Saw Palmetto Berry as a Treatment for BPH

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Phytotherapeutic agents are often prescribed in Europe for the treatment of benign prostatic hyperplasia with lower urinary tract symptoms and are commonly used in the United States in over-the-counter preparations. Saw palmetto berry is the most popular of these agents, and in vitro some studies suggest that liposterolic extract of the plant has antiandrogenic effects that inhibit the type 1 and type 2 isoenzymes of 5α-reductase; however there are no clinical studies that show any decrease in serum dihydrotestosterone or prostate-specific antigen. Its efficacy in the treatment of lower urinary tract symptoms has not been conclusively proven. Clinical efficacy was suggested by a meta-analysis of Permixon, a formulation of saw palmetto, but the meta-analysis was done on suboptimal studies. One trial supports the equivalency of Permixon to finasteride in treating moderate to severe symptoms of benign prostatic hyperplasia, with less decrease in sexual function. However, without a control/placebo arm, the actual efficacy of the agents cannot be determined. Other than occasional gastrointestinal upset, no other side effects have been reported. [Rev Urol. *2001;3(3):134–138*]

Key words: Phytotherapy • Benign prostatic hyperplasia • Saw palmetto • 5α-reductase

Phytotherapeutic agents are becoming more popular in the treatment of benign prostatic hyperplasia (BPH). They are commonly prescribed in Europe in the treatment of lower urinary tract symptoms (LUTS) with BPH. In addition, they are commonly self-prescribed by patients in the United States as they are available over the counter without a prescription. Access to these agents has become easier with the expansion of health food stores and vitamin shops. Additionally, on the Internet there are more than one hundred Web sites advertising and selling phytotherapeutic agents. Thirty to ninety percent of patients seen by urologists for BPH/LUTS may be taking these agents.[1-3] One of the most commonly used agents is saw palmetto berry extract.

Serenoa repens (Saw Palmetto Berry Extract)

Saw palmetto berry (SPB) extract is the most popular phytotherapeutic agent used in the treatment of BPH/LUTS. SPB is derived from the berry of the American dwarf tree (*Serenoa repens, Sabal serrulata*). The plant is found in many areas of the southeastern United States.[4] Reports of SBP use in treatment of prostatic conditions date to the 1800s.[5]

One of the main difficulties in assessing the efficacy of phytotherapeutic agents and SPB is the lack of any standard formulation. These products are categorized as foods by the U.S. Food and Drug Administration. Therefore there is little regulation in their production and distribution. Different brands of SPB may show marked variation in content. Thus studies using one brand of SPB cannot be compared to other forms of SPB.[3,6] Permixon, produced by a French pharmaceutical company, is the most extensively studied form of SPB. Permixon is available in the United States via the Internet. It is a hexane extract of the American dwarf palm tree, *Serenoa repens*. Permixon is composed of free (90%) and esterified (7%) fatty acids, and smaller amounts of sterols, polyprenic compounds, flavonoids, and other substances.[3,6,7]

Table 1
Possible Mechanisms of Action of the Extract of *Serenoa repens**

1. Antiandrogenic activity
2. Inhibitory effect on type 1 and type 2 isoenzymes of 5α-reductase
3. Inhibition of prolactin and growth factor-induced cell proliferation
4. Antiestrogenic effect
5. Anti-inflammatory effect
6. Antiedema effect

**Most studies were performed with Permixon brand saw palmetto berry.*

Mechanism of Action

Numerous mechanisms of action of SPB have been proposed, including antiandrogenic effects, inhibition of type 1 and type 2 isoenzymes of 5α-reductase, inhibition of growth factors, and an anti-inflammatory effect (see Table I). Most in vitro studies that have sought to elucidate the mechanisms of action of SPB extract have been performed using Permixon, the liposterolic extract of SPB. In recent publications, it has been postulated that the liposterolic extract of *S. repens* has antiandrogneic effects,[8] inhibits the type 1 and type 2 isoenzyme of 5α-reductase,[9-11] inhibits prolactin and growth factor-induced cell proliferation,[12,13] and has antiestrogenic[14] and anti-inflammatory[15] effects.

