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Saw Palmetto and Benign Prostatic Hyperplasia

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Abstract: Benign prostatic hyperplasia (BPH) is a common health issue that affects 8% of all men at the age of 40, 60% of men in their 70s, and 90% of those greater than 80 years of age. One-fourth of these men will develop moderate to severe lower urinary tract symptoms that greatly affect their quality of life. Recent evidence suggests that the use of saw palmetto leads to improvements in urinary function for those suffering from BPH. The favorable comparison of saw palmetto with tamsulosin, a well-known first line agent in the treatment of urinary tract symptoms, demonstrates promise towards a beneficial effect of this herbal agent, with very few, if any, adverse effects. However, what degree of this beneficial activity is due to placebo effects is yet to be determined. In addition, the precise mechanism of action of saw palmetto in men with BPH remains unclear.

Keywords: Benign Prostatic Hyperplasia (BPH); Lower Urinary Tract Symptoms; Saw Palmetto; *Serenoa repens*; Tamsulosin; Placebo Effect.

Introduction

Benign prostatic hyperplasia (BPH) is a common health problem in men. Though rarely a cause of mortality, it presents a considerable source of morbidity to aging men through its associated symptoms and complications (La Vecchia *et al*., 1995). Hyperplasia of the prostate is extremely common, with a rapidly increasing prevalence with advancing age starting in the fourth decade of life (Barry, 1990). Hyperplasia is seen in 8% of men at the age of 40, 60% of men in the 70s, and 90% in those greater than 80 years of age (Barry, 1990). A quarter of these men will develop moderate to severe lower urinary tract symptoms (LUTS) that patients describe as greatly affecting their quality of life. As shown in community-based studies, BPH has a severe negative impact on the health-related quality of life of men affected

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by the disease (Girman *et al*., 1999). The clinical effects of BPH are varied; bladder outlet obstruction can lead to recurrent urinary tract infections, bladder calculi, hematuria, and even end stage renal disease. However, the primary manifestation of BPH is LUTS generally classified as irritative (urgency, frequency, nocturia) or obstructive (straining, hesitancy, dribbling, retention). The patient's dissatisfaction with such urinary symptoms has generally been agreed upon as the predominant factor in the choice of therapy.

Despite the efforts of the medical community to relieve symptoms of BPH, many patients are not satisfied with the results of conventional therapy. There is growing evidence from clinical trials that phytotherapeutic agents may lead to subjective and objective symptom improvement beyond a placebo effect. Among them, saw palmetto is the most commonly used herb for the treatment of BPH. This article reviews the effects of saw palmetto on BPH.

Saw Palmetto

Saw palmetto (*Serenoa repens*) is the most popular herbal therapy used in the treatment of LUTS in men with BPH (Lowe and Ku, 1996). Historically, Native Americans have used the berry of the American dwarf palm tree indigenous to the southeastern United States in botanical medicines for disorders of the urinary tract. The active components are thought to be a combination of free fatty acids, phytosterols and other compounds extracted from the saw palmetto berry. Permixon is the most widely used and most extensively investigated form of saw palmetto, however it is only available in Europe and not in the US (Carraro *et al*., 1996). Thus, the outcomes of these studies may have little bearing on the treatment effect to be expected by American consumers using other saw palmetto products.

Effects and Possible Mechanisms of Action

A variety of mechanisms for the action of saw palmetto have been proposed (Goepel *et al*., 1999; Di Silverio *et al*., 1992). However, it is most commonly accepted that saw palmetto acts as an inhibitor of 5-alpha reductase, the enzyme responsible for the conversion of testosterone (T) to its more potent form in the prostate, dihydrotestosterone (DHT) (Delos *et al*., 1994; Bayne *et al*., 1997). A number of *in vitro* studies have been performed using Permixon with human tissue such as skin fibroblasts, primary cultures of BPH cells, and other models which have demonstrated a decrease in DHT levels, thought to be due to inhibition of 5-alpha reductase types 1 and 2 activity (Delos *et al*., 1994; Bayne *et al*., 1997; Sultan *et al*., 1984; Carilla *et al*., 1984).

Several small studies demonstrate *in vivo* activity of saw palmetto on human subjects. In one study, 25 patients selected for open prostatectomy for the treatment of BPH were randomized to either no treatment or 3 months treatment with Permixon (Di Silverio *et al*., 1998). After surgical resection, testosterone, DHT and growth factor levels were measured on the prostate specimen. The periurethral prostatic tissue was found to have the highest levels of all three measured factors while the subcapsular zone of the prostate had the lowest levels. DHT and growth factor levels were significantly decreased throughout the prostate in men receiving Permixon and testosterone levels were elevated, suggesting a 5-alpha

reductase effect of saw palmetto. The effect of saw palmetto on prostatic androgens and growth factors was similar to a previous study by the same group utilizing finasteride, an established 5-alpha reductase inhibitor (Di Silverio *et al*., 1998). Although a small study, it appeared that Permixon leads to important changes in prostatic androgen levels primarily within the tissue adjacent to the urethra.

