

# **A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the treatment of androgenetic alopecia.**

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**BACKGROUND:** Androgenetic alopecia (AGA) is characterized by the structural miniaturization of androgen-sensitive hair follicles in susceptible individuals and is anatomically defined within a given pattern of the scalp. Biochemically, one contributing factor of this disorder is the conversion of testosterone (T) to dihydrotestosterone (DHT) via the enzyme 5-alpha reductase (5AR). This metabolism is also key to the onset and progression of benign prostatic hyperplasia (BPH). Furthermore, AGA has also been shown to be responsive to drugs and agents used to treat BPH. Of note, certain botanical compounds have previously demonstrated efficacy against BPH. Here, we report the first example of a placebo-controlled, double-blind study undertaken in order to examine the benefit of these botanical substances in the treatment of AGA. **OBJECTIVES:** The goal of this study was to test botanically derived 5AR inhibitors, specifically the liposterolic extract of *Serenoa repens* (LSEsr) and beta-sitosterol, in the treatment of AGA. **Subjects:** Included in this study were males between the ages of 23 and 64 years of age, in good health, with mild to moderate AGA. **RESULTS:** The results of this pilot study showed a highly positive response to treatment. The blinded investigative staff assessment report showed that 60% of (6/10) study subjects dosed with the active study formulation were rated as improved at the final visit. **CONCLUSIONS:** This study establishes the effectiveness of naturally occurring 5AR inhibitors against AGA for the first time, and justifies the expansion to larger trials.

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**Tissue effects of saw palmetto and finasteride: use of biopsy cores for in situ quantification of prostatic androgens.**

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**OBJECTIVES:** To determine the effects of a saw palmetto herbal blend (SPHB) compared with finasteride on prostatic tissue androgen levels and to evaluate needle biopsies as a source of tissue for such determinations. **METHODS:** Prostate levels of testosterone and dihydrotestosterone (DHT) were measured on 5 to 10-mg biopsy specimens (18-gauge needle cores) in three groups of men with symptomatic benign prostatic hyperplasia: 15 men receiving chronic finasteride therapy versus 7 untreated controls; 4 men undergoing prostate adenectomy to determine sampling variability (10 specimens each); and 40 men participating in a 6-month randomized trial of SPHB versus placebo, before and after treatment. **RESULTS:** Prostatic tissue DHT levels were found to be several times higher than the levels of testosterone (5.01 versus 1.51 ng/g), that ratio becoming reversed (1.05 versus 3.63 ng/g) with chronic finasteride therapy. The finasteride effect was statistically significant for both androgens ( $P < 0.01$ ), and little overlap of individual values between finasteride-treated and control patients was seen. In the randomized trial, tissue DHT levels were reduced by 32% from 6.49 to 4.40 ng/g in the SPHB group ( $P < 0.005$ ), with no significant change in the placebo group. **CONCLUSIONS:** For control versus finasteride-treated men, the tissue androgen values obtained with needle biopsy specimens were similar—both for absolute values and the percentage of change—to those previously reported using surgically excised volumes of prostatic tissue. The quantification of prostatic androgens by assay of needle biopsies is thus feasible and offers the possibility of serial studies in individual patients. The SPHB-induced suppression of prostatic DHT levels, modest but significant in a randomized trial, lends an element of support to the hypothesis that inhibition of the enzyme 5-alpha reductase is a mechanism of action of this substance.

## **Serenoa repens (Permixon) inhibits the 5alpha-reductase activity of human prostate cancer cell lines without interfering with PSA expression.**

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The phytotherapeutic agent *Serenoa repens* is an effective dual inhibitor of 5alpha-reductase isoenzyme activity in the prostate. Unlike other 5alpha-reductase inhibitors, *Serenoa repens* induces its effects without interfering with the cellular capacity to secrete PSA. Here, we focussed on the possible pathways that might differentiate the action of Permixon from that of synthetic 5alpha-reductase inhibitors. We demonstrate that *Serenoa repens*, unlike other 5alpha-reductase inhibitors, does

