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

Harry G. Preuss, MD, MACN, CNS[1]; Charlyn Marcusen PhD[1]; James Regan MD[2]; Ira W. Klimberg MD[3]; Timothy A. Welebir MD[4]; William A. Jones MD[4]

[1] Department of Physiology and Biophysics, Georgetown University Medical Center, Washington, DC 20007
[2] Department of Urology, Georgetown University Hospital, Washington, DC 20007
[3] Urology Center of Florida, Ocala, FL 34474,
[4] Boise, ID 83701

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

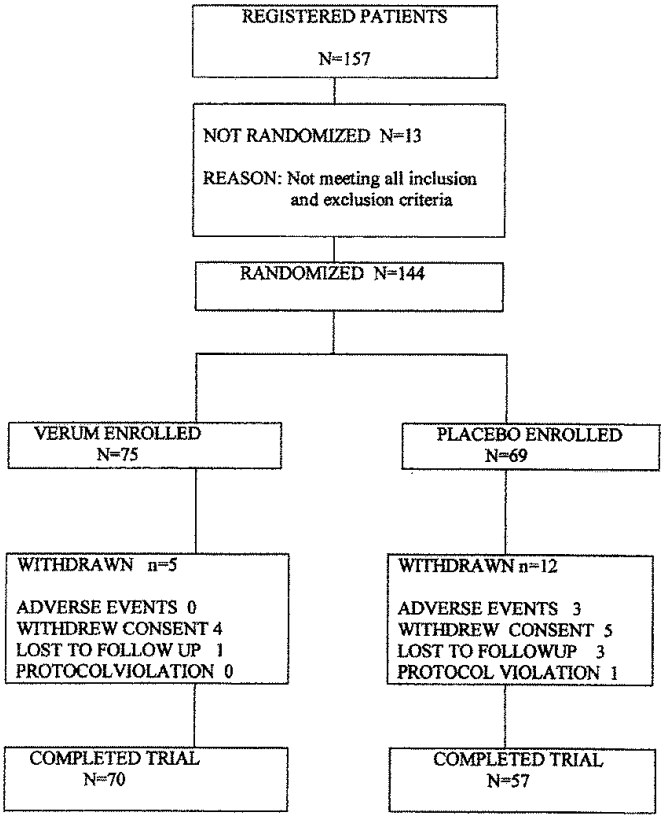

Figure 1. Progress through the various stages of the trial, including flow of participants and withdrawals.

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.

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).

References

1. Preuss HG, Adderly B. The Prostate Cure. New York, NY: Crown Publishing, 1998;pp 1-106.
2. Ebeling L. The therapeutic results of defined pollen extract in patients with chronic prostatitis. In: Schmiedt E, Alken JE, Bauer HW (eds). Therapy of Prostatitis. Munchen: Zuchkschwerdt Verlag, 1986;pp 154-160.
3. Becker H, Ebeling L. Conservative treatment of benign prostatic hyperplasia (BPH) with Cernitin N. Results of a placebo-controlled double-blind study. Urologe B 1988;28:301-306.

