

What Do I Tell Patients About Saw Palmetto for Benign Prostatic Hyperplasia?

Christopher J. Kane, MD^{a,b,*}, Omer A. Raheem, MD^{a,b},
Stephen Bent, MD^c, Andrew L. Avins, MD, MPH^d

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- Saw palmetto • Benign prostatic hyperplasia
- Lower urinary tract

HISTORY OF HERBAL THERAPIES FOR BENIGN PROSTATIC HYPERPLASIA

Historically, herbal therapy is considered to be the mainstay of complementary and alternative medicine for the treatment of benign prostatic hyperplasia (BPH).¹ Millions of people worldwide, including in the United States, use herbal agents to treat symptoms of BPH and prevent its progression.² Despite their widespread use for maintaining prostatic health in older men, the long-term efficacy and safety of over-the-counter phytotherapies for lower urinary tract symptoms (LUTS) attributable to BPH are not clear.

BPH is a common cause of morbidity among older men in the United States and other developed countries. Although BPH is a histologic process and its exact cause is unknown, this condition confers morbidity primarily through LUTS. Additionally, men with BPH, and particularly those with larger prostates as a result of BPH, are at an increased risk for complications, such as acute urinary retention, and may progress to requiring surgical treatment for BPH. In fact, although the availability of effective medical therapy has reduced the need for transurethral resection of the prostate (TURP), the traditional surgical

treatment for BPH, the Centers for Disease Control's National Hospital Discharge Survey reports that 132,000 TURP procedures were performed in the United States in 2000. Although a working epidemiologic definition of symptomatic BPH is still being debated, the clinical manifestations of BPH are generally agreed upon. Clinical BPH, defined as an American Urological Association Symptom Index (AUASI) score greater than 7 (moderate to severe LUTS) and a depressed peak uroflow rate (<15 mL/s), affects 17% of men aged 50 to 59 years, 27% of men aged 60 to 69 years, and 35% of men aged 70 to 79 years.³

Men with bothersome LUTS caused by BPH can choose from a spectrum of traditional medical treatments, including alpha blockers and 5-alpha reductase inhibitors, minimally invasive therapies that use heat to damage or destroy prostate tissue, TURP, and other surgical therapies.⁴ The Medical Treatment of Prostatic Symptoms trial tested finasteride and doxazosin, alone and in combination, for the prevention of BPH progression.⁵ BPH progression was defined as a confirmed increase in an AUASI score by at least 4 points, acute urinary retention, incontinence, urinary tract infection or urosepsis, or new renal insufficiency. Almost all progression events were in the first 2 categories.

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^a Division of Urology, Department of Surgery, University of California San Diego, 200 West Arbor Drive, 8897, San Diego, CA 92103-8897, USA

^b Urologic Cancer Unit, Moores UCSD Cancer Center, 3855 Health Sciences Drive, La Jolla, CA 92093, USA

^c Department of Medicine, University of California San Francisco, San Francisco, CA, USA

^d Kaiser Permanente, Northern California Division of Research, Oakland, CA, USA

* Corresponding author. Division of Urology, Department of Surgery, University of California San Diego, 200 West Arbor Drive, 8897, San Diego, CA 92103-8897.

E-mail address: ckane@ucsd.edu

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Finasteride is a 5-alpha reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone, the major intraprostatic androgen, and reduces prostate size. Doxazosin blocks alpha-adrenergic receptors in the lower urinary tract, resulting in a reduction in smooth muscle tone in the prostate and bladder neck. Alpha-blockers rapidly improve voiding symptoms and urinary flow rate, and the improvements are long lasting. Common side effects are dizziness, retrograde ejaculation, and postural hypotension. The 5-alpha reductase inhibitors reduce prostate volume and decrease the risk of urinary retention and the need for surgical intervention. The reduction in prostate volume takes months. Common side effects are decreased ejaculate volume and, rarely, erectile dysfunction. For men with severe symptoms and large prostates, combination therapy was more effective than either therapy alone, but was associated with a greater risk of side effects and greater cost. Combination finasteride and doxazosin therapy is an attractive option, given the different mechanisms of action.⁵

Almost 30 phytotherapeutic compounds are currently available for the treatment of BPH. Those that have been studied most are extracts of the fruit of *Serenoa repens*, the saw palmetto dwarf palm that grows in the Southeastern United States. Second to saw palmetto is the extract of the bark of *Pygeum africanum*, the African plum tree.^{6,7} The proposed mechanisms of action for saw palmetto include 5-alpha reductase inhibition, intraprostatic androgen receptor blockage, and adrenergic receptor antagonism, as well as an anti-inflammatory effect.⁸ In vitro studies have shown that *Pygeum* extracts have antiinflammatory and immunomodulatory properties, effects on bladder contractility, modulation of androgen production, and direct effects on the function of prostate epithelium.^{7,9} Although there is conflicting evidence in the literature concerning the efficacy and safety of saw palmetto in the treatment of men with LUTS secondary to BPH, a recent meta-analysis of saw palmetto conducted by the Cochrane Review committee concluded that there is no observed benefit of using saw palmetto in the treatment of LUTS related to BPH, compared with placebo.¹⁰

EVIDENCE OF CURRENT USE OF SAW PALMETTO AND OTHER HERBAL AGENTS IN TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

