Saw Palmetto
Summary

Commercial source of product: The commercial saw palmetto products and the medically active constituents are derived from the ripe fruits of *Serenoa repens* (Bartram) Small. Commercial saw palmetto preparations include the partially dried or dried fruit, in the whole or powdered (fine and very fine) form. These bulk materials are used to make teas, capsules, tinctures, liquids, and semi-solid extracts with or without standardization of varying strengths. A liposterolic oily extract (LESP), prepared with either *n*-hexane, 90% ethanol w/w or by supercritical fluid extraction with CO_2, standardized to 70 to 95% free fatty acids, has been used for the symptomatic treatment of lower urinary tract symptoms (LUTS) secondary to mild to moderate benign prostatic hyperplasia (BPH). Although the industry is beginning to institute and mandate good manufacturing procedures among its members, the health care practitioner and consumer should be aware that commercial preparations can vary in quality and strength from one manufacturer to another.

Chemistry:

The principle chemical constituents consist of:

Phytosterols, fatty acids, carbohydrates, monoacylglycerides, and selected other compounds. Of these, the probable active compounds are among the phytosterols, fatty acids and their ethyl esters, and monoacylglycerides.

Reported use:

Traditional and Folk Medicine Use: Saw palmetto has been used in males to tone and strengthen the reproductive system and specifically for symptoms of prostatic enlargement. In women, it has been used occasionally to reduce ovarian enlargement, and increase the size of small, undeveloped mammary glands. In both sexes, it has been used as a general tonic, for genitourinary problems, to increase sexual vigor, and as a diuretic.

Modern Medical Use

Twenty-nine published studies on the use of saw palmetto for the treatment of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) were identified in a search of the international medical literature conducted through August 1999 (see Appendix A for bibliographic list). This search identified seven placebo-controlled trials (14-16, 18, 19, 24, 75), one active-controlled trial vs. finasteride (13), one active-controlled study vs. an alpha-adrenergic blocking drug (70), and one meta-analysis (1), all meeting a USP quality standard of Level II or higher. The products tested in these studies were commercial liposterolic extracts of saw palmetto given at a dose of 160 mg twice a day.

These studies provide evidence of moderate scientific quality that commercial extracts of saw palmetto at a dose of 160 mg twice a day are more effective than a placebo in relieving lower urinary tract symptoms of benign prostatic hyperplasia including frequency, urgency, dysuria, nocturia, and impaired urinary flow. These effects are reported to begin within 30 days of treatment and to continue through at least 6 months, the longest period studied to date. There is a large placebo effect in studies in this field. Saw palmetto extracts do not significantly

affect prostatic size or reduce PSA (Prostate Specific Antigen) levels in the blood; nor do they appear to alter sexual function. Common side effects are mild and not consistently different from those reported in patients on placebo. No serious adverse events are known to be associated with saw palmetto.

Global Contemporary Use:

Countries in which data from prescription and over-the-counter pharmacy sales and use are available indicate that in many European countries plant extracts, including saw palmetto, are used for patients with early and moderate outflow tract obstruction due to BPH. The German Commission E has evaluated saw palmetto as safe and effective for urination problems due to benign prostatic hyperplasia stages I and II (acc to Alken).

Dosage range:

Note: All dosage ranges given are adult doses unless otherwise specified.

Traditional Preparations:

Tea—1 to 2 grams per day. As a decoction, bring to a boil 1 cup of water and one third the total daily dose of saw palmetto fruits and simmer gently for 5 minutes. Drink 1 cup three times daily. As this is a hydrophilic extract process, it contains few lipophilic components.

Liquid Extract— (BPC 1934P), 1:1 herb to extract ratio (HER), 0.6 to 1.5 mL three times daily.

Tincture— 80% alcohol (fresh fruit, 1:2[HER], dried fruit, 1:5[HER]), 1 to 2 mL three to four times daily.

Clinical Trial Preparations:

Liposterolic Extract (LESP)— 320 mg orally once daily or 160 mg twice daily (liquid or solid), with an approximate 10:1 herb to extract ratio (HER), standardized to 70 to 95% free fatty acids, has been studied for symptomatic treatment of BPH stage I and II.

All doses should be taken with food to minimize gastric disturbances.

Precautions/potential risks:

Use of saw palmetto in children and pregnant or breast-feeding women has not been studied and such use is not recommended. No drug interactions or medical contraindications have been reported with use of saw palmetto. Although no clinical evidence has been reported to date, the possibility of endocrine or alpha-adrenergic blocking effects in combinations with other drugs cannot be excluded, as scientific studies of interactions with other drugs have not been conducted. Patients should have a medical examination before using saw palmetto for the treatment of benign prostatic hyperplasia to rule out prostate cancer.

Side/adverse effects:

Clinical studies indicate that saw palmetto is well tolerated by most patients, with the primary reported side effects being mild gastrointestinal complaints such as nausea and diarrhea. A systematic review of saw palmetto found a withdrawal rate from clinical studies of 9.1% for S. repens, 7% for placebo, and 11.2% for finasteride. Saw palmetto has not been reported to be toxic in humans or animals.

SAW PALMETTO PROTOCOL

Search Strategy

Five electronic databases, (EMBASE, MEDLINE, NAPRALERT, ChemAbstracts and Cochrane Library) were searched with follow-up checking of bibliographies through August 1999 using the following terms: *Serenoa repens, Sabal serrulata,* saw palmetto, sitosterols, phytosterols, cabbage palm, American dwarf palm, benign prostatic hyperplasia, and lower urinary tract symptoms. Foreign and domestic references of pertinent articles, reviews, meta-analyses and clinical trials were identified and reviewed during this search.

Selection Criteria

Eligible trials for the effects of saw palmetto on lower urinary tract Symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) were limited to randomized controlled trials (RCTs) that compared the botanical with placebo, no saw palmetto, or an appropriate active or historical control and included men with diagnosed BPH. All studies using combination products were eliminated except in the case of meta-analysis. There were no qualifiers applied for size or duration of the study. All types of studies in humans were used to assess adverse clinical effects.

Data Abstraction and Analysis

To facilitate comparisons, abstraction was carried out using a standard data abstraction form. The checklist along with specific criteria for levels of evidence (see appendix B) set out by the panel, were the basis of the overall rating of the studies. Authors were not contacted regarding the studies nor was there any attempt to obtain raw data for statistical evaluation; thus it is possible that some of these studies would be considered of highest quality if more thorough descriptions of procedures were available from the authors. This report considers quality of methodology based *only* on the report of the study in the scientific journal in which it was published. Evidence tables were used to compare relationships between clinical outcomes, participant characteristics, and methodological characteristics. Statistical analysis, when reported, was checked for appropriateness.

Description

Nomenclature

Botanical name: *Serenoa repens* (Bartram) Small (69)
Synonyms: *Serenoa serrulata* (Michaux) Nichols or *Sabal serrulatum* Schultes or *Sabal serrulata* (Michaux) Nutall ex Schultes (5, 6).
Family: Arecaceae (*alt.* Palmae) (5, 7, 8).
Common names: Saw Palmetto, American dwarf palm tree, cabbage palm, sabal (5, 7).

Plant description/distribution

Saw palmetto is native to and grows wild in North America, forming colonies in sandy soils from Texas and Louisiana, east to South Carolina, and south to Florida (8, 6). It is widely distributed also in

various islands in the Bahamas and Cuba (71). This species grows on acid or alkaline soils, on sandy dune hammocks, pinelands, or prairies, and is the predominant shrub in the fire flatwood ecosystem (9). Its most extensive development occurs in the lower coastal plains of Georgia and Florida (6).

The plant is an evergreen shrub, usually 2 to 10 feet tall, with creeping or horizontal rhizomes (6, 9). Occasionally the species reaches the size of a small tree, up to 20 to 25 feet (6). The common name, saw palmetto, derives from the ascending fan-shaped leaves, erect, 1 to 2.5 feet broad, stiff, and glabrous (non-hairy) (8,9). In the Northern Hemisphere, blooming occurs from April to early June and fruits ripen during September and October (6). Fruits are subspherical to ovoid drupes, green to yellow before ripening and bluish-black to dark brown when ripe.

