Saw Palmetto

Species (Family)

Serenoa serrulata Hook., F. (Arecaceae/Palmae)

Synonym(s)

Sabal, *Sabal serrulata* (Michx.) Nutt. & Schult., Serenoa, *Serenoa repens* (Bartram) Small

Part(s) Used

Fruit

Pharmacopoeial and Other Monographs

BHP 1996[G9]
BPC 1934[G10]
Complete German Commission E[G3]
Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]

Legal Category (Licensed Products)

GSL[G37]

Constituents[G22,G64]

Carbohydrates Invert sugar 28.2%, mannitol, high molecular weight polysaccharides (e.g. MW 100 000) with galactose, arabinose and uronic acid[1] identified as main sugar components for one.

Fixed oils 26.7%. Many free fatty acids and their glycerides. Monoacylglycerides (1-monolaurin, 1-monomyristicin).[2] Oleic acid (unsaturated) and capric acid, caproic acid, caprylic acid, lauric acid, myristic acid, palmitic acid and stearic acid (saturated).

Steroids β-Sitosterol, campesterol, stigmasterol and other compounds.[3–5]

Other constituents Flavonoids (e.g. rutin, isoquercitrin, kaempferol),[5] pigment (carotene), resin, tannin and volatile oil 1.5%.

Most commercial preparations of saw palmetto contain lipophilic extracts.[G56]

Food Use

Saw palmetto is not used in foods. In the USA, saw palmetto is listed by the Food and Drugs Administration (FDA) as a Herb of Undefined Safety.[G41]

Herbal Use

Saw palmetto is stated to possess diuretic, urinary antiseptic, endocrinological and anabolic properties. Traditionally, it has been used for chronic or subacute cystitis, catarrh of the genitourinary tract, testicular atrophy, sex hormone disorders and specifically for prostatic enlargement.[G7,G32,G64] Modern interest in saw palmetto is focused on its use in the treatment of symptoms of benign prostatic hyperplasia (BPH).

Dosage

Dried fruit 0.5–1.0 g or by decoction three times daily.[G7]

Extract 320 mg lipophilic ingredients extracted with lipophilic solvents (hexane or ethanol 90% v/v).[G3]

Clinical trials have assessed the effects of lipophilic extracts (containing lipids and sterols) of saw palmetto usually at a dosage of 160 mg twice daily.

Pharmacological Actions

Several pharmacological activities have been documented for saw palmetto *in vitro* and *in vivo* (animals). Several of these properties, such as inhibition of 5-α-reductase activity, inhibition of androgen binding and spasmolytic activity, are thought to explain, at least in part, the effects of saw palmetto in BPH. However, the clinical significance of the *in vitro* inhibition of 5-α-reductase activity by saw palmetto has not been clearly established (*see* Clinical studies). 5-α-Reductase is the enzyme that catalyses the conversion of testosterone to 5-α-dihydrotestosterone (DHT) in androgen target tissues, including the prostate. DHT is more potent than testosterone, and is thought to be implicated in the development of BPH. There is evidence that 5-α-reductase activity is higher in cells obtained from BPH tissue than from normal prostate tissue.

In vitro and animal studies

A lipidic (liposterolic) extract of saw palmetto was found to inhibit 5-α-reductase-mediated conversion of testosterone to dihydrotestosterone, and 3-ketosteroid reductase-mediated conversion of dihydrotestosterone to an androgen derivative.[5] Other *in vitro* studies have shown that an ethanolic extract of saw palmetto (IDS-89) inhibited 5-α-reductase activity in the epithelium and stroma of human BPH tissue in a concentration-dependent manner.[7] The IC_{50} was around 2.2 mg/mL. This study also demonstrated that the inhibitory effect of IDS-89 was mainly due to the fatty acid constituents of a saponifiable subfraction of the extract, as non-saponifiable and hydrophilic subfractions showed little or no inhibition of 5-α-reductase activity. Inhibition of 5-α-reductase by a liposterolic extract of saw palmetto has also been documented in porcine prostatic microsomes.[8]

