tissue. During the course of the study there was a marked fall in the serum concentration of AP in both groups.

The PAP and PSA determinations in the serum show a clear difference in the effectiveness of the two preparations. Prostatic acid phosphatase (PAP) is a highly tissue-specific enzyme which is normally passed into the seminal fluid. All pathological changes of the prostate, whether carcinoma, benign hyperplasia or prostatitis, lead to an increase in the concentration of this enzyme in the peripheral blood. In Group A the PAP concentration fell, the decrease being not only clinically relevant but also statistically significant ($p < 0.05$), from 3.5 to 2.7 ng/ml, i.e. the serum concentration reached the normal range, the upper limit of which, measured by the RIA method , is 2.8 ng/ml. Group B, with a high baseline value, showed a similar initial fall from 4.4 to 3.7 ng/ml, which remained at this level until the end of the study, and thus did not reach the normal range (Fig. 1).

The prostate-specific antigen (PSA) originates from the epithelium of the excretory ducts of the

glandular complex and shows a maximum physiological concentration in the serum of 2.3 ng/ml. In benign prostatic hyperplasia concentrations of up to 12 ng/ml are reached. β-sitosterol lowered the serum concentration from the start to the end of the study by only 0.5 ng/ml (from 12.9 to 12.4 ng/ml). This value is not statistically significant and also there is no detectable trend. Statistically significant and also there is no detectable trend. Statistically significant ($p < 0.01$), and in our opinion clinically relevant, on the other hand, is the fall in the PSA value in the pollen-extract group. Here the value fell from 8.25 to 5.8 ng/ml, i.e. a decrease of 2.45 ng/ml was obtained (Fig. 2).

For the other clinico-chemical parameters, namely iron, total protein, albumin, calcium, anorganic phosphate, bilirubin, LDH, GPT (ALT), GOT (AST), triglycerides, cholesterol, cholinesterase, copper, magnesium and zinc, no significant changes were recorded, between the baseline and final values. Only in the values for leukocytes, erythrocytes, haematocrit, haemoglobin and CPK is there a trend towards a slight fall in both groups, so that on the basis of this spectrum of parameters the relative innocuity of both preparations can be confirmed.

Discussion

Prostatic acid phosphatase (PAP) is a glycoprotein with a relatively low carbohydrate content of only 6%. Under normal physiological conditions this enzyme is passed from the prostate to the seminal fluid in which, together with hyaluronidase, it influences the fluidity of the semen (8). Because of secretory obstruction a benign prostatic hyperplasia is always accompanied by raised internal pressure in the glandular complex. This raised pressure leads to compressive cellular lesions and cytolysis, as a result of which the PAP concentration in the peripheral blood increases. During the course of the study the mean value of the PAP concentration in Group A fell below the upper limit of the normal rage (Fig. 1), while in Group B there was an initial improvement, but then no further change in the mean value for the rest of the period of the study.

In healthy subjects the prostate-specific antigen (PSA) is to be found in high concentrations only in the semen. In the peripheral blood it is normally present only in a very low concentration (up to 2.3 ng/ml) (5), but increases markedly (up to 12 ng/ml) in the presence of cellular lesions of the excretory ducts resulting from a benign prostatic hyperplasia. Like the PAP concentration, that of the PSA also shows a marked fall under pollen extract therapy, from 8.25 ng/ml (Day 0) to 5.8 ng/ml (Day 42), while underβ sitosterol therapy the values fall only slightly (Fig. 2).

The fall in the serum concentrations of these two highly prostate-specific markers (PAP and PSA) permits the conclusion to be drawn that the cellular lesions of the glandular tissue resulting from prostatic changes show marked improvement under treatment with pollen extract. Presumably the internal pressure in the glandular complex due to the secretory obstruction also subsides. The concentrations of the mediators of inflammation, of the prostaglandin and leukotriene types, are certainly also reduced. In this way the vicious circle of a self-perpetuating inflammatory process can be broken, since the excessive secretion of prostaglandin is always set in motion by cellular lesions and persists for as long as these lesions are present. Thus with these values it can be confirmed that Cernilton^{R} exerts an anti-inflammatory effect.

On the basis of the measurement values presented here the use of Cernilton^{R} can be recommended for the indication, “benign prostatic hyperplasia in Stages I and II”, provided the residual urinary volume is still under 100 ml. Cernilton^{R} reduces the symptomatolofy of prostatic hyperplasia. The antiinflammatory and micturition-improving effects are confirmed by the various measurement data. We consider very important the fact that the preparation is extremely well tolerated.

The conservative drug therapy of benign prostatic hyperplasia is also of great significance, both in the hospital environment and in general practice, in view of the fact that the proportion of the general population over the age of 50 will in future be even greater than it is today.

Keywords: Prostatic hyperplasia, benign, Cernilton^{R}, β-sitosterol, Prostatic acid phosphatase, Prostate-specific antigen.

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Table 1: Statistical data (age, height, weight) in the two comparative groups (x±s)

Group	n	Age (years)	Height (cm)	Weight (kg)
A (Cernilton^{R})	19	68.9 ± 15.13	171.5 ± 8.28	76.3 ± 10.32
B (B-sitosterol)	20	73.0 ± 10.9	171.1 ± 6.8	73.9 ± 9.9

Table 2a: Concomitant diseases and general condition of the patients of Group A

Patient No.	Concomitant diseases	General Condition
5	Arteriosclerosis, cerebral sclerosis	Poor
9	Moderate hypertension, diabetes mellitus	Good
12	Moderate hypertension, diabetes mellitus, cholelithiasis, coronary sclerosis	Satisfactory
13	Osteoarthritis of the hip, arteriosclerosis, hypertension, coronary sclerosis	Satisfactory
15	Hypertension, coronary sclerosis	Good
18	-	Good
19	-	Satisfactory
21	Nephrolithiasis	Satisfactory
23	Spondylarthrosis, arteriosclerosis	Satisfactory
24	Coronary sclerosis, angina pectoris	Poor
27	-	Good
30	Generalized osteoarthritis, diabetes mellitus	Poor
31	Coronary sclerosis	Satisfactory
32	Moderate hypertension, coronary sclerosis	Poor
33	-	Satisfactory
36	Arteriosclerosis, coronary sclerosis	Good
37	Duodenal ulcer	Good
38	Glaucoma, bronchial asthma, coronary sclerosis	Satisfactory

Table 2b: Concomitant diseases and general condition of the patients of Group B

Patient No.	Concomitant disease	General condition
1	Slight hypertension	Satisfactory
2	Slight hypertension	Satisfactory
3	Nephrolithiasis, diabetes mellitus, angina pectoris	Poor
4	Slight hypertension, varicose veins	Poor
6	Slight hypertension	Satisfactory
7	Moderate hypertension, spondylosis	Satisfactory
8	Spondylosis, spondylarthropathy	Good
10	Moderate hypertension	Good
11	Slight hypertension, coronary sclerosis	Satisfactory
14	Arteriosclerosis, Parkinson's disease	Satisfactory
16	Cerebral sclerosis	Satisfactory
17	Cor pulmonale	Satisfactory
20	-	Good
22	Generalized osteoarthritis	Satisfactory
25	Angina pectoris	Poor
26	Cor pulmonale, arteriosclerosis, chronic obstructive bronchitis	Satisfactory
28	Slight hypertension, angina pectoris	Good
29	Slight hypertension, cerebral sclerosis, cerebral insufficiency, coronary sclerosis	Satisfactory
34	Angina pectoris, coronary sclerosis	Satisfactory
36		Satisfactory

Table 3: Baseline status and course of the subjective complaints
(A = Cernilton^{R} group, B=B-sitosterol group)

Complaints	Group	n	Day 0	Day 14			Day 42		
				No change	Reduced	Absent	No change	Reduced	Absent
Painful micturition	A B	19 20	13 14	7 10	6 4	0 0	1 1	7 9	5 4
Changes in urinary stream	A B	19 20	9 16	3 12	4 4	2 0	2 1	1 9	6 6
Pollakisuria	A B	19 20	15 13	10 10	5 2	0 1	1 2	6 5	8 6
Vesical tenesmus	A B	19 20	4 5	4 3	0 1	0 1	2 0	1 4	1 1
Polyuria	A B	19 20	1 3	1 2	0 1	0 0	0 0	1 3	0 0
Incontinence	A B	19 20	2 0	1 0	1 0	0 0	1 0	0 0	1 0
Urinary dribbling	A B	19 20	4 5	3 3	1 2	0 0	2 2	1 1	1 1
Pain or feeling of pressure	A B	19 20	7 4	5 1	2 3	0 0	0 0	5 3	2 1

Table 4: baseline status and course of the urinary findings (A = Cernilton^{R} , B = β-sitosterol group)

	Day 0		Day 14		Day 42	
	A n	**B n**	**A n**	**B n**	**A n**	**B n**
Erythrocytes						
None	15	14	17	14	18	13
Few	4	4	2	4	1	5
Moderately numerous	-	-	-	-	-	-
Numerous	-	-	-	-	-	-
Leukocytes						
None	3	1	3	2	5	4
Few	8	8	12	10	11	9
Moderately numerous	7	8	4	8	2	6
Numerous	1	3	-	-	1	1
Epithelial cells						
None						
Few	18	17	16	16	19	16
Moderately numerous	1	1	2	2	-	2
Numerous	-	-	-	-	-	-
	-	-	1	-	-	-
Bacteria						
None	13	12	15	12	16	13
Few	3	5	3	8	3	7
Moderately numerous	2	3	1	-	-	-
Numerous	1	-	-	-	-	-

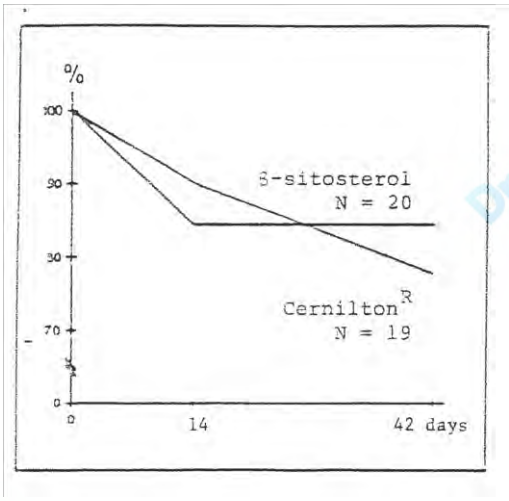

Fig. 1: Significant reduction ($p < 0.05$) of the serum PAP in %, after 6 weeks Cernilton^{R} therapy. A comparable effect with β-sitosterol cannot be demonstrated*.

*The absolute values before and after treatment are, in the Cernilton^{R} group 3.5 ± 1.67 ng/ml (Day 0) and 2.7 ± 1.11 ng/ml (Day 42), and in the β-sitosterol group 4.4 ± 5.68 ng/ml (Day 0) and 3.7 ± 4.42 ng/ml (Day 42). Normal serum PAP value, by radioimmunoassay (RIA) = ≥ 2.8 ng/ml.

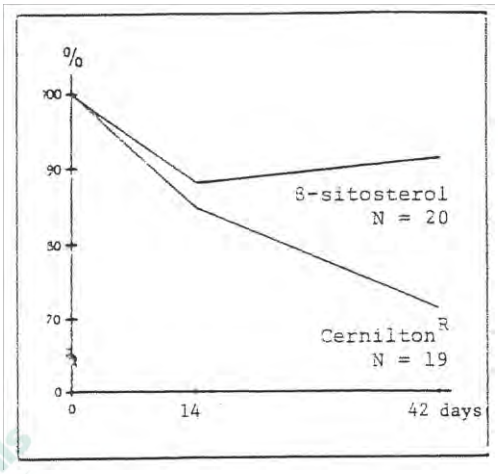

Fig. 2: Significant reduction ($p < 0.01$) of the serum PSA in %, after 6 weeks Cernilton^{R} therapy. A comparable effect with β-sitosterol cannot be demonstrated**.

**The absolute values before and after treatment are, in the Cernilton^{R} group 8.25 ± 10.77 ng/ml (Day 0) and 5.8 ± 6.56 ng/ml (Day 42), and in the β-sitosterol group 12.9 ± 14.55 ng/ml (Day 0) and 12.4 ± 13.57 ng/ml (Day 42). Normal serum PSA value, by radioimmunoassay (RIA) = ≥ 2.3 ng/ml.

PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

A systematic review of Cernilton for the treatment of benign prostatic hyperplasia

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Objective To systematically review the evidence for the clinical effects and safety of the rye-grass pollen extract (Cernilton) in men with symptomatic benign prostatic hyperplasia (BPH).

Methods Trials were identified by searching Medline, specialized databases (EMBASE, Cochrane Library, Phytodok), bibliographies, and contacting relevant trialists and manufacturers. Randomized or controlled clinical trials were included if: men with symptomatic BPH were treated with Cernilton; a control group received either placebo or pharmacological therapy; the treatment duration was ≥ 30 days; and clinical outcomes were reported.

Results In all, 444 men were enrolled in two placebo controlled and two comparative trials lasting 12- 24 weeks. Three studies used a double-blind method although the concealment of treatment allocation was unclear in all. Cernilton improved 'self-rated urinary symptoms' (the proportion reporting satisfactory or improving symptoms) vs placebo and another plant product, Tadenan. The weighted mean (95% confidence interval) risk ratio (RR) for self-rated improvement vs placebo was 2.40 (1.21-4.75) and the weighted RR vs Tadenan was 1.42 (1.21-4.75). Cernilton reduced nocturia compared with placebo or Paraprost (a mixture of amino acids); against placebo, the weighted RR was 2.05 (1.41-3.00), and against Paraprost the weighted mean difference for nocturia was -0.40 times per evening (-0.73 to 0.07). Cernilton did not improve urinary flow rates, residual volume or prostate size compared with placebo or the comparative study agents. Adverse events were rare and mild; the withdrawal rate for Cernilton was 4.8%, compared with 2.7% for placebo and 5.2% for Paraprost.

Conclusions The Cernilton trials analyzed were limited by their short duration, limited number of enrolees, omissions in reported outcomes, and the unknown quality of the preparations used. The comparative trials had no confirmed active control. The available evidence suggests that Cernilton is well tolerated and modestly improves overall urological symptoms, including nocturia. Additional randomized placebo and active-controlled trials are needed to evaluate the long-term clinical effectiveness and safety of Cernilton.

Key words: Cernilton, plant extracts, benign prostatic hyperplasia, BPH, efficacy

Introduction

The LUTS associated with BPH are common in ageing adult men [1]; in the USA, population studies show that the frequency of moderate to severe LUTS is 8-31% among men in their fifth decade and up to 44% among men in their seventh decade [2]. The cost of managing BPH is >$4 billion per year [3]. The primary aim of treatment in the vast majority of men is to relieve these bothersome obstructive and irritative symptoms.

Treatment options for symptomatic BPH include lifestyle change, medical, device or surgical therapy [4]. Phytotherapy, i.e. the use of plant extracts, is becoming widely used to manage BPH [5]; the use of phytotherapeutic agents is common in Europe and increasing in the Western hemisphere. In Germany, phytotherapy is the primary treatment for mild to moderate urinary obstructive symptoms and represents >90% of all drugs prescribed for treatment of BPH [6]. Phytotherapeutic agents are readily available in the USA as nonprescription dietary supplements and often recommended in 'natural health-food' stores or books for the self treatment of BPH symptoms [7].

Cernilton, prepared from the rye-grass pollen *Secale cereal*, is one of several phytotherapeutic agents available for the treatment of BPH. It is used by millions of men worldwide and is a registered pharmaceutical product throughout Western Europe, Japan, Korea and Argentina (data from the manufacturer, AB Cernelle, Engelholm, Sweden, 1999). In the USA, Cernilton is used as a nutritional supplement by ≈5000 men (D. Ruyan, Cernitin American, personal communication). One dose of Cernilton contains 60 mg of Cernitin T60, a water-soluble pollen extract fraction, and 3 mg of Cernitin GBX, an acetone-soluble pollen extract fraction (Cernelle AB). The acetone-soluble fraction contains β-sterols [8]. Several *in vitro* studies undertaken to investigate the mechanism of action suggest that Cernilton has antiandrogenic effects [9], may relax urethral smooth muscle tone and increase bladder muscle contraction [10], or may act on the a-adrenergic receptors and relax the internal and external sphincter muscles [11].

Despite many studies showing *in vitro* activity [9-11], the clinical effectiveness of Cernilton for the treatment of LUTS remains unclear. The objective of the present study was to systematically review the existing evidence for the clinical effectiveness and safety of Cernilton. Specifically, we assessed whether
Cernilton is more effective than placebo or as effective as other pharmacological therapies in improving the obstructive and irritative urinary symptoms associated with BPH.

Methods

Inclusion criteria and the identification of relevant trials

Randomized (RCTs) or controlled clinical trials (CCTs) were included if men had symptomatic BPH; the treatment intervention was Cernilton (Cernitin) or a preparation of *Secale cereale*; a control group received either placebo or pharmacological therapy for BPH; and the treatment duration was ≥30 days.

Medline (from 1966 to November 1998) was searched using a combination of the optimally sensitive search strategy for trials from the Cochrane Collaboration with the medical subject headings 'prostatic hyperplasia', 'phytosterols', 'plant extracts', 'pollen', 'sitosterols', *Secale cereale*, 'Cernilton.tw', and 'Cernitin.tw' including all subheadings [12]. EMBASE was searched from 1974 to 1997 (performed in July 1997) in a similar approach to the one used for Medline. The private database Phytodok (Munich, Germany) and the Cochrane Library, including the database of the Cochrane Prostate Group and the Cochrane Field for Complementary Medicine, were also searched similarly. The reference lists of all trials found were searched for additional trials. We attempted to solicit trialists identified, asking them to identify any further published or unpublished trials; there were no language restrictions.

Data extraction and study appraisal

Study characteristics, demographic information, enrolment criteria and outcomes were extracted independently by two reviewers. Authors or sponsors of the trials were petitioned for required missing or additional information. Extracted data were reviewed by the principal reviewer and discrepancies resolved by discussion. The number and age of enrolees, and dose and duration of treatment, were recorded. The main outcome was the efficacy of Cernilton vs placebo or control in improving urological symptom scores (e.g. the IPSS). The following secondary outcomes were also assessed: nocturia (times/evening); peak and mean urine flow; postvoid residual urine volume (PVR); and prostate size. One study used the Uroflow Index, a formula developed to examine urinary flow measurement based on maximum and mean flow [13]. The number of and reason for men withdrawing from the trial or being lost to follow-up were assessed, as were treatment-related side-effects.

The overall study quality was assessed according to the scale developed by Schulz *et*

al. [14]. The quality of the concealment of treatment allocation is assigned a score from 1 to 3, (1 for the poorest quality and 3 the best). Trials in which concealment was inadequate (e.g. alternation or reference to case-record numbers or to dates of birth) were given a score of 1. Trials in which the authors either did not report their approach to allocation concealment or reported an approach that did not fall into one of the other categories were given a score of 2. Trials deemed to have taken adequate measures to conceal allocation, e.g. central randomization, were scored as 3.

Statistical methods

Summary treatment effect sizes were determined for Cernilton vs placebo and vs pharmacological therapies. Weighted mean differences (WMDs) and their 95% CI were calculated [15]. Heterogeneity was assessed using a chi-squared test; if there was evidence of heterogeneity then a random-effects model was used. For continuous measurements, a difference between treatment means and its correlated se of the difference were calculated using the methods of Lau [16] and Laird [17]. To assess the percentage of patients having an improvement in urological symptoms a modified intention-to-treat analysis was conducted (i.e. men who withdrew or were lost to follow-up were considered to have had worsening symptoms) [18]. Chi-square tests were used to analyze bivariate comparisons.

Results

Four studies met the inclusion criteria from a total of six [19-24] identified through the combined search strategy. Two trials were excluded because they had no control groups [23,24]. The concealment of treatment allocation was rated as unclear in the four studies reviewed, although two indicated randomization [19,22]. Three trials reported using a double-blind method [19,20,22]. Two studies were placebo-controlled [19,20] and two were 'active controlled' trials. The 'active-controlled' trials included Tadenan, a phytotherapeutic extract from the African plum plant, *Pygeum africanum* [21], and Paraprost (Nikken Kagakusha, Japan), a pharmacological treatment for BPH used primarily in Japan, and containing 265 mg of l-glutamic acid, 100 mg of lalanine and 45 mg of aminoacetic acid [22].

A total of 444 participants were enrolled in the four trials (163 in the placebo-controlled and 281 in the 'active controlled' trials). Table 1 describes the participants, intervention, follow-up period, number of participants randomized, number who withdrew or were lost to follow-up, double-blind method status, and adverse effects. The mean (range) age of the enrolees was 69 (42-89) years and the duration of the trials was 12-24 weeks. The overall mean (range) rate of reported withdrawals or losses to follow-up was 6.3 (0-11.7%) (n = 28).

Table 1 The description of the individual studies

	Study			
Characteristic	*[19]*	*[20]*	*[21]*	*[22]*
Participants	Symptomatic BPH Stage II–III (Vahlensieck)	Men with BOO from	Men with BPH; assessed	Men with BPH; global
BPH; modified Boyarsky	using authors' symptom	physician assessment;		
PVR >150 mL	scale; flow rate ⩾150 mL/s; US estimate of PVR and prostate size	score; uroflowmetry; US of PVR and prostate size	symptom score (graded 0–3 for nocturia, dysuria, hesitancy, etc.) peak flow 10 mL/s (> 150 mL); PVR < 50 mL	
Mean (range) age (years)	66.6 (not reported)	68.6 (59–89)	? (50–68)	70 (54–68)
Intervention	1. Cernilton 2 caps × 3/day; 2. Placebo	1. Cernilton 2 caps × 2/day; 2. Placebo	1. Cernilton 2 caps × 3/day for 2 weeks then 1 cap × 3/day; 2. Tadenan 2 tabs × 2/day	1. Cernilton (63 mg) 2 caps × 2/day; Paraprost 6 g tab 2/day
Follow-up (weeks)	12	24	16	12
No. enrolled (withdrawals)	103 (7)	60 (7)	89 (0)	192 (14)*
Quality scale score†	2	2	2	2
Double-blind method	Yes	Yes	No	Yes
Adverse events	Mild nausea (1)	None	None	None

*Efficacy was studied in only 159 patients. †Bbased on Schulz *et al.* [14]. US, ultrasonography.

Table 2 The summary of the outcome data

	Study							
	[19]		[20]		[21]		[22]	
Mean (SD) variable‡	Cernilton	Control	Cernilton	Control	Cernilton	Control	Cernilton	Control
Symptom score or rating								
Baseline	–	–	'Overall improvement'		+ve response		11.5 (3.5)	11.4 (4.0)
Follow-up	–	–					5.2 (2.5)	4.3 (2.7)
Difference	–	–	69%	29%†	78%	55%*	−6.3	−7.1
Nocturia (times/night)								
Baseline			Improved		–	–	3.7 (0.5)	4.0 (0.8)
Follow-up	'Improved' or symptom-free				–	–	2.8 (0.6)	3.2 (1.1)
Difference	69%	37%†	60%	30%	–	–	−0.9	−0.8
Peak urinary flow rate (mL/s)								
Baseline	0.74 (0.27)	0.72 (0.34)	10.3 (5.2)	11.8 (6.4)	12.59 (3.0)	13.54 (3.2)	9.29 (4.99)	9.34 (4.86)
Follow-up	0.86 (0.25)	0.82 (0.31)	10.5 (5.1)	12.1 (5.1)	15.51 (4.3)	15.18 (4.5)	10.94 (5.09)	10.57 (4.82)
Difference	0.12	0.10	0.2	0.3	3.02	1.64	1.65	1.23
PVR (mL)								
Baseline	45.6 (30.4)	47.8 (32.8)	145.4 (107.5)	93.4 (91.4)	77.0 (15.7)	61.0 (14.1)	54.2 (78.84)	33.1 (40.06)
Follow-up	22.5 (20.9)	37.0 (28.9)	101.9 (87.3)	113.4 (87.3)	45.0 (21.0)	50.0 (15.8)	25.2 (28.22)	23.8 (28.59)
Difference	−23.1	−10.8*	−43.5	20.0*	−32.0	−11.0	−29.0	−9.26

*$P < 0.05$; †$P < 0.01$, otherwise not significant. ‡Except for the values in [20], which are mean (sem).

Table 2 shows the summary of outcome data for urological symptoms scores, nocturia, peak urinary flow rate and PVR. Three studies reported symptom scores or measured the symptom improvement, nocturia was reported in three, peak urinary flow rate in four studies and four provided information related to PVR. Differences in the control agents and methods of reporting results did not permit all studies to be combined in a quantitative meta-analysis. However, the results from all studies were consistent with an improvement in symptoms and urinary flow measures, as described below.

Mean differences in outcomes

Cernilton was comparable with both Paraprost and Tadenan in improving urological symptoms based on the IPSS (Paraprost) and two undefined symptom scales evaluating obstructive or irritative symptoms. For the IPSS, the mean (95% CI) difference (MD) was 0.90 (-0.43 to 2.23), with a percentage improvement from baseline of 55% for Cernilton and 62% for Paraprost [22]. For the trial comparing Cernilton with Tadenan, the MD for the obstructive scale score was -0.70 (-1.78 to 0.40; % improvement from baseline, Cernilton 63%, Tadenan 46%) and for the irritative scale -0.90 (-2.26 to 0.46; % improvement from baseline, Cernilton 68%, Tadenan 40%) [21].

Table 3 A comparison of Cernilton and placebo for nocturia and PVR in the two RCTs

	Study		
Variable	[19]	[20]	Total
Reported improvement in nocturia			
Cernilton (*n*/*N*)	33/48	17/31	50/79
Placebo (*n*/*N*)	16/48	7/26	23/74
Weight (%)	67.8	32.2	100
Relative risk (95% CI fixed)	2.06 (1.32–3.21)	2.04 (1.00–4.14)	2.05 (1.41–3.99)
PVR (mL)			
Cernilton (*n*)	48	28	76
Mean (SD)	22.5 (42.08)	101.9 (134.46)	–
Placebo (*n*)	48	24	72
Mean (SD)	37.0 (41.08)	113.4 (124.48)	–
Weight (%)	94.8	5.2	100
WMD (95% CI fixed)	−14.5 (−30.94 to 1.94)	−11.5 (−81.93 to 58.93)	−14.35 (−30.35 to 1.66)

Cernilton was better than placebo, Paraprost and Tadenan in the self-reported improvement of symptoms. The mean (95% CI) risk ratio (RR) vs placebo was 2.40 (1.21-4.75) (percentage of men reporting improvement, Cernilton 69%, placebo 29%) [20]. The RR vs Tadenan for a positive overall therapeutic response was 1.42 (1.21-4.75; % of patients who reported improvement, Cernilton 78%, Tadenan 55%). Cernilton reduced nocturia compared with the controls (Table 3; 30.8% absolute improvement) [19,20] and against Paraprost, the MD was -0.40 times per evening (-0.73 to -0.07).

Urinary flow measures were not significantly different between men treated with Cernilton and the placebo or active controls. The mean (95% CI) differences for peak urinary flow and the Uroflow Index were 1.60 (-5.77 to 2.59) mL/s and 0.04 (-0.11 to 0.19) mL/s, respectively [19,20]. Against Paraprost, the MD was 0.37 (-1.90 to 2.64) mL/s for peak urinary flow rate (4.6% absolute improvement) and 0.39 (-0.80 to 1.58) mL/s for the mean flow rate [22]. Against Tadenan, the MD was 0.33 (-2.00 to 2.66) mL/s (8.7% absolute improvement) [21].

Cernilton modestly reduced the PVR in the two placebo controlled studies (Table 3; 36.5% absolute improvement vs placebo) [19,20]. Cernilton was comparable with the control agents; the MD was -5.00 (-14.98 to 4.98) mL vs Tadenan and 1.40 (-20.00 to 22.80) mL vs Paraprost [21,22]. No significant differences in prostate size were evident when compared with Tadenan, with a MD of -2.09 (-10.21 to 7.97) mL, and Paraprost, with a MD of -1.12 (-10.21 to 7.97) mL. One placebo-controlled study, reporting changes for three variables (circumference, transverse diameter and anteroposterior diameter) of the prostate, found a 'statistically significant reduction in the anteroposterior diameter' after treatment with Cernilton [20].

Adverse effects

In the short-term, Cernilton was well tolerated; the only reported adverse effect associated with the use of Cernilton was one case of mild nausea [20]. Withdrawal rates were Cernilton 4.8%, placebo 2.7% and Paraprost 5.2% (P = 0.26 for Cernilton vs placebo and P = 0.33 vs Paraprost).

Discussion

This is the first systematic review summarizing the evidence from RCTs or CCTs about the efficacy and safety of Cernilton; the results suggest that Cernilton improved subjective symptoms and nocturia compared with placebo, Paraprost and Tadenan. Cernilton produced a similar response to the comparative study agents in improving urinary symptoms when evaluated by symptom scores. Only one adverse effect was reported, indicating that Cernilton was well tolerated; the withdrawal rate was <5%.

In contrast to the modest improvement in subjective symptom outcomes, Cernilton did not significantly improve objective measures such as peak and mean urinary flow rates when compared with placebo and the control study agents. Although Cernilton was analogous to Paraprost and Tadenan in improving peak flow rates and reducing PVR and prostate size, these results were limited by the lack of confirmed active controls to validate the comparisons.

Methodological issues

Although the results suggest that Cernilton provides modest benefit to men with BPH, the studies assessed for this review were limited by several factors. The concealment of treatment allocation was deemed unclear in all four trials and may be indicative of the questionable methodological quality of the studies meeting the inclusion criteria. Two of the studies reported random allocation with no detail of the method of concealment and three reported using a double-blind method. One trial did not report random allocation or a double-blind method [21]. Inadequate concealment of randomization and blinding are known to affect the sizes of the outcomes [25].

The treatment duration was short, with no studies lasting longer than 24 weeks. Cernilton dosages were not reported in three studies and whether a standardized preparation was used is also unknown. Additionally, fewer than 500 men were evaluated. Therefore, the long-term efficacy and safety of Cernilton, and its effectiveness in preventing complications of BPH such as acute urinary retention or the need for surgical interventions, is unknown. Only one study reported results from a standardized and validated urological symptom scale, the IPSS [22], although a modified Boyarsky Scale was

used in one [20], the others reporting various outcome variables. Therefore, the effect sizes should be interpreted with caution until future RCTs are conducted [26].

Such RCTs should be of sufficient size and duration to detect important differences in outcome, including urological symptom scale scores (e.g. the IPSS), mean and peak urine flow, voided volume, prostate size, PVR, and the development of acute urinary retention or need for surgical intervention. Studies are needed to compare Cernilton, α-blockers, 5α-reductase inhibitors and other phytotherapeutic agents, e.g. extracts of *Serenoa repens* (saw palmetto) [5,27]. Studies should also use standardized doses of Cernilton products that have been analyzed for purity and potency by an independent laboratory to ensure the quality of the product.

Additionally, cost-effectiveness studies should be conducted to evaluate the long-term cumulative costs associated with plant extracts, including the potential need for surgical intervention. The cost of a 90-day supply of Cernilton (three tablets/day, suggested use 2-4 tablets daily) is ≈US $40.00. In comparison, the cost of a 90-day supply of finasteride or terazosin (5 mg/day) is ≈$200 and $120, respectively. Alpha-blockers appear to be the preferred medical therapy for improving urological symptoms and urinary flow [28]. However, the costs of the initial medication may not reflect the total charges incurred for the treatment of BPH-related conditions. Finasteride has been shown to reduce the need for surgical intervention in about 6% of men who have large prostates and moderate to severe symptoms [29]. The comparative total cumulative costs of medical or surgical management alone, and a combination of medicine and surgery caused by any failure of the initial medical management (mixed therapies), has been shown to depend on the age of the patient at onset of therapy and the avoidance of mixed therapies [30]. Medical management (including phytotherapeutic agents such as Cernilton) in younger patients appears to be costly over time unless it can also reduce urinary retention or the need for surgery. In men with mild to moderate symptoms of BPH that do not interfere with lifestyle watchful waiting remains a good initial option [31].

In conclusion, additional randomized placebo and active-controlled studies are needed to evaluate the clinical effectiveness of Cernilton. Until the results of such studies are available, the present systematic review provides the most complete assessment of the efficacy and safety of Cernilton in the treatment of mild to moderate BPH. The available evidence suggests that Cernilton is well tolerated and modestly improves subjective urological symptoms. Cernilton was not shown to improve urinary flow measures compared with placebo. The long-term effectiveness and safety of Cernilton, and its ability to prevent complications from BPH, are unknown.

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Results of Treatment with Pollen Extract (Cernilton® N) in Chronic Prostatitis and Prostatodynia

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Summary— We report the results of a prospective study with the pollen extract, Cernilton® N, in a dose of 1 tablet *tid* for 6 months for the treatment of chronic prostatitis syndrome in 90 patients. The factors documented before and after 3 and 6 months' treatment were digital rectal examination (DRE) of the prostate, uroflowmetry, bacterial studies, leucocyte counts in urine and measurement of complement C3/coeruloplasmin in the seminal fluid.

The patients were divided into 2 groups: those without associated complicating factors (CFs) (n=72) and those with complicating factors, i.e. urethral strictures, prostatic calculi, bladder neck sclerosis (n=18). In the group without CFs, 56 (78%) had a favourable response; 26 (36%) were cured of their symptoms and signs and 30 (42%) improved significantly with an increase in flow rate, a reduction in leukocyturia in post-prostate massage urine (VB3) and a decrease in complement C3/coeruloplasmin in the ejaculate. In the patients with CFs only 1 patient showed a response. Complicating factors should be considered in patients who fail to respond to treatment within 3 months. Cernilton® N was well tolerated by 97% of patients.

Controversy surrounds the aetigology and clinical significance of the painful prostate and the diagnosis of chronic prostatitis and prostatodynia is seldom based on sound diagnostic criteria (Drach, 1980). Even when the diagnosis of chronic bacterial or non-bacterial prostatitis and prostatodynia has been reached, the results of treatment are ofter disappointing (Pfau, 1986).

Clinical studies with the pollen extract, Cernilton® N (A.B. Cernelle, Sweden), have revealed symptomatic improvement in prostatic inflammatory disease and benign prostatic hyperplasia (Denis, 1966; Ebeling, 1986; Becker and Ebeling, 1988, 1991; Buck *et. al.,* 1989, 1990). We present the results of a prospective study on the efficacy of Cernilton® N in the treatment of chronic non-bacterial prostatitis and prostatodynia.

Patients and Methods

Ninety patients aged from 19 to 90 years (mean 47.2±SD 17.6) with symptoms of prostatitis of at least 1 year's duration, in whom bacterial localization studies were negative, were entered into the study. Thirty patients had had at least 2 previous episodes of bacterial prostatitis and/or urinary tract infection treated with antibiotics, but were entered into the study during an infection-free period.

The diagnosis was based upon bacterial localization studies of pre- and post-massage urine samples and expressed prostatic secretion (EPS) (Meares and Stamey, 1968). Leucocyte counts in the sediment from the first voided 10 ml of urine (VB1), mid-stream urine (VB2) and first voided 10 ml of after massage (VB3) were performed using a counting chamber and calculating the number of leucocytes/µl (MD-Kova-system®) Sieck, 1983).

Additional investigation (ultrasonography, voiding and/or retrograde cystourethrography and endoscopy) revealed other pathology in 18 patients. These complicating factors were bladder neck sclerosis (10), urethral strictures (5) and extensive prostatic calcification (3). Eight patients had undergone a previous transurethral or open prostatectomy (7 for benign prostatic hyperplasia (BPH) and 1 for chronic prostatitis).

Forty-four patients (49%) had received treatment with various drugs, including antibiotics, anti-inflammatory agents and other empirical remedies, during the 3 months prior to entering the trial; 37 patients had improved.

Cernilton® N (Pharma Stroschein (liscensed by Cernitin SA, Lugano, Switzerland; Hamburg, Germany) was given in a dose of 1 tablet *tid* and in most cases treatment was continued for 6 months. The following factors were recorded before treatment and after 3 and 6 months' therapy: (i) symptoms of discomfort and pain were graded as absent, mild, moderate and severe; (ii) nocturia, frequency and dysuria were scored according to Boyarsky *et al.* (1977); (iii) the findings of rectal palpitation of the prostate; (iv) uroflowmetry; (v) leucocyturia in VB2 and VB3; (vi) bacteriuria; (vii) complement C3 and coeruloplasmin in the ejaculate (scored semi-quantitatively combining the values of complement C3/coeruloplasmin/dl according to a modified scheme of Blenk and Hofstetter (1975) as follows; 1 =<1.5 mg/negative; 2=1.5-<2 mg/ <0.5 mg; 3=2-4 mg/ 0.5-1 mg; 4=3-8 mg/>1-3 mg).

Complement C3 and coeruloplasmin were determined after the ejaculate had been liquefied and centrifuged for 5 min at 11,266 U/min resp. at 10,500 g. The radial immunodiffusion of the supernatant sample was performed with LC-Partigen® C 3c and LC-Partigen® plates (Behringwerke AG, Marburg, Germany). In addition to the sample, a control from calibrated standard serum was placed on the plates (dilution 1:20 for complement C3, dilution 1:11 for coeruloplasmin). The amount of complement C3 and coeruloplasmin was calculated from the diameter of the samle precipitate according to the calibration curve from calibrated standard serum of complement C3 and coeruloplasmin (Behringwerke AG, Marburg, Germany).

A "cure" was defined as a complete response with a return to normal of all factors, an "improvement" as a partial symptomatic and objective response and "no improvement" as persistence of symptoms or signs or deterioration. The biometrical evaluation was performed by descriptive analysis of the factors before and after treatment as well as a comparison of changes at 3 months and 6 months. The following tests were used: (i) the *t* test for related samples for a comparison of uroflow measurements; (ii) the Wilcoxon matched-pairs signed-rank test using chi^2 approximation for comparison of the leucocytes in VB3; (iii) the sign test for the scored complement C3/coeruloplasmin in the ejaculate; (iv) the Pawlik corrected contingency coefficient for qualitative and the Spearman rank correlation coefficient for quantitative correspondence between the changes of leucocyturia in VB3 and the peak urine flow rate.

Results

At the commencement of the study the patients' clinical symptoms were maily moderate or mild; the prostate was enlarged in 56% and tender in 94%. On the basis of significant differences at initial presentation and the response to treatment the patients were separated into 2 groups: those without (n=72) and those with (n=18) complicating factors. Complement C3 in the ejaculate was >1.5 mg/dl in all cases.

Symptoms

Almost all of the patients complained of frequency and dysuria, while pain was present in about two-thirds. Patients with associated CFs responded poorly to treatment, whereas in those without CFs the symptoms were markedly reduced after 6 months' treatment (Table 1).

In patients without CFs the prostate reverted to a normal size in 15/39 cases; its consistency improved in 37/68 cases and it was no longer tender on palpation in 47/71 cases after treatment. These signs worsened in 5 patients. The findings on palpation of the prostate in the group with associated CFs were either unchanged or had deteriorated.

Table 1 Response to Treatment in 72 Patients without Complicating Factors

Symptom	*Cured (%)*	*Improved (%)*	*No.*
Discomfort	68	9	53
Pain	69	12	49
Nocturia	56	30	54
Frequency	49	26	72
Dysuria	52	12	69

Uroflowmetry

In contrast to the patients with CFs, where all uroflow parameters became worse, there was a significant improvement in the time to peak flow and increased voided volume in the patients without CFs (P<0.05). Micturition and flow time remained unchanged. In patients with CFs the peak urine flow rate showed a slight decrease from 11.9±3.9 to 10.5±2.6 ($\bar{x}$±SD). In patients without CFs the mean peak flow rate before treatment was 15.9±SD 5.2 ml/s; this increased to 19.0±SD 7.2 ml/s at 3 months (P<0.001) and to 23.9±SD 10.6 ml/s at 6 months (P<0.001; comparing 6 with 3 months: P<0.001).

Leucocyturia in VB3 (L-VB3)

In patients with CFs the L-VB3 increased from a median of 80 to 185 leucocytes/µl (P<0.001). Comparing the number of leucocytes before and after treatment in patients without CFs the L-VB3 decreased from a median of 50 to 20 leucocytes/µl (P<0.001). In these patients the pre-treatment mean leucocyte count fell from 85±SD 89.9 leucocytes/µl to 69.1±SD 121.8 at 3 months and to 42.2±SD 62.6 leucocytes/µl at 6 months (control vs 3 vs 6 months P<0.001; comparing 6 with 3 months: P<0.001). The individual changes documented separately as pre and post values at different baseline levels of leucocyturia, *i.e.* <50, 50-99, 100-1000 leucocytes/µl, are shown in Figure 1.

L-VB3 and PUFR (peak urine flow rate)

Correlation of the changes in L-VB3 with the PUFR in patients without CFs showed that the leucocyte count decreased in 52 cases while the PUFR increased, but the PUFR fell in 3 patients. An increase in L-VB3 occurred together with a decrease in PUFR in 8 cases and an increase in PUFR in 9 cases. There was a highly significant negative correlation between L-VB3 and PUFR (CC corr= 0.720; r= -0.56). Because of the wide distribution pattern of the leucocytes in VB3, individual differences between the baseline values and the control after treatment were ranked separately for L-VB3 and PUFR according to the definition of rank 1 as the strongest increase plotted as the combined ranks of the individual changes for both parameters (Fig.2).

Complement C3/coeruloplsmin

Patients without CFs showed a decrease in complement C3/coeruloplasmin in the ejaculate after 3 months (P<0.001) and a further decrease after 6 months (P<0.001; comparing 6 with 3 months: P=0.005). Patients with CFs showed an increase in these indices of inflammation (P=0.07) (Table 2).

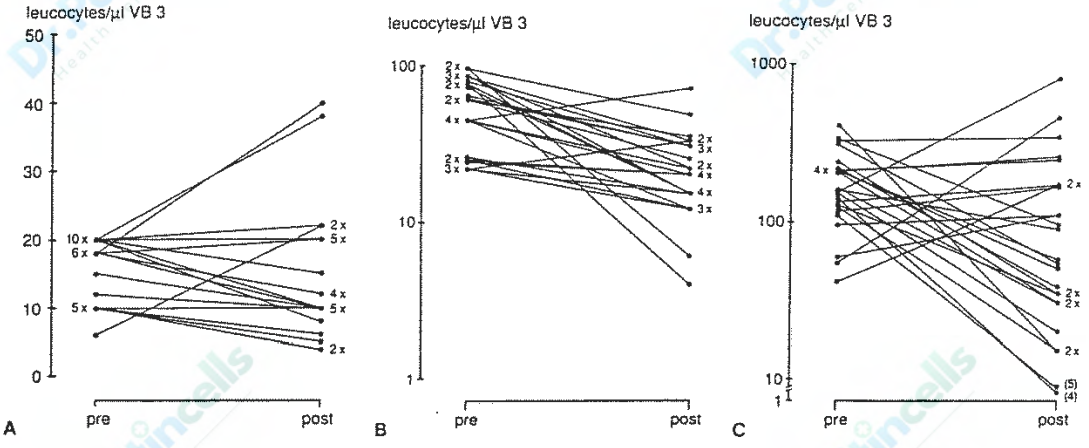

Fig. 1 Individual courses of leucocyturia in VB3 in 72 patients without complicating factors, plotted separately according to baseline values (pre: < 50, 50–99, 100–1000 leucocytes/µl) or control (post) values. The numbers on the left and right sides of the lines refer to the number of patients with the corresponding baseline or post-treatment value, *e.g.* 10 × in Figure 1A represents 10 patients with the same baseline value of 20 leucocytes/µl VB3. The numbers (5) and (4) in Figure 1C represent the post-treatment values of leucocytes/µl VB3 in 2 patients which are not assessable from the Figure owing to the broken axis of ordinate.

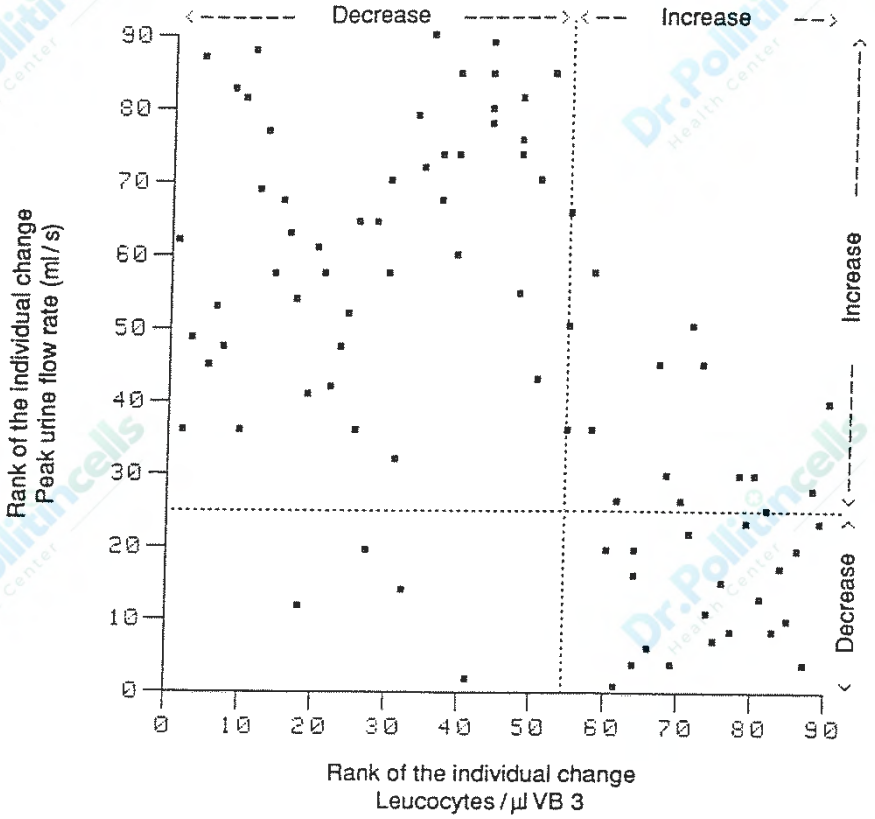

Fig. 2 Scattergram of the combined ranked individual changes in leucocyturia in VB3 (L-VB3) and peak urine flow rate (PUFR) in 90 patients with chronic prostatitis syndrome comparing the values before and after treatment. High inverse qualitative ($CC_{corr} = 0.720$) and quantitative ($r_s = 0.565$) correlation between the changes of L-VB3 and PUFR. Rank 1 = strongest decrease, rank 90 = strongest increase, parallel lines to ordinates = no change (conversion point).

Table 2 Complement C3/coeruloplasmin/dl Ejaculate before and after 3 ($P < 0.001$) resp. 6 Months ($P < 0.001$; $P = 0.005$ comparing 6 with 3 months) of Treatment in Patients without Complicating Factors and before and after Treatment in Patients with Complicating Factors (CF) ($P = 0.07$)

	No CF			*With CF*	
Complement C3/coeruloplasmin	*Pre* *No.*	*3 months* *No.*	*6 months* *No.*	*Pre* *No.*	*Post* *No.*
< 1.5 mg/negative	—	3	11	—	—
1.5–< 2.0 mg/< 0.5 mg	8	36	40	4	—
2.0–< 4.0 mg/< 0.5–1 mg	46	30	13	11	9
3.0–< 8.0 mg/< 1–3 mg	17	2	5	1	7
Missing values	1	1	3	2	2

Assessment of efficacy

There was an overall clinical response in 56/72 patients (78%) without CFs; 26 of these (36%) were cured of symptoms and signs and the remainder (42%) were improved. In 16 patients (22%) there was no response. In patients with CFs only 1 improved and the remaining 17 showed no response. Treatment was discontinued in 12 paitents because of an ineffective response or clinical deterioration. The most frequent cause of deterioration was symptomatic bacteriuria (83%) and these

patients were treated with antibacterial therapy. CFs were present in 67% of all patients in whom treatment was discontinued.

Treatment was well tolerated by 97% of patients. Three complained of a mild to moderate degree of meteorism, heartburn or nausea which did not require discontinuation of treatment.

Discussion

Cernilton® N was found to be effective in the treatment of patients with chronic non-bacterial prostatitis and prostatodynia. Patients with complicating factors due to incidental lower urinary tract pathology (e.g. bladder neck sclerosis, urethral stricture or extensive prostatic calcification) failed to respond and a high percentage of these developed bacteriuria.

Complement C3 in the ejaculate is regarded as an extremely sensitive index of an inflammatory process in the prostate or adnexae (Blenk and Hofstetter, 1991), even in patients with minor and/ or focal pathological changes within the gland that do not necessarily lead to an increase in the number of leucocytes in the expressed prostatic secretion or the VB3. Comparison of the baseline values of complement C3/coeruloplasmin and L-VB3 showed a high concentration of complement C3 in the ejaculate even in patients with a low leucocyte count in VB3 (i.e. prostatodynia). The decline in the complement C3/coeruloplasmin values with pollen extract in these patients suggests that inflammation of oedema may also be a feature of prostatodynia (di Trapani et al., 1988; Vahlensieck and Dworak, 1988).

Barbalias (1992) reported an increase in the maximum urethral closure pressure (MUCP) in patients with the prostatitis syndrome resulting in a simultaneous diminution in urinary flow rates. It is suggested that local inflammation may irritate adrenergic endings and cause a high MUCP. Our finding of an inverse correlation between inflammation and uroflow supports this hypothesis and the decrease in complement C3 leads us to speculate that local irritation may also be responsible in patients with prostatodynia. Takeuchi et al. (1981) reported a significant decrease in the MUCP from 92±SD 23 to 58±SD 19 cm H_2O with a reduction in the prostatic profile length and prostatic urethral resistance with pollen extract in patients with BPH. The concluded that this finding may be related to the eradication of oedema and inflammation in the periurethral area.