The use of herbal therapies by adults in the United States has increased significantly in the last decade. It is estimated that 1 in every 5 people in the United States uses an herb to treat a condition

or promote health.¹¹ Likewise, herbal therapy for BPH is rapidly gaining popularity in the Western world. A 2002 nationwide survey found that approximately 2.5 million men used saw palmetto for treatment of BPH in the United States.¹ It is estimated that up to 90% of patients newly diagnosed with BPH have already tried an herbal treatment by the time they were referred to a urologist.^{2,12}

The trend in using phytotherapy for BPH can be partly explained by positive views of herbal therapies and personal values and beliefs.¹³ However, the published literature raises concerns about the safety and efficacy of herbal treatments for BPH.¹⁴

Plant extracts are widely used by men with BPH in the United States and usually sold as dietary supplements. In Europe, these extracts are often prescription drugs.^{15,16} A nationwide German study reported that 50% of urologists preferred saw palmetto over pharmaceutical agents for treatment of BPH.¹⁷

In a 2002 Cochrane meta-analysis of the effectiveness of saw palmetto extracts for men with BPH, 21 randomized trials 4 to 48 weeks in duration were identified, with 3193 total subjects. Data from the trials indicated that, compared with placebo, saw palmetto reduced nocturia by 0.76 times per night (10 trials), increased the odds of self-rated improvement 1.76 fold (6 trials), and improved peak flow rates by 1.86 mL/s (9 trials).¹⁸ Adverse effects were mild and infrequent. Methodological problems noted within the trials included lack of standardized symptom scores and short study durations. The most common dosage was 160 mg twice daily, but a comparative trial showed similar effectiveness with the more convenient dosage of 320 mg once daily.¹⁹

There has been strong interest among numerous investigators, particularly urologists, to further examine the safety and efficacy of phytotherapy for BPH in the form of large multicenter clinical trials, such as the Complementary and Alternative Medicines for Urological Symptoms (CAMUS) trial. If the results of these ongoing clinical trials show effectiveness at reducing LUTS, men with BPH might find herbal therapy preferable to medical therapy because of the appeal of naturalistic herbal therapy and minimal side effects.

COLLECTION OF RELEVANT STUDIES FOR THIS REVIEW

The authors performed PubMed (www.pubmed.gov), Web of Science (www.isiwebknowledge.com), and Cochrane library (www.cochrane.org) world literature searches for articles in the English language. The search terms saw palmetto and BPH or herbal agent and BPH returned 35 studies

published between 2000 and 2011 worldwide. Nineteen randomized clinical trials (RCT) were identified, but only 8 RCT were included (≥ 100 patients) (**Table 1**); 4 meta-analysis studies (≥ 2 clinical studies) (**Table 2**), 7 experimental basic scientific studies, 2 prospective studies, and 3 retrospective studies (**Table 3**) were related to saw palmetto or herbs and BPH. Most of the world literature, in descending order, is from the United States,⁹ United Kingdom,⁴ Spain,⁴ Germany,⁴ Italy,⁴ France,⁴ Russia,² Romania,¹ Turkey,¹ Australia,¹ and Brazil.¹ All large RCTs and meta-analyses were carefully selected and reviewed.

THE CURRENT AVAILABLE HERBAL AGENTS USED IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

Table 4 lists most currently available herbal agents, dosages, and adverse effects. The current published evidence of using saw palmetto and other herbal agents is briefly discussed next.

Saw Palmetto

The mechanism of saw palmetto is poorly defined. Investigators have proposed antiandrogenic activity via 5- α reductase inhibition and subsequent prevention of the conversion of testosterone to dihydrotestosterone,⁷ an antiinflammatory effect,¹⁶ competitive inhibition of androgen binding, decrease in the bioavailability of the sex hormone-binding globulin (SHBG),¹⁵ and inhibition of growth factor-induced prostatic cell proliferation.^{16,20,21}

In 2009, a detailed Cochrane Review analyzed 9 RCTs of saw palmetto with 2053 total patients. Five trials with 820 patients evaluated saw palmetto alone or combined with nettle root, beta-sitosterol, vitamin E, or tamsulosin versus placebo.^{22–26} Four trials with 1233 participants evaluated saw palmetto alone versus control.^{27–30} The most common commercialized extract of saw palmetto was Permixon (Pierre Fabre M dicament, Castres, France). The review concluded that saw palmetto was well tolerated but failed to improve urinary symptom score compared with placebo.¹⁰

A recent Italian study was conducted to evaluate the effect of saw palmetto in reducing intraoperative and postoperative complications of men undergoing surgical treatment (TURP or open prostatectomy) for BPH. The 114 patients were randomized to receive either pretreatment with saw palmetto or no pretreatment. No intraoperative complications occurred and no blood transfusions were required in the pretreatment group ($P < .001$). Additionally, the postoperative course was statistically significantly more favorable in the pretreatment group. This

study suggests that pretreatment with saw palmetto before surgery for BPH is an effective measure for decreasing potential intraoperative and postoperative complications.³¹

Pygeum

Experimental studies have shown that *Pygeum* exerts an antiinflammatory effect, modulates androgen production, and decreases hypersensitivity of the detrusor muscle of the urinary bladder.^{7,9} In a large European multicenter study, the effectiveness of *Pygeum* was examined against tamsulosin and finasteride in 2351 men with LUTS/BPH. Marked improvement of patients' urinary symptoms was observed in patients taking tamsulosin (68%) or finasteride (57%), but there was 43% improvement in patients who were on *Pygeum*.³² In a meta-analysis of 2 studies, Mantovani³³ systematically examined the role of saw palmetto and *Pygeum* on patients with BPH. A total of 70 men participated in 2 studies. In the first study, patients were treated with 320 mg daily saw palmetto for 30 days. In the second study, patients received 320 mg of saw palmetto daily or 25 mg of *Pygeum* daily for 30 days. Both studies demonstrated marked improvement in urinary symptoms and prostate size, and general tolerability of the herbal agents.³³