Commercial source

The commercial saw palmetto products and the medically active constituents are derived from the ripe (fresh, partially dried, or dried) fruits of *Serenoa repens* (Bartram) Small. The majority of the world's supply of saw palmetto fruits comes from an area near Cape Canaveral, Florida (6). Commercial saw palmetto preparations include the dried or partially dried fruit, whole or ground into a powder (fine and very fine). These bulk materials are used to make teas, capsules, tinctures, liquid extracts, and semi-solid extracts with or without standardization. A liposterolic oily extract (LESP), extracted either with *n*-hexane, 90% alcohol w/w or prepared by supercritical fluid extraction with CO_2, and standardized to 70 to 95% free fatty acids has been used and clinically studied for the treatment of benign prostatic hyperplasia (BPH) stages I and II (10). The liposterolic extracts used in the clinical trials are licensed products primarily manufactured in Europe to specific standards and manufacturing processes. Such extracts are also manufactured and distributed in the United States under various trade names.

Note: Health care professionals and consumers should be aware that herbal products generally are marketed in the United States as dietary supplements and are regulated by the Dietary Supplement Health and Education Act (DSHEA). This legislation authorizes the FDA to issue "good manufacturing practice" (GMP) regulations, that describe mandatory conditions under which dietary supplements must be prepared, packed, or held. Due to the diversity of products classified as dietary supplements, the issuing of GMPs is very complex. The FDA has proposed such mandates but they are not yet official. While the law requires that dietary supplements adhere to GMPs, currently there are no uniform requirements. Consequently, the responsibility for producing products of good quality and with standardized practices rests solely with the manufacturer and is voluntary. Some commercial products may contain plant parts other than those considered active or desirable. The quality, purity, and strength of herbal products may also vary with the seasons, the geographical source of the plants, the time and conditions of harvest, the drying and processing procedures used for the raw material, and the formulation and manufacturing of the final dosage form.

USP-NF Standards

The *NF* monograph for saw palmetto requires a lipophilic extract content of not less than 7% and that the sum of the percentages of all fatty acids be not less than 9%, and specifies appropriate botanical characteristic (macroscopic and microscopic), chemical identification, and a limit for pesticides. Microbial limits, Total ash, Acid-insoluble ash, Heavy metals, Volatile oil content, and Foreign organic matter are also specified. A mixture of 11 methyl esters of fatty acids (methyl laurate, methyl oleate, methyl myristate, methyl palmitate, methyl palmitoleate, methyl linoleate, methyl linolenate, methyl caproate, methyl caprylate, methyl caprate, and methyl stearate) serve as marker substances for saw palmetto (35, 42).

Note: Manufacturers are not required to adhere to the USP-NF standard. If a manufacturer voluntarily elects to claim NF status on the product label, however, then the product must meet the USP-NF standard.

Chemistry

Numerous fatty acids, their ethyl esters, and sterols have been isolated from saw palmetto. Possible active constituents include phytosterols (β-sitosterol and β-sitosterol 3-*O*-β-D-glucoside), free fatty acids (capric acid, caproic acid, caprylic acid, lauric acid, myristic acid, oleic acid, linoleic acid, linolenic acid, palmitoleic acid, palmitic acid, and stearic acid), and their ethyl esters and glycerides (1, 5, 42). Specifically, two monoacylglycerides, 1-monolaurin and 1-monomyristin, have shown moderate biological activity (11). Other constituents are carbohydrates (invert sugar, mannitol, high molecular weight polysaccharides with galactose and arabinose), aromatic acids (ferulic acid and vanillic acid), anthranilic acid, and syringaldehyde (5, 12).

Reported uses

Folk medicine and traditional systems of medicine

Saw palmetto was one of the most important foods for Florida's pre-Columbian, non-horticultural peoples and later Creek immigrants. Even today, among the older Seminole population the fruit is still consumed in moderate quantities and a sweetened traditional drink called "shiope sofkee" is made from the juice (48). The Native Americans of the southeast regions considered saw palmetto useful as a nutritional tonic (a use to which the high oil content in the nuts and flesh of the fruits probably contributed), as a diuretic, a sedative, and an aphrodisiac. The steam from cooking fruits was inhaled for use in bronchitis and to relieve irritated mucous membranes and as an expectorant (45).

Saw palmetto was largely unknown by the European and American medical communities until the second half of the 19th century (45).

The plant was first considered a nutritive tonic and a useful remedy for relieving local irritations of the mucus membranes of the respiratory, digestive, and reproductive tracts. Over time it became widely used for the relief of urinary difficulty and pain in men with benign prostatic hyperplasia (3). Benefit was attributed to an ability to increase bladder tone and reduce urinary urgency, allowing better contraction and expulsion of urine with reduced pain. Saw palmetto also was used for

certain uro-genital disorders in women, including ovarian enlargement, dysmenorrhea, and for stimulating mammary gland secretion. (3, 44). Saw palmetto was also frequently used to relieve chronic bronchial coughs and laryngitis (3, 4).
The traditional preparations available were of three main types:
The fluid extract— 1:1 HER (herb to extract ratio), as defined in the USP 1916, consisted of the powdered fruits, extracted with a menstrum of alcohol and water through the process of percolation. A standard dose was 1 ml taken at various intervals throughout the day (41).
Aromatic oil— The pulp of the fruit yields by pressure 1.5% aromatic oil of a fruity odor. It is brownish-yellow to dark red, soluble in alcohol, ether, chloroform, and benzene (43).
Fixed fatty oil— Obtained exclusively from the nut, is chemically different from that derived from the pulp. It is a thick liquid of a greenish color, only slightly soluble in alcohol, insoluble in water, and soluble in benzene, chloroform, and ether (44). It was also noted that the same pungent greenish oil was present in a distillation of the fresh fruits mixed with water and it separated out from the fluid extract prepared with the fresh fruits.

Global contemporary practice
The German Commission E has evaluated saw palmetto as safe and effective for urination problems in benign prostatic hyperplasia stages I and II (acc to Alken). Countries in which data from prescription and over-the-counter pharmacy sales and use are available indicate that in many European countries plant extracts, including saw palmetto, are used for patients with early and moderate outflow tract obstruction due to BPH (68, 5). In Germany and Austria, herbal medicines are the first-line treatment more than 90% of the time for patients with early and moderate outflow tract obstruction due to BPH (68). Over 50% of German urologists are reported to prefer herbal medicines to chemically derived agents in the treatment of mild to moderate symptoms (68).

Modern medical use
Twenty-nine published studies on the use of saw palmetto for the treatment of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) were identified in a search of the international medical literature conducted through August 1999 (see Appendix A for bibliographic list). Ten of these studies were considered to be trials of sufficient size, duration, and quality to permit scientific assessment of the efficacy of saw palmetto for this use. These studies are summarized in the evidence tables at the end of this monograph. This body of evidence consists of seven placebo-controlled trials (14-16, 18, 19, 24, 75), one active-controlled trial vs. finasteride (13), one active-controlled study vs. an alpha-adrenergic blocking drug (70), and one meta-analysis of 18 published studies (1). The meta-analysis included studies containing saw palmetto in combination with other botanical ingredients, which accounts for the larger number of studies in this publication than are included in the evidence tables in this monograph.
Study duration ranged from 21 days to 26 weeks. Specific end points varied somewhat, and rating scales used to measure symptoms were often not standardized. It is not clear that any of the published studies was monitored to international standards. All studies were considered to be Level II in quality, although within this category some studies

were much better reported than others. Trials were judged Level II in quality because of inadequate descriptions of the statistical analyses, the method of blinding and randomization, rating scales used, incomplete reporting of the data, and improper design.

The botanical preparations tested in the nine clinical trials were not identical. All studies used liposterolic extracts but with differing extraction procedures; however, all extracts contained a total amount of 70 to 95% fatty acids, esters, and sterols. Six of the studies used products produced by *n*-hexane extraction (13, 15, 18, 19, 70, 75), two by supercritical carbon dioxide extraction (14, 16), and one by alcohol extraction (24). The meta-analysis contained trials using saw palmetto products produced by varying extraction procedures and in combination with other botanicals. In all studies the dose of saw palmetto extract given was 160 mg twice a day.