Cernilton® N is an extract from several pollens. Its pharmacological action could be ascribed to inhibition of the cyclo-oxygenase and 5-lipoxygenase enzyme in the biosynthesis of prostaglandins and leucotrienes as demonstrated by the *in vitro* studies of Loschen and Ebeling (1991). A dose-related inhibition of noradrenaline-induced contractions of the rat and mouse urethra with pollen extract has been observed (Kimura et al., 1986; Nakase et al., 1988). In addition, extract of pollen was shown to inhibit the growth of the rat prostate and immortal prostate cancer cell lines in culture (Ito et al., 1986; habib et al., 1990). From this broad spectrum of pharmacodynamic activity it is difficult at the present time to define a precise mode of action.

This study has shown a progressive improvement in the clinical course of patients with chronic prostatitis and prostatodynia over a 6-month period. This confirms the observation of Buck et al. (1989) that a 3-month period treatment with pollen extract is required before significant improvement occurs. This favourable response indicates that Cernilton® N has an important therapeutic role in the treatment of these conditions. Futher studies are necessary to elucidate its precise mode of action.

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Regulation of Prostate Growth in Culture with the Pollen Extract, Cernilton T-60, and the Impact of the Drug on the EGF Tissue Profiles

F.K. Habib

Introduction

A major difference between the prostate and other accessory reproductive glands is the susceptibility of the prostate to hyperplasia in again men. Indeed, benign hyperplasia of the prostate (BPH) affects most males over 60 years of age and causes enlargement of the inner gland. When the urethra becomes constricted, treatment is required to relieve the kidney and circulation system of the damaging effects of back pressure.

Surgery in the form of transurethral resection still remains the “gold standard” for the treatment of outflow tract obstruction (1) but recently attention has also focused on alternative forms of therapy, namely hormonal (2, 16), 5α-reeducates inhibitors (11), and α-adrenergic blockers (5). However, the long-term prognosis for medical treatment has been poor and many of the endocrine and pharmacological agents presently in use have side effects (4). This has prompted the medical and scientific community to consider new lines of treatment of BPH. One recent development was sudden and unexpected interest in phytotherapy, which was in part instigated by the encouraging results and the undoubted beneficial effects of the pollen extract, Cernilton, in the symptomatic relief of BPH (1).

The mechanism by which the pollen induces its effect on the hyperplastic prostate is not yet clear even though extensive experimentation has been undertaken by many workers (8, 9, 10). Notably however, the bulk of the earlier research was focussed on experiements with animal tissue, which constitutes an unsatisfactory model for the human gland. Additionally, the few studies on the human prostate were carried out either on whole organ homogenates or on prostate epithelical cell lines (8), both of which ignore the potential heterogeneity of the cellular activity within the gland and the importance of stroma / epithelial interactions. Futhermore, the immortal cell lines represent a highly selective cell population which might have undergone phenotypic changes and may therefore be distinctive from the cells of orgin.

In attempt to overcome these earlier limitations, efforts in our laboratory have been directed towards developing primary culture of the human prostate and the serial culture of epithelial and fibroblast cells from BPH employing defined media. Initially, progress was slow and attempts to find the optimal concentration of ingredient to permit the growth of the cells and increase their plating efficieny were repeatedly frustrated. However, thanks to our collaboration with Dr. D. *Chaproniere,* to whom much of the credit for the earlier work goes (3), combined with the perseverance of the chief tissue culturist, Mrs. *Margaret Ross,* we managed to overcome many of the initial obstacles and finally establish a reliable technique for the serial culture of both prostate stroma and epithelial cells in serum-free medium (manuscript in preparation). This model was subsequently adapted to our Cernilton studies in which the experiements were confirned to the water-soluble Cernitin T-60 fraction; this fraction accounts for approximately 60% of the pollen extract. Detail of the procedures followed and summary of our findings on the characterization of the cultured cells along with the impact of the Cernitin T-60 are described within.

This chapter also includes some preliminary data on growth factor profiles in prostate tissue specimen and in expressed prostate secretions (EPS) obtained from a group of BPH patients

receiving the pollen extract. The relevance of growth factors peptides and particularly epidermal growth factor (EGF) to the prostate stems from their ability to maintain and regulate prostat growth either by acting in tandem with androgens or possbiliy even by by-passing the steroid hormomes and imprinting their own characteristics on the gland (7, 12). Recent reports on the preferential accumulation of EGF in BPH when compared to normal prostate tissue (6, 14) supports the belief that this peptide might be implicated in the pathogenesis of this condition. Since the action of Cernilton in the prostate has been found not to be mediated via the androgen delivery system of the cell (8), we are now looking at the possibility of an association between the expression of some of these growth factors and their response to Cernilton in patients receiving the drug.

Serial Culture of Prostate Epithelial and Fibroblast Cells

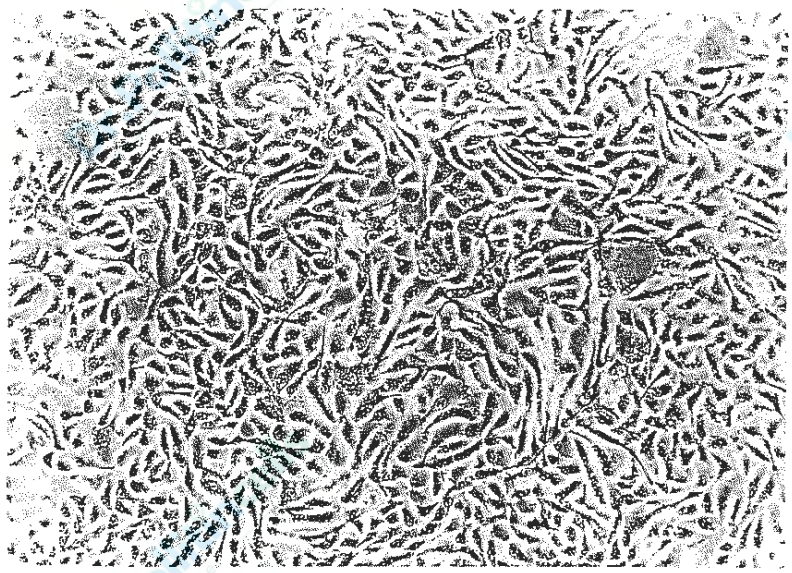
BPH specimens obtained by transurethral resection were transported under sterile conditions to the laboratory in transport medium. Acini and fibroblast cells were released from prostate tissue by collagenase digestion and primary and sub-cultures were grown by plating onto plastic culture flasks and incubating at 37°C in a 95% air-5% CO_2 humidified atmosphere. By using this sytem it was possible to establish and serially culture pure populations of both epithelial (Fig **1a**) and fibroblasts (Fib **1b**) cells in well-defined media. For epithelial cells the WAJC404 medium (3) was serum free and was supplemented with insuling (2.5µg / ml), EGF (10 ng / ml), dexamethasone (1µM), and choleratoxin (10µg / ml); this medium selects against the growth of the fibroblast cells. Four days after inculation of the epithelial cells onton T-75 flasks, the acini demonstrated good spread, and confluence was usually reached by day five. Fibroblast cells were maintained in RPMI1640 supplemented with fetal calf serum (10%) and penicillin and streptomycin (10µg / ml each). Fibroblast cells were initially slow in growing and confluence was reach usually after ten days.

Verification of the culture as prostatic fibroblast and epithelial cells is accomplished by immunocytochemical staining employing a variety of antiobodies including those for vimentin, desmin, prostatic-specific antigen (PSA), prostatic acid phosphatase (PAP), and cytokeratin. Assessment of the staining patterns and their intensities was always undertaken by an independent pathologist. A typlical pattern of the staining profiles obtained is illustrated in Table **1**.

In addition to the immunostaining (Table **1**), the cells were also examined by phase contrast microscopy. Analysis of the photomicrographs (Figs. **1a** and **1b**) suggest that the resultant epithelial monolayers contain very little or no contaminants – any residual fibroblasts will be totally destroying by the epithelial growth medium. Futhermore, the bulk of the epithelial cells appear to be of a secretory nature since PAP and PSA are strongly expressed (Table **1**). The epithelial cells also stain uniformly for cytokeratin and recognize the antibody for the epidermal growth factor receptor. This confirms our earlier findings on the presence of EGF-receptors in epithelial cells of human prostate tissue (14).

In contrast, the fibroblast cells failed to stain for PAP and PSA but were positively labeled by antibodies for vimentin and desmin. Somewhat surpisingly, the fibroblast cells were also outlined by the antibodies for cytokeratin and for Human Milk Fat Globulin (HMFG), which are exclusively epithelial in nature. This raises the possilbity that the fibroblast cells might contain small contaminats of a secondary cell. Closer examination of those fibroblastic cells by microscopy highlights the presence of small numbers of epithelial-like cells amongst the stromal monolayers. The secondary cells could be either non-secretory epithelial or endothelial cells which maintain an ,,epithelioid”-like appearance, but this needs to be confirmed. The presence of the fibroblast contaminants was also confirmed by flow cytometry and we are at present attempting to segregate the two cell populations employing a cell sorter. Interestingly, however, the “epithelioid”-like material appears not to multiply but remains constant throughout each passage and might merely act as a supportive matrix for the fibroblast.

a



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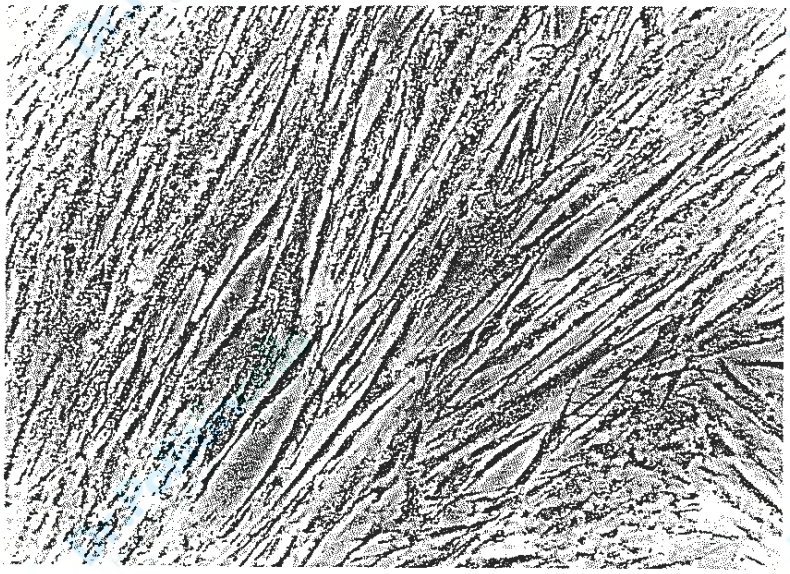

Fig. 1 Phase-contrast micrograph of a primary culture of epithelium (1 a; × 100) and a serial culture of fibroblast (1 b; × 200) from a patient with benign prostatic hyperplasia.

Markers used	Fibroblast cells	Epithelial cells
Prostatic acid phosphatase	–	++
Prostatic specific antigen	–	++
Epidermal growth factor receptor	–/+	++
Cytokeratin	–/+	++
Vimentin	++	–/+
Desmin	+	–
HMFG (Human Milk Fat Globulin)	–/+	++

Intensity of staining: (++) strongly positive; (+) moderately positive; (–/+) patchy; (–) negative.

Tab. 1 Immunocytochemical Staining of Epithelial and Fibroblast Cells in Culture.

The Effect of T-60 on Epithelial and Stromal Cell Growth in vitro

Dose response curves of Cernitin T-60 treatment were determined using the following method: triplicate determinations for each treatment were performed in 96 well culture plates; each well was seeded with 2.5 x 10^4 cells and incubated overnight at 37°C in the medium under defined incubation conditions. The following day, the Cernitin T-60 stock solution was serially diluted in the defined medium to yield a concentration varying from 0.05-1mg / ml. Controlled cultures received culture medium alone. For the dose response curve studies, the cells were exposed to Cernitin T-60 for a total period up to 4 days with changes of freshly diluted T-60 in medium every 2 days. For the time course study, cells were treated in the presence and absence of T-60 a total period of 7 days. After the incubation periods, the cells were pulse-labelled with radiolabelled thymidine whilst remaining in the defined medium for a further 24 hours.

For the determination of the rate of the DNA synthesis the cells were trypsinized and 10% ice cold tricholoacetic acid was added for 2 hours. The cells were subsequently harvested onto filter mats, dried at 60°C for 30 minutes and each disc of filter paper containing the precipitable material was then counted in scintillation fluid. The results illustrated in Fig **2** (fibroblast cells) and Fig. **3** (epithelial cells) are expressed as the percentage of ^{3}H-thymidine incorporated relative to the untreated control. These demonstrate that the effect of Cernitin T-60 on stroma and epithelial cells is biphasic: initially and at the low concentrations of T-60 (up to approximately 0.1 mg / ml) we detect significant stimulation, particularly in the fibroblast cells which show after 2 days of exposure an increase of appromately 75% in DNA synthesis. However, exposure to higher concentrations of the T-60 inhibits the uptake of thymidine and after 3-4 days exposure we do find that the concentrations of T-60 (P > 0.25 mg / ml) almost totally inhibit the fibroblast growth.

Although the epithelial cells do also show an inhibition in cell growth which is time-and concentration-dependent, it appears that the epithelial cells are slightly more resistant to the pollen extract than the fibroblast cells. Though there is initially a minute stimulation in the DNA synthesis of up to 25% after 2 days of exposure (results not shown), this is rapidly reserved, and inhibition is observed at approximately the same concentrations of T-60 as those required to induce the same effect with the fibroblast but following longer periods of response to the Cernitin T-60 (Fig. **3**).

EGF Concentrations in Prostate Tissue and Prostate Secretions following Cernitin Treatment

Prostate tissue was obtained at the time of transurethral resection from 19 patients with the BPH; the patients had been enterend into a Cernilton double-blind placebo-controlled study over a six-month period. The tissue was transported immediately to the laboratory in iced saline, dry blotted, snap-frozen in liquid nitrogen and stored at -70°C until analysis. Matching expressed prostatic secretions (EPS) were collected by transrectal massage before the commencement of the trial and at approximatelty three-month intervals with the last specimen obtained immediately prior to transurethral resection whilst the patient was under either regional or general anesthesia. The fluid was collected into 1-ml insulin syringes, frozen without delay, and stored at -70°C until needed.

Studies on EPS Specimens

Pre- and post-treatment samples of EPS were obtained from 8 patients in the Cernilton treatment group and 5 patients in the placebo group; the mean length of treatment with Cernilton was 147 ± 42 days. A comparison of EGF concentrations in both group before commencement of treatment revealed to significant difference (P > 0.5; Fig. **4**). Similarly, comparison of the EGF concentrations in samples before and after treatment also showed no significant difference (P > 0.5); these data are illustrated in Fig. **4**. In addition we have also examined the changes in EGF concentrations of consecutive samples of EPS from individual participants in the double-blind placebo-controlled study; the patterns obtained are illustrated in Fig. **5**. Clearly, there are no consistent patterns of change which could be of use for monitoring response to treatment.

Studies on Prostate Tissue

In addition to the measurements undertaken on EPS, we have also measured the ECG

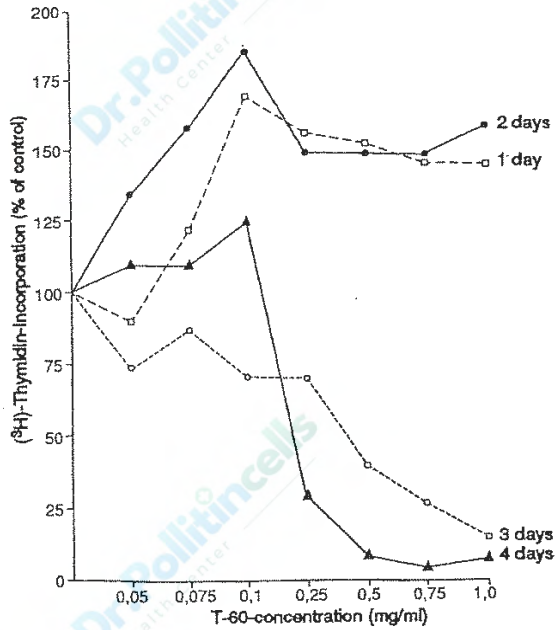

Fig. 2 Effect of T-60 concentration on fibroblast cell survival. Fibroblast cells (2.5×10^4 cells/well) were plated overnight in 96 well plates. Increasing concentrations of T-60 were added for varying times. (^{3}H)-thymidine was then added for 24 hours and the cells were trypsinized in 10 % TCA. The cells were then harvested onto filter mats, dried and counted in scintillation fluid. The data is normalized relative to the untreated control (100 %).

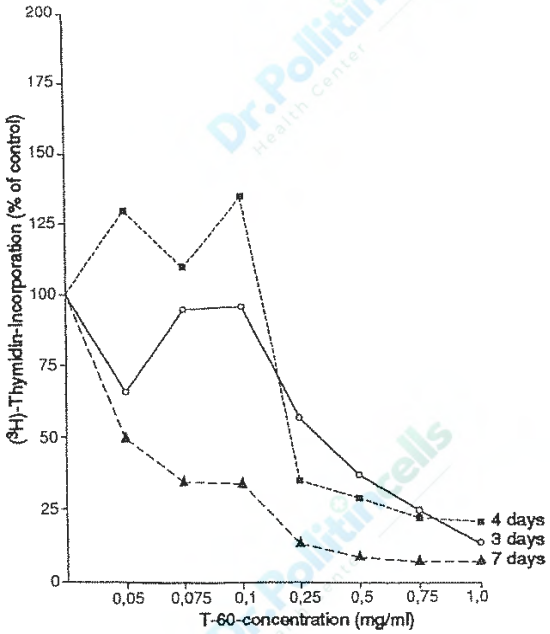

Fig. 3 Effect of T-60 concentration on epithelial cell survival. Details were identical to those followed for the fibroblast cells as detailed in legend to Fig. **2**.

concentrations in prostate tissue obtained from 15 BPH patients undergoing prostatectomy. These were compared to the concentrations found in a parallel group of 7 patients who were taking Cernilton as part of the double-blind placebo-controlled study. The data was expressed as ng EGF / mg protein in the tissue and the results obtained for the individual patients are outlined in Table **2**. Although the levels of EGF in the treated group appeard to be considerably lower than those measured in the controlled group, the difference is not statistically different. However, it should be noted that the population receiving the Cernilton tablet is comparatively small and the results obtained might have been slightly biased by the fact that 2 out of 7 patients showed relatively high concentrations of EGF whereas the remainder of the population had levels considerably lower than those measured in any of the other individuals in the controlled group. We are at present extending this study to incorporate a further 20 patients on the drug in the hope that this might show some light no the mechanism of action of Cernilton and whether the differences between the control and test groups are genuine and reflect actual changes in the metabolic pathways of the gland following treatment with the pollen extract.

Conclusion

The precise mode of action of Cernilton in BPH is not clearly understood even though many studies have been undertaken to elucidate the mechanism by with this pollen extract promotes

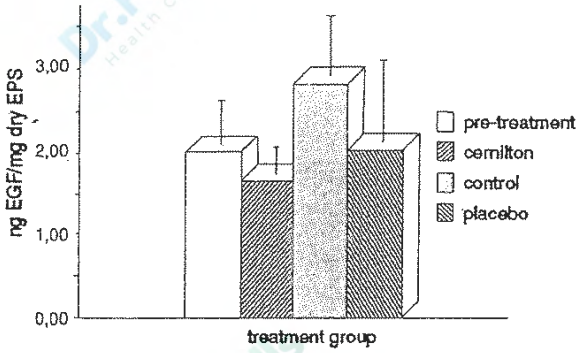

Fig. 4 EGF concentrations in expressed prostate fluid (EPS). Aliquots of EPS were taken from a group of patients who had entered the double-blind placebo trial of Cernilton, and EGF was measured in samples taken at the start and towards the end of the trial. The concentrations in the treated group were compared to those on placebo. Results are expressed as mean ± SEM for 8 patients in the treated group and 5 patients on placebo. Bars show SEM.

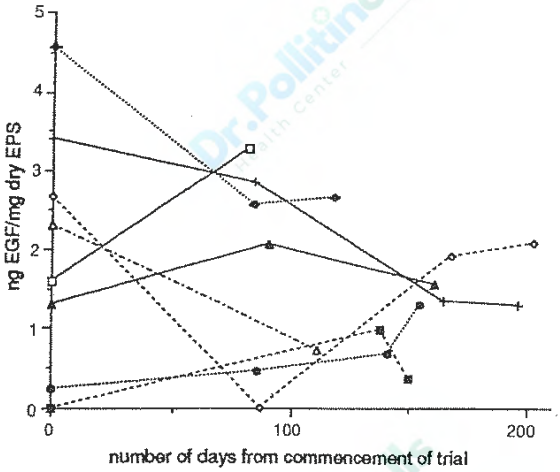

Fig. 5 EGF concentrations in consecutive EPS specimens taken from patients receiving Cernilton. For each patient EPS specimens were obtained before commencement of treatment and then at approximately 3 and 6 months into the trial.

symptomatic relief in patients with BPH. The earlier studies concentrated mainly on animal models and as reported by *Ito* et al. (9), Cernilton produced in mature Wistar rats a significant reduction in the size of the prostate as well as in PAP concentrations whilst also inducing a parallel increase in blood and tissue zinc concentrations. Additionally, Cernitin T-60 produced relaxtion of the smooth muscle of the mouse and increased the contraction of the bladder muscle in a concentration-dependent manner (10).

In view, however, of the specie differences in prostate anatomy and function, a fundamental distinction must be made between animal studies and experiements on human tissue. The attentions of this laboratory were therefore focused initially on the immortal human prostate cell lines which demonstrated an inhibitory response following treatment with Cernitin T-60 (7). Interestingly, the inhibitory effect was far more marked in the hormone unresponsice cell line when compared to the androgren-sensitive human prostate cells. Human prostate cell lines derived from non-prostatic tissue failed to exhibit a similar sensitivity to the pollen-extract (7).

Although the usage of immortal cell lines in our earlier studies was most helpful in dentifying the specificity and selectivity of the drug, their use is somewhat limited because of: (a) the cancer nature of the continuous cells whilst Cernilton is prescribed purely for BPH; (b) immortal cells are identical clones and do not therefore take account of the morphological heterogeneity of the prostate; and (c) continuous cell lines may undergo phenotypic changes and this might render them distinctive from the cells of origin. In view of these limitations we have decided to continue our work on Cerntin T-60 employing the well-established cultures of epithelial and fibroblast cells from human hyperplastic prostats (3, 15). Those studies were facilitated by our ability to establish and serially culture pure populations of epithelial and fibroblast cells in a well-defined serum-free medium. By using this system the specifc characteristics of Cernitin T-60 could be assessed in a cohesive and systematic fashion.

Clearly, the data outlined in this report indicates that Cernitin T-60 is a powerful mitogenic inhibitor of fibroblastic and epithelial

Control group	EGF concentration	Cernilton Group	EGF concentration
J. W.	1.50	W. F.	3.45
J. G.	1.35	C. F.	2.43
J. N.	2.09	C. S.	1.51
D. D.	1.61	K. B.	0.45
G. T.	2.07	A. S.	0.31
H. H.	1.20	T. S.	1.10
R. H.	2.84	R. H.	0.89
A. C.	3.98		
W. T.	3.67		
W. B.	4.38		
W. H.	1.50		
K. H.	3.40		
H. J.	2.57		
K. N.	3.00		
T. S.	1.76		
hEGF-Concentrations (µg EGF/mg Protein)			
Mean± S.D.	2.39 ± 0.85		1.45 ± 1.31

proliferation. Although the mechanism involved is not as yet understood, we have evidence derived from our earlier studies (8) to indicate that these responses are not medicated via the androgenic pathways. We have therefore decieded to look at the impact of Cernitin T-60 on the expression of growth factors which have been implicated in the growth of the prostate cells. Though the results on the prostate fluid indicate little difference in EGF concentrations between the control and test groups, the evidence derived in this report suggests that there might be some impact on the epidermal growth factor concentration of the tissue.

EGF is a well-established secretory product of the prostate and is retained in large concentrations by BPH when compared to the normal gland (6). This retention might be associated with the high concentrations of the EGF receptors found BPH which must sequester the growth factor for internal use (14). We are not too clear on the mechanism responsible for this build-up of EGF receptors and whether it is a causal factor or merely a result of the development of hyperplasia. We are also not cerntain whether there is an association between these abnormal growth factor concentrations and the dihydrotestosterone levels which have previously been linked to the growth of the gland (17). Significantly however, our most recent studies reveal no correlation between EGF recpetors and the endocrine status of the gland, suggesting that androgens do not modulate EGF-receptor expression in the prostate (13). Since the action of Cernilton on the prostate seems also to be independent of the endocrine functions of the gland, the impact of the pollen exract on the tissue EGF concentrations might be of significant importance, not only in controlling the abnormal growth of the gland but also in pinpointing new pathways relating to the pathogenesis of BPH.

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Usefulness of Cernilton in the treatment of benign prostatic hyperplasia

Int Urol Nephrol 1996; 28(1):49-53

Dutkiewicz S

A total of 89 patients with benign prostatic hyperplasia (BPH) were treated pharmacologically for 4 months: 51 received Cernilton and 38 Tadenan (controls). Significant subjective improvement was found in 78% of the patients in the Cernilton group compared to only 55% of the Tadenan-treated patients. The obstructive and irritative symptoms responded best to the therapy. In the Cernilton-treated patients a significant improvement in the uroflow rate, decrease in residual urine and in prostate volume were found. This study shows that Cernilton is an effective therapy for patients with BPH.

Diagnosis and Treatment of Chronic Prostatitis

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Introduction

Chronic prostatitis is one of genital disease frequently occurring in grown-up men, but its diagnosis is in many cases difficult, if it may seem easy at a glance. At present there is no proper therapy for chronic prostatitis, although marked results are now obtainable in acute cases thanks to the recent development in chemotherapeutics.

The present report concerns the author's experience with CERNILTON, a pollen preparation produced by AB Cernelle. Diagnosis and treatment of this disease are also dealt with.

Diagnosis

In chronic prostatitis complaints of patients are diverse. Thus, often the disease is erroneously diagnosed as chronic cystitis, prostatomegaly, neurogenic cystitis, etc. Leader describes that chronic prostatitis is a stagnant uninfectious lesion resulting from an inflammation in the past. However, in many cases organisms are not detectable or, if detected, cannot be precisely related to the disease. Moreover, there are patients who complain of various symptoms even though tests reveal no abnormal findings in urine, prostatitc secretion, etc., thus making the diagnosis more difficult.

In making a diagnosis of chronic prostatitis, it is first necessary to examine thoroughly the patient's anamnesis and present state of illness. As shown in Table 1, the symptoms of chronic prostatitis can be classified into 4 groups: symptoms of urethra, symptoms of rectum, symptoms of genital organs, and disturbance of sexual function. Various diseases are associated with these symptoms. According to Schnierstein, of the patients with these symptoms, 30% are suffering from true chronic prostatitis, 30% from rectal disturbance, and 30-40% from neurosis of genital organs.

Secondly, it is important to know the patient's sexual anamnesis, such as marital status, with or without children, ages of children, frequency of sexual intercourse, masturbation, nocturnal pollution, and disturbances in libido, erection, ejaculation, and orgasmus, though such questions difficult to make. If all these are considered, a fairly correct diagnosis can be made.

Of course, findings of palpation differ with state of inflammation of the prostate. Cases with comparatively new inflammations usually present a state in a) (Table 2), cases with old obsolete inflammations the state in b), and cases with localized inflammations in state in c). Thus, all inflammations are not necessarily associated with prostatic fluid or tenderness. Some cases are utterly free of fluid and tenderness and yet with a hard prostate. In such cases it may be necessary to suspect prostatic cancer.

Clinical examinations are also important. Urine test is an important means to find out where the lesion exists: urethra, prostate or urinary bladder. The best procedure employed is: first collect voided urine 10-20 cc, then take out urine in the bladder, and lastly collect voided urine after massaging prostate. Examination of semen

is also necessary since chronic prostatitis is frequently associated with vesiculitis. Next important is x-ray examination. Chronic prostatitis often shows the same symptoms as ureterolithiasis, prostatomegaly and urethral stricture. Therefore, it is necessary to take the x-ray of the urinary tract and then the ureterogram. If it is chronic prostatitis, Ask-Upmark says, there will be observed an infiltration of contrast media into the prostate, but, as he also says, the absence of the infiltration does not necessarily deny chronic prostatitis. The author has also tried ureterography on his cases. Indeed, as shown in Fig. 1, there were cases which showed infiltration of contrast media into the prostate, but it seems that such cases are rather rare. Finally, regarding cystoscopy, Schnierstein recommends that it be avoided in general. In some cases, however, cystoscopy is essential for distinction of the disease from others and thus cannot be uniformly forbidden. If all that have been said above are well taken into consideration, a reliable diagnosis of chronic prostatitis can perhaps be expected.

According to the author's experience in the past 4 years, as shown in Table 3, chronic prostatitis occurs most frequently in patients of the twenties and, when patients are old, prostatomegaly will come to be associated making the diagnosis more difficult and leaving only a few cases to be treated as true chronic prostatitis.

Subjective symptoms of chronic prostatitis are as shown in Table 4. Among them pollaksuria is most commonly observed, and it seems that a great number of patients are with complaints of urethral symptoms.

Table 5 shows palpation findings of the prostate. Patients with tenderness are noted in 42 cases, or 82%. It is believed that tenderness provides an important clue to the diagnosis of chronic prostatitis.

The urinary findings are given in the upper columns of Table 6. As may well be expected, WBC, RBC, and bacteria are more frequently revealed in those cases which received massage. The alterations of WBC, RBC, and bacteria after massage are shown in the lower columns of Table 6. While more cases showed increase after massage, decrease was also observed in a considerable number of cases. Thus, diagnosis cannot be made solely from urinary findings.

Treatment

Based chiefly on the theory of stagnant inflammation advocated by Leader, treatment of chronic prostatitis has hitherto consisted of massage and warming of the prostate, to which sulfonamides, antiphlogistic enzymes and antibiotics are added. Although in some cases this kind of treatment may take effect, in most cases the symptoms recur, with one symptom disappearing and a new one appearing. Therefore, complete cure is extremely difficult with this treatment.

The author has recently tried pollen preparation CERNILTON on 30 cases of patients diagnosed to be suffering from chronic prostatitis, the samples of which were supplied by Tobishi Pharmaceutical Co., Ltd.

CERNILTON has been employed as a tonic in patients of convalescent phase following treatment of infectious diseases or operation until 1960, when Ask-Upmark described it to be effective in chronic prostatitis. In 1961 Jonsson used it in 10 cases. Then, in 1962 Leander carried out a double blind test in a total of 179 cases. He said that about 90% of cases treated with CERNILTON showed disappearance or improvement of symptoms and about 50% of those treated with placebos showed improvement of symptoms. Considering, however, that all cases were given massage about once a week, he said the effective rate of CERNILTON would be roughly between 60 and 80%.

In the present experiment, other drugs were not combined in the cases treated with CERNILTON, and massage was given at intervals of 5-7 days merely for the purpose of urinary examination.

Improvements in subjective symptoms are shown in Table 8, with marked effects obtained in the CERNILTON-administration group. The palpation findings are given in Table 9, also showing marked improvement in the CERNILTON-administration group. The urinary findings are treated in Table 10 (only urine collected after massage was examined), with a slightly better result obtained in the CERNILTON- administration group.

The criteria of evaluation were based on improvements in subjective and objective symptoms (urinary findings were not taken into consideration):

-Markedly effective: Cases where both subjective and objective symptoms nearly completely disappeared.

-Effective: Cases where symptoms were improved with one or more symptoms still persisting.

-Ineffective: Cases where no improvement was noted at all.

Results obtained according to these criteria are shown in Table 11. As may be noted therefrom, of all the cases treated with CERNILTON, only one case (dysuria) was utterly unresponsive. Symptoms were improved in 3 days in the earliest case, but on the average they were improved in about a week, which is significantly shorter than the length required in the control group. The dosage was uniformly 6 tablets per day in all cases. No side-effects were evidenced at all.

Concluding Remarks

Diagnosis of chronic prostatitis is extremely difficult. However, if the patient's anamnesis is accurately grasped, palpation of the prostate is properly made, and examinations of urine, semen, and x-ray are carried out systematically, it is believed an exact diagnosis can be made.

Hitherto, prolonged treatment has been instituted for this disease, yet repeated recurrence of symptoms has been quite common. With the pollen preparation CERNILTON, the author has been able to obtain improvement in a relatively short period of time, with an effective rate of over 80% as against 60-80% obtained by Leander.

Table 1. Symptoms of Chronic Prostatitis

1. Symptoms of urinary tract	:	Pollakisuria Dysuria Vesical tenesmus Discomfort on urination Pain on or after urination Feeling of residual urine
2. Symptoms of rectum	:	Rectal tenesmus Rectal oppression
3. Symptoms of genital organs	:	Sense of disturbance in genital organs, groin, sacrum and perineum Pubic pain Prostatorrhea Spermatorrhea Hemospermia Pyospermia
4. Disturbance of sexual function	:	Libido impediment Erection impediment

Table 2. Palpation findings of prostate

a) Size : Normal
Hardness : Elastic, soft
Surface : Uneven
Diffused or Localized tenderness
Tiny quantity of prostatic fluid
Increased WBC in prostatic fluid

b) Prostatic atrophy
Hardness : "Narbig" hard
Surface : Smooth or uneven
No prostatic fluid

c) Size : Normal or slightly swollen
Localized infiltration and tenderness

Table 3. Age

Under 20 years old	3 cases
20—29 years old	21 cases
30—39 years old	10 cases
40—49 years old	11 cases
Above 50 years old	6 cases

Table 4. Subjective Symptoms

Pollakisuria	26 cases
Pain after urination	14 cases
Feeling of residual urine	13 cases
Perineum pain	12 cases
Pain on urination	11 cases
Dysuria	9 cases
Abdominal pain	8 cases
Discomfort on urination	7 cases
Lumbago	4 cases
Bleeding after urination	3 cases
Bloody semen	3 cases
Pain on ejaculation	2 cases
Itching of urethra	2 cases
Urethral secretion	1 case
Anal pain	1 case

Table 5. Palpation Findings of Prostate

Tenderness	42 cases
Swelling	11 cases
Hardening	8 cases
Discharge of pus	1 case
Atrophy	1 case

Table 6. Urinary Findings

	Before Massage	After Massage
W.B.C.	39 cases	45 cases
R.B.C.	27 cases	31 cases
Microbes	9 cases	16 cases

Alterations after Massage

	Decreased	Increased
W.B.C.	11 cases	27 cases
R.B.C.	8 cases	25 cases
Microbes	5 cases	12 cases

Table 7. Composition of Cernilton

A. Kinds of Pollens

1.	Timothy	26 %
2.	Maize	26 %
3.	Rye	40 %
4.	Pine	5 %
5.	Orchard grass	2 %
6.	Alder	1 %

B. Contents in one tablet

1.	Cernitin GBX	3 mg
2.	Cernitin T 60	60 mg
3.	Calcium glyconicum	70 mg
4.	Saccharum lactis	70 mg
5.	Calcium phosphoricum dibasicum	140 mg
6.	Acidum alginicum	10 mg
7.	Potato starch	20 mg
8.	Pigmentum	3 mg
9.	Magnesium stearatum	4 mg
10.	Talcum	20 mg

Table 8. Improvement of Subjective Symptoms

	Cernilton + Massage			Other Drugs + Massage + Warming		
	Unchanged	Improved	Disappeared	Unchanged	Improved	Disappeared
Pollakisuria	0	4	14	0	3	5
Pain after urination	0	0	11	0	1	1
Feeling of residual urine	1	3	5	0	3	1
Perineum pain	1	2	7	0	1	1
Pain on urination	0	0	2	0	0	2
Dysuria	1	1	2	2	2	2
Abdominal pain	0	0	5	1	1	1
Discomfort on urination	0	0	7	0	0	0
Lumbago	0	1	1	1	0	1
Bleeding after urination	0	1	2	0	0	0
Bloody semen	0	0	0	0	3	0
Impotence	0	0	0	3	0	0
Pain on ejaculation	0	0	0	0	0	2
Itching of urethra	0	0	2	2	0	0
Urethral secretion	0	0	0	0	0	1
Anal pain	0	0	0	0	1	0

Table 9. Improvement of Objective Symptoms

	Cernilton + Massage			Other Drugs + Massage + Warming		
	Unchanged	Improved	Disappeared	Unchanged	Improved	Disappeared
Tenderness	3	6	14	5	6	7
Swelling	1	2	3	1	5	0
Hardening	3	2	1	0	1	0
Discharge of pus	0	0	1	0	0	0
Atrophy	1	0	0	0	0	0

Table 10. Urinary Findings

	Cernilton + Massage			Other Drugs + Massage + Warming		
	Unchanged	Decreased	Disappeared	Unchanged	Decreased	Disappeared
W.B.C.	9	10	9	2	9	4
R.B.C.	5	6	9	1	5	2
Microbes	2	0	7	0	1	1

Fig. 1. Urogram of Chronic Prostatitis

No.	Age	Length of adm. (days)	Subjective Symptoms	before adm.	after adm.	Objective Symptoms	before adm.	after adm.	Results
1	44	12	Lower abdominal pain Pain after urination Lumbago	+ + +	— — —	Prostate hardened	++	+	Effective
2	48	10	Pain after urination Pollakisuria Urethral bleeding	+ + +++	— — —	Prostate tender	+	±	Effective
3	28	19	Lower abdominal pain Pain on urination Dysuria	+ +++ +++	— — ±	Prostate tender	+	—	Effective
4	54	21	Pain after urination	+	—	Prostate swollen Prostate tender	+ ++	— +	Effective
5	25	7	Pollakisuria Pain of perineum	+ +	— —	Prostate tender	+	—	Markedly effective
6	17	5	Discomfort on urination Pain on urination Pain of perineum Feeling of residual urine	+ + + ++	— — — +	Prostate tender	+	+	Effective
7	27	14	Dysuria	+	+	No findings			Ineffective
8	30	36	Pain after urination Pollakisuria Pain of perineum Lower abdominal pain	+ ++ + +	— — — ±	Prostate tender	++	—	Markedly effective

No.	Age	Length of adm. (days)	Subjective Symptoms	before adm.	after adm.	Objective Symptoms	before adm.	after adm.	Results
9	41	11	Discomfort on urination Pain after urination Pollakisuria	+ ++ +++	— — ±	Prostate tender Prostate hardened	++ +	± ±	Markedly effective
10	32	9	Discomfort on urination Pain after urination Pollakisuria Pain of perineum	+ ++ ++ +	— — + +	Discharge of pus	+	—	Effective
11	33	7	Pain after urination Dysuria Lower abdominal pain	+ + +	— — —	No findings			Markedly effective
12	48	5	Pain on urination Pollakisuria Bleeding after urination	+ + +	— — —	Prostate tender	+	—	Markedly effective
13	26	12	Pollakisuria Bleeding after urination	++ ++	— +	Prostate tender Prostate swollen	+ +	+ —	Effective
14	25	21	Pain on urination Pollakisuria Feeling of residual urine	+ + ++	— — —	Prostate tender	+	—	Markedly effective
15	40	3	Discomfort on urination Pain after urination Feeling of residual urine	+ ++ +	— — —	No findings			Markedly effective
16	28	5	Discomfort on urination Pain on urination Pollakisuria Feeling of residual urine	++ + + +	— — ± +	Prostate tender	+	—	Effective

No.	Age	Length of adm. (days)	Subjective Symptoms	before adm.	after adm.	Objective Symptoms	before adm.	after adm.	Results
17	50	14	Pain on urination Pollakisuria	+ ++	— —	Prostate tender	+	—	Markedly effective
18	37	9	Discomfort on urination Pollakisuria Feeling of residual urine	+ ++ +	— — —	No findings			Markedly effective
19	24	7	Pain of perineum	+	—	Prostate tender			Markedly effective
20	54	9	Pain on urination Discomfort on urination Pollakisuria Feeling of residual urine	+ + ++ ++	— — — —	Prostate tender	+	—	Markedly effective
21	61	6	Pollakisuria	+++	—	Prostate hardened	+	+	Effective
22	23	11	Pain after urination Pain of perineum Pollakisuria	+ + +	— — —	Prostate tender Prostate swollen	+ +	± —	Markedly effective
23	21	7	Pollakisuria Pain of perineum	+ ++	— +	Prostate tender Prostate hardened	+ +	± +	Effective
24	40	15	Pain of perineum	+	±	Prostate tender Prostate swollen	+++ ++	+ +	Effective

No.	Age	Length of adm. (days)	Subjective Symptoms			Objective Symptoms			Results
				before adm.	after adm.		before adm.	after adm.	
25	45	20	Lumbago Pain after urination	+ +	— —	Prostate tender Prostate atrophyed	+++ ++	— +	Markedly effective
26	20	25	Pain on urination Itching of urethra Feeling of residual urine	+ + +	— — ±	Prostate tender Prostate swollen	++ ++	— —	Markedly effective
27	52	5	Itching of urethra Pollakisuria Feeling of residual urine	+ ++ +++	+ +	Prostate tender Prostate hardened	+ +	+ +	Effective
28	29	5	Pain after urination Pollakisuria Pain of perineum	+ + +	— — —	Prostate tender Prostate swollen	+++ +	+ +	Effective
29	24	35	Lower abdominal pain Pain on urination Pain of perineum	+ + +	— — —	Prostate tender Prostate swollen	++ +	— —	Markedly effective
30	17	20	Pollakisuria Dysuria Feeling of residual urine	+++ + +	— — —	Prostate tender	++	—	Markedly effective

PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Inhibition of Growth of Human Benign Prostatic Hyperplasia by Cernilton N in the Nude Mouse Model

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1989

Introduction

In spite of the high incidence of benign prostatic hyperplasia (BPH) a conservative therapy for this disease has still not been established (1,2). The reasons for this are the following: On the one hand, the symptomatology in patients with BHP is due to various different factors, which leads to uncertainty regarding the objective parameters to be considered in clinical trials (2); also, all clinical investigations of the treatment of BPH present the problem of a high placebo effect. On the other hand, the aetiology of prostatic hyperplasia is still unexplainable, due to lack of suitable experimental models (2,3). This makes the search for casual factors on which to base a conservative therapy difficult.

At present, mainly phytotherapeutic agents are used for conservative treatment up to Stage II of the disease according to the classification of Vahlensieck (4, 5). We have established the heterotransplantation of human BPH tissue into the nude mouse as a model for the evaluation of the aetiology of BPH and of drug therapies and their mechanisms (6). Within the framework of these investigations we have studied the plant-based preparation Cernilton N in this model, since in a clinical trial it had been possible to show a significant effect with Cernilton N in comparison with placebo (7). The aim of these first investigations is to answer the question whether a significant effect on the growth of a hormonally stimulated BPH can be demonstrated in our model.

Materials and Methods

All the NMRI nu/ nu mice are kept in a special laboratory, under sterile conditions with a constant relative humidity of 55% and a constant temperature of 27 C. They receive a standard diet of Altromin (Lage) and water.

The human BPH tissue is obtained, by the transvesical prostatectomy, from two patients with BPH.

The tissue is cut into small pieces under sterile conditions and reference tissue is kept on one side for the histological assessment.

Within one hour, pieces measuring 3x3x3 mm are transplanted into both sides of the thorax of the mice.

The test animals are three-month-old male NMRI nu/ nu mice, orchiectomized one day previously.

At the same time, silicone implants with 5-alpha-dihydrotestosterone (DHT) and oestradiol (E_2) are implanted subcutaneously, for hormonal stimulation of the tissue, as described by Steenbrugge (8).

Three groups, each of 4 animals (= 8 tumours), are formed per tumour-line. Groups II and III receive the silicone implants with DHT (serum level for DHT: 8.0 ng/ ml) and E_2 (serum level for E_2: 400 pg/ ml) for the hormonal stimulation. Group I serves as control (serum levels of DHT and E_2 below the measurable levels):

The mice of Group I are also treated with the pollen extract, Cernilton N (Extract. pollinis sicc. 2.5:1), in the dose of 10 mg/25 g body weight, twice a week, p.o., through stomach tube. Based

on body weight, this dosage is equivalent to 50 times the dosage in humans (in order to obtain a speeded up effect). The size of the tumours is measured once a week, with a calliper. Their volume is calculated by means of the formula, length of tumour x width of tumour $^{2}/_{2}$, as described earlier (9).

After 2 months the animals are sacrificed and the tissue removed for histological examination.

The human character of the tissue is checked by semi-quantitative determination of the human LDH isoenzymes (electrophoresis), also 2 months after the heterotransplantation.

Statistical analyses are performed by and independent investigator, whereby the t-test is used for comparison of mean values in 2 comparative groups and a one-way analysis of variance for comparison of the mean values in 3 comparative groups.

Results

In all cases the BPH tissue was histologically vital two months after transplantation, with no signs of necrosis or rejection.

In group I (control group) the volume of the tumours did not change significantly during the two months in the body of the mouse.

In the other two groups the volume of the transplanted tumours increased in the course of the two months. In comparison with the control group this increase in volume is statistically significant ($p < 0.05$). The increase observed in Group III (treatment-group) is, however, significantly less than that in Group II ($p < 0.008$).

The volumes of the transplanted prostate tissue before and two months after transplantation are shown in Table 1 and the growth curves are presented in Figure 1.

All the transplanted prostate-tissue preparations show an epidermoid metaplasia. A difference between the two groups with hormonal stimulation could not be demonstrated histologically.

Discussion

A statistically significant inhibition of growth through the application of Cernilton N can be demonstrated for human BPH in the nude mouse model. This result concurs with the results of the clinical trial (7). On the other hand, however, it must be born in mind that the transferability of these findings to man is limited. The doses of the stimulant hormones on the one hand and of the therapeutic agent on the other, which are used in order to achieve the speeding-up effect, are both unphysiologically high. Also, in man the size of the prostate alone is insufficient to explain the whole pathological picture (2).

A conclusion regarding a possible mechanism of action cannot be drawn on the basis of our results. Also the histological picture, due to the lack of differences between groups, provides no information on the mechanism of the inhibition of growth of the tumour. However, an inhibition of the enzymes, 5-alpha-reductase and aromatase, can be excluded, since the end-products of the biochemical reactions catalyzed by these enzymes are substituted.

The model described here is nevertheless suitable, through further investigations of the prostate tissue, to contribute to clarification of the mechanisms of action.

Cernilton N is capable, under experimental conditions, of exerting an objectively evaluable effect on the growth of human BHP tissue.

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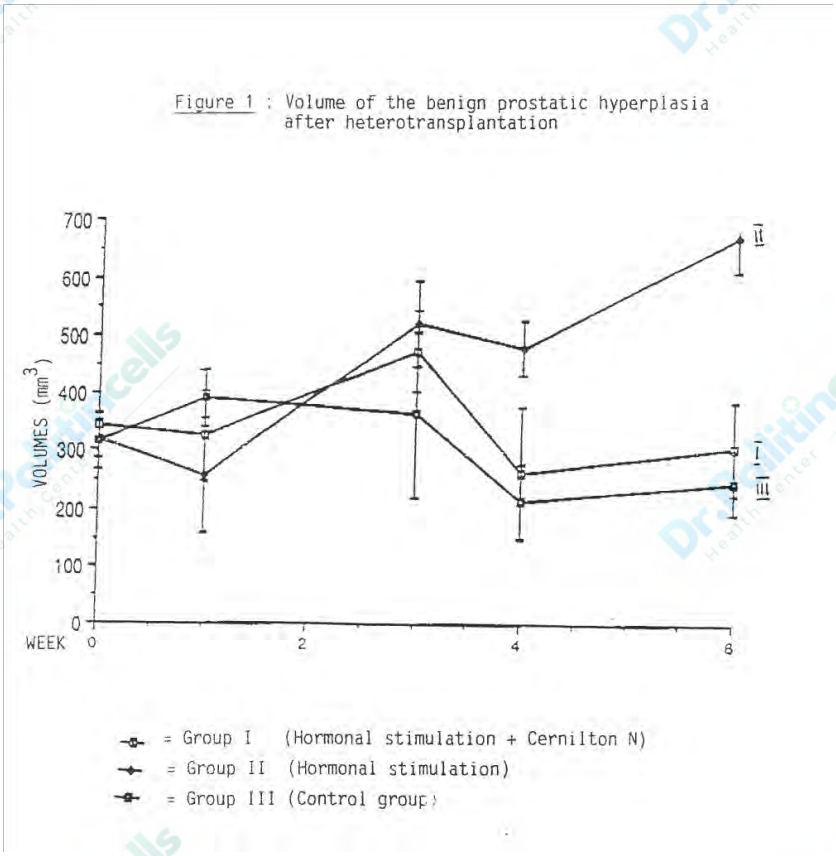
Table 1: Volume of BPH – Mean values (MV) Sunday 29.4.90, 20.36 hrs

Time	Group I MV	Group II MV	Group III MV	Group I s	Group II s	Group III s	p
Baseline	343.0	318.3	315.9	6.1	32.7	48.7	0.940
1st week	324.8	256.0	390.4	78.1	99.5	50.8	0.076
3rd week	473.5	522.2	363.1	72.8	75.0	141.9	0.046
4th week	282.8	479.8	213.8	112.5	48.0	63.7	0.008
6th week	307.0	673.0	246.3	79.3	58.4	54.0	0.001



Pharmacological Studies on Cernilton, a New Remedy for Prostatitis and Prostatomegaly (2)

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I. Introduction

CERNILTON contains two major ingredients, Cernitin T-60 (T-60) and Cernitin GBX (GBX) mixed at a ratio of 20:1. The drug is clinically effective in the treatment of prostatomegaly.

In the present study acute toxicity test was carried out with CERNILTON (Cer) with a view to determine the LD_{50} in rats and mice and observe symptoms produced at a large dose. Subacute toxicity test was carried out with Cer, T-60 and GBX in rats and chronic toxicity test with Cer. Observations were made on physical development and general toxic symptoms. Liver function test, pathohistological examinations and other tests were also carried out.