Nettle Root

Previous studies have shown that nettle root has antiinflammatory effects, binds to SHBG, and inhibits cellular proliferation. It also inhibits sodium-potassium ATPase action (Na-K ATPase).^{24,34} The safety and efficacy of nettle root was investigated over a 96-week period in 219 men with moderate/severe LUTS caused by BPH.³⁵ Participants were randomized to receive a placebo or a fixed dose of 160 mg *Sabal* fruit extract combined with 120 mg nettle root extract (PRO 160/120) over 24 weeks, followed by another 24-week control period during which all participants received PRO 160/120. In the final 48-week follow-up period, all participants received PRO 160/120. International Prostatic Symptom Scores (IPSS), urinary flow rates, and residual urine volumes improved significantly in the treatment group, thus providing evidence of a clinically relevant benefit of using PRO 160/120 over a period of 96 weeks.³⁵

PUMPKIN SEEDS

Pumpkin seeds are antihelmintic agents, but they decrease the binding capacity of androgen receptors to testosterone through competitive binding. They also have diuretic properties.³⁶ In

Table 1
Randomized clinical trials evaluating saw palmetto and other herbal agents in BPH

First Author	Year of Publication	Journal	Study	N	Main Findings/Conclusions
Anceschi	2010	Minerva Urol Nefro	RCT	114	This study suggests that pretreatment with saw palmetto before surgery for BPH is effective in reducing intraoperative and postoperative complications.
Bercovich	2010	Urologia	RCT	NA	A new plant extract (Pluvio), which contains avocado, soya oil and nettle root, was compared with controls in men with BPH. IPSS, uroflow, postvoid residual volume, prostate volume, and PSA were measured. This study showed that Pluvio is highly effective for the treatment of BPH.
Lee	2009	Clinical Trials	RCT/CAMUS	3300	This RCT is the largest to evaluate saw palmetto for the treatment of BPH to date and the only one to include a dose-ranging protocol. The results of this study will provide the most definitive test of the efficacy of saw palmetto in men with BPH.
Lopatkin	2007	Int Urol Nephrol	RCT	219	This study was designed to evaluate the safety and efficacy of a combined agent (160 mg <i>Sabal</i> fruit extract and 120 mg nettle root extract in men with BPH. IPSS was reduced by 53% ($P < .001$), peak and average urinary flow increased by 19% ($P < .001$), and residual urine volume decreased by 44% ($P = .03$). This study concludes that treatment with PRO 160/120 provides a clinically relevant benefit.
Bent	2006	NEJM	RCT/STEP	225	This study examined the role of saw palmetto in BPH treatment. No significant difference between the saw palmetto and placebo groups was identified over a 1-year period.
Hutchison	2006	Eur Urol	RCT/TRIUMPH	NA	Tamsulosin, finasteride, saw palmetto and <i>Pygeum</i> were all assessed in treating LUTS/BPH patients. Drug treatments were associated with some improvement compared with watchful waiting for most patients. Tamsulosin was the most effective in improving urinary symptoms (68%). Additionally, <i>Pygeum</i> therapy was shown to significantly improve urinary symptoms (43%).
Engelman	2006	Arzneimittelforschung	RCT	140	A combination of 160 mg <i>Sabal</i> fruit extract and 120 mg nettle root extract (PRO 160/120), compared with tamsulosin in treatment of BPH. Primary outcomes were IPSS and adverse events. The study supports noninferiority of PRO 160/120 in the treatment of LUTS caused by BPH.

Popa	2005	MMW Fortschr Med	RCT	NA	This study recommends the use of the combined <i>Sabal</i> extract and nettle root extract (PRO 160/120) in the treatment of BPH.
Zlotta	2005	Eur Urol	RCT	NA	This study compares saw palmetto, tamsulosin, and finasteride. After 3 months, there were no statistically significant differences between the 3 treatment groups in terms of IPSS and slight improvement in sexual performance. This study demonstrates that saw palmetto has no negative impact on male sexual function.
Debruyne	2004	Eur Urol	RCT/PERMAL	704	This study compares saw palmetto and tamsulosin for the treatment of BPH and concluded that 320 mg daily saw palmetto is slightly superior to 0.4 mg daily tamsulosin.
Willets	2003	BJUI	RCT	100	Saw palmetto was compared with placebo. This study concluded that there is no significant beneficial effect of saw palmetto over placebo.
Melo	2002	Int Braz J Urol	RCT	NA	This study analyzed the effect of combined <i>Pygeum</i> and nettle root extract, compared with placebo. This combination produced clinical and urodynamic effects similar to placebo.
Sökeland	2000	BJUI	RCT	431	This study compared combined <i>Sabal</i> and nettle root extract (PRO 160/120) to finasteride in patients with BPH. It showed that efficacy of both PRO 160/120 and finasteride was equivalent. Additionally, PRO 160/120 had better tolerability than finasteride.
Marks	2000	J Urol	RCT	44	This study compared the effects of saw palmetto to placebo and concluded that saw palmetto appears to be a safe, highly desirable option for men with BPH.
Glemain	2002	Prog Urol	RCT/OCOS	352	This study compared a combination of tamsulosin and saw palmetto with tamsulosin alone. It concluded that the addition of saw palmetto or tamsulosin did not provide any significant benefit.
Preuss	2001	Int Urol and Nephro	RCT	NA	This study examined the efficacy of a combination of rye grass, saw palmetto, beta-sitosterol, and vitamin E compared with placebo. After 3 months, the combined therapy had significantly lessened symptoms of BPH and no significant adverse side effects were noted.