not inhibit binding between activated AR and the steroid receptor-binding consensus in the promoter region of the PSA gene. This was shown by a combination of techniques: assessment of the effect of Permixon on androgen action in the LNCaP prostate cancer cell line revealed no suppression of AR and maintenance of PSA protein expression at control levels. This was consistent with reporter gene experiments showing that Permixon failed to interfere with AR-mediated transcriptional activation of PSA and that both testosterone and DHT were equally effective at maintaining this activity. Our results demonstrate that despite *Serenoa repens* effective inhibition of 5 $\alpha$ -reductase activity in the prostate, it did not suppress PSA secretion. Therefore, we confirm the therapeutic advantage of *Serenoa repens* over other 5 $\alpha$ -reductase inhibitors as treatment with the phytotherapeutic agent will permit the continuous use of PSA measurements as a useful biomarker for prostate cancer screening and for evaluating tumour progression. (c) 2004 Wiley-Liss, Inc.  
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## **Saw Palmetto induces growth arrest and apoptosis of androgen-dependent prostate cancer LNCaP cells via inactivation of STAT 3 and androgen receptor signaling.**

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PC-SPEs is an eight-herb mixture that has an activity against prostate cancer.

Recently, we purified Saw Palmetto (*Serenoa repens*) from PC-SPEs and found that Saw Palmetto induced growth arrest of prostate cancer LNCaP, DU145, and PC3 cells with ED50s of approximately 2.0, 2.6, and 3.3  $\mu$ mol/ml, respectively, as measured by mitochondrial-dependent conversion of the the 3-(4, 5-dimethylthiazol-

2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. Saw Palmetto induced apoptosis of LNCaP cells in a time- and dose-dependent manner as measured by TUNEL assays. Also, Saw Palmetto increased the expression of p21waf1 and p53 protein in LNCaP cells. In addition, we found that Saw Palmetto down-regulated DHT- or IL-6-induced expression of prostate specific antigen in conjunction with down-regulation of the level of androgen receptor in the nucleus as measured by Western blot analysis. Moreover, Saw Palmetto down-regulated the IL-6-induced level of the phosphorylated form of STAT 3 in LNCaP cells. Furthermore, Saw Palmetto inhibited the growth of LNCaP cells present as tumor xenografts in BALB/c nude mice without adverse effect. These results indicate that Saw Palmetto might be useful for the treatment of individuals with prostate cancer.

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INTRODUCTION: Increasing attention has been focused on the use of phytotherapeutic agents to alleviate the symptoms of benign prostatic hyperplasia (BPH) in recent times. The best described and studied phytotherapeutic agent is Serenoa repens (SR). MATERIALS AND METHODS: This prospective study was designed to have 3 arms including SR 320 mg per day (N = 20), Tamsulosin (TAM) 0.4 mg per day (N = 20) and SR + TAM (N = 20) to reveal the superiority or equivalence between these treatment regimens in BPH. RESULTS: The groups were not statistically different with regard to increase in maximal urinary flow rate (Q (max)) and decrease in International Prostate Symptom Score (I-PSS) (P > 0.05). No adverse effect was detected in SR therapy group. CONCLUSION: Treatment of BPH by both SR and TAM seems to be effective alone. None of them had superiority to another and additionally, combined therapy (SR + TAM) does not provide extra benefits. Furthermore SR is a well-tolerated agent that can be used alternatively in the treatment of LUTS due to BPH.

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**BACKGROUND:** Several of the proposed mechanisms for the actions of the liposterolic extract of saw palmetto (SPE) are exerted on known risk factors for prostate cancer (CaP). This study investigated whether SPE could prevent the progression of CaP in a transgenic adenocarcinoma of the mouse prostate (TRAMP) model. **METHODS:** Two different doses of SPE designed to deliver 50 mg/kg/day SPE and 300 mg/kg/day SPE were administered in a custom diet to TRAMP mice for 12 or 24 weeks. Body and organ weights were used to evaluate toxicity, and radioimmunoassay was used to measure plasma and tissue androgen levels to monitor effects of SPE on 5 $\alpha$  reductase activity. Prostate tissues were evaluated histologically to determine the effect of treatment on tumor grade, cell proliferation, and apoptosis. **RESULTS:** Treatment with 300 mg/kg/day SPE from 4 to 24 weeks of age significantly reduced the concentration of 5 $\alpha$ -dihydrotestosterone (DHT) in the prostate and resulted in a significant increase in apoptosis and significant decrease in pathological tumor grade and frank tumor incidence. **CONCLUSIONS:** Dietary supplementation with SPE may be effective in controlling CaP tumorigenesis. SPE suppression of prostatic DHT levels lends support to the hypothesis that inhibition of the enzyme 5 $\alpha$ -reductase is a mechanism of action of this substance. (c) 2007 Wiley-Liss, Inc.