Five of the seven placebo-controlled trials (14, 16, 18, 19, 75) reported significant improvement in lower urinary tract symptoms in patients with benign prostatic hyperplasia. Symptom improvement for nocturia ranged from 33 to 74% over baseline for saw palmetto vs. 13 to 47% for placebo. Significant improvement was also reported in maximum (19 to 51%) and mean (26 to 61%) urinary flow rates. The meta-analysis (1) found overall improvement rates of 23% (74% on drug vs. 51% on placebo) in patient-assessed rating scales and of 25% (63% on drug vs. 38% on placebo) in physician-assessed rating scales. Statistically significant improvement also occurred in nocturia (25%), peak urine flow (24%), mean urine flow (28%), and residual volume (43%).

Two of the seven placebo-controlled trials (15, 24) reported no significant improvement in lower urinary tract symptoms or urine flow in patients treated with commercial extracts of saw palmetto.

In a large active-controlled study of 1098 patients (13), a saw palmetto product given at a dose of 160 mg twice a day was compared with finasteride, 5 mg once a day, for a period of 26 weeks. Symptom scores were reduced by a mean of 38% in both groups, and mean flow rates increased significantly in both groups. Finasteride, as expected, produced an 18% decrease in prostatic size vs. 6% for saw palmetto. Because of the low dose, and because no placebo control arm was included in the study, finasteride has not been shown to produce statistically significant improvement in symptoms during the first 6 months of its administration, this study, in spite of its large size, does not provide strong evidence for the effectiveness of saw palmetto. However, this study does provide good data on the comparative side effects of the two interventions. Twice as many dropouts occurred in the saw palmetto group (28 patients vs. 14 patients). Common side effects were similar in both groups. Mean sexual function score decreased significantly in the finasteride group but not in the saw palmetto group. PSA levels decreased by 41% in the finasteride group, but no significant change occurred in the saw palmetto group.

In a relatively small comparative study vs. alfuzosin, an alpha-adrenergic blocking drug (70), symptom scores and flow rates improved in both groups over the 3 weeks of the study. Changes tended to be greater in the alfuzosin group, but the difference between groups was statistically significant only for total symptom and obstructive symptom scores. No placebo control group was included in the study.

In summary, the medical literature contains five placebo-controlled trials and one meta-analysis providing evidence for the efficacy of commercial extracts of saw palmetto for the treatment of lower urinary tract symptoms of benign prostatic hyperplasia. Two placebo-controlled trials have found no evidence of efficacy. In a large comparative study vs. finasteride and a smaller comparative study vs. an alpha-adrenergic blocking drug, saw palmetto produced generally similar symptomatic improvement, but these studies provide no clear evidence with respect to efficacy because of their design.

Dosage range

When using dietary supplements and botanical products in the United States, the consumer and health care practitioner should be aware that the quality, standards, and strength can differ from one manufacturer to another, depending on the raw materials and process used for extraction. An encapsulated powdered fruit product has a dosage range like that of the bulk herb (1 to 2 grams per day) while the dosage of a preparation extracted with 90% alcohol with a 10:1 herb to extract ratio (HER) will be very different than that extracted with 80% alcohol and a 1:4 HER. In such cases the knowledge of the herb to extract ratio is critical for making a dosage decision.

Note: All dosages given are adult doses unless otherwise specified and they are approximate ranges as the individual strength of different commercial preparations varies.

Traditional preparations*:*

Tea— 1 to 2 grams per day. As a decoction, bring to a boil 1 cup of water and one third the total daily dose of saw palmetto fruits and simmer gently for 5 minutes. Drink 1 cup three times daily (5, 53, 62).

Note: This preparation results in an extraction of primarily the non-lipophilic components.

Tincture— 80% alcohol (fresh fruit, 1:2 (HER), dried fruit, 1:5 (HER), 1 to 2 mL three times daily (44, 53).

Liquid Extract —1:1 HER (BPC 1934) 0.6 to 1.5 mL three times daily.

Clinical trial preparations:

Liposterolic Extract (LESP)— 160 mg orally twice daily or 320 mg once daily of a liposterolic extract (LESP) prepared with either *n*-hexane, 90% ethanol w/w, or by supercritical fluid extraction with CO_2 and standardized to 70 to 95% free fatty acids has been studied for symptomatic treatment of urinary complications of BPH (1,13-16,18, 19,24,70,75). This results in an extract of about a 10:1 concentrate compared to the original dried fruit, which corresponds to about 3 grams of dried fruits daily. These oily extracts are, in most cases, directly encapsulated into soft gelatin capsules without any additional auxiliaries (65). Although these preparations are standardized to the same marker compounds, differences do exist among the liposterolic extracts when prepared by different extraction procedures. What exactly these differences are and their therapeutic significance has yet to be elucidated.

All doses should be taken with food to minimize gastric disturbances.

Product information

Availability
Saw palmetto is available in the United States, as capsules, liquid or semi-solid extracts, tinctures, teas, and a liposterolic extract (LESP) prepared with *n*-hexane, 90% ethanol w/w, or by supercritical fluid extraction with CO_2 and standardized to 70 to 95% free fatty acids These are manufactured from the bulk materials of dried or partially dried fruit, whole and powdered.

Combinations
Saw palmetto is often combined with pumpkin seed oil or extract, nettle root extract, and *Prunus africana* extract. Many countries in Europe, particularly Germany, use these phytotherapeutic agents alone or in combination to treat prostatic problems (45). There are many combination products available in the United States combining these and other entities with saw palmetto.

Packaging and storage
Serenoa repens preparations should be stored away from light in a well-closed container below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer (42).

Pharmacology
The mechanism by which saw palmetto may be useful to treat the symptoms of benign prostatic hyperplasia is not completely understood. *In vitro* pharmacodynamic studies indicate that *S. repens* may have multiple mechanisms of action in BPH. The mechanisms most likely involved include inhibition of type 1 and type 2 isoforms of 5α-reductase, inhibition of binding of dihydrotestosterone to cytosolic androgen receptors in prostate cells, and $alpha_1$-adrenergic blocking activity. Mechanisms also possibly involved but less well demonstrated are inhibition of prolactin and growth factor–induced prostatic cell proliferation, an antiestrogenic activity, and/or an anti-inflammatory effect (50 27).

Inhibition of 5α-reductase activity
In vitro
Saw palmetto may act by inhibiting 5α-reductase, the enzyme responsible for conversion of testosterone to dihydrotestosterone (DHT). Several *in vitro* experiments in cultured human foreskin fibroblasts have found extracts of *Serenoa repens* to be strong and specific inhibitors of the enzyme 5α-reductase (20, 50, 54, 55). Studies using an eukaryotic (baculovirus-directed insect cell) expression system found that LESP (liposterolic extract) inhibits activity of both isoenzymes of 5α-reductase, whereas finasteride selectively inhibits type 2 (21). Moreover, finasteride demonstrates a competitive inhibition, while LESP displays noncompetitive inhibition of the type 1 isozyme (22, 23). Similarly, an experiment performed on rat prostate gland cells using an *n*-hexane extract of *Serenoa repens* at an IC_{50}= 88.2 ± 2.6 μg/mL showed specific inhibition of the enzyme 5α-reductase, which thereby slowed the conversion of testosterone to DHT (17).

In vivo human/animal

A 7-day study in which testosterone-stimulated, castrated rats were given an *n*-hexane extract of *Serenoa repens* at doses of 180 or 1800 mg per day found no 5α-reductase inhibition nor decrease in serum DHT (25). A similar 7-day study in healthy male volunteers given 160 mg twice daily found similar results (26). As an explanation for the conflicting observations from previous studies (20, 46), the authors suggest that the high doses used in the prior studies resulted in the non-specific inhibition of 5α-reductase and androgen binding. They contend that the doses used by the earlier investigators were supraphysiologic and thus not clinically relevant.

Alpha$_1$ adrenergic blocking activity

In vitro

Several phytotherapeutic agents, including saw palmetto extract oils, were tested for their ability to inhibit [^{3}H] tamsulosin binding to human prostatic α_1-adrenoceptors and [^{3}H]prazosin binding to cloned human α_{1A}-and α_{1B}-adrenoceptors in rat-1 cells. All saw palmetto extracts inhibited radioligand binding to human alpha$_1$-adrenoceptors in a non-competitive, concentration-dependent manner (60). Extract oils and powders were tested. For the two extract powders, maximum inhibition was obtained with 125 and 160 μg/mL and was 74 ± 4% and 59 ± 17%, respectively. The saw palmetto oils behaved slightly differently. They inhibited [^{3}H]prazosin binding almost completely.