Abbreviations: IPSS, International Prostatic Symptoms Score; NA, not available; OCOS, Omix contre Omix + *Serenoa repens*; STEP, Saw Palmetto Treatment of Enlarged Prostates; TRIUMPH, TransEuropean Research Into the Use of Management Policies for LUTS suggestive of BPH in Primary Health care.

Table 2
Meta-analysis evaluating saw palmetto and other herbal agents

First Author	Year of Publication	Journal	Study Design	Main Findings/Conclusions
Mantovani	2010	Minerva Urol Nefrol	Analysis of 2 studies	This meta-analysis concluded that a daily dose of 320 mg of saw palmetto can significantly reduce symptoms related to BPH with a good tolerability.
Tacklind	2010	Cochrane Database Sys Rev	Cochrane Reviews	This systematic meta-analysis showed that saw palmetto provides no improvement in urinary symptoms secondary to BPH, compared with placebo. Additionally, it found that saw palmetto was well tolerated.
Boyle	2004	BJUI	Meta-analysis	This meta-analysis showed significant improvement in LUTS and flow rate in patients treated with saw palmetto for BPH, compared with placebo.
Buck	2004	J Urol	Meta-analysis	This meta-analysis suggested a wide spectrum of activity of saw palmetto. However, the precise mechanism of action remained unclear. Balance and caution are needed when extrapolating the results of in vitro laboratory studies to the complex human situation.

a randomized study, the preparation curbicin, obtained from pumpkin seeds and dwarf palm plants (*Cucurbita pepo* and *Sabal serrulata*), was compared with a placebo in the treatment of BPH. A total of 53 patients participated, and after 3 months, urinary flow, micturition time, residual urine, and frequency of micturition significantly improved in the treatment group, indicating that pumpkin seeds were beneficial in treating BPH.³⁶

African Wild Potato

African wild potato extract blocks the production of cyclooxygenase-1 (COX-1) and COX-2 prostaglandin biosynthesis. It also has antiinflammatory and free-radical scavenging activity.³⁷ Some specific African wild potato extracts, taken alone or in combination with other sources of beta-sitosterol, seem to reduce urinary symptoms and improve quality of life.^{37,38}

Beta-sitosterol

Beta-sitosterol inhibits 5-alpha reductase enzyme activity and has potent antiproliferative effects on the prostate, possibly by inhibiting growth factors.^{39,40} In vitro experimental studies have

shown the inhibitory effect of beta-sitosterol on multifunctional growth factors.^{37,40}

Lycopene

Lycopene reduces proliferation of prostatic epithelial cells and improves urinary symptoms.⁴¹ However, there is no strong published evidence to support the use of lycopene supplements to treat or prevent BPH. Previously published data have shown that increased consumption of tomato products and other lycopene-containing foods might reduce the occurrence or progression of prostate cancer.⁴²

Red Clover

Studies of red clover in animal models have identified antiandrogenic and apoptosis effects on prostate cells.^{43,44} However, there is no clear evidence that red clover reduces urinary symptoms in men with BPH.

Rye Grass Pollen

Rye grass pollen acts as an alpha-adrenergic receptor antagonist, is antiinflammatory, and inhibits prostate cancer cell growth. The most used

extract of rye grass pollen is Cernilton. Some studies have reported decreased prostate size, improved urinary flow, and decreased residual urine volume in men treated for BPH with Cernilton.⁴⁵ Others reported no effect on objective BPH measures.⁴⁶ It is unknown whether or not rye grass pollen is comparable to finasteride or tamsulosin; however, it is comparable to *Pygeum*.⁴⁶

Selenium

Selenium activates glutathione peroxidase, which reduces oxidative stress by handling free radicals and hydrogen peroxide. In addition, studies of selenium have reported contradictory evidence regarding its effect on prostate cancer risk. Population studies suggest that higher serum or toenail selenium levels are associated with a decreased risk of prostate cancer.⁴⁷ A recent Italian experimental study evaluated the antiinflammatory effects of saw palmetto, lycopene, selenium, and an association of the 3 on rat prostates. The saw palmetto-lycopene-selenium association caused a greater inhibitory effect on the expression of (COX)-2, indicating anti-BPH properties.⁴⁸

Vitamin E

Research suggests that vitamin E might have an antiproliferative effect on benign hyperplastic prostate cells.⁴⁹ Several large RCTs provide conflicting evidence regarding vitamin E supplementation and prostate cancer.⁵⁰ The best evidence indicates that taking vitamin E supplements does not significantly reduce the risk of developing prostate cancer.⁵⁰

Garlic

Garlic acts as a smooth muscle relaxant, and there is also preliminary evidence suggesting that garlic extract might help improve urinary flow, decrease urinary frequency, and reduce other symptoms associated with BPH and prostate cancer.⁵¹ Additional preliminary evidence suggests that taking garlic supplements might decrease the risk of developing prostate cancer; however, the mechanism of action is unclear.⁵²