4. Becker H, Ebeling L. Phytotherapy of BPH with Cernitin N. Results of a controlled clinical study. Urologe B 1991;31:113-116.
5. Buck AC, Cox R, Rees RWM, Ebeling L. Treatment of chronic prostatitis and prostadynia with pollen extract. Br J Urol 1989;64:496-499.
6. Buck AC, Cox R, Rees RWM, Ebeling L, John A. Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, Cernitin. A double-blind, placebo-controlled study. Br J Urol 1990;66:398-404.
7. Ohkoshi M, Kawamure N, Nagakubo I. Evaluation of Cernitin in chronic prostatitis. Japanese J Urol 1967;21:73-85.
8. Takeuchi H, Yamauchi Al, Ueda T, Hiraga S. Quantitative evaluation on the effectiveness of Cernitin on benign prostatic hypertrophy. Hinyoki Kiyo 1981;27:326-327.
9. Brauer H. The treatment of benign prostatic hyperplasia with phytopharmacia; a comparative study of Cernitin and beta sitosterol. Therapeiwoche 1986;36:1686-1696.
10. Rugendorff EW, Weidner W, Ebeling L, Buck C. Results of treatment with pollen extract (Cernitin N) in prostadynia and chronic prostatitis. Br J Urol 1993;71:433-438.
11. Yasumoto R, Kawanishi H, Tsujino T, Tsujita M, Nishisaki N, Horii A, Kishimoto T. Clinical evaluation of long-term treatment using Cernitin pollen-extract in patients with benign prostatic hyperplasia. Clinical Therapeutics 1995;17:82-87.
12. Rhodes L, Primka RL, Berman C, Vergu HG, Gabriel M, Pierre-Malice M, Gibelin B. Comparison of finasteride (Proscar), a 5a reductase inhibition. The Prostate 1993;22:43-51.
13. Sultan C, Terraza A, Divillier C. Inhibition of androgen metabolism and binding by a liposterolic extract of Serenoa repens B in human foreskin fibroblasts. J Steroid Biochem 1984;20: 515-521.
14. Carraro JC, Raynaud J., Koch G, Chisolm GD, DiSiverio F, Teillae P, Da Silva FC, Cauquit J, Chopin DK, Hamdy M, Hanus M, Hauri D, Kalinteris A, Marencak J, Perier A, Perrin P. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia; a randomized international study of 1,098 patients. The Prostate 1996;29:231-240.
15. Posker GL, Brogden RN. Serenoa repens (Permixon). A review of its pharmacology and therapeutic efficacy in benign prostatic hyperplasia. Drug and Aging 1996;9:379-395.
16. Denis LJ. Editorial review of “Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia; a randomized international study of 1,098 patients.” The Prostate 1996;29:241-242.
17. Braeckman J. The extract of Serenoa repens in the treatment of benign prostatic hyperplasia: a multicenter open study. Curr Therap Res 1994;56:776-785.
18. Champault G, Bonnard AM, Cauquil J, Patel JC. Medical treatment of prostatic adenoma. Controlled trial PA 109 vs placebo in 110 patients. Ann Urol 1984;18:407-410.
19. Klippel KF, Hitl DM, Schipp B. A multicenter, placebo-controlled, double-bllind clinical trial of B-sitosterol (Phytosterol) for the treatment of benign prostatic hyperplasia. Br J Urol 1997;80:427-432.
20. Berges RR, Windeler J, Trampisch HJ. The B sitosterol study group: Randomized, placebo-controlled clinical trial of B-sitosterol in patients with benign prostatic hyperplasia. The Lancet 1995;345:1529-1532.
21. Vahlensieck W, Rutishauser G (eds). Benign Prostatic Diseases. Georg Thieme Verlag:Stuttgart-New York, 1992;pp 1-207.
22. McConnell JD, Wilson JD, George FW, Geller G, Walsh PC, Ewing LL, Isaacs J, Soner, E. An inhibitor of 5-alpha reductase, MK-906 suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. J Urol 1989; 141:280 (abstract).
23. Gormley GJE, Stoner E, Breuskewitz RC, Imperato-McGinley J, Walsh PC, McConnell JD, Andrioli GL. The effect of finasteride in men with benign prostatic hyperplasia. N Eng J Med 1992; 327:1185-1191.
24. Leper H. Role of alpha-andrenergic blockers in the treatment of benign prostatoc hyperplasia. Prostate 1990;3(suppl):75-84.
25. Consumers Union. Complete Drug Reference. Yonkers NY: Consumers Union, 1997;p 1540.
26. Loschen G, Ebeling L. Hemmung der arachindonsaure-kaskade durch einen extrakt aus roggenpollen. Arzneimittelforschung 1991;41:162-167.
27. Breu W, Hagenlocher M, Redl K, Tittel G, Stadler F, Watner H. Anti-inflammatory activity of sable fruit extracts prepared with supercritical carbon dioxide. Arzneim Forsch Drug Research 1992;42:547-551.