Antiandrogenic and antiestrogenic activity

In vitro

The antiandrogen effects of saw palmetto have been reported in several *in vitro* experiments demonstrating its inhibitory effect on the binding of DHT to androgen receptors in the cytosolic component of prostate cells (20, 30, 46, 58). One *in vitro* experiment using isolated rat prostate found that a saw palmetto *n*-hexane extract at concentrations of 0.33 mg/mL inhibited the binding of a synthetic androgen to cytosolic receptor sites (46). Results of another *in vitro* experiment demonstrated that a liposterolic extract of *Serenoa repens* inhibited binding of dihydrotestosterone to androgen receptor sites in cultured human foreskin fibroblast (20). Experiments using human tissue samples (i.e., abdominal wall skin, myometrium, prepuce, and vaginal skin) found that *n*-hexane extract of *Serenoa repens* inhibited dihydrotestosterone and testosterone binding by approximately 40% (30). The authors of an experiment to study the effects of a liposterolic extract of saw palmetto (LESP) on two prostatic cancer cell lines differing in androgen responsiveness also concluded that their findings supported anti-androgenic activity of the extract. Variable concentrations (≤10 mg/mL to ≥25 mg/mL) of an *n*-hexane_preparation antagonized androgen-stimulated cell growth in a concentration-dependent manner (58). Binding of DHT receptors is not an unequivocal finding, however. One study further tested the effect of saw palmetto on DHT binding using a liposterolic extract produced by supercritical CO_2 extraction. No effect on the (3H) dihydrotestosterone binding either with an undiluted extract or with dilutions up to 1:1000 was observed (54).

In vivo animal

A study using hormone-treated castrated rats found that administration of an *n*-hexane extract of saw palmetto for 90 days inhibited hormone-induced total prostate weight, with maximum benefits beginning 30 days after treatment was begun (28). A similar study used xenografts of human benign hyperplastic prostate tissue transplanted into three groups of athymic nude mice. In groups II and III the tissue was stimulated with the hormones 5α-dihydrotestosterone and estradiol. Group I received no treatment and served as the control. In addition, animals of group III were treated with the lipophilic extract of saw palmetto. Significant inhibition of tissue growth was observed in group III as compared with group II ($P<0.05$). However, histologically no differences were visible between groups II and III. In group I (the control) atrophy of the graft was observed as expected (73).

Other hormonal effects

In vitro

Several researchers (56, 57) have investigated the inhibition of prostate growth by blocking the binding of prolactin to specific receptors in the prostate and/or interfering with signal transduction processes. Pretreatment of Chinese hamster ovary cells with 1 to 10 mg/L of LESP completely inhibited the effects of prolactin on various pathways of receptor signal transduction and ultimately prolactin-induced prostatic growth (56). Human prostate tissue samples biopsied from patients with BPH were cultured *in vitro* with the presence or absence of basic fibroblast growth factor (b-FGF) or epidermal growth factor (EGF)(57). The saw palmetto extract did not significantly inhibit basal cell proliferation at any dose when separately compared with b-FGF. However, when saw palmetto was incubated with either b-FGF or EGF, it significantly inhibited both b-FGF and EGF-induced cell proliferation at the highest dose of 30 μg/mL.

In vivo human

In an effort to demonstrate that LESP has a multi-site mechanism of action, twenty-five men with BPH were randomly assigned to two treatment groups, a control group receiving no treatment and a treatment group receiving 320 mg per day of an *n*-hexane extract for 3 months. Each patient then underwent suprapubic biopsies from three prostatic regions: periurethral, subcapsular, and intermediate. The concentration of testosterone (T), dihydrotestosterone (DHT), and epidermal growth factor (EGF) in each prostatic region was measured by radioimmunoassay. Each prostatic region was evaluated with radioimmunoassay for levels of testosterone (T), dihydrotestosterone (DHT), and epidermal growth factor (EGF). Those treated with saw palmetto exhibited regionally distinct, statistically significant reductions in prostatic DHT and EGF levels along with an increase in T levels. Lower DHT (2363 ± 553 pg/gram, ($P < 0.001$) and EGF (6.98 ± 2.48 μg/gram tissue, $P <0.001$) values in the periurethral zone and an increase in T values in all three prostatic regions, with the highest values seen in the periurethral area (1023 ± 101 pg/gram tissue, $P < 0.001$) demonstrate the capacity of the extract to inhibit *in vivo* 5α-reductase in human pathological prostate. These biochemical effects, particularly in the periurethral region, may be associated with the clinical improvement of the obstructive symptoms of BPH (59).

Another study in BPH patients receiving 160 mg of a saw palmetto extract twice a day for 30 days reported no change in plasma concentrations of testosterone, follicle-stimulating hormone, or luteinizing hormone (29). The authors concluded that saw palmetto does not act via systemic changes of hormone levels.

Anti-inflammatory activity
In vitro
Several studies demonstrated that inhibition of synthesis of inflammatory metabolites of arachidonic acid, through a double blocking of cycloxygenase and lipoxygenase pathways, could be involved in the anti-inflammatory and antiedematous properties shown by the *S. repens* extract (31, 32). An *in vitro* study of LESP prepared by supercritical fluid extraction with carbon dioxide, separated into three fractions, found the fraction containing the acidic lipophilic compounds to be a dual inhibitor of cyclo-oxygenase and 5-lipoxygenase in the acidic lipophilic fraction, while the fatty alcohols and sterols were inactive (31). Another *in vitro* study demonstrated the potent inhibition of the production of 5-lipoxygenase metabolites (especially leukotriene B4) by LESP (Permixon®) The production of 5-lipoxygenase metabolites was inhibited at concentrations as low as 5 μg/mL and 50% inhibition was achieved with concentrations of approximately 13 μg/mL (32).

Antispasmodic activity
In vitro
The spasmolytic effects of two lipophilic extracts from saw palmetto (total lipidic and saponifiable) were studied on isolated smooth muscle of rat uterus, bladder, and aorta. The antispasmodic activity appeared to be related to inhibition of calcium influx and an activation of the sodium/calcium ion exchanger (33). Follow-up research suggested that cyclic AMP might be a possible mediator, together with the involvement of post-transcriptional induction of protein synthesis (34).

Pharmacokinetics

Pharmacokinetics is one of the most difficult aspects of botanical products to measure and identify. Most often not all constituents are known and, of those identified, their therapeutic contribution to the whole is largely unknown. The best attempt at pharmacokinetic understanding at this point is to measure an identified surrogate or marker compound, realizing that this may be a substitute for the active, or more likely, various active components. These are not fully understood and the relevance of the clinical information provided must be evaluated on a case-by-case basis.

Distribution
The only available distribution information is from a study in rats given a radioactive *n*-hexane liposterolic extract of saw palmetto. Recovery of the radioactive labeled isolates of lauric acid, oleic acid, and β-sitosterol revealed that tissue concentrations were highest in abdominal fat tissue, prostate, and skin, with lesser amounts distributed to the liver and urinary bladder (35).

Half-life
No reports in the literature were found that clearly identified the components studied. Elimination half-life and peak serum were reported from one study done on 12 healthy young men; however, in this particular study the second component was not identified but appeared consistently among the extracts studied (61).

Peak serum concentration
No reports in the literature were found that clearly identified the components studied.

Precautions/Potential risks

Mutagenicity
Five different *in vitro* assays followed by *in vivo* oral administration to mice resulted in no mutagenic incidence with saw palmetto. There was no indication of dose given or duration of study (77).

Pregnancy/Reproduction
Studies conducted at the University of Pavia, in Italy, found no indication of teratogenic effects at doses up to 600 mg/kg in both rats and rabbits. Further, when both male and female rats were given doses up to 600 mg/kg per day for 10 weeks prior to mating and during gestation, no effects on fertility or offspring were noted (77). No clinical studies in pregnant humans have been reported. The use of saw palmetto in pregnancy has not been tested scientifically and is not recommended (7,62).

Breast-feeding
It is not known if saw palmetto constituents are distributed into breast milk; however, because of potential hormonal effects, use of saw palmetto in lactating women is not recommended (7).

Pediatrics
There are no reported studies of *Serenoa repens* in the pediatric population. The use of saw palmetto has not been studied scientifically in children, and is not recommended.

Geriatrics
Older adults have been included in the clinical studies of *Serenoa repens* and no age-related adverse events have been reported.