Prickly Pear Cactus

Cactus acts as an antioxidant, and preliminary evidence suggests that some patients who take powdered prickly pear cactus flowers, 500 mg 3 times daily for 2 to 8 months, have subjective improvements in symptoms, such as urgency and feelings of fullness in the bladder.⁵³

***Saxifraga Stolonifera* Meerb**

This Chinese herb has been studied as a potential treatment for men with BPH.⁵⁴ A recent randomized trial compared the symptomatic effects on patients with BPH treated either with alpha blocker or *Saxifraga stolonifera* Meerb. Although this Chinese herb was effective in improving quality of life, prostate volume, and maximum uroflow rate for men with BPH, it was less effective than alpha blocker in improving IPSS.⁵⁴ Further studies are required to thoroughly investigate its potential role in treating men with BPH, with particular emphasis on its molecular basis.

Saireito

It is known that Saireito acts as a diuretic. A study of its efficacy in treating men with BPH has been reported.⁵⁵ Twelve men diagnosed with BPH who failed traditional medical therapy and still reported nocturnal frequency participated in the study. Nocturnal frequency decreased significantly and the results suggest that Saireito can be used as an effective treatment for nocturia in patients with BPH.⁵⁵

Green Tea

Green tea and androgens are among the oldest medicinal agents used in traditional Chinese medicine. Epigallocatechin-3-gallate, a catechin in green tea, can modulate the production of androgens and other hormones. This property could be useful for treating hormone-related diseases, including BPH and androgen-dependent and androgen-independent prostate cancers.^{56,57}

Fengweicao Granule

This Chinese herbal preparation is made from *Pteris multifida*. In a recent randomized trial, 108 patients with BPH received Fengweicao granule, and 47 BPH patients received finasteride. After 3 months, both groups had considerable improvement in IPSS, uroflow rates, and residual urine volumes, but no significant change in prostate volume was observed. The investigators concluded that Fengweicao granule has a positive effect in treating BPH.⁵⁸

Ganoderma lucidum

Ganoderma lucidum is another Chinese herb proven to be effective in men with LUTS caused by BPH.⁵⁹

Qianlie Sanyu

Qianlie sanyu is another Chinese herb proven to be effective in men with LUTS caused by BPH.⁶⁰

Table 3
Other studies evaluating saw palmetto and other herbal agents

First Author	Year of Publication	Journal	Study Design	N	Main Findings/Conclusions
Bonvissuto	2011	Urology	Experimental	NA	A combination of lycopene, selenium and saw palmetto caused an inhibitory effect on prostate of rat. This association might be useful in the treatment of BPH.
Sinescu	2011	Urol Int	Prospective	120	Long-term treatment with 320 mg saw palmetto proved to be efficient in reducing urinary symptoms and improving sexual function in men with BPH.
Quiles	2011	Prostate	Experimental	6	This study suggests that <i>Pygeum</i> has an antiproliferative effect on prostate fibroblasts and myofibroblasts but not on smooth muscle cells.
Pais	2011	Adv Ther	Experimental	NA	A novel saw palmetto extract shown to effectively inhibit 5-alpha reductase enzyme activity that has been linked to BPH. This study confirms the effect of saw palmetto on prostate, compared with finasteride.
Agbabiaka	2009	Drug Saf	Retrospective	NA	This study evaluated the safety of saw palmetto and recommended higher quality reporting to improve safety assessments in the future.
Scholtyssek	2009	Biochem Biophys Res Commun	Experimental	NA	This study showed the potential usage of saw palmetto and its extracts as antitumor agents.
Avins	2008	Compl Ther Med	Subanalysis	225	This study examined the safety and efficacy of saw palmetto in men with BPH. No significant differences were observed between saw palmetto versus placebo regarding adverse events.

Hizl	2007	Int Urol Nephrol	Prospective	60	This study evaluated the efficacy of saw palmetto alone versus tamsulosin and saw palmetto versus tamsulosin alone for patients with BPH. Both saw palmetto and tamsulosin seem to be effective in treating BPH.
Schleich	2006	Planta Med	Experimental	NA	This study compared the antiandrogenic activity of <i>Pygeum</i> , saw palmetto, and pumpkin seeds in treatment of BPH and prostate cancer. Results showed that <i>Pygeum</i> has the highest antiandrogenic effect and may provide a novel approach for the prevention and treatment of BPH and prostate cancer.
Habib	2004	Prostate Cancer and Prostatic Diseases	Comparative analysis	NA	This study indicated that sources of saw palmetto vary significantly between brands. It also evaluated the safety and efficacy of saw palmetto in BPH as well as its therapeutic benefits, compared with available medications.
Talpur	2003	Mol Cell Biochem	Experimental	NA	This study evaluated the antiandrogenic effects of saw palmetto and rye grass on prostatic enlargement in rats. Saw palmetto and rye grass influence prostatic hyperplasia via effects on androgen metabolism.
Vacherot	2003	Prostate	Experimental	NA	This study evaluated the role of saw palmetto as an antiandrogenic agent on human prostatic stroma and epithelium specimens obtained from men with BPH. Induction of apoptosis and inhibition of cell proliferation are likely the basis for the clinical efficacy of saw palmetto.

Abbreviation: NA, not available.