However, most of these in vitro studies were performed in cell cultures or used supraphysiologic dosages of SPB extract. Therefore the significance of the results is uncertain.

In a recent ex vivo study, Di Silverio and associates[16] supported the concept that the liposterolic extract of SPB (Permixon) has antiandrogenic effects that inhibit the type 1 and type 2 isoenzymes of 5α-reductase. In a randomized study, 33 patients with BPH underwent suprapubic prostatectomy after being treated with finasteride (5 mg/day for 3 months), flutamide (750 mg/day for 2 months), Permixon (320 mg/day for 3 months), or after receiving no treatment. None of these treatments caused a significant alteration in tissue concentrations of testosterone. However, both Permixon and finasteride exhibited a 50% reduction in prostate dihydrotestosterone (DHT) levels ($P < .01$) compared with flutamide or with no treatment. For both agents, this effect was primarily in the periurethral tissues.

In contrast, Weisser and colleagues[17] performed a prospective, randomized double-blind trial using an extract of *Sabal serrulata* (IDS-89) to determine the possible influence on epithelial and stromal enzymes in BPH tissue. Patients were treated with either placebo or IDS-89 for 3 months, at which time they underwent suprapubic prostatectomy. The tissues were evaluated for 5α-reductase, 3α-and 3β-hydroxysteroid oxidore tase, and creatine kinase activity. There was no difference in 5α- reductase and 3α-reductase and 3β-hydroxysteroid activity in those treated with IDS-89 versus placebo. However, creatine kinase activity was statistically significantly increased in patients treated with IDS-89. Because the synthesis of creatine kinase is estrogen dependent, it is possible that IDS-89 might affect the balance of androgens in relation to estrogens. The clinical significance of this possibility is not known.

Analysis showed mild to moderate improvement in symptom score and urinary flow.

Pathologic comparisons of those pretreated with *S. serrulata* were compared with those who were given placebo. Those pretreated with *S. serrulata* showed a significant reduction in periglandular and stromal edema, mucoid degeneration, intraglandular congestion, and "congestive prostatitis." Again the clinical significance of these pathologic findings is not clear.[18]

Not all in vivo studies are in

agreement. Rhodes and associates[19] did not demonstrate any inhibition of DHT binding to rat prostatic androgen receptor nor inhibition of DHT activity.

Additionally, several clinical studies measured serum testosterone, DHT, prostate-specific antigen (PSA), and follicle stimulating hormone (FSH) levels in patients given SPB extracts for variable periods of time up to 6 months.[19-23] None of these studies showed any alteration in testosterone, DHT, PSA, and FSH levels. Therefore, the effect on hormone metabolism and 5α-reductase activity by *S. repens* (including Permixon) has yet to be determined conclusively.

Clinical Studies

The efficacy of SPB in the treatment of LUTS has never been conclusively proven in double-blind, randomized placebo-controlled trials. There have been numerous randomized trials which were summarized by Wilt and colleagues.[7] These authors analyzed and interpreted 18 randomized clinical trials involving more than 2,900 men with symptomatic BPH. The results of their analysis showed mild to moderate improvement in symptom score and urinary flow without decreasing prostate size. The drug-effect improvement in symptom score was 1.41. The drug-effect improvement in peak urine flow was 1.93 ml/sec. The side effects were comparable with placebo and were reportedly mild. However, many of the studies analyzed were relatively small, and not every study demonstrated significant improvement. This study was flawed and probably inaccurate due to variability of the different products reviewed, publication bias of the studies selected, and the methodology utilized for interpreting the diverse data.

