

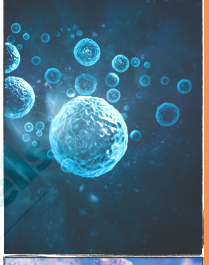
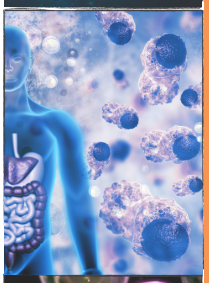
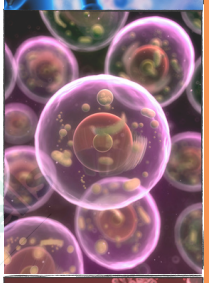
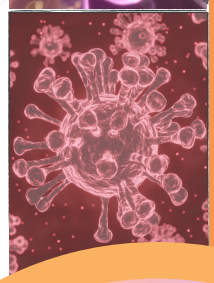

16 RESEARCH PROPOSAL

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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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16 งานวิจัย เกี่ยวกับเกสรดอกไม้ และ Saw Palmetto

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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 months, a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) compared to placebo can significantly lessen nocturia 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; B-sitosterol; Cernitin; Frequency, Natural means to treat; Nocturia, Natural means to treat; Saw Palmetto

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 placebo over 90 days. To accomplish this, we examined a combination of cernitin, saw palmetto, B-sitosterol, and vitamin E[1]. 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 Figure 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 the 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 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 phytosterol (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, 9, 11]. 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 Future Tech, 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 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 days 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 up at $p<0.05$.

PROFILE OF A RANDOMIZED CONTROLLED TRIAL

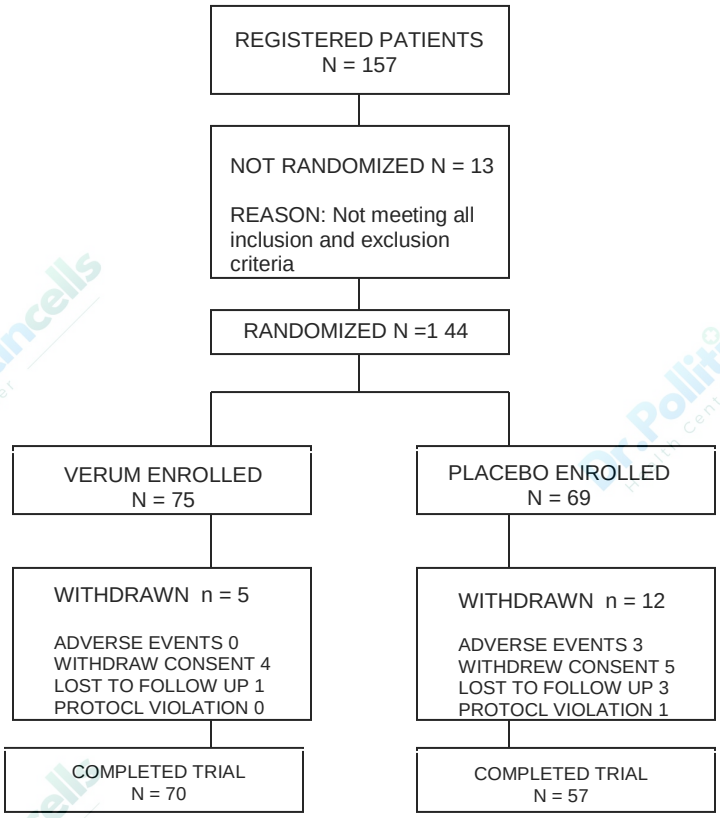

Figure 1. Progress through the various stages of the trial, including flow of participants and withdrawals.

*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

Results

As shown in Figure 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 Figure 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 only 2 patients complaining of gastrointestinal distress were in the placebo group.

The questions asked in the American Urological Associating (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 are being sought. Table 3 depicts the mean AUA scores and the statistics performed by Mixed ANOVA at the 3 time pints. Results from Question #7 concerning nocturia showed that there was 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 from the objective measurements. The PSA scores, maximal and average urinary flow rates, and residual volumes shoed no statistically significant differences when comparing the test and placebo groups.