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**BACKGROUND:** Phytotherapy is a third approach for treating lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH). The lipido-sterolic extract of the fruit of *Serenoa repens* is one of the more widely used phytotherapeutic agents in this regard. **MATERIALS AND METHODS:** The effect of an ethanolic extract of *S. repens* (10-1000 microg/ml) was tested in hormone-sensitive LNCaP, MCF-7 and hormone-insensitive DU 145, MDA MB231 prostate, breast carcinoma cell lines, renal Caki-1, urinary bladder J82, colon HCT 116 and lung A 549 cancer cells. Its cell growth inhibitory and apoptosis-inducing effects were tested using WST-1 assay and flow cytometry (Annexin V/PI stain) and/or by colorimetric assay (APOPercentage assay). **RESULTS:** The *S. repens* extract induced a dose-dependent antiproliferative effect on all human malignant cells tested, with GI50 values between 107 and 327 pmicro/ml. In hormone-sensitive prostate LNCaP and breast MCF-7 cell lines, the effect of extract expressed in GI50 was 2.2- and 2.5-fold more potent ( $p < 0.01$ ) than in hormone-insensitive DU 145 and MDA MB231 cells. The proportion of apoptotic cells, except in A549 cells, lay between 22.5-36.3%. *S. repens* extract did not induce apoptosis in lung cancer A 549 cells. **CONCLUSION:** This study showed that the antiproliferative effect exerted by the ethanolic extract of *S. repens* is at least triggered by induction of apoptosis. These in vitro data provide some information that may be useful for clinical use and render *S. repens* extract an interesting tool for new applications.

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**OBJECTIVES:** To elucidate the in vitro and ex vivo effects of saw palmetto extract (SPE) on autonomic receptors in the rat lower urinary tract. **METHODS:** The in vitro binding affinities for alpha 1-adrenergic, muscarinic, and purinergic receptors in the rat prostate and bladder were measured by radioligand binding assays. Rats received vehicle or SPE (0.6 to 60 mg/kg/day) orally for 4 weeks, and alpha 1-adrenergic and muscarinic receptor binding in tissues of these rats were measured. **RESULTS:** Saw palmetto extract inhibited specific binding of [3H]prazosin and [N-



methyl-3H]scopolamine methyl chloride (NMS) but not alpha, beta-methylene adenosine triphosphate [2,8-(3)H]tetrasodium salt in the rat prostate and bladder. The binding activity of SPE for muscarinic receptors was four times greater than that for alpha 1-adrenergic receptors. Scatchard analysis revealed that SPE significantly reduced the maximal number of binding sites (Bmax) for each radioligand in the prostate and bladder under in vitro condition. Repeated oral administration of SPE to rats brought about significant alteration in Bmax for prostatic [3H]prazosin binding and for bladder [3H]NMS binding. Such alteration by SPE was selective to the receptors in the lower urinary tract. CONCLUSIONS: Saw palmetto extract exerts significant binding activity on autonomic receptors in the lower urinary tract under in vitro and in vivo conditions.

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PC-SPEs is an eight-herb mixture that has an activity against prostate cancer. Recently, we purified Saw Palmetto (*Serenoa repens*) from PC-SPEs and found that Saw Palmetto induced growth arrest of prostate cancer LNCaP, DU145, and PC3 cells with ED50s of approximately 2.0, 2.6, and 3.3 microl/ml, respectively, as measured by mitochondrial-dependent conversion of the the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. Saw Palmetto induced apoptosis of LNCaP cells in a time- and dose-dependent manner as measured by TUNEL assays. Also, Saw Palmetto increased the expression of p21waf1 and p53 protein in LNCaP cells. In addition, we found that Saw Palmetto down-regulated DHT- or IL-6-induced expression of prostate specific antigen in conjunction with down-regulation of the level of androgen receptor in the nucleus as measured by Western blot analysis. Moreover, Saw Palmetto down-regulated the IL-6-induced level of the phosphorylated form of STAT 3 in LNCaP cells. Furthermore, Saw Palmetto inhibited the growth of LNCaP cells present as tumor xenografts in BALB/c nude mice without

adverse effect. These results indicate that Saw Palmetto might be useful for the treatment of individuals with prostate cancer.