Drug interactions and/or related problems
The possibility of endocrine or alpha-adrenergic blocking effects in combination with other drugs cannot be excluded, as scientific studies of interactions with other drugs have not been conducted.

Laboratory value alterations
There have been no reports of laboratory value alterations in humans or animals due to use of saw palmetto.

Medical considerations/Contraindications

No medical contraindications have been reported with the use of saw palmetto. There is no reliable clinical information about use of saw palmetto in patients suffering from hormonal-dependent diseases other than benign prostatic hyperplasia (7). However, the possible antiandrogenic and antiestrogenic activity of the plant constituents should be taken into consideration when evaluating its use under these circumstances.

Patients should have a medical and urological evaluation before beginning treatment with saw palmetto to rule out prostate cancer, nephritis, urinary tract infections, and other nephrourologic disorders (37). Although there have been anecdotal reports in the literature (76) that saw palmetto decreases Prostate Specific Antigen (PSA) levels, this has not been found in clinical trials (13, 38, 63). Unlike finasteride, the extract does not appear to lower serum PSA concentrations and has minimal effect on the prostate volume. (13,38, 63)

Patient monitoring

No tests for monitoring are necessary specifically for patients taking saw palmetto. All patients with symptomatic benign prostatic hyperplasia should be followed medically because of the potential need for further intervention in progressive disease (37).

Side/Adverse effects

A systematic review of saw palmetto found a withdrawal rate from clinical studies to be 9.1% *S. repens*, 7% placebo, and 11.2% finasteride (1). The pooled tolerability data from those 18 randomized trials indicate that *S. repens* is well tolerated. Gastrointestinal complaints (i.e., abdominal pain, diarrhea, constipation, and nausea) were the most frequently reported adverse events (1). A large randomized multicenter trial of 1098 patients reported a hypertension rate of 3.1% for saw palmetto (versus 2.2% with finasteride)(13). Other reported side effects in this study with an occurrence rate of 1% or more include abdominal pain, back pain, decreased libido, impotence, headache, and urinary retention. No statistically significant differences were noted between the two treatment groups for any intercurrent event.

Toxicity

In acute toxicity studies conducted on the mouse, rat, and dog over 13 to 26 weeks, the LD_{50} could not be determined on any of the animals. With intraperitoneal injections at doses of 1080 mg/kg the rat exhibited clinical signs of depression, dyspnea, and greasy fur; however, the rat and dog given oral doses of 50 grams/kg and 10 grams/kg, respectively, exhibited no adverse clinical signs. The authors concluded that the LD_{50} should be considered higher than these doses (77).

Status

Regulatory status

Country	Regulatory Status
Austria	Approved as a drug with RX only status (74).
Canada	Saw palmetto is authorized for sale as a traditional herbal medicine with the indication of increasing the flow of urine (64).
Denmark	Approved as a drug with OTC status for use in various urinary problems associated with BPH (45).
France	It has OTC status but is primarily prescribed by a physician (45,74).
Germany	The German Commission E has evaluated saw palmetto as safe and effective for urination problems in benign prostatic hyperplasia stages I and II (acc to Alken). It has OTC status but is primarily prescribed by a physician (45,74).
Italy	Approved as a drug with RX only status (45).
Spain	The standardized liposterolic extracts are approved as a drug with RX only status. Non-standardized extracts are approved as dietary supplements (45).
Sweden	Approved as a drug with OTC status for use in various urinary problems associated with BPH (45).
Switzerland	Approved as a drug with OTC status for use in various urinary problems associated with BPH (45).
United States	Saw palmetto is not approved as a drug product for any therapeutic use in the U.S. Provided claims are not made that cause a product to be subject to regulation as a drug, products containing this substance may be marketed as "dietary supplements." Dietary supplements are not subject to pre-market review or approval by the Food and Drug Administration (FDA) (39).

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Saw palmetto extract for the treatment of benign prostatic hyperplasia (BPH)

AUTHOR/ STUDY/ RATING	METHODS/GOALS	PARTICIPANTS	OUTCOMES
Braeckman J, 1997 (14) *Sponsors: Not specified* *Evidence Rating*: **IIA**	*What was tested: S. repens* (Prostaserene®) orally 160 mg bid vs. placebo *Goal:* confirm efficacy and tolerance of *S. repens* extract vs placebo in symptomatic BPH *Study design*: Randomized, double-blind, placebo-controlled, multicenter *Treatment duration*: 3 months *Assessment:* 0, 30, 60, 90 d QOL questionnaire, DRE, prostate volume by ultrasound, PVR volume *Randomization:* – independent center randomized *N based on power analysis?* Yes *Statistical analyses* – Student's t-test, chi-square, Fischer's exact, ANOVA	*Inclusion criteria*: Hyperplasia of prostate, flow rate between 5 and 15 mL/s *Exclusion criteria*: Debilitating concomitant disease, > 80 yrs. old, cancer, residual volume > 60 mL, using other BPH treatment, prostate abnormalities *Total N:* 238 (205 evaluable) *N per group*: 99 placebo, 106 *S. repens* *Dropouts per group*: 4 placebo, 5 *S. repens* lost to follow-up or withdrew consent before day 30. 24 patients did not fill inclusion criteria, 229 evaluated for safety, 205 evaluated for efficacy	*Author's major conclusions*: *S. repens* improvement statistically superior to placebo and well tolerated Urinary volume difference (placebo – tx) 40 mL (95% CI 6, 75) Total symptom score, (placebo – tx) at 60 d. .97 difference (95% CI 0.2, 1.74) Total symptom score, (placebo – tx) at 90 d 1.40 difference (95% CI 0.58, 2.23) Treatment Placebo Frequency 51% imp 32% imp $p < 0.05$ Nocturia 67% imp 47% imp $p < 0.05$ Dysuria 44% imp 19% imp $p < 0.01$ Urgency 57% imp 21% imp $p < 0.01$ Patient/physician evaluations and hesitancy $P < 0.01$ *(values not reported)*. Nonsignificant results at $p \geq 0.05$ for prostate volume, max and mean flow rate, residual volume, perineal heaviness *(all not reported)*, and side effects *Side effects:* Both groups reported GI upset, headache, allergic rx; treatment group reported 2 patients with increased blood pressure. Overall 9.1% treatment vs. 8.3% placebo reported

COMMENTS: This study is very well conducted, but does not include intent-to-treat analysis. The urological symptom score was not a standardized scale. It consisted of a questionnaire divided into symptom groups, frequency, nocturia, dysuria, hesitancy, and perineal heaviness, scored 0 to 3; urgency scored 0 to 4. Reduction in mean total symptom scores between treated and placebo groups of .97 was significant at day 60 ($P<0.05$) and 95% CI(0.2, 1.74) and of 1.40 ($P<0.01$)with 95% CI (0.58, 2.23) at day 90. Urinary volume of treated group improved significantly ($P<0.05$) from approximately 260 to 300 mL observed at 90 days. The data show statistically significant improvement in total symptom scores at 60 and 90 days and at 90 days in frequency, nocturia, urgency, dysuria and urinary volume. Study shows no improvement in any symptoms at 30 days, and no significant improvement in max or mean flow rates or prostatic volume at any time. A disconcerting baseline comparison shows total symptom score to be significantly higher in treatment group; this was not accounted for in study analysis. Statistical analysis and methodology were all appropriate and well described.

AUTHOR/ STUDY/ RATING	METHODS/GOALS	PARTICIPANTS	OUTCOMES
Wilt TJ, et al., 1998 (1) *Sponsor:* Dept. of Veterans Affairs Coordinating Center of the Cochrane Collaborative Review Group *Evidence Rating:* **IIB**	*What was tested*: Saw palmetto extract; alone or in combination *Goal:* Conduct a quantitative meta-analysis of the existing evidence regarding the therapeutic efficacy and safety of *S. repens* *Type of study:* Meta-analysis *Treatment duration:* mean duration of all studies: 9 weeks *N based on power analysis?* Yes	*Inclusion criteria:* RCTs, control groups used, $\geq$ 30 d evaluation time, men with symptomatic BPH used in studies *Exclusion criteria: N*o clinical outcomes reported *N per group:*18 studies, N = 2939 *Dropouts per group*: Avg. 9.6%	*Author's major conclusions:* Saw palmetto leads to decreased symptom scores and increased urinary flow measures compared with placebo and has similar improvements when compared with finasteride. Significant results, $P < 0.05$, in favor of *S. repens* for: Mean urinary flow *28% improvement vs. placebo* Peak urinary flow *24% improvement vs. placebo* Residual urine *43% decrease vs. placebo* Nocturia *25% improvement vs. placebo* Urinary symptom score *28% improvement vs. placebo* Patient/physician evaluations *approx. 25% improvement vs. placebo*. Nonsignificant results, $p \geq 0.05$, reported for prostate size and adverse effects *Side effects:* 1.3% reported adverse side effects in treatment group compared to 0.9% in placebo group (not significant). Both groups reported erectile dysfunction and GI effects

COMMENTS: This is a very well conducted meta-analysis which includes all available evidence at time of publication. One problem noted is that the meta-analysis included studies with inadequate treatment allocation; however, authors state that excluding these studies did not drastically change results. Statistical analysis and study description were excellent.