Table 4
Summary of currently available herbal agents for benign prostatic hyperplasia

Herb	Scientific Name	Family	Dosage	Adverse Effects
Antiandrogenic				
Saw palmetto	<i>Serenoa repens</i>	Arecaceae	Dried: 160 mg twice daily; Liquid: 0.6–1.5 mL or 0.5–1.0 g of berries in 150 mL of water 3 times daily	Nausea, vomiting, constipation, diarrhea, headache, hypertension, mild pruritus, decreased libido, and ejaculatory/erectile dysfunction
Antiproliferative				
Pygeum	<i>Pygeum africanum</i>	Rosaceae	Dried: 50 mg twice daily	Nausea, gastric pain, constipation, diarrhea, dizziness, headache, insomnia, restlessness, and visual disturbance
Nettle root	<i>Urtica dioica</i>	Urticaceae	Dried: 600–1200 mg daily Liquid: 1.5–7.5 mL daily	Mild gastric upset, allergic skin reactions, and sweating
Pumpkin seeds	<i>Cucurbita pepo</i>	Cucurbitaceae	Dried: 5 g twice daily	Potential electrolytes loss
African wild potato	<i>Hypoxis hemerocallide</i>	Hypoxidaceae	Dried: 60–130 mg divided into 2–3 doses daily	Nausea, vomiting, indigestion, diarrhea, constipation, anxiety, ventricular tachycardia, bone marrow suppression in patients with HIV disease, reduced absorption and blood levels of alpha- and beta-carotene and vitamin E
Beta-sitosterol	22,23-dihydrostigmasterol	Beta-sitosterol	Dried: 60–130 mg divided into 2–3 doses daily	Nausea, indigestion, diarrhea, constipation, erectile dysfunction, loss of libido, reduced absorption and blood levels of alpha- and beta-carotene and vitamin E
Lycopene	All-trans lycopene	Lycopene	Dried: 15 mg twice daily	Reduced plasma PSA level

Red Clover	<i>Trifolium pratense</i>	Fabaceae	Dried: 40–80 mg daily for 3 months	Rashlike reactions, myalgia, headache, nausea, and vaginal spotting; large amounts can induce bleeding
Antiinflammatory				
Rye grass pollen	<i>Secale cereale</i>	Poaceae	Dried: 126 mg 3 times daily	Nausea, abdominal distention and heartburn
Nutrients				
Selenium	Selenium	Selenium	For prostate cancer prevention, 200 mcg daily	Nausea, vomiting, abdominal pain, nail changes, fatigue, irritability, alopecia, and weight loss
Vitamin E	Alpha-tocopherol	Vitamin E	For prostate cancer prevention, 50–100 IU daily	Nausea, diarrhea, intestinal cramps, fatigue, weakness, headache, blurred vision, rash, gonadal dysfunction, and creatinuria
Miscellaneous				
Garlic	<i>Allium sativum</i>	Alliaceae	NA	Mouth/breath odor, gastrointestinal irritation, heartburn, flatulence, nausea, vomiting, and diarrhea
Prickly pear cactus	<i>Opuntia ficus-indica</i>	Cactaceae	Dried: 500 mg 3 times daily for 2–8 mo	Mild diarrhea, nausea, increased stool volume, abdominal fullness, and headache
Saxifraga stolonifera Meerb	saxifraga	Chinese herb	NA	NA
Saireito	Saireito	Chinese herb	Dried: 5.4 g daily	NA
Green tea	Green tea	NA	NA	NA
Fengweicao granule	Fengweicao	Pteris multifida	Dried: 5 g twice daily	NA
<i>Ganoderma lucidum</i>	Ganoderma	NA	Dried: 6 mg daily	NA
Qianlie Sanyu	Qianlie	NA	NA	NA
Bushenhuoxue	Bushenhuoxue	NA	NA	NA

Abbreviation: NA, not available.

Bushenhuoxue

Bushenhuoxue is another Chinese herb proven to be effective in men with LUTS caused by BPH.⁶¹

Saw Palmetto Treatment of the Enlarged Prostate Study

The Saw Palmetto Treatment of Enlarged Prostates (STEP) study was the first randomized, placebo-controlled trial of saw palmetto to be funded by the National Institutes of Health (NIH) and was designed to address the methodological weaknesses of earlier studies. Specifically, the STEP study initially convened an expert review panel from the National Center for Complementary and Alternative Medicine (NCCAM) to solicit and review applications from manufacturers of saw palmetto in an effort to identify and select the highest-quality product. The product selected for the trial was manufactured by Indena USA and was confirmed to have 92.1% total fatty acids and 0.33% total sterols, a standard that meets recommended guidelines from the US Pharmacopeia and other authorities on herbal products.²⁵ The study medication was produced in 1 batch to optimize consistency and was tested at the midpoint of the study and confirmed to have a consistent level of the proposed active ingredients.

Other methodological improvements in the STEP study included the relatively large sample size (225 participants), the long duration of follow-up (1 year), and the assessment of the adequacy of blinding. Earlier studies had not described the process of developing an adequately blinded placebo for saw palmetto, which has a bitter taste and a pungent odor. If participants in the treatment groups knew they were taking saw palmetto, then the observed benefits in earlier studies could have been at least partially caused by a placebo effect. In the STEP study, participants were asked at the end of the study which group they thought they had been assigned to, and a similar number in both groups thought they were taking saw palmetto (40% in the active group and 46% in the placebo group, *P* = .38), suggesting that blinding was effective.