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## All About SUPPLEMENTS

### Saw Palmetto

This Plant-Derived Remedy Benefits Prostate Health, Modulates Hormones, and May Help Prevent Hair Loss By Armond Scipione



As men grow older, many experience declining prostate health that significantly affects their lifestyle and well-being. One of the most common conditions threatening the prostate gland is benign prostatic hypertrophy. This swelling of the prostate gland can lead to myriad symptoms such as increased urinary frequency, weak urinary stream, and difficulty initiating urination.

For more than a century, saw palmetto (*Sabal serrulata*) has been recognized for its ability to relieve swelling of the prostate gland. In fact, saw palmetto is one of the most popular plant-derived remedies for benign prostatic hypertrophy. Doctors in Germany, Austria, and Italy use saw palmetto, along with other plant extracts like pygeum and nettle root, as a first-line treatment for enlargement of the prostate gland.<sup>1</sup>

By helping to prevent the conversion of testosterone to its potent metabolite dihydrotestosterone (DHT),<sup>2-6</sup> saw palmetto may have important implications for preventing hormone-related cancers in men, such as prostate cancer. Saw palmetto's ability to modulate hormonal balance also makes it a promising candidate for preventing and treating hair loss, with initial studies demonstrating positive effects.<sup>7</sup>



## Benefits for Prostate Health

Benign prostatic hypertrophy (BPH) is a common condition that becomes increasingly prevalent in aging men. BPH affects 8% of all men at the age of 40, 60% of men in their seventies, and 90% of men in their eighties.<sup>8</sup> One fourth of these men will develop moderate-to-severe lower urinary tract symptoms that will greatly affect their quality of life.<sup>8</sup> The prostate gland's sole function is to secrete fluid containing substances needed for reproduction. This process requires an extremely high concentration of androgen hormones in the prostatic tissues. BPH seems to be related to the prostate's long-term exposure to the



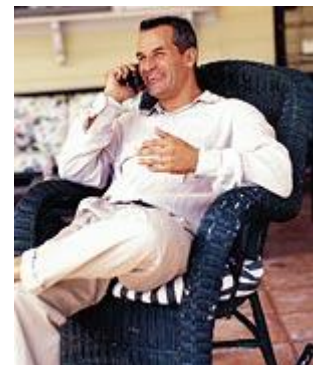
strong androgen dihydrotestosterone (DHT), as well as to estrogens.<sup>9</sup> The enzyme necessary to convert testosterone into DHT is called 5-alpha-reductase.

Research has shown that saw palmetto is an effective inhibitor of 5-alpha-reductase activity in prostate gland tissue.<sup>2-6</sup> In patients with BPH, saw palmetto relieved urinary symptoms as effectively as the pharmaceutical 5-alpha-reductase inhibitor, finasteride (Proscar®).<sup>9</sup> In addition to inhibiting 5-alpha-reductase activity, saw palmetto exerts anti-inflammatory effects that also may have complementary effects on prostate health.<sup>9</sup>

Extensive research supports saw palmetto's benefits for prostate health. An analysis of 2,939 men with symptomatic BPH found that those taking saw palmetto extract reported greater improvement of urinary tract symptoms and urinary flow measures compared to control subjects. Furthermore, the experimental group saw a decrease in episodes of nocturia (nighttime urination) and an improvement in peak urinary flow.<sup>1</sup>

In one trial, researchers assessed the efficacy of 160 mg of saw palmetto given twice daily for two years. The study enrolled men with clinically diagnosed BPH and complaints of prostate symptoms.

The patients were evaluated at 6, 12, 18, and 24 months. At each subsequent evaluation, the patients' quality of life and maximum urinary flow had improved, and both prostate size and symptoms had decreased. The study participants reported that sexual function remained stable for the first year of treatment and significantly improved during the second year. Another study examined men aged 45 or older with moderate-to-severe symptoms of BPH. After receiving placebo for one month, the men were randomly assigned to



receive either saw palmetto or placebo for an additional six months. The men were evaluated using the International Prostate Symptom Score and measurement of urinary flow rate. The saw palmetto group experienced a significant decrease in its prostate symptom scores. Moreover, its quality-of-life scores increased to a greater degree than in those taking a placebo. The researchers concluded that saw palmetto significantly improved urinary symptoms compared to placebo.<sup>11</sup>

## Potent Hormone-Modulating Effects

Growing numbers of aging adults are turning to a novel therapy called hormone restoration to fight the signs of aging and regain their youthful vitality. Proper hormone restorative therapy involves balancing and maintaining youthful levels of the body's key hormones. For optimal health, pregnenolone, dehydroepiandrosterone (DHEA), progesterone, cortisol, estrogen, testosterone, and DHT all need to be in proper balance.