II. Methods of Tests

1. *Acute Toxicity Tests of T-60, GBX and Cer*

Method: Animals used were Donryu strain rats (bodyweight 150-180 g) and ddN strain mice (bodyweight 20-25 g) of both sexes at 6-8 weeks of age, each group consisting of 5-10 animals. The sample drugs were given by three routes: oral, subcutaneous (only males), and intraperitoneal (only males). Following medication, animals were observed hourly for 6 hours and then only daily 7 days as to acute toxic symptoms and presence of death. Dead animals were subjected to laparotomy and the thoracic and abdominal organs were macroscopically observed. The LD_{50} was calculated on the basis of the total number of deaths in 7 days by means of the Probit method. T-60 and Cer were dissolved or suspended in 1% CMC and GBX was suspended in olive oil. The volume was so adjusted that the animals would receive 20 ml/ kg by oral route, 10 ml/ kg by the subcutaneous route, and 5 ml/ kg by the intraperitoneal route.

Dose (Table 1): According to the report by Tor Magnusson, the LD_{50} of T-60 is 5g/ kg by intraperitoneal route in mice. The dose levels were set up on the basis of this report.

2. *Subacute Toxicity Tests of T-60, GBX and Cer*

Donryu strain rats of both sexes weighing about 80g were used. The animals were raised under controlled conditions (room temperature 25±1°C, humidity 55±5%) and a total of 12 groups was set up, each group consisting of 10 males and 10 females. Four groups of animals were used for each sample drug. Sample drugs were given by the oral route with the aid of a gastric sound, once daily over a period of 35 days.

The dose levels were determined on the basis of the data obtained by Tor Magnusson as well as the results obtained in our laboratory concerning the LD_{50} of T-60, GBX and Cer. It was also

taken into consideration that chronic toxicity test was to be carried out.

T-60 and Cer were suspended in 1% CMC solution. Concentrations were so adjusted that the maximum daily volume would be 4 ml/100g for T-60 and 2 ml/100g for Cer. Original solution (specific gravity 0.94) was used for GBX.

Observations were made on the following items: a) body weight: Determined daily until the end of administration. b) Food consumption: Determined for 10 days after the 25th day of administration. c) Observation of toxic symptoms: Daily until the end of administration. d) Blood test: Blood was collected from 10 animals (5 males, 5 females) in each group before administration and on the 30th day of administration. RBC count, hemoglobin value (cyanmethemoglobin method), WBC count, and WBC percentage were determined. e) Urine: Urine was collected from 10 animals (5 males, 5 females) in each group before administration and at the end of administration. Sugar, protein and urobilinogen were examined with Uristix (Ames Co.). The volume and color of urine were also examined. f) Liver function test: BSP excretion test was performed by Gaebler's method prior to autopsy at the end of administration. Hepatosulphalein was injected in doses of 10 mg/ kg into the vein of a hind limb and the amount of excreted dye was measured after 5 min. In addition, serum GOT and GPT levels were measured using ESGOT testing agent. g) Total cholesterol, total protein, blood sugar: Total protein was measured simultaneously with liver function test. Blood sugar was measured by Somogyi-Nelson's method and cholesterol level by Zak-Henly's method. h) Autopsy: 1) Macroscopic observation of organs: Major organs. 2) Weight: Hypophysis, thymus, heart, liver, kidneys (bilateral), adrenal glands (bilateral), spleen, prostate, testis (unilateral), epididymus (unilateral) and spermatocyst. 3) Pathohistological examinations: Brain, lungs, heart, liver, spleen, kidneys, stomach, intestine, pancreas, thymus, adrenal, spermatocyst and bone marrow. Each organ was fixed with 10% formalin solution and embedded in paraffin. It was then sliced and stained with hematoxylin eosin for microscopic observations.

3. *Chronic Toxicity test of Cer*

The conditions of animal breeding and method of administration were the same as in the subacute toxicity test. The drug was given for 180 days. Five dose groups were set up on the basis of the results obtained in the subacute toxicity test. T-60 was first dissolved in 1% CMC solution, after which GBX was added and mixed well with a homogenizer. The drug was so adjusted in concentration that the maximum volume would be 1ml/100g.

Items of observation were as follows. a) Body weight. b) Food consumption. c) Toxic symptoms. d) Blood test. e) Urine test. f) Liver function test. g) Total cholesterol, total protein, blood sugar. h) Autopsy.

III. Results

1. Acute Toxicity Tests of T-60, GBX and Cer
A. Observation of toxic symptoms and death
a. Rats

1) *T-60 administration groups*

a) Oral route: Though varying in intensity, symptoms were similar in all groups, regardless of sex. Animals crouched immediately after administration. Piloerection and decreased activity ensued. None, however, died and all the animals returned to normal after 6-24 hours.

b) Subcutaneous route: Symptoms were essentially the same as those observed in a) in all five groups. However, animals screamed for 5-10 seconds as if complaining of pain when injected subcutaneously. Subcutaneous induration was present at the site of injection for three days and then disappeared. Death occurred in no cases even by this route.

c) Intraperiotoneal route: Crouching, piloerection, decreased activity, and apprehension were noted. In survivals these symptoms disappeared after 6-12 hours, but in

dead cases the symptoms did not disappear and the animals died after 24 hours in the state of natural death.

2) *GBX administration groups*

a) Oral route: Crouching, piloerection and decreased activity were seen from about 3 min after administration, but no specific symptoms were shown. All animals recovered after 6 hours and survived.

b) Subcutaneous route: Death occurred in no cases, and symptoms were same as those seen in a). The site of injection presented swelling and induration as in the case of T-60, but they disappeared in about 5 days.

c) Intraperitoneal route: Death occurred by the third day. Symptoms noted were crouching, decreased activity and slight tremor. In the 1.95 and 2.34g/ kg dose groups, where all animals survived, the symptoms disappeared after 24 hours.

3) *Cer administration groups*

a) Oral route: Crouching, piloerection, decreased activity, and apprehension occurred from about 2 min after administration, but no specific toxic symptoms were seen. All animals recovered and returned to normal after 24 hours. Death was not noted.

b) Subcutaneous route: Symptoms were similar to those observed in a) and no specific toxic symptoms were disclosed. Some cases developed slight inflammation at the site of injection which lasted 3 days. Screaming lasting several seconds was noted at the time of injection, but death occurred in no cases.

c) Intraperitoneal route: Besides the symptoms observed in a) and b), slight general tremor was noted. In survivals the animals recovered after 12-24 hours, while in dead cases the symptoms persisted and the animals died within 24 hours. No further deaths, however, occurred during the 7 days of observation.

b. Mice

1) *T-60 administration groups*

a) Oral route: Difference due to sex was not noted. Intensity of symptoms varied somewhat with doses, but generally symptoms were same as those observed in rats. In other words, piloerection, decreased activity and tremor were noted, but they disappeared after 24 hours. In dead cases these symptoms were marked and animals died within 24 hours.

b) Subcutaneous route: For a few seconds after administration the animals ran about within the cage as if complaining of pain. Activity decreased somewhat more by this route than by the oral route, though it returned to normal after 6 hours. Death occurred between the 24th and 72nd hours of administration. Inflammation manifested at the site of injection in all cases as in rats, but likewise it disappeared in about 72 hours.

c) Intraperitoneal route: In dead cases in the large dose group, the animals developed piloerection, crouching, tremor of extremities and eventually died. In survivals symptoms as piloerection, decreased activity, and slight tremor were noted, but they disappeared after 6 hours.

2) *GBX administration groups*

a) Oral route: As with T-60 administration, symptoms were same in both sexes and slightly varied in intensity with doses. Namely, piloerection and decreased activity occurred immediately after administration, and in the large dose group slight general tremor was noted. Some cases developed diarrhea which lasted about 48 hours. Dead cases were all noted within 24 hours.

b) Subcutaneous route: In the large dose group the animals jumped around in the cage immediately after administration, showed piloerection, crouching, and staggering after one minute and died after 24-72 hours. In the small dose group these symptoms appeared too, but

they disappeared after 48 hours. Inflammation at the site of injection was more marked than with T-60 administration but disappeared after 4 days.

c) Intraperitoneal route: Piloerection, decreased activity, and slight tremor appeared immediately after administration. Death occurred in some cases after 24-120 hours. Recovery was slow in survivals but they returned to normal by the 6th day.

3) *Cer administration groups*

a) Oral route: Symptoms were similar to those observed with T-60. Piloerection, decreased activity, and tremor were seen. Death occurred within 24 hours. These symptoms also occurred in survivals but they disappeared after 6 hours.

b) Subcutaneous route: As with oral administration, piloerection, decreased activity and tremor appeared. However, they were of slighter degree than with subcutaneous injection of T-60. Death occurred within 48 hours.

c) Intraperitoneal route: In the large dose group, the same tremor as seen with T-60 administration appeared and death ensued. In survivals in the small and medium dose groups, piloerection, decreased activity, and slight tremor all appeared, but they disappeared within 10 hours.

B. LD_{50} (Table 2)

The LD_{50} in rats was not obtainable by the oral and subcutaneous routes because all animals survived even at the maximum permissible dose. However, by the intraperitoneal route, the toxicity of the sample drugs was considerably high. The LD_{50} was 7.58g/ kg for T-60, 3.31 for GBX, and 6.66 for Cer. GBX was the most toxic while T-60 and Cer were approximately of the same degree.

In mice the LD_{50} was successfully obtained by routes. As a result, it was found that GBX was the least toxic by the subcutaneous route. On the other hand, by the intraperitoneal route, GBX was the most toxic of all sample drugs. Of the three routes, the intraperitoneal route was the most toxic while the oral and subcutaneous routes were approximately of the same degree.

2. Subacute Toxicity Tests of T-60, GBX and Cer

A. Body weight and death (Figs. 1,2,3)

a. T-60 administration groups

1) Control group: The control group receiving 1% CMC solution at a dose of 40ml/ kg showed normal weight increases both in males and females.

2) T-60 6.0g/kg group: The males showed normal weight increases at the control group and registered a greater weight increase than the control group throughout the period, with a difference of about 14 g at the end of administration. In females weight decrease was noted around the 25th day of administration, but as a whole they showed the same weight increase tendency as the control group. Death occurred in one male and one female, on the 23rd and 24th day, respectively.

3) T-60 12.0g/kg group: Weight increase in males slowed down transiently from about the 20th day, but generally the tendency was the same as that of the control group. Females showed a greater weight increase than the control throughout the period, with a difference of about 5g on the 30th day of administration. The difference, however, was not statistically significant. Death occurred in one male and one female on the 33rd and 21st day respectively.

4) T-60 24.0g/kg group: Males showed a greater weight increase than the control group up to the 20th day as in the previous two groups, but from about the 25th day weight increase slowed down markedly, with practically no weight increase shown up to the end of administration. The body weight on the 30th day was about 30g less than that of the control group, thus with a significant difference between the two groups. In females weight increase slowed down from about the 20th day, the body weight being lower than that of the control group by about 5g on the 30th day. Death occurred in

2 males (9, 32nd day) and 3 females (26, 20, 32nd day).

b. GBX administration groups

1) Control group: The control group receiving 1% CMC solution at a dose of 10 ml/kg showed normal weight increases both in males and females.

2) GBX 5.0g kg group: Both males and females showed normal weight increases, and the body weight at the end of administration was about the same as that of the control group. Death occurred in one male on the 33rd day.

3) GBX 10g/kg group: In males weight increase slowed down from about the 20th day, and the body weight was about 30g lower than that of the control group in the 30th day, with significant difference. Females showed normal weight increases. The bodyweight at the end of administration was little different from that of the control group.

4) GBX 20g/kg group: In males weight increase slackened more than in the previous 3 groups, and although it subsequently recovered, the body weight on the 30th day was about 40g lower than that of the control group. The difference was of significance. In females, contrarily, weight increase progressed quite favourably and the body weight was about 12g higher than of the control group on the 30th day. Death occurred in one male (14th day) and 3 females (6, 9, 32nd day).

c. *Cer administration groups*

1) Control group: The control group, which was given 20ml/kg of 1% CMC solution, showed normal weight increases in both sexes as the control groups of T-60 and GBX. Death occurred in one male, but this was due to an error in administration.

2) Cer 6.3g/ kg group: Both males and females showed exactly the same weight increase as the control group up to the 20th day, but then it was slightly inhibited. Difference in body weight, however, was noted at the end of administration in comparison with the control group. One male died on the 34th day.

3) Cer 12.6g/kg group: Males had a slightly greater weight increase than the control group from about the 15th day, with a difference of about 5g on the 30th day of administration. Females showed exactly the same weight increase as the control group, with no difference in body weight at the end of administration. Death occurred in 2 males (22, 34th day) and one female (31st day).

4) Cer 25.2g/kg group: Weight increase slowed down from about the 5th day in both sexes lasting until the end of administration. In males, although there was no weight decrease, the difference with the control group reached as much as 20g on the 30th day. In females, a transient weight decrease was noted on the 30th day, and the difference with the control group at the end of administration was about 16g, with significant difference. Death occurred in no cases.

B. *Food consumption (Table 3)*

Food consumption tended to decrease in both males and females with all sample drugs as compared with that in the control group. This tendency was particularly marked in the T-60 24.0g/kg, GBX 20.0g/kg, and Cer 25.2g/kg groups where the food consumption was only about half that of the control group.

C. *Observation of toxic symptom*

a. *T-60 administration groups*: In the 12.0g/kg and 24.0g/kg groups, piloerection, soft feces and depression appeared from about the 15th day. In addition, mild tremor of forelimbs, salivation, face-washing and coughing appeared every day 5-10 min after administration, disappearing gradually after 10 min with animals coughing repeatedly. Toward the end of administration, tremor of forelimbs intensified with a longer recovery time required, and in all cases loss of appetite, emaciation and piloerection were noted persistently.

b. *GBX administration groups*: From about the 15th day, in addition to the aforementioned symptoms of piloerection and soft feces, forward opening of forelimbs was noted in the 10.0g/kg and 20.0g/kg groups, beginning from immediately to 5 min after administration. From about 5-10 min after administration salivation, face-washing, tremor of forelimbs, searching behaviour, and coughing appeared, and animals, after repeating face-washing and severe tremor of forelimbs, moved toward recovery after 30-40 min of administration. In the 20.0g/kg group there was found mixed in soft feces something whose colour was indicative of the sample drug. Loss of appetite, emaciation and depression were markedly observed in the latter period of administration.

c. *Cer administration groups*: In the 12.6g/kg and 25.2g/kg groups about two-thirds of the animals showed salivation, face-washing, chronic tremor of forelimbs and coughing about 10 min after administration from about the 20th day. These symptoms continued for about 20 min and then gradually improved. In the 25.2g/kg group several animals developed searching behaviour. It gradually improved after the animals repeated coughing and face-washing. Furthermore, loss of appetite, emaciation, piloerection, and soft feces were persistently observed until the end of administration.

D. Blood tests (Table 4, 5, 6)
a. T-60 administration groups

1) RBC: RBC was slightly decreased in the experimental groups as compared to that in the control group. Significant difference was noted between the T-60 24.0g/kg and control groups in both sexes.

2) Hemoglobin: Hemoglobin was decreased in the experimental groups as compared to that in the control group. The males of all groups and the females of the 12.0g/kg and 24.0g/kg groups showed significant difference from the control group.

3) WBC: WBC showed no marked changes in males. In females it increased more in the experimental groups than in the control group, with significant difference noted in the cases of 12.0g/kg and 24.0g/kg groups.

4) WBC percentage: Neutrophiles, basophiles, acidophiles and lymphocyte were all within normal limits in distribution, and no morphologically abnormal cells were disclosed.

b. *GBX administration groups*

1) RBC: RBC showed no marked changes in the experimental groups as compared to that in the control group on the 30th day.

2) Hemoglobin: Hemoglobin decreased in the females of the 10.0g/kg group as compared to that in the control group, with significant difference. No marked changes were noted in the other groups.

3) WBC: In males all experimental groups showed a decreasing tendency in comparison to the control group, with significant difference in the case of the 20.0g/kg group. In females no such tendency was revealed.

4) WBC percentage: WBC percentage showed no specific abnormalities, and no morphologically abnormal cells were disclosed.

c. *Cer administration groups*

RBC, hemoglobin, WBC and WBC percentage as determined on the 30th day show no marked changes in the experimental groups as compared to those in the control group. Morphologically abnormal cells were not revealed.

E. *Urine tests*

Toward the end of administration sugar was detected in the Cer 25.2g/kg group and protein and urobilinogen in the GBX 20.0g/kg group, in 3-4 cases each, but the levels were not significantly high. Results obtained both before and after administration showed no abnormalities. Comparison between the

experimental and control groups also showed no abnormalities. The urinary volume tended to increase in the experimental groups. The color tone was normal.

F. Liver function test (Tables 7, 8, 9)
a. T-60 administration groups

1) BSP excretion test: In males BSP excretion was delayed in the experimental groups in comparison to that in the control group, with significant difference noted in the cases of the 6.0g/kg and 12.0g/kg groups. No such delay was seen in females.

2) Transaminase: In males GOT and GPT were lower in the experimental groups than in the control group, with significant difference in the cases of the 6.0g/kg and 24.0g/kg groups, the former both in GOT and GPT and the latter in GOT. In females both GOT and GPT showed no significant difference between the experimental and the control group.

b. GBX administration groups

1) BSP excretion test: The experimental groups showed no tendency of delayed excretion in both sexes in comparison to the control group. Rather, excretion was somewhat delayed in the control group.

2) Transaminase: GOT showed no difference between the experimental and control groups in both sexes. GPT was slightly raised in the experimental groups in both sexes, with significant difference from the control in the cases of the females of the 5.0g/kg group.

c. Cer administration groups

1) BSP excretion test: In males excretion tended to delay in all experimental groups with increase in dosage, but no significant difference was noted from the control. In females, delayed excretion was not revealed at all.

2) Transaminase: In males both GOT and GPT were lower in the experimental groups than in the control group, with significant difference in the cases of the 12.6g/kg and 25.2g/kg groups, the former in GPT and the latter in both GOT and GPT. In females both GOT and GPT were lower in the 6.3g/kg and 25.2g/kg groups. In the 12.6g/kg group GOT and GPT tended to rise, but the difference was not significant from the control.

G. Total cholesterol, total protein, blood sugar (Tables 7, 8, 9)

a. *T-60 administration groups*: Total cholesterol was raised in the males of the 12.0g/kg and 24.0g/kg groups compared to that in the control group. It was found lowered in the females of the 24.0g/kg group, with significant difference from the control. Blood sugar tended to rise with increase in dosage in females and total protein registered a significantly high value in the males of the 24.0g/kg group. Otherwise, there was no difference from the control.

b. *GBX administration groups*: Total cholesterol was lowered in the females of the 10.0g/kg group, with significant difference from the control. Otherwise, there was no difference between the experimental and control groups in both sexes. Blood sugar was higher in the experimental groups in both sexes, with significant difference in the cases of 5.0g/kg group (males), 10.0g/kg group (females), and 20.0g/kg group (both sexes) and 10.0g/kg (females) groups than in the control group, with significant difference.

c. *Cer administration groups*: Total cholesterol tended to increase in the experimental groups in both sexes as compared to that in the control group. The difference was significant in the case of the 25.2g/kg group (males). Blood sugar was lower in the 6.3g/kg and 12.6g/kg groups in both sexes than the control but was higher in the 25.2g/ kg group in both sexes. The difference, however, was not significant. Total protein in the experimental groups showed no difference from the control in both sexes.

H. Autopsy

a. *Macroscopic observation of organs*: No specific changes were disclosed in the thoracic,

abdominal, and endocrinological organs. Smear specimens of the seminal vesicle, epididymus and testis showed no abnormalities. It is unlikely that the testicular function was impaired.

b. Organ weight (Tables 10, 11, 12, Fig. 4)
1) T-60 administration groups

a) Hypophysis: The weight showed no marked variations between the experimental and control groups. A higher weight than the control with significant difference, however, was noted in the males of the 12.0g/kg group and the females of the 24.0g/kg group.

b) Thymus: The weight was lower in the males of the 24.0g/ kg group and the females of the 12.0g/kg and 24.0g/kg groups than the control, each with significant difference.

c) Heart: The weight tended to be decreased in the high-dose groups in both sexes. In the 24.0g/kg group it was decreased in both sexes, with significant difference from the control.

d) Liver: There was no difference between the experimental and control groups in both sexes.

e) Kidney: Here, too, the weight tended to be decreased in the high-dose groups in both sexes, with significant difference bilaterally between the 24.0g/kg and control groups in males.

f) Adrenal gland: In males the weighy tended to increase in the experimental groups as compared to that in the control group, with significant difference in the cases of the 12.0g/kg group (bilateral) and the 24.0g/kg group (left). In females the weight was little affected except that it was slightly increased in the 6.0g/kg group.

g) Spleen: Except that the weight was decreased in the 24.0g/kg group in both sexes, there was no marked difference between the experimental and control groups.

h) Prostate: The weight decreased as the dosage was increased, and significant difference was noted between the control and the 12.0gkg and 24.0g/kg groups.

i) Testis, epididymus: None of the experimental groups showed difference with the control group.

j) Seminal vesicle: The weight was higher in the 6.0g/kg group than the control, but was lower in the 24.0g/kg group with significant difference.

2) *GBX administration groups*

a) Hypophysis: The weight was increased in the males of the 10.0g/kg group, with significant difference from the control. Otherwise, no difference was revealed between the experimental and control groups in both sexes.

b) Thymus: In males, the weight tended to decrease as the dose was increased, while in females the decreasing tendency was evident.

c) Heart: In males the weight was lower in the 20.0g/kg group, with significant difference from the control, but in females it was rather increased in all experimental groups.

d) Liver: The weight tended to be increased in the experimental groups in both sexes, but none of the groups showed any significant difference with the control group.

e) Kidneys: In males the weight tended to decrease as the dosage was increased, and significant difference was noted between the 20.0g/kg and the control groups (left). In females, contrarily, the weight increased with dosage, with significant difference from the control in the case of the 20.0g/k group (left).

f) Adrenal glands: The weight increased with dosage in experimental groups in both sexes. In the 20.0g/kg group significant difference was noted from the control in the left kidney in both sexes. In the right kidney, the males of all experimental groups showed significant difference from the control.

g) Spleen: In males the weight tended to decrease with increase in dosage. In females an increasing tendency was noted, but neither showed significant difference from the control.

h) Prostate: The weight was lower in the experimental groups than the control, but not so evidently as in the T-60 administration groups. The relation to dosage was not clear.

i) Testis, epididymus: The weight of the testes in the 20.0g/kg group and that of the epididymus in the 5.0g/ kg and 10.0g/kg groups were lower than the control, with significant difference.

j) Seminal vesicle: the weight was lower in all the experimental groups, with significant difference from the control in the case of the 20.0g/kg group.

3) *Cer administration groups*

a) Hypophysis: The weight was increased in the males of the 12.6g/kg and 25.2g/kg groups in the females of the 6.3g/kg group, with significant difference from the control.

b) Thymus: It weighed less in the females of the 25.2 g/kg group than in the control group, with significant difference. Otherwise, there was no difference between the experimental and control groups in both sexes.

c) Heart: None of the experimental groups showed great difference from the control group in both sexes.

d) Liver: The weight tended to increase with dosage in the experimental groups in both sexes. The difference between the 25.2g/kg group and the control was significance in both sexes.

e) Kidneys: As in the liver, the weight tended to increase with dosage in both sexes in the experimental groups, and the 25.2g/kg showed significant difference from the control.

f) Adrenal glands: The weight was increased in experimental groups in both sexes except in the 6.3g/kg group. Significant difference was noted from the control in the 6.3g/kg (right, both sexes), 12.6g/kg (bilateral, both sexes) and 25.2g/ kg (bilateral, both sexes) groups.

g) Spleen: Except that the weight was lower in the females of the 25.2g/kg group, with significant difference from the control, no great difference was noted between the experimental and control groups.

h) Prostate: The weight was higher in the experimental groups but with no significant difference. A correlation between dosage and weight was not revealed.

i) Testis: the weight increased as the dosage was increased in the experimental groups, with significant difference in the cases of the 12.6g/kg and 25.2g/kg groups.

j) Epididymus: No difference was shown between the experimental and control groups.

k) Seminal vesicle: All experimental groups showed a higher weight, but with no significant difference.

4) *Weight of prostate per 100g of body weight (Fig. 4)*

a) T-60 administration groups: As the dosage was increased, the weight tended to decrease in the experimental groups, with significant difference from the control in the cases of the 12.0g/kg and 24.0g/kg groups.

b) GBX administration groups: With increase in dosage, a slight weight-increasing tendency was noted in the experimental groups, but the difference was of no significance.

c) Cer administration groups: The weight was slightly higher in the experimental groups, but with no significant difference.

c. Pathohistological observations
1) T-60 administration groups

a) Control group

(1) Prostate: The parenchyma of the prostate was composed of glandular ducts. The ducts

had no clear-cut basal membranes and the interior surface was covered with glandular epithelium. The width of the ducts varied greatly depending on the height of the ducts. For convenience' sake the letters X and Y will be used here, the former indicating narrow glandular ducts and the altter wide ducts. There appearded three types of glandularducts: X ducts, dilated X ducts, and Y ducts. Seminal ductules with abundant polynucleic gigantic cells, which seemed to be Sertoli's cells, were found in some areas. Otherwise, there were no abnormal findings.

(2) Liver: Venous congestion and slight deposit of fat droplets were seen. No other abnormal findings were obtained.

No abnormalities were found in the other organs.

b) T-60 6.0g/kg group

(1) Prostate: Findings varied from case to case, some consisting of only Y ducts and others X and dilated X ducts.

(2) Testis: Marked degeneration of seminal ductules and atrophic seminal ductules rich in gigantic cells were seen in a small number of cases.

(3) Liver: Fat deposit, diffuse cellular atrophy, and cellular dissociation were noted. They were severe in degree.

(4) Hypophysis: Congestion was disclosed in a small number of cases.

c) T-60 12.0g/kg group

(1) Prostate: Similar findings were obtained in all cases. It consisted mainly of X ducts, mixed with dilated X ducts.

(2) Testis: No specific findings were obtained.

(3) Liver: The changes were particularly evident in females and atrophied liver cells and pimelosis were markedly seen. In a small number of cases pimelosis was quite marked, and moreover intrasinusoidal congestion was associated.

(4) Kidney: Congestion and urinary cast were noted in about half the cases.

(5) Hypophysis: Marked congestion and congestive edema was seen in a small number of cases.

d) T-60 24.0g/kg group

(1) Prostate: Slight degeneration of ducts was noted in about half the cases. Findings, however, were not uniform, some cases consisting of X and Y ducts and others dilated X or Y ducts.

(2) Testis: Hypoplasia of seminal ductules and necrosis due to coagulation of sperms were noted in a small area in all cases.

(3) Liver: Atrophy of cells and scattered fatty droplets were shown in about half the cases. Marked congestion was noted in a few cases.

(4) Kidneys: A moderate degree of congestion was shown in all cases. Otherwise, there were no specific findings.

(5) Pancreas: Localized vacuolation or pimelosis of the acinus was observed in a small number of cases.

(6) Hypophysis: All cases showed slight congestion.

(7) Thyroid: In many cases colloid was thin (some cases devoid of it) and the epithelium was vacuolated.

2) GBX administration groups

a) Control group

(1) Prostate: In all cases it consisted of X ducts and dilated X ducts. In a small number of cases Y ducts were also noted.

(2) Testis: No abnormal findings.

(3) Liver: Very slight cellular dissociation, congestion and scattered fatty droplets were shown in a small number of cases.

No changes were disclosed in the other organs.

b) GBX 5.0g/kg group

(1) Prostate: In many cases Y ducts were somewhat abundantly noted, but generally the findings were similar to those in the T-60 6.0g/kg group.

(2) Testis: No specific findings.

(3) Liver: Diffuse cellular atrophy and fatty droplets were observed.

(4) Kidney: No specific findings.

(5) Hypophysis: Congestion was seen in all cases.

No specific findings were obtained in the other organs.

c) GBX 10.0g/kg group

(1) Prostate: Findings were similar in all cases. The prostate consisted mainly of X ducts, and dilated X ducts were few.

(2) Testis: No specific findings.

(3) Liver: Atrophy of cells and deposit of fat droplets were noted as in the T-60 12.0g/kg group. They were less marked than those in the T-60 administration groups but more marked than those in the Cer administration groups.

(4) Hypophysis: Congestion or congestive edema was seen in about half the cases.

d) GBX 20.0g/kg group

(1) Prostate: Some cases consisted of X and dilated X ducts while others consisted mainly of Y ducts.

(2) Testis: No specific findings.

(3) Liver: Cellular dissociation and localized cellular atrophy were noted in many cases, but fat scarcely appeared.

(4) Kidney: No specific findings.

(5) Hypophysis: Somewhat marked congestion was disclosed in about half the cases.

(6) Thyroid: The colloid was thin and the epithelium was vacuolated.

3) Cer administration groups

a) Control group

(1) Prostate: The prostate consisted of X ducts in about half the cases. In the other half it consisted of X ducts and dilated X ducts.

(2) Testis: No specific findings.

(3) Liver: Slight congestion and deposit of fatty droplets were noted in all cases.

(4) No specific findings.

(5) Hypophysis: Acidophilic cells were slightly increased in a small number of cases.

No specific changes were shown in the other organs.

b) Cer 6.3g/kg group

(1) Prostate: In many cases it consisted of X ducts and dilated X ducts, while in some cases Y ducts were markedly observed.

(2) Testis: Slight hypoplasia of sperms was shown in a small number of cases.

(3) Liver: In about half the cases deposit of fatty droplets and diffuse cellular atrophy were slightly noted.

No specific changes were seen in other organs.

c) Cer 12.6g/kg group

(1) Prostate: It consisted of X ducts in all cases, mixed with Y ducts in a few cases. Slight degeneration or disappearance of glandular

ducts was noted in most cases, but the degree was slight. The stroma showed no abnormalities.

(2) Testis: Seminal ductules suggestive of hypoplasia of sperms were locally noted immediately below the capsule.

(3) Liver: Slight cellular atrophy, dissociation of cell cords, and deposit of fatty droplets were seen.

(4) Kidney: Slight congestion of the cortico-medullary border zone and glomeruli and urinary casts occurred in about half the cases.

(5) Hypophysis: Increased acidophilic cells were seen in a small number of cases.

d) Cer 25.2g/kg group

(1) Prostate: In most cases X ducts were dilated, some with degeneration or disappearance of the glandular epithelium. The degree of change varied with cases. Y ducts were generally scarce.

(2) Testis: Seminal ductules suggestive of hypoplasia of sperms were disclosed in a small number of cases, but degeneration or necrosis was not observed. Generally findings were scarce.

(3) Liver: Slight cellular atrophy and deposit of scattered fatty droplets occurred in about half the cases.

(4) Kidney: Only slight congestion of glomeruli was noted in about half the cases, and the renal tubules showed no changes at all.

(5) Hypophysis: Only acidophilic cells were slightly increased.

(6) Thyroid: The colloid was thin and sometimes absent, and the epithelium was vacuolated in many cases.

3. Chronic Toxicity Test of Cer

A. Body weight and death (Fig. 5)

a. Control group: The control group, which received 10ml/kg of CMC solution, showed normal weight increases in both sexes.

b. Cer 1.6g/kg group: In males the body weight was greater than the control, by about 20g on the 30th day and by about 35g on the 105th day. Thereafter, it decreased transiently. After the 135th day increase and decrease occurred alternately and the difference with the control at the end of administration was about 12g. In females weight increase became somewhat unsteady after the 135th day and the body weight slightly decreased after the 165th day. However, the tendency was the same as that of the control as a whole. Death occurred in one male and one female, on the 134 and 166th day respectively.

c. Cer 3.2g/kg group: The body weight in males showed no decrease up to the 165th day and was about 20g greater than the control. After the 165th day it slightly decreased so that the difference with the control was only about 5g at the end of administration. In females, the body weight ceased increasing after the 105th day and then slightly decreased after the 165th day. At the end of administration it was about 10g smaller than the control. One male died on the 117th day.

d. Cer 6.3g/kg group: As in the previous two groups, the males showed normal weight increase up to the 165th day without weight decrease, and the body weight was about 20g greater than the control. However, toward the end of administration the body weight decreased slightly so that the difference with the control ended up with about 14g. In females, the weight increase slowed down after the 105th day and the body weight at the end of administration was about 1.5g smaller than the control. One male died on the 165th day.

e. Cer 12.6g/kg group: The males showed a slower weight increase than the control and the three previous groups. This tendency was intensified after the 105th day and the body weight at the end of administration was about 40g smaller than the control with significant

difference. In females, the body weight ceased increasing after the 120th day. On the contrary, it tended to decrease and the difference with the control at the end of administration was about 16g, though with no significant difference. Death occurred in 2 males, on the 124th and 164th day.

B. Food consumption (Table 13)

The food consumption decreased from about the second month in the 12.6g/kg group (both sexes) and from about the fourth month in the 6.3g/kg group (both sexes). The other groups showed no great difference with the control, but generally the consumption tended to decrease as the dosage was increased.

C. Observation of toxic symptoms

The toxic symptoms were nearly the same as those observed in the subacute toxicity test. In the 1.6 and 3.2g/kg groups, beginning from about the 90th day, there occurred immediately after administration face-washing, coughing and slight general tremor in about one-third of the cases lasting about 15 min. At the time of recovery the animals were slightly in sedation. The intensity of symptoms did not change until the end of administration. Piloerection was also noted. Generally speaking, the intensity of symptoms was stronger in males. In the 6.3g/kg and 12.6g/kg groups the same symptoms as seen above appeared from about the 70th day and tremor of forelimbs, searching behavior, coughing, face-washing and salivation from about the 100th day. The symptoms lasted about 15 min and then gradually moved toward recovery. Toward the end of administration loss of appetite, emaciation and piloerection occurred in all cases and alopecia in one male.

D. Blood tests (Tables 14, 15)

a. WBC: No marked difference was noted between the experimental and control groups when comparison was made before administration, on the 90th day and 180th day. Nevertheless, the number was found to be smaller than the control in the males of the 6.3g/kg group on the 180th day and in both sexes of the 12.6g/kg group, all with significant difference.

b. Hemoglobin: Except that the males of the 6.3g/kg group were smaller in number than the control with significant difference on the 90th day, there was no difference between the experimental and the control groups in both sexes at all time periods.

c. WBC: Some difference was noted between the experimental and the control groups before administration and on the 90th day in both sexes, but the difference was not significant. On the 180th day, however, the males of all experimental groups showed a smaller value than the control, with significant difference in the cases of the 1.6g/kg, 3.2g/kg and 12.6g/kg groups. In females, WBC was slightly increased in all experimental groups, but no significant difference was noted.

e. WBC percentage: As in the subacute toxicity test, the results showed no marked difference in cell distribution between the experimental and control groups at all time periods. No morphologically abnormal cells appeared.

E. Urine tests

No abnormal findings were obtained in sugar, protein, and urobilinogen. The urinary volume, however, tended to increase in the experimental groups.

F. Liver function test (Table 16)

a. BSP excretion test: No tendency of excretion delay was noted in the experimental groups in both sexes as compared to the control. In the females of the 3.2g/kg group the excretion was even faster than the control.

b. Transaminase: GOT and GPT were not increase with dosage in the experimental groups in both sexes, but GPT in the males of the 3.2g/kg group showed a higher value than the control and GOT in the females of the 12.6g/kg

group a lower value, each with significant difference was noted.

G. Total cholesterol, total protein, blood sugar (Table 16)

a. Total cholesterol: There was no definite tendency noted. In males the 3.2g/kg and 6.3g/kg groups showed the same value as the control, the 1.6g/kg group a lower than the control, and the 12.6g/kg group showed a slightly higher value than the control, but no significant difference was noted.

b. Total protein: The males of the 1.6g/kg and 3.2g/kg groups showed a lower value than the control, with significant difference. In females, there was no difference between the experimental and the control groups.

c. Blood sugar: Males generally showed a higher value than the control in all groups, but the correlation to dosage was not evidenced. However, in females, the value tended to increase with dosage and significant difference from the control was noted in the 3.2, 6.3, and 12.6g/kg groups.

H. Autopsy

a. Macroscopic observation of organs: In a few cases in the 6.3g/kg and 12.6g/kg groups there was noted a chronic inflammatory picture in the lung. Otherwise, no macroscopic changes were noted in the thoracic, abdominal or endocrine organs. Smear specimens of the seminal vesicle, epididymus and testis showed no abnormalities. It is unlikely that the function of the testis was impaired.

b. Organ weight (Table 17, Fig. 6)

1) Hypophysis: The weight was lower in the males of the 12.6g/kg group and in the females of all experimental groups than the control, with significant difference.

2) Thymus: The weight tended to decrease with increase in dosage in all experimental groups in both sexes, with significant difference from the control in the cases of the 6.3g/kg (males) and 12.6g/kg (both sexes) groups.

3) Heart: Except that the females of the 1.6g/kg group were greater than the control, there was no difference between the experimental and control groups.

4) Liver: Males showed no difference between the experimental and control groups, but the females of the experimental groups were generally greater than the control, with significant difference.

5) Kidney: It weighed less in the males of the 12.6g/kg group in the bilateral kidneys than the control, with significant difference. Otherwise, there was no difference between the experimental and control groups.

6) Adrenal gland: Generally, the weight tended to increase in the experimental groups in both sexes, with significant difference from the control in the cases of the 1.6g/kg (females), 3.2g/kg (males) and 6.3g/kg (males) groups.

7) Spleen: In males, the weight was decreased in the 12.6g/kg group, with significant difference from the control. The other three groups showed a slightly higher weight than the control. In females, all experimental groups showed a higher weight than the control, and the weight tended to increase, with dosage. The difference with the control was significant in the cases of the 3.2g/kg, 6.3g/kg and 12.6g/kg groups.

8) Prostate: It weighed less in all the experimental groups, and furthermore the weight tended to decrease as the dosage was increased. The difference with the control was significant in the cases of the 3.2g/kg, 6.3g/kg, and 12.6g/kg groups. Even in terms of weight per 100g of body weight, the tendency was of the same and significant difference was noted in the 3.2g/kg, 6.3g/kg, and 12.6g/kg groups.

c. Pathohistological findings

1. Control group

a) Prostate: The glandular ducts folded and were covered with relatively high epithelium which was slightly protruding like papilloma. They were composed of two types of ducts, one type of being a narrow lumen (hereinafter abbreviated as X) and the other being a wide lumen with low epithelium (hereinafter abbreviated as Y). Marked widening of lumen was seen in some Y ducts and the epithelium underwent squamous metaplasis in response to the widening. However, falling-off or disappearance of the epithelium was not observed.

b) Testis: The pictures of seminal ductules varied slightly with cases depending on the stage of spermatogenesis, such as delayed spermatogenesis (hereinafter abbreviated as C), homogenous coagulation (D), numerous Sertoli's cells (E), and transitory impairment of maturation of sperms (F). Degeneration of spermatoblasts (G) was not found at all.

c) Liver: Slight dissociation and partial atrophy of liver cells with fatty droplets were disclosed in a small number of cases. But generally lesions were scarce. Congestion occurred in no cases.

d) Kidneys: Deposit of basophilic crystals in the area between the cortex and medulla, slight congestion of stroma or urinary casts were observed in a small number of cases.

e) Spleen: The pulp slightly coarse, and the blood volume varied with cases.

f) Thymus: The medulla was wide and the cortex developed well, but the cellular density was coarse in many cases.

g) Adrenal gland: In general, the cortex was of uniformly light staining and in some cases distinction of different layers was rather difficult. Severe congestion was also seen in the area between the cortex and medulla in some cases.

h) Thyroid: Colloid was thin. The epithelium was entirely within normal limits.

i) Hypophysis: Acidophiles increased in number in many cases. The organ was slightly edematous, and hemorrhage was seen in a few cases.

No specific findings were obtained in the heart, lungs, brain, pancreas, digestive tracts, bone marrow and ovary.

2) Cer 1.6g/kg group

a) Prostate: The epithelium of X ducts was vacuolated and fell off at time. On the other hand, Y ducts showed marked squamous metaplasia in a few cases, but the difference with the control was not significant.

b) Testis: The findings C, D, E and F were seen sporadically in the normal seminal ductules.

c) Liver: Slight but wide-spread atrophy of liver cells, associated with irregularly-sized nuclei, was seen in a small number of cases. Congestion and fatty droplets were noted sporadically.

d) Kidney: Mild congestion and urinary casts were found in the greater majority of the cases in both sexes. In females, concentric round or irregularly-shaped basophilic crystals, which had been seen in the control group, were found in the parenchyma in the cortico-medullary border area.

e) Spleen: The pulp was congestive and coarse and was deficient in cells in general.

f) Pancreas: Partial atrophy and vacuolation of the acinus and mild edema of stroma were seen in a small number of cases.

g) Thymus: The parenchyma was coarse and the cortical cells also under-developed in a small number of cases. Cellular necrosis was found in one case.

h) Adrenal gland: In the greater majority of cases the fat was deficient and the cortex was uniformly of light staining. In a few cases there occurred severe congestion in the zonal cortex.

i) Thyroid: In most cases it lacked colloid and the epithelium underwent squamous metaplasia at times.

j) Hypophysis: In males acidophiles increased, but in females it consisted chiefly of main cells.

k) There was no great difference between the control and experimental groups in regard to other organs; brain, heart, lungs, digestive tracts, ovary and bone marrow.

3) Cer 3.2g/kg group

a) Prostate: Falling-off or degeneration of epithelium of X ducts was seen in many cases. In general, X ducts were slightly enlarged and Y ducts rather decreased.

b) Testis: The findings C, E, F were seen more frequently in this group than in the previous two groups. However, they were not so severe as to cause dysfunction.

c) Liver: Findings were similar to those seen in the 1.6g/kg group. Atrophy of liver cells, congestion, and deposit of fatty droplets were seen in a few cases.

d) Kidney: The basophilic crystals seen in the 1.6g/kg group were noted in all females, but none in males. Mild congestion and swelling of main tubules were found in nearly all cases. Granule-form deposit was present in Bowman's capsule in a few cases.

e) Spleen: The lymphatic tissue was decreased. The pulp was coarse and deficient in cells. Congestive edema was seen in a few cases.

f) Heart: Histocytes somewhat increased in the pericardium forming small cell foci. In one case they penetrated into the myocardium and in another case they formed round cellular infiltration in the myocardium.

g) Thymus: Both cortex and medulla were coarse and lacked cellular density.

h) Adrenal gland: Congestion was generally noted in females. In males congestion was not evident, and the cortex was of light staining and lacked fat.

i) Thyroid: Scanty colloid. The epithelium was somewhat atrophied and vacuolated in many cases.

j) Hypophysis: As in the 1.6g/kg group, acidophilic cells were increased in males while in females it consisted chiefly of main cells.

No specific findings were obtained in other organs as lungs, digestive tracts, pancreas, ovary and bone marrow.

4) Cer 6.3g/kg group

a) Prostate: Y ducts were fewer than X ducts. In X ducts, some cases were with necrosis of hyaline degeneration of the epithelium, others with stenotic ducts or higher epithelium, while still others with vacuolation or falling-off of epithelium. Y ducts under marked squamous metaplasia. An intermediate type between X ducts and Y ducts was also seen. The stroma was not affected very much, although serious infiltration was seen in some.

b) Testis: All the findings C, D, E and F were observed in mature seminal tubules corresponding to the stages of spermatogenesis. In most cases the tubules were normal and completely free from disturbances interfering with spermatogenesis.

c) Liver: Mild diffuse atrophy of liver cells was seen in a few cases, and the degree was somewhat stronger than that in the 3.2g/kg group. The severity of congestion varied with cases, but was not necessarily stronger than that in the previous three groups.

d) Kidney: Deposit of basophilic crystals was noted in the corticomedullary border area in females. In males this was not noted at all. Turbid swelling, degeneration or necrosis of the epithelium of the renal tubules occurred in no cases.

e) Spleen: The pulp was enlarged and in some cases it became coarse due to congestive edema. Reticulum cells, hematopoietic cells or giant cells were sparse, and deposit of hemosiderin was not evident.

f) Heart: Histocytes and round cells infiltrated beneath the pericardium and then through the stroma to the superficial layer of the myocardium. This was found in one case.

g) Pancreas: Sporadic small acinous atrophy and vacuolation or fatty degeneration of the epithelium was seen in a few cases.

h) Thymus: Serous infiltration of the cortex and medulla was seen over a wide area in a few males. In females the parenchyma was dense in all cases and hemorrhage occurred in no cases.

i) Adrenal gland: Severe congestion and dissociation of cortical cells were found in a few cases. Generally fat was scanty.

j) Thyroid: In general colloid was scanty. Vacuolar swelling and falling-off of the epithelium were seen in some cases.

No specific changes were seen in the brain, hypophysis, lungs, digestive tracts, ovary and bone marrow.

5) Cer 12.6g/kg group

a) Prostate: The findings were nearly the same as those in the 6.3g/kg group. In some cases the epithelium of X ducts completely degenerated and disappeared retaining only the basal membrane, in some other cases vacuolar degeneration and atrophy of the epithelium was noted, and in still other cases Y ducts underwent squamous metaplasia of the epithelium.

b) Testis: Degenerative cells of findings C, D, E, F and G of seminal tubules appeared somewhat more in this group than in the 6.3g/kg group. Of these, seminal tubules with coagulative necrosis and slight calcification (D) and those which consisted of only Seltori's cells (E) were relatively abundantly noted. Nevertheless, most seminal tubules were normal and such marked degeneration as indicating loss of testicular function occurred in no cases.

c) Liver: Diffuse liver atrophy occurred somewhat more frequently in this group than in the 6.3g/kg group. Irregularly-sized nuclei, congestion, and deposit of fatty droplets were extensively noted. Moreover, they were severe in degree.

d) Kidneys: Congestion was considerably severe in both sexes. Turbid swelling of main renal tubules was noted in some cases, and in females basophilic crystals were noted in all cases.

e) Spleen: Lymphatic follicles were slightly atrophied and the pulp was edematous. Giant cells and hemosiderin were not particularly evident.

f) Pancreas: Partial vacuolation of the acinus and fatty droplets occurred in a few cases, the degree being about the same as that in the 6.3g/kg group.

g) Adrenal gland: In males the blood and fat were scarce and the cortex was of light staining. Contrarily, in females, the organ was congestive and contained abundant fat.

h) Hypophysis: Main cells comprised the greater part of the parenchyma and acidophilic cells were sparse. Cells were generally full and congestion was only sporadically seen. In one case a large follicle consisting of mucoid epithelium was noted.

No specific changes were noted in other organs as brain, heart, lungs, digestive tracts, thyroid, ovary, and bone marrow.

IV. Summary

Acute, subacute and chronic toxicity tests were carried out with T-60, GBX and Cernilton using rats and mice, and the following results were obtained.

1. Acute toxicity test

The LD_{50} as determined in Donryu stain rats was high with each sample drug, and there was no difference between sexes. The lethal dose was the smallest by the intraperitoneal route with all sample drugs, whereas the LD_{50} was unobtainable by the oral and subcutaneous routes. In ddN strain mice the results were the same. As in rats, the lethal dose was the smallest by intraperitoneal route, although the sensitivity was somewhat higher than in rats. By the oral and subcutaneous routes, GBX showed the lowest toxicity both in rats and mice. The toxicity was of the same degree both with T-60 and Cer and symptoms manifested at an early period. By the subcutaneous route, GBX exhibited the strongest toxicity both in rats and mice. The toxic symptoms seen with T-60 and Cer at a large dose were piloerection and depression occurring from immediately after to 10 min. after administration and tremor and gait disturbance after 10-30 min. In death cases these symptoms lasted 1-3 hours. Such symptoms also occurred in survivals, but they were rather slight in degree and the animals recovered in about 24 hours. With GBX no specific symptoms occurred and only piloerection, depression, emaciation, local swelling and enduration were noted by the oral and subcutaneous routes. By the intraperitoneal route slight tremor was noted additionally. In death cases food consumption and body weight decreased and animals died in 2-6 days after showing emaciation.

2. Subacute toxicity test

With T-60 suppression of weight increase appeared at a dose of 24.0g/kg in both sexes, with significant difference noted between the males and the control. Death also occurred in a few cases at this dose. With GBX suppression of weight increase occurred evidently in the males of the 10.0g/kg and 20.0g/kg groups, with significant difference from the control. Death occurred in a few cases in each of the 10.0g/kg and 20.0g/kg group. With Cer there was no marked influence noted in either sex, but in the 25.2g/kg group suppression of weight increase occurred in both sexes, with significant difference from the control in the case of females. Death occurred in 2-3 cases in each group.

Toxic symptoms were the same with all sample drugs.

General toxic symptoms appeared from the 15-20th day. Salivation, face-washing, coughing, tremor of forelimbs, and searching behavior occurred 5-20 min after administration lasting 10-20 min, and then from about 30-40 min after administration the animals gradually moved toward recovery after repeating the symptoms of coughing, face-washing, and slight tremor of forelimbs. Toward the end of administration loss of appetite, emaciation, piloerection and depression were markedly observed in all large-dose groups.

RBC, hemoglobin and WBC counts showed significant difference between experimental and control groups at times with T-60 and GBX, but not with Cer.

Results of BSP excretion test were similar with both T-60 and Cer. Namely, excretion was delayed only in males. With GBX delayed excretion was not revealed. GOT and GPT were not raised with any of the sample drugs. Total cholesterol in the T-60 administration groups and blood sugar and total protein in the GBX administration groups were higher than the control with significant difference. In the Cer administration groups total cholesterol slightly increased. Blood sugar was not found related to dosage.

In organ weight some changes were noted in the hypophysis in the Cer administration groups. The weight of the thymus tended to decrease in the experimental groups with all sample drugs. At a large dose the difference with the control was considerably great. The weight of the liver tended to increase with dosage in the GBX and Cer administration groups. It decreased, however, in the T-60 administration groups. The kidney weight increased with dosage in both sexes of the T-60 administration groups and the males of the GBX administration groups.