Inclusion and exclusion criteria in the STEP study were set to be consistent with most prior, large, randomized controlled trials of pharmaceutical drugs for BPH. Men were older than 49 years and had moderate to severe symptoms (defined as an AUASI score of at least 8) and a peak urinary flow rate less than 15 mL/s. The study recruited 225 men and randomly assigned them to the same dosage of saw palmetto used in the vast majority of prior studies (160 mg twice daily). The STEP study had a high completion rate (96%)

and medication adherence rate (92% of study medication consumed), and the active and placebo groups showed no significant differences with respect to baseline characteristics.

The predefined primary outcome of the study showed that saw palmetto had no effect on urinary symptoms. As in most studies of BPH, there was a small decrease in symptom scores during the placebo run-in period. After that, the AUASI score decreased 0.68 points in the saw palmetto group versus 0.72 points in the placebo group (difference in change in AUASI scores between groups 0.04 points, 95% confidence interval -0.93 to 1.01). The lack of effect of saw palmetto can be visualized in Fig. 1, where the lines showing changes in symptom scores in the 2 groups almost overlap. The STEP study also found that saw palmetto had no effect on urinary flow rates. The rate of serious and nonserious adverse events was similar in both groups, providing some evidence that saw palmetto is safe. The STEP study provided compelling evidence that saw palmetto is not an effective treatment for BPH, and suggested that the positive results of some earlier studies may have been caused by their methodological weaknesses. One significant limitation of the STEP study was that it only assessed 1 dose of saw palmetto and, therefore, could not assess whether higher doses or a longer duration of treatment might produce beneficial effects. Consequently, the CAMUS study was designed to address the possibility that higher doses of this herb might produce beneficial effects.

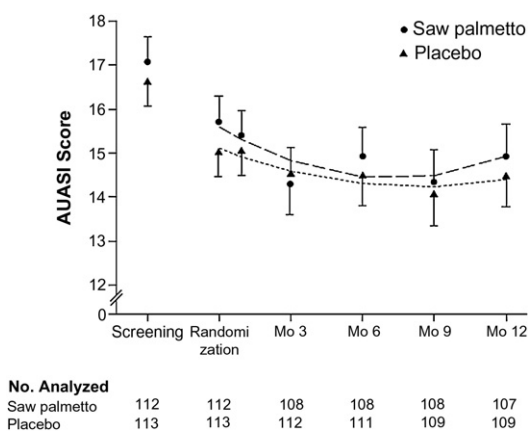


Fig. 1. Mean (±standard error) change in the American Urological Association Symptom Index (AUASI) scores in the saw palmetto and placebo groups. Values at screening represent prerandomization screening values. The full range of the scale is from 0 to 35, with higher numbers indicating more severe symptoms. (Adapted from Bent S, Kane C, Shinohara K, et al. Saw palmetto for benign prostatic hyperplasia. N Engl J Med 2006;354:557-66; with permission.)

The Complementary and Alternative Medicines for Urological Symptoms study

Among the many difficulties inherent in the study of phytotherapies is the choice of the product and the dose. Because part of the justification for studying phytotherapies is the perceived effectiveness of the supplement among large numbers of individuals who choose to self-medicate, it is important to replicate, as closely as possible, the actual conditions of use among the public. However, for many phytotherapies, there is great variation in the types of available products as well as the doses used. Hence, researchers are faced with difficult choices in conducting clinical studies and often have little theoretical or prior phase II work to guide the optimal choice of product to test.

Such was the case after the publication of the STEP trial of saw palmetto. Although the investigators chose a high-quality, well-characterized saw palmetto extract produced by an experienced European manufacturer, they were also aware that this extract was only one such product on the market and others were also widely used.⁶² Second, the investigators chose to test the most commonly used dosage of saw palmetto, 320 mg/d (administered as 160 mg twice daily),¹⁰ although higher doses have been used by men in the community. When the negative results of the STEP study were published, there were inevitable (and reasonable) concerns raised about the dose and product used in the trial and whether alternative products at higher doses might provide a demonstrable benefit. In addition, because it was a single-center trial, the generalizability of the results was of concern.

To address these concerns, the National Institute of Diabetes, Digestive, and Kidney Diseases, NCCAM, and the Office of Dietary Supplements jointly sponsored a large, multicenter, randomized double-blind clinical trial of 3 escalating doses of an alternative saw palmetto extract. This study, called the CAMUS trial, began enrollment in July 2008, with the intent of recruiting 369 men for an 18-month dose-escalation study (clinical trials.gov identifier # NCT00603304).

The CAMUS study was designed to specifically address areas of uncertainty raised by the STEP study. First, the investigators decided against a single dose of the extract in favor of a dose-ranging approach, starting with the widely used dosage of 320 mg/d (in a single dose for participant convenience), followed by a doubling, then tripling of the initial dose over the follow-up period. Second, because of the lipophilic nature of many of the extract's constituents, it was also felt that

several months at each dose would be required to provide a fair test of efficacy; therefore, dose escalations were done at 6-month intervals. Third, the saw palmetto extract chosen was produced by an experienced manufacturer using an extraction technique (ethanolic extraction) different from the CO₂ extraction technique used to manufacture the product tested in the STEP study.