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 your 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 have to push or strain to being 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 many 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 score from 7 questions indicate severity of BPH:

0-7 = mild prostatism
8-18 = moderate prostatism
19-35 = severe prostatism

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]
Q 1-7	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 x 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

	Vernum		Placebo	
	Basline	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.

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 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.

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 last 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 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%, $p=0.009$. 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 time 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 to 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 known about defined pollen extract referred to as cernitin. We are unaware of any 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 percent [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 percent of cases. In a double-blind, placebo-controlled study performed in 1988 in collaboration with 6 practicing urologists, 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 anti-congestive- 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 percent [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 improved subjective findings in the present study, it is not clear why improved changes in objective criteria were not also seen. However, this situation is not unusual when considering other reports. Examination of many 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.

Conclusions

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 significantly relief for 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.

Acknowledgements

This study was supported by Rexall/Sundown, Inc, Boca Raton, FL through the National Research Council for Health, Washington DC and Meridian ID. The authors gratefully acknowledge the following individuals for their outstanding contribution to the study: Denise G. Tobar (ID), Tracey Smithee (ID), D Russell Locke MD (FL), Ellen Metivier (FL), Fran McTiernan (FL), Joanne Nasworth (FL), Beth Soles (FL), Virginia B. King (FL), Victoria Benson (NRCH), and Jennifer Atagi (NRCH).

Note

1. Cernitin AF™, Rexall/Sundown, Boca Raton FL.

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Comparison of Saw Palmetto (extract and whole berry) and Cernitin on prostate growth in rats

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Abstract

Pharmaceuticals such as finasteride and alpha blockers are used to treat symptoms of benign prostatic hyperplasia (BPH) and are known to cause severe adverse reactions. Accordingly, a search for safer, natural products has been undertaken. Two natural agents (nutraceuticals) have come under recent scrutiny; because natural products, in general, often have evidence of long term safety. The present study compares the *in vivo* effects on androgen-induced prostatic enlargement in rats of two nutraceuticals – the widely recognized Saw Palmetto (*Serenoa repens*) and the less well-known Cernitin (defined pollen extract). Non- castrated rats, had a mean prostate weight of 124 mg ± 8.8 (S.E.M) compared to the 24.5 ± 1.9 (S.E.M.) of the castrated rat followed under the same regimen ($p<0.01$). When castrated rats were given testosterone, the mass increased significantly to 250.0 mg ± 31.7 (S.E.M.) ($p<0.01$). In the five remaining groups, castrated rats receiving testosterone were given finasteride, an extract of Saw Palmetto, crushed whole berry derived from Saw Palmetto fruit, a water soluble and fat soluble extract of Cernitin or a combination of the Saw Palmetto extract and Cernitin. All treatments decreased the size of the prostate to roughly the same size as in the non-castrated rats, a size that was significantly smaller than castrated rats treated with testosterone in the same manner ($p<0.01$). A second study examining non-castrated rats treated with very high doses of testosterone showed similar results. In both studies, the nutraceuticals generally decreased body weight. In conclusion, these studies show the ability of Saw Palmetto (whole berry and extract) and Cernitin to influence prostatic hyperplasia via effects on androgen metabolism. (Mol Cell Biochem **250**: 21-26, 2003)

Keywords: benign prostatic hyperplasia (BPH), finasteride, alpha blockers, Saw Palmetto, Cernitin, androgen-induced prostatic hyperplasia; castrated and non-castrated rats

Introduction

Benign prostatic hyperplasia (BPH) is the most common non-cancerous tumor in men and ranks with prostate cancer as the two most common prostate disorders affecting middle-aged and older men [1]. BPH is basically enlargement of the prostate, which is common in older men. Epidemiological studies have revealed that when a man reaches approximately 40 years of age the prostate gland starts enlarging. More than 50% of men ages 60 years have BPH, while 90% of men in their 70's and 80's have BPH. BPH is a secret, silent disease which progresses with aging and the irritating symptoms of BPH are prevalent throughout our society [1-3]. Common symptoms of this prostate perturbation include a weak urinary

stream, incomplete bladder emptying, difficulty in starting urination, frequent urination (especially at night), nocturia (excess urination at night), urgency (difficulty in postponing urination), painful and difficult urination (dysuria), and interruption of the stream (stopping and starting) [1].