More and more men are using testosterone therapy to regain their youthful vigor. Testosterone not only can transform itself into DHT via the 5-alpha-reductase enzyme, but also can convert to estradiol via the aromatase enzyme. These are undesirable effects, since elevated DHT may lead to enlargement of the prostate and possibly to loss of scalp hair.<sup>7,12</sup> Furthermore, elevated estradiol in men has been linked to gynecomastia (breast enlargement in men), decreased sexual function, and weight gain.<sup>13,14</sup>

Fortunately, such side effects of testosterone therapy can be avoided by taking some simple steps. Studies show that an extract of saw palmetto can block the conversion of testosterone to DHT.<sup>3</sup> Research has also shown that zinc may block testosterone's conversion (aromatization) to estradiol. In a study published in the Journal of Nutrition, researchers examined the effects of zinc deficiency on androgen metabolism and aromatization. The formation of estradiol from testosterone was significantly greater in rats fed a zinc-deficient

diet than in freely fed rats. The researchers concluded that zinc deficiency reduces circulating testosterone concentrations, alters hepatic steroid metabolism, and may increase circulating estradiol concentrations.<sup>15</sup> Ensuring adequate zinc status may thus help prevent the undesirable conversion of testosterone to estradiol.

## Preventing and Managing Hair Loss

Intriguing research suggests that supplementation with saw palmetto may prove useful in preventing and managing hair loss. It has been estimated that there are between 100,000 and 150,000 hairs on the human scalp. On average, between 50 and 150 hairs may be lost each day. Baldness occurs when this hair loss occurs at an abnormally high rate or when hair replacement occurs at an abnormally slow rate. About 95% of all cases of hair loss are the result of androgenic alopecia, or male pattern hair loss.

Biochemically, one contributing factor to this disorder is the conversion of testosterone to DHT via the 5-alpha-reductase enzyme.<sup>7,16,17</sup> Accordingly, agents that block the 5-alpha-reductase enzyme are attracting attention as treatments for androgenic alopecia.



Finasteride, marketed under the brand names Propecia® and Proscar®, is an FDA-approved treatment for men with androgenic alopecia. Clinical studies in balding men have demonstrated that finasteride reduces scalp DHT levels and improves hair growth, confirming DHT's role in the pathophysiology of androgenic alopecia.<sup>17</sup> Studies have shown that both finasteride and saw palmetto are effective inhibitors of the 5-alpha reductase enzyme.<sup>2-6,9,17</sup> However, researchers have also discovered that finasteride is associated with a greater risk of erectile dysfunction, ejaculatory disorders, and decreased

libido.<sup>18</sup> Thus, many men are seeking effective solutions for hair loss that are free of these side effects.

One study sought to examine saw palmetto's effects in treating androgenic alopecia. The study followed 19 healthy men, aged 23-64, with mild-to-moderate androgenic alopecia. The men were given either 200 mg of saw palmetto and 50 mg of beta-sitosterol twice a day or a matching placebo for an average of 4.6 months. Overall hair assessment was determined using a standardized scale. The patients were asked to evaluate any changes with respect to their current satisfaction with their hair. Assessments were performed at baseline and at the study's completion. Sixty percent of the study subjects were rated as improved at the final visit.<sup>7</sup> Larger, gender-specific clinical trials are needed to further elucidate these promising initial findings.

## Summary

For over 200 years, saw palmetto has been used to prevent and improve the symptoms associated with benign prostatic hypertrophy in men.<sup>1</sup> Growing evidence indicates that supplementing with saw palmetto may also positively modulate the complex system of hormone metabolism in men and women alike. Saw palmetto's effects on hormone metabolism may have important implications for hormone restoration programs as well as for supporting healthy hair growth and preventing hair loss.

Saw palmetto has no known drug interactions, and reported side effects are minor and rare.<sup>5,12,19,20</sup> However, some health care practitioners have noted that high doses of saw

palmetto may lead to a loss of libido in both men and women.<sup>21</sup> Life Extension suggests a daily dose of 160 mg of saw palmetto for women and 160-320 mg for men.

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