There are at least two isoenzymes of 5-α-reductase (5-α-reductase types I and II), and several studies have documented that a liposterolic extract (Permixon) of saw palmetto inhibits both isoenzymes in prostate epithelial cells[9,10] and fibroblast cells.[10] Several other studies have documented inhibition of 5-α-reductase activity by liposterolic extracts of saw palmetto *in vitro*; these studies have been summarised elsewhere.[5,G50] Permixon was reported to inhibit 5-α-reductase activity without affecting the secretion of prostate-specific antigen (PSA) by epithelial cells, suggesting that use of saw palmetto extract should not interfere with PSA measurements for prostate-cancer screening.[9]

Anti-androgenic activity has been documented for a hexane liposterolic extract (Permixon) of saw palmetto. *In vitro* studies in rat prostate tissue and human foreskin fibroblasts indicated that this extract competitively inhibited the binding of dihydrotestosterone to cytosolic and nuclear androgen receptor sites.[6,11] By contrast, an alcoholic extract of saw palmetto appeared to be without androgen receptor-binding activity.[12]

Liposterolic extracts of saw palmetto have also been investigated in animal models of BPH. A liposterolic extract (Permixon) of saw palmetto 50 mg/kg body weight administered for 30 days to castrated rats with oestradiol/testosterone-induced prostate enlargement resulted in significant reductions in the wet weight of the dorsal region of the prostate, compared with control.[13] Another study in rats compared the effects of a liposterolic extract of saw palmetto with those of the 5-α-reductase inhibitor finasteride in rat prostate hyperplasia induced by hyperprolactinaemia.[14] It was reported that the liposterolic extract of saw palmetto inhibited rat prostate hyperplasia in the lateral lobe induced by hyperprolactinaemia, and that finasteride did not antagonise the action of prolactin. By contrast, a study in dogs with BPH reported a lack of effect for saw palmetto extract on prostatic weight, prostatic volume, prostatic histologic scores, prostatic ultrasonographs and serum testosterone concentrations.[15] In the study, 20 dogs with BPH, determined by raised prostatic volume and prostatic volume per kilogram body weight, received saw palmetto extract (type of extract not specified) 1500 mg daily in meatballs ($n = 8$), 300 mg daily in meatballs ($n = 6$) or unmedicated meatballs ($n = 6$), for 91 days. Dogs included in this study did not have clinical signs of BPH (i.e. decreased urinary flow and residual urine volume) that often occur in human males with BPH. Dogs did not appear to be randomly assigned to treatment, and the mean prostatic volume in the control group was higher than that in the active treatment groups before treatment, although it was stated that this was not statistically significant. Assessments and data analysis were carried out by blinded investigators.

In a study using human prostate tissue, a liposterolic extract of saw palmetto (Permixon) 30 μg/mL significantly inhibited basic fibroblast growth factor-induced proliferation of human prostate cell cultures, compared with control, although the extract did not affect basal prostate cell proliferation.[16] An unsaponified fraction of the extract also markedly inhibited basic fibroblast growth factor-induced cell proliferation, but had only a minimal effect on basal cell proliferation. In a study using stromal and epithelial tissue from normal prostate and from patients with BPH, cell numbers and proliferative indices were found to be higher in BPH tissue than in tissue from normal prostates.[17] In tissue from patients with BPH who had been treated with a liposterolic extract of saw palmetto (Permixon), there was significant induction of apoptosis and inhibition of cell proliferation, compared with tissue from patients with BPH who had not received saw palmetto extract. In another *in vitro* study, incubation with Permixon 10 μg/mL also increased the apoptotic index for prostate epithelial cells by 35%.[10]

Other *in vitro* studies have explored the effects of saw palmetto extract and its constituents on human prostatic cancer cells and other tumour cell lines. An extract of saw palmetto fruit, prepared by supercritical fluid extraction with carbon dioxide, induced cell death in LNCaP cells (a hormonal therapy-resistant prostatic cancer cell line) in a concentration-dependent manner.[18] This confirms the findings of previous studies demonstrating the effect of a liposterolic extract of saw palmetto (Permixon) on the mortality rate of LNCaP cells: increased mortality was observed