In the past, treatment options for prostate enlargement focused mainly on surgery [4]. Over the last few years, prescription drugs have also been used to initiate therapy against prostatic perturbations in their early stages. One highly recognized pharmaceutical (finasteride, Proscar™) works chiefly to inhibit the activity of 5-alpha reductase and the formation of dihydrotestosterone (DHT), which is considered a major cause of prostatic hyperplasia [5-7]. Another agent (terazosin, Hytrin™) is an alpha blocker that relaxes the muscle tissue of the prostate and thus relieves the pressure around the urethra [8,9]. However, surgery and pharmaceuticals carry a high monetary cost and the added risk of developing potentially debilitating side effects [1,3]. Accordingly, there is a need to develop safer and better therapeutic agents. One potential is avenue is the use of natural products to treat BPH a concept that has been pioneered in Europe and Japan [10-13].

The present study compares the *in vivo* effects of the widely recognized Saw Palmetto (*Serenoa repens)* and the less well-known Cernitin (defined pollen extract) on prostatic enlargement in rats. Furthermore, we also compared the effects of a standard Saw Palmetto extract against crushed whole berries from the Saw Palmetto tree.

Materials and methods

Saw Palmetto, Cernitin, and other chemicals

The Saw Palmetto extract (lot code 199633 – 45% fatty acids) and the Saw Palmetto berry powder (lot code 9809555 – 8.49% fatty acids) were obtained from Rexall/Sundown (Boca Raton, FL, USA). Cernitin (T63) 20:1 mixture of water-soluble T60 and alcohol-soluble GBX, was obtained from Graminex (Saginaw, MI, USA). Finasteride was obtained from Georgetown University Medical Center Pharmacy (Washington, DC, USA). All other chemicals used in this study were obtained from Sigma Chemical Company (St. Louis, MO, USA) and were of analytical grade or the highest commercial grade available.

Animals and treatment

To examine the ability of phytochemicals to influence androgen-stimulated prostate growth, six regular and 42 castrated male Sprague-Dawley rats, weighing between 50-100g were purchased from Taconic Farms, Germantown, NY, USA. The *in vivo* assay used to determine androgen-stimulated prostate growth was patterned as described earlier [11]. Throughout the study, rats were fed standard rat chow and drank water *ad libitum.* Six rats were assigned to one of eight groups based upon their daily protocol. The Saw Palmetto extract dosage was selected based on the studies conducted by Rhodes *et al.* [13]. No previous determination study was conducted for Cernitin T63, we used a dosage similar to that of Saw Palmetto extract.

The regimen for the first 7 days among eight different groups was as follows:

Group 1 Normal, non-castrated rats receiving the vehicle, methylcellulose, alone via gavage

Group 2 Castrated rats receiving the vehicle, methylcellulose, alone via gavage

Group 3 Castrated rats gavaged with methylcellulose similar to the second group

Group 4 Castrated rats gavaged with 10mg of finasteride in methyl cellulose

Group 5 Castrated rats gavaged with Saw Palmetto extract (200 mg) in methylcellulose

Group 6 Castrated rats gavaged with a preparation of crushed berries obtained

from Saw Palmetto fruit (200 mg) in methylcellulose

Group 7 Castrated rats gavaged with Cernitin T63 (200 mg/ day) in methylcellulose

Group 8 Castrated rats gavaged with Saw Palmetto extract (200 mg/ day) plus Cernitin T63 (200 mg/ day) in methylcellulose

From days 8-17, rats in groups 1 and 2 received a daily subcutaneous injection of 0.1 ml of saline, while the rats in groups 3-8 received a daily injection of 20 µg testosterone enanthate in a 0.1 ml volume. Groups 2 and 3 were distinguished by the injection of saline or testosterone. All groups (1-8) were continued on their same daily oral regimens. Body weights were measured on day 8 and the last day of the study, which was 10 days later.

Upon completion of the study, prostates were removed and wet/dry prostate weights were measured. DNA and RNA concentrations were measured using a Qiagen RNA and DNA Kit (Qiagen, Valencia, CA, USA) and a BioRad Smatspec 3000 Spectrometer.

On day 8, we injected each rat's right paw with 0.1 ml of incomplete Freund's adjuvant after initial measurements of paw thickness were made with sensitive calipers (day 0). Thereafter, the right and left paws (control) of each rat were measured 1 day, 3 days, and 7 days after testosterone dosing was initiated.