A meta-analysis completed by Lowe and associates[24] reviewed all recent placebo-controlled trials for Permixon brand SPB; these 7 studies were all of short duration (less than 3 months). In summary, there was an improvement in symptoms (nocturia was the only symptom that occurred in all studies) and urine flow rate when compared to placebo. Nocturia decreased by an additional 0.5 times per night over than placebo. The increase in peak urine flow was an additional 1.5 mL/sec over than placebo. However, the clinical significance of these small magnitudes is uncertain.

Perhaps the most widely quoted study of SPB using Permixon involved a comparison to finasteride, the 5α-reductase inhibitor. This was a 6-month, randomized, double-blind, placebo-controlled study of 1,098 patients. Symptom scores were improved to an equal extent in both groups (37% with Permixon versus 39% with finasteride). Peak flow also improved to a similar extent in both groups (2.7 mL/sec with Permixon versus 3.2 mL/sec with finasteride). The differences were significant compared with baseline for both drugs. There was also a statistically significant decrease in residual urine in the finasteride group. PSA levels were unchanged in the Permixon group and fell in the finasteride group by 41%. Prostate size decreased more in the finasteride group than in the Permixon group (by 18% versus 6%).[25]

This well-designed and well-executed trial supports the equivalency of Permixon to finasteride in treating men with moderate to severe symptoms of BPH, with less decrease in sexual function than is found with finasteride. However, the lack of a placebo group clouds the efficacy issue.[26,27] Because the study was only 6 months in duration, it is possible that the effect is due to the placebo effect and will eventually fade with time.[28] Additionally, the study by Lepor and colleagues[29] indicated that finasteride was not statistically better than placebo in men that had relatively small prostates. Therefore, comparing Permixon with finasteride might simply be showing equivalency to placebo.[26,27]

Comparing Permixon with finasteride in a group of patients with small prostates might simply be showing equivalency to placebo.

In one placebo-controlled study, 176 of 215 nonresponders to placebo were randomized to receive Permixon 160 mg twice daily or placebo for 30

Main Points

- Thirty to ninety percent of patients seen by urologists for BPH/LUTS may be taking phytotherapeutic agents.
- Saw palmetto use in the treatment of prostatic conditions has been reported since the 1880s.
- Studies suggest antiandrogenic effects that inhibit the type 1 and type 2 isoenzymes of 5α-reductase, but these effects have yet to be determined conclusively.
- The safety of saw palmetto extract compares well with finasteride, with fewer sexual side effects.

days.[30] Subsequent evaluation showed that dysuria, daytime frequency, nocturia, and peak urinary flows were all improved in Permixon-treated patients compared to baseline values and placebo-treated patients. However, at the end of the study, when the patients and physicians were asked to assess global efficacy of the different treatments, there was no statistical difference in satisfactory responses between Permixon therapy (71% and 57%) and placebo treatment (68% and 47%) respectively. Thus this study of Permixon therapy did not show any actual perceived clinical benefit by the patients or their physicians.

Urodynamic Effects

In a 6-month, open-label study utilizing SPB extract (Nutraceutical Corp, Ogden, UT), 50 men were evaluated urodynamically at baseline and at completion of the study.[23] The International Prostate Symptom Score (IPSS) (mean +/- standard deviation) improved from 19.5 +/- 5.5 to 12.5 +/- 7.0 ($P < .001$). Although an improvement of more than 50% in IPSS was identified in 21%, 30%, and 46% of patients at 2, 4, and 6 months, respectively, no demonstrable changes in peak urinary flow rate, postvoid residual urine, or detrusor pressure at peak flow were found. This study demonstrated no correlation between relief of urodynamic signs of obstruction and a decrease in LUTS. Without an appropriate control, the attributable drug effect of SPB extract cannot be demonstrated.[31] Thus the effect may be largely attributable to the placebo effect.[23]

Summary of the Clinical Trials

The uncontrolled and comparative trials utilizing SPB extract without placebo control are not useful in defining the efficacy of SPB in the treatment of BPH. The randomized placebo-controlled studies are hampered by short duration, variable inclusion/exclusion criteria, and lack of uniform symptom score analyses.[1] The meta-analysis of Permixon suggests clinical efficacy. However, the meta-analysis was done on suboptimal studies.