with saw palmetto extract 50 μg/mL, compared with control.[19] Further investigation identified myristoleic acid as a component of saw palmetto extract that caused cell death. The EC_{50} for both the extract and myristoleic acid was around 100 μg/mL.[18] Following incubation of LNCaP cells with saw palmetto extract 130 μg/mL or myristoleic acid 100 μg/mL, the proportions of apoptotic and necrotic cells were 16.5% and 46.8%, respectively, for the extract, and 8.8% and 81.8%, respectively, for myristoleic acid. An extract of saw palmetto obtained by supercritical extraction with carbon dioxide inhibited the invasion of PC-3 cells (derived from human adenocarcinoma of the prostate) into Matrigel *in vitro* in a concentration-dependent manner at concentrations in the range 1–10 μg/mL.[20] However, LNCaP cells and SKRC-1 cells (derived from human renal carcinoma) were unaffected by the extract. The extract was also shown to inhibit the activity of urokinase-type plasminogen activator, a protease enzyme that is necessary for tumour-cell invasion into basement membranes. The monoacylglycerides 1-monolaurin and 1-monomyristicin isolated from saw palmetto demonstrated *in vitro* activity against renal (A-498) and pancreatic (PACA-2) human tumour cells (EC_{50} for 1-monolaurin: 3.77 μg/mL and 2.33 μg/mL, respectively; EC_{50} for 1-monomyristicin: 3.58 μg/mL and 1.87 μg/mL, respectively).[2] However, only borderline cytotoxicity was observed against PC-3 cells (EC_{50} for 1-monomyristicin: 8.84 μg/mL).[2]

Spasmolytic activity has also been documented for saw palmetto and it has been suggested that this may contribute to the herb's effects in BPH. An ethanolic lipidic extract was reported to produce a concentration-dependent relaxation on rat uterus tonic contraction induced by vanadate (EC_{50} 11.41 μg/mL).[21] Further investigation suggested that a mechanism for the observed effect could be interference with intracellular calcium mobilisation, possibly mediated via cyclic AMP. Other *in vitro* studies demonstrated that a lipophilic ethanolic extract of saw palmetto 0.3–0.75 mg/mL reduced norepinephrine (noradrenaline)-induced contractions in rat deferential duct. Further study indicated that the relaxant effect of saw palmetto extract results from either α-adrenoceptor blockade or from calcium-blocking activity.[22]

Other activity *In vivo* oestrogenic activity in the rat has also been documented for an alcoholic extract.[23] Activity was attributed to the high content of β-sitosterol, a known oestrogenic agent, present in saw palmetto.

In vivo anti-oedema activity in the rat has been documented for a hexane extract of saw palmetto, acting by inhibition of histamine-induced increase in capillary permeability.[24] Low doses of an aqueous extract were effective in carrageenan-induced paw oedema and pellet tests in the rat, although the extract was not found to influence the proliferative stage of inflammation.[1,25] The observed anti-inflammatory activity was attributed to a high molecular weight polysaccharide (approximately 100 000). Polysaccharides possessing immunostimulating activity have also been documented for saw palmetto and were stated to contain a high content of glucuronic acid.[1,25]

An extract (SG-291) prepared from saw palmetto fruits by supercritical fluid extraction with carbon dioxide was reported to inhibit both cyclooxygenase and 5-lipoxygenase *in vitro* (IC_{50} 28.1 μg/mL and 18.0 μg/mL, respectively).[26] Further study indicated that the component(s) of saw palmetto extract that inhibits these enzymes must be within the acidic lipophilic fraction. Subsequent studies have documented that a liposterolic extract of saw palmetto (Permixon) significantly inhibited the production of 5-lipoxygenase metabolites, including leukotriene B_4, by human polymorphonuclear neutrophils at concentrations of saw palmetto extract of 5 μg/mL and above.[27]

Clinical studies

Pharmacokinetics Some data on the pharmacokinetics of saw palmetto extracts in healthy male volunteers ($n = 12$) come from an open, randomised, single-dose bioequivalence study of a 320-mg capsule of a liposterolic extract of saw palmetto compared with two capsules of saw palmetto extract 160 mg as the reference preparation.[28] The plasma concentration–time curves were reported to be almost identical for both preparations. The maximum concentration (C_{max}) for saw palmetto extract 320-mg capsule and 2 × 160-mg capsules was 2.54–2.61 μg/mL and 2.57–2.67 μg/mL, respectively, and time to C_{max} (T_{max}) was 1.58 and 1.5 hours for the 320-mg capsule and 2 × 160-mg capsules, respectively. Another study explored the bioavailability and pharmacokinetic profile of a rectal formulation of saw palmetto extract 640 mg in healthy male volunteers ($n = 12$).[29] The mean maximum plasma concentration of the second component of saw palmetto was almost 2.6 μg/mL at around 3 hours after drug administration.