Contrarily, it decreased in the females of the GBX administration groups and both sexes of the Cer administration groups. With regard to the adrenal gland, the weight increased with dosage in both sexes in all administration groups except in the females of the T-60 administration groups. The spleen showed no definite tendency. At a large dose, however, all administration groups showed a lower weight than the control in both sexes except in the females of the GBX administration groups. The prostate decreased in weight as the dosage was increased in the T-60 and GBX administration groups. In the Cer administration groups the weight was greater than the control. In terms of weight per 100g of body weight, a decreasing tendency was noted in the T-60 administration groups and an increasing tendency in the GBX administration groups. In the Cer administration groups it increased slightly more than the control, but with no significant difference. The weight of the testis showed a decreasing tendency in the GBX administration groups and an increasing tendency in the Cer administration groups. The weight of the spermatocyst was decreased in the T-60 and GBX administration groups and increased in the Cer administration groups.

Pathohistological findings at a small dose were as follows. The prostate showed no great difference among the various groups receiving T-60, GBX, and Cer. The difference with the control was not great either, and there was no tendency of the development of the glandular ducts being suppressed. The testis and liver showed pathological changes in the T-60 and Cer administration groups, but not in the GBX administration groups. The kidney showed no changes with any of the sample drugs.

At a medium dose, Cer produced some changes in the glandular ducts of the prostate. With T-60 and GBX no specific changes were produced. The glandular ducts consisted mostly of high epithelium in all administration groups receiving T-60, GBX and Cer. The testes showed no changes with T-60 and GBX. However, spermatogenesis was slightly suppressed with Cer. In the liver Cer produced the least changes, followed by GBX and T-60 in that order. The kidney was not changed with GBX. The changes were approximately of the same degree and same frequency with Cer an T-60. In the hypophysis acidophilic cells were increased with Cer.

At a large dose, the prostate was composed of high epithelium in many cases in the Cer administration groups. In the T-60 and GBX administration groups dilated ducts were found mixed. Degeneration of X ducts was seen with all sample drugs. In the Cer administration groups, in particular, it occurred in nearly all cases, although the degree was about the same as that in the T-60 and GBX administration groups.

The testis was affected more in the T-60 administration groups than in the other administration groups. In the GBX administration groups it was not affected at all. The findings of the liver varied greatly among the three administration groups, the Cer administration groups showing less findings than the T-60 administration groups and the GBX administration groups showing no difference with the control group. The kidney, too, was little affected by the administration of GBX. However, congestion was seen with Cer and T-60, which occurred far more frequently with the latter. In the hypophysis congestion did not occur with Cer, but instead acidophilic cells were increased. With administration of T-60 and GBX, congestion was noted.

It can be said from the foregoing that hyperplasia of the prostate was suppressed somewhat more strongly with Cer than with T-60 and GBX, but the liver, kidney and other organs were less affected with Cer than with T-60.

3. Chronic toxicity test

In the large-dose group receiving 12.6g/kg, the animals showed normal weight increases as the control group in both sexes except that the weight increase was suppressed after the 100th day of administration. Death occurred in 1-2

cases in each group but no animals died due to drug poisoning. With administration of Cer, face-washing, coughing and general tremor of light degree were noted in the 1.6g/kg and 3.2g/kg groups from immediately after to 15 min after administration beginning from about the 90th day. In the 6.3g/kg and 12.6g/kg groups the foregoing symptoms manifested from about the 70th day; from about the 100th day tremor of forelimbs, searching behavior, coughing, face-washing, and salivation occurred. Toward the end of administration loss of appetite, emaciation and piloerection were markedly noted in the 12.6g/kg group in both sexes. RBC and WBC counts, hemoglobin value, and WBC percentage all showed no marked alterations except that RBC and WBC counts were found increased or decreased around the 180th day in the males of the 1.6g/kg, 3.2g/kg, and 12.6g/kg groups. The urinary volume was somewhat increased, but otherwise no abnormalities were noted in urine in the experimental groups. BSP excretion and transaminase activity, too, showed no great difference between the experimental and control groups. Blood sugar was increased with dosage and significant difference was noted from the control in the case of females in the 3.2g/kg, 6.3g/kg, and 12.6g/kg groups. Total cholesterol was increased with significant difference from the control in the males of the 12.6g/kg group. Total protein was decreased in the males of the 1.6g/kg and 3.2g/kg groups, with significant difference from the control. Macroscopically, no specific changes were found in the organs. The weights of the hypophysis, prostate, thymus, adrenal gland, and spleen were decreased, especially that of the prostate which was only about 2/3 of the control.

Pathohistologically, specific findings were obtained in the prostate and testis. In the case of the prostate, when continuous administration was carried out at a small dose (1.6g/kg), the epithelium of the glandular ducts vacuolated or fell off. At a medium or large dose (3.2-12.6g/kg) degeneration, necrosis or atrophy of the epithelium occurred in many cases. Changes in the seminal ductules in the testis varied considerably. At a medium dose (3.2g/kg) thre occurred delayed spermatogenesis, increased Sertoli's cells, and suppression of maturation of spermatid. In the 6.3g/kg group, in addition to these, degeneration of spermatid was abundantly seen. In the 12.6g/kg group calcification as well as coagulative necrosis of seminal ductules was noted in many cases. In all groups, however, the seminal ductules were not all degenerated; rather, a great majority of ductules presented normal pictures. Smear specimens of the seminal vesicle, testis and epididymus showed no abnormalities, and it was unlikely that the function of the testis was impaired.

The liver showed congestion, deposit of fatty droplets and cellular atrophy in a few cases in the 1.6g/kg group. These changes intensified slightly with dosage and occurred in many cases in the 12.6g/kg group. In the kidney deposit of basophilic crystals was noted in the cortico-medullary border zone in many cases, including the control group. The signification of this manifestation is not clear. Congestion was noted in the control groups as well as in the experimental groups. In the experimental groups, however, it increased in intensity and frequency as the dosage was increased, and in the 12.6g/kg group turbid swelling of renal tubules was disclosed in some cases. Changes were also noted in other organs as the heart, lung, thymus, pancreas, and thyroid, but they were not considered due to administration of the drug since they were also noted in the control group and since the dose-response correlation was not established.

V. Discussion and Concluding Remarks

The LD_{50} of Cer, T-60 and GBX as determined in rats and mice was very large by the oral route. Moreover, toxic symptoms disappeared within a short period of time. The influence on symptoms, development, blood, and organ weight varied little with the sample drugs. However, considering that sugar was detected in the urine in the Cer 25.2g/kg group and that the blood sugar level was raised in the T-60

24.0g/kg and Cer 25.2g/kg groups, continuous administration at a large dose may cause disturbance in the metabolism of sugar. Pathohistological findings at a large dose were degeneration of the epithelium of glandular ducts, hypoplasia of sperms in the testis, fat deposit in the liver, atrophy and congestion of liver cells, and congestion and urinary casts in the kidney. Taking all findings into consideration, the influence on the prostate was the strongest with Cer and other organs were the strongest with T-60. In chronic toxicity test where rats were used, the findings were nearly the same as those seen in the subacute toxicity test. Deposit of basophilic crystals was noted in the kidney and turbid swelling in the epithelium of the renal tubules. In the pancreas partial vacuolation, pimelosis, and atrophy of the acinus were shown, but as they were also seen in the control group, they may bear some connections with the aforementioned rise in blood sugar level.

As seen above, prolonged and missive administration of Cer may cause specific disturbances in the prostate, testis, liver, and kidney and as functional disturbance rise in blood sugar level. Yet, it must be remembered that disturbances would occur only when the drug is administered at the high dosage of 6.3g/kg or 12.6g/kg, which is about 800-1,200 times the normal human dose. On the other hand, the maximum safety dose in rats is about 3.2g/kg, or about 400 times as much as the normal human dose. From all these it is concluded that the toxic symptoms will not likely to manifest in the form of side-effects on clinical levels.

Tab. 1 Dosegs of acute toxicity.

Animal	Route	Sex	T 60	GBX	Cer
			Dose (g/kg)	Dose (g/kg)	Dose (g/kg)
Donryu rats	p.o.	♂	17.92—34.40	20.74—43.00	18.84—27.09
		♀	17.02—34.40	20.74—43.00	18.84—27.09
	s.c.	♂	7.20—14.95	12.00—21.74	10.89—15.69
		♀	——	——	——
	i.p.	♂	5.50—11.40	1.95— 6.99	3.65—13.07
		♀	——	——	——
ddN mice	p.o.	♂	25.05—39.70	39.70—79.50	31.50—46.12
		♀	17.90—44.60	33.71—83.97	18.84—39.00
	s.c.	♂	4.15—21.50	13.50—48.58	9.98—17.68
		♀	——	——	——
	i.p.	♂	3.98—20.10	1.13— 2.81	4.00—14.54
		♀	——	——	——

Tab. 2 LD 50 of T-60, GBX and Cer

( ) shows fiducial limits

animal	route	sex	Cernitin T 60	Cernitin GBX	Cernilton
Donryu rats	p.o.	♂	34.40g/kg <	43.00g/kg <	27.01g/kg <
		♀	34.40g/kg <	43.00g/kg <	27.01g/kg <
	s.c.	♂	14.95g/kg <	20.74g/kg <	15.69g/kg <
		♀	——	——	——
	i.p.	♂	7.58g/kg (7.14— 8.04)	3.31g/kg (2.99— 3.66)	6.66g/kg (6.02— 7.35)
		♀	——	——	——
ddN mice	p.o.	♂	31.90g/kg (30.38—33.50)	55.45g/kg (49.30—62.25)	37.78g/kg (36.35—39.27)
		♀	27.75g/kg (26.66—28.89)	52.25g/kg (50.21—54.38)	27.61g/kg (26.54—28.71)
	s.c.	♂	9.47g/kg (8.78—10.21)	26.13g/kg (24.47—27.92)	13.06g/kg (12.51—13.63)
		♀	——	——	——
	i.p.	♂	8.31g/kg (7.63— 9.07)	1.72g/kg (1.64— 1.81)	6.94g/kg (6.33— 7.61)
		♀	——	——	——

Tab. 3 Food consumption during T-60, GBX, and Cernilton administration (35 days).

sample	T-60				GBX				Cernilton			
	control	6.3 g/kg	12.6 g/kg	25.2 g/kg	control	6.0 g/kg	12.0 g/kg	24.0 g/kg	control	5.0 g/kg	10.0 g/kg	20.0 g/kg
dose	18.35	14.80	14.31	8.00	17.80	14.19	17.80	7.69	19.67	16.97	14.81	12.67
	15.72	12.95	12.25	7.8	14.90	14.00	16.00	7.94	15.42	13.10	14.13	13.44

(g/animal/day)

Tab. 4 Changes in blood picture during 35 days of Cernitin T-60 administration (p.o.).
(average of five cases)

Sex	Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Baso-phile %	Acido-phile %	Neutrophile % staff	Neutrophile % segment	Lympho-cytes %	Mono-cytes %	Others %
♂	before	control	6.29±0.37	9.8±0.43	7.86±0.73	0.2	1.0	1.0	22.4	73.8	1.6	0
		6 g/kg	4.86±0.29	10.0±0.60	7.18±0.62	0	2.2	1.6	27.2	65.6	3.4	0
		12 g/kg	5.62±0.60	9.1±0.36	6.84±0.66	0.2	2.0	1.4	20.0	72.8	3.6	0
		24 g/kg	5.42±0.32	10.6±0.47	7.96±0.46	0.4	2.2	1.6	25.2	67.6	3.0	0
	after 35 days	control	7.13±0.47	13.8±0.25	9.7 ±0.31	0.2	0.8	1.4	26.4	69.0	2.2	0
		6 g/kg	6.11±0.26	12.4±0.45*	8.80±0.33	0.2	0.4	2.0	23.6	70.8	2.8	0.2
		12 g/kg	6.55±0.27	12.2±0.41*	10.12±0.48	0.2	1.2	1.4	22.0	73.2	2.0	0
		24 g/kg	5.80±0.23*	12.7±0.23*	8.80±0.33	0	3.0	1.4	29.0	64.4	2.2	0
♀	before	control	5.49±0.27	9.6±0.35	7.16±0.66	0.2	0.6	1.4	27.0	68.8	2.0	0
		6 g/kg	5.35±0.33	10.1±0.24	7.22±0.90	0.2	1.0	1.2	23.6	71.0	3.0	0
		12 g/kg	5.25±0.26	9.1±0.36	6.86±0.50	0.2	2.0	1.2	18.8	75.6	2.2	0.2
		24 g/kg	4.87±0.33	9.0±0.37	7.04±0.41	0	0.4	0.8	31.0	62.8	4.8	0
	after 35 days	control	6.96±0.28	13.8±0.26	7.64±0.71	0	0.8	1.4	24.8	69.2	3.8	0
		6 g/kg	6.92±0.40	13.8±0.61	9.18±0.48	0	2.8	1.2	25.4	70.0	2.6	0
		12 g/kg	6.17±0.27	12.6±0.39*	10.76±0.85*	0	1.8	1.0	26.8	67.8	2.6	0
		24 g/kg	5.95±0.34*	12.5±0.39*	9.19±0.47*	0	1.4	1.8	22.2	72.0	2.6	0

± : standard error * : $P < 0.05$ significant

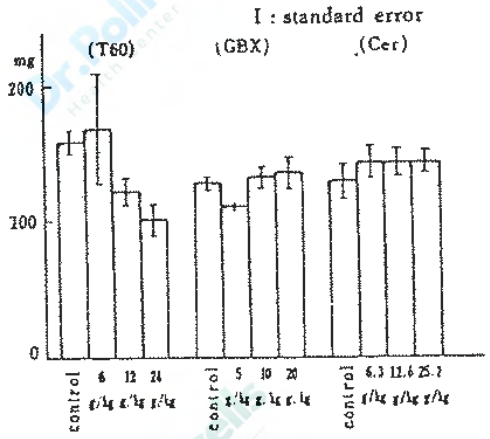

Fig. 4 Average prostate weight after 35 days T-60, GBX and CERNILTON administration (p. o.)
(Prostate weight/100 g body weight)

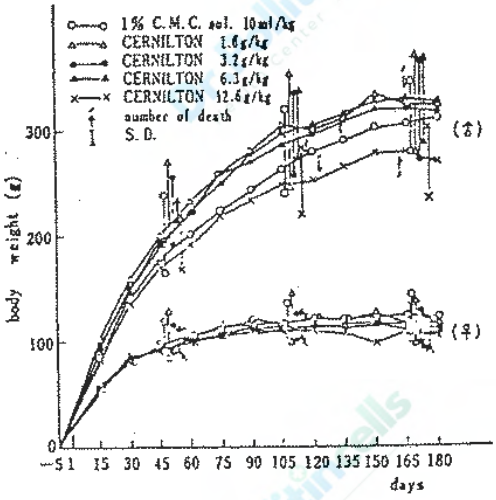

Fig. 5 Body weight increase in rats receiving CERNILTON daily for 180 days (p. o.)

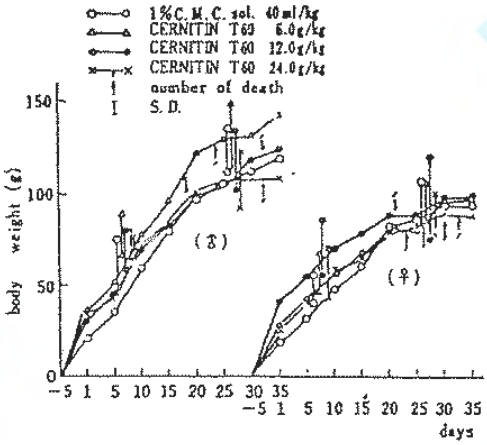

Fig. 1 Body weight increase in Rats receiving T-60 daily during 35 days. (p.o.)

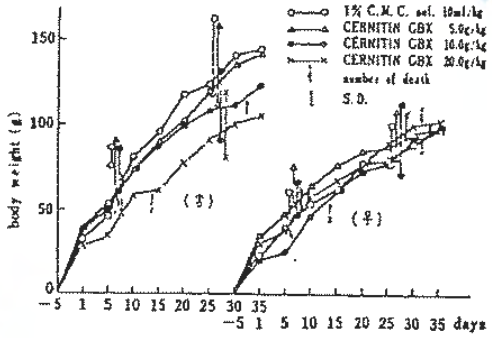

Fig. 2 Body weight increase in rats receiving GBX daily during 35 days (p. o.)

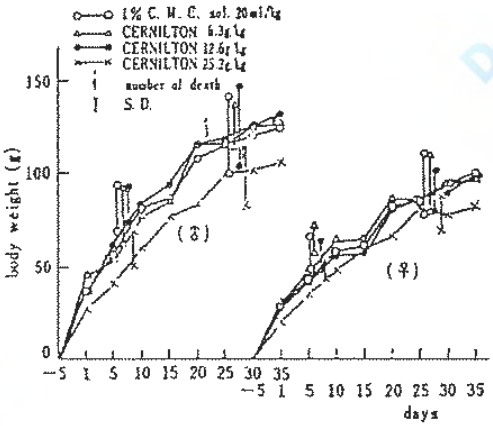

Fig. 3 Body weight increase in rats receiving CERNILTON daily during 35 days (p. o.)

Tab. 5 Changes in blood picture during 35 days of Cernitin GBX administration (p.o.)
(average of five cases)

Sex	Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Baso-phile %	Acido-phile %	Neutrophile %		Lympho-cytes %	Mono-cytes %	Others %
								staff	seg-ment			
♂	before	control	5.44±0.23	8.6±0.48	7.44±0.65	0.2	1.4	1.4	29.6	63.2	4.0	0.2
		5 g/kg	5.09±0.10	7.9±0.30	7.54±0.49	0	1.4	1 2	23.4	68.4	3.6	0
		10 g/kg	4.52±0.14	9.4±0.68	7.80±0.31	0.2	1.0	1.4	23.6	70.6	3.2	0
		20 k/kg	5.22±0.18	9.8±0.33	7.82±0.57	0.2	0.8	0.8	31.6	62.0	4.4	0.2
	after 35 days	control	6.01±0.20	12.5±0.30	10.38±0.25	0	1.8	1.0	27.2	66.6	2.8	0
		5 g/kg	6.07±0.40	12.5±0.26	9.98±0.94	0	2.4	1.6	22.2	72.0	1.6	0.2
		10 g/kg	5.80±0.20	12.5±0.30	9.62±0.67	0	0.8	2.4	24.0	70.4	2.4	0
		20 g/kg	5.89±0.56	12.8±0.34	8.72±0.56*	0.2	0.8	1.2	28.6	67.2	2.0	0
♀	before	control	5.95±0.16	9.5±0.41	6.40±0.25	0.4	2.0	1.6	21.4	70.0	3.4	0.2
		5 g/kg	5.32±0.45	8.0±0.27	7.64±0.48	0	1.4	0.6	14.4	70.4	5.0	0.2
		10 g/kg	6.08±0.34	9.2±0.42	6.24±0.50	0	1.6	1.0	23.8	70.4	3.2	0
		20 g/kg	5.04±0.22	10.4±0.41	7.56±0.38	0.2	0.6	2.6	27.6	64.0	4.8	0.2
	after 35 days	control	5.95±0.19	13.4±0.39	10.94±0.79	0	1.2	1.4	21.4	74.0	2.0	0
		5 g/kg	6.07±0.26	13.0±0.14	11.20±0.52	0.2	1.0	1.4	21.0	74.6	1.8	0
		10 g/kg	6.23±0.26	11.8±0.27*	8.94±0.51	0	2.0	1.6	26.4	67.6	2.2	0.2
		20 g/kg	6.27±0.25	12.5±0.43	9.42±0.53	0	1.0	0.6	21.0	75.6	1.8	0

± : standard error * : $P < 0.05$ significant

Tab. 6 Changes in blood picture during 35 days Cernilton administration (p.o.)
(average of five cases)

Sex	Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Baso-phile %	Acido-phile %	Neutrophile %		Lympho-cytes %	Mono-cytes %	Others %
								staff	seg-ment			
♂	before	control	5.57±0.16	10.3±0.57	9.92±0.79	0	0.8	1.2	30.6	65.6	3.8	0
		6.3 g/kg	5.70±0.28	9.2±0.30	8.18±0.23	0	0.8	1.6	24.0	70.0	3.6	0
		12.6 g/kg	5.61±0.47	10.3±0.46	8.68±0.43	0	0.8	1.4	24.6	69.2	3.8	0
		25.2 g/kg	5.04±0.22	10.4±0.41	8.56±0.38	0	0.8	0.8	23.4	74.8	1.8	0
	after 35 days	control	6.56±0.34	13.0±0.14	10.10±0.56	0	1.6	1.2	28.4	66.6	2.2	0
		6.3 g/kg	6.10±0.34	13.0±0.14	9.86±0.50	0	2.0	1.4	25.4	68.8	2.4	0
		12.6 g/kg	6.06±0.21	12.6±0.19	9.98±0.51	0.2	1.4	2.0	28.6	65.8	2.0	0
		25.2 g/kg	7.13±0.47	13.8±0.25	9.70±0.31	0	0.6	1.6	26.6	67.8	3.4	0
♀	before	control	5.65±0.20	10.0±0.53	8.56±0.88	0	0.6	1.2	25.8	68.8	3.6	0
		6.3 g/kg	6.11±0.52	9.0±0.15	8.00±0.54	0.2	0.8	1.4	26.4	69.0	2.2	0
		12.6 g/kg	5.96±0.14	10.7±0.83	7.42±0.44	0	0.8	1.6	27.0	67.0	3.6	0
		25.2 g/kg	5.19±0.25	9.7±0.44	7.18±0.21	0	1.2	1.4	26.2	68.2	3.0	0
	after 35 days	control	6.18±0.22	13.2±0.14	8.76±0.47	2.0	0	0.8	28.4	66.6	2.2	0
		6.3 g/kg	6.67±0.24	13.5±0.26	9.88±0.70	0	1.2	1.0	25.6	69.6	2.6	0
		12.6 g/kg	5.86±0.14	13.2±0.32	9.18±0.53	0	1.6	0.4	20.4	74.8	2.8	0
		25.2 g/kg	6.96±0.28	13.8±0.26	7.64±0.71	0	2.0	0.8	22.4	72.2	2.6	0

± : standard error

Tab. 7 Hepatic function on 35 th day of T-60 administration (p.o.)

Sex	Dose	BSP (%)	Transaminase (Karmen unit)		Cholesterol (mg/dl)	Blood suger (mg/dl)	Total protein (g/dl)
			GOT	GPT			
♂	control	10.4±3.8	91.8±6.0	31.3±2.2	49.7±3.4	95.6±32.5	7.1±0.3
	6 g/kg	20.5±3.0*	70.5±2.2*	24.0±1.4*	55.9±2.9	72.7± 3.8	7.4±0.2
	12 g/kg	20.5±1.7*	78.3±2.7	28.0±1.3	70.6±4.6*	69.8±26.1	7.6±0.2
	24 g/kg	13.1±2.8	68.3±0.6*	25.0±3.6	64.0±2.7*	112.8± 3.4	8.0±0.1*
♀	control	12.1±1.4	71.2±2.4	25.6±0.6	58.3±4.9	88.5±16.5	7.6±0.2
	6 g/kg	12.6±1.5	70.3±3.5	24.3±1.5	56.0±3.6	55.7± 0.6	7.4±0.1
	12 g/kg	8.2±2.0	67.0±4.4	25.5±1.8	51.1±1.9	133.4±12.6	7.8±0.1
	24 g/kg	8.8±2.8	71.0±5.6	31.3±7.1	40.0±3.2*	100.4±36.6	7.6±2.5

± : standard error * : P <0.05 significant

Tab. 8 Hepatic function on 35 th day of GBX administration (p.o.)

Sex	Dose	BSP (%)	Transaminase (Karmen unit)		Cholesterol (mg/dl)	Blood suger (mg/dl)	Total protein (g/dl)
			GOT	GPT			
♂	control	23.7±2.7	85.4±3.3	28.4±1.9	54.2±4.1	72.8± 1.8	7.4±0.2
	5 g/kg	9.2±2.1*	92.0±3.0	31.3±4.3	56.5±1.6	141.4±14.5*	7.8±0.1*
	10 g/kg	14.1±3.1*	84.8±6.0	29.0±1.8	60.5±1.9	124.9±17.9	7.5±0.1
	20 g/kg	7.8±5.0*	78.8±0.8	29.0±1.5	57.1±3.1	136.9±12.9*	7.2±0.2
♀	control	8.0±1.3	73.8±4.1	22.8±0.8	50.2±3.6	76.8± 6.0	7.0±0.2
	5 g/kg	5.6±1.0	74.5±7.3	29.5±1.0*	49.2±2.6	100.9±12.1	7.7±0.2*
	10 g/kg	4.2±1.0*	66.0±2.6	25.7±1.5	36.6±3.8*	129.0± 8.1*	7.7±0.2*
	20 g/kg	6.0±1.5	70.3±3.8	26.5±3.0	40.4±1.8	133.4± 9.1*	7.5±0.2

± : standard error * : P <0.05 significant

Tab. 9 Hepatic function on 35 th day of Cernilton administration (p.o.).

Sex	Dose	BSP (%)	Transaminase (Karmen unit)		Cholesterol (mg/dl)	Blood suger (mg/dl)	Total protein (g/dl)
			GOT	GPT			
♂	control	10.4±3.8	91.8±6.0	31.3±2.2	49.7±3.4	95.6±32.5	7.1±0.3
	6.3 g/kg	15.1±3.8	78.8±3.3	28.8±1.9	51.5±2.8	56.2±11.4	7.8±0.1
	12.6 g/kg	14.0±4.4	78.5±2.9	24.0±0.8*	55.3±5.5	59.4± 6.8	7.5±0.2
	25.2 g/kg	18.0±6.6	71.0±1.2*	26.8±1.5*	60.8±6.0	111.8± 5.8	7.6±0.1
♀	control	12.1±1.4	71.2±2.4	25.6±0.6	58.3±4.9	88.5±16.5	7.5±0.5
	6.3 g/kg	7.6±1.1*	68.4±4.2	23.2±1.2	66.2±3.6	76.5±14.6	7.6±0.1
	12.6 g/kg	7.5±1.9	77.3±4.6	26.3±1.6	63.7±6.4	72.8±14.1	7.7±0.1
	25.2 g/kg	9.4±2.2	63.8±3.8	21.3±1.3	74.8±4.6*	117.1± 7.3	7.4±0.4

± : standard error * : P <0.05 significant

Tab. 10 Average organ weight after 35 days

Sex	Dose	Hypophisis (mg)	Thymus (mg)	Heart (mg)	Liver (g)	Kidney (mg)	
						L.	R.
♂	control (8)	9.0±0.3	323.9±32.5	818.3±39.0	6.90±0.41	808.5±39.0	817.4±34.7
	6 g/kg (9)	9.4±0.8	374.0±42.4	924.0±30.1*	7.74±0.39	922.9±27.2*	879.7±31.7
	12 g/kg (9)	10.9±0.4*	335.1±19.1	878.9±23.8	6.90±0.25	795.7±24.5	807.9±19.3
	24 g/kg (7)	8.7±0.4	218.6±20.6*	715.9±23.3*	6.58±0.21	678.1±18.4*	674.6±21.6*
♀	control (10)	12.0±0.5	437.7±33.0	754.1±19.3	6.59±0.32	730.3±26.2	738.4±25.4
	6 g/kg (9)	10.7±1.8	440.4±26.4	812.7±28.8	6.38±0.16	778.0±31.1	752.3±37.5
	12 g/kg (9)	11.2±0.8	327.3±23.8*	713.3±24.5	6.58±0.24	744.9±35.8	733.4±37.6
	24 g/kg (7)	18.1±1.9*	347.0± 9.1*	655.9±28.1*	6.03±0.44	686.3±30.6	659.4±30 3

± : standard error * : P<0.05 significant ( ) : number of cases

Tab. 11 Average organ weight after 35 days

Sex	Dose	Hypophisis (mg)	Thymus (mg)	Heart (mg)	Liver (g)	Kidney (mg)	
						L.	R.
♂	control (10)	8.5±0.5	359.3±18.4	904.7±29.0	7.22±0.30	901.2±27.1	860.5±24.8
	5 g/kg (9)	7.8±0.5	338.8±28.6	901.2±30.0	8.21±0.25*	885.1±33.1	863.2±29.6
	10 g/kg (8)	9.8±0.4*	347.9±14.3	878.9±34.7	8.29±0.26*	877.0±31.3	860.3±36.6
	20 g/kg (9)	8.6±0.9	293.4±26.1	794.7±30.9*	8.83±0.29*	828.9±21.5*	806.2±26.7
♀	control (10)	12.4±2.7	408.6±10.0	765.0±24.5	6.61±0.39	756.8±34.6	737.4±16.4
	5 g/kg (9)	12.8±1.0	383.2±33.3	794.6±26.2	7.74±0.35*	731.2±30.3	716.9±34.2
	10 g/kg (7)	12.7±1.1	388.9±24.6	782.6±27.2	8.10±0.24*	838.1±32.6	816.9±26.9
	20 g/kg (7)	12.6±0.5	384.1±21.1	837.0±39.2	8.81±0.51*	917.3±41.0*	837.0±33.3

± : standard eror * : P<0.05 significant ( ) : number of cases

Tab. 12 Average organ weight after 35 days

Sex	Dose	Hypophisis (mg)	Thymus (mg)	Heart (mg)	Liver (g)	Kidney (mg)	
						L.	R.
♂	control (9)	9.0±0.3	323.9±32.5	818.3±39.0	6.90±0.41	808.5±39.0	817.4±34.7
	6.3 g/kg (9)	9.7±0.4	343.0±13.2	886.2±20.1	7.07±0.12	858.8±20.6	836.2±17.0
	12.6 g/kg (8)	10.1±0.4*	328.6±18.3	834.8±31.1	7.43±0.30	888.1±25.9	849.5±35.7
	25.2 g/kg (10)	11.2±0.4*	353.5±17.7	851.5±29.5	10.40±0.31*	1043.4±32.6	1035.7±30.0*
♀	control (10)	12.1±0.8	403.6±19.5	735.3±22.9	6.59±0.27	730.3±23.1	738.4±38.2
	6.3 g/kg (9)	15.6±1.1*	419.1±50.1	788.7±28.8	6.79±0.23	752.0±22.6	761.3±34.4
	12.6 g/kg (9)	14.4±1.3	385.1±24.0	789.0±29.3	6.76±0.22	763.0±26.7	751.0±26.4
	25.2 g/kg (10)	10.9±0.4	280.1±14.0*	709.0±15.8	9.24±0.30*	814.2±29.3	760.8± 8.4

± : standard error * : P<0.05 significant ( ) : number of cases

Cernitin T-60 administration (p.o.).

Adrenal (mg)		Spleen (mg)	Prostate (mg)	Testis (mg)	Epididymis (mg)	Seminal vecicle (mg)
L.	R.					
15.9±1.4	16.8±1.0	492.8±43.7	390.7±38.0	1029.4±29.6	434.3±28.3	695.6±101.2
20.3±1.9	17.2±2.0	588.2±20.2	405.6±40.1	1014.5±54.1	429.9±18.2	842.2±132.8
21.2±1.6*	20.6±1.0*	485.3±25.5	273.0±16.9*	1009.7±75.0	463.1± 9.9	649.4± 20.2
20.1±0.9*	19.1±0.9	419.0± 5.7	209.4±28.2*	1014.0±45.0	411.6±51.6	467.9± 29.1*
33.2±0.5	32.5±1.2	426.5±50.7				
38.8±1.6*	39.3±1.8*	467.6±25.9				
31.9±2.4	31.0±2.3	494.0±41.4				
32.1±1.6	28.3±3.0	338.9±36.6				

Cernitin GBX administration (p.o.).

Adrenal (mg)		Spleen (mg)	Prostate (mg)	Testis (mg)	Epididymis (mg)	Seminal vecicle (mg)
L.	R.					
13.7±1.2	11.5±1.1	553.5±28.2	306.7±18.1	1072.7±26.7	504.2± 9.6	741.2±74.0
16.0±0.5	14.2±0.5*	491.0±19.3	271.9±14.5	1068.6±45.4	404.8±12.4*	618.6±55.1
16.5±0.7	15.0±0.8*	477.1±27.6	300.0±24.7	1049.0±37.3	428.8±10.3*	645.8±45.3
19.1±0.8*	17.0±0.7*	432.1±77.4	280.0±28.3	1002.0±20.3*	501.8±51.4	408.1±17.8*
34.8±1.8	34.9±1.4	504.6±29.2				
38.2±1.4	39.7±3.8	532.7±40.0				
34.9±2.3	37.7±3.1	507.0±31.6				
42.6±3.0*	38.4±2.1	543.0±21.6				

Cernilton administration (p.o.).

Adrenal (mg)		Spleen (mg)	Prostate (mg)	Testis (mg)	Epididymis (mg)	Seminal vecicle (mg)
L.	R.					
15.9±1.4	16.8±1.0	492.8±43.7	290.7±38.0	1029.4±29.6	434.3±28.3	695.6±101.2
14.8±0.8	14.1±0.8*	488.4±13.8	322.6±22.1	1053.4±23.3	433.9± 8.0	715.3± 50.2
19.8±0.5*	19.5±0.5*	533.1±31.2	322.8±23.6	1115.6±24.3*	481.6± 9.7	894.3± 55.3
27.7±0.4*	27.1±0.3*	474.0±23.6	320.2±19.7	1150.4±30.2*	460.2±14.6	864.6± 56.8
34.2±1.6	28.8±1.7	474.0±29.1				
33.3±2.4	34.6±1.7*	537.7±49.7				
40.7±2.2*	38.7±1.0*	451.6±21.9				
39.3±1.2*	41.3±1.5*	392.3±15.6*				

Tab. 13 Food consumption during Cernilton administration (180 days). (g/animal/day)

Sex	Months / Dose	before	1	2	3	4	5	6
♂	control	14.92	16.01	20.00	18.90	20.40	20.03	19.81
	1.6 g/kg	16.58	20.20	22.09	20.94	21.03	21.43	19.10
	3.2 g/kg	15.82	19.32	19.64	21.95	20.65	18.57	18.19
	6.3 g/kg	16.54	18.84	19.04	19.56	17.76	17.79	14.40
	12.6 g/kg	15.38	15.85	14.85	16.03	14.00	15.10	14.19
♀	control	13.92	14.22	13.68	12.66	13.13	10.39	12.41
	1.6 g/kg	13.66	14.06	13.57	12.62	12.76	13.50	12.87
	3.2 g/kg	13.68	14.39	12.38	11.85	11.76	12.17	12.14
	6.3 g/kg	14.40	14.79	12.19	11.48	11.27	10.99	11.41
	12.6 g/kg	14.14	13.24	10.23	10.16	10.14	9.70	8.91

Tab. 14 Changes in blood picture during 180 days Cernilton administration (p.o.). (male rats)

Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Basophile %	Acidophile %	Neutrophile staff	Neutrophile segment	Lymphocytes %	Monocytes %	Others %
before	control	6.53±0.44	10.6±0.28	12.80±0.10	0	1.2	1.0	31.2	62.8	3.8	0
	1.6 g/kg	7.35±0.27	10.3±0.35	11.84±0.82	0	2.2	1.0	30.0	65.4	3.2	0.2
	3.2 g/kg	6.87±0.37	10.6±0.26	10.84±0.98	0	1.4	1.2	28.8	66.4	2.2	0
	6.3 g/kg	6.80±0.84	10.1±0.38	10.28±1.03	0	1.2	1.6	31.0	62.2	3.8	0.2
	12.6 g/kg	7.03±0.34	9.8±0.24	10.36±0.71	0	1.0	0.8	25.2	70.0	3.0	0
after 90 days	control	7.57±0.24	13.4±0.31	10.42±1.35	0.2	3.6	0.8	27.6	66.4	1.4	0
	1.6 g/kg	7.40±0.26	13.3±0.25	10.36±0.71	0.2	2.0	0.8	25.0	71.6	0.4	0
	3.2 g/kg	8.01±0.36	13.1±0.08	9.36±1.24	0.2	2.8	1.0	22.8	71.0	2.2	0
	6.3 g/kg	7.89±0.23	12.3±0.23*	8.86±0.60	0	1.6	2.2	28.2	77.6	2.4	0
	12.6 g/kg	8.23±0.28	13.2±0.17	12.3 ±0.90	0.2	3.2	0.6	28.0	65.8	3.0	0.2
after 180 days	control	7.11±0.52	11.6±0.78	12.00±0.55	0	1.8	1.6	30.2	64.8	1.6	0
	1.6 g/kg	6.91±0.52	12.6±0.96	7.98±0.28*	0	1.6	1.0	30.4	65.8	1.2	0
	3.2 g/kg	7.07±0.24	12.6±0.44	9.30±0.70*	0	1.8	1.0	25.6	69.6	1.8	0.2
	6.3 g/kg	6.55±0.41	12.8±0.32	10.64±1.06	0	1.2	0.4	29.8	66.2	2.4	0
	12.6 g/kg	6.54±0.49	12.5±0.69	9.52±0.76*	0.2	1.2	0.8	22.6	72.6	2.6	0

± : standard error * : $P < 0.05$ significant

Tab. 15 Changes in blood picture during 180 days Cernilton administration (p.o).
(female rats)

Test	Dose	Red 10^6/mm³	Hemoglobin g/dl	White 10^3/mm³	Baso-phile %	Acido-phlie %	Neutrophile % staff	Neutrophile % segment	Lympho-cytes %	Mono-cytes %	Others %
before	control	7.35±0.43	11.6±0.35	12.00±0.99	0	2.4	1.0	25.2	67.2	4.0	0.2
	1.6 g/kg	7.35±0.52	11.8±0.36	10.44±0.87	0	2.6	1.2	32.4	59.2	4.6	0
	3.2 g/kg	6.94±0.44	11.2±0.36	8.28±0.38	0	0.8	1.2	24.8	69.8	3.2	0.2
	6.3 g/kg	6.84±0.34	10.9±0.13	10.44±0.53	0	2.2	1.2	20.0	73.4	2.8	0.4
	12.6 g/kg	6.64±0.48	10.9±0.42	12.08±1.25	0.4	2.6	1.0	25.4	67.0	3.6	0
after 90 days	control	7.12±0.55	12.0±0.40	11.00±1.39	0	2.2	0.6	26.0	68.0	4.0	0
	1.6 g/kg	7.95±0.27	11.2±0.23	10.46±0.36	0	3.4	0.2	29.0	65.4	2.0	0
	3.2 g/kg	8.39±0.25	12.3±0.55	10.84±0.60	0.6	2.2	0.4	28.2	65.8	2.8	0
	6.3 g/kg	8.09±0.35	12.3±0.34	8.70±0.67	0	1.6	0.2	22.2	72.0	4.0	0
	12.6 g/kg	7.53±0.23	12.1±0.35	11.20±0.81	0	4.6	0	28.2	65.2	2.0	0
afte 180 days	control	7.19±0.15	13.2±0.50	8.24±0.62	0	0.8	1.4	38.0	58.6	1.0	0.2
	1.6 g/kg	7.37±0.35	14.5±0.57	9.44±0.38	0	1.2	0.6	24.0	72.6	1.6	0
	3.2 g/kg	7.42±0.42	12.4±0.28	9.48±0.73	0	2.2	0.6	28.2	68.0	1.0	0
	6.3 g/kg	6.57±0.33	12.7±0.26	10.16±0.77	0	1.6	1.6	31.4	63.2	2.2	0
	12.6 g/kg	6.03±0.32*	12.6±0.34	9.50±0.64	0.2	4.8	1.8	28.0	65.6	2.0	0

± : standard error * : $P < 0.05$ signficant

Tab. 16 Hepatic function on 180 th day Cernilton administration (p.o.)

Sex	Dose	BSP (%)	Transaminase(Karmen unit) GOT	Transaminase(Karmen unit) GPT	Cholesterol (mg/dl)	Blood surger (mg/dl)	Total protein (g/dl)
♂	control	46.7±4.3	70.2± 7.2	41.4±6.3	96.4± 4.6	84.4±19.2	8.6±0.2
	1.6 g/kg	55.9±3.8	75.8± 2.1	31.5±1.0	68.1± 3.4*	108.5± 7.6	7.9±0.1*
	3.2 g/kg	50.7±8.0	64.8± 1.8	28.5±1.3	80.5±10.0	95.1± 6.4	7.8±0.2*
	6.3 g/kg	46.5±4.3	85.8± 6.5	33.8±5.3	93.7±10.7	97.8± 6.3	8.4±0.1
	12.6 g/kg	47.6±4.4	67.8± 4.2	34.0±4.1	144.2±20.2*	113.5± 8.9	8.9±0.3
♀	control	50.4±7.2	80.6± 5.7	29.2±0.8	120.1±10.6	88.3± 3.8	8.9±0.3
	1.6 g/kg	44.5±7.0	74.8± 4.1	28.0±1.1	106.8± 8.6	80.6± 8.4	9.1±2.8
	3.2 g/kg	29.7±1.9*	87.2±13.6	40.0±7.7*	106.2± 8.8	100.0± 2.3*	8.8±2.1
	6.3 g/kg	41.5±4.4	66.8± 5.5	21.8±5.7	99.7± 7.9	163.0±13.4*	8.3±0.2
	12.6 g/kg	50.2±4.2	64.6± 2.5*	35.0±3.8	140.0± 8.3	169.8±12.0*	9.0±0.1

± : standard error * : $P < 0.05$ significant

Tab. 17 Average organ weight after 180 days Cernilton administration (p.o.)

Sex	Dose	Hypophisis (mg)	Thymus (mg)	Heart (mg)	Liver (g)	Kidney (mg)		Adrenal (mg)		Spleen (mg)	Prostate (mg)
						L.	R.	L.	R.		
♂	control (10)	11.5 ±0.5	302.2 ±13.6	1333.5 ±66.9	11.09 ±0.47	1488.9 ±69.3	1427.2 ±61.9	21.9 ±1.0	22.6 ±0.9	755.1 ±56.4	753.8 ±69.0
	1.6 g/kg (9)	12.6 ±0.6	277.5 ±14.1	1419.3 ±38.7	11.66 ±0.49	1396.8 ±65.1	1336.9 ±59.8	23.6 ±0.9	24.0 ±1.1	774.4 ±29.9	659.9 ±75.5
	3.2 g/kg (9)	10.3 ±1.1	250.4 ±22.3	1457.4 ±28.2	11.42 ±0.37	1468.1 ±42.7	1410.9 ±40.2	26.9 ±1.8*	28.1 ±1.1*	794.6 ±52.7	500.8 ±37.3*
	6.3 g/kg (9)	11.0 ±0.4	237.9 ±25.3*	1469.6 ±25.3	11.67 ±0.31	1543.1 ±32.9	1491.8 ±21.8	25.6 ±1.1*	23.1 ±1.1	797.8 ±32.8	491.4 ±45.1*
	12.6 g/kg (8)	9.6 ±0.5*	189.5 ±16.8*	1264.3 ±32.5	10.37 ±0.35	1303.3 ±53.1*	1211.6 ±39.3*	23.4 ±1.4	22.9 ±1.8	562.4 ±16.5*	403.8 ±35.3*
♀	control (10)	14.4 ±1.4	196.8 ±12.1	824.1 ±15.7	6.71 ±0.34	784.7 ±31.0	784.9 ±27.8	27.9 ±0.7	28.5 ±1.2	460.0 ±21.0	
	1.6 g/kg (9)	11.1 ±0.4*	200.7 ± 3.8	907.4 ±35.2*	7.09 ±0.28	811.5 ±23.6	852.1 ±70.8	32.4 ±1.4*	33.2 ±1.3*	504.0 ±15.8	
	3.2 g/kg (10)	11.2 ±0.4*	195.8 ±10.4	888.3 ±28.2	9.27 ±0.26*	870.4 ±30.6	837.8 ±21.4	29.2 ±1.1	27.4 ±1.3	543.4 ±22.2*	
	6.3 g/kg (10)	11.2 ±0.4*	179.0 ± 9.2	822.9 ±12.3	7.01 ±0.13	769.4 ±16.2	763.2 ±19.9	29.7 ±0.9	30.3 ±0.8	542.2 ±21.4*	
	12.6 g/kg (10)	10.4 ±0.3*	163.3 ± 8.5*	863.1 ±21.3	7.19 ±0.20	770.5 ±25.2	771.5 ±18.7	28.2 ±0.5	25.5 ±1.1	607.0 ±45.0*	

±: stadard error *: $P < 0.05$ significant ( ): number of cases

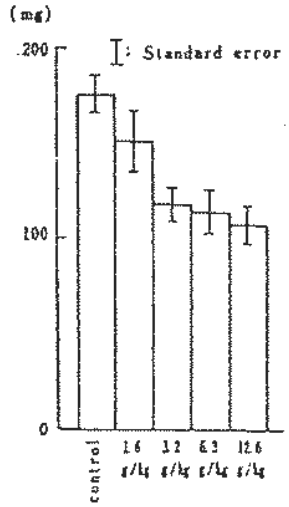

Fig. 6 Average prostate weight after 180 th day CERNILTON administration (p. o.) (prostate weight/100 g body weight)

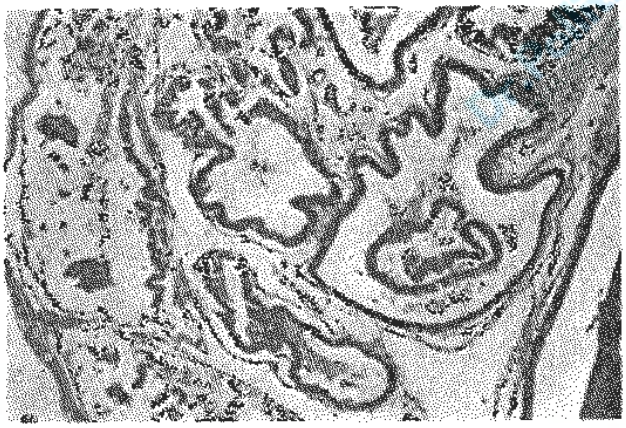

Photo 1. Prostate. Cernilton 12.6g/kg group, male (survival). Glandular ducts A (signifying Undilated glandular ducts with relatively thick epithelium which creased and protruded in the ducts like papilloma) were slightly dilated and the epithelium partially fell off and disappeared.

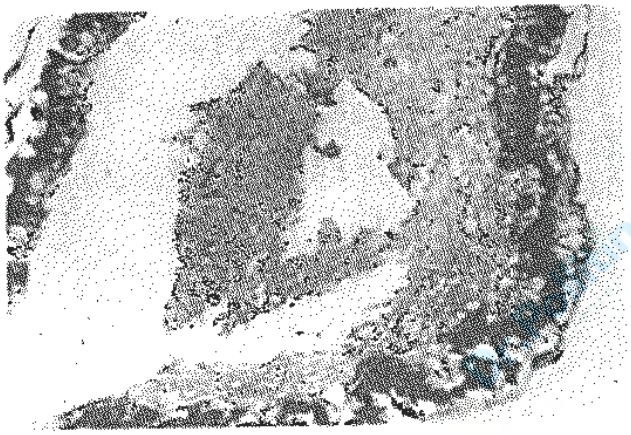

Photo 2: Prostate. Cernilton 12.6g/kg group, male (dead, 124th day). Glandular ducts B (signifying markedly dilated glandular ducts whose epithelium underwent squamous metaplasia) were partially but markedly atrophied in the epithelium.

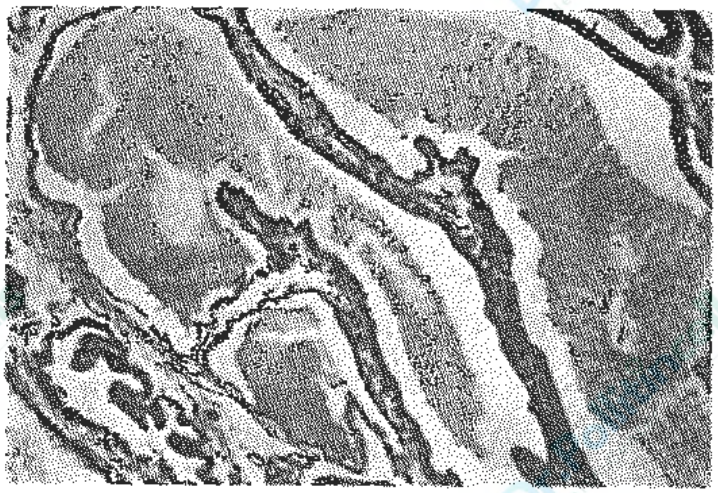

Photo 3. Prostate. Cernilton 12.6g/kg group, male (survival). Glandular ducts A were extensively degenerated and atrophied.

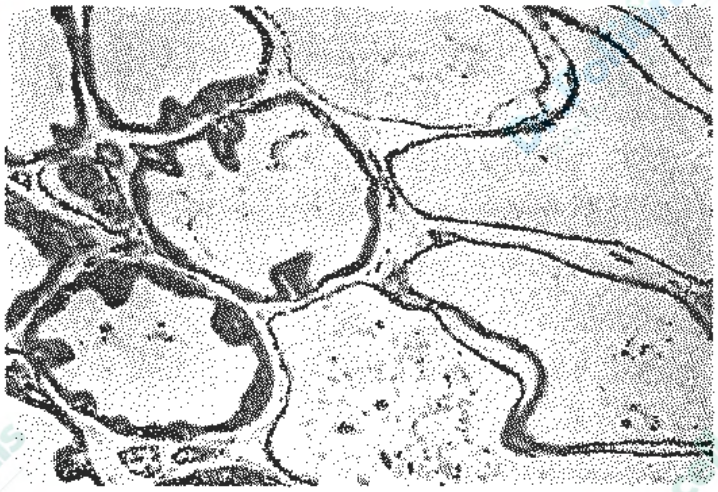

Photo 4. Prostate. Cernilton 12.6g/kg group, male (survival). Extensive vacuolation of the epithelium.