AUTHOR/ STUDY/ RATING	METHODS/GOALS	PARTICIPANTS	OUTCOMES
Cukier, 1985 (18) Sponsor: Fabre Laboratories *Evidence Rating:* **IIA**	*What was tested*: Permixon 160 mg (bid) vs. placebo *Goal: E*valuate effect of *S. repens* extract on functional symptoms of BPH *Type of study:* Randomized, double-blind, placebo-controlled, multicenter *Treatment duration:* 69 d *Assessment:* 0, 30, 69 d Symptoms, global evaluation by physician and patient, and residual volume by ultrasound *Randomization:* Coded/packaged by lab *N based on power analysis?* Yes	*Inclusion criteria:* > 60 yrs old, prostatism diagnosis, no complications, at least 6 months of symptoms *Exclusion criteria:* Concomitant disease, need surgery, concurrent BPH therapy, antibiotics, anti-inflammatories, or agents liable to affect functional symptoms *N per group:* 76 placebo, 70 *S.repens* Total N = 168 (146 evaluable) *Dropouts per group*: 14 Permixon, 8 placebo	*Author's major conclusions:* Significant effect for Permixon on every symptom, good tolerance, placebo effect did occur. Diurinal frequency and nocturia reported as significant improvement and differences were more marked by the end of the trial Significant results, P < 0.05, in favor of Permixon: Treatment / Placebo Diurnal pollakiuria: 19.5% dec / 1.3% dec Nocturnal pollakiuria: 33% dec / 15% dec Severe nocturia (> 3 times/night): 25% dec / 5% dec Dysuria: 47% imp / 30%imp Residual urine: 15% dec / 52% inc Physician/patient assessments: 67% imp / 27% imp Nonsignificant results, P > = 0.05, reported for tolerance *Side effects:* Treatment group four cases of intolerance (5%) vs. seven cases of placebo group (9%). Placebo events not well described; treatment side effects included hypertension (1) and tinnitus (1) non-specific complaints (2)

COMMENTS: Although seemingly complete, this study was not described well enough to be considered high scientific quality. Results and statistical analysis in particular were not clear enough to determine if proper procedures had been used. No intent-to-treat analysis was performed.

AUTHOR/ STUDY/ RATING	METHODS/GOALS	PARTICIPANTS	OUTCOMES
Carraro, 1996 (13) *Sponsor:* Not specified *Evidence Rating:* **IIA** (**IC** if considered ONLY for adverse events)	*What was tested*: *S. repens (*Permixon®) 160 mg bid vs. Finasteride 5 mg qd *Goal:* Determine whether Permixon® and finasteride are equivalent in relieving symptoms of moderately severe BPH *Type of study:* Randomized, double-blind, multicenter *Treatment duration:* 26 wks, *Assessment:* 0, 6, 13, 26 wks. IPSS,QOL, sexual function questionnaire, urinary flow rates, at weeks 13/26, prostate volume, PVR by ultrasound, PSA *Randomization:* Computer coded *N based on power analysis?* No *Statistical analyses:* ANOVA, intent-to-treat, Wilcoxon rank sum test, Fischer's exact test	*Inclusion criteria:* Diagnosed BPH by DRE & IPSS score > 6, age > 50 yrs, max flow 4–15 mL/s, urine volume ≥ 150 mL, PVR < 200 mL, prostate size > 25mL, PSA < 10 ng/mL, if prostate < 60 mL, PSA < 15 ng/mL for prostates > 60 mL *Exclusion criteria:* Cancer of prostate, concomitant disease, prior treatment with finasteride or Permixon, diuretics, antiandrogens or alpha-blockers within the last 3 months *Total N:* 1098 (1069 evaluable received the study drug and were reevaluated at least once 536 Permixon, 533 finasteride) *N per group:* 553 Permixon, 545 finasteride	*Author's major conclusions:* Large improvements in symptoms noted for both groups; finasteride and Permixon equally effective for BPH symptoms. Significant results at 26 weeks, P < 0.05, in favor of finasteride: *S. repens* / finasteride Max urinary flow rate: 25% inc / 30% inc (mean change mL/sec): **2.7(2.1,3.1) / 3.2(2.8,3.8) Prostate volume: 6% dec / 18% dec Overall withdrawal rate: 16% / 11% Significant results at 26 weeks, P < 0.01, in favor of Permixon: Sexual function score: 6% inc / 9% dec Serum PSA levels: 3% inc / 41% dec Nonsignificant results at 26 weeks, P > 0.05: Mean urinary flow rate: 15% inc / 20% inc IPSS score*: 37% dec / 39% dec (mean decrease): **5.8 / 6.2 Quality of life*: 69% inc / 73% inc

		Dropouts per group: 86 Permixon; 61 finasteride	*Side effects:* 28 withdrawals due to side effects in Permixon group vs. 14 in finasteride group. Events experienced in equal proportions by both groups. Hypertension (3.1%), decreased libido(2.2%) most common in Permixon group; decreased libido(3%), abdominal pain (2.8%), and impotence (2.8%) were most common in finasteride group

* Not significant between groups but significant (P<0.001) from baseline ** 95% CI

COMMENTS: This is a technically excellently conducted and reported clinical trial. Because of the lack of a placebo group and the short duration, this study does not allow for determination of the true effects of Permixon. The comparison against finasteride, however, makes for an excellent comparison of side effects and adverse events. This is one of the few trials that included a 2 week wash-out for those with prior alpha-adrenergic receptor antagonists or *P. africana* exposure. No power analysis was performed, but the obviously large sample size is assumed big enough to make adequate comparisons. The IPSS total score, QOL, max and mean flow rate improved significantly from baseline for both groups but there was no significant difference between groups.

AUTHOR/ STUDY/ RATING	METHODS/GOALS	PARTICIPANTS	OUTCOMES
Descotes, 1995 (75) *Sponsor:* Not specified *Evidence Rating:* **IIA**	*What was tested*: *S. repens (*Permixon®) 160 mg bid vs. placebo *Type of study:* Randomized, double-blind, placebo-controlled, multicenter *Goal:* Assess efficacy and tolerability of S. *repens* extract in patients with symptomatic BPH *Treatment duration:* 30 d *Assessment:* 0 and 30 d Irritative symptom scores, urodynamics, physician and patient global assessment *Randomization:* Not adequately described *N based on power analysis?* No *Statistical analyses:* Wilcoxon and chi-square test	*Inclusion criteria:* BPH Alken stage I/II, nocturnal urination ($\geq$ 2 x per night), dysuria reported for > 8 wks, max flow rate $\geq$ 5 mL/sec *Exclusion criteria:* Incontinence, major concomitant disease, history of BPH surgery, placebo responders following 30 day run-in *Total N* = 215 (176 evaluable) *N per group:* 82 Permixon, 94 placebo *Dropouts:* 52 total, 27 due to initial inclusion error, 9 for protocol violation, 2 withdrew, 1 lost to follow-up	*Author's major conclusions:* Permixon significantly more effective than placebo; large placebo improvements also noted Significant results, $P < 0.05$, in favor of Permixon Treat. / Placebo Max urinary flow rate: 29% inc / 9% inc Daytime frequency: 11% dec / 3% dec Nighttime frequency: 33% dec / 18% dec Dysuria: 31% dec / 16% dec Nonsignificant results, $P > 0.05$, reported for: Patient efficacy evaluation: 71% / 68% Physician evaluation*: 57% / 47% Tolerability: 96% / 99% *Side effects:* 1 Permixon patient dropped out due to fatigue, depression, and stomach upset

* number of patients that expressed satisfaction with the treatment

COMMENTS: Although this is one of the few trials with a 30 day placebo run-in, this study had a number of flaws that somewhat undermine the quality of the study, including lack of description of randomization procedure, failure to complete or discuss power analysis, lack of intent-to-treat analysis, and placebo preparation not described . The trial duration, 30 days, is much shorter than most other saw palmetto trials. Side effects were not specifically reported other than noting overall tolerability.