Pharmacodynamics The inhibitory effects of saw palmetto extract on 5-α-reductase activity documented *in vitro* (*see* Pharmacological Actions, *In vitro* and animal studies) have been confirmed in some studies in humans, and refuted by others.

In one study, 25 men with symptomatic, established BPH were randomised to receive either a liposterolic extract of saw palmetto (Permixon) 320 mg/day for three months ($n = 10$), or no treatment ($n = 15$).[30] At the end of the treatment period, analysis of samples of BPH tissue, obtained by suprapubic prostatectomy, showed that dihydrotestosterone concentrations were significantly reduced and that testosterone concentrations were significantly higher in the treatment group, compared with the control group ($p < 0.001$ for both). A significant reduction in concentrations of epidermal growth factor in total BPH tissue was also observed in the treatment group, compared with the control group ($p < 0.01$). The reported biochemical effects were most evident in BPH tissue from the periurethral region.

In another study, biopsy specimens of the prostate were taken from 44 men with symptomatic BPH participating in a randomised, placebo-controlled trial of a herbal combination preparation containing saw palmetto lipoidal extract 106 mg together with nettle root extract, pumpkin seed oil, lemon bioflavonoid extract and vitamin A.[31,32] There were no statistically significant differences in median tissue dihydrotestosterone and testosterone concentrations between the treatment and placebo groups at baseline. At the end of the study, mean tissue dihydrotestosterone concentrations decreased significantly in the treatment group, compared with baseline values ($p = 0.005$), whereas there was no significant change in dihydrotestosterone concentrations in the placebo group. However, in a separate analysis, it was reported that the median change in tissue dihydrotestosterone concentrations for the treatment group (1.38 ng/g) did not differ significantly from the corresponding change in the placebo group (0.87 ng/g). The findings of this study should be interpreted cautiously as it is possible there are other explanations for the observed effect.

Another randomised, double-blind trial involving 18 men with BPH compared saw palmetto extract (IDS-89; Strogen) 640 mg three times daily (i.e. six times the normal dose) for three months with placebo.[33] This high dose of saw palmetto extract achieved only a moderate decrease in 5-α-reductase activity.

An open, randomised, placebo-controlled study involving 32 healthy male volunteers compared the effects of a liposterolic extract of saw palmetto (Permixon) 80 mg twice daily for seven days with those of finasteride 5 mg daily for seven days on inhibition of 5-α-reductase activity.[34] Serum dihydrotestosterone concentrations were reported to decrease significantly with finasteride, compared with baseline values, but no significant changes were observed for the saw palmetto and placebo groups. Thus, this study did not support a mechanism of action for saw palmetto in BPH by inhibition of 5-α-reductase activity.

Alpha-adrenoceptor blocking activity has also been documented for saw palmetto extract *in vitro*,[22] although this has been refuted in a study involving healthy volunteers.[35] In a double-blind, placebo-controlled, four-way, crossover study, 12 healthy male volunteers received three different saw palmetto extract preparations (Prostagutt uno, Prostess uno, Talso uno) 320 mg daily for eight days each, separated by wash-out phases of at least two weeks. It was reported that none of the study medications showed signs of α_1-adrenoceptor subtype occupancy as determined by a radioreceptor assay.

Therapeutic effects Numerous clinical studies have investigated the effects of saw palmetto in men with BPH.

A systematic review and meta-analysis included 18 randomised clinical trials (16 of which were double-blind) of saw palmetto extracts involving a total of 2939 men with BPH.[36] This work has also been published as a Cochrane systematic review.[37] The review included 10 studies which compared saw palmetto extracts alone with placebo, three comparing saw palmetto extracts in combination with other herbals with placebo, two comparing saw palmetto extracts alone with an active control, one comparing saw palmetto extracts in combination with other herbals with an active control, one comparing saw palmetto extract with another herb and with placebo, and one comparing oral saw palmetto extract with a rectal formulation of saw palmetto extract. The mean duration of the included studies was nine weeks (range 4–48 weeks).