In a separate study, 35 non-castrated rats were injected daily with either saline or testosterone enanthate, 20 mg. This was a 1000-fold increase in the dose of testosterone. Treatment groups received the same doses by gavage of finasteride, whole berry Saw Palmetto, Saw Palmetto extract, Cernitin and a combination of Cernitin and Saw Palmetto extract as in the initial study.

Statistical analyses

Results from the two studies are presented as mean ± S.E.M. The statistics were performed by one-way analysis of variance (ANOVA). Where a significant effect of treatment was detected by ANOVA ($p<0.05$), the Dunnett *t*-test was used to establish which differences between means reached statistical significance ($p<0.05$) [14].

Results

In the first experiment the non-castrated rats gavaged with only methylcellulose had a mean prostate weight of 124 mg ± 8.8 (S.E.M.) compared to the 24.5 mg ± 1.9 (S.E.M.) of the castrated rat followed under the same regimen, i.e. approximately a 5-fold difference in size at the end of the trial period (Table 1). When castrated rats receiving only methylcellulose were given testosterone enanthate, the mean increase in size was almost 10 fold, i.e. 250.0 mg ± 31.7 (S.E.M.). In the five remaining groups, castrated rats receiving testosterone were given finasteride, an extract of Saw Palmetto (SPE), crushed whole berry derived from Saw Palmetto fruit (WBSP), a water soluble and fat soluble extract of defined pollen extract in a 20:1 ratio (Cernitin T63), or a combination of the SPE and Cernitin T63. All treatments decreased the size of the prostate to roughly the same size as in the non-castrated, control rats. At the doses used, finasteride decreased prostate size the most, but the decreased size was not statistically different from the other groups receiving the natural therapies. Two additional points of interest stand out: first, the crushed whole berry of Saw Palmetto fruit was as effective as the extract and the combination of the SPE and Cernitin T63 was no better in reducing prostate size than each alone in this model.

When the prostatic tissues were examined further, the concentrations of DNA and RNA in the prostate were essentially similar. In addition, the dry/wet weight ratio of the prostates among the groups were virtually similar.

In Figure 1, we examined more closely the effects of the various regimens on body weight changes over the 10 day experimental period

when the rats were receiving different therapeutic regimens. Compared to the untouched control rats (group 1), those receiving the castration procedure and no testosterone (group 2) showed a similar mean body weight gain. The addition of testosterone caused an increased body weight (group 3) as did the rats given finasteride in addition to testosterone (group 4). These increases, however, were not statistically significant. Comparing natural products to regular or castrated controls, the groups gavaged with SPE (group 5) and WBSP (group 6), and Cernitin T63 plus SPE (group 8) showed significantly reduced body weight gain. This was not seen with the group receiving Cernitin T63 alone (group 7).

In this same study, the effects of the various therapeutic agents on paw edema were also examined (Table 2). Using the left paw as control, we found no consistent differences in response of the edema when the animals were receiving SPE, Cernitin T63, or a combination of both over the course of the various regimens.

In a second, separate study, where groups of five non-castrated rats were challenged with the 20 times more testosterone than in the original studies (20 mg), the prostate sizes increased markedly, i.e. from a mean of 90 mg ± 16.5 (S.E.M) to 621 mg ± 57.0 (S.E.M.). The addition of finasteride, SPE, WBSP, Cernitin T63 and the combination of SPE plus Cernitin T63 all decreased prostate size significantly when compared to the group gavaged with the carrier alone. In the contrast to the first study, the combination of Cernitin T63 plus SPE caused a greater reduction in weight when compared to the additions of each ingredient alone (Table 3).

When changes in body weight over the study period were examined, rats gavaged with finasteride, WBSP, Cernitin T63, and the combination of Cernitin T63 and SPE showed less gain when compared to control.