The inclusion criteria specified in the final protocol for the CAMUS required that participants be men aged at least 45 years, with an AUASI score between 8 and 24 and a peak urinary flow rate greater than 4 mL/s. Exclusion criteria were any prior procedure for BPH, taking a drug known to affect urinary function, serum creatinine greater than 2.0 mg/dL, evidence of liver dysfunction or coagulopathy (or anticoagulant use) at baseline, prostate-specific antigen (PSA) greater than 10 ng/mL, urinary incontinence, cancer in the prior 5 years or cancer of the prostate or bladder at any time, neurologic condition affecting urinary function, and evidence of prostatitis or recurrent urinary tract infection. The primary outcome was change in the AUASI; secondary outcomes included participant global assessment of urinary function, the BPH Impact Index, peak uroflow, postresidual urine volume, PSA level, measurements of sexual and ejaculatory function, incontinence, perceived sleep quality, and the NIH Chronic Prostatitis Index. Assessments of symptomatic adverse events and detailed laboratory measurements were conducted at regular intervals.⁶³

Recruitment for the CAMUS study was completed in April 2009 and the final participant was closed out in October 2010. Results of the trial are expected to be published in 2011. The CAMUS study is the largest placebo-controlled trial of saw palmetto to date and the only one to include a dose-ranging protocol.¹⁰ The results of this study will provide the most definitive test of the efficacy of saw palmetto in men with LUTS and will likely have a major impact on future studies of botanic therapies for BPH as well as the clinical use of saw palmetto extracts.

SAFETY OF SAW PALMETTO EXTRACTS

Despite the large number of saw palmetto studies, there exist surprisingly little data on the safety of the extract. Most trials have not employed thorough methods for assessing potential adverse effects and few have conducted any laboratory assessments for subclinical toxicities. Most studies were of short duration (<3 months) and had small sample sizes. There are a small number of published case reports of adverse events potentially linked to the

use of saw palmetto,⁶⁴⁻⁶⁸ but most of these do not clearly establish saw palmetto as the causative agent.

The best data available on the safety of saw palmetto are from the STEP study.²⁵ As noted, the STEP trial included a large number of longitudinal laboratory measurements as well as regular, detailed assessments of symptomatic adverse events. A detailed analysis of the safety data from STEP has been published.⁶⁹

Reassuringly, the examination of the STEP safety data revealed no evidence of clinically meaningful adverse effects attributable to saw palmetto. Although there were substantially more serious adverse events reported in participants randomized to placebo (18 in the placebo group vs 8 in the saw palmetto group), a large number of these occurred in a single individual, skewing the comparison. There was no significant difference in the percentage of participants in each treatment group who suffered at least 1 serious adverse event (5.4% in the active-treatment group vs 9.7% in the placebo group, $P = .31$) and most of these were not life threatening.^{25,69}

Nonserious adverse events were approximately evenly distributed between the two treatment groups in STEP. The mean number of nonserious adverse events per person in the placebo and saw palmetto groups was 0.51 versus 0.47, respectively ($P = .72$). The proportion of participants experiencing at least 1 nonserious adverse event was also similar between the two groups (30.1% vs 34.8%, $P = .48$).^{25,69}

Examination of the laboratory data from STEP was reassuring in that only a few significant differences between groups were observed, approximately the number that would be expected to arise by chance when conducting a large number of hypothesis tests; none of these differences were considered clinically meaningful. Importantly, there was no difference between the groups in changes in the levels of PSA over the course of the trial.^{25,69}

Few other studies have reported comprehensive data on saw palmetto safety. One large study, a comparison of saw palmetto with tamsulosin among 704 participants over 1 year, found no effect on PSA levels over time.²⁷ Other studies have also found no effects of saw palmetto on PSA levels^{25,26,70}; one small study (of biologic outcomes) did perform extensive laboratory testing on the trial participants and found no evidence of toxicity attributable to saw palmetto.⁷¹ The most important data on saw palmetto safety will come from the CAMUS study, which has also included comprehensive adverse-event assessments as well as numerous longitudinal laboratory measurements.

A high-quality systematic review of potential adverse events associated with saw palmetto gathered data from the published literature; several governmental reporting agencies from North America, Europe, and Australia; saw palmetto manufacturers; and herbalist organizations.⁷² The investigators found no firm evidence of toxicity associated with saw palmetto. The most commonly reported side effects were "abdominal pain, diarrhea, nausea, fatigue, headache, decreased libido and rhinitis."⁷² However, the quality of the data was generally poor and no clear causal association with saw palmetto could be established, particularly because the rates of adverse events were similar in the saw palmetto and control groups among the comparative studies. No drug interactions were identified in this study or in a review specifically examining the potential for interactions between phytotherapies and prescription medications.⁷³

On balance, saw palmetto appears to be quite safe, with no substantial toxicities noted in any studies. However, the generally small sample sizes of the studies do not provide sufficient statistical power to rule out the possibility of uncommon but serious toxicity. In addition, the duration of all of the studies were short in comparison to the many years that patients might be expected to use the supplement. The one exception is the effect of saw palmetto on PSA levels, for which substantial data show a lack of effect of the botanic on this parameter.

RECOMMENDATIONS

The best current evidence suggests that saw palmetto is no more effective than placebo in treating lower urinary tract symptoms caused by BPH. The CAMUS trial will determine whether higher doses of saw palmetto may be efficacious. Until the CAMUS results are reported the authors do not recommend saw palmetto for men with troublesome LUTS caused by BPH. However, the authors do not strongly discourage its use when men currently taking saw palmetto have confidence in its efficacy, because they may be enjoying a placebo effect and it does appear to be safe. There is no good clinical evidence that other herbal preparations are beneficial for men with LUTS caused by BPH.

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