In another small study, Marks *et al*. (2001) found a decrease in prostatic DHT levels on prostate biopsy specimens in 44 men after the administration of saw palmetto. After a baseline prostate biopsy, 44 men were randomized to receive saw palmetto or placebo for 6 months. A repeat biopsy was then performed and prostatic testosterone, DHT and epithelial tissue measurements were made. A significant 32% decrease in prostatic DHT levels and a 40% decrease in prostate epithelial tissue were found. In comparison, patients receiving finasteride had an 80% decrease in prostatic DHT and a 50% decrease in epithelial tissue (Marks *et al*., 2001). Interestingly, the finasteride treatment group also demonstrated decreases in serum DHT, serum PSA, and prostate volume, whereas the saw palmetto group showed no change in serum DHT, PSA, or prostatic volume.

Significant 5-alpha reductase activity with saw palmetto has not been demonstrated in other studies (Rhodes *et al*., 1993; Strauch *et al*., 1994). In one study, finasteride, but not Permixon, inhibited prostatic growth in rats stimulated with testosterone and DHT (Rhodes *et al*., 1993). Strauch *et al*. (1994) demonstrated among 32 male volunteers without BPH that treatment with finasteride for 7 days led to a decrease in serum DHT levels but no change was seen with Permixon. Significant changes in serum DHT levels among men treated with Permixon have also not been demonstrated by other investigators (Lowe and Fagelman, 1999).

Despite the fact that saw palmetto has been shown to have *in vivo* 5-alpha reductase activity, several human trials call into question the clinical relevance of this activity (Carraro *et al*., 1996; Gerber *et al*., 1998; Braeckman, 1994). Though saw palmetto may decrease intra-prostatic levels of DHT, does this necessarily translate into the same clinical effect as finasteride? Finasteride will lead to an approximate 50% decrease in serum PSA levels, an effect that does not occur with saw palmetto (Carraro *et al*., 1996; Gerber *et al*., 1998; Braeckman, 1994). Also, while finasteride will lead to a 20%–30% reduction in prostate size when administered for 6–12 months, minimal or no reduction in prostate size has been shown in large clinical trials using saw palmetto (Carraro *et al*., 1996; Gerber *et al*., 1998; Braeckman, 1994).

A mechanism to support the discrepancy between conventional 5-alpha reductase inhibitors and Permixon has been proposed by Bayne *et al*. (2000). Using tissue cultures of human prostate, epididymis, testis, kidney, skin and breast, the lipidosterolic extract of saw palmetto has been shown to be specific to the lipid environment of the prostatic nuclear membrane. Disruption of this membrane by Permixon could lead to an indirect inhibition of the membrane bound 5-α reductase. Marks *et al*. (2000) presented histologic evidence in a study of 44 men who underwent biopsy evaluation of the prostate before and after treatment with saw palmetto for 6 months. Significant increases in prostatic epithelial contraction and in the percentage of atrophic glands among those receiving saw palmetto was found compared to those treated with the placebo. These saw palmetto-induced histologic changes in the prostate may begin to explain symptomatic improvement in men with BPH.

Clinical Relevance

Though used clinically to treat BPH since the late 1800s, it was not until the 1980s that the first clinical trials testing the efficacy of palmetto in men were published. These studies were often limited by the inclusion of a small numbers of patients and brief treatment intervals of one to three months (Champault *et al*., 1984; Cukier *et al*., 1985; Descotes *et al*., 1995; Emile *et al*., 1983; Reece Smith *et al*., 1986). Champault *et al*., in a study of 110 men, found that the use of saw palmetto subjectively improved symptoms of nocturia and dysuria in men with BPH (Champault *et al*., 1984). However, at the time of this study, validated questionnaires such as the International Prostate Symptoms Score (I-PSS) were not yet developed. Also, the duration of the effect of saw palmetto could not be established, as follow-up was for only 1 month. Several years later, Smith *et al*. in a double-blind trial, reported an equal improvement of subjective and objective measures among patients with BPH treated with Permixon and placebo (Reece Smith *et al*., 1986). Due to conflicting findings, the limitations of small patient numbers, and brief treatment intervals, skepticism regarding the efficacy of saw palmetto for the treatment of BPH remained.

With the increasing interest in alternative therapies over the past decade, following a latent period in the study of saw palmetto, several large-scale clinical trials were performed to determine the efficacy of this herbal remedy (Carraro *et al*., 1996; Gerber *et al*., 1998; Braeckman, 1994; Wilt *et al*., 1998). Braeckman *et al.* in a non-randomized study of 505 men with mild to moderate voiding symptoms, demonstrated an improvement in I-PSS to 12.4 from a baseline of 19.0 after treatment with saw palmetto for 3 months (Braeckman, 1994). In addition, an increase from 9.8 ml/sec to 12.2 ml/sec in the mean peak urinary flow rate and a small, but statistically significant, decrease in prostate volume of 9.2% was seen in the same group of men. Ultimately, 88% of patients and physicians were satisfied with the results of saw palmetto in this study. However, due to the lack of placebo controls, it is difficult to draw conclusions regarding the true effectiveness of saw palmetto from this study alone.