In conclusion, the efficacy of SPB extract in the treatment of LUTS secondary to BPH has yet to be conclusively determined. Long-term, placebo-controlled trials are needed to determine the efficacy of SPB.

Safety of SPB

In general there are very few adverse affects to SPB. In a study of 1,098 patients, when Permixon was compared to finasteride there was no change in PSA of standard blood tests during a six-month period. In addition, the safety of the drug compared well with finasteride, with fewer sexual side effects.[25,32]

The safety of Strogen, a European SPB extract, was demonstrated in a 3-year study of 453 men. Occasional gastrointestinal upset was reported. No other side effects were reported. The use of SPB extract has not been associated with erectile dysfunction, ejaculatory disturbance, or altered libido.[32,33]

Evaluations of SPB extract have not been performed in the United States as they are not required by law. Herbal medicines are regulated as dietary supplements under the 1994 Dietary Supplement Health and Education Act. Under this law, herbal products can be sold without any specified efficacy or safety testing provided the product was marketed in the United States before October 15, 1994. The burden of product safety falls on the manufactures. Approval by the Food and Drug Administration is not required to sell these products.[32]

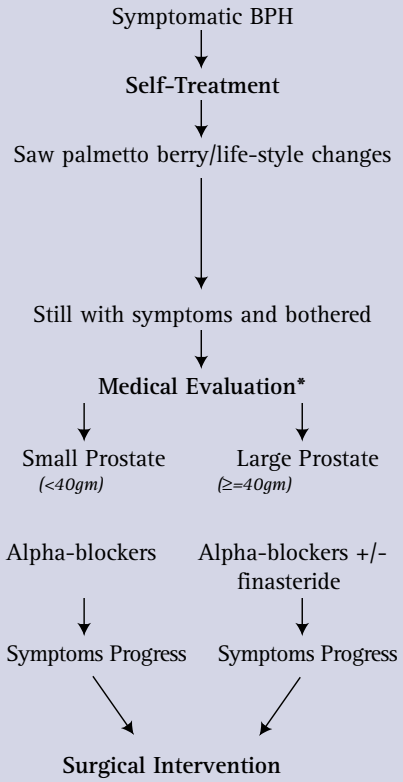
Advice to Patients

There is no standard of care with regards to management of patients who are taking phytotherapeutic agents, including SPB, for LUTS/BPH. When patients present to urologists while taking phytotherapeutic agents, they are usually still symptomatic; otherwise they probably would not be seeing a urologist. Patients should be counseled that the efficacy, mechanisms of action, and long-term side effects of these agents are not known. If a patient refuses "traditional medical" therapy such as alpha-blockers, then phytotherapeutic agents are a reasonable alternative as long as the patient understands the current limitations of these agents. For patients with moderate to severe symptoms, traditional medical therapy should be undertaken. For patients with urinary tract infections, urinary retention, bladder calculi, or decreased renal function, aggressive medical and surgical therapy should be undertaken.

For those interested in utilizing saw palmetto berry, the authors recommend buying the least expensive brand and trying it for one month. If after 3 months and trying three different brands of SPB, the patient's symptoms have not improved sufficiently (causing the patient less bother), then standard medical surgical therapy is indicated.[1] Table 2 shows a decision-making list for the medical management of BPH utilizing SPB.

In conclusion, the efficacy of SPB extract in the treatment of LUTS secondary to BPH has yet to be conclusively determined. Long-term, placebo-controlled trials are needed to determine the efficacy of SPB.

Table 2
Decision Tree for the Medical Management of Benign Prostatic Hyperplasia (BPH)



**History, physical exam, digital rectal exam, urine analysis, creatinine, and PSA.*

†Laser therapy, internal urethral stents, transurethral needle ablation of the prostate, transurethral electrovaporization of the prostate, or high-intensity focused ultrasound.