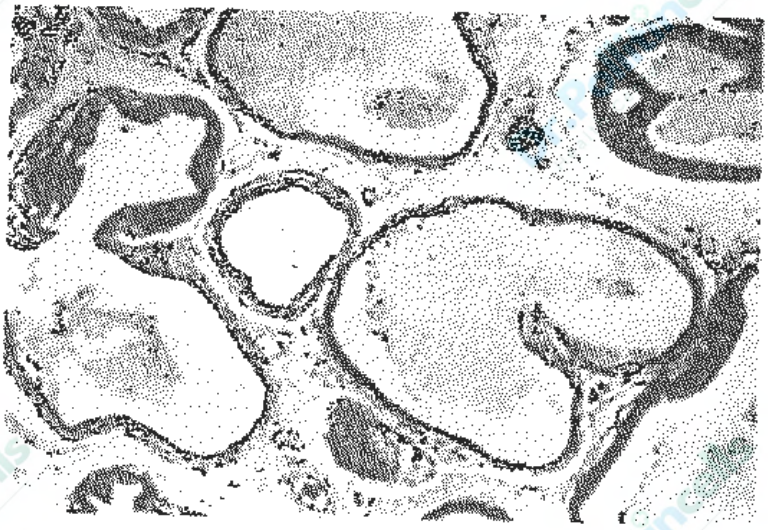

Photo 5. Prostate. Cernilton 12.6g/kg group, male (survival). Glandular ducts A were slightly dilated. Adjacent to them were dilated ducts that lost epithelium.

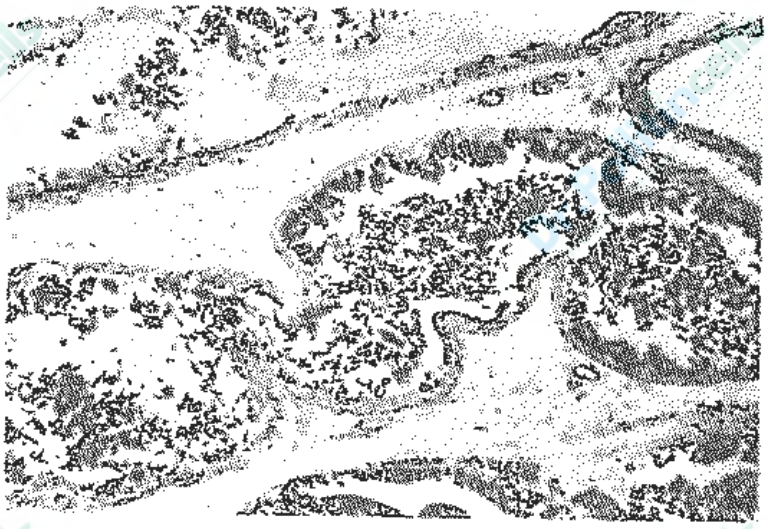

Photo 6. Prostate. Cernilton 6.3g/kg group, male (survival). Glandular ducts that lost most of the internal integument of the epithelium.

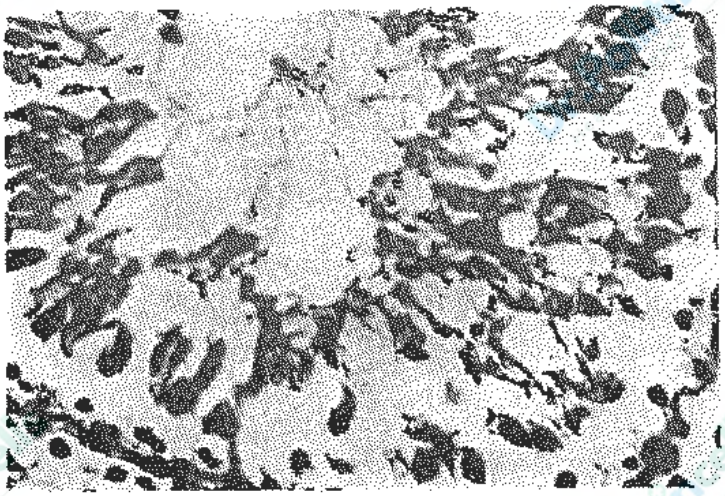

Photo 7. Testis. Cernilton 12.6g/kg group, male (survival). Spermatids showed hypoplasia and only Sertoli's cells were conspicuously seen. Suppression of naturation was of course noted.

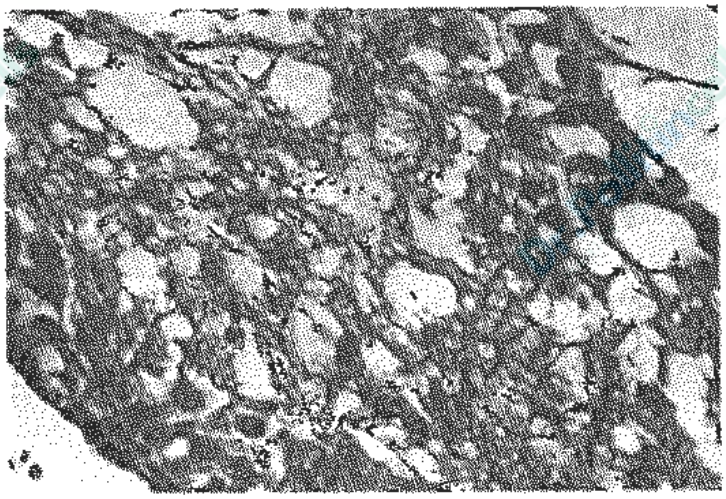

Photo 8. Testis. Cernilton 12.6g/kg group, male (survival). Maturation of spermatids was suppressed and the ducts underwent coagulative necrosis.

A preliminary investigation on the therapeutic effect of Cernilton in chronic prostatovesiculitis

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INTRODUCTION

It has been known for many years that chronic prostatovesiculitis is a very common disease. The highest incidence of cases reported in the literature on the subject is provided by Wiseman (1931). He accounted for 200 male patients selected at random, the majority of whom having sought medical advice on the grounds of extraurogenital symptoms. 54% percent of these cases were found to exhibit clinical signs of chronic prostatovesiculitis. Pelouze (1939) reported an incidence of 30-40% of all males over the age of 40 years, and Gartman (1960) gives a figure in excess of 40% in a material of 919 apparently healthy males aged between 17-40 years (routine military examination). Although Farman and McDonald (1961) do not state any incidence figures, they agree with Pelouze that this disease is probably the most prevalent chronic infection in men over 40 years of age.

The symptomatology of chronic prostatovesiculitis is extremely vague and, from his material, Gartman was able to record no less than 178 different symptoms (sic!). Because of the great variety of symptoms, and despite the fact that the symptoms occurring most frequently only constitute a fraction of the total number, diagnosis is seldom confirmed at an early stage. This delay leads both to a marked resistance to therapy and to a marked recidivism, two notable characteristics of the disease. The combination of these two characteristics often causes deviations from the normal in the psyche of the patients who may, for instance, become fixed in a sexual impotency that might otherwise have disappeared after a short time.

In spite of the fact that chronic prostatovesiculitis has been a well-known syndrome for so long therapeutic advances in this field have been negligible. Chemotherapeutics and antibiotics are of some value in the acute stage or during exacerbation periods, but they are worthless in the chronic course. The conservative treatment still consists of stripping and expulsions at regular intervals. The experienced urologist first handles the patient by stripping (to empty the gland and to diagnose the secretion) and follows up with massage (to eliminate adhesions and to stimulate the blood flow). Treatment given by an inexperienced person will, for the most part, only lead to negative results, and the patient will become disinclined to complete the treatment. This was illustrated by some American statistics which showed that only one-half of the patients persisted whereas the remaining number oscillated between different physicians only to find that the treatment recommended was practically identical and without any significant modification. In many cases, they gave up trying and only returned to the doctor when various sequalae became apparent (pelveospondylitis, uropolyarthritis, or sacral rhizopathy).

Cernilton was first mentioned as a possible therapeutic agent in chronic prostatovesiculitis in 1959 when Dr. Ask-Upmark, Sweden, published a short report on a typical case. The disease was so persistent that not even an antibiotic dose as large as 150 g chloromycin, administered over a two-month period, could prevent a relapse. The patient then began to take Cernilton on his own initiative. At that stage, the patient had been suffering from the disease for 5 years with practically continuous distress. He became symptom-free very rapidly and remained so, the last report being noted two years later. The only occasion upon which he experienced any distress during these two years was during a two-week trip

when he did not have access to the tablets. Owing to the rebellious nature of his particular case, the result naturally attracted attention. Later, Jönsson (1961) reported 10 cases who had received Cernilton for more than a year. As a result of his observations, Jönsson held the opinion that continued experimental therapy was motivated and emphasized the very great advantages which could be derived from a test series employing placebo tablets.

A preliminary Investigation

This investigation was based on a material consisting of 179 cases of chronic prostatovesiculitis selected from open urological praxis. The minimum observation period following the introduction of Cernilton was 4 months (14%) and the maximum period was 23 months (1 case). The mean observation period was 10 months. The entire investigation period dated from Dec. 1, 1959 to Oct. 31, 1961. Cases which had been under observation for less than 4 months by the terminal date, and those who came under observation afterwards, will be reported in a later article planned to cover a 3-year period and approximately 500 cases.

CERNILTON

The preparation was placed at the disposal of the author by the manufacturers, AB Cernelle, Vegeholm, Sweden. The raw material consists of an extraction taken from a given admixture of four types of pollen. The extraction is autolyzed and microbially digested before being spray dried. The purpose of this digestion is to break down any allergens which might be present. When the preparation is ready for use, it does not contain any precipitable protein and it is rich in certain B-vitamins. Tests have also been performed in order to determine whether the steroids present in the preparation contain the therapeutically active component. However, no results are available at the time of writing.

Patient material

The 179 cases were selected from about 400 cases available at the time in question. 80 cases were eliminated from the total when it was found that the placebo tablets given initially differed from the real Cernilton tablets both in colour and consistancy. Other cases were eliminated because they had undergone surgery or some other manipulation (apart from panendoscopes for diagnostic purposes), and, further, all cases suffering from serious diseases outside the urogenital tract. Cernilton treatment was not employed in cases of ascertained or suspected malignant degeneration of the gland although the material does include a few cases exhibiting a concurrent, but negligible, benign enlargement of the gland which, however, in no way affected the actual infection.

The age distribution of the material is given in Fig. 1. It should be noted that prostatovesiculitis can occur at any age; there are references in literature to new-born infants with the disease (Mann, Giannastasio).

Fig. 2 provides information concerning the duration of distress prior to the introduction of the therapy.

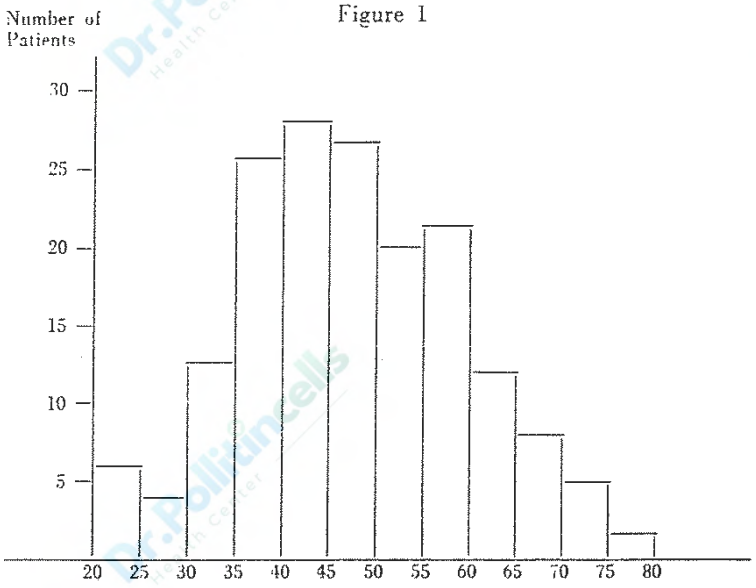
The patient material was not sufficiently large to permit the same age distribution in the different groups.

Method

The investigation was planned partly as a double-blind test and the material was divided into two groups for the treatment.

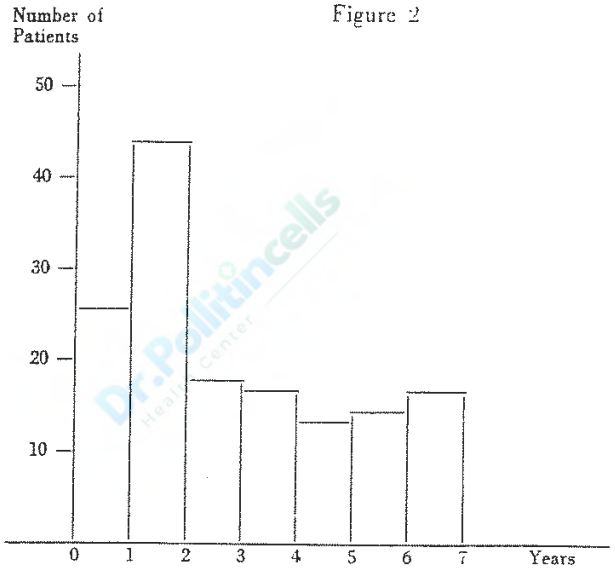
A. In this group, comprising 65% of the cases, the patients were supplied with Cernilton on prescription (druggist's Cernilton). The physician in charge was therefore fully aware of the nature of the preparations.

Figure 1



Age distribution of the patient material.

Figure 2



Duration of symptoms prior to combined Cernilton + conservative therapy.

B. In this group, comprising 35% of the cases, the patients received either placebo or the real tablets (code Cernilton). The physician in charge did not have access to the code and was therefore unaware of the nature of the preparation. The code number was noted in the journal and the results assessed objectively. This procedure made it possible to determine whether the physician exerted any influence over the patients (psychic supportation) when he knew the true composition of the tablets. Once the aforementioned eliminations had been made and the selection of patients completed, the tablets used all had exactly the same shape, size, smell, taste, and appearance.

All the patients underwent a complete urological examination including urography, urethrocystrography and, when necessary, panendoscopy. In connection with these examinations, the patients were given chemotherapy for a few days but otherwise during the course of the treatment, both chemotherapeutics and antibiotics were to all intents and purposes banned.

Ataractics were administered when the patient exhibited an obvious psychogenic state. When impotence persisted even after the secretion had become normalized, hormone treatment was introduced (i.m. injections of hormone derivatives).

The conservative treatment — in 2/3rds of the cases in combination with druggist's Cernilton and in 1/3rd with code Cernilton —consisted of expulsion and subsequent massage performed initially once a week to once in 10 days. Concurrent to the normalizing of the secretion and to the reduction of the secretionary stasis in the gland, the interval between expulsions was extended to 2—3 up to 4 weeks, and even longer in some cases.

The dosage of both druggist's and code Cernilton was the same: 4 tablets each morning swallowed whole or chewed as preferred. More recently, a double dose has been given during the first 2—3 weeks, the patient being supplied with 4 tablets in the morning and another 4 at lunchtime.

Evaluation

Although the symptomatology of chronic prostatovesiculitis is very heterogeneous, the object of the therapy is quite definite: to achieve, as quickly and as effectively as possible, improved drainage of the gland and, simultaneously, to eliminate the prevailing stasis of the secretion which contains greater or lesser quantities of pus. When evaluating the results, two clinical findings have been most intensely investigated: the appearance of the secretion and urethrocystoscopy and microscopy, and the content of the prostate gland and the vesicles on rectal palpation. When an infection is in progress, the prostate and the vesicles have a doughy consistancy, they are tender when palpated and they contain a more or less pus-filled secretion. When therapy is successful, evacuation is improved and, consequently, the secretionary stasis is eliminated. This can be easily confirmed by palpation. Concurrently, the secretion reverts to normal and this too is easily confirmed by direct microscopy. A secretion containing a count of more than 10 white blood cells per field (enlargement x 240 diameters) is obviously pathological but even a secretion containing 4—6 cells per field should be considered pathological if these white blood cells form aggregations. A secretion is considered normal when the number of white blood cells does not exceed 6 and occur individually. A healed gland has a tough, indurated consistancy, is no longer tender when palpated and does not retain any secretion.

The therapy results were assessed as being positive when there was no more than one exacerbation in the course of six months and two exacerbation periods during a time of one year or longer. Most of these mild relapses were due to the fault of the patient who, since he became symptom-free at relatively early stage, became nonchalant in following up his treatment. However, these relapses were generally harmless and could be coped without difficulty. A temporary doubling of the Cernilton dose brought about a rapid improvement.

Results and Discussion

One the basis of the above, the results were assessed for three groups:

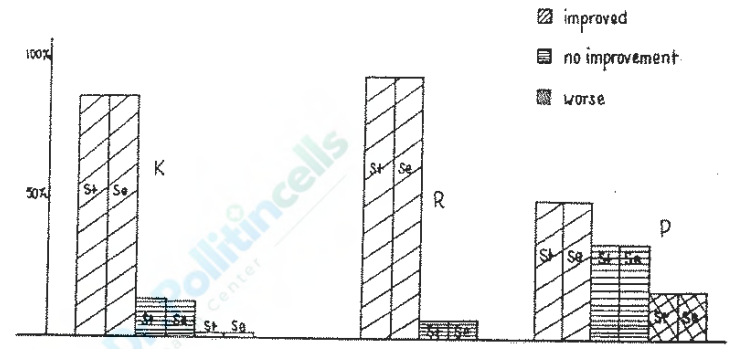
a) Tablet composition known to the physician in charge (Fig.3 (K)).
Total: 118 cases.

B) Real Cernilton tablets in the code group (Fig. 3 (R)).

C) Placebos (Fig. 3 (P)).
Total B) + C): 61 cases.

Figure 3

Cernilton effect on prostatovesiculitis.
Changes in stasis and secretion in per cent of patients in each group.



St = Stasis
Se = Secretion

It can be seen from Fig. 3 that the effect of the tablets in the K and R groups is practically identical. The number of symptom-free or considerably improved patients is about 90%. This also serves to show that the personal influence of the doctor is negligible and can be discounted entirely in the final results.

The improvement shown by the patients in the placebo group (P) is about 50%. Since the total material received absolutely uniform conservative treatment, the results of this preliminary investigation can be expressed as follows:

The results of the combination of conservative and Cernilton therapy were 60-30% better than those achieved with conservative treatment alone.

Taking into account the marked resistance of the disease to earlier therapeutic measures, its frequency, and, not least, the complications occurring later and leading to a high degree of invalidity if left untreated, this therapeutic result must be acknowledged with satisfaction.

It can further be seen from the figures that the pus content of the secretion and the secretionary stasis run a parallel course during changes in the state of the disease. The occurrence of a pus-containing secretion when the gland is indurated and free from secretion is highly exceptional. Apart from the two main symptoms mentioned, attention has been paid to only one other of the numerous symptoms reported, namely the sacral rhizopathies described by Bohm, Franksson and Peterson (1956). The author of the present paper felt this to be motivated since the connection between chronic prostatovesiculitis and sacral rhizopathy has not been elucidated and further, as the patient can nearly always give a clear picture of the area of pain, diagnosis of this particular syndrome is not difficult. However, so far the results of Cernilton therapy have not provided any statistically significant values in any direction.

A number of other observations have been made concerning miction frequency, elimination of residual urine, etc., but these symptoms have not been dealt with statistically.

Cernilton appears to have an antiphlogistic effect. The results obtained also indicate that the preparation improves or facilitates the drainage of the gland. The active component(s) of the substance has not been isolated. A new and thorough double blind test with synthetic tablets containing exactly the same composition of vitamins and amino acids as Cernilton and with real Cernilton tablets will be commenced very shortly. Further, a test series is planned involving the use of only pollen steroids for the purpose of isolating and defining the active therapeutic component.

Complications

Cernilton treatment has not given rise to any serious complications. One case developed an obvious gynecomastia after two months of treatment. During this time, his prostatovesiculitis had improved considerably and the preparation could be discontinued, and he subsequently received only conservative therapy. The gynecomastia disappeared shortly afterwards. One other patient complained of a swelling sensation in the mammae although no changes in glandular substance could be confirmed. This symptom also disappeared rapidly when Cernilton was withdrawn. There were no other cases of similar side effects and it is obviously impossible to form any opinion of the hormonal effect on the basis of these two solitary cases (out of a material which, to date, consists of more than 500 cases).

A number of patients exhibiting clearly allergic reactions have been treated. The therapy has not caused any exacerbation although in a couple of cases it was found necessary to reduce the dose because of intestinal symptoms arising during therapy. As similar intestinal symptoms also occurred in a few isolated non-allergic patients, these symptoms can hardly be registered as allergic. Helander has, in fact, stated that the substance does not cause any allergic reactions when administered orally. However, in two cases included in a section of the primary material not included here, treatment had to be discontinued owing to nausea and pruritis. As soon as the drug was eliminated, the symptoms disappeared. When the substance is to be administered to patients who are highly allergic, the author suggests commencing the treatment with a small dose (e.g. 1 tablet each morning and, if not distress is experienced, gradually increasing to normal dose). In summarizing the complications, it can be stated without reservation that side effects were negligible and without any practical importance to the results as a whole.

Summary

A preliminary report is given of a current investigation on the effect of Cernilton in the treatment of chronic prostatovesiculitis. The investigation indicates the conservative treatment in combination with Cernilton gives results which are 60—80% better than those obtained with conservative treatment alone.

The author wishes to express this thanks to Dr. H. Palmstierna for his extremely valuable assistance in planning the investigation and in treating the results.

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PROSTATE SUPPORT:

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Alternative Therapies for Benign Prostatic Hyperplasia

Cydney E. McQueen, PharmD, and Kelly M. Shields, PharmD

Benign prostatic hyperplasia (BPH) is a non-cancerous increase in the tissue mass of the prostate, the muscular gland that produces seminal fluid. BPH is one of the most common medical conditions affecting older men. It may be diagnosed because of urinary symptoms, or identified when a large prostate is found during a routine screening rectal exam. Many men simply have a slow worsening of symptoms throughout their lifetimes, usually beginning in their 50's. Subclinical disease is very common: Approximately 80% of men older than age 60 will have histological changes indicative of BPH upon biopsy; by age 85, this percentage rises to 90%.[1] Some of these patients have severe disease progression, which can lead to incontinence, formation of calculi, frequent urinary tract infection, or permanent urinary tract damage.

Despite the possibility of progression and the bothersome symptoms, many men – perhaps half of those with the condition – never seek medical advice or treatment for BPH symptoms even when those symptoms are severe enough to warrant surgical intervention.[2] Patients may believe that urinary symptoms are part of the normal aging process, that nothing that can be done, or that the available treatments have unacceptable side effects.

Etiology/ Pathophysiology

BPH is related to age-associated changes in the body's hormone levels.[3] Although the clinical ramifications of these hormone changes are not completely characterized, it is known that the levels of serum testosterone decrease while dihydrotestosterone (DHT), the principle androgen responsible for prostatic growth,[4,5] accumulates. Until recently, it was believed that estradiol, converted from testosterone via the aromatase pathway, was implicated in initiating hyperplasia in the stroma and epithelium of the prostate.[4] That now seems unlikely.[6]

Factors that may accelerate disease progression are not well enumerated. Diet is one factor that has been implicated in the development of BPH. A Western diet characterized by high fat intake appears to be linked to earlier onset of BPH.[7,8] One study indicated that low intake of vegetables is positively associated with BPH risk,[9] whereas another drew a correlation between alcohol consumption (more than 25 ounces/ month) and BPH risk.[10] However, each of these studies had limitations and did not demonstrate a clear, direct correlation. Symptoms may be worsened by various factors such as evening intake of liquids, decongestant use, or caffeine, alcohol, or spicy food intake.

Symptoms

Urinary symptoms experienced by patients with BPH can be classified as obstructive or irritative (see Table 1). Obstructive symptoms, sometimes referred to as "voiding symptoms," include a decrease in the force of the urinary stream, difficulty in maintaining or initiating the stream, "dribbling" after ending the stream, or the inability to completely void the bladder. Although some obstructive symptoms can be directly correlated with restriction of urethral flow, others seem to be caused by a decrease in

strength of the detrusor muscle or an increase in the excitability of the bladder muscle. Irritative symptoms of BPH also are referred to as “storage symptoms” and include dysuria, urge incontinence, urgency, nocturia, and increased frequency of urination during the day. These seem to be related to irritation of the epithelium of urethral and bladder structures.[3,4]

The International Prostate Symptoms Score (IPSS) is a validated instrument that is widely accepted for staging the severity of the disease via scoring of subjective symptoms. It also is known as the American Urological Association Urinary Symptoms Index for Prostatism (AUA Index) and is a patient-completed instrument.[4] (See table 2). Score ranges equate to “mild” (0-7), “moderate” (8-19), and “severe” (20-35) symptoms. The Boyarsky Index and the Madsen-Iversen Score are additional instruments that are physician-completed.[11] Other instruments include the BPH Impact Index (BII), and various health-related quality of life (QOL) measurements. Interestingly, the severity of the symptoms experienced does not always correlate directly with the measured extent of glandular enlargement or with the objective measurements utilized to monitor disease progression.

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Objective measurements include uroflowmetry, such as the maximum flow rate (MFR) in millimeters of urine passed per second (also termed peak urine flow rate) and post-void residual urine (PVR). Prostate volume usually is measured by transrectal ultrasonography.[3,4] Normal MFR ranges decrease with age. Generally, rates of less than 15 mL/s are considered to be diagnostic of a urinary flow problem; however, because of lower rates often found in older men, MFR rates alone do not indicate the need for therapy. They must be correlated with other physical findings and symptoms.[11]

Conventional Disease Management/ Treatment

“Usual” disease management can differ significantly based on the stage of the disease and the impact of symptoms on the patient’s lifestyle. The emphasis of BPH treatment has changed over the last several years from surgical intervention to medical intervention.[2,11] The first medical approach usually is “watchful waiting” – a recognition that the problem exists. Initiation of pharmacological treatment is delayed until symptoms become more bothersome to the patient. The next step generally involves α-1 blockers (doxazosin, tamulosin, or terazosin). These agents relax muscles of the prostate and bladder neck, thus providing symptomatic relief. They are associated with side effects including hypotenstion, dizziness, fatigue, and changes in sleep patterns. Another drug treatment choice is finasteride (a 5-α reductase inhibitor), which decreases the conversion of testosterone to the more active DHT. This agent has been associated with an increased incidence of sexual dysfunction.

A final choice for treatment is surgical intervention, which generally achieves the greatest degree of efficacy. Surgical options include: localized cryotherapy or thermal therapy, transurethral incision of the prostate (TUIP), transurethral resection of the prostate (TURP), electrovaporization (modified TURP),

laser surgery, or open prostatectomy. These procedures are costly and confer an increased risk of complications, such as bleeding, infection, incontinence, and sexual dysfunction.[3,4,11,12] All of the above treatment options, with the exception of watchful waiting, are associated with adverse effects and significant cost. For these and other reasons, patients and clinicians are beginning to consider the use of alternative therapies to treat BPH.

All of the treatments that will be discussed here are phytomedicinal in nature and are either whole extracts from botanical sources, or single extracted or manufactured constituents originally from botanical sources. Several of these treatments have been used in other parts of the world for many years. In fact, phytomedicinals are the initial treatments of choice in countries such as France and Germany. Many treatments show significant placebo effects in clinical trials; an examination of multiple BPH treatment trials provided estimates of this effect that ranged from 30% to 40%.[2] The maximal placebo effect usually is seen in the first 4-6 months of therapy.[2]

Pumpkin Seed

The use of pumpkin seed (*Cucurbitae peponis*) for treatment of symptoms associated with BPH has been approved by the Commission E, the German regulatory body responsible for phytomedicinals.

Pumpkin seed is theorized to act by displacing DHT from androgen receptors on human fibroblasts[13] or by antiandrogenic/anti-inflammatory effects.[14] Pumpkin seeds contain phytosterols and, therefore, may bind to androgen receptors. However, there are no human studies to support these proposed mechanisms. In addition, there have been a very limited number of clinical trials evaluating its efficacy, none of which are published in English.

Friedrich et al evaluated the efficacy of 1-2 capsules of Prosta Fink Forte, a brand-name standardized extract, in the treatment of 2,245 patients who were classified as “Alken stage I or II” (this scale has not been equated to other standardized scales).[15] The trial abstract reports that the results demonstrated a decrease in IPSS and quality of life improvement.

The average daily dose is 10 grams of the ground seeds in either single or divided doses.[14,16,17] No adverse reactions or interactions with other drugs have been reported with the use of pumpkin seeds.[14-17]

β-Sitosterol

β-Sitosterol is a dietary supplement used for cholesterol level modification as well as for the treatment of BPH. It is one of the principal phytosterols in pygeum, another supplement used to treat BPH symptoms.

The mechanism of action of the sitosterols is not well understood. Multiple mechanisms have been proposed and include antiandrogenic and antiestrogenic effects, inhibition of prostaglandin synthesis, and anti-inflammatory action.[12,16]

A limited number of trials have evaluated the efficacy of β-Sitosterol. The β-sitosterol study group examined 200 patients and evaluated the efficacy of Harzol® brand β-sitosterol (extracted from African star grass [*Hypoxis rooperi*]) 20 mg three times per day for six months to treat the symptoms of BPH.[18] The researchers noted a significant decrease in modified Boyarsky score (6.7 in the treatment group vs. 2.1 in the placebo group) after four weeks of intervention. The study also showed statistically significant improvement in all of the following parameters in the treatment and placebo groups, respectively: IPSS (7.4 point vs. 2.1 point reduction), QOL (1.4 vs. 0.2 reduction), MFR (5.2 mL/s vs. 1.1 mL/s increase), median flow rate (3.0 mL/s vs. 0.3 mL/s increase), voiding time (15.5 s reduction vs. 2.8 s increase), and RUV (35.4 mL vs. 11.6 mL reduction). Those participants who continued in the β-sitosterol treatment group maintained the improvement in all parameters, but did not demonstrate further improvement during an 18-month follow-up to the study.[19]

Table 1
Symptoms of benign prostatic hyperplasia

Obstructive
Decreased force of urine stream
Hesitancy or difficulty in initiating stream
Straining to urinate
Dribbling after urination
Incomplete emptying of bladder
Urinary retention
Irritative
Increased urination frequency
Nocturia
Dysuria
Urgency
Urge incontinence

A separate trial compared the efficacy of Azuprostat® 130 mg daily and placebo over a six-month period in 177 patients with symptomatic BPH.[20] The treatment group showed a statistically significant decrease in IPSS scores in favor of the treatment group compared to placebo, 8.2 vs. 2.8, as well as marked changes occurred during the first month of therapy, and then additional improvements were demonstrated more slowly throughout the course of treatment.

Very few adverse effects have been reported; the most common side effect is GI disturbance. Two incidents of sexual dysfunction have been reported.[18] The daily dose range is 60-130 mg of β-sitosterol. Theoretically, interactions could include an additive effect with antihyperlipidemics. For that reason, firm adherence to scheduled cholesterol monitoring is recommended for patients on lipid-lowering medications.

Rye Grass

Rye grass pollen extract is supplement traditionally used for the relief of BPH symptoms. It is believed to work by multiple mechanisms that include antiandrogenic effects, increased bladder muscle control, relaxation of urethral smooth muscle,[21] and inhibition of prostaglandin and leukotriene synthesis.[22]

Several studies have evaluated the efficacy of a particular brand of extract called Cernilton®. One randomized, double blind, clinical trial evaluated Cernilton 126 mg twice daily for six month vs. placebo in 60 patients awaiting operative treatment for outflow obstruction.[23] The results indicated statistically significant improvement in symptoms of nocturia and incomplete emptying. The study also showed a statistically significant decrease in anteroposterior diameter (18.2% in the Cernilton group vs. 4.6% in the placebo group) and a decrease in residual urine volume (101.9 ± 87.3 mL vs. 113.4 ± 87.3 mL). The authors also reported no adverse effects in the treatment group.

One study in 159 patients compared Cernilton to Paraprost®, another product used for BPH symptoms that is a mixture of the amino acid L-glutamine, L-ariginine, and glycine.[24] The study noted significant improvements in the Cernilton group in respect to RUV, MFR, and prostate weight. The investigators determined that the intervention was “moderately effective” in 49.1% of the Cernilton patients as compared to 41.2% in Paraprost group. There were no adverse effects or clinical abnormalities noted.

Another study evaluating Cernilton 126 mg twice daily for 12 weeks in 79 men with mild-to-moderate symptomatic BPH concluded that the rye grass pollen extract caused improvement from baseline in all subjective symptoms measured as well as in flow rate and residual urine volume.[25] The symptoms examined were urgency/discomfort, dysuria, nocturia, incomplete emptying, prolonged voiding, delayed voiding, intermittency, and post-void dribbling. One major limitation to the validity of the study was the lack of a control group.

A more recent study evaluated the efficacy of Cernilton compared to Tadenan® in 89 patients (ages 50-68 years) with Stage I BPH.[22] Tadenan is *Pygeum africanum* extract standardized to 14% triterpenes and 0.5% n-docosanol. The results indicated that both products provided increased flow rate and decreased urine volume.

Table 2

American Urological Association (AUA) Urinary Symptom Index for Prostatism

Symptom	Score: Not at All	< 1 in 5 Times	< ½ the Time	= ½ the Time	> ½ the Time	Almost Always
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month or so, how often have you found you stopped and started several times when you urinated?	0	1	2	3	4	5
4. Over the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the past month or so, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 times	1 time	2 times	3 times	4 times	5 times

Interpretation of AUA Symptom IndexAUA Symptom Score = Sum of Questions 1-7 = _____

Mild prostatism ≤ 7

Moderate prostatism 8-18

Severe prostatism > 18

Highest possible score = 35

Adapted from: Barry M, et al. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol* 1992;148:1549-1557.

In addition, both treatment groups noted an improvement in subjective symptom scores. However, methodological limitations of the study limit its usefulness in clinical decision-making.

Additional studies evaluating the efficacy of Cernilton in the treatment of BPH have reported significant improvements in objective as well as subjective parameters; however, these studies have not been published in English and, therefore, the quality of methodology could not be evaluated.[26,27]

Clinical trials have reported no adverse effects associated with rye grass pollen extract therapy.[24-27] The typical dose of extract studied in trials is 126 mg twice or three times daily for 3-6 months. There are no known interactions with prescription medications. Recommended monitoring is limited to that associated with the disease state.

Stinging Nettle Root

The root of the stinging nettle (*Urtica dioca*) contains polysaccharides which are believed to be responsible for its anti-inflammatory effects. Unidentified components present in certain aqueous, but not lipophilic, extracts reduce the binding of sex hormone binding globulin (SHBG) to prostatic membrane receptors[28] and inhibit 5-α-reductase and prostatic aromatase.[13]

Although four double-blind, placebo-controlled studies have been performed, the quality of the evidence could not be analyzed for this review, because none of the trials have been published in English. Tertiary sources have summarized the results of the trials, which included a total of 210 patients. The most recent trial reported a significantly larger decrease in the IPSS for the nettle root group, but differences in MFR, PVR and QOL score were not significant. Other trials reported an improvement in symptoms, as well as significant improvements in urinary output and MFR and a reduction of SHBG.[13]

An observation study of 67 patients with BPH, ages 53-87 years, was conducted using an aqueous alcohol extract of *Urtica dioica* and *Urtica urens* (dog nettle) roots for six months.[29] The investigators documented clinically

Table 3

Clinical trials of alternative therapies for benign prostatic hyperplasia

Supplement	Dose	Urodynamics	Symptoms	Prostate Size	PSA	Nocturia	Side Effects	Efficacy Evidence
Pygeum (14% triterpenes and 0.5% n-docosanol)	75-200 mg/d	+	+	—	U	+	GI discomfort constipation, nausea, diarrhea	Good
Saw Palmetto (> 85% fatty acids and sterol)	160 mg bid	+	+	—	—	+	GI discomfort headache, dizziness, impotence (with high doses)	Good
Stinging Nettle (hydroalcoholic root extract)	600-1,200 mg/d	+	+	—	U	+	GI distress, skin reactions, hyperhidrosis	Fair
Rye Grass Pollen Cernilton®	126 mg bid or tid	+	+	+	U	+	None reported	Fair
β-Sitosterol	60-130 mg QD	+	+	—	U	U	GI upset, nausea, diarrhea	Fair
Pumpkin Seed	10 g/d ground seed	U	+	U	U	U	None reported	Poor

Legend: + = positive effect; — = no effect; U = unknown effect

Efficacy Evidence

Excellent: Several well-designed, controlled human trials with minimal limitations
Good: Controlled human trials, with moderate design limitations
Fair: Controlled human trials, with major design limitations or very small populations
Poor: Few uncontrolled human studies

significant reductions from baseline in episodes of nocturia and corresponding decreases in post-void bladder volume. Prostate volume, as measured by ultrasound, was unchanged.

Stinging nettle root is well tolerated. A six-month study in 4,087 patients were reported very few adverse events. These were GI distress, allergic skin reactions, and hyperhidrosis. There are no known drug interactions with stinging nettle root, although there is a theoretical interaction with finasteride, based on the possibility of a clinically significant level of 5-α-reductase inhibition. Until more is known, concomitant use with finasteride should be avoided or carefully monitored.

Doses of stinging nettle root used in majority of clinical trial ranged from 600 to 1,200 mg/d of hydroalcoholic root extract. Patients who choose to use stinging nettle need to be aware that products are available that use the leaves and other above ground parts of the plant; these products have different chemical components and indications and cannot be used interchangeably.[14]

Pygeum africanum

The lipid-soluble constituents within the bark of the pygeum tree are the most pharmacologically active. The bark contains approximately 14% triterpenes; ferulic acid esters, such as n-docosanol and n-tetracosanol; and several phytosterols.[13,30,31] The anti-inflammatory activity associated with pygeum is due primarily to the action of the triterpenes, which inhibit enzymes implicated in connective tissue deterioration.[13,32] Prostaglandin formation within the prostate also is inhibited.[33] The phytosterols components inhibit prostaglandin synthesis and compete with precursors of androgens.[13] N- docosanol, specifically, has been demonstrated to decrease levels of testosterone, luteinizing hormone (LH), and prolactin in animal studies,[31] although one human study examining testosterone, follicle-stimulating hormone, LH, and estrogens did not find significant changes.[34] Pygeum also has an effect on glandular epithelium, causing "normalization" of histological changes. Inhibition of fibroblasts proliferation and increase in prostatic secretions have been noted, as well as estrogenic and antiestrogenic activity.[35] The

slight decrease in prolactic (which stimulates intraprostatic DHT synthesis and testosterone uptake) and possibly in testosterone; a decrease in proliferation of fibroblasts within the gland;[36,37] and a reduction in the excitability of the detrusor muscle[37] all contribute to alleviation of obstructive symptoms. Irritative symptoms may be relieved more by the increase in prostatic secretions. Although pygeum does inhibit 5-α-reductase, as well as the androgen receptors' binding of DHT, these actions are so minimal they probably are clinically insignificant.[34]

Although 46 investigations of pygeum extract have been conducted to date, only 11 have been placebo-controlled trials. A review of available trials, completed in 1995, concluded that pygeum extract did provide some benefit for both objective and subjective BPH symptoms and should be investigated further in comparison to standard pharmacological treatments.[37] The 43 trials covered in the analysis included a total of 2,262 patients.

Of the placebo-controlled studies, the largest to date (n=263) was published in German by Barlet et al in 1990.[38] A moderately detailed description of the trial was based on an English translation was published in 2000.[39] Results of this trial showed statistically significant improvement compared to placebo for symptoms of daytime and nighttime micturations, residual urine volume (24.5% and 3.5% reduction, respectively), urine volume (12% and 3.2% increase, respectively) and MFR (17.2 and 4.3% increase, respectively), with no change in the prostate volume.

A more recent meta-analysis of pygeum trials was published in 2000.[40] Eighteen trials met the inclusion criteria for the meta-analysis and presented the experiences of 1,562 patients. Thirteen trials were placebo-controlled and five were compared to other treatments such as NSAIDS or other herbal products. No comparisons to finasteride or α-blockers have been conducted. Twelve of the 13 placebo-controlled trials reported more improvement in outcome measures for pygeum groups and one did not find any difference in outcomes. Based on the effect size calculated for each of the trials, an overall effect size was estimated using six trials, an overall effect size was estimated using six trials of pygeum (n=474) that were judged by the authors to be sufficient for result pooling. The overall summary effect size of -0.8 (95% CI, -1.4 to -0.3) calculated by the authors is equivalent to an improvement that is both large and statistically significant. A summary effect size for improvement in nocturia was calculated separately and also was -0.8 (95% CI of -1.4 to -0.1), a moderate to large effect. The authors concluded that overall results of the analysis support improvements in urinary symptoms, peak urine flow, and nocturia that are moderate and statistically significant and that *Pygeum africanum* extracts may be an effective short-term treatment option for patients with BPH symptoms.

Pygeum is well tolerated. Adverse effects reported in studies are mild and include nausea, constipation, diarrhea, and gastrointestinal discomfort.[37,38,40] No interactions with any pharmaceutical agents have been identified or reported, although the possibility of additive hormonal effects should be kept in mind.

Doses used in clinical trials have ranged from 75 to 200 mg/d. One trial compared a 100 mg/d dosage given once daily or in two divided doses and found no difference in outcome.[41] The extract should be standardized to contain 14% triterpenes and 0.5% n-docosanol.

Saw Palmetto

The lipophilic extract of *Serenoa repens* (also known as *Sabal serrulata*) inhibits 5-α-reductase activity, theoretically decreasing the amount of DHT produced from testosterone. Although finasteride more specifically inhibits type two 5-α-reductase, *Serenoa repens* (saw palmetto) inhibits both types one and two.[42] The extent and significance of this activity in vivo is not completely understood, and measurements of the reductase activity are not always significantly decreased.[43] In addition, saw palmetto may decrease prolactic and have anti-inflammatory

activity, as well as inhibit fibroblast and epidermal growth factors. Although antiestrogenic effects may exist, this action has not been well described.

Saw palmetto is the most investigated of all natural product therapies used for treatment of BPH. A systematic review of saw palmetto trials was published in 1998.[44] The investigators analyzed 18 of the 24 trials located in an exhaustive literature search. Analysis revealed 24-28% improvements in nocturia, MFR, mean urine flow, and "urinary tract symptoms" compared to placebo. Improvements were similar when compared to finasteride. The authors concluded that saw palmetto extracts do improve BPH symptoms and that improvements are similar to those experienced with finasteride treatments; however, fewer adverse effects were reported in the saw palmetto groups.

One of the placebo-controlled studies is of particular interest because of the investigators' attempt to reduce the influence of the placebo effect (i.e., BPH symptoms are known to be associated with placebo response rates of 30-40% or more clinical trials[2]). Descotes et al designed a trial in which all patients with a 30% or greater improvement in symptom scores during a 30-day placebo run-in period were excluded from the study population. The remaining patients (n=176) were randomized to receive placebo or a standardized saw palmetto extract 160 mg (Permixon®) twice daily for 30 days. Results included a significantly greater increase in MFR in the Permixon group (28.9% vs. 8.5% for Permixon and placebo, respectively). There also was a significant difference between groups in the decrease of nocturnal urinations (-32.5% vs. -17.7% for Permixon and placebo, respectively). Despite the differences in these more objective parameters, however, the patient-based and physician-based global assessments of efficacy did not reveal significant differences, although they did favor Permixon. The investigators concluded that the overall clinical significance of Permixon treatment probably was less than what might be indicated by the statistically significant differences between treatment groups.[45]

A three-year observational study of the IDS 89 extract of saw palmetto in 435 patients noted an increase in MFR of 6.1 mL/s (13.4 mL/s to 19.5 mL/s) and a 50% reduction in RUV (64 ± 41 mL to 32 ± 36 mL). Nocturia resolved or improved in 73.3% of patients. According to the Boyarsky scale, 53-80% of patients were classified as symptom-free or improved. The investigators noted that the deterioration rate at three years for the 315 patients who completed the study was significantly lower than would be expected in BPH patients not receiving pharmacological or surgical treatment.[46]

Additionally, the standardized saw palmetto lipophilic extract, Permixon, has been compared to the 5-α-reductase inhibitor finasteride.[47] Patients (n=1,098) were randomized to receive Permixon 160 mg twice daily or finasteride 5 mg once daily for 26 weeks. The primary outcome measure was improvement in the IPSS. Assessments of QOL, sexual function, prostate-specific antigen (PSA), urodynamics, and prostate volume were also performed. The IPSS decreased by 37% and 39% and MFR increased by 25% and 30% in the Permixon and finasteride groups, respectively. QOL improved approximately 40% in both groups. Differences were noted between the Permixon and finasteride groups for prostate volume, which decreased 6% vs. 18% respectively, and for PSA, which was unaffected by Permixon, but decreased 41% in the finasteride group. Adverse event reports indicated that sexual function was less affected by Permixon than by finasteride.

Saw palmetto generally is well tolerated. A few reports include adverse events of nausea, headache, dizziness, dysuria, and GI discomfort. A three-year study in 435 patients reported mild adverse events in 34 patients.[13] High doses have been associated with impotence and decreased libido. Although no interactions with pharmaceutical agents have been specifically identified, recommendations to avoid use in

conjunction with hormonal or antihormonal therapies seem sound, based on the known pharmacological actions.

Saw palmetto products should be standardized to contain 85% or more fatty acids and sterols. The dose is 160 mg twice daily and may be taken with meals if GI upset occurs.

Conclusions

The most important contradiction to any alternative or complementary therapy is lack of a medical diagnosis. As with any BPH therapy, the possibility of prostate cancer must be eliminated before patients begin any symptomatic treatment.

Monitoring of patients taking any of the alternative treatments discussed should be the same as for any BPH patient: digital rectal exam to observe for increase in prostate size, a scored symptom questionnaire, and a regular serum PSA. An increase in or exacerbation of symptoms may indicate the necessity for uroflowmetry studies, urine culture, or biopsy. In addition, an inquiry into any possible side effects should be a part of any regular clinic visit.

Because BPH usually is a long-term, slowly processing disease state whose standard treatment often includes “watchful waiting,” the use alternative therapies for symptom reduction can be very appropriate. Unfortunately, those products tested in BPH clinical trials are not widely accessible in the United States. Therefore, successful treatment requires products standardized to the same component percentages as the tested products, good patient education to ensure safety, and reasonable patient and physician expectations.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Clinical Evaluation of Cernilton in Adenoma of the Prostate

By Doctors Jorge Toro, Assistant Director of the Urology Service, and Carlos Giudice, Clinical Assistant

Frequently the urologist is confronted with patients suffering from adenoma of the prostate who, for certain reasons, cannot in the immediate future be submitted to any sort of surgical treatment.

A significant number of such cases having been confirmed in our Urology Service at the Italian Hospital in Buenos Aires, it was decided to determine what effect CERNITIN exerted in this type of condition.

CERNITIN is a microbiological extract of dried pollen obtained under optimum conditions of standardization.

This extract contains various active principles: 21 difference amino-acids, lipids, saccharides, phospholipids, a minute percentage of oestrogens, enzymes, DNA, RNA, vitamins (not vitamin B_{12}) and minerals.

As long ago as 1960, Ask-Upmark of Sweden was reporting that CERNITIN was effective in the treatment of prostatitis. The mode of action of CERNITIN has not yet been determined, but what can be considered proven is a decongestant effect with a marked specific affinity for prostatic tissue, and a capacity to improve defense mechanisms against infection and inflammation in general.

Although the mode of action of CERNITIN is not yet clear, the following are, briefly, some of the theories and investigations which have taken place, which will surely in the future help to elucidate it:

1. From experiments conducted by Sir Alic-Isaac it appears that CERNITIN may be able to augment the production of INTERFERON (a protein produced by the cells for defense against viruses.)
2. Cernitin may have a stimulant effect upon the THYMUS, and it is already known that this gland plays an important role in the body's defences against infections.
3. Finally we report an article in Acta Chemica Scandinavica Vol. 24, 1970 – pp.3672, in which Dr. Kvanta mentions the fact that he has proved that CERNITIN has an inactivating effect upon STREPTOLYSIN (a toxin produced by streptococci).

From all these observations and facts it would appear that CERNITIN may take effect by means of a combination of different modes of action.

Materials and methods

100 patients were included in this investigation divided into 4 Groups (see diagram) according to their symptomatology.

Group 1: Patients who presented with minimal prostatism; that is, with commencing dysuria, slight polyuria, nocturia once or twice, clear abacterial urine and no residual urine.

Rectal examination revealed a prostate normal as to size, shape and consistency.

Group 2: Patients who presented with prostatism and increased dysuria and polyuria, both by day and by night, clear urine, residual urine of 60 c. c., and slight bacteriuria

Rectal examination: enlarged prostate with the features of an adenoma.

Group 3: Patients who present with marked dysuria, burning on micturition, a feeling of hypogastric fullness, nocturia, cloudy urine, bacteriuria of more than 150.000 colonies per millilitre and residual urine of 150 to 250 c.c.

Rectal examination: enlarged prostate with loss of median sulcus, smooth surface and elastic consistency.

Group 4: Patients consist of some with a large volume of residual urine and others with a total acute retention of urine, with pyuric cloudy urine, sometimes blood-stained. Their general condition is only fair.

The age of the 100 patients varied between 55 and 70 years.

Dosage and Results

The most frequently-used dose of Cernilton was 6 tablets daily, taken before meals (Giúdice), or else 3 or 4 tablets daily taken in the morning (Toro) both over a prolonged period.

Rearing in mind the symptomatology, urinalysis and the absence or presence of residual urine (Groups 1 and 2) we preferred to prescribe 4 tablets daily for 3 weeks, followed by a pause of 10 days and then continuing up to a total dosage of 100 tablets.

In this group of 40 patients we noticed, within a few days of starting the treatment, an improvement in their symptoms, and their total disappearance after the full dosage mentioned had been taken.