Compared with placebo, saw palmetto extracts led to a decrease in urinary symptom scores and nocturia, and improvements in self-rating of urinary symptoms and peak urine flow.[37] Compared with finasteride, saw palmetto extracts achieved similar improvements in urinary symptom scores and peak urine flow. This systematic review was considered to have provided good evidence that saw palmetto is effective in men with symptoms of BPH, although there is scope for further trials.[37,38]

Several other clinical studies of saw palmetto extracts in BPH have now been published since the Cochrane systematic review, although few have comprised rigorous study design capable of testing efficacy, and several have investigated combination preparations of saw palmetto with other herbs.

A short report describes a randomised, double-blind, placebo-controlled trial of saw palmetto extract (LG-166S) 160 mg twice daily for six months in 101 men with BPH.[39] This study reported statistically significant differences in symptom scores between the treatment group and the placebo group at the end of the study ($p < 0.001$).

In a study involving 75 men with mild/moderate BPH according to their International Prostate Symptom Score (IPSS), participants received a liposterolic extract of saw palmetto (Permixon) 160 mg twice daily for nine weeks ($n = 57$).[40] A control group ($n = 18$) did not receive any medical treatment for BPH, and there was no random allocation to treatment, although it was stated that baseline parameters were comparable between the two groups. It was reported that, at the end of the study, IPSS and quality-of-life scores, compared with baseline values, significantly improved in Permixon-treated men ($p < 0.001$). There were no significant differences in these parameters, compared with baseline values, for the control group.

Two randomised studies involving men with symptomatic BPH have compared the effects of different regimens of saw palmetto extract.[41,42] A multicentre, randomised, single-blind trial involving 132 men with BPH compared the effects of saw palmetto extract (Prostaserene) 320 mg once daily with 160 mg twice daily for one year.[41] Another study compared a liposterolic extract of saw palmetto (Permixon) 320 mg daily with 160 mg twice daily for three months in 100 men with symptomatic BPH.[42] For each regimen, both studies reported significant improvements in the mean IPSS, maximum and mean urinary flow rates and residual urine volume, at the end of the studies, compared with baseline values. However, as these studies did not include a placebo-control group, the possibility that the observed effects are placebo effects cannot be excluded.

Several other open, uncontrolled studies of saw palmetto extracts (alone or in combination with other herbs), several of which were drug-monitoring studies which also assessed effectiveness, have reported improvements in symptoms of BPH at the end of treatment, compared with baseline values.[43–47] Doses assessed in these studies were usually 160 mg two or three times daily for up to three years. These studies are discussed in more detail later (*see* Side-effects, Toxicity).

The effects of a combination herbal preparation containing saw palmetto lipoidal extract 106 mg together with nettle root extract, pumpkin seed oil, lemon bioflavonoid extract and vitamin A, were assessed in a six-month, randomised, double-blind, placebo-controlled trial involving 44 men with symptomatic BPH.[32] At the end of the treatment period, a slight decrease in symptom score and an increase in urinary flow were observed for both groups, compared with baseline values. These changes were greater in the treatment group, compared with the placebo group, but this difference was not statistically significant. In another randomised, double-blind, controlled trial involving 543 men with BPH, participants received a combination of saw palmetto extract 160 mg and nettle root extract 120 mg (Prostagutt forte) daily, or finasteride 5 mg daily, for 48 weeks.[48] Data from a subgroup of 431 participants with ultrasonographic measurements were analysed. Mean maximum urinary flow and IPSS improved in both groups, compared with baseline values; there were no statistically significant differences between the two groups.

