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Review Article

SAW PALMETTO FOR THE TREATMENT OF MEN WITH LOWER URINARY TRACT SYMPTOMS

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ABSTRACT

Purpose: A comprehensive review of the literature on the use of saw palmetto in men with lower urinary tract symptoms is provided.

Materials and Methods: A literature search of studies that have assessed the mechanism of action and clinical results of saw palmetto in men with benign prostatic hyperplasia was performed.

Results: A variety of potential mechanisms of action of saw palmetto have been demonstrated through in vitro studies, including 5-α reductase inhibition, adrenergic receptor antagonism and intraprostatic androgen receptor blockade. Clinical evidence of the relevance of these effects is largely unavailable. The use of saw palmetto in men with benign prostatic hyperplasia is safe with no recognized adverse effects. No effect on serum prostate specific antigen has been noted. Placebo controlled trials and meta-analyses have suggested that saw palmetto leads to subjective and objective improvement in men with lower urinary tract symptoms. However, most studies are significantly limited by methodological flaws, small patient numbers and brief treatment intervals.

Conclusions: Evidence suggests that saw palmetto may have a significant effect on urinary flow rates and symptom scores compared to placebo in men with lower urinary tract symptoms. However, large scale, placebo controlled trials are needed to assess the efficacy of saw palmetto.

KEY WORDS: prostatic hyperplasia; medicine, herbal; urologic diseases; prostate

Increasing attention has been focused on phytotherapy, which is the use of plants and plant extracts to treat a variety of medical conditions.[1,2] It is estimated that $1.5 billion per year are spent in the United States for such products and overall use is growing rapidly.[3–5] Reasons for the increasing popularity of alternative medical approaches include dissatisfaction with conventional treatments, the need for personal control, and a philosophical congruence between alternative therapies and patient values and beliefs.[6–8] In a national survey alternative medicine users tended to be more educated, have a poorer overall health status and were more likely to have urinary tract problems.[6] The latter finding correlates well with the rapid increase in the use of medicinal botanicals by men with lower urinary tract symptoms.[9,10] Most patients do not rely primarily on alternative therapies[6] and many use phytotherapeutic agents with approved prescription drugs.[10]

With the increased popularity of alternative medicines has come increased scrutiny regarding their efficacy and safety.[11] Although there is a general perception that herbal products are at worst a harmless placebo, growing evidence suggests that this is not always true. DiPaola et al reported that an herbal mixture, PC-SPES, which is purported to bolster the immune system of men with prostate cancer, has significant estrogenic activity.[12] Use of this agent has been associated with estrogen related side effects, such as venous thrombosis, and may be inappropriate for patients receiving other hormonal agents or confound followup for those with prostate cancer by altering prostate specific antigen (PSA) levels. There are likely many other known and unknown potentially adverse interactions between nonprescription "dietary supplements" and conventional medicines.[13,14]

Herbal remedies have become particularly popular for men with lower urinary tract symptoms since the primary goal of treatment in most with benign prostatic hyperplasia (BPH) is a subjective decrease in voiding symptoms.[9,15,16] The frequently observed significant decrease in symptom scores and increase in urinary flow rates in men receiving placebo,[17] as well as the unpredictable natural history of BPH,[18] have led some to suggest that "maybe a placebo for BPH is not so terrible."[19] Although this view may be true, there is general support for continued evaluation of the many herbal agents that have been advertised to "promote prostate health."[9,15,20] The most popular agent is saw palmetto (Serenoa repens), which is derived from the berry of the American dwarf palm tree (see figure).[9] This plant is also known by its botanical name, Sabal serrulata, and found in many areas of the southeastern United States.[21] Although reports on the use of saw palmetto to treat a variety of prostatic conditions date to the 1800s, many misconceptions and unknown factors remain regarding its use in men with BPH.

FORMULATIONS AND PROPOSED MECHANISMS OF ACTION

A difficulty in assessing the use of herbal preparations is the lack of standardization of these products. Since they are generally categorized as food additives by the Food and Drug Administration there is little or no oversight of their production and distribution in the United States. The absence of

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Saw palmetto extract is derived from American dwarf palm tree, Serenoa repens, which is found in Florida and other areas of southeastern United States.

regulatory control is likely to lead to marked differences in purity and content among herbal products.[11,22] Therefore, results achieved with 1 form of saw palmetto cannot be reliably extrapolated to other products from different manufacturers.