With regard to Groups 3 and 4, the treatment followed was 6 to 8 tablets a day up to a total of 100. We also prescribed antibiotics after appropriate urine culture. In this group of 60 patients, within a few days of the commencement of treatment, we observed a great improvement in the symptoms, mainly in frequency and nocturia.

10% of these patients showed no response to the treatment given.

Secondary Effects

In all the cases treated we encountered no allergic reactions, gastritis or hepatic intolerance. Some patients complained of abdominal distension, which improved with reduction of dosage. These side-effects were insignificant, and did not modify the final results.

Conclusions

Cernilton appears to have a decongestant and antiphlogistic effect upon the prostate gland, for which reason the subjective and objective symptomatology disappears or improves, which fact persuades us to continue with this treatment. The advantages of this preparation lie in its harmlessness and the possibility of carrying out prolonged courses of treatment.

	Group 1	Group 2	Group 3	Group 4
Number of cases	15	25	38	22
Average age	55-70	55-70	55-70	55-70
Urinalysis	Abacterial	Abacterial	Urinary infection	Urinary infection more than 100.00 colonies
Symptoms	Commencing dysuria Polyuria		Dysuria, polyuria, burning on micturition, nocturia	Incomplete or complete retention or urine. Hematolpyuria

Note: We are using Cernilton in acute and chronic prostato-cystitis, chronic urethritis and the cystitis syndrome in the female.

In view of the few cases so far treated, we have not yet reached a definitive conclusion.

PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Clinical evaluation of Cernilton in chronic prostatitis

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1. Introduction

Chronic prostatitis and spermatocytosis are known to have long persistence of subjective symptoms. The diseases are not fully defined yet, and it is speculated that many of the cases classified as falling in these diseases are of primary psychosomatic origin.

As early as 1960 Ask-Upmark of Sweden reported that a pollen preparation was effective in the treatment of prostatitis. Though its mechanism of action is not known, the preparation is considered to prevent growth of bacteria and exert roborant and desensitizing actions.

The purpose of this trial was to study the effectiveness of Cernilton, a pollen preparation used for treatment of prostatitis in Europe, by a double blind test using placebos.

2. Composition

Pollen species used in Cernilton are:

Timothy	26 %
Maize	26 %
Rye	40 %
Pine	5 %
Orchard grass	2 %
Alder	1 %

One Cernilton tablet contains:

Cernitin GBX	3 mg
Cernitin T60	60 mg
Calcium gluconate	70 mg
Lactose	70 mg
Calcium hydrogen phosphate	140 mg
Alginic acid	10 mg
Potato starch	20 mg
Pigment	3 mg
Talc	20 mg

One placebo contains:

Lactose	180 mg
Avicel (microcrystal cellulose)	60 mg
Dextrin	152 mg
Carbon wax	20 mg
Pigment	3 mg

3. Subjects and Method of Administration

The subjects were selected from among the patients with prostatitis and non-gonorrheal urethritis visiting the Outpatient Clinic. Those with acute inflammatory symptoms were excluded.

Administration was made once daily, 4 tablets in the morning. Patients with even-numbered dates of birth were given Cernilton while those with odd-numbered dates were given placebos. Administration was made in such a way that neither patients nor physicians would know which was given.

4. Grading System and Criteria of Evaluation

A. Grading System

1. Subjective Symptoms
   Disappearance……...2 points
   Some improvement……1 point

2. Number of leukocytes in urine after massage of prostate
   Less than 15 in one visual field (magnified 100 times)……normal
   Decrease from above 15 to normal…….2 points
   Decrease by more than 15……1 point

3. Number of bacteria in urine after massage of prostate
   Disappearance…….. 2 points
   Number decreased……1 point

4. Other findings
   Decreased hardness of prostate…...1 point
   Improvement of leukocytosis…….1 point
   Disappearance of comma shreds….1 point

B. Criteria of Evaluation

Effective: Cases with a total of 3 or more points or with normal findings in all items.
Slightly Effective: Cases with a total of 1-2 points.
Ineffective: Cases with no points

5. Therapeutic results

Cernilton was given in 17 cases. Of these, the clinical courses were followed in 14 cases, and the results were: “effective” in 10 cases, “slightly effective” in 3 cases, and “ineffective” in 1 case. Placebos, on the other hand, were given in 21 cases, and the clinical courses were followed in 16 cases, with “effective” in 7 cases and “ineffective” in 9 cases.

In subjective symptoms, disappearance was noted in 10 cases and subsidence in 4 cases in the Cernilton group, with all cases showing some sort of improvement. In the placebo group, disappearance was seen in 5 cases, subsidence in 2 cases, no-change in 7 cases, and exacerbation in 2 cases. The results show a great difference, but it must be emphasized that objective evaluation of subjective symptoms is all but impossible.

The findings in urinary deposits after the massage of the prostate were, in the Cernilton group, normalization in 5 cases, improvement in 1 case, persistence of abnormal state in 2 cases, exacerbation in 1 case, and persistence of normal state in 4 cases; result was unknown in one case because the urine was not examined. In the placebo group, normalization was noted in 3 cases, improvement in 2 cases, persistence of abnormal state in 3 cases, and persistence of normal state in 8 cases; exacerbation was not noted.

The findings in bacteria in the urine after the massage of the prostate were: disappearance in 3 cases, no-change in 2, and persistence of normal state in 9 in the Cernilton group and disappearance in 1 case, no-change in 2, reappearance in 1, and persistence of normal state in 12 in the placebo group.

6. Cases

Several cases are illustrated below.

Case 1. 26. Effective
Chief Complaints: heavy pressure sensation in the lower abdomen and abnormal sensation in the penis.

Findings and Treatment:
March 24: Prostate normal on palpation. No tenderness. Deposits of urine examined after massage of prostate. RBC8- 10/1GF. WBC slightly increased/ 1GF. Epithelial cells 3-4/ 1GF. Culture of bacteria, negative. Peripheral blood examined. WBC 5300. Hemogram, slight shift to the left. Administration of Cernilton started.

April 1: 32 tabs of Cernilton given in 8 days with persistence of chief complaints. Medication continued.

April 12: 60 tabs of Cernilton given in 15 days. Abnormal sensation in the penis disappeared (29 days).

May 21: 116 tabs of Cernilton given. Heavy pressure sensation in the lower abdomen subsided. No tenderness. Deposits of urine reexamined after massage of prostate. RBC not found. WBC 8-10/1 GF. Epithelial cells 5 6/1 GF. Culture of bacteria, negative. No side-effects.

Remarks: The chief complaints persisted for a long time, but urinary findings were markedly improved.

Case 2. 23. Effective.
Chief complaints: Initial voiding pain.

Findings and Treatment:
March 24: Prostate normal in size and hardness, but tenderness present. Examination of urinary deposits after massage of prostate: RBC 10-13/ 1 GF, WBC 20-30/ 1GF, cocci positive.

April 2: Chief complaints, left untreated for a week, persisted without improvement. Administration of Cernilton started.

May 31: 56 tabs of Cernilton given in 14 days. Chief complaints subsided on the 6th day. Prostate normal. Tenderness disappeared. Examination of urinary deposits after massage of prostate: RBC 1/2 – 3GF, WBC 5-6/ 1GF, culture of bacteria negative.

June 14: 112 tabs of Cernilton given in 14 days. Medication discontinued.

Remarks: This is a case in which both subjective and objective symptoms have disappeared.

Case 3. 27. Effective.
Chief complaints: Sense of urinary retention.

Findings and Treatment:
March 25: Findings in urine and prostate both within normal limits. Slight tenderness seen. Administration started.

April 1: 28 tabs of Cernilton given in 7 days without improvement of chief complaint. Urinary findings after massage of prostate: RBC (-), WBC 5-8/ 1GF, epithelial cells 1/1 – 2GF, culture of bacteria negative.

April 15: 140 tabs of Cernilton administered in 35 days, with improvement of chief complaint.

April 28: 196 tabs of Cernilton in 49 days. Chief compliant disappeared completely. Medication withdrawn. No side-effects.

Remarks: This is a case in which only subjective symptoms were found. In all three cases, the initial effect appears to have taken place after administration of more than 10 days.

Case 9. 23. Cernilton effective, placebo ineffective.

Chief complaint: Sense of urinary retention.

Findings and Treatment:
Dec. 3: Induration found in right lower part of prostate. E.coli 56540/ ml revealed after massage. Urocydal and Wintomylon given.

March 28: Anti-inflammatory agents and antibiotics had no effect, though given for 4 months. Slight voiding pain appeared. Induration still noted in the prostate. Pseudomonas 5600/ ml noted in urine after massage of prostate. Examination of peripheral blood: WBC 5000, hemogram no shift to the left. Administration of placebo started to observe the course.

April 11: 56 placebo tablets given in 14 days. Total voiding pain somewhat exacerbated.

May 23: 168 placebo tablets given in 42 days. Total voiding pain subsided but sense of urinary retention persisted. Induration noted in prostate. Examination of urinary deposits after massage of prostate: RBC(-), WBC 10 11/ 1FG, St. epidermis 6 160/ml. Administration of Cernilton started.

June 13: 84 tablets of Cernilton administered in 21 days. Voiding pain disappeared and sense of retention subsided.

July 4: 168 tablets of Cernilton in 42 days. Subjective symptoms all disappeared and induration not palpable.

Remarks: This is a case which has been completely cured with Cernilton. The

patient was not informed of the change of drugs during the treatment.

Case 10. 47. Cernilton effective, placebo ineffective.

Chief Complaint: Dull pain in the perineum.

Findings and Treatment:

March 17: Prostate somewhat enlarged with tenderness. Examination of urinary deposits after massage of prostate: RBC (-), WBC 1 2/ 1GF, epithelial cells 1/ 1GF, culture of bacteria negative. Administration of Cernilton started.

April 4: 68 tabs of Cernilton administered in 17 days. Chief complaint and tenderness disappeared and prostate became normal in size. Medication withdrawn.

April 27: Chief complaint recurred. Prostate normal in size. Examination of urinary deposits after massage of prostate: RBC (-), WBC 1-2/ 1GF, bacteria negative. Administration of placebo started.

May 13: 56 placebo tablets given in 14 days with no improvement of chief complaint. Placebo withdrawn.

7. Side Effects

No complaints compatible with side-effects were noted among the cases studied (Cernilton group 17 cases, placebo group 21 cases). Neither were abnormal objective symptoms noted, in the cases where clinical courses were followed.

Reportedly, Cernilton must be administered in the morning as it produces a caffeine-like action. This, however, was observed in none of our cases. Case 12 mistakenly took the drug in the afternoon for some days, but he said he did not suffer from insomnia at all. One of the authors, too, had 4 tablets at 10 o' clock every night for 5 days; and he did not experience excitement or insomnia, either. This may be a matter of individual susceptibility. Yet, our impression is that the drug is not necessarily one to be taken in the morning.

8. Discussion

There are no definite criteria for diagnosis of prostatitis at present. On the contrary, the presence of chronic prostatitis itself is sometimes doubted. Generally, positive finding in the culture of bacteria and increase in the number of leukocytes in urinary deposits after the massage of the prostate, are the criteria used for diagnosis of chronic prostatitis, through diagnosis based solely on tenderness has also been employed since old times.

On the other hand, it comes gradually to be known that chronic prostatitis is often attributable to allergy. It was Stewart and Wray who first described pathological changes of allergic prostatitis, and many cases of eosinophilic granulomatous prostatitis have since been reported. In some cases asthma is claimed associated. Since Cernilton has the actions of desensitization and increasing physical resistance, as well as bacterial and bacteriostatic actions, it can be expected to exert considerable effects on pathological changes of allergic prostatitis, granting that the mechanism of action is not precisely known.

The cases of prostatitis selected for the present study were mainly diagnosed on the basis of subjective symptoms and findings on palpation. Thus, many cases showed no abnormal findings in the secretion of the prostate or in the urine. Care, however, was taken to select only such cases as would comply with the diagnostic criteria laid down by Campbell in his text-book. Naturally, some cases of psychosomatic origin were included. On the other hand, the cases where placebos proved effective were not necessarily of psychosomatic origin. A good number of them can be considered to have healed spontaneously. Yet the fact that the rate of effectiveness was higher than 90% in Cernilton group as against below 50% in the placebo group, suggests that the there must have been cases where Cernilton was indicated. This is supported by the significant difference of effects registered in the two cases where both Cernilton and placebos were employed and

further by the fact that improvement of subjective symptoms was more difficult to obtain in the placebo group.

Cernilton was administered over periods ranging from 10 to 56 days, but no side-effects were noted. It is considered that a longer period of administration is possible. The onset of effect was rather slow, taking place in 7-10 days. Therefore, administration should at least be maintained for two weeks. Recurrence of symptoms was noted in two cases after withdrawal of the drug. Since the drug is experimentally confirmed to cause little toxicity, maintenance of medication even after disappearance of symptoms is advisable.

More describes that chronic prostatitis is found in more than 35% of male adults over the age of 35, while, according to another report, it is found in 85% of male adults over the age of 30. The participating factors are trauma, drinking and car-driving, and the incidence may even increase in future. In most cases bacteria are either totally absent or only sparsely detected, and thus positive use of antibiotics is not justified. On the other hand, long-term administration of anti-inflammatory drugs does not always result in improvement of symptoms. In this sense, the pollen preparation Cernilton points to a new approach. It may not be effective in all cases of chronic prostatitis, but it certainly can be effective in many such cases, especially those of allergic origin. For treatment of acute prostatitis, however, it is desirable to use antibiotics since Cernilton does not possess potent bactericidal action. Finally, it is reported that the drug is to be carefully administered to patients allergic to pollen.

Conclusions

Cernilton and placebos have been used for treatment of chronic prostatitis and following results obtained:

1. Of a total of 14 cases in the Cernilton group, 10 cases were effective and 3 cases slightly effective.
2. Results obtained in the placebo group were much less favourable, effective in 7 cases and ineffective in 9 cases.
3. Side-effects were observed in none of the 38 cases studied.

Table 1. Cernilton Group

No.	Age	Dosage tab. × time	Adm. Days	Combined Drugs	Effects	Subjective symptoms	After Massage of Prostate: Urinary findings	After Massage of Prostate: Bacteria in Urine	Remarks
1.	26	4 × 1	43	—	Effective	+ + → +	++ → —	—	Tenderness of prostate disappeared.
2.	23	,,	28	—	,,	++ → —	+	+ → —	,,
3.	27	,,	49	—	,,	+ + → —	—	—	Same patient as No. 9 in Table 2.
4.	33	,,	10	—	,,	+ + → —	+ → ±	+ → —	
5.	38	,,	21	—	,,	+ + → —	—	—	
6.	44	,,	56	Urocydal 21 days before Cernilton	,,	+ + → —	+ + → —	—	
7.	32	,,	42	—	,,	+ + → —	—	—	Recurred after withdrawal.
8.	34	4 × 1 2 × 1	7 28	—	,,	++ → —	—	—	
9.	23	4 × 1	42	Placebos 42 days before Cernilton	,,	++ → ±	+ → —	—	Same patient as No. 9 in Table 2.
10.	47	,,	24	—	,,	+ + → —	+ → —	—	Later changed to placebo same patient as No. 10 in Table 2.
11.	57	,,	21	—	Slightly effective	+ + → —	?	—	Ureteral calculus subsequently found and treatment changed.
12.	61	,,	56	Panvitan 3 tabs daily	,,	+ + → —	+ +	+	Induration of prostate disappeared.
13.	52	,,	10	Antibiotics	,,	+ + → +	+ → —	+	Hypertrophy of prostate associated.
14.	37	,,	14	—	Ineffective	+ + → +	+ → ++	—	Same patient as No. 16 in Table 2.

Table 2. Placebo Group

No.	Age	Dosage tab. × time	Days Adm.	Combined Drugs	Effects	Subjective symptoms	After Massage of Prostate: Urinary findings	After Massage of Prostate: Bacteria in Urine	Remarks
1.	38	4 × 1	49	—	Effective	+ + → +	+ → —	+ → —	
2.	60	,,	28	—	,,	+ + → —	++ → +	—	
3.	53	,,	7	—	,,	+ + → —	++ → +	—	
4.	31	,,	14	—	,,	+ + → —	—	—	
5.	33	,,	35	—	,,	+ + → —	+ → —	—	
6.	41	,,	21	—	,,	+ + → —	—	—	
7.	25	,,	42	—	,,	+ + → —	+ + → —	—	
8.	27	,,	27	—	Ineffective	+ +	—	—	Vaginal trichomonas found transitorily in urine.
9.	23	,,	42	—	,,	+ +	+	+	Same patient as No. 9 in Table 1. Subsequently changed to Cernilton.
10.	47	,,	14	Cernilton 24 days before placebo	,,	— — → +	— —		Same patient as No. 10 in Table 1.
11.	21	,,	28	—	,,	+ +	—	—	
12.	29	,,	14	—	,,	+ +	—	—	
13.	42	,,	7	—	,,	+ +	—	— → +	
14.	60	,,	28	—	,,	+ +	+	—	
15.	33	,,	21	—	,,	+ +	+	—	
16.	52	,,	10	—	,,	+ → + +	—	+	Same patient as No. 16 in Table 1.

Biometric Analysis of a Retrospective Documentation Study of Cernilton®N in the Treatment of Patients with Chronic Symptomatic Prostatitis

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Summary

A retrospective documentation study of the efficacy and tolerability of Cernilton®N in the treatment of chronic bacterial prostatitis was conducted by Dr.Dr.med. Erwin W. Rugendorff (Study Director), Giessen, Germany, between January and October 1988. The study included 40 patients between 23 and 69 years of age who were started on treatment with Cernilton®N between January and April 1988. The following parameters were determined before the start and at the end of Cernilton N therapy:

Clinical Features

- Discomfort
- Pain
- Nocturia
- Pollakiuria
- Dysuria

Uroflometry

- Micturition volume
- Peak urine flow
- Mean urine flow
- Flow time
- Micturition time
- Flow rise time
- Uroflow index

Findings on palpation

- Size of the prostate
- Consistency of the prostate
- Tenderness

- Tenderness of the prostate

Leukocyturia

- Leukocytes in midstream urine
- Leukocytes in post-massage urine

Bacteriuria

Ejaculate findings:

- C_{3c}/ ceruloplasmin
- IgG
- Antichlamydia IgA

Adverse drug reactions

Reasons for premature discontinuation of therapy

Assessment of tolerability and efficacy

Results

1. History

   - Acute bacterial infection: *n* = 32
   - TUR-P: *n* = 3
   - Prostatectomy: *n* = 0
   - Previous therapy in the preceeding 3 month: *n* = 15
   - Complicating factors: *n* = 14
     [1. Urethrostenosis: *n* = 4]
     [2. Prostatic calculi: *n* = 3]
     [3. Sclerosis of the bladder neck: *n* = 7]
   - Concomitant diseases: *n* = 8

2. Clinical features and laboratory parameters on admission:

   The patients complained of mild-to-moderate symptoms on admission. Uroflometry detected abnormalities (mean uroflow index = 0.91); the white cell count in the postmassage urine was significantly increased (range 45-610, median 128 WBC/ml); and the C_{3c}/ ceruloplasmin and IgG concentrations in the ejaculate were elevated.

3. Complicating factors:

   The clinical features were, to a large extent, influenced by the presence of complicating factors. While the incidence of manifest symptoms was lower before treatment, the impairment of urine flow was more pronounced.

4. Cernilton®N therapy:

Cernilton®N therapy was provided on a fixed dosing regimen: 1 tablet t.i.d. The duration of therapy varied between 25 and 196 days; the median duration was 146 days. Treatment was discontinued prematurely in 24 cases for the following reasons:

- Freedom from symptoms: *n* = 3
- Marked improvement: *n* = 6
- Ineffectiveness: *n* = 1
- Exacerbation: *n* = 13
- Dropout for personal reasons: *n* = 1

Early dropout reasons are primarily ineffectiveness of therapy/ exacerbation of the disease, while the majority of the patients who discontinued therapy prematurely in the second quarter of the study had achieved either freedom from or a marked improvement in their complaints.

5. Changes in clinical features on Cernilton® N therapy:

In the absence of complicating factors, the following percentages achieved freedom from the following complaints on Cernilton® N therapy:

- Discomfort: 89.5%
- Pain: 83.3%
- Nocturia: 53.8%
- Pollakiuria: 56.0%
- Dysuria: 86.4%

In the presence of complicating factors, however, the response rates to Cernilton® N therapy was significantly lower.

6. Uroflometry:

In the absence of complicating factors, the urine flow parameters showed the following average improvements

- Micturition volume: - 6.1 ml
- Peak urine flow: + 3.0 ml/sec
- Mean urine flow: + 2.7 ml/sec
- Flow time: - 7.1 sec
- Micturition time: - 7.3 sec
- Flow rise time: - 3.0 sec
- Uroflow index: + 0.22

In the presence of complicating factors, uroflometry showed a slight tendency for deterioration. The between-subset (without vs. with complicating factors) differences proved to be significant for peak urine flow, mean urine flow, and uroflow index.

Thus, an increase in the uroflow index was reported for 92.0 percent of patients without complicating factors, while as few as 36.4 percent of those with complications achieved such an improvement.

7. Findings on palpation:

The subset of patients without complicating factors experienced marked improvements in the findings on palpation. Thus, 75.0 percent had nontender prostates after Cernilton® N therapy, while as few as 33 percent of the complicated cases were asymptomatic in this respect.

8. Leukocyturia:

Lower white cell counts in the urine were recorded for the following percentages of patients:

Midstream urine:

- Without complicating factors: 73.1%
- With complicating factors: 28.6%

Post-massage urine:

- Without complicating factors: 80.8%
- With complicating factors: 28.6%

9. Bacteriuria:

Bacteria were again found in the urine in the following percentages of patients:

- Without complicating factors: 15.4%
- With complicating factors: 49.9%

10. Ejaculate findings:

Reductions in the C_{3c}/ ceruloplasmin concentrations were determined for the following percentages of patients:

- Without complicating factors: 80.8%
- With complicating factors: 28.6%

IgG was elevated in

- 7.7% of the patients without complications
- 50.0% of the patients with complications

The majority of patients without complicating factors were either unchanged or achieved improvement.

12 . Antichlamydial IgA:

No change.

13. Adverse drug reactions:

There was no report of an adverse drug reaction.

14. Assessment of tolerability:

Tolerability was rated as good in 35 patients and as fair in 5.

15. Assessment of efficacy:

Efficacy was judged as follows:

Judgment	Without complications	With complications
Normalization	3 (11.5 %)	1 (7.1 %)
Improvement	18 (69.2 %)	3 (21.4 %)
No improvement	5 (19.2 %	10 (71.4 %)
Comparison	p = 0.005 (chi-square test)	

The response was

- 80.8% without complicating factors
- 28.6% with complicating factors

Table of Contents

1. Study Objective

A retrospective documentation study of the efficacy and tolerability of Cernilton® N in the treatment of chronic bacterial prostatitis was conducted.

The present exposé reports about the biometric analysis of the clinical data.

2. Methods

The present retrospective documentation study includes patients with chronic bacterial prostatitis started on Cernilton® N therapy between January and April 1988. The study parameters were determined at baseline (before the start of the study) and at the end of therapy. The study period was > = 6 months for non-dropouts.

Enclosed CRF shows the scope of the clinical and laboratory workup done in the individual patients.

Outcome is assessed by comparing the results obtained for the study parameters before and after treatment. In addition, a comparison is made between

- The patients without complicating factors
  and
- Those with complicating factors (urethrostenosis, prostatic calculi, sclerosis of the bladder neck).

These two subsets are compared by

- The chi-square test for frequency distributions;
- Student's t-test for baseline means and mean pre-post differences (parametric test); and
- The U-test for baseline medians and median pre-post differences (non-parametric test).

The nonparametric statistic is used for testing the white cell count per ml urine.

Both documented parameters and selected derived parameters are included in the statistical analysis.

- *Normal range of peak urine flow:*

  The reference value + -20% range is used as the normal range. The micturition volume-dependent reference values are as follows:

Micturition volume	Reference value
"200 ml" = < 250 ml	22.5 ml/sec
"300 ml" = 250 - < 350 ml	26 ml/sec
"400 ml" = 350 - < 450 ml	28 ml/sec
"500 ml" = > = 450 ml	30 ml/sec

- *Normal range of mean urine flow:*

  The reference value + -20% range is used as the normal range. The micturition volume-dependent reference values are as follows:

Micturition volume	Reference value
"200 ml" = < 250 ml	15 ml/sec
"300 ml" = 250 - < 350 ml	17 ml/sec
"400 ml" = 350 - < 450 ml	20 ml/sec
"500 ml" = > = 450 ml	23 ml/sec

- *Assessment of uroflow index:*

Normal:	> = 1.2
Reduced:	0.8 - < 1.2
Markedly reduced:	< 0.8

The uroflow index I is calculated from the following formula:

$$I = \frac{\text{peak urine flow + Mean urine flow}}{[(\text{micturition volume}/400) + 0.75] * 20}$$

- *Normal range of white cells in the urine:*

Normal:	< = 20 ml urine*
Elevated:	> 20 ml urine

*Urine: Midstream urine
Postmassage urine

- *Ejaculate IgG determination:*

Normal:	0 mg/dl
Elevated:	1 - 20 mg/dl
Markedly elevated:	> 20 mg/dl

3. Patients

The retrospective documentation study included 40 patients with chronic bacterial prostatitis. Their age ranged between 23 and 69 years (median 42 yrs); their mean height was 176 cm, and their mean weight, 75.4 kg (Table 1). Three patients with concomitant BPH, whom we did not exclude from analysis, will be dealt with specifically in Section 6. Prominent history features include (Table 1):

- Acute bacterial infection: *n* = 32
  [bacterial prostatitis: *n* = 32; bacterial urethritis: *n* = 14]
- Previous therapy in the preceding 3 months: *n* = 15
- Complicating factors: *n* = 14
  [1. Urethrostenosis: *n* = 4]
  [2. Prostatic calculi: *n* = 3]
  [3. Sclerosis of the bladder neck: *n* = 7]
- Concomitant diseases: *n* = 8

The patients typically complained of mild-to-moderate symptoms on admission (Table 2). The following mean values were obtained for the uroflow parameters*:

- Micturition volume: 277 ml
- Peak urine flow: 17.7 ml/sec
- Mean urine flow: 9.5 ml/sec
- Flow time: 31.7 sec
- Micturition time: 33.2 sec
- Flow rise time: 10.2 sec
- Uroflow index: 0.91

The prostate was enlarged in 52.5 percent and tender in 85.0 percent of patients. Merely one patient showed a WBC count > 20/ml in the midstream urine. However, all patients had elevated WBC counts in postmassage urine (range: 45-610/ml; median: 128/ml). The C_{3c}/ ceruloplasmin and IgG concentrations in the ejaculate were elevated in all patients; 25.0 percent tested positive for antichlamydial IgA (Table 2).

Documented patients with complicating factors differed markedly from those without complications

- By a reduced incidence of the cardinal clinical features.
- By a more pronounced impairment of urine flow.
  (Table 3)

4. Cernilton® N Therapy

Cernilton® N was prescribed at a dosage of 1 tablet t.i.d. None of the patients included in this retrospective documentation study had his dose modified or his therapy suspended.

The treatment was continued for 25-196 days (median 146 days). Twenty-nine patients discontinued therapy prematurely (< 180 days). Five patients who had almost completed the “180-day minimum” (duration of therapy: 144, 158, 162, 163, 177 days) and another 4 patients who had achieved improvement in their signs and symptoms were obviously not classified as *dropouts*.

Early discontinuation of therapy was primarily due to exacerbation of the disease/ ineffectiveness of treatment (Table 4). Premature termination as a consequence of improvement occurred no earlier than after 3 months’ treatment in the present study cohort.

Treatment was discontinued prematurely in 24 cases for the following reasons:

- Freedom from symptoms: n = 3
- Marked improvement: n = 6
- Ineffectiveness: n = 1
- Exacerbation of the disease: n = 13
- Dropout for personal reasons: n = 1

5. Results

5.1 **Clinical Features**

The percentages of patients with the various clinical features before and after Cernilton® N therapy are shown in Table 5 and Figures 1 through 5:

- Discomfort (Figure 1)
- Pain (Figure 2)
- Nocturia (Figure 3)
- Pollakiuria (Figure 4)
- Dysuria (Figure 5)

The patients of the subset without complicating factors experienced marked improvements. The following percentages of patients achieved freedom from complaints:

- Discomfort 89.5%
- Pain 83.3%
- Nocturia 53.8%
- Pollakiuria 56.0%
- Dysuria 86.4%

The presence of complicating factors results in lower response rates (cf. Figure 6); in particular, there is a comparatively elevated incidence of deterioration. Estimative chi-square tests revealed parallel differences between the subsets “without” and “with” risk factors for the five cardinal features, the differences being marginal, as emerges from the p-values.

5.2 Uroflometry

Table 6 shows the distribution of the uroflometry parameters. The pre-post difference in micturition volume is small. Also, the difference between patients without and those with complicating factors is a minor one.
Differences are, however, noted for the following parameters:

Peak urine flow (p = 0.020):
- Without complicating factors: +3.0 ml/sec
- With complicating factors: -1.7 ml/sec

Mean urine flow (p = 0.004):
- Without complicating factors: +2.7 ml/sec
- With complicating factors: -0.8 ml/sec

Flow time (p = 0.013):
- Without complicating factors: -7.1 sec
- With complicating factors: +1.3 sec

Uroflow index (p = 0.006):
- Without complicating factors: +0.22
- With complicating factors: -0.03

For the latter parameter, the overall change results from an average increase from 0.97 to 1.20 for uncomplicated patients and an essentially unchanged result for “high risk” patients (mean change from 0.77 to 0.75). While consistent influences of complicating factors emerge for the other parameters, these fail to attain the level of statistical significance also for high-risk patients, although there is a tendency for improvement. Figures 7 through 13 visualize the average values of the uroflometry parameters before and after Cernilton® N therapy:

- Micturition volume (Figure 7)
- Peak urine flow (Figure 8)
- Mean urine flow (Figure 9)
- Flow time (Figure 10)
- Micturition time (Figure 11)
- Flow rise time (Figure 12)
- Uroflow index (Figure 13)

The tables that follow complement the quantitative analysis of uroflometry by providing a qualitative pre-post comparison of urine flow and uroflow index:

Pre-post comparison of **peak urine flow** (qualitative)						
Post / Pre	Without complications			Complications		
	Below normal	Normal	Above normal	Below normal	Normal	Above normal
Below normal	12	2	1	11	-	-
Normal	-	6	3	2	1	-
Above normal	-	1	-	-	-	-

Pre-post comparison of **mean urine flow** (qualitative)						
Post / Pre	Without complications			Complications		
	Below normal	Normal	Above normal	Below normal	Normal	Above normal
Below normal	16	5	1	12	-	-
Normal	1	2	-	2	-	-
Above normal	-	-	-	-	-	-

Pre-post comparison of **uroflow index** (qualitative)						
Post / Pre	Without complications			Complications		
	< 0.8	0.8 to <1.2	> =1.2	< 0.8	0.8 to <1.2	> =1.2
<0.8	2	2	2	6	1	-
0.8 to <1.2	-	8	6	1	2	-
> =1.2	-	-	5	-	-	1

Marked gradual effects on the uroflow index emerged for the subset without complicating factors. These are particularly prominent for the individual tendency of the uroflow index:

Change	Without complications		Complications	
Increase	23	(92.0 %)	4	(36.4 %)
No change	--	(0.0 %)	1	(2.8 %)
Decrease	2	(8.0 %)	6	(54.5 %)

The differences between the subsets without and with complications are statistically significant ($p = 0.002$). The trend in the uncomplicated subset (23:2) is quite obvious ($p < 0.001$ in the signed rank test).

5.3 Findings on Palpation

Normalization of the enlarged prostate at baseline is achieved in 6/12 uncomplicated patients but in none of those with complicating factors. In fact, two patients of the latter group experienced deterioration (Table 7). As regards the consistency of the prostate, 16/26 patients without complications showed improvement while merely 2/14 of those with complications did so (Table 7). Similar results are obtained for tenderness (2 consistently negative cases of both subsets are not included).

Change	Complications NO	YES
Deteriorated	3	8
Unchanged	2	-
Improved	1	-
Asymptomatic	18	4
% asymptomatic	75.0	33.3
Comparison	$p = 0.016$ (chi-square test)	

The presence of complicating factors also proved to be a limiting factor for the response of the parameter tenderness of the prostate.

For graphic representations of tenderness please refer to Figures 14 and 15:

- Intensity of tenderness (Figure 14)
- Change in tenderness (Figure 15)

5.4 Leukocyturia

While the majority of the patients of the uncomplicated subset showed reductions in their white cell counts in the midstream urine in the course of therapy, the high-risk patients predominantly had higher WBC counts (Table 8; $p < .001$ for the between-subset comparison of the median change in white cell count). The within-patient pre-post comparison demonstrates reductions in the WBC count

- In 73.1% of the subset without complications, and
- In 28.6% of the subset with complications

(p = 0.005 for the between-subset comparison of the within-patient pre-post change).

Change	Without complications		Complications	
Decrease	19	(73.1 %)	4	(28.6 %)
No change	2	(7.7 %)	-	(0.0 %)
Increase	5	(19.2 %)	10	(71.4 %)

The 19:5 trend (decrease:increase) for uncomplicated cases attains the level of statistical significance (p = 0.007) in the signed rank test.

The increase in the white cell count was beyond the upper limit of normal

- In *n* = 1 patient in the subset without complications, and
- In *n* = 5 patients in the subset with complications

Pre-post comparison of **midstream urine WBC count** (qualitative)				
Post / Pre	Without complications		Complications	
	< = 20	> 20	< = 20	> 20
< = 20	24	1	9	5
> 20	1	-	-	-

The white cell count in postmassage urine decreased in the majority of patients without complications, but tended to increase in most of the high-risk patients (Table 8; p = 0.002 for the U-test subset comparison). The whitin-patient pre-post comparison demonstrates reductions in the WBC count.

- In 80.8% of the subset without complications, and
- In 28.6% of the subset with complications

(p = 0.001 for the between-subset comparison of the within-patient pre-post change).

Change	Without complications		Complications	
Decrease	21	(80.8 %)	4	(28.6 %)
Increase	5	(19.2 %)	10	(71.4 %)

The 21:5 trend (decrease/increase) for uncomplicated cases attains the level of statistical significance (p = 0.002) in the signed rank test.

The reductions in the white cell count was tantamount to normalization

- In *n* = 3 patients of the subset without complications, and
- In *n* = 1 patient of the subset with complications.

Pre-post comparison of postmassage urine WBC count (qualitative)				
Post / Pre	Without complications		Complications	
	< = 20	> 20	< = 20	> 20
< = 20	-	-	-	-
> 20	3	23	1	13

Figure 16 visualizes the leukocyturia findings.

5.5 Bacteriuria

Ten patients again had bacteria detected in their urine in the course of CERNILTON® N therapy, namely

- 4/26 (15.4%) of the patients without complications, and
- 6/14 (49.9%) of the high-risk patients.

5.6 Ejaculate Findings

The pre-post comparison of the ejaculate findings yields the following results (Table 9):

C3c/ceruloplasmin		
Change	Without complications	Complications
Improvement	21 (80.8 %)	4 (28.6 %)
No change	1 (3.8 %)	1 (7.1 %)
Deterioration	4 (15.4 %)	9 (64.3 %)
Comparison	*p* = 0.004 (chi-square test)	

IgG		
Change	Without complications	Complications
Improvement	8 (30.8 %)	3 (21.4 %)
No change	16 (61.5 %)	4 (28.6 %)
Deterioration	2 (7.7 %)	7 (50.0 %)
Comparison	*p* = 0.009 (chi-square test)	

The tendencies for improvement in the subset of uncomplicated cases are quantified by p = 0.001 (21:4) and p = 0.109 (8:2), respectively.

Figure 17 visualizes the ejaculate findings.

5.7 Antichlamydial IgA

No changes were seen on CERNILTON® N therapy.

5.8 Adverse Drug Reactions

There were no adverse drug reactions.

5.9 Assessment of Tolerability and Efficacy

Tolerability was rated as good in 35 patients and as fair in 5 (Table 10). The judgment of efficacy was significantly affected by the presence of complicating factors (urethrostenosis, prostatic calculi, sclerosis of the bladder neck; Table 10). The response rate was

- 80.8% in the subset without complicating factors, and
- 28.6% in the subset with complicating factors.

6. Specific Cases

6.1 Concomitant BPH

Three patients with existing prostatic hyperplasia (BPH) were included in the retrospective documentation study. The following therapeutic responses were obtained:

Pat #1 (absence of complicating factors):

- Improvement in all clinical symptoms;
- Increase in peak and mean urine flow;
- Reduction in flow time, micturition time, and flow rise time;
- Increase in uroflow index from 0.63 to 0.74;
- Normalization of the consistency of the prostate;
- Decrease in tenderness;
- Reduction in white cell count in the urine;
- Decrease in C_{3c}/ ceruloplasmin levels;
- Judgment of efficacy: Improvement.

Pat #12 (sclerosis of the bladder neck):

- No change in clinical features;
- No improvement in urine flow; decrease in uroflow index from 1.07 to 0.94;
- Palpation findings unchaged ;
- Increase in WBC count in postmassage urine;
- Ejaculate unchanged;
- Judgment of efficacy: No improvement.

Pat #14 (sclerosis of the bladder neck):

- Improvement in all clinical symptoms other than dysuria;
- No improvement in urine flow; uroflow index unchaged (0.66);
- Tenderness on palpation improved;
- Decrease in WBC count in post-massage urine from 312 to 92/ ml;
- Decrease in C_{3c}/ ceruloplasmin levels;
- Decrease in IgG;
- Judgment of efficacy: Improvement.

Given the impact of complicating factors on therapeutic effects, the presence of BPH does not cause an additional impairment.

6.2 Patient #26 (absence of complicating factors)

Patient #26 had been admitted to the study with a significantly elevated micturition volume.

- Improvement in all clinical symptoms;
- Normalization of urine flow;
- Tenderness on palpation improved;
- Decrease in WBC count in postmassage urine from 315 to 52/ ml;
- Decrease in C_{3c}/ ceruloplasmin levels;
- Judgment of efficacy: Improvement.

Given the overall consistent pattern of changes in the clinical features on Cernilton® N therapy, exclusion of patient #26 from analysis should be limited to the uroflometry parameters.

7. Data Listings

The individual data are collated in 4 lists:

- Demographics & History (List 1)
- Concomitant diseases/ therapy/ comedications (List 2)
- Clinical features & lab tests (List 3)
- ADR/ dropouts/ judgments (List 4)

Appendices

1 CRF	(6 pages)
10 tablets	(18 pages)
17 figures	(17 pages)
4 data listings	(21 pages)

PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Chronic Prostatitis

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Chronic prostatitis, which is one of the most common diseases with which the adult male is afflicted [1, 2], covers a wide range of symptoms originating in the prostate. Gartman [3] collected 178 of these symptoms related to the strategic position of the prostate to the urinary, genital and gastro-intestinal tract. A classification based on histological appearance by Swinney [14] divides the clinical heterogeneous group of chronic prostatitis in a true inflammatory group, a group with no evidence of inflammatory changes and a third small group of granulomatous prostatitis first described by Tanner and McDonald [5]. A new extract Cernitin (2) was introduced in 1959 by Ask-Upmark [6] in the therapy of this syndrome. This paper gives the preliminary results in small group of patients treated with this product in combination with a study of some constituents of prostatic fluid in this disease.

Methods and materials

Thirty one patients with a presumptive diagnosis of chronic prostatitis were considered potential candidates for admission to the study. The presumptive diagnosis was based on a careful history after which the patients underwent complete urological evaluation. This evaluation included weight and height, general and neurological findings, rectal findings with touch diagrams, residual urine, hemogram, serum phosphatase and lactic dehydrogenase (LDH), sedimentation rate, urinary sediment, urine and prostatic secretion cultures and antibiograms and urography. Prostatic secretion was obtained through massage of the prostate.

In several selected instances cystometry, transrectal prostatic biopsy and cysto-urethroscopy were performed. After this evaluation all patients with present urologic abnormalities or infections were excluded from the study and treated following standard urological concepts. The other patients, ten in total, which had received four days of sulfatherapy during the urological manipulations were treated with vitamins for a total period of six weeks. After this period a new urinesediment and urineculture was obtained. When these results were negative and when the syndrome of chronic prostatitis, <<a contradictio in terminis in this case>> was still present, Cernitin therapy was started. Four tablets were given in the morning for a total of twelve weeks to seven patients. After six weeks and at the end of the therapy the prostate was again massaged. Where prostatic secretion could be obtained total protein, LDH and acid phosphatase were determined and compared to similar determinations in the serum. Pherograms of protein and the isozymes of LDH and acid phosphatase were also determined. The total LDH and phosphatase were determed by the procedure of Berger and Broida [7] and Sigma technique [8] respectively. Total protein was determined by the biuret method [9]. The protein and enzyme pherograms were carried out according to a microelctrophoretic technique previously described [10] with modifications for the isozymes of LDH [11] and acid phosphatase [12]. The repeated touch diagram of the prostate attempted to define size, consistency, sensitivity and discernible longitudinal sulcus [13]. This

rectal examination and massage in order to obtain prostatic fluid, executed after voiding, to clear the urethra, was the only form of treatment besides extract. Moderate restriction of alcohol was also advised.

A second group of five patients hospitalized for cerebral commotion was utilized as a control group to the remaining seven patients.

Results

In the group of seven patients with a syndrome compatible with chronic prostatitis but where no evidence of infection was detected, the following data were obtained.

The mean age was 36 (22-44). Slight urinary problems were present in each instance which was mainly the reason for their reference. These included frequency (4), urgency (4), hesitation (2), discomfort when urinating (7). None of them complained of urethral discharge. Three of them complained of loss of sexual desire and four had regular pain in one of the testicles, groin, or perineum. Five of them had some signs of neuropsychiatric irritability including anxiety, nervousness, and fatigue. All laboratory studies were normal in the seven patients including serum and acid phosphatase and LDH. The serum LDH isozymes were normal in each sample. The prostatic secretion obtained in five patients and which could only be collected in three cases after receiving therapy, was colorless in all instances. Acidity, total protein, total acid phosphatase, and total LDH determined in nine instances, are shown in table I. Quantitated pherograms of protein, LDH and acid phosphatase (Fig. 1, 2, 3) from these samples are shown in table II.

The average size of the touch diagram exceeded the normal size (2 a 3 cm wide, 2.5 cm long and 2 cm thick at the heaviest point) in five out of seven patients combined with softer consistency and tenderness in at least one out of three occasions of rectal examination. Transrectal biopsy of the prostate performed in two instances revealed fibrosis in both and lymphocytic infiltration in one occasion.

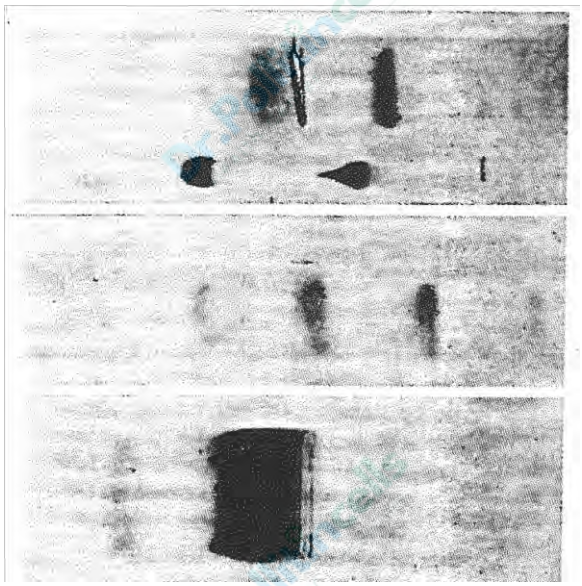

Fig. 1 – Photograph of pherogram of prostatic secretion. Three main fractions are clearly visible.
Fig. 2 – Photograph of LDH enzymogram of prostatic secretion. Five fractions are visible with a predominance of the middle fractions.
Fig. 3 – Photograph of acid phosphatase activity after electrophoretic separation by Gomori technique. Two fractions are present. The fraction to the left is albumin visualized by precipitation.

Following therapy, improvements of symptoms occurred in all seven patients. Therapy was discontinued in three of them. The other four still admitted slight abnormalities on close questioning and were kept on continuous therapy. In two out of three patients the sexual desire improved with disappearance of the symptoms. In the control group of five patients all laboratory investigations were normal. Rectal massage provided only two instances enough fluid for examination. The laboratory results obtained in these patients are presented in table I and II.

Discussion

A bacterial chronic prostatitis is a clinical syndrome which is vaguely defined, comprising a variable set of characteristic symptoms and findings on rectal examination of the prostate. Its only objective evidence is the histological aspect of deformed acini by an excess of fibromuscular

TABLE I

Values of total LDH, acid phosphatase and total protein in serum and prostatic secretion in patients with chronic prostatitis syndrome, * after six weeks of treatment, ** after twelve weeks of treatment and in a control series. Acidity of prostatic secretion is added in the last column.

Patients	Total LDH		Acid phosphatase		Total proteins		Acidity (Prostatic secretion)
	BB	Units	BB	Units	g %	g %	
R.T.	240	7.400	0.63	2.000	7.2	0.8	6.5
	—	*8.600	—	1.600	—	0.9	6.5
	—	**7.800	—	1.900	—	1.3	6.8
W.V.	320	9.200	0.53	1.600	6.8	1.5	6.7
	—	*6.800	—	1.800	—	0.8	6.5
M.H.	220	4.250	0.45	800	7.5	3.6	6.4
F.F.	200	6.700	0.53	1.750	7.1	1.8	6.2
	—	*7.200	—	1.900	—	1.1	6.5
M.F.	300	5.700	0.20	1.800	6.7	0.9	6.6
Controls							
L.P.	320	6.300	0.56	1.600	7.6	0.9	6.3
J.W.	180	8.250	0.49	1.500	6.8	2.4	6.5
A.P.	140	4.800	0.32	2.400	7.1	1.3	6.6

TABLE II

Representative example of quantitated electrophoretic study of prostatic secretion of one patient (W.V.)

Proteins	Fraction I	Fraction II	Fraction III
	15 %	38 %	47 %

LDH Isozymes	I	II	III	IV	V
	7.26 %	23.30 %	35.37 %	22.94 %	6.13 %

Acid Phosphatase	Fraction I	Fraction II
	86 %	14 %

stroma. This feature however is difficult to assess in a small surgical specimen which excludes the prostatic biopsy from the normal clinical evaluation of these patients. The aetiology is unknown and hypothesis range from psychomatic and autoimmune diseases. Therapy of course is not well defined and various measures including repeated prostatic massage to verbalization of symptoms have all been advocated [3]. A new form of treatment was studied by Leander, G. [14] and Jönson, G. [14] consisting of the oral administration of an extract of pollen, Cernitine, with no bacteriostatic or bacteriocidal effect *in vitro* and mainly consisting of amino-acids, vitamins, and unknown steroids. Therapeutic relief was obtained in a large variety of patients with chronic prostatitis including bacterial and abacterial cases. These results can be compared to the symptomatic relief by amino-acid therapy in benign prostatic hypertrophy as reported by Damrau [15].

A successful clinical result was obtained with Cernitine in a group of patients with abacterial prostatitis. It should be noted however that the extensive questioning and investigation in these cases might already relief some of these patients from their symptoms [16] and larger series will have to prove any statistical therapeutic effect of Cernitin against placebo. It can be conceived that Cernitin may have similar symptomatic relief effect in cases of true inflammatory prostatitis in combination with adequate chemotherapy. No adverse or side effects were noted in any patient. Attempts were made to determine biochemical parameters for the clinical diagnosis of chronic prostatitis by the determination of total serum LDH and acid phosphatase, serum LDH isozymes and acidity, total protein, total LDH, acid phosphatase and the pherogram of the proteins and the isozymes of LDH and acid phosphatase in the prostatic secretion as compared to a control group. These attempts were futile as shown in table I and II.

It showed also that no substantial difference occurred in any of these parameters after Cernitine therapy.

However, several interesting observations could be made concerning the results of the prostatic secretion. All obtained specimen had an acid reaction in contradiction to reports in the literature [17] where alkalinity of the prostatic secretion in described as a regular observation in chronic prostatitis. The total protein content of the prostatic secretion ranged between 0.89 mg percent to 3.6 mg% which are somewhat higher than the figures of Mann [18]. Electrophoretic separation of these proteins provided an identical pherogram both in diseased and control patients with three main fractions (Fig. 1). These fractions have been earlier described by Nylander [19]. No significant variations were noted in these fractions between the two groups as compared to previous reports of Soanes [20, 21]. This may be due to the absence of infection in these experiments since leukocytes or bacterial contamination may be responsible for the alteration of the protein spectrum in these reports. The total LDH activity and acid phosphatase activity were marked in both groups and can be compared to the recently provided figures of Grayhack (22). The activity of LDH isozymes was mostly divided between the three middle fractions (Fig. 2). Five fractions were present in every instance. No relation of any particular enzymatic shift could be noted in relation to age, disease or therapy. The acid phosphatase of the prostatic secretion was composed of several fractions. We were able to obtain two fractions (Fig 3) in three instances, one main fraction in the a region, one smaller fraction in the b region. This phenomenon was already reported by Estborn [23] but received no further attention. Further investigation seems in order to study this duplicity of phosphatase in relation to the importance of this enzyme in clinical urology.

Conclusions

Seven patients with clinical syndrome of abacterial chronic prostatitis were treated with Cernitine. Subjectif relief was obtained in all cases. Statistical evaluation by double blind studies is necessary for definite evaluation. Attempts for determination of biochemical parameters in this disease regarding protein, LDH and acid phosphatase determinations were completely negative.

Summary

Seven patients suffering from the clinical syndrome of <<abacterial chronic prostatitis>> according to their symptoms and rectal examination were treated with Cernitin (Cernilton, AB Cernelle, Sweden) for twelve weeks. Relief of symptoms was complete in three marked in four. Further experiments for statistical evaluations are mandatory.