Discussion

Standard treatment options for symptoms emanating from prostatic enlargement focus principally on surgery and pharmaceuticals such as finasteride (Proscar™) and alpha blockers (Hytrin™) [1]. However, many patients seek to avoid these treatments, partially due to adverse reactions associated with these regimens. Finasteride, a synthetic 4-azasteroid compound and a specific inhibitor of 5-alpha-reductase, converts the androgen testosterone into dihydrotestosterone (DHT). It is worthwhile to mention that DHT is a potent stimulator of prostate gland growth and is responsible for the overproduction of prostate cells, which ultimately results in prostate enlargement. Finasteride

Table 1. Androgen stimulation of prostate in castrated rats

Group	In BW (g)	F BW (g)	Pros Size (mg)	DNA (μg/10 mg)	RNA (μg/10 mg)	Dry/wet (%)
Baseline	121.4 ± 8.8	169.5 ± 5.0	124.0 ± 8.8	10.4 ± 0.8	38.8 ± 1.8	0.27 ± 0.059
Cas	124.7 ± 2.5	178.5 ± 2.1	24.5 ± 1.9	10.4 ± 0.8	37.6 ± 1.9	0.26 ± 0.037
Cas + T	133.7 ± 4.3	194.0 ± 4.6	250.0 ± 31.7	10.3 ± 0.9	36.9 ± 1.9	0.23 ± 0.007
Cas + T + Pros	137.3 ± 2.5	197.0 ± 4.9	77.5 ± 11.0*	10.7 ± 0.9	41.6 ± 4.2	0.27 ± 0.012
Cas + T + SPE	130.3 ± 5.1	169.3 ± 7.8	103.0 ± 13.6*	8.9 ± 0.5	38.2 ± 2.6	0.24 ± 0.014
Cas + T + SPWB	132.8 ± 4.2	170.8 ± 7.3	122.6 ± 11.2*	9.5 ± 1.3	36.9 ± 2.5	0.29 ± 0.060
Cas + T + T63	132.3 ± 3.3	190.4 ± 6.4	141.4 ± 17.2*	9.0 ± 0.4	42.9 ± 3.1	0.26 ± 0.059
Cas + T + Comb	128.7 ± 3.7	173.9 ± 5.3	122.3 ± 10.6*	9.5 ± 1.6	38.8 ± 2.2	0.25 ± 0.024

Each value is the mean ± S.E.M. from 6 rats. See 'Materials and methods' for details. *Statistically significantly different from C + T. C – castrated; T – testosterone enanthate (20 μg subcu daily); Pros – finasteride (0.15 mg po daily); SPE – Saw Palmetto extract (200 mg po daily); SPWB – whole berry Saw Palmetto (200 mg po daily); T63 – Cernitin (200 mg po daily); Comb – same dose of SPE and T63 together.

has been demonstrated to cause a number of adverse events including decreased libido, ejaculatory disorders, impotence, reduced sex drive, and increases in the overall testosterone level, which results in increased body hair [15,16]. In Europe and Japan, use of natural products derived from plants has been used to treat prostatic perturbations in order to derive a favorable ratio between therapeutic benefits and adverse reactions. A major attractiveness of natural compounds, for the most part, lies in their fewer serious adverse side effects compared to drugs. Two potentially useful natural products could be useful therapeutic agents – SPE [10] and the relative newcomer on

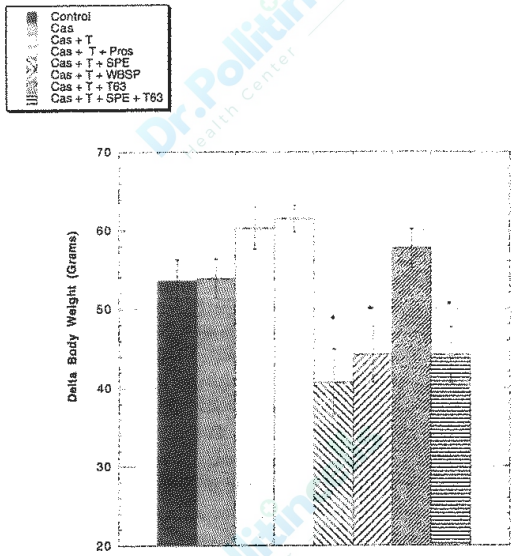

Fig. 1. Effects of nutraceuticals alone and combined on body weight during a 10 day study period in the first experiment. Mean ± S.E.M. is depicted ($p < 0.01$).

the block, Cernitin T63 [11]. Many large trials have found that SPE and Cernitin T63 improved

prostatic symptomatology and even compared favorably with finasteride when compared head to head [17-31]. Recently, combining both natural products was shown to have therapeutic effects in a randomized, placebo-controlled, double-blind trial [32].