References

1. Lowe FC: What I tell patients about phytotherapeutic agents for benign prostatic hyperplasia. *AUA News*. 1998;September/October:12.
2. Gerber GS, Bales G, Kirsh E, Christiano AP. Medicinal botanicals in the treatment of lower urinary tract symptoms (LUTS): a demographic analysis of awareness and use at the University of Chicago. *J Urol*. 1998;159:334, abstract 1282.
3. Lowe FC, Ku JC. Phytotherapy in treatment of benign prostatic hyperplasia: a critical review. *Urology*. 1996;48:12.
4. Lowe FC, Fagelman E. Phytotherapy in the treatment of BPH: an update. *Urology*. 1999;53:671-678.
5. Dreikorn K. Other medical therapies. In: Denis L, Griffiths K, Murphy G, eds. *Proceedings of the Fourth International Consultation on Benign Prostatic Hyperplasia (BPH), Paris, July 2-5, 1997*. Plymouth, UK: Health Publication, Ltd.; 1998:635-659.
6. Gerber GS. Saw palmetto for the treatment of men with lower urinary tract symptoms. *J. Ord*. 2000;163;1408-1412.
7. Wilt TJ, Ishani A, Stark G, et al. Saw palmetto extracts for treatment of benign prostatic hyperplasia. A systematic review. *JAMA*. 1998;280:1604-1609.
8. Ravenna L, Di Silverio F, Russo M, et al. Effects of the lipidosterolic extract of Serenoa repens (Permixon) on human prostatic cell lines. *Prostate*. 1996;29:219-230.
9. Di Silverio F, D'Eramo G, Lubrano C, et al. Evidence that *Serenoa repens* extract displays an antiestrogenic activity in prostatic tissue of benign prostatic hypertrophy in patients. *Eur Urol*. 1992;21:309-314.
10. Iehle C, Delos S, Guirou O, et al. Human prostatic steroid 5(reductase isoforms: a comparative study of selective inhibitors. *J Steroid Biochem Mol Biol*. 1995;54:273-279.
11. Bayne CW, Grant ES, Chapman K, et al. Characterisation of a new coculture model for BPH which expresses 5(-reductase types I and II: the effects of Permixon on DHT formation (abstract 70). In: Denis L, Griffiths K, Murphy G, eds. *Proceedings of the Fourth International Consultation on Benign Prostatic Hyperplasia (BPH), Paris, July 2-5, 1997*. Plymouth, UK: Health Publication, Ltd.; 1998:70.
12. Vacher P, Prevarskaya N, Skryma R, et al. The lipidosterolic extract from Serenoa repens interferes with prolactin receptor signal transduction, *J Biomed Sci*. 1995;2:357-365.
13. Paubert-Braquet M, Raynaud JP, Braquet P, et al. Permixon [lipid sterolic extract of *Serenoa repens* (LSESr)] and some of its components inhibits β-FGF- and EGF-induced proliferation of human prostate organotypic cell lines (abstract 74). In: Denis L, Griffiths K, Murphy G, eds. *Proceedings of the Fourth International Consultation on Benign Prostatic Hyperplasia (BPH), Paris, July 2-5, 1997*. Plymouth, UK: Health Publication, Ltd.; 1998:74.
14. Paubert-Braquet M, Raynaud JP, Braquet P, et al. Permixon lipid sterolic extract of *Serenoa repens* (LSESr) inhibits estrogen-androgen-induced prostate enlargement in the rat. *Pharmacol Res*. 1995; 31(suppl):31-35.
15. Paubert-Braquet M, Cousse H, Raynaud JP, et al. Effect of lipidosterolic extract of *Serenoa repens* (Permixon) on the ionophore. A 23187-stimulated production of leukotriene B4 (LTB4) from human polymorphonuclear neutrophils (abstract 72). *Fourth International Hyperplasia (BPH), Paris, July 2-5, 1997*. page 73.