The study of protein, lactic dehydrogenase, and acid phosphatase in serum and prostatic secretion established no parameters for diagnostic or therapeutic evaluation.

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Report on the clinical evaluation of "Cernilton" preparation in cases of chronic prostatitis

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The trial treatment of nine patients has been in progress since April 1965. Preparations of "Cernilton" in tablet form were placed at our disposal for these trial experiments by the Berlin Institute of Medicine.

Nine cases of clinically established prostate diseases, i.e. prostatitis, were treated. The following symptoms were observed in all instances:

9 cases of micturition disturbances
9 cases of cohabitation difficulties
9 cases of leukocytes in the ejaculate

All the patients were found to suffer from lowered libido and painful orgasms, and six of them exhibited manifestations of impotence. The practice of coitus interruptus was denied in all cases. In three cases the diagnosis was confirmed by histological excision, which revealed adenomatosis of the prostate with leukocyte infiltration. Haemospermia was detected in five cases.

Cultures of ejaculates from all nine cases revealed two cases of haemorrhagic ejaculates, two cases of greenish streptococci, two cases of haemolytic streptococci and one case of Peseudomonas aeruginosa. Apathogenic bacteria were found in three cases. All the ejaculates contained leukocytes and bacteria. Two cases with haemorrhagic discharges were observed, and a previous history of venereal infection (gonorrhea) was reported for two patients. One patient exhibited a predisposition to allergy.

Suicide had previously been attempted by two patients and grave depressive manifestations were observed in four others.

No pathological changes in the kidneys, urethra, or bladder could be established, i.e. no calculus, pyelonephritis or malformations could be confirmed.

Comprehensive re-examinations undertaken in 1966, revealed that all the patients had responded with a definite improvement. The following conclusions could be drawn from the use and evaluation of the drug to date:

In agreement with the findings of other investigators, it is apparent that scientific exactitude in the treatment of this subject is not possible.

In establishing criteria for cure or improvement, the following tests were undertaken:

1. Urine examination
2. Ejaculate examination
3. Examination of bacterial culture of ejaculate

4. Subjective report by the patient
5. Palpation findings

Chronic prostatitis is understandably difficult to define, since a considerable diversity of changes can take place in the prostate, that cannot always be definitely differentiated from each other. The diagnosis is thus best confirmed by histological examination. Biopsy specimens were therefore used in two cases. In the other cases, the material examined was the ejaculate and not the product of stripping, which had been studied by other investigators. As mentioned above, non-pathogenic bacteria were found in all cases, as well as large numbers of leukocytes.

As the test group consisted of no more than nine patients, no purpose could be served by grouping with relation to venereal disease. It may however be mentioned that, at the end of the treatment, previous infection of the urinary tract was of no fundamental importance.

In contrast to the observation period of 3 months, practiced by many of the West German workers, our own observations were carried over three years.

1. In all the nine cases, the ejaculate examinations showed the ejaculates to be free from leukocytes and bacteria after a protracted course of one Cernilton tablet taken three times daily.
2. Cultivated specimens of ejaculate and urine did not reveal the presence of pathogenic bacteria.
3. All the patients exhibited a considerable improvement both mentally and physically, with the result that some of the patients discontinued medication with Cernilton during the final 6-12 month. Only in three cases is Cernilton still being taken (3 x 1 tablets daily), but even these patients experience both physical and mental well-being.

The appearance of discharges has ceased, cohabitation difficulties no longer occur and pains radiating to the perineum and sacral region have disappeared.

Micturition disturbances could no longer be observed, neither could side-effects of after-effects following treatment with Cernilton be confirmed.

In conclusion it may be said that treatment of nine patients with one Cernilton tablet taken three times daily for a period of two years and longer brought about a healing of the condition, and that the pollen preparation Cernilton is a very suitable agent in the treatment also of severe and stubborn cases of chronic prostatitis. It would be a commendable advance if treatment with this pollen preparation were to become incorporated into recommended therapeutic praxis.

PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Prostatitis

Pygeum africanum

A tropical African evergreen tree.

Administration of extracts of the bark (standardized to contain 14% beta-sitosterol and 0.5% n-docosanol) may be beneficial at a dosage of 50 to 100 mg twice daily.

Experimental Study

18 pts. with benign prostatic hypertrophy or chronic prostatitis and, simultaneously, sexual disturbances, received an extract of *Pygeum africanum* (Tadenan®, Roussel Pharma) 200 mg daily. After 60 days, the extract had improved all the urinary parameters that were investigated. Also, sexual behavior was reported to be improved despite a lack of change in the levels of sex hormones or in nocturnal penile tumescence and rigidity. No side effects were observed (*Carani C, Salvoli V, Scuteri A, et al. [Urological and sexual evaluation of treatment of benign prostatic disease using Pygeum africanum at high doses.] Arch Ital Urol Nefrol Androl 63(3):341-5,1991) (in Italian).*

Combination Treatment

Flower Pollen Extract

Administration of standardized extract of flower pollen (Cernilton®) may be beneficial.

Note: In vitro studies suggest that Cernilton® is a potent cyclo-oxygenase and lipoxygenase inhibitor and a smooth muscle relaxant (Buck AC, Rees RW, Ebeling L. Treatment of chronic prostatitis and prostatodynia with pollen extract. Br J Urol. 64(5):469-9, 1989).

Experimental Study

90 pts. with chronic prostatitis received Cernilton N one tablet 3 times daily. After 6 mo., in the 72 patients without complicating factors (urethral strictures, prostatic calculi or bladder neck sclerosis), 56 (78%) had a favorable response; 26 (36%) were cured of their signs and symptoms, and 30 (42%) improved significantly with an increase in flow rate, a reduction in leukocyturia in the post-prostate massage urine and a decrease in complement C3/ceruloplasmin in the ejaculate. In the 18 pts. with complicating factors, however, only 1 pt. showed a response; thus complicating factors should be considered in pts. who fail to respond to treatment within 3 months. The extract was well tolerated by 97% of pts. *(Rugendorff EW, Weidner W, Ebeling L, Buck AC. Results of treatment with pollen extract (Cernilton N) in chronic prostatitis and prostatodynia. Br J Urol. 71(4):433-8, 1993).*

Experimental Study

25 pts. with chronic prostatitis received Cernilton tablets. Improvement of subjective symptoms and objective findings was noted in 96% and 76%, respectively. Sonographic findings showed 33-100% improvement in 4 objective parameters. No side effects were observed *(Suzuki T, Kurokawa K, Mashimo T, et al. [Clinical effect of Cernilton in chronic prostatitis.] Hinyokika Kiyo. 38(4):489-94, 1992) (in Japanese).*

Experimental Study

13/15 pts. with chronic prostatitis and prostatodynia with a mean duration of 3.3 yrs. were treated with Cernilton 2 tabs twice daily. 7 had complete and lasting symptom relief, while 6 had marked improvement. Most pts. who responded (11/13) did not start to show

improvement until 3 mo. after starting treatment, and symptoms recurred in 2 pts. who stopped treatment. No adverse reactions were seen (*Buck AC, Rees RW, Ebeling L. Treatment of chronic prostatitis and prostatodynia with pollen extract. Br J Urol. 64(5): 496-9, 1989*).

Experimental Study

32 pts. with chronic prostatitis received Cernilton 6 tabs daily. After an average of 6 weeks, improvement of subjective symptoms and objective findings was noted in 74.2% and 65.6%, respectively. The effective rate was 75%. No subjective side effects or abnormal changes in laboratory data were observed *(Jodai A, Maruta N, Shimomae E, et al. [A long-term therapeutic experience with Cernilton in chronic prostatitis.] Hinyokika Kiyo. 34(3):561-8, 1988) (in Japanese).*

Experimental Study

Based on a grading system using both objective and subjective measures of 14 pts. with non-gonorrheal prostatitis and urethritis given Cernilton 4 tabs daily, it was 'effective' in 10 (71%) and 'slightly effective' in 3 (21%). Of 16 pts. given placebo it was 'effective' in 7 (44%) and 'slightly effective' in none. Subjective symptoms disappeared in 10 pts. (71%) and diminished in 4 (29%) while the rest had some degree of improvement in the Cernilton group. In the placebo gp., subjective symptoms disappeared in 5 pts. (31%), diminished in 2 (13%), and worsened in 2 (13%). In the Cernilton group, there was normalization of the urinary sediment in 5 pts. (36%) improvement in 1 (7%), persistence of the abnormal state in 2 (14%), exacerbation in 1 (7%), and continuation of the normal state in 4 (29%) (the result in 1 pt. is unknown). In the placebo gp., there was normalization in 3 pts. (19%), improvement in 2 (13%), persistence of the abnormal state in 3 (13%) and persistence of the normal state in 8 (50%). For the Cernilton gp., urinary bacteria following prostatic massage disappeared in 3 pts. (21%), failed to change in 2 (14%), and remained normal in 9 (64%). For the placebo gp., bacteria disappeared in 1 pt. (6%), failed to change in 2 (13%), reappeared in 1 (6%) and remained normal in 12 (75%). There were no notable subjective or objective side effects *(Ohkoski M, Kawamura N, Nagakubo I. [Clinical evaluation of Cernilton in chronic prostatitis.] Rev Med Suiza. 2(16):436-9. 1970)(in Spanish).*

See Also

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Quantitative Evaluation on the Effectiveness of Cernilton® on Benign Prostatic Hypertrophy

H. Takeuchi et al. (Endocrinological Dept., Faculty of Medicine, Tokyo Medical & Dental University) (Hinyok Kiyo, Volume 27, No. 2, February 1981)

Introduction

Prostatomegaly is a very common disease in elderly men. It consists of a glandular, proliferative change occurring in the interior of the bladder and urethra. There are histopathological features, with proliferation not only of the glandular tissue but also of muscle and connective tissue. From the pathological point of view this is not genuine neoplasia but hyperplasia: the gland retains its normal exocrine function. The aetiology of the enlargement is still not certain, but a model experiment on dogs has shown that androstanediol secreted by the testes is involved, with estradiol as an accelerating factor.

This fact strongly suggests the participation of the endocrine function of the testes in the genesis of the disease.

The characteristics of an enlargement of this kind are also important from the therapeutic point of view. For example, if there is hormone imbalance with reduced sexual activity, the secretions accumulate in the tissue of the enlarged gland, leading to so-called “congestive prostatism”, with the formation of what is virtually a cyst. Therefore if the secretions are suitably eliminated the entire prostate gland will shrink.

From the clinical point of view prostatomegaly is a nodular proliferation (adenoma), which is located mainly in the right and left lobes of the prostate gland and pushes the latter outwards, not only forming a capsule, but also pressing it down and flattening it out. This increases urethral resistance during micturition and leads to various subjective symptoms; moreover there is obstruction of the lower urinary tract, with secondary effects on the bladder and upper urinary tract, finally leading to systemic symptoms. However, there is not necessarily any relation between the degree of obstruction and the size of the adenoma; there tends to be a closer relationship with either the site of enlargement, oedema of surrounding tissue, or infections complications. Frequency, which is regarded as an early symptom of this disease, or delayed and prolonged micturition, narrowing of the stream of urine, decline in ejaculatory power etc., which are regarded as symptoms of irritation, appear at an early stage, depending on the site of enlargement. On the other hand, there are not a few cases where the disease remains at the stage of “silent prostatism”, even with a prostatomegaly of 10-20g. Clinical problems of this kind, in conjunction with the above-mentioned pathological and physiological characteristics, suggest the possibility of some palliative method of treatment for the disease as opposed to the conventional prostatectomy. This would not be merely symptomatic but directed towards the eradication of the cause.

If this position is adopted, not only the basic problem of reduction of the adenoma, but also accessory problems of oedema of the neck of the urinary bladder accompanying the adenoma, stasis of the prostatic secretion and infections complications will form the object of therapy. At the moment hormones,

plant or animal organ extracts etc. are regarded as effective against this disease. However, not only the mode of action but also the usefulness of such preparations is still under review.

Although the pollen preparation Cernilton®, which has long been regarded as useful against prostatitis mainly in Northern Europe, has been regarded as indicated for prostatomegaly, both for its effect against inflammation and its action in inhibiting the growth of the prostate gland (2), there have been few studies of its actual use and effectiveness against prostatomegaly (3, 4). The present study is concerned with 25 cases of prostatomegaly chosen at random from patients assessed as not requiring an immediate operation, and investigates the preparation's effectiveness both from the point of view of subjective symptoms and from a physical examination of prostate gland, with the aim also of throwing some light on its mode of action.

Subjects of Investigation and Method

(A) Subjects: the subjects were 25 cases chosen at random from patients with prostatomegaly at the Endocrinological Department of the Faculty of Medicine, Tokyo Medical & Dental Hospital. The following were the exclusion criteria when selecting these cases:

1. Those not complaining of difficulty in micturition;
2. Those at stage III or later of the disease; with a residual urine volume of more than 250 ml;
3. Those receiving some other preparation for prostatomegaly up to one week before the start of the trial;
4. Patients with complications, such as mental disorder, neurological disease (neurogenic bladder, including diabetes);
5. Patients with urethral stricture;
6. Patients with hardening of the neck of the urinary bladder;
7. Patients with the complication of cancer of the prostate gland;

(B) Method and period of administration of the preparation: Cernilton was administered 3 times a day orally, 2 tablets at a time, for 3 months continuously. Concurrent drugs were given as little as possible: when complications made this inevitable only drugs were allowed which were judged to have no effect on prostatomegaly.

(C) Test items: Before and after the 3-months trial period and at suitable intervals during the trial subjective symptoms were ascertained and objective data investigated according to the following schedule:

a) Enquriy into subjective symptoms: The items investigated in the enquiry into subjective symptoms and the gist of questions were as follows

1. Frequency of micturition during day and at night;
2. Whether or not acute poor stream was present;
3. Prolonged micturition: (i) comes out smoothly
   (ii) takes some time
   (iii) takes a very long time
4. Delayed micturition: (i) very frequent, as when young
   (ii) sometime between each
   (iii) a long time between each

5. Staining during micturition:	(i) micturition is usually possible without being particularly aware of it; (ii) sometimes it is not possible to micturate unless one consciously puts an effort into the abdomen; (iii) micturition is not possible unless one continually puts an effort into it during the act.
6. Decline in vigor of urine stream:	(i) the thickness and force of the stream are no different from when the patient was young; (ii) the stream is weak, or intermittent; (iii) it comes out only in drops and hardly at all.
7. Feeling of residual urine	(i) Nil (ii) Present slightly (iii) Present

b) Enquiry into objective symptoms: The items of the objective enquiry were as follows

1. Findings on rectal examination;
2. Measurement of residual urine;
3. Ultrasonic planigram method (using an Aloka ECHO VISION SSD-120, a planigram of the prostate was obtained via the rectum and used to measure the maximal antero-posterior diameter of the prostate (in cm), maximal transverse diameter (cm) and length (cm), also obtaining the presumed weight of the prostate (g));
4. Measurement of urine flow (using a DISA 2100 URO system, a curve was drawn of the urine flow per second, and the maximum flow rate, MFR ml/ sec, average flow rate (ml/ sec), micturition volume (ml), micturition time (sec) and residual urine volume (ml) were calculated) ;
5. Urethral pressure profile (UPP) (using a DISA 2100 URO system, a curve was drawn of the UPP and the maximum urethral pressure (cm H_20), maximum urethral closure pressure (MUCP cm H_20) and prostatic profile length (PPL cm) were obtained, also calculating the prostatic urethral resistance (PUR g/cm) integrated within the PPL range on the basis of the PPL curve and MUCP standard curve).

c) General tests: The following were also investigated in the general tests:-

1. Hematology: red cell count, white cell count, platelet count, hematocrit (Ht = %), haemoglobin (Hb = g/ dl), leukocyte differential (eosinophils, basophils, band cells, segmented neutrophils, lymphocytes, monocytes).
2. Serum chemical tests: GOT (U/L), GPT (U/L), alkaline phosphatase (U/L), acid phosphatase (K. A. units), BUN (mg/ dl), creatinine (mg/ dl), total protein (TP= g/ dl), cholesterol (mg/ dl), triglyceride (mg/ dl), Na (mEq/ l), K (mEq/1), Cl (mEq/l), P (mg/ dl), Ca (mg/dl).
3. Urological tests: protein, sugar ½ estimated amount and deposit.

d) Assessment of effectiveness: The assessment of the effectiveness of Cernilton in relation to subjective and objective symptoms accompanying Prostatomegaly was according to the following standards:

1) Assessment of effectiveness against subjective symptoms: after 3 months of treatment the patient was questioned regarding changes before and after the treatment in the six items mentioned in the gist of the enquiry, namely frequency of micturition (especially at night), prolonged micturition, delayed micturition, straining during micturition, decline in force of urine

stream and feeling of residual urine, and an assessment was made on a scale of 3 grades: improvement, no change and deterioration. On the basis of these findings a total assessment was then made of:

(i) markedly effective, where there was no item which had deteriorated and 4 or more items had improved.
(ii) effective, where there was no item which had deteriorated and 1-3 items had improved.
(iii) no change, where there was no change in any item, and
(iv) ineffective, where even though there were improved items there was deterioration even in only one item.

2) Judgement of effectiveness against objective symptoms: when it was found in the objective findings that the difference between pre- and post-trial values for the 4 items of: residual urine, prostate weight ascertained by the ultrasonic planigram method, maximum flow rate (MFR) obtained by uroflowmetry, and urethral resistance obtained from the UPP, was 50% in the case of residual urine and more than 20% for the other items, this was assessed as improvement or deterioration, “no change” being cases where the figure was within these limits. The following total assessment was then made:-

(i) markedly effective, where there were 2 or more items on the improvement side;
(ii) effective, where there was 1 more item on the improvement side;
(iii) no change, where there was the same number of deterioration and improvement items, or where all items showed no change;
(iv) ineffective, where the deterioration items were more numerous.

3) Method of overall evaluation of therapeutic effectiveness: the therapeutic effectiveness of this preparation in prostatomegaly as regards subjective and objective symptoms was assessed by the following criteria:-

(i) markedly effective, where the findings both for subjective and objective symptoms were markedly effective or effective;
(ii) effective, where the findings were markedly effective or effective for subjective symptoms but no change for objective symptoms;
(iii) ineffective, where either subjective symptoms or objective symptoms or both were ineffective.

e) Statistical evaluation: The numerical values for the test items of the objective findings and general tests were summed for all patients for each item; the t value was ascertained by each of the differences between pre- and post-trial values, and a two-way test of significance at the 5% level was conducted using a table of t values.

Trial Findings

The age of subjects of the test ranged from 53 to 77, the average age being 67 (S. D. = 6 years). 6 cases had previously received drug treatment for prostatomegaly – either a vegetable extract or a Gestageno hormone preparation. No effectiveness was found with either of these preparations. Complications notified were 1 each of emphysema, cardiac insufficiency and hypertension; during the course of testing 2 cases of prostatic calculus, 1 of prostatitis and 1 of cystitis came to light.

The chief complaints of the 25 subjects were difficulty of micturition 18 (72%), frequency (20%) and residual urine sensation 2 (8%). 3 cases (12%) had experienced acute poor stream in the past. Enquires revealed that all cases had had some difficulty in micturition, whose details are shown in Table 1:

beginning with the most frequent 96% had prolonged micturition, 92% had delayed micturition, 84% had nocturnal frequency, 68% had a decline in the force of the urine stream, 68% experienced strain during micturition and 32% had a feeling of residual urine.

The preparation was administered with relative precision: apart from 1 case where acute poor stream occurred, an operation was indicated and the preparation was terminated in month 2, all cases continued taking it for 3 months or more. No cases received any concurrent drugs.

A) Therapeutic effectiveness of Cernilton against subjective symptoms

Although there was some fluctuation in the effect against subjective symptoms during the course of administration of the preparation, the impression at the end of 3 months treatment could be classified fairly well into the 3 grades of: improvement, no change and deterioration. Table 2 lists cases of improvement for the various symptoms: starting from the high effectiveness rate end, the figure was 54% for prolonged micturition, 50% for nocturnal micturition, 50% for residual urine sensation, 47% for decline in force of urine stream, 41% for straining during micturition and 22% for delayed micturition. As an overall judgment of these findings, one could hardly say that the effectiveness of the preparation against subjective symptoms was outstanding, although the start of emission of urine did improve and there was a relative improvement in the force of flow. The feeling of residual urine, frequency and other symptoms of irritation of the bladder neck were alleviated. However, this does not mean that there was any marked shortening of the time required for micturition. It would appear that this was due to an increase in diurnal urinary volume due to a decrease in the frequency of micturition.

The overall assessment of the effectiveness of this preparation against subjective symptoms was: markedly effective, 2 cases (8%); effective, 14 cases (56%); no change, 5 cases (20%); and ineffective, 4 cases (16%). The efficiency rate was assessed as 64% (Table 6).

B) Therapeutic effectiveness of Cernilton against objective symptoms

Table 3 summarizes the pre-test and post-trial figures for various measurement values in the objective findings.

a) Residual urine volume: in 15 out of 25 cases (60%) residual urine was detected after the start of the trial in amounts of 10-90ml (33±25ml). At the end of the trial 1 case had a fresh occurrence of acute poor stream; apart from inserting an indwelling urethral catheter, there was no occurrence of residual urine and in 3 out 15 cases it disappeared, in 3 cases it lessened and in 2 cases it increased. The volume of residual urine in the 15 cases at the end of the trial ranged from 0 to 120 ml (28±26ml). The t value was 0.38, and there was no significant difference in the residual urine volume after the trial (Table 3).

b) Ultrasonic planigram method: The findings of measurement of the prostate gland by the ultrasonic planigram method showed that the antero-posterior diameter before the trial was 2.0-3.8 cm (2.6±0.5cm); this tended to increase slightly to 2.5-3.6 cm (3.0±0.4 cm) after the trial. The findings were similar for transverse diameter and length: the transverse diameter before the trial had been 3.2-4.5 cm (3.8±0.5cm), and this tended to increase slightly to 3.6-4.4 cm (4.0±0.4 cm) and length from 3.0-5.0 cm (3.9±0.6 cm) to 3.5-5.0 cm (4.2±0.6 cm). this also affected the weight: where this had been 11.7-44.9 g (23.7±10.4 g) before the trial, it had increased to 20.9-56.6 g (31.2±14.8 g) after it. However, these figures were not statistically significant.

c) Uroflowmetry: The urine flow curve, maximum flow rate (MFR), average flow rate, volume passed, time of urination, residual urine etc. were measured by this method, but since apart from

MFR the measurement levels were greatly influenced by the urine volume in the bladder during measurement they were excluded from the investigation. The MFR was 3.6-15.7 ml/sec (8.7±4.3 ml/sec) before the test and tended to increase: figures for after the test were 7.6-15.1 ml/sec (11.8±3.5 ml/sec). The t value was -1.90 and the significance level was under 10%: although this does not come within the standard 5% of the two-way test, in a one-way test as to whether the urine flow rate increases over the course of the trial, it would come within the 5% figure and would be significant. Consequently, although this difference is not clearly evident, the indications are that Cernilton tends to increase the flow of urine. This is also connected with the number of subjects, but would appear to be a problem related to the length or shortness of the trial period.

d) U.P.P.: The prostatic profile length (PPL) was 2.5-6.6 cm (4.2±1.3 cm) before the trial and tended to decrease slightly after the trial to 2.9-4.3 cm (3.4±3.5cm). The maximum urethral closure pressure (MUCP) was 35-120 cmH_20 (92±23 cmH20) before the trial and clearly decreased after the trial to 45-85 cmH20 (58±19 cmH_20). The t value here was 2.71, with significance at the 5% level. The prostatic urethral resistance (PUR) showed a wide distribution of 7-57 g/cm (28±14 g/cm) before the trial and a clearly lower value of 8-14 g/cm after it (12±3 g/cm). This corresponds to the decline in MUCP: t=2.17 (P<0.05), and here too this can be described as a significant decline.

e) Overall assessment of effectiveness against objective symptoms: the following is a summary of findings before and after the administration of Cernilton of organic measurements of the prostate by the ultrasonic planigram method and of functional measurements from residual urine, uroflowmetry and UPP.

The size of the prostate gland itself did not decrease during the trial period of 3 months but on the whole rather tended to increase, with the result that the character of the disease in question was not checked. However, since there were no controls to whom Cernilton was not administered, it is not impossible that the rate of growth of the organ in question slackened. However, the measurements of the functional effects of prostatomegaly on the mechanism of urination showed a general trend for the better. This took the form of a decline in the prostatic profile length (PPL) in the urethral plane and a decrease in urethral closure pressure, indicating a reduction in urethral resistance and an improved urine flow rate. From this it may be presumed that there was release from a state of constriction due to some factor from the bladder neck to the external sphincter of the bladder. It would appear most appropriate to regard this as an elimination of the oedema and inflammation of the area in question or else of the stasis of prostatic secretions, and the mode of action of Cernilton relates to this point.

Table 6 shows the overall assessment findings for the effectiveness of this preparation against objective symptoms. They were: markedly effective, 0 cases (0%); effective, 9 cases (36%); no change, 13 cases (42%); and ineffective, 3 cases (12%).

C) <u>Effect of Cernilton on general test findings</u>:

Tables 4 and 5 summarize the haematological and serum chemical test findings for before and after the Cernilton trial.

a) Hematological tests: There was only one case that showed a white cell count before the trial of 12,800 and both before and after the trial showed red cell, white cell and platelet counts, also Ht and Hb levels, more than 10% outside the normal range. The same patient had a complication of cystitis. In the white cell differential, band cells tended to be common and segmented neutrophils

infrequent both before and after the trial: remembering that all the counts were done by the same technician, there may have been some problems in assessment. In any case, if a comparison is made of pre-trial results, band cells tend to decrease and lymphocytes to increase and the statistical significance of this cannot be denied. As regards other constituents, no abnormal values or variations were observed either before or after the trial.

There appears to be a possibility that the increase in lymphocytes was connected with the immune action of the preparation, and the assessment was that this cannot be disregarded.

b) Serum chemical tests: Abnormal values for serum constituents were 2 cases of a slight rise in GOT and GPT (less than twice normal), 3 cases of a rise in BUN (23-25 mg/dl) and Cr (1.4-1.6 mg/ dl) and 5 cases of a rise in triglyceride (181-233 mg/dl), the number of patients involved being 8. In no other case was there more than 10% variance from normal in the test items. Furthermore, also including patients who showed abnormal values, no variations exceeding 10% were found in any patient or test item in the comparison of pre- and post-trial findings. However, acid p-ase and triglyceride showed a general tendency to decrease and Cl to increase.

The tendency for acid p-ase to decrease would seem to be significant in the consideration of the inhibitory effect of this preparation on the prostate gland. If this preparation is regarded as having the effect of reducing triglyceride, this is useful information, quite apart from this trial. The fact that a pre-trial level of 101 mEq/ l Cl became 109 mEq/l after the trial is a considerable change, suggesting that there is an effect in stabilizing the blood electrolyte levels.

c) Urological tests: No abnormal findings were made apart from an increase in white cells in the deposit before and after the trial in one case.

D) Overall assessment of therapeutic effectiveness of Cernilton against prostatomegaly

The therapeutic effectiveness of Cernilton against Prostatomegaly is shown in Table 6: a high rate of effectiveness of 64% was shown against subjective symptoms, but the improvement in objective findings was not outstanding at 36%. In the assessment of the two combined there were 8 cases of markedly effective (32%) and 8 of effective (32%), giving an effectiveness rate of 64%. There was almost complete agreement between the improvement in subjective and objective findings: the 9 cases where there was effectiveness against objective symptoms all showed an improvement in subjective symptoms – markedly effective or effective. In 2 cases there was deterioration in both subjective and objective findings, and in 3 cases there was deterioration in one or the other, with the other unchanged. Therefore in no instance did a case where there was effectiveness against subjective symptoms become unchanged or ineffective in the overall assessment.

General Discussion

Cernilton consists of “Cernilton pollen extract” extracted from a mixture in certain proportions of the pollen of 8 plant species grown in South Sweden. The allergens are dissolved and removed, and the constituents are water-soluble Cernitin T-60 (T-60) and oily Cernitin GBX (GBX). The component ratio of the former to the latter is 20 to 1 and 1 tablet of Cernilton contains 63 mg of the preparation.

The pharmacological effect of Cernilton, as reported by Ishikawa et al.[5)] and Ozaki et al.[6)], can be summarized as follows. In animal (rat) experiments no abnormal symptoms were exhibited even with 20 times the human dose: however with…* units there were difficulties in walking, and when the dose was repeated face-washing, coughing and tremor throughout the body. Both T-60 and GBX, after a temporary rise in blood pressure, led to a dose-dependent fall in blood pressure and respiratory stimulation, which

was more marked with T-60. Against smooth muscle GBX brought about an acceleration of spontaneous movements and T-60 also caused twitching. There was an inhibitory effect from both preparations against croton oil oedema after 1 and 24 hr, against ovalbumin oedema from GBX after 24 hr and by the filter paper pellet method from T-60. Large doses of Cernilton brought about impairment of liver function, increase in suprarenal gland weight, weight loss of prostate gland and thymus gland and interference with sperm production. Degenerative atrophy of the epithelium was noted in the prostate gland. T-60 had this effect but not GBX. Cernilton had the effect of increasing total cholesterol and blood sugar in the serum and reducing total protein. According to Kimura et al.[7)], the antigenicity or immunogenicity of both drugs is either extremely slight or nil.

In view of the above facts it can be stated that the characteristic pharmacological effect of Cernilton is a relatively marked anti-inflammatory action, with hardly any side effects worthy of note; moreover it works rather specifically against the prostate gland, combining this with an inhibitory effect. However, one can hardly say that there is any satisfactory evidence to support the finding that this preparation has a specific effect against prostatitis. Consequently our view before the present trial was that one should not expect any great therapeutic effectiveness against prostatomegaly. Nevertheless, the clinical findings obtained in this trial provided ample evidence for the usefulness of the preparation against prostatomegaly.

Organic measurements of the prostate gland by the ultrasonic planigram method showed that the administration of Cernilton could not completely reduce its size (Fig. 1), but the functional measurements of the effect of the prostate gland on the urination mechanism showed that Cernilton reduced the length of the urethra occupied by the prostate gland and also reduced the urethral closure pressure and markedly reduced the urethral resistance as a whole (Fig. 2). This indicates an organic change in the interior of the posterior urethra from the bladder neck to the external sphincter. Although no detailed proof could be obtained, this probably involved an elimination of the inflammatory oedema in this area and of accumulated secretions in the prostatic duct. Apparently because of this, the urine flow rate increased and the subjective symptoms of irritation of the bladder neck decreased markedly. Thus the findings of this trial provided objective data to support the traditional view that the preparation improves subjective symptoms.

It cannot be concluded from the above results that prostatomegaly is radically reduced and eliminated with a resultant cure by administering the preparation, but it can be said that it is a quite useful symptomatic treatment for this disease. Although the majority of cases of prostatomegaly do not cause serious disease, they do involve quite distressful subjective symptoms for the patient, and treatment would be adequate which would lead to their eradication for a certain time. In this sense a lack of side effects is the most important property, and a condition is that there should of course be no inhibition of liver, kidney and heart functions, nor of testicular function. During this trial none of the 25 patients complained of subjective side effects, nor were there any signs thereof in the various tests. The normalization of the left shift in the white cell differential and of a high serum triglyceride level would tend to be rather in the patient's favour.

It has been shown above that Cernilton has no side effects and was effective against 64% of cases of prostatomegaly. Although its mode of action could be conjectured along general lines, would it not be possible to make an estimate of its usefulness before treatment in each individual case? It was therefore decided to ascertain the correlation coefficient between the various objective measurements and the degree of improvement of subjective symptoms with a scale of: markedly effective = 4, effective = 3, no change = 2, and ineffective = 1, and the figures obtained were residual urine 0.34, prostate gland weight – 0.42, MFR – 0.02 and urethral resistance – 0.21. i.e. the preparation was found to be effective whatever the objective findings, meaning that the therapeutic effectiveness of the preparation could not be predicted on the basis of tests such as these. Thus it would appear to be indicated to administer the

preparation to all patients: either over a long period with the aim of improving the subjective symptoms of patients where an immediate operation is not indicated or for a certain time just before an operation with the aim of improving urinary function.

The effectiveness rate of this preparation against prostatomegaly, 64%, if compared with the 91% reported by Akasaka[4], and the 10 out of 12 cases reported by Ineda (83%)[5], is much lower but is the same as the 63% of Kimura et al.[8] (5 out of 8 cases) and the 69% of Taguchi et al.[9]. This is also because of the different standards used in judging effectiveness by these authors, and no sweeping statement can be made. In any case the finding that this preparation is effective against subjective symptoms accompanying prostatomegaly is common to all these authors.

Summary and Concluding Remarks

When 6 tablets per day of Cernilton were administered to 25 cases of prostatomegaly the following findings were made:

1. The improvement of subjective symptoms was most striking for prolonged micturition difficulty (54%), followed by nocturnal frequency (50%) and then residual urine sensation (50%), decline in force of urine stream (47%), straining during urination (41%), delayed micturition (22%).
2. The effectiveness for subjective symptoms as a whole was: markedly effective 8%, effective 56%, no change 20% and deterioration 16%, with an effectiveness rate of 64%.
3. As regards residual urine, there were many cases where this decreased but also some where it increased: on average pre-treatment 32.5±25.0 ml became post-treatment 27.9±25.6, with no significance in the change.
4. In the measurements of the prostate gland by the ultrasonic planigram method there was a slight tendency for antero-posterior diameter, transverse diameter and length to increase, while the weight increased from a pre-treatment 23.7±10.4 g to a post-treatment 31.2±14.8 g, so that it can be concluded that this preparation does not cause the prostate gland to shrink.
5. Where the maximum urine flow rate before treatment by the uroflowmetry method had been 8.7±4.3 ml/sec, this became 11.8±3.5 ml/sec after treatment, so that it was clearly established that this preparation improves urine flow.
6. In the measurements by the urethral pressure profile method the length of the prostatic urethra decreased as a result of administering this preparation. The maximum urethral closure pressure also decreased, and there was a significant drop in the urethral resistance from a pre-treatment 28±14 g/cm to a post-treatment 12±3 g/cm.
7. The effectiveness of this preparation against objective symptoms was assessed as: markedly effective 0 cases (0%), effective 9 cases (36%), no change 13 cases (42%) and ineffective 3 cases (12%).
8. On the basis of haematological and serum chemical tests, no changes could be detected indicating any harm inflicted by this preparation on the human body.
9. No subjective or objective side effects at all were noted.

On the basis of the above findings it can be assumed that Cernilton removes the oedema of the urethral mucosal surface from the bladder neck to the external sphincter which accompanies prostatomegaly, and so improves urination and alleviates the irritation experienced subjectively in the bladder neck. In view of the complete absence of observed side effects, it is concluded that this preparation is indicated for all cases of prostatomegaly and that its effectiveness can be relied on.

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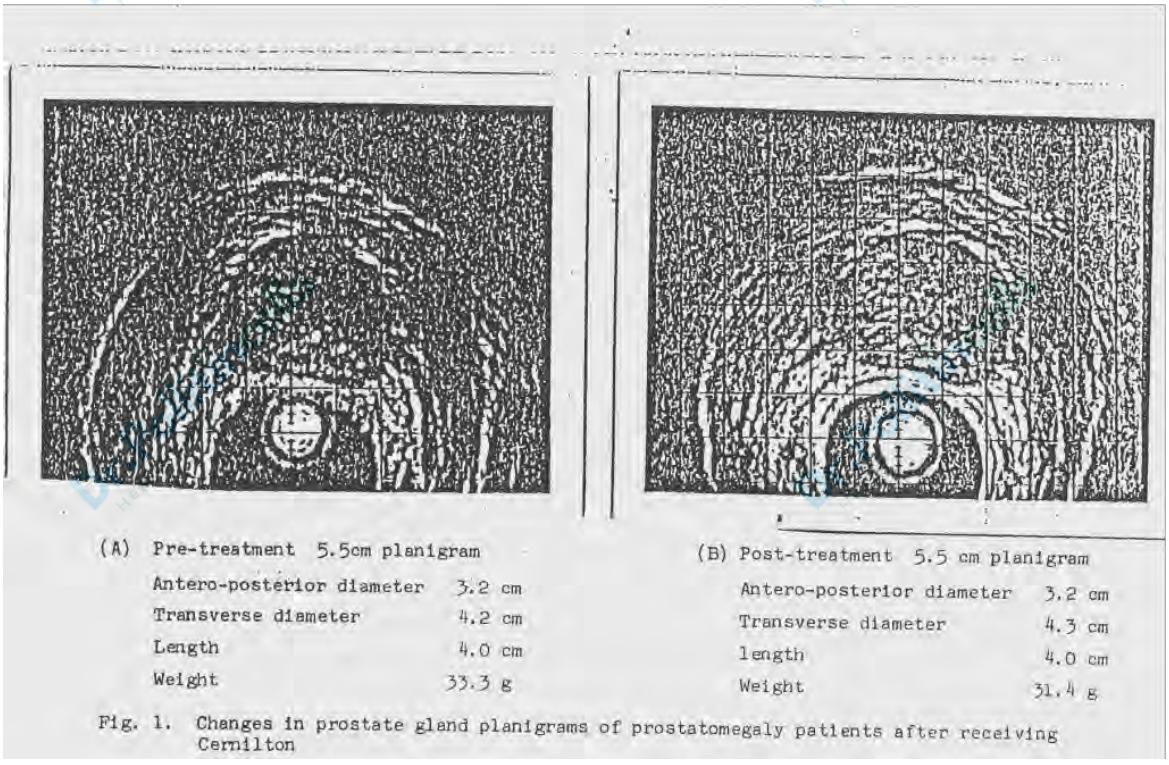

(A) Pre-treatment 5.5cm planigram

Antero-posterior diameter	3.2 cm
Transverse diameter	4.2 cm
Length	4.0 cm
Weight	33.3 g

(B) Post-treatment 5.5 cm planigram

Antero-posterior diameter	3.2 cm
Transverse diameter	4.3 cm
length	4.0 cm
Weight	31.4 g

Fig. 1. Changes in prostate gland planigrams of prostatomegaly patients after receiving Cernilton

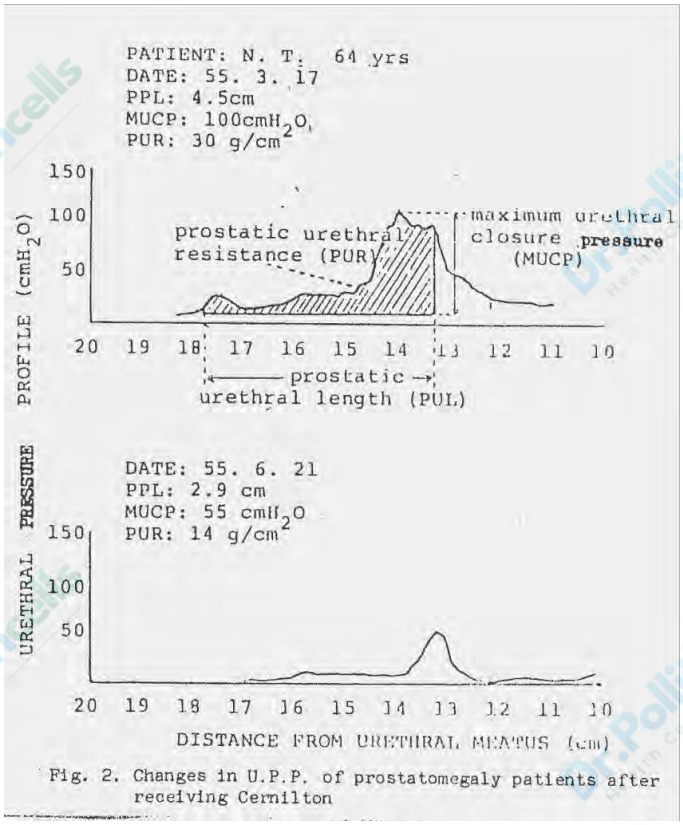

Fig. 2. Changes in U.P.P. of prostatomegaly patients after receiving Cernilton

Table 1. Subjective symptoms in 75 prostatomegaly cases

Type and degree of subjective symptoms		Number of cases (%)
Nocturnal frequency	more than 4 times	5 cases
	2 - 3 times	16 (84%)
	0 - 1 time	4
Prolonged micturition	++ (3)	2
	+ (2)	22 (96%)
	- (1)	1
Delayed micturition	+ (2)	23 (92%)
	- (1)	2
Straining in micturition	++ (3)	1
	+ (2)	16 (68%)
	- (1)	8
Decline in force of urine stream	++ (3)	2
	+ (2)	15 (68%)
	- (1)	8
Residual urine sensation	++ (3)	1
	+ (2)	7 (32%)
	- (1)	15

Table 2. Effectiveness of Cernilton against subjective symptoms of prostatomegaly

Subjective symptoms	Number of cases	Number of cases who improved	Effectiveness rate
Nocturnal frequency	20	10	50%
Prolonged micturition	24	13	54
Delayed micturition	23	5	22
Straining in micturition	17	7	41
Decline in force of urine stream	17	8	47
Residual urine sensation	8	4	50

Table 3. Effectiveness of Cernilton against objective symptoms of prostatomegaly

Type of objective symptoms		Pre-treatment	Post-treatment	t value (result of 2-way test)
Residual urine volume (ml)		32.5 ± 25.0	27.9 ± 25.6	0.38
Ultrasonic planigram method :	antero-posterior diameter (cm)	2.6 ± 0.5	3.0 ± 0.4	- 1.32
	transverse diameter (cm)	3.8 ± 0.5	4.0 ± 0.4	- 0.74
	length (cm)	3.9 ± 0.6	4.2 ± 0.6	- 0.10
	weight (g)	23.7 ± 10.4	31.2 ± 14.8	- 1.25
Uroflowmetry :	MFR (ml/sec)	8.7 ± 4.3	11.8 ± 3.5	- 1.90 ($p<0.10$)
U.P.P. :	PPL (cm)	4.2 ± 1.3	3.4 ± 0.6	1.27
	MUCP (cmH_2O)	92.0 ± 23.0	58.0 ± 19.0	2.71 ($p<0.05$)
	PUR (g/cm)	28.0 ± 14.0	12.0 ± 3.0	2.17 ($p<0.05$)

Table 4. Change in haematological valves after administering Cernilton

Test item		Pre-treatment value	Post-treatment value	t value (result of 2-way test)
Red cell count X 10^4		460.9 ± 38.4	449.4 ± 44.9	0.61
White cell count		6900.0 ± 2500.0	6600.0 ± 1300.0	0.27
Platelet count X 10^4		25.7 ± 6.8	27.7 ± 3.6	- 0.67
Ht (%)		42.1 ± 2.5	41.0 ± 3.8	0.81
Hb (g/dl)		14.5 ± 0.9	13.9 ± 1.3	1.37
White cell differential	eosinophils	2.0 ± 1.4	3.0 ± 3.3	- 0.80
	basophils	0.89 ± 0.78	0.60 ± 0.89	0.63
	band cells	30.3 ± 6.9	18.4 ± 6.2	3.20 (p<0.05)
	segmented cells	34.9 ± 11.9	30.4 ± 10.3	0.68
	lymphocytes	29.7 ± 10.2	42.2 ± 11.3	- 2.12 (p<0.10)
	monocytes	5.6 ± 2.4	5.4 ± 2.6	0.11

Table 5. Changes in seven chemical tests after administration of Cernilton

Test		Pre-treatment level	Post-treatment level	t value (result of 2-way test)
GOT	(U/l)	22.0 ± 8.0	26.0 ± 14.0	- 0.86
GPT	(U/l)	23.0 ± 14.0	30.0 ± 30.0	- 0.77
Alkaline p-ase	(U/l)	82.0 ± 22.0	85.0 ± 21.0	- 0.31
Acid p-ase	(K.A.U.)	2.9 ± 0.5	2.6 ± 0.4	1.41
BUN	(mg/dl)	16.0 ± 4.0	15.0 ± 5.0	0.30
Cr	(mg/dl)	1.1 ± 0.2	1.1 ± 0.1	- 0.20
TP	(g/dl)	7.1 ± 0.4	0.9 ± 0.4	1.29
Cholesterol	(mg/dl)	189.0 ± 44.0	199.0 ± 51.0	- 0.49
Triglyceride	(mg/dl)	135.0 ± 55.0	122.0 ± 52.0	0.52
Na	(mEq/l)	141.0 ± 2.0	141.0 ± 2.0	- 0.29
K	(mEq/l)	4.1 ± 0.3	4.0 ± 0.5	0.30
Cl	(mEq/l)	104.0 ± 2.0	106.0 ± 3.0	- 2.32 (p<0.10)
P	(mg/dl)	2.7 ± 0.5	2.6 ± 0.2	0.45
Ca	(mg/dl)	9.1 ± 0.5	8.9 ± 0.4	0.99

Table 6. Therapeutic effectiveness of Cernilton against prostatomegaly

Degree of therapeutic effectiveness	Subjective symptoms	Objective symptoms	Total assessment
markedly effective	2 cases (8%)	0 cases (0%)	8 cases (32%)
effective	14 (56%)	9 (36%)	8 (32%)
no change	5 (20%)	13 (52%)	4 (16%)
ineffective	4 (16%)	3 (12%)	5 (20%)
total	25 (100%)	25 (100%)	25 (100%)

PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Randomized Trial of a Combination of Natural Products (Cernitin, Saw Palmetto, B-Sitosterol, Vitamin E) on Symptoms of Benign Prostatic Hyperplasia (BPH)

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Abstract

Because benign prostatic hyperplasia (BPH) is relatively common, it is important to discover safe and effective means to treat this often debilitating perturbation. Accordingly, we examined the effectiveness of a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) in treating symptoms of BPH. We undertook a randomized, placebo-controlled, double-blind study. Patients were enrolled from 3 urological practices in the USA. 144 subjects were randomized for study. 17 subjects eventually withdrew, leaving 70 patients in the test group and 57 in the placebo group to complete the study. Inclusion criteria consisted of a diagnosis of BPH, no evidence of cancer, and a maximal urinary flow rate between 5 and 15 ml/second. Patients received either placebo or the combined natural products for 3 months. Evaluations were performed via the American Urological Association (AUA) Symptom Index score, urinary flow rate, PSA measurement, and residual bladder volume. Nocturia showed a markedly significant decrease in severity in patients receiving the combined natural products compared to those taking placebo ($p<0.001$). Daytime frequency was also lessened significantly ($p<0.04$). When the average individual total AUA Symptom Index score in the test group was compared to that in the placebo group at the end of the study, the difference proved highly significant ($P<0.014$). PSA measurements, maximal and average urinary flow rates, and residual volumes showed no statistically significant differences. When taken for 3 monts, a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) compared to placebo can significantly lessen noturia and frequency, and diminish overall symptomatology of BPH as indicated by an improvement in the total AUA Symptom Index score. The combination of natural products caused no significant adverse side effects.

Key Words: Benign Prostatic Hyperplasia, Natural means to treat; Nocturia, Natural means to teat; Frequency, Natural means to treat; Cernitin; Saw Palmetto; B-Sitosterol

Introduction

Despite availability of numerous positive reports, it is not generally recognized in the USA that certain natural products can overcome many troublesome symptoms emanating from benign prostatic hyperplasia (BPH) [1]. Three natural products possessing such potential are: a collection of pollens called cernitin [2-11], saw palmetto (*Serenoa repens*) [12-18], and B-sitosterol [19,20]. Some antioxidants, such as vitamin E, are also believed to be helpful in the treatment [1].

Virtually all studies on the effects of natural agents have been performed in Europe and Asia. This may be the principal reason behind the poor recognition in the USA of the therapeutic benefits of natural products in alleviating symptoms of BPH. Therefore, we undertook a multicenter, randomized, placebo-controlled, double-blind study in the USA to determine how a combination of these products might influence common perturbations of BPH. Our major objectives were to assess both subjective criteria (American Urological Association Symptom Index) and objective criteria (average and maximal urinary flow rates, post void residual urinary volume in the bladder, and PSA score) comparing natural products to placebo over 90 days. To accomplish this, we examined a combination of cernitin, saw palmetto, B-sitosterol, and vitamin E. The first 3 components have been found singly in clinical studies to possess the potential to benefit the often debilitating symptoms caused by BPH [1].

Materials and Methods

Plan

As depicted in Fig. 1, 144 subjects were enrolled at the 3 sites (Washington, DC; Florida; and Idaho) in this multicenter clinical trial. Patients for study were solicited through advertisements in local newspapers and from patient data bases in the investigators' urology practices. 17 subjects eventually withdrew, leaving 70 patients in the test group and 57 in placebo group to complete the study. After signing informed consent in the presence of the principal investigator or his designee at the site, patients received a numbered bottle of pills from the study coordinator at each site. Care was taken so that the pill forms of placebo and test could not be identified by sight, smell or taste. Only the clinical monitor at a separate site from where the studies took place possessed the code, so that neither the doctors nor patients were aware of what was being given or taken.

Inclusion criteria consisted of the following. A diagnosis of BPH was necessary. There was to be no evidence of cancer by digital rectal and/or PSA examinations. The maximal urinary flow rates were to be between 5 to 15 ml /second for a voided volume in excess of 100 ml. The patient had to read, speak, and clearly understand English, and written informed consent to participate in the trial had to be obtained. These studies were approved by separate Institutional Review Boards (IRB) for each of the 3 locations.

Exclusion criteria consisted of an age greater than 80 years; the presence of any tumor, malformation, or infection of the genitourinary tract; any severe concomitant medical condition that would make it undesirable in the clinician's opinion for the subject to participate in the trial or would jeopardize compliance with the trial protocol; severe laboratory abnormalities at baseline according to the WHO recommendations for grading of acute and subacute toxicity (Grade 2-4); medical treatment for BPH with finasteride (Proscar) within the last 3 months and all other medical treatment for BPH within the last 4 weeks; and patients currently being treated with antibiotics for genitourinary tract infections.