Saw palmetto is one of the eight herbal ingredients contained in a commercial preparation known as PC-SPES; the other herbal ingredients are chrysanthemum, isatis, licorice, *Ganoderma lucidum*, *Panax pseudoginseng*, *Rabdosia rubescens* and *Scutellaria* (scullcap). The combination preparation has been investigated for oestrogenic activity, and is currently of interest for its potential effects in the treatment of hormone-sensitive prostate cancer.[49]

Side-effects, Toxicity

A systematic review and meta-analysis of 18 randomised clinical trials of saw palmetto extracts (*see* Pharmacological Actions, Clinical studies, Therapeutic effects) reported that adverse effects with saw palmetto were generally mild and comparable to those with placebo.[37] Gastrointestinal effects were reported in 1.3% of men taking saw palmetto extracts, placebo (0.9%) and finasteride (1.5%). Study withdrawal rates for men taking saw palmetto, placebo and finasteride were 9.1%, 7.0% and 11.2%, respectively. The authors of the review concluded that saw palmetto extracts are associated with fewer adverse treatment effects than is finasteride, but that little is known about the long-term safety of saw palmetto extracts.

In a drug-monitoring study involving 1334 men with BPH, the tolerability of saw palmetto extract 160 mg twice daily for 12 weeks was reported to be 'good' or 'excellent' by more than 95% of participants.[46] This is similar to a finding from a three-year prospective, uncontrolled study involving 435 men with BPH, in which the tolerability of saw palmetto extract (IDS-89) 160 mg twice daily was classified as 'good' or 'very good' by both physicians and patients for 98% of participants.[45] A total of 46 adverse

events was reported in 34 patients. Of these, 30% were gastrointestinal disturbances. The withdrawal rate from the study was 1.8%, mostly because of digestive disturbances ($n = 3$) and tumours ($n = 3$). Non-serious adverse effects (4.95–6.63%), mainly minor gastrointestinal effects, such as gastralgia, nausea, diarrhoea, constipation and anorexia, as well as vertigo, headache, dry mouth and pruritus, were reported in an open study involving 413 men with BPH who received saw palmetto extract 160 mg twice daily for three months.[44] An observational study involving 2080 patients with BPH who received a combination of saw palmetto extract (WS-1473) and nettle root extract (WS-1031) reported that the tolerability of the preparation was classified by physicians to be 'good' or 'very good' for the majority of participants.[47] Mild adverse effects were reported in 15 patients (0.72%).

Studies assessing the equivalence of two different regimens of saw palmetto extract (320 mg once daily and 160 mg twice daily) report that adverse events occurred with a similar frequency in both groups.[41,42] Most events were deemed to be unrelated or unlikely to be related to treatment with saw palmetto extract.

Toxicity Incubation of high concentrations of saw palmetto extract (Permixon) 9.0 mg/mL for 48 hours inhibited sperm motility, compared with control.[50]

Contra-indications, Warnings

In view of the reported anti-androgen and oestrogenic activities, saw palmetto may affect existing hormonal therapy, including the oral contraceptive pill and hormone replacement therapy.

Pregnancy and lactation The safety of saw palmetto has not been established. In view of the lack of toxicity data and the documented hormonal activity, the use of saw palmetto during pregnancy and lactation should be avoided.

Pharmaceutical Comment

Several pharmacological activities have been documented for saw palmetto *in vitro* and *in vivo* (animals). Some of these properties, such as inhibition of 5-α-reductase activity, inhibition of androgen binding and spasmolytic activity, are thought to explain, at least in part, the effects of saw palmetto in benign prostatic hyperplasia (BPH). However, some experimental and clinical studies report conflicting results, particularly with regard to the inhibition of 5-α-reductase activity and α-adrenoceptor blocking activity by saw palmetto extracts. Thus, the mechanism(s) of action of saw palmetto extracts in BPH remain unclear. This is not surprising, given that, at present, the exact cause of BPH is unknown. In addition to the effects of saw palmetto in experimental models of BPH, immunostimulant and anti-inflammatory activities have been documented in laboratory studies.

Results of clinical studies indicate that saw palmetto is a potential agent for the treatment of BPH. However, this is not an indication suitable for self-diagnosis and self-treatment, and over-the-counter use of saw palmetto extract for BPH should be under medical supervision. Data from randomised clinical trials and drug-monitoring studies indicate that, generally, saw palmetto is well-tolerated;[51] adverse events are mild and relate mainly to gastrointestinal symptoms. However, in view of the lack of toxicity data and the documented pharmacological actions of saw palmetto, excessive use should be avoided.

References

See also General References G3, G5, G9, G10, G22, G31, G32, G36, G41, G50, G56 and G64.

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