Interestingly, the hypothesized mechanisms of action for Saw Palmetto and Cernitin T63 are essentially similar [1]. Among other mechanisms, benefits of both are attributed to their ability to affect the androgen metabolism. Saw Palmetto and perhaps Cernitin T63 simulate finasteride by preventing conversion of testosterone to DHT. DHT is the androgen associated with undesired prostate growth during aging. Saw Palmetto and Cernitin T63 not only lower the rate of DHT formation but block the ability of DHT to bind cells, preventing the action of hormone [31] (Table 1). SPE may also demonstrate potent anti-inflammatory activity as it has been shown to reduce prostate inflammation and pain [32]. Furthermore, inhibition of prolactin and growth factor induced cell proliferation may be another mechanistic avenue of cytoprotection of enlarged prostate by Saw Palmetto.

The ability of Saw Palmetto to influence androgen metabolism has been well studied (Table 4). SPE was found to inhibit 5-alpha

Table 2. Effect of various regimens on raw paw edema

Group	Day 0	Day 1	Day 3	Day 7
Regular	31.6 ± 0.3/31.5 ± 0.4	33.9 ± 0.4/62.2 ± 1.4	30.9 ± 0.4/54.8 ± 1.0	33.4 ± 0.8/50.5 ± 0.9
Cas	31.7 ± 0.7/31.7 ± 0.6	35.0 ± 0.6/54.5 ± 1.9	30.0 ± 0.5/47.5 ± 1.3	30.8 ± 0.7/44.7 ± 1.4
Cas + T	32.0 ± 0.3/32.1 ± 0.3	35.7 ± 0.7/57.8 ± 1.3	30.3 ± 0.5/45.8 ± 1.8	33.8 ± 0.8/47.3 ± 1.0
Cas + T + Pros	32.2 ± 0.3/32.2 ± 0.3	35.6 ± 0.6/59.6 ± 1.5	29.2 ± 0.8/44.8 ± 2.3	32.4 ± 0.8/46.4 ± 1.1
Cas + T +SPE	30.2 ± 0.8/30.0 ± 0.4	35.2 ± 0.9/57.7 ± 2.2	31.8 ± 0.2/46.3 ± 1.6	30.0 ± 0.4/43.0 ± 1.8
Cas + T +SPWB	31.3 ± 0.2/31.3 ± 0.2	35.0 ± 0.9/61.0 ± 1.4	31.1 ± 0.3/57.4 ± 1.8	29.8 ± 0.8/44.3 ± 0.6
Cas + T +T63	30.3 ± 0.2/30.2 ± 0.2	34.5 ± 0.4/59.5 ± 2.0	33.7 ± 0.4/53.5 ± 4.2	30.6 ± 0.4/45.6 ± 0.9
Cas + T +Comb	30.7 ± 0.2/30.3 ± 0.4	34.0 ± 0.7/57.7 ± 0.6	30.5 ± 0.8/54.2 ± 1.3	28.2 ± 0.6/43.2 ± 0.9

Each value is the mean ± S.E.M. from 6 rats. See 'Materials and methods' for details. Cas – castrated; T – testosterone enanthate (20 μg subcu daily); Pros – finasteride (0.15 mg po daily); SPE – Saw Palmetto extract (200 mg po daily); SPWB – whole berry Saw Palmetto (200 mg po daily); T63 – Cernitin (200 mg po daily); Comb – same dose of SPE and T63 together.

Table 3. Androgen-stimulation of prostate in regular non castrated rats

Group	Number	Initial BW (g)	Final BW (g)	Prostate size (mg)
Control	5	141 ± 7.7	186 ± 8.7	90 ± 16.5
T	5	150 ± 1.3	200 ± 4.2	621 ± 57.0
T + Pros	5	144 ± 8.4	179 ± 7.6	401 ± 18.0*
T + SPE	5	146 ± 3.8	188 ± 6.0	454 ± 53*
T + SPWB	5	142 ± 9.5	166 ± 11.7	453 ± 11.3*
T + T63	5	162 ± 9.0	197 ± 5.7	514 ± 52.6*
T + SPE + T63	5	147 ± 5.9	176 ± 5.4	368 ± 11.4*#*