Study Design

The study design included a 3-month participant commitment to adhere to the following schedule. The patients were to take 2 pills of the combined natural products or placebo each day over 90 days. The test group received a total daily dose of cernitin 378 mg, saw palmetto complex and phytosterols (saw palmetto fruit standardized to 40% to 50% free fatty acids and B-sitosterol standardized to 43%) 286 mg, and vitamin E 100 IU. They were to make 3 clinic visits.

- Visit 1 (Baseline)
- Visit 2 (Day 45)
- Visit 3 (Day 90)

Procedures

The following procedures were performed on each study participant:

1. Physical Examination (Visits 1 and 3)
2. Laboratory Evaluation (Visits 1-3)
3. American Urological Association (AUA) Symptom Score (Visits 1-3)
4. Urinary flow evaluation (Visits 1-3)
5. Post void residual bladder volume (Visits 1-3)

Analytical Approaches

The target sample size was projected by evaluating previous clinical trials using cernitin for the treatment of BPH which were conducted outside the United States [3,4,6,8,911]. Cernitin clinical trials with similar outcome measures, demonstrating statistically significant findings averaged n=55.5. Since one half of the studies were open label, conservative action dictated at least doubling the "n" to ensure adequate statistical power. The randomization unit was a cluster method. A stratification with minimization procedure by site was used to increase the likelihood of a balanced distribution. Data were analyzed by FutureTech, Inc. of Boise, Idaho. The analyses examined the changes in individuals of all study variables over the course of the study comparing the test group receiving cernitin, saw palmetto, B-sitosterol, and vitamin E to the placebo group. Two statistical analyses were conducted on each question or parameter. The first analysis used a general linear model

PROFILE OF A RANDOMIZED CONTROLLED TRIAL

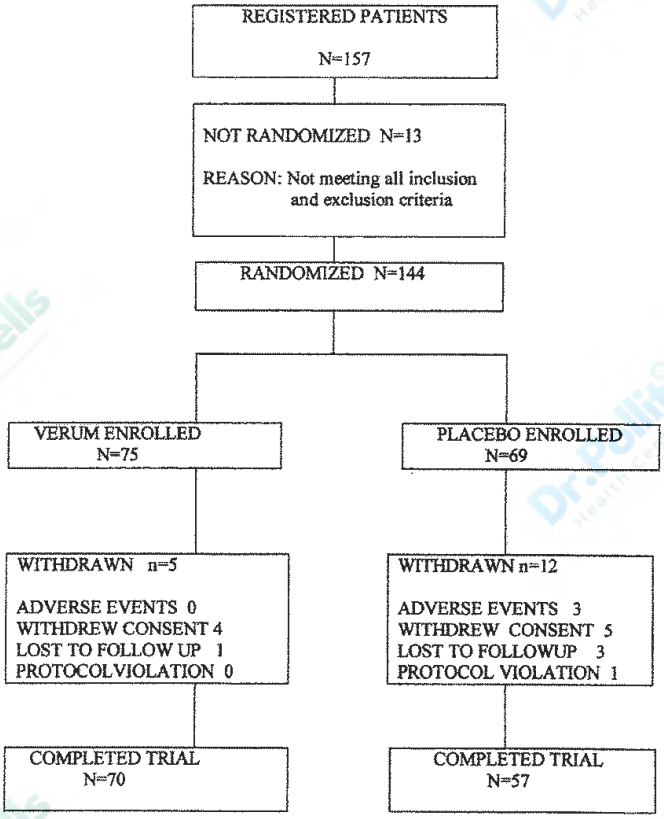

Figure 1. Progress through the various stages of the trial, including flow of participants and withdrawals.

mixed measures analysis of variance (Mixed ANOVA). This analysis takes into account the relative amount of change between groups over time. Of particular interest is the group by time interaction. This is indicative of a difference between the test (active) group and the placebo group from baseline to 45 day to 90 day assessments. Such an analysis will reveal significant differences between baseline and 90 day assessments as well as 45 day to 90 day assessments. The second analysis used the independent t-test on change scores (i.e., day 90 score – baseline score). The absolute amount of change was analyzed. For both analyses, statistical significance was set at $p<0.05$.

Results

As shown in Fig. 1, 144 patients of the 157 registered were eventually randomized – 75 to the test group and 69 to the placebo group. Five of 75 (6.7%) test patients did not complete the study, whereas 12 of 69 (17.4%) failed to complete the study in the placebo group. The information on the randomized patients who remained and withdrew before completing the study are depicted in Fig. 1. All the adverse events severe enough to cause termination, i.e., 3, occurred in the placebo group. One patient in the placebo group was removed from the study for protocol violation. Five patients in the test group either withdrew consent or were lost to follow-up compared to 8 patients in the placebo group. Concerning all adverse events listed in Table 1, 7 (10%) occurred in the test group and 9 (16%) in the placebo group. Interestingly, flatulence was reported by 3 in the test group, but the only 2 patients complaining of gastrointestinal distress were in the placebo group.

The questions asked in the American Urological Association (AUA) Symptom Index are listed in Table 2, and the scoring system for the first 6 questions is described just below them. Note that question 7 is slightly different from the first 6 questions in that the number of trips to the bathroom during the night is being sought. Table 3 depicts the mean AUA scores and the statistics performed by Mixed ANOVA at the 3 time points. Results from Question #7 concerning nocturia showed that there was a markedly significant decrease in severity in patients receiving the test substances compared to those taking placebo ($p<0.001$). Daytime frequency (question 2) was also lessened significantly in the test group compared to placebo ($p<0.04$). When the average individual total AUA Symptom Index score in the test group was compared to that in the placebo group, the difference proved highly significant ($P<0.014$). Table 4 shows the average changes in the AUA Symptom Index parameters between the test and placebo groups over the 90 days of study. Again, nocturia ($P<0.001$), frequency ($p<0.031$) and total AUA score ($P<0.009$) improved significantly in test compared to placebo groups.

Table 5 provides the data for the objective measurements. The PSA scores, maximal and average urinary flow rates, and residual volumes showed no statistically significant differences when comparing the test and placebo groups.

Discussion

Benign prostatic hyperplasia (BPH) presents a difficult, widespread problem [1,21]. Common symptoms of obstructive BPH are often disabling and include a weak urinary stream, a sense of incomplete bladder emptying, difficulty initiating urination, frequency, nocturia, urgency, and poorly controlled stopping and starting of the urinary stream (Table 2). Previously, treatment options for prostate enlargement focused primarily on surgery. However many adverse symptoms attributed to the operative procedure may persist after surgery -- post urination dripping, severe incontinence, and even a decline in sexual function. Because of the potential for these significant side effects, prescription drugs are often chosen by many as initial therapy against BPH, especially when the symptoms are mild or moderate.

Table 1. Adverse events

Event	Verum	Placebo
Flatulence	3	0
Lower abdominal rash	0	1
Dizziness	0	1
Headache	1	1
Nausea/GI distress	0	2
Urinary tract infection	1	0
Ear infection	0	1
Lumbar spine surgery (spur)	0	1
Herpes zoster	1	0
Elevated blood pressure	0	1
Chest pain	0	1
Right arm laceration	1	0

Table 2. American urological association symptom index

Question 1. Emptying. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Question 2. Frequency. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?

Question 3. Hesitancy. Over the past month or so, how often have you found that you stopped and started again several times when you urinated?

Question 4. Urgency. Over the past month or so, how often have you found it difficult to postpone urination?

Question 5. Weak Stream. Over the past month or so, how often have you had a weak urinary stream?

Question 6. Straining. Over the past month or so. how often have you had to push or strain to begin urination?

For questions 1–6, score:

0 for not at all
1 for less than 1 time in 5
2 for less than half the time
3 for about half the time
4 for more than half the time
5 for almost always

Question 7. Nocturia. Over the last month or so, how may times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning? (0, 1, 2, 3, 4, or 5)

Sum of scores from 7 questions indicate severity of BPH:

0–7 = mild prostatism
8–18 = moderate prostatism
19–35 = severe prostatism

Finasteride prevents production of dihydrotestosterone (DHT) from testosterone by inhibiting the activity of the conversion enzyme, 5-alpha reductase. This is important, because DHT is associated with BPH [22]. However, the beneficial effects of finasteride lasts only as long as the drug is being taken and must be given for many months before finasteride can be assessed as to effectiveness. Further, a decreased libido is an unwanted side effect in some men [23]. Another class of drugs has also been used to treat BPH. Alpha blockers are employed to relax the muscle tissue of the prostate in order to relieve the pressure around the urethra [24]. By relaxing the smooth muscles in the prostate, these agents essentially open the bladder and urethra and allow easier flow. However, adverse reactions can be serious and include chest pain, light-headedness, weakness, fast and/or irregular heartbeat, shortness of breath, nasal congestion, swelling of the extremities, and impotence [25].

Recently, many have turned to the use of natural products to overcome or at least ameliorate symptoms of BPH. The public often prefers natural compounds, because of a perception that they have fewer serious side effects compared to drugs. Among the natural agents most widely used outside the USA are a defined pollen mixture called cernitin (rye, timothy, corn), saw palmetto, and B-sitosterol. Various agents used to lessen free radical formation such as vitamin E have been reported to be useful additions as well. In the present investigation, we examined an over-the-counter product with the trade name Cernitin AF™ containing the aforementioned agents.

We carried out a multicenter, randomized, double-blind, placebo-controlled study on 70 patients in the test group and 57 patients in the placebo group to determine how patients with BPH would respond to the combination of natural products. A markedly significant beneficial response was noted by the lessening of nocturia, frequency, and overall AUA Symptom Index scores, even when assessed by different statistical methodologies (Tables 3 and 4). Although there was a general improvement of symptomatology associated with taking placebo, the improvements from the combined natural products compared to placebo in some parameters were dramatic: nocturia 258%, $p < 0.001$; frequency 242%, $p = 0.040$; and overall AUA Symptom Index score 90%, $p = 0.009$.

Table 3. Mean scores from the American urological association symptom index

Q#	Parameter	Baseline	Day 45	Day 90	p
Q1	Emptying	2.37/2.30	1.91/1.98	1.58/1.62	ns
Q2	Frequency	3.34/2.82	2.54/2.29	2.48/2.57	0.040[1]
Q3	Hesitancy	2.72/2.42	1.98/2.21	1.72/1.86	ns
Q4	Urgency	2.57/2.46	2.05/2.10	1.94/2.23	ns
Q5	Weak stream	3.62/3.35	3.01/2.66	2.48/2.57	ns
Q6	Straining	1.70/1.83	1.12/1.57	1.00/1.20	ns
Q7	Nocturia	2.58/2.47	1.95/2.07	1.61/2.19	<0.001[1]
Q1–7	Total AUA score	18.9/17.7	14.6/15.0	12.7/14.5	0.014[1]

Means (70 verum and 57 placebos) for baseline, 45 days and 90 days are shown. First number in the group represents mean of verum group at the time indicated. the second is mean of placebo group at the time indicated. Statistics by Mixed ANOVA.
[1] = statistically significant examining Time × Group Interaction.

Table 4. Change in AUA symptom index over 90 days (70 patients on verum and 57 on placebo)

AUA Questions	Verum	Placebo	% Improvement[1]	p
Emptying				
Question 1	−0.783 ± 0.171	−0.702 ± 0.182	+12%	0.748
Frequency				
Question 2	−0.855 ± 0.185	−0.250 ± 0.207	+242%	0.031[2]
Hesitancy				
Question 3	−0.971 ± 0.194	−0.589 ± 0.205	+65%	0.181
Urgency				
Question 4	−0.594 ± 0.164	−0.232 ± 0.260	+156%	0.225
Weak stream				
Question 5	−1.174 ± 0.186	−0.804 ± 0.208	+46%	0.186
Straining				
Question 6	−0.696 ± 0.169	−0.643 ± 0.195	+8%	0.838
Nocturia				
Question 7	−0.971 ± 0.119	−0.271 ± 0.118	+258%	<0.001[2]
Total AUA score				
Question 1–7	−6.171 ± 0.766	−3.241 ± 0.774	+90%	0.009[2]

Mean ± SEM is shown for 70 patients in the verum group and 57 patients in the placebo group.
− = improvement in symptoms, + = worsening of symptoms (Based on scale 0–5, being worst)
[1]Indicates % improvement in verum score over placebo
[2]Statistically significant by unpaired t test.

Table 5. Objective criteria for cernitin AF study after 90 days

	Verum		Placebo	
	Baseline	After 90 days	Baseline	After 90 days
Bladder volume (ml)	58.9 ± 11.4	57.5 ± 12.8	59.6 ± 12.8	40.7 ± 10.4
PSA (units)	2.6 ± 0.3	2.6 ± 0.4	1.9 ± 0.3	2.6 ± 0.7
AFR (ml/min)	6.0 ± 0.4	6.0 ± 0.5	6.1 ± 0.5	6.8 ± 0.5
MFR (ml/min)	11.2 ± 0.8	11.8 ± 0.7	12.1 ± 0.9	13.1 ± 1.0

Means ± SEM are shown for 70 patients in the verum group and 57 patients in the placebo group.
AFR = average flow rate, MFR = maximal flow rate.

To derive an even greater understanding of the significance of the effect on nocturia, we focused on patients with the greatest distress, i.e., those who at the beginning of the study micturated 3 or more times during the night. Of the 33 patients taking the combined natural products, 29 of 33 (88%) showed improvement in the AUA Symptom Index compared to 14 of 24 patients

(58%) receiving placebo (p=0.004). The decrease of -1.145 + 0.103 (SEM) in the test group means that the patients micturating 3-4 times a night, on an average, were now more apt to void only twice a night. We did a similar analysis on frequency. In those patients having frequency (as defined by Question 2 in table 2) 3 times or greater during the day, 32 of 47 (68%) test patients showed some improvement, whereas only 15 of 34 (44%) placebo patients reported improvement (p=0.013). The decreased frequency of -1.362 + 0.203 (SEM) in the test group meant that the average frequency of 4 decreased below 3. Residual urinary volume in the bladder, average and maximal flow rates, and PSA were not significantly different between test and placebo groups at the end of the 3 month treatment period. No significant adverse side effects were discerned in those taking the combined natural products.

Of the natural compounds involved in this study, perhaps the least is know about defined pollen extract referred to as cernitin. We are unaware of any other major study carried out in the USA on this agent. Therefore, we will discuss cernitin in more detail than the other natural products. In 1967, Ohkoshi, Kawamura and Nagakubo of Keio University reported that cernitin was effective in the treatment of 30 patients with chronic nonbacterial prostatitis and prostadynia [7]. Takeuchi investigated both subjective and objective effects of cernitin on 25 men with BPH and reported favorable results, especially for nocturia, in 64 per cent [8]. In 1986, a field study of 2,289 patients being treated by 170 urologists was undertaken [2]. Cernitin improved symptoms in 64 to 82 percent, in contrast to a low rate of adverse reactions found in 2.9 per cent of cases. In a double-blind, placebo-controlled study performed in 1988 in collaboration with 6 practicing urologist, Becker and Ebeling [3] examined 48 patients taking cernitin and compared them with an equal number of patients receiving placebo over a 12 week interval. Nocturia was claimed by 97% of the patients as a symptom of their disorder. There was a significant improvement using cernitin compared to placebo in nocturia, i.e., 69% vs. 37% (p<0.005). Not only the sensation of residual urine but the actual volume of residual urine was significantly reduced by the flower pollen extract. Mild nausea was reported in one patient.

Cernitin has a number of physiological effects that could benefit BPH. It has an anticongestive-antiinflammatory action which could lessen external pressure on the urethra [1]. These effects may be due to inhibition of prostaglandin and leukotriene biosynthesis. It has been noted that the activities of 5-lipoxygenase and cyclo-oxygenase enzymes are markedly reduced and the arachidonic cascade is interrupted by cernitin [25]. Additional pharmacological effects reported for the pollen preparation are: inhibition of prostate cell growth in animals, influence on contractility of bladder and urethral smooth muscle as well as diaphragms of animals, and an influence on the metabolism of dihydrotestosterone [26].

Saw palmetto (*Serenoa repens*) is an extract of the pulp and seeds of a dwarf, scrubby palm tree native to the West Indies and the Atlantic coast of the United States. It is generally accepted that saw palmetto works, at least in part, by the same major mechanism as finasteride, i.e., preventing the conversion of testosterone to DHT [12]. However, saw palmetto not only lowers the rate of DHT formation, but blocks the ability of DHT to bind to cells, preventing the action of hormone on receptors [13]. In addition, *Serenoa repens* may prevent severe inflammatory responses via a dose-related effect on the arachidonic acid cascade through a double blocking of cyclo-oxygenase and lipoxygenase pathways [27]. In one study examining 110 subjects, it decreased night time urination by 45 percent, increased urinary flow rate more than 50 percent, and reduced the amount of urine left in the bladder after urination by 42 per cent [18]. In other large trials, improvement in prostatic symptomatology was readily noted and saw palmetto even compared favorable with Hytrin (alpha blocker)

and/or Proscar (finasteride) in affecting the symptomatology of BPH when these agents were compared head to head. [14-18].

B-sitosterol is a phytopharmacological agent containing many phytosterols [19,20]. In a randomized double blind study reported in the Lancet [20], 200 patients with symptoms of BPH from 8 private urological practices were treated for 6 months with either 20 mg of B-sitosterol or placebo. At the end of 6 months, modified Boyarsky scores decreased statistically in the B-sitosterol-treated group compared to the placebo group. Reduction took place in the prostatic volume, the quality of life score improved, the peak urine flow increased, the mean voiding time and the urinary volume retention also improved from the initial scores in the sterol group, whereas no changes were noted in the placebo group. Importantly, no severe adverse reactions were attributed to B-sitosterol.

In light of the subjective findings, it is not clear why changes in objective criteria were not seen in the present study. However, this is not unusual. Examination of other BPH clinical studies reveals a lack of consistent findings among both subjective and objective parameters even in those investigations deemed positive through overall assessment [1-21]. PSA is not known to change in response to saw palmetto intake [12-18] and has been shown only once to decrease in the case of cernitin usage [9]. Buck et al [6] found no change in urinary flow rates in response to cernitin, but Braeckman found significant change in his investigation of saw palmetto [17]. Both the former citations reported significant changes in residual urine volume. Considering everything, we believe that our subjective changes are real and indicate a definite benefit from the use of this combination of natural products despite the lack of objective support.

Conclusion

We cannot state with certainty whether we could have accomplished the same results in our study by using only one or 2 of the ingredients present in the combination of natural products. Cernitin [1-11], saw palmetto [12-18], and B-sitosterol [19,20] have been shown to be effective, at least to some extent, when used individually. Because each agent has slightly different actions and different time frames of action, it seemed wise initially to examine a combination to determine clinical utility. Accordingly, we know from our results that a combination of cernitin, saw palmetto, B-sitosterol and vitamin E provided significant relief from some of the most irritating symptoms resulting from BPH. Further studies directly comparing combinations with individual components must be carried out in the future. In summary, this combination of natural products when taken over 3 months significantly lessened nocturia and frequency, diminished overall symptomatology of BPH as indicated by the improvement in the total AUA symptom index scores while causing no significant adverse side effects.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Therapeutic Results of Defined Pollen-Extract in Patients with Chronic Prostatitis or BPH Accompanied by Chronic Prostatitis

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Introduction

Depending mainly upon analysis of prostatic fluid and angloamerican classification divides the benign painful diseases of the prostate into four categories: Acute bacterial prostatitis, chronic bacterial prostatitis, non-bacterial prostatitis, and prostatodynia (1).

According to findings of *Weidner* (2) the largest group, the prostatodynia (vegetative urogenital syndrome), covers 52.4%. Besides clinical symptoms and normal laboratory findings the following urodynamics changes are characteristic: Elevation of the maximum urethral closure and reduced peak urine flow rates (3,4,5).

In approximately 40% of non-bacterial prostatitis the microbiological examination is negative (2) whereas by definition leucocytosis in the prostatic fluid can be demonstrated. The prostatic congestion, pathomorphologically considered as congestion of secretion and edemas in the prostate (6) can appear in every form of prostatism (7).

This demonstrates that antibiotics are indicated for a small number of patients only. Predominantly an anti inflammatory resp. symptomatic therapy is required.

The use of the pollen-extract in the treatment of benign prostatic diseases as BPH and prostatitis has already been described since 1960 and leads to clinical improvement of symptoms and positive changes by objective parameters.

In a double-blind study with 61 patients and a simultaneously carried out open examination with 118 patients *Leadner* (9) stated in the verum-group a normalization of initially pathological palpation findings and leucocytosis of prostatic fluid in 94% of patients with chronic prostatitis who were treated with pollen-extract. 6% of the patients showed unchanged results, aggravations were not observed. In the placebo-group 48% showed normalization, 34% demonstrated an unchanged status and in 18% of the patients the findings were deteriorated. The results of treatment in the open trial revealed only small differences in comparison to therapeutic effects in the verum-group which can be rated as accidental. *Takeuchi* (10) demonstrated in a clinical study with 25 BPH-patients in stage 1 or 2 under treatment with pollen-extract besides the elevation of peak urine flow rate a significant ($p < 0.05$) decrease of maximum urethral closure pressure with a corresponding diminished resistance of the prostatic part of the urethra.

Pharmacologically the pollen-extract is characterized by antiinflammatory and prostate cell selective growth inhibiting properties. Furthermore a specific affinity to the prostate could be demonstrated (11,12).

The aim of this field study was to control the acceptance and effectiveness of this drug on a large number of patients with chronic prostatic complaints, i.e. symptoms of chronic prostatitis or BPH, and to evaluate the possible role of the pollen-extract in their conservative treatment.

Methods

2,289 patients were divided according to the diagnoses given by 170 urologists based on clinical symptoms, palpation and laboratory findings as well as residual urine volume resp. uroflow measurements into three groups: 583 (25,4%) cases of chronic prostatitis (P), 590 (25,8%) cases of BPH accompanied by prostatitis (BP) and 1116 (48,8%) cases of BPH (B). The BP- and B-group was subdivided into stage 1, 2, and 3 (14).

The treatment with pollen-extract was in 84% of the cases in a dosage of 3 x 2 tablets/ day in the first week and continued in 78.5% with 3 x 2 tablets/ day up to twelve weeks.

Typical symptoms and palpation findings classified as light, medium or severe were recorded and evaluated before, during, and after therapy up to twelve weeks.

The residual urine volume determined by sonography, X-ray or catheterization, uroflow measurements as peak urine flow rate, urine volume voided and flow time, laboratory parameters as leukocytes in urine sediment or expressed prostatic secretions were controlled before and during treatment.

The courses of clinical signs and symptoms and the change of the objective parameters were documented. A further assessment was carried out by comparing the data before and after treatment.

Side effects, statements regarding the tolerance and a general assessment about the treatment with pollen-extract were investigated. Statistical analysis was performed as chi-square tests, variance analysis, split-plot variance analysis and factor analysis.

Results

The age distribution showed a prevalence of the chronic prostatitis in the 4th and 5th decade whereas the BPH with prostatitis was diagnosed mainly in 60-70 years old men. The B-group represented the oldest patient-group (table 1).

Typical for patients with chronic prostatitis are also symptoms other than difficulties on micturition. These complaints reappeared in the BP-group in a less extensive form but compared to the B-group the significant difference is obviously (figure 1a). The correspondence between the P- and BP-group was similar regarding the leukocytes in prostatic expressate (figure 1b) and the >>painful prostate<< on palpation (figure 1c).

Depending on the respective complaints improvement or absence of symptoms were stated in 64% to 82%.

The palpated size of the prostate diminished more markedly in the BP-group compared to the B-group. A significant reduction in the P-group was found in 55.9% of the patients with initially enlarged prostate (n=169, n=302). The changes regarding the >>painful prostate<< on palpation are demonstrated by table II. The microscopic estimates of leucocytes in the prostatic expressate after therapy revealed for all diagnostic groups a decreased number of leucocytes ≤ 10/ HPF in 59% of the cases with initial findings >10 leucocytes/ HPF (n=291, n=493).

The residual urine volume diminished significantly ($p < 0.001$) in all stages (figure 2a) and showed a continuous decrease with the length of therapy (table III).

The peak urine flow rate increased in all groups significantly ($p < 0.001$) about 3 to 4 ml/sec comparing the pre/post-values (figure 2b and table IV). Concomitantly the urine volume voided increased and the flow time was reduced.

The general assessment of the therapy with pollen-extract by physician and patient was very good or good in 72.2% resp. 75%. Side effects (i.e. slight and temporary GIT disturbances)

[1] 1 tabl. Contains: Extr Pollin. sicc. (Cernitin T60) 60mg, Extr. Pollin. dialys. (Cernitin GBX) 3mg.

were described in 66 cases (2.9%), in 1.2% the treatment was discontinued.

Table I. Age distribution in the diagnostic groups (P = chronic prostatitis, B = BPH, BP = BPH with prostatitis).

Parameter	Age range/Statistic	P	B	BP
Patients		583	1.116	590
Age, years	minimum	17	21	22
	maximum	85	97	94
	median	40.3	67.0	60.3
	mean	40.6	66.6	60.3
	standard deviation	12.0	9.3	11.7
	≤ 30	126	2	6
	31–40	170	4	22
	41–50	184	48	87
	51–60	61	210	182
	61–70	26	440	160
	71–80	12	328	113
	> 80	1	67	17
	negative	3	17	3
Stage of BPH	1		324	259
	2		598	244
	3		109	40
	negative		85	47

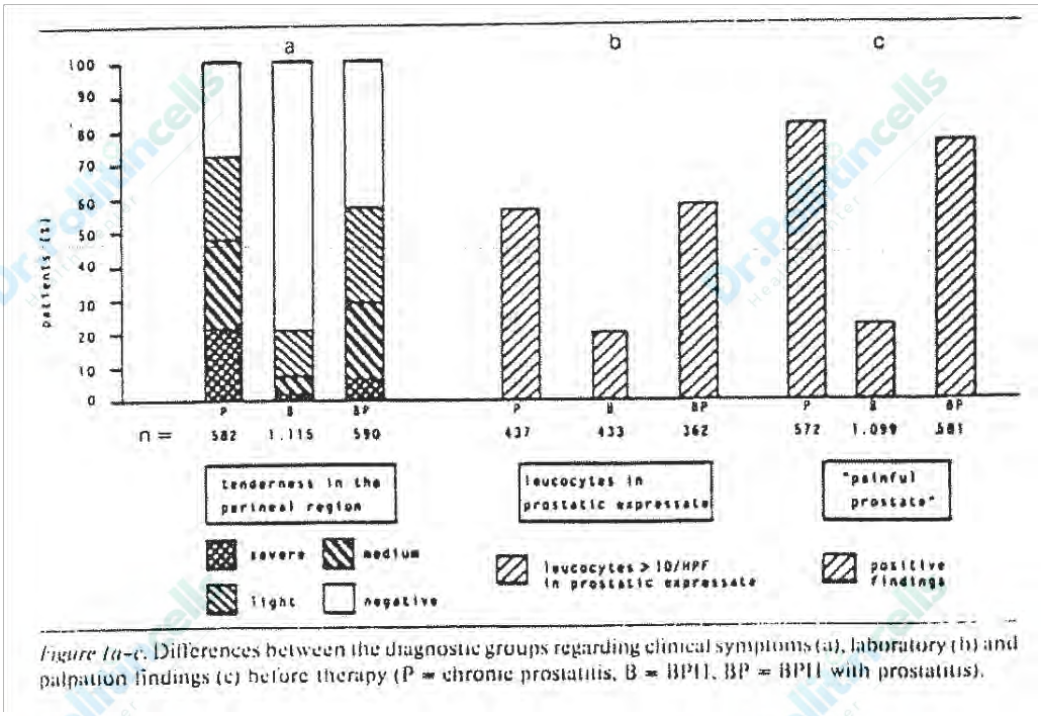

Figure 1a–c. Differences between the diagnostic groups regarding clinical symptoms (a), laboratory (b) and palpation findings (c) before therapy (P = chronic prostatitis, B = BPH, BP = BPH with prostatitis).

Table II. »Painful prostate« on palpation. Comparison of the pre/post-data. Significant ($p < 0.001$) differences in the findings before and after treatment with pollen-extract.

Intensity, scores	Chronic prostatitis		BPH		BPH with prostatitis	
	pre, n	post, n	pre, n	post, n	pre, n	post, n
Severe	96	4	12	–	56	3
Medium	196	26	62	5	186	22
Light	164	159	174	68	194	128
Negative	95	362	812	987	124	407
% negative	17.2	65.7	76.6	93.1	22.1	72.7

Course under therapy	Chronic prostatitis		BPH		BPH with prostatitis	
	n	%	n	%	n	%
Unchanged (all)	93		811		123	
Aggravated	4	0.9	1	0.4	3	0.7
Unchanged positive	50	10.9	41	16.5	47	10.8
Improved	135	29.5	31	12.4	103	23.6
Asymptomatic	269	58.7	176	70.7	284	65.0

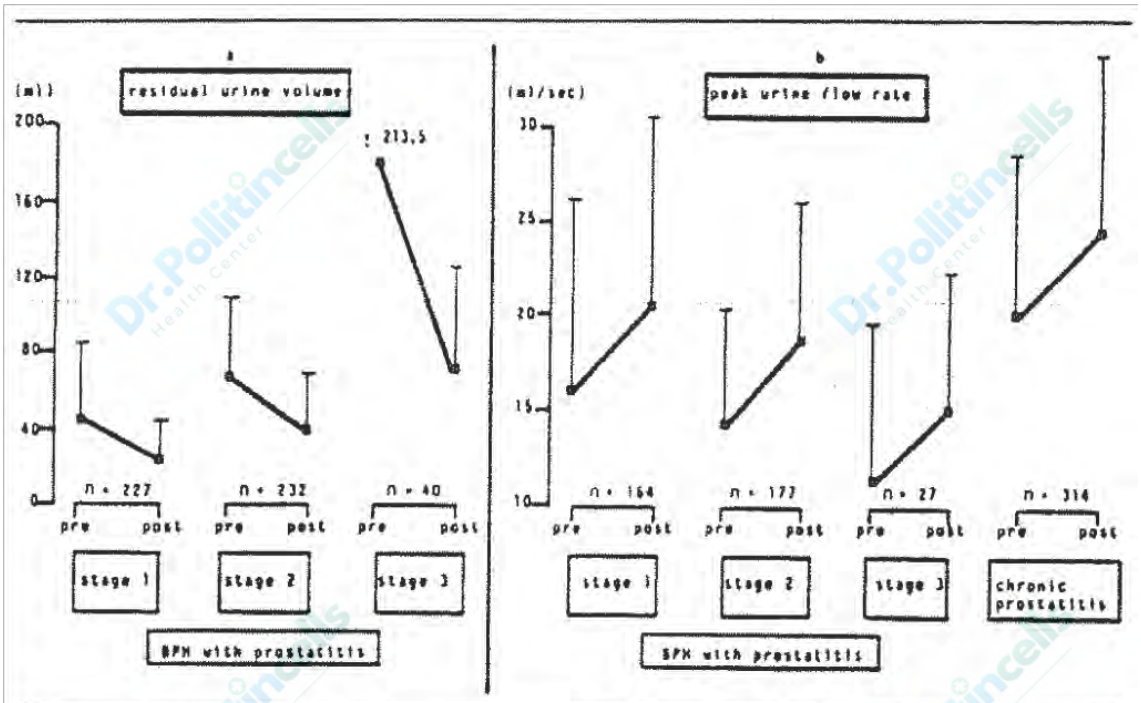

Figure 2a–b. Comparison of pre/post-findings regarding residual urine volume (a) and peak urine flow rate (b). Significant ($p < 0.001$) decrease of residual urine volume in BPH (stage 1–3) with prostatitis, significant ($p < 0.001$) increase of peak urine flow rate in patients with chronic prostatitis or BPH (stage 1–3) with prostatitis under the treatment with pollen-extract.

Table III. Residual urine volume (ml) under treatment with pollen-extract. Continuous decrease with the length of therapy. Significant ($p < 0.001$) differences in the findings before and after treatment.

	Time of control	BPH with prostatitis	
		x̄	s
Treatment over 12 weeks (n = 175)			
	pre	67.3	73.6
	2 weeks	50.0	46.2
	6 weeks	41.7	42.0
	12 weeks	32.0	35.7
Pre/post-comparison (n = 542)			
	pre	62.9	76.6
	post	34.2	34.2
	difference	−28.7	

Table IV. Peak urine flow rate (ml/sec) under treatment with pollen-extract. Continuous increase with the length of therapy. Significant ($p < 0.001$) differences in the findings before and after treatment.

	Time of control	Chronic prostatitis		BPH with prostatitis	
		x̄	s	x̄	s
Treatment over 12 weeks		n = 95		n = 119	
	pre	20.7	9.6	14.6	7.9
	2 weeks	22.6	8.8	16.3	7.5
	6 weeks	24.2	8.8	18.8	9.2
	12 weeks	26.1	8.8	20.0	9.3
Pre/post-comparison		n = 314		n = 403	
	pre	19.8	8.5	15.0	8.2
	post	24.1	8.9	19.3	8.9
	difference	+4.3		+4.3	

Discussion

The objective criteria for therapeutic effectiveness as residual urine volume, peak urine flow rate, urine volume voided, flow time and leucocytes findings show in their course and by comparison the status before and after therapy significant changes which are accompanied by improved palpation findings and a continuous decline of symptom-scores indicating the subjective relief in patients.

Under differential therapeutic aspects the conservative treatment of benign and chronic prostatic diseases is to consider as a predominantly antiinflammatory resp. symptomatic one. The findings of *Weidner* (2) regarding the various forms of chronic >>prostatitis<< confirm that at least in 68.3% of patients an antibiotic therapy is not primarily indicated.

The pre/post-comparison of leucocyte findings in the prostatic expressate reveals a decrease on ≤ 10 leucocytes/ HPF in 59% of all cases with initial values > 10/ HPF.

These results confirm previous findings by *Leander* (9). The differences regarding the percentage of improvement resp. normalization

are explainable by his definition of the pathological value as ≥ 10 leucocytes/ field (x 240).

Therefore it can be concluded that the pharmacologically demonstrated antiinflammatory property leads to clinical effects in human too.

The etiology of the prostatodynia remains uncertain. Whereas *Vahlensieck* (6) distinguishes between the static, vegetative and sexual dependent causes of prostatic congestion, a primary abnormality involving the pelvic sympathetic nervous system in most patients or tension myalgia of the pelvic floor is suggested by *Meares* et al. (4, 5).

The urodynamic findings in this study, i.e. significant ($p < 0.001$) increase about 3 to 4 ml/ sec of peak urine flow rate with concomitantly higher values of urine volume voided and reduced flow time, are investigated in the P- and BP-group, suggesting a homogenous effect of the pollen-extract on the bladder outflow obstruction.

Under treatment with pollen-extract a significant ($p < 0.05$) decrease of maximum urethral closure pressure with decreased resistance of the prostatic part of the urethra was demonstrated in BPH-patients (10).

These findings, due to the antiinflammatory and decongestive effects of this drug, give evidence for the therapeutic benefit of the pollen-extract in patients with non-bacterial prostatitis or prostatodynia since improvement of clinical symptoms and palpation findings occurs concomitantly.

The investigated parameter, evaluated before, during and after treatment with pollen extract, show in the B- and BP-group a reduction of residual urine volumes, elevated peak urine flow rates and voided urine volumes at simultaneously reduced flow times with improvement of both obstructive and irritative symptoms as well as laboratory and palpation findings.

Comparing the course of kinetics between the two hyperplasia-groups B and BP in regard of clinical symptoms, residual urine volume, uroflow and palpation findings it demonstrated even in different before findings a parallel development. This allows the conclusion, that within the BPH frame besides hyperplastic obstruction edematous resp. inflammatory as well as congestive changes in the prostatic tissue reach clinical effectiveness.

These results indicate an applicability of the pollen-extract in patients with BPH (with or without concomitant prostatitis) and suggest in addition therapeutic effects on the so-called non-pathogen post TURP-prostatitis, which is pathohistologically demonstrated in over 50% of patients after prostatectomy (8).

Due to the large number of substances in pollen the identification of (the) active substance(s) of the pollen-extract is difficult and not yet succeeded, but the demonstration of 5 different phytosteroles and of a biological active peptide looks promising as it is known that both peptides and sterols can influence the intracellular metabolism in biological systems (13).

In summary, the results of the multi-center study suggest a rationality for application of the pollen-extract in patients with non-pathogen dependent chronic prostatitis, prostatodynia, prostatic congestion, BPH with and without concomitant prostatitis and TURP-prostatitis.

The positive tolerance of the pollen-extract meets the requirement for a satisfying compliance in chronic and benign prostatic diseases and in thus indicated long-term treatment.

Further investigations with double-blind test design have to establish these encouraging results also to evaluate the degree of spontaneous improvement and placebo-effect.

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PROSTATE SUPPORT:

GRAMINEX Flower Pollen Extract

Use of natural products to treat benign prostatic hyperplasia (BPH) and chronic non-bacterial prostatitis: emphasis on Cernitin®

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Many males throughout the world, both young and old, suffer severely from the ravages of cardiovascular disorders and cancers, but another important area of specific concern receiving less attention involves a small gland of the reproductive tract called the prostate [1]. The prostate is very important for a number of health reasons. Malignancy of this gland is recognized as the most common cancer among men (1 out of 10) and, unfortunately, is the second most fatal. It has been estimated that over 300,000 men will develop prostate cancer in the coming year, and more than 40,000 will succumb to it. It is important to note that the prostate gland is also the origin of an even more widespread problem – benign prostatic hyperplasia surpasses that of prostatic cancer – nearly 60% of men over the age of 40 have an enlarged prostate, and the incidence increases to over 80% by the age of 80 [2-5]. Over $1 billion dollars are spent each year on treatment for prostatic enlargement.

The major function of the prostate, a gland associated with the male reproductive system, is to produce and discharge a various alkaline liquid that provides a major portion of the seminal fluid. This gland is made up of both muscular and glandular tissue. It produces semen to carry sperm in the ejaculate. Sperm are protected, at least to some extent, and can survive longer after ejaculation because of the environment afforded by the presence of prostatic fluid. Prostatic fluid also contains prostaglandins, which are fatty acids that, similar to hormones, affect smooth muscle fibers and blood vessel walls.

Although the prostate plays no direct role in the functioning of the male urinary system, many urinary perturbations occur when it expands via growth due to its location at the outlet of the bladder [1,6]. The prostate is located in front of the rectum and below the urinary bladder. Importantly, it surrounds the urethra, a tube which carries urine from the bladder to the tip of the penis for expulsion. The gland is the size of a pea at birth and grows slowly until puberty. Driven by sex hormones, the prostate grows at a faster pace. During the 20s and 30s, the gland is characteristically the size of a walnut, weighing roughly one ounce. Around age 45, cells in the prostate multiply once more causing the gland to grow up to 10 times the normal adult size [7].

Common symptoms of obstructive BPH include (1) a weak urinary stream, (2) a sense of incomplete bladder emptying, (3) difficulty initiating urination, (4) frequent urination (especially at night when it is referred to as nocturia), (5) urgency (difficult postponing urination), and (6) interruption of the stream (stopping and starting). The typical sufferer usually becomes aware of the problem when the urge to urinate becomes more frequent than expected. The person suffering from BPH rarely can sit through a movie or concert – he is the one that requests the aisle seat on an airplane in order not to disturb his fellow passengers by his

frequent sojourns to the restroom. At night, trips to the bathroom caused by nocturia steadily increase, so that there is a definite impingement on sleep. Accordingly, any experiencing of such urinary frequency should lead to suspicion of the disorder. In view of the rising life expectancy of the male population, knowledge of the means with the best risk/ benefits ratio to treat BPH in its various stages will become more important.

In the past, treatment options for prostate enlargement focused on surgery. Over the last few years, prescription drugs have been used to initiate therapy against BPH in its early stages. One highly recognized group of agents works chiefly to inhibit the activity of 5-alpha reductase (finasterides). Another group works to relax the muscle tissue of the prostate and thus relieve the pressure around the urethra (alpha blockers). Unfortunately, surgery and pharmaceuticals used to treat BPH carry a high cost and the added risk of potentially debilitating side effects. In recent years, emphasis has been placed upon the use of natural compounds to ameliorate the symptoms of BPH and chronic non-bacterial prostatitis. The attractiveness of natural compounds, for the most part, lies in their fewer serious side effects compared to drugs. In many cases, natural products work similar to many pharmaceuticals used to treat BPH. Some plant extracts not only lower the rate of DHT formation like finasterides, but block the ability of DHT to bind to cells, preventing the action of hormone. They may also relax the musculature involved in urination similar to alpha blockers. In addition, they may prevent severe inflammatory responses similar to drug inhibitors of the prostaglandin cascade (COX 2 inhibitors).

A number of natural products have been recognized as having some therapeutics use for prostate problems. The natural product most used for prostate problems is saw palmetto [8-13]. A number of clinical studies have substantiated the efficacy of saw palmetto usage in treating BPH [14-19]. *Pygeum africanum* contains phytosterols which have been purported to have anti-inflammatory properties [20]. When 263 German men were tested with *Pygeum africanum,* urinary symptoms improved in 66% compared to 31% in the placebo group. Occasional gastrointestinal upset seems to be the major adverse side effect.

Less work has been performed using the stinging nettle (Urtica dioica) to ameliorate BPH [21,22]. Of late, much attention has been focused on beta-sitosterol [23]. Beta-sitosterol is a phytopharmacological agent containing many phytosterols. In a randomized, double-blind study reported in the Lancet [24], 200 patients with symptoms of BPH from eight private urological practices were treated for six months with either 20 mg of beta-sitosterol or placebo. At the end of six months, modified Boyarsky scores [25] decreased significantly in the beta-sitosterol treated group compared to placebo. Reduction took place in prostatic volume, the quality of life score improved, the peak urine flow increased, and the mean voiding time and urinary volume retention also improved from the initial scores in the sterol group, whereas no changes were noted in the placebo group. Importantly, no severe adverse reactions were attributed to beta-sitosterol.

Compared to other natural products, a defined flower pollen extract called “Cernitin” has received less recognition in the USA as a therapeutic agent for prostate perturbations [26]. Ironically, it may be the best natural product for this condition yet recognized. In 1950, a beekeeper in a tiny Swedish village found a way to collect pollen artificially [27]. Initially, the flower pollen was used as a prophylactic agent against infections. Later the extraction process was modified so that the active pollen was released and was non-allergenic. Oily Cernitin GBX and water soluble Cernitin T60 are important extracts of a mixture of three different pollen strains: timothy, maize, and rye. Found in the pollen are peptides, carbohydrates, fatty acids, vitamins, minerals, nucleic acids, and enzymes. Whatever the original hypothesis concerning overall health, Cernitin proved specifically useful in treating BPH [28].

Many types of clinical trials of all varieties examining the therapeutic benefits of Cernitin on prostate perturbations, including randomized, multi-center, double-blinded, and placebo-controlled, have been published. The most significant investigations have been performed in Europe (Germany, Britain, Switzerland) and Japan. End points for examination have included both subjective (various questionnaires and history of symptom amelioration) and objective (flow rates, residual urine volumes, estimation of prostate size, and concentration of prostatic specific antigen [PSA evaluation]) criteria. The overall trend in all these trials, both open and blinded, was to show an improvement in the symptoms and signs of BPH and chronic prostatitis, whether subjective and/or objective criteria were used. Following are brief descriptions of some clinical investigations:

1. Using pollen extract, Leander [29] found a 60-80% improvement over placebo in symptoms of obstruction, probably through elimination of inflammatory edema.
2. In 1967, Ohkoshi, Kawamura and Nagakubo of Keio University, reported impressive results in 30 patients with prostatitis and/or urethritis [30]. Examining 14 patients receiving Cernitin, it was found that treatment was successful in 10, slightly effective in three, and ineffective in only one case.
3. Takeuchi [31] investigated both subjective and objective effects on Cernitin on 25 men with BPH. There was a 50% improvement of nocturnal micturition.
4. Inada et al., reported favorable effects in 12 patients suffering from prostatic hypertrophy [32]. They reported that five cases had “effective” results, five showed “slightly effective” results and two reported “ineffective” results.
5. In 1986, a field study of 2,289 patients being treated by 170 urologists was undertaken [33]. Improvement of symptoms was reported in 64-82%, in contrast to a low rate of adverse reaction found only in 2.9% of cases.
6. Brauer [34] compared the effects of Cernitin and beta-sitosterol in 39 patients. A significant reduction in circulating levels of PSA with Cernitin therapy indicated a reduction of cell lesions in BPH. In contrast, no such change occurred with beta-sitosterol treatment. Although flow pollen extract proved superior to beta-sitosterol in many respects, the mean values for residual urine volume fell under 15 ml for both at the end of the treatment.
7. In a double-blind, placebo-controlled study performed in 1988 in collaboration with six practicing urologists, Becker and Ebeling examined 48 patients taking Cernitin and compared them with an equal number of patients receiving placebo over a 12-week interval [35]. The results showed that there was a significant improvement using Cernitin compared to placebo of nocturia, i.e., 69% vs. 37% ($p<0.005$). Not only the sensation of residual urine but the actual volume of residual urine was significantly reduced by flower pollen extract. Mild nausea was reported in one patient.
8. In a follow-up, open study emanating from the above double-blinded study, 92 patients, all receiving Cernitin, were evaluated [36]. There was a marked improvement in nocturia and residual urine volume. Differences between Cernitin and placebo groups during the initial double-blind phase were balanced out after the switch from the placebo to Cernitin.
9. In an open trial using the defined Cernitin pollen extract on 15 patients with chronic prostatitis or prostadynia, Buck and his colleagues reported that 13 obtained either complete and lasting relief of symptoms or marked improvement – only two patients failed to respond [37].
10. In a paper appearing one year later, Buck, et al., performed a larger study on 57 patients with outflow obstruction due to BPH [38]. This was double-blind, placebo-controlled trial to evaluate the effect of a six-month course of pollen extract on symptomatology. The overall subjective improvement with the defined Cernitin pollen extract of 69% more than doubled that of the placebo group (30%). The investigators reported a significant decrease in residual urine with Cernitin and in the antero-posterior diameter of the prostate by ultrasound assessment.
11. Rugendorff, et al. [39], performed a prospective, case-controlled, open trial to treat chronic prostatitis and prostadynia. In 90 patients who were treated for six months,

freedom of symptoms and normalization of the palpation finding were obtained in 50-70% of patients without complicating factors.

12. Braun and Peyer [40] in a 1993 double blind, placebo-controlled investigation on 44 patients with Grade I and II BPH assessed the validity of treatment with flower pollen extract on subjective and objective parameters. They found by using questionnaires, echography, and laboratory analysis of PSA that flower pollen extract had a clear benefit over placebo. In 25 patients receiving verum compared to 19 receiving placebo, there was a significant reduction in the mean number of both diurnal and nocturnal micturitions with flower pollen extract ($p<0.05$). Using ultrasonic measures, the mean volume of the prostate decreased significantly more in the verum group (-29% vs -8.8%, $p<0.05$). More reduction in residual urine volume and PSA levels were noted in the verum group.
13. An open post-marketing observation study in which 208 doctors participated investigated the efficacy and tolerability of Cernitin in the treatment of BPH stage I-II according to Aiken [41]. One thousand seven hundred ninety-eight patients were treated for 24 weeks. Improvements in all irritative symptoms in 50-80% were noted, and residual urine volume improved. Adverse effects were noted in 15 patients (0.8%). The perturbations were mainly gastrointestinal symptoms, and termination of treatment because of adverse effects was seen only in four patients.
14. In Japanese study published 1995, 79 patients were treated with Cernitin pollen extract [42]. At a dosage of 126 mg tid, symptom scores based on a modified Boyarsky rating scale [25], uroflowmetry, prostate volume, and residual volume were measured. Urine maximum flow increased significantly from 54.2 ml to less than 30.0 ml. When 28 patients who had received treatment for one year were examined, a mean decrease of prostatic volume of 26.5 cm3 was found.

We undertook a randomized, placebo-controlled, double-blind study using a combined treatment of Cernitin, saw palmetto, vitamin E and beta-sitosterol [43]. Patients were enrolled from 3 urological practices in the USA. One hundred forty-four subjects were randomized for study. Patients received either placebo or the combined natural products for 3 months. Evaluations were performed via the AUA Symptom Index scores, urinary flow rates, PSA measurements, and residual bladder volumes. Nocturia showed a markedly significant decrease in severity in patients receiving the combined natural products compared to those taking placebo ($p<0.001$). Daytime frequency was also lessened significantly ($p<0.04$). When the average individual total AUA Symptom Index score in the verum group was compared to that in the placebo group, the difference proved highly significant ($p<0.014$). PSA measurements, maximal and verage urinary flow rates, and residual volumes showed no statistically significant differences.

The major mechanism behind the beneficial action of Cernitin is believed to be inhibition of edema formation and prevention of inflammation in the prostate. Inflammation of the prostate can cause edema of the interstitial tissue surrounding the acini and ducts of the glands leading to poor drainage. This, in turn, creates difficulty in voiding, dysuria, frequency, and nocturia – symptoms which have been shown to improve with flower-pollen extract usage. In addition, pollen extract has been reported to reduce prostatic volume and residual volume, and improves voiding difficulties and urinary flow rates of patients with BPH. Obviously, pain may be due to such processes and will remit if these perturbations are overcome. It is believed that the anti-congestive action is based upon the inhibition of prostaglandin and leukotriene and cyclo-oxygenase enzymes are markedly reduced and the arachidonic cascade is interrupted [28].

Additional pharmacological effects reported for the pollen are: inhibition of prostate cell growth in animals, influences on contractibility of bladder and urethral smooth muscle, as well as diaphragms of animals, and influences on metabolism of dihydrotestosterone [28]. In conclusion, the combined mechanisms behind

the effects of Cernitin pollen extract will go a long way to ensure overall prostate health.

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