The most widely studied form of saw palmetto is Permixon.†[23] In Europe herbal agents are more widely accepted by patients and physicians than in the United States. In France, Germany and Austria phytotherapeutic compounds are among the most frequently prescribed agents for the majority of men with lower urinary tract symptoms.[4,16,24] Permixon, which is not presently available in the United States, is a hexane extract of the American dwarf palm tree consisting of free (90%) and esterified (7%) fatty acids as well as small amounts of sterols, polyprenic compounds, flavonoids and other substances.[16,25] Most of the basic research concerning the proposed mechanisms of action of saw palmetto has been performed using Permixon.

Although many potential mechanisms by which saw palmetto may relieve urinary symptoms in men with BPH have been suggested and studied (see Appendix), the most widely held belief is that this herbal product is a naturally occurring 5-α reductase inhibitor.[23,26] The human prostate contains types I and II of this enzyme, which catalyze the conversion of testosterone to dihydrotestosterone.[27,28] Since dihydrotestosterone has an important role in the development of BPH, the use of 5-α reductase inhibitors, such as finasteride, have been demonstrated to lead to shrinkage of the prostate with relief of urinary symptoms in many patients.[29] Finasteride is a selective, competitive inhibitor of type II 5-α reductase, which has long been considered to be the most important isozyme in the prostate.[28,30] The type I isozyme predominates in the liver and skin,[31] and has been more recently noted in prostatic tissue.[32,33] Finasteride inhibits type I activity to only a minor degree and this isozyme may contribute to ongoing prostatic dihydrotestosterone production in patients treated with this drug.[28] The function and relative importance of type I 5-α reductase in the prostate remain largely unknown at this time.

In vitro studies have shown that saw palmetto is a noncompetitive inhibitor of type I 5-α reductase and uncompetitively inhibits the type II isozyme.[26,34] Since 5-α reductase is a nuclear membrane associated enzyme and fatty acids are an important component of such membranes, it has been suggested that saw palmetto acts at least partly due to modulatory effects by its lipid component on the enzyme environment.[26,35] Although these studies have convincingly demonstrated 5-α reductase inhibition by saw palmetto, the clinical relevance of these effects remains far less clear. A decrease in serum dihydrotestosterone was noted only in men treated with finasteride in a study of healthy volunteers 20 to 30 years old randomized to receive finasteride, Permixon or placebo for 1 week.[36] Similarly, finasteride but not Permixon inhibited prostate growth in castrate rats stimulated with testosterone or dihydrotestosterone.[30] Conversely, a statistically significant reduction in dihydrotestosterone in periurethral prostatic tissue was reported in men treated with Permixon for 3 months compared to controls.[37] Saw palmetto had minimal effects on prostate volume and no effect on serum PSA in clinical studies of men with BPH treated for 6 months.[20,25] Overall, in vitro 5-α reductase inhibition reported in several studies may be partly attributed in some to the use of supraphysiological doses of saw palmetto. To date convincing evidence to suggest that saw palmetto has significant, clinically relevant effects as a 5-α reductase inhibitor is still largely lacking.

The second most widely accepted mechanism of action by which saw palmetto has been suggested to improve voiding symptoms in men with BPH is through inhibition of dihydrotestosterone binding to the cytosolic androgen receptor in prostatic cells.[23,38,39] Dihydrotestosterone binding has important effects on gene transcription and regulation of specific biological responses.[23] In vitro studies have demonstrated that Permixon leads to competitive inhibition of radiolabeled dihydrotestosterone binding to the androgen receptor in human foreskin fibroblasts and rat cytosolic receptors.[23,38,39] In studies using the prostatic cell line LNCaP, which is responsive to androgenic stimulation, concentrations greater than 25 mg./l. Permixon had an antiproliferative effect.[40] These effects may be mediated by androgen receptor mutations in the LNCaP cells.[23] No antiproliferative effect was seen in similar experiments on androgen independent PC3 cells.[40] However, when PC3 cells were cotransfected with wild type androgen receptors, Permixon inhibited androgen induced transcription, suggesting antiandrogenic action.[23,40] As noted with 5-α reductase effects seen with saw palmetto, the clinical relevance of androgen receptor binding inhibition in relieving voiding symptoms remains unproved.

A variety of other proposed mechanisms of action of saw palmetto have also been evaluated.[23,41–46] Although androgens have a primary role in the development of BPH, there is evidence suggesting that androgen dependent epithelial growth in the prostate is stimulated at least partly by estrogen dependent stromal proliferation.[43,47] Saw palmetto was able to inhibit the nuclear estrogen receptors in prostatic tissue samples from patients receiving placebo or the herbal agent for 3 months before open prostatectomy.[43] Saw palmetto has also been demonstrated to have anti-inflammatory effects in the prostate through inhibition of arachidonic acid metabolites and reactive oxygenated species produced by

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neutrophils.[23,46] Other effects of saw palmetto in vitro include inhibition of fibroblast growth factor induced prostatic epithelial proliferation and modulation of prolactin induced prostatic growth by receptor signal transduction.[44,45] In a recently reported study saw palmetto extracts were demonstrated to have α-adrenergic inhibitory properties mediated by noncompetitive antagonism.[48] Finally, antiedematous effects of saw palmetto on prostatic tissues in animal models have also been reported.[23] It is not evident which if any of these proposed mechanisms is responsible for improvement in voiding symptoms in men with BPH treated with saw palmetto. However, most patients are satisfied with a decrease in urinary symptoms even if it is not completely clear how or why this improvement has occurred.