16. Di Silverio F, Sciarra A, DíEramo G, et al. Response to tissue androgen and epidermal growth factor concentrations to the administration of finasteride, flutamide and *Serenoa repens* in patients with BPH (abstract). *Eur Urol*. 1996;30(suppl 2):80.
17. Weisser H, Tunn S, Behnke B, et al. Effects of the *Sabal serrulata* extract IDS 89 and its subfractions on 5α-reductase activity in human; benign prostatic hyperplasia. *Prostate*. 1996, 28:300-306.
18. Helpap B, Oehler U, Weisser H, et al. Morphology of benign prostatic hyperplasia after treatment with Sabal extract IDS 89 or placebo. *J Urol Pathol*. 1995;3:175-182.
19. Rhodes L, Primka RL, Berman C, et al. Comparison of finasteride (Proscar), a 5α-reductase inhibitor, and various commercial plant extracts in in vitro and in vivo 5α-reductase inhibition. *Prostate*. 1993;22:43-51.
20. Casarosa C, Coscio di Coscio M, Fratta M: Lack of effects of a liposterolic extract of *Serenoa repens* on plasma levels of testosterone, follicle stimulating hormone, and luteinizing hormone. *Clin Ther*. 1988;5:585-588.
21. Strauch G, Perles P, Vergult G, et al. Comparison of finasteride (Proscar) and *Serenoa repens* (Permixon) in inhibition of 5α-reductase in healthy male volunteers. *Eur Urol*. 1994;26:247-252.
22. Braeckmann J. The extract of *Serenoa repens* in the treatment of benign prostatic hyperplasia: a multicenter open study. *Curr Ther Res*. 1994;55:776-785.
23. Gerber GS, Zagaja GP, Bales GT, et al. Saw palmetto (*Serenoa repens*) in men with lower urinary tract symptoms: effects on urodynamic parameters and voiding symptoms. *Urology*. 1998;51:1003-1007.
24. Lowe FC, Roehrborn CG, Robertson C, Boyle P. Meta-analysis of clinical trials of Permixon. *J Urol*. 1998;(2)159:257, abstract 986.
25. Carro JC, Raynaud JP, Koch G, et al. Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostatic hyperplasia: a randomized international study of 1089 patients. *The Prostate*. 1996;29:231-240.
26. Lowe FC, Fagelman E. Phytotherapy in the treatment of benign prostatic hyperplasia. *Curr Opin Urol*. 1998;8:27-29.
27. Lowe FC. Saw palmetto berry in the treatment of benign prostatic hyperplasia. *Clin Res Reg Affairs*. 1997;14:53-66.
28. Denis LJ. Review of "Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostatic hyperplasia: a randomized international study of 1089 patients." *The Prostate*. 1996;29:241-242.
29. Lepor H, Williford WO, Barry MJ, et al. The efficacy of terazosin, finasteride or both in benign prostatic hyperplasia. *N Engl J Med*. 1996;335:533-539.
30. Descotes JL, Rambeaud JJ, Deschaseaux P, et al. Placebo-controlled evaluation of the efficacy and tolerability of Permixon in benign prostatic hyperplasia after exclusion of placebo responders. *Clin Drug Invest*. 1995;9:291-297.
31. Lowe FC. Saw palmetto (*Serenoa repens*) in men with lower urinary tract symptoms: effects on urodynamic parameters and voiding symptoms [editorial comment]. *Urology*. 1998;51:1007.
32. Marks LS, Tyler VE. Saw palmetto extract: newest (and oldest) treatment alternative for men with symptomatic benign prostatic hyperplasia. *Urology*. 1999; 53:457-461.
33. Bach D, Edeling L. Long-term drug treatment of benign prostatic hyperplasia: results of a prospective 3 year multicenter study using Sabal extract IDS 89. *Phytomedicine*. 1996;3:105-111.