In a more recent double-blind, placebo-controlled study by Gerber *et al.* (2001), 85 men with LUTS were randomized to receive either placebo or saw palmetto. Baseline I-PSS, sexual function and urinary flow rates were obtained. After a treatment period of 6 months, follow-up data showed an improvement in symptom score without worsening of sexual function, but no change in urinary flow rate. In a previous study, Gerber *et al.* (1998) have shown no improvement in any urodynamic parameter, including peak flow rate, detrusor pressure, or post-void residual in men treated with saw palmetto. In contrast, Willets *et al.* (2002) recently published a study showing no significant difference between treatment with saw palmetto or placebo. In a similar study design, 100 men with LUTS were randomized to receive either saw palmetto or placebo and at 4-month follow-up, no significant beneficial effect of saw palmetto was found with regards to IPSS or peak urinary flow rate. However, the initial I-PSS was significantly less in the Permixon group. It has been established that the magnitude of improvement in I-PSS is directly related to initial severity of symptoms (Debruyne *et al*., 2002), possibly explaining the lack of difference in symptom score improvement in this study.

In a meta-analysis of 2939 men, Wilt *et al*. (1998) evaluated the combined results of patients treated with saw palmetto. This study included results from 18 trials and the authors concluded that men treated with saw palmetto had an overall improvement of 1.9 ml/sec in mean peak urinary flow rate and a mean decrease of 1.4 points in symptom score as compared with controls. Despite the large number of patients included in this meta-analysis, the findings of this study are limited due to the short 9-week mean duration of the 18 studies used. In addition, several of the trials did not include a placebo group or involved the use of saw palmetto in combination with other herbal agents. Boyle *et al*. (2000) more recently published another meta-analysis of 2859 patients. The common end-points examined were peak flow rate and nocturia, as most of the studies included did not utilize a symptom score. The improvement in flow rate (2.2 mL/s) and nocturia (0.5 episodes) were both significant, however slight, lending to the evidence of the efficacy of saw palmetto as compared with the placebo.

One of the largest single studies of saw palmetto is a European multi-center trial of 1098 men randomized to receive either Permixon or finasteride for 6 months (Carraro *et al*., 1996). Statistically significant improvements from baseline in symptom score and peak urinary flow rate were seen in both groups, although the flow rate increase was slightly greater among men treated with finasteride. While side effects in both groups were low, patients receiving Permixon did have a lower incidence of sexual dysfunction than those treated with finasteride. Prostate size, as measured by transrectal ultrasound, decreased by 18% in patients treated with finasteride compared to 6% in the Permixon treatment group. In addition, there was a decrease of 41% in serum PSA levels seen with finasteride, but essentially no change in this serum cancer marker was associated with Permixon. Despite the lack of clinically evident 5-alpha reductase activity in men administered Permixon, as demonstrated by the lack of change in serum PSA and prostate volume, IPSS and quality of life scores improved by 39% and 41% respectively in this treatment group compared to 37% and 38% with finasteride. However, in the large American VA Cooperative Trial, finasteride was found to be no more effective than placebo (Lepor *et al*., 1996). Thus, without a control group in the European study, it is possible that the improvement of symptom scores and quality of life with Permixon and finasteride may be primarily due to a placebo effect.

In another large study, Debruyne *et al*. (2002) published a double-blind, prospective trial including 1111 men with symptomatic BPH. Patients from 11 European countries were randomized to treatment with Permixon or tamsulosin and follow-up was obtained at 1 year. After a year of treatment, the I-PSS decreased significantly without a difference between the two groups. Both groups showed a similar increase in peak flow rates, but only the Permixon group showed a decrease in prostate volume (0.99cc versus a 0.22cc increase in the tamsulosin group). Though no statistically significant difference in sexual function score existed between the two groups, ejaculation disorders were significantly less frequent in those treated with Permixon. Without a control group, this study cannot prove the individual efficacy of either Permixon or tamsulosin, but does demonstrate equivalence between the two products.

Summary

Recent evidence suggests that the use of saw palmetto leads to subjective and objective improvement in urinary function. The favorable comparison of saw palmetto with tamsulosin, a well-known first line agent in the treatment of LUTS, demonstrates promise towards a beneficial effect of this herbal agent. Yet, what degree of this is due to placebo effect is yet to be determined. However, very few, if any, adverse effects have been noted with saw palmetto, especially in regards to sexual function. In addition, saw palmetto has been well documented to have no effect on serum PSA levels and histologic studies have revealed its ability to cause changes within prostatic tissue. As discussed in this article, the precise mechanism of action of saw palmetto in men with BPH remains unclear. At present, men considering the use of saw palmetto can be told that it is safe, will not mask the detection of prostate cancer, and may lead to a mild to moderate improvement in symptoms.

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