NONPLACEBO CONTROLLED CLINICAL TRIALS

Although the efficacy of saw palmetto can only be determined reliably through placebo controlled studies, clinically relevant information can be gained from comparative and observational trials. Saw palmetto has been tested against finasteride[25,49] and a variety of α-blockers[50,51] in men with lower urinary tract symptoms in randomized trials without a placebo arm. In the largest study of saw palmetto reported to date 1,098 men at 87 centers in Europe were randomized to receive finasteride or Permixon for 6 months.[25] All patients had a minimum International Prostate Symptom Score of 6 or greater, peak urinary flow rate 4 to 15 ml. per second and prostate volume greater than 25 ml. Both groups had virtually identical improvement in symptom score (37% to 39% decrease) and there was a slightly greater increase in peak flow rate in those treated with finasteride (3.2 versus 2.7 ml. per second in the Permixon group). Saw palmetto was well tolerated with no significant side effects. In addition, men receiving Permixon reported significantly less sexual dysfunction than those treated with finasteride. Despite comparable clinical efficacy in relieving voiding symptoms, men receiving Permixon had only a 6% decrease in prostate volume compared to 18% among finasteride treated patients. Serum PSA decreased by a mean of 41% in those receiving finasteride, while there was essentially no change in men treated with Permixon. Although improvements in symptom scores in this study did not appear to be related to pretreatment prostatic volume,[52] these results strongly suggest that saw palmetto does not have significant 5-α reductase inhibiting activity compared to finasteride. However, the most important result is the demonstrated equivalent efficacy of saw palmetto and finasteride in men with lower urinary tract symptoms.

Superior results were achieved in men receiving adrenergic antagonists in 2 trials comparing the efficacy of saw palmetto and α-blockers.[50,51] Semino et al treated 45 men with prazosin or saw palmetto for 12 weeks and, although standardized symptom scores were not used, the former was slightly more effective in relieving irritative symptoms.[49] In a study of 63 men randomized to receive alfuzosin or saw palmetto for only 3 weeks those treated with the α-blocker had superior improvement in symptom scores and urinary flow rates.[50] The small numbers of patients as well as brief duration of treatment in these trials make it difficult to assess adequately the relative efficacy of α-blockers and saw palmetto in relieving voiding symptoms. Treatment with saw palmetto for 3 months was considered effective by 88% of physicians and patients in an observational study of 505 men with mild to moderate lower urinary tract symptoms.[53] Side effects were reported by 5% of patients and primarily limited to minor gastrointestinal symptoms. Finally, urodynamic effects were studied in 50 patients who received saw palmetto for 6 months.[20] Although an improvement in the International Prostate Symptom Score of 50% or more was noted in 46% of cases, there was no significant change in peak flow rate, residual urine volume or detrusor pressure. These uncontrolled trials suggest that saw palmetto is well tolerated and leads to subjective improvement in many patients with lower urinary tract symptoms. However, no satisfactory information to suggest that improvements are due to anything more than a placebo effect can be gained from these studies.

PLACEBO CONTROLLED TRIALS

Although a number of placebo controlled studies have been published on the effects of saw palmetto in men with lower urinary tract symptoms, most are significantly flawed due to a variety of factors.[54–62] Limitations include treatment intervals of only 1 to 3 months, small numbers of patients and failure to use standardized testing instruments, such as symptom scores (see table). Since many trials were performed before the introduction of standardized symptom questionnaires, subjective treatment responses in regard to frequency, nocturia, dysuria and other symptoms were variably assessed, making comparisons among studies difficult.[15]

Two meta-analyses of the results of treatment with saw palmetto in men with BPH have been presented.[4,63] Lowe et al analyzed the results of 11 randomized trials (8 placebo controlled, 3 versus finasteride or α-blockers) and 2 large, open label studies of patients treated with Permixon.[63] These 13 studies represented all of the available clinical trial data concerning Permixon at the time, for a total of 2,859 men. The authors found little information common to all of the studies, although data on peak flow rates and nocturia were available for 11. The results suggested that Permixon increases peak urinary flow by an estimated 1.87 ml. per second more than placebo. The reduction in nocturia compared to placebo was 0.55 voiding episode a night. Both of these changes were highly statistically significant ($p < 0.001$).