Each value is the mean ± S.E.M. from 6 rats. See 'Materials and methods' for details. *Significantly different from T; #significantly different from T + SPE, T + WBSP and T + T63. T – testosterone enanthate (20 µg subcu daily); Pros – finasteride (0.15 mg po daily); SPE – Saw Palmetto extract (200 mg po daily); T63 – Cernitin (200 mg po daily); WBSP – whole berry Saw Palmetto (200 mg po daily).

reductase and receptor binding of androgens in cultured human foreskin fibroblasts [31]. In contrast, Rhodes *et al.* [13] found different results when comparing the effects of *Sereona repens* (Permixon) and finasteride using an antiandrogen assay. While finasteride inhibited 5-alpha reductase activity and not the binding of DHT to prostatic androgen receptors, *Sereona repens* did neither. Kamijo *et al.* [33] had examined the effects of Cernitin T63 on experimental nonbacterial prostatitis in rats but not androgen-stimulated prostate growth.

In the present study, we compared the abilities of finasteride, Saw Palmetto and Cernitin T63 to influence androgen metabolism in the prostate. We corroborated that injections of testosterone into castrated and non-castrated rats increased prostate mass via hyperplasia. We found that the oral intake of finasteride; Saw Palmetto, either as an extract or crushed whole berries; and Cernitin T63 (combined T60 water soluble and GBX oil soluble extracts) overcame much of the androgen-stimulated prostate growth in castrated and non-castrated rats. When massive doses of testosterone were given in the second study, the combination of both Saw Palmetto and Cernitin T63 overcame the androgen effect more than either one alone. However, this may be a dose-dependent effect, i.e. increasing the dose of either agent alone might have produced similar results as the combination. Nevertheless, the potential for additive effects of independent agents is plausible.

The two natural ingredients are also postulated to have anti-inflammatory and smooth muscle relaxant effects through a dose-related effect on the arachidonic acid cascade through a double blocking of cyclooxygenase and lipoxygenase pathways [34,35]. We did not see this in our anti-androgen model. The similar and unchanging dry to wet prostate weight ratios suggest no difference in tissue water content among any group over the course of study (Table 1). Also, the rat paw assay showed no effects of any gavaged substance on the produced edema (Table 2).

Table 4. Hypothesized major mechanisms of action of Saw Palmetto and Cernitin on androgen metabolism

1.	Inhibits 5 alpha reductase
2.	Inhibits 3 alpha reductase
3.	Inhibits binding of DHT to cytosolic receptors Inhibits translocation of the DHT-receptor to the nucleus
4.	Demonstrates anti-inflammatory activity
5.	Inhibits prolactin and growth factor induced cell proliferation

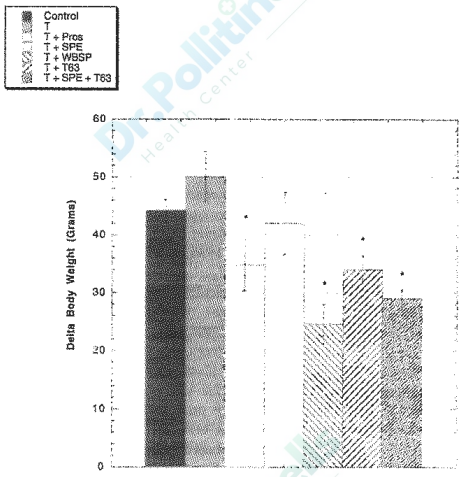

Fig. 2. Effects of nutraceuticals alone and combined on body weight during a 10 day study period in the second experiment where excessive doses of testosterone were given. Mean ± S.E.M. is depicted ($p < 0.01$).

It is unclear why Saw Palmetto and Cernitin T63 appeared to slow body weight gain. We surmised this by examining both Figs 1 and 2 (Cernitin T63 did not have any effect in the first study on castrated rats, but did in the second study on non-castrated rats: SPE decreased weight gain in the first study but not in the second). Unfortunately, we did not measure the food intake in either study to determine if varying weight changes could be due to different food intakes.

In conclusion, these studies corroborate the potential of Saw Palmetto (whole berry and extract) and Cernitin T63 to influence prostatic hyperplasia via effects on androgen metabolism

Acknowledgement

The authors thank Ms. Kristine Strong for technical assistance.

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