AUTHOR/ STUDY/ RATING	METHODS/GOALS	PARTICIPANTS	OUTCOMES
Boccafoschi C et al, 1983 (19) *Sponsor:* Not specified *Evidence Rating:* **IIA**	*What was tested*: *S. repens (*Permixon®) 160 mg bid vs. placebo *Goal:* Compare *S. repens* extract to placebo in the treatment of BPH *Type of study:* Randomized double-blind, placebo-controlled *Treatment duration:* 60 d *Assessment:* 0, 30, 60 d Symptom evaluation, urodynamics, prostate size, DRE, global judgment of efficacy *Randomization:* Used but not adequately described *N based on power analysis?* No *Statistical analyses:* ANOVA, Student's t-test, chi-square	*Inclusion criteria:* Clinically treatable prostatic adenoma *Exclusion criteria:* Serious concomitant disease *Total N:* 22 *N per group:* 11 Permixon, 11 placebo *Dropouts per group*: 0	*Author's major conclusions:* Permixon effective and distinguishable from placebo Significant results, $P < 0.05$, in favor of Permixon: Treatment / Placebo Voiding volume: 42% dec / 2% inc Max urinary flow rate: 43% inc / 19% inc Mean urinary flow rate: 55% inc / 26% inc Dysuria: 37% dec / 18% dec Nocturnal pollakiuria: 55% dec / 32% dec Physician evaluation: 82% good/fair / 27% good/fair *Nonsignificant, P > 0.05, results:* Voiding duration: 6% dec / 12% dec Residual volume: 47% dec / 44% dec Diurnal pollakiuria: 29% dec / 29% dec Pelvic heaviness sensation: 40% dec / 29% dec *Side effects:* No major side effects reported. One Permixon patient reported diffuse heatburn

COMMENTS: Reporting deficiencies including description of randomization, lack of power analysis, and lack of intent-to-treat analysis. Statistical analysis seemed appropriate. Significant improvement in favor of the treatment group was reported for flow rate with a 4 mL/sec increase vs. 2 mL/sec increase for placebo. Similarly the post void residual volume decreased by 48 mL in the treatment group and only 30 mL for placebo.

STUDY/. RATING	METHODS	PARTICIPANTS	OUTCOMES
Reece Smith 1986 (15) *Sponsor:* Not specified *Evidence Rating:* **IIA**	*What was tested*: Permixon 160 mg bid vs. placebo *Goal:* Compare effect of Permixon and placebo in BPH *Type of study:* Randomized, double-blind, placebo-controlled *Treatment duration:*12 wks., *Assessment:* 0,2,4,8,12 wks and 6 m Medical exam, urinary flow rate, residual volume by ultrasound, symptom questionnaire *Randomization:* Numbered folders *N based on power analysis?* No *Statistical Analysis:* paired and unpaired t-tests, Mann-Whitney U test	*Inclusion criteria:* Urological waiting list, presence of urological symptoms *Exclusion criteria:* Malignant prostatic disease *Total N* = 80 (70 evaluable) *N per group:* Permixon 33, placebo 37 *Dropouts per group*: Total 10(groups not identified) 2 due to severe nausea and vomiting, 4 lost to follow-up, 3 required surgery, 1 was non-compliant	*Author's major conclusions:* Significant improvements in both groups; Permixon indistinguishable from placebo. No significant between-treatment results reported Residual urine volume varied erratically in both groups; there were no significant changes in mean within or between groups Significant results from baseline within both groups but not between groups, $P < 0.01$ for both : Treatment / Placebo Urinary flow rate: 35% inc / 35% inc Significant results from baseline within groups but not between groups for Symptoms reported by both investigators and patients Micturation difficulty: 52% dec / 48% dec Urgency: 37% dec / 58% dec Hesitancy: 59% dec / 77% dec Nocturia: 36% dec / 36% dec *Side effects:* Three Permixon patients reported nausea and vomiting side effects; one additional Permixon patient stopped treatment for 1 day due to dizziness

COMMENT: The methodological evaluation of this study highlighted minor flaws, including lack of power analysis and lack of intent-to-treat analysis and no placebo run-in.

AUTHOR/ STUDY/ RATING	METHODS/GOALS	PARTICIPANTS	OUTCOMES
Mattei FM et al, 1990 (16) *Sponsor:* Not specified *Evidence Rating:* **IIA**	*What was tested*: *S. repens* extract 160 mg (LG 166/S) bid vs. placebo *Goal:* Evaluate *S. repens* extract clinically for its effects and tolerance in BPH *Type of study:* Randomized, double-blind, placebo-controlled *Treatment duration:* 3 m *Assessment:* 0, 30, 60, 90 d Symptom score, residual volume, prostate size by ultrasound *Randomization:* Used but not described *N based on power analysis?* No *Statistical Analysis:* ANOVA, Student's t-test, Scheffe's multiple comparisons, chi-square	*Inclusion criteria:* Moderate BPH (impediment of normal voiding) *Exclusion criteria:* Concomitant disease including UTI, need of surgery *Total N* = 40 *N per group:* 20 *S. repens*, 20 placebo *Dropouts per group*: At least 1 *S. repens*, 1 placebo both for gastritis; others not reported	*Author's major conclusions:* *S. repens* demonstrated symptom improvement superior to placebo Significant results, $P < 0.05$, in favor of *S. repens:* Treatment / Placebo PVR volume: 59% dec / NS Mean change: 65 mL Dysuria: 79% dec / 10% dec (mean score change): 1.5 / 0.2 Sensation incomplete voiding: 69% dec / 18% dec (mean score change): 1.1 / 0.1 Perineal pressure: 87% dec / 9% dec Frequency (*value not reported*) Nocturia *(value not reported)* Nonsignificant, $P > 0.05$ results: Prostate diameter: 3% inc / 3%inc Adenoma size *(not reported)* *Side effects:* None reported; incomplete discussion of side effects

COMMENTS: This study has numerous flaws. Full statistical analysis was not reported, method of randomization was not described, no intent-to-treat analysis was performed, no power analysis was used to determine sample size, and no homogeneity baseline comparison was performed between treatment and placebo groups. In contrast to all other studies in this field, the placebo effects were apparently small.

AUTHOR/ STUDY/ RATING	METHODS/GOALS	PARTICIPANTS	OUTCOMES
Grasso, 1995 (70) *Sponsor:* Not specified *Evidence Rating:* **IIA**	*What was tested*: Alfuzosin 2.5 mg tid vs. *S. repens* (Permixon®) 160 mg bid *Goal:* Compare the efficacy and safety of *S. repens* vs Alfuzosin in symptoms of BPH *Type of study:* Randomized, double-blind, comparative, parallel group *Treatment duration:* 3 wks *Assessment:* 0 and 21 d Boyarsky scale, symptom evaluation, urodynamics *Randomization:* Adequate *N based on power analysis?* No *Statistical Analysis:* ANOVA, Chi-square	*Inclusion criteria:* Age 50 to 80 yrs, BPH diagnosis, max flow rate < 15 mL/s, voided volume ≥ 150 mL, nocturia (≥ 2 x per night) *Exclusion criteria:* Concomitant urologic, severe cardiac, renal or hepatic disorders, hypertensive meds or drugs that could interfere with treatment, placebo responders after 7 day run-in *Total N* = 63 *N per group:* 32 Alfuzosin, 31 *S. repens* *Dropouts per group*: 0	*Author's major conclusions:* Both groups showed improvement Significant effects in favor of Alfuzosin, P < 0.05: Alfuzosin / *S. repens* Total symptom 39% dec / 27% dec Obstructive symp. scores 38% dec / 23% dec No significant differences p > 0.05, Mean flow rate 47% inc / 18% inc (mL/sec difference) 2.1 inc / 0.9 inc Max flow rate 51% inc / 27% inc (mL/sec difference) 4.7 inc / 2.7 inc Irritative symptoms 40% dec / 30% dec Daytime frequency* 69% imp / 52% imp Nocturia* 69% imp / 65% imp Other minor urodynamic symptoms(terminal dribbling, hesitancy, urgency, etc) *Side effects:* None reported in Alfuzosin group, 1 Permixon patient complained of pruritus

***** Percent of patients who improved by at least 1 point on the rating scale.

COMMENTS: Although this study did include an intent-to-treat analysis, a 7-day placebo run-in, and good statistical and methodological reporting, no power analysis was conducted and no placebo group was used. A shorter duration was used for this study, which was justified by the authors by stating that Alfuzosin, the comparison drug, is effective almost immediately.