The second meta-analysis was performed using the results of 18 randomized, controlled trials (2,939 patients), including several in which men receiving saw palmetto were compared to those treated with other pharmacological agents.[4] In addition, 3 of the trials assessed results achieved with saw palmetto combined with other phytotherapeutic agents and 1 bioequivalence study with no control arm was included in the meta-analysis. Mean duration of the 18 studies was only 9 weeks (range 4 to 48). Since standardized symptom scores were used in only 3 studies, subjective voiding changes were assessed by patient self-rating and/or changes in nocturia

Results of placebo controlled trials of saw palmetto in men with lower urinary tract symptoms[23]

References	No. Pts. Randomized	Study Duration (mos.)	Significant Improvement in Symptoms vs. Placebo	Peak Flow Rate (cc/sec.)		
				Before Saw Palmetto	After Saw Palmetto	p Value
Descotes et al[54]	176	1	Yes	11.7	15.1	<0.05
Cukier et al[61]	146	2–3	Yes	Not available		
Champault et al[56]	88	1	Yes	5.4	8.1	<0.001
Boccafoschi and Annoscia[58]	22	2	Yes	9.6	13.7	<0.05
Reece Smith et al[55]	70	3	No	6.1 (estimated)	8.2	Not significant
Tasca et al[60]	27	2	No	12.9	16.3	Not significant
Emili et al[62]	30	1	No	10.3	13.7	Not significant

alone in most. Therefore, none of the 18 studies met the generally accepted criteria for assessing treatment results in men with lower urinary tract symptoms.[64] Despite these limitations, the authors reported that saw palmetto significantly relieved voiding symptoms and improved peak urine flow by 1.93 ml. per second compared to placebo.

Although meta-analysis represents an important statistical method which may be helpful in summarizing the results of different research studies of related problems, several difficulties may limit the reliability of results.[65–67] The primary literature on which the meta-analysis is based must be of good quality.[67] Quantitative findings of interest must be expressed on a common scale.[65] Reviews of meta-analyses by independent experts have frequently demonstrated a variety of major problems in implementation of the technique leading to the presentation of misleading results.[66,68] Bailar has stated that "any attempt to reduce the results [of a meta-analysis] to a single value, with confidence bounds, is likely to lead to conclusions that are wrong, perhaps seriously so."[65] Finally, in a comparison of the findings of large randomized, controlled trials and results of meta-analyses published earlier on the same topics, outcomes of 35% of trials were not predicted accurately by the preceding meta-analysis.[67] However, despite these limitations, there is evidence to suggest that saw palmetto is associated with improvements in flow rates and symptoms in men with lower urinary tract symptoms compared to controls. Further support for the use of saw palmetto awaits the results of large scale, placebo controlled trials.[69]

CONCLUSIONS

Saw palmetto extracts remain the most popular medicinal botanical used by men to treat voiding symptoms secondary to BPH. A variety of in vitro studies have demonstrated multiple potential mechanisms of action of saw palmetto, including 5-α reductase inhibition, adrenergic receptor blockade and inhibition of dihydrotestosterone binding to the cytosolic androgen receptor. However, evidence that these effects are seen in vivo to a clinically relevant degree has not been presented to my knowledge. Large clinical trials of men with BPH have demonstrated the safety of saw palmetto, which is associated with no significant adverse effects and no alteration of serum PSA. Although a number of placebo controlled trials have shown significant improvements in symptoms and flow rates, they generally have included small numbers of patients and been of short duration. The findings of meta-analyses regarding the results achieved with saw palmetto have also suggested the benefits of this agent. However, multiple methodological difficulties make it difficult to accept the reliability of these conclusions. Until data from large scale, placebo controlled studies are presented questions will remain regarding the efficacy of saw palmetto in men with lower urinary tract symptoms.

Photograph provided by Linda Schurman.

APPENDIX: PROPOSED MECHANISMS OF ACTION OF SAW PALMETTO IN MEN WITH LOWER URINARY TRACT SYMPTOMS

Inhibition of 5-α reductase
Inhibition of dihydrotestosterone binding to the cytosolic androgen receptor
α-Adrenergic receptor blockade
Inhibition of the nuclear estrogen receptors in prostatic tissue (anti-estrogenic effects)
Anti-inflammatory effects within the prostate
Decreased prostatic edema
Inhibition of fibroblast growth factor induced prostatic epithelial proliferation
Modulation of prolactin induced prostatic growth by receptor signal transduction

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