AUTHOR/ STUDY/ RATING	METHODS/GOALS	PARTICIPANTS	OUTCOMES
Lobelenz J., 1992 (24) *Sponsor:* Not specified *Evidence Rating:* **IIA**	*What was tested*: S. repens (Sabal) 100 mg tid vs. placebo (sabal extract manufactured by Dr. Willmar Schwabe, Germany) *Goal:* Evaluate effect of *S. repens* extract on symptoms of BPH *Type of study:* Randomized, double-blind, placebo-controlled *Treatment duration:* 6 wks *Assessment:* 0, 15, 29, 43 d Urodynamic parameters *Randomization:* Computer program *N based on power analysis?* No	*Inclusion criteria:* BPH Alken stages I/II, max flow rate < 20 mL/s *Exclusion criteria:* not given *Total N* = 60 *N per group:* 30 Sabal, 30 placebo *Dropouts per group*: Not given	*Author's major conclusions:* Therapy results more favorable under active treatment, but no statistically significant differences found Nonsignificant results at 6 weeks, P > 0.05, Treat / Placebo Max micturitional volume: 10% inc / 5% inc Mean change: 1.2 mL/sec / 0.6mL/sec Mean urine flow: 11% inc / 5% inc Mean change: 0.6 mL/sec / 0.3mL/sec *Side effects:* None reported

COMMENTS: This study contains fairly major flaws in reporting, including incomplete description of both statistical analysis and general methodology of study. Exclusion criteria and dropouts were not reported, and no power analysis was completed.

KEY:
BID— Twice daily
BPH — Benign prostatic hyperplasia
CI —- Confidence interval
D—Day
DEC—Decrease
DRE — Digital rectal exam
GI—Gastro-intestinal
INC—Increase
IMP—Improve
IPSS — International Prostatic Symptom Scale (7 symptoms, each scored 0-5, max score 35 as most severe symptoms)
LG 166/S—Manufactured by Sanofi Winthrop, Germany, using a hypercritical CO_2 extraction process.
LUTS —Lower urinary tract symptoms
M—Month
PSA— Prostate specific antigen
PVR— Prostate residual volume
PERMIXON®— Manufactured by Pierre Fabre, France, using a hexane extraction process.
PROSTASERENE®— Manufactured by Therabel Pharma, Belgium, using a hypercritical CO_2 extraction process
QD— Daily
QOL — Quality of life
SABAL — Manufactured by Wilmar Schwabe, Germany, using a 90% ethanol extraction process.
TID—Three times daily
UTI—Urinary tract infection

APPENDIX A

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APPENDIX B

	A	B	C
I	**RCT** ➢ Highest quality ➢ Adequately powered ➢ Comprehensively reported ➢ Well-designed and executed in all respects	**Meta-Analysis** ➢ A representative universe of RCT's that meet inclusion/exclusion criteria ➢ Results are based mostly on Level IA quality trials ➢ Comprehensively reported – pooling methods/statistical analysis well described	**Epidemiological Studies** ➢ For safety and drug adverse event associations of high scientific credibility ➢ Case-control, cohort or other appropriate design ➢ Case selection minimizes and controls for confounding factors ➢ No serious methodological flaws
II*	**RCT** ➢ Methodological flaws, if present, may not be serious enough to undermine the conclusions ➢ Methods of analysis or reporting may be less completely described	**Meta-Analysis** ➢ Universe of RCTs that meet inclusion/exclusion criteria may be less representative ➢ Results are based primarily on Level IIA quality trials ➢ Comprehensively reported – pooling methods/statistical analysis well described	**Epidemiological Studies** ➢ For safety and drug adverse event associations ➢ Uncontrolled long-term post-marketing surveillance studies
III	**Inconclusive Studies** ➢ Non-randomized trials for efficacy ➢ Studies containing serious methodological flaws ➢ Efficacy studies lacking an appropriate control ➢ Inappropriate size or duration to be of any value		
IV	**Anecdotal Evidence** ➢ Case reports ➢ Descriptive rather than experimental studies ➢ Considered useful for hypothesis generation		

* Minimum level of evidence for botanical articles that would be considered for admission to the USP

CRITERIA FOR LEVELS OF EVIDENCE

Level I: Randomized Controlled Trials, Meta-Analyses and Epidemiological Studies of Highest Quality

A. Randomized Controlled Trial (RCT)

The study is a randomized controlled trial that is adequately powered to show a treatment effect vs. placebo or an appropriate active or historical control. The report of the study must describe the objectives and design of the study, the endpoints measured, the method of randomization, the method of blinding, the assessment of outcome, and the statistical analysis employed, including the handling of dropouts and withdrawals (e.g., intention-to-treat vs. per protocol analyses). The results must be presented comprehensively, not selectively. Sponsorship of the study and the measures taken to assure the validity and integrity of the data (e.g., monitoring) should be noted. The study may not have a methodological flaw, or a potentially biased statistical analysis that is serious enough to undermine the conclusions of the study.

B. Meta-Analysis

The study contains a representative universe of RCTs in the worldwide medical literature that meet the pre-specified inclusion and exclusion criteria of the meta-analysis, at least some of which are Level IA in quality. The report of the meta-analysis must describe in detail the inclusion/exclusion criteria, the methods used to minimize selection bias, the method of pooling data, and the statistical analysis used. The study may not have methodological flaws sufficient to undermine the conclusions of the study.

C. Epidemiological Study

For the demonstration of drug-adverse event (AE) associations (but not drug efficacy), the study is a case-control study (or other epidemiological study of appropriate design) that demonstrates a drug-AE association of high scientific credibility, i.e., an association that is biologically plausible, has a non-marginal relative risk and a low probability of error. The report must describe in detail the method of selecting cases and controls and the measures taken to minimize selection bias and to control for confounding variables. The study may not have methodological flaws sufficient to undermine the conclusions of the study.

Level II: Randomized Controlled Trials, Meta-Analyses and Epidemiological Studies of Moderate Quality

A. Randomized Controlled Trial

The study is a randomized controlled trial that is designed to show a treatment effect vs. placebo, an active control, or a historical control. However, the report lacks a sufficient description of the methods or analyses, particularly with respect to specified endpoints,

randomization, blinding and/or the statistical analysis, to meet a IA level of quality. Evidence of quality control of the data though independent monitoring is usually lacking. The study may have significant methodological flaws, or uncertainties in the statistical analysis, but none that is overt and serious enough to undermine the conclusions of the study. Many clinical studies reported in the older medical literature or in non-peer-reviewed journals may meet this description.

B. Meta-Analysis

The study is a meta-analysis of a sample of trials that is less than the full universe of published trials meeting the pre-specified inclusion or exclusion criteria or is composed only of studies that are Level IIA in quality, but in other respects is appropriately conducted and reported.

C. Epidemiological Study

For the demonstration of a drug-AE association, the study is a case control study (or other epidemiological study of appropriate design) that would meet the standards of a Level IA study except that the relative risk and/or the P value marginal. Serious drug-related AE's identified in large, uncontrolled, long-term studies or in post-marketing surveillance belong in this category.

Level III: Inconclusive Studies

This level includes non-randomized trials, efficacy studies lacking an appropriate control group, studies with methodological flaws serious enough to render them uninterpretable, and studies that are too small or of insufficient duration to be of value. The conclusions of Level III studies are not necessarily incorrect, but they cannot be shown by scientific methods to be correct. Level III studies can be useful as hypothesis-generating studies but are ordinarily considered inconclusive in supporting the overall efficacy assessment of a drug.

Level IV: Anecdotal Evidence

This level includes case reports and/or papers reporting a series of cases. Such reports are not necessarily incorrect, but are generally considered as descriptive rather than experimental, and hypothesis-generating at best.