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V 06/15

Serenoa repens

Saw Palmetto

HERBAL MONOGRAPH
FOR PRACTITIONERS ONLY

BOTANICAL NAME:

Serenoa repens

BOTANICAL SYNONYMS:

- Serenoa repens – also known as Sabal serrulata.[i]

(Named in honour of the American botanist Sereno Watson)

COMMON NAME:

- Saw Palmetto
- American Dwarf Palm Tree [ii]
- Dwarf Palm Tree [iii]
- Dwarf Palmetto [iv]
- Fan Palm [v]
- Sabal [vi]
- Sabal Fructus [vii]
- Serenoa [viii]

OTHER NAMES:

- **Danish** – Savpalme
- **German** – Zwegpalme, Sabalfruchte
- **French** – Palmier de l'Amerique du Nord

SYNONYMS:

- *Brahea serrulata* (Michx.) H.Wendl. [ix]
- *Chamaerops serrulata* Michx. [x]
- *Corypha repens* Bartr. xi
- *Sabal serrulata* (Michx.) Nichols; Nuttal. ex Schult. [xii]
- *Serenoa serrulata* Hook.[xiii]
- *Serenoa serrulata* Roem. et Schult. [xiv]
- *Serenoa serrulatum* (Michx.) Benth et Hook [xv]
- *Serenoa serrulatum* Schult. [xvi]

BOTANICAL FAMILY:

Palmae

PARTS USED:

Berries

SUMMARY

The Saw Palmetto berry has a long history of traditional use by the Native American Indians who used it for the treatment of various conditions including urinary problems and as a food. It was described as the "old man's friend" in King's American Dispensatory in 1898 [xvii] and has long been used in the treatment of benign prostatic hyperplasia (BPH).

Saw Palmetto (Serenoa repens) has garnered much attention in urology and numerous clinical trials have investigated its effects. The overwhelming weight of the evidence supports its use in mild to moderate BPH, comparing its efficacy to finasteride, a pharmacological 5-α reductase inhibitor.

Saw Palmetto has been shown to inhibit 5-α reductase, [xviii xix]reducing the conversion of testosterone to dihydroxytestosterone, a more potent androgen, believed to be a major driver of BPH. It also has a vast array of actions that contribute to its beneficial effects in BPH, including inhibition of cyclooxygenase (COX)-2, [xx xxi]epithelial growth factor (EGF), [xxii] interleukin-12 (IL-12) [xxiii] and insulin-like growth factor-1 (IGF-1). [xxiv] It has also been shown to increase prostate epithelial cell apoptosis in vivo. [xxv] Interestingly, it does not reduce the volume of the prostate or circulating PSA levels and some researchers believe its ability to mitigate the urinary symptoms of BPH are in part due to its ability to bind to α 1-adrenergic and muscarinic (acetylcholine) receptors in the urinary tract triggering a relaxation effect in the bladder. [xxvi]

Saw Palmetto is also used in other androgen driven conditions such as androgenic alopecia, polycystic ovarian syndrome (PCOS) and acne, and may have application in prostatitis. It has an excellent safety profile, comparable to that of placebo. Research shows that urinary symptoms are incredibly common in Australian men as they age, affecting around 26.4% of men in all ages and 48.3% in those aged over 65 years, [xxvii] highlighting the need for Saw Palmetto in every well stocked dispensary.

DOCTRINE OF SIGNATURES:

It is thought that the Native American Indians observed the wild animals closely and noticed that they lost weight when food was least available but gained it again after eating the ripe Saw Palmetto berries, which led to its use as a food.

While no information exists about the doctrine of signatures in regards to Saw Palmetto, one American herbalist has hypothesised that the Native American Indians may have made the link between Saw Palmetto and the urinary tract as the juice from the berries is reported to look and smell like urine.

ENERGETICS:

Pungent, sweet and warming

Astrology - Thought to be ruled by the planet Pluto as are other plants believed to have an effect on reproductive organs.

DESCRIPTION:

Saw Palmetto is a low lying scrubby palm with a dense crown of leaves that is indigenous to the south-east of the United States of America, from South Carolina to Florida, and is often found growing in the sandy soil under pine forests.

It has a characteristic creeping rhizome, which rises a short distance above the ground at one end. Most roots are shallow and grow in the upper 30cm of the soil; however some may extend to several feet further down in well drained sandy soil. Using growth rate studies some plants are estimated to be over 500 years old. [xxviii]

Generally leaves are green in colour except when found growing along Florida's East Coast where they tend towards light bluish green. Mature, fan shaped leaves are palmate and grow up to 90 cm wide; sharp spine-like projections are often found along the edges of the leaves, creating a saw-like margin which is associated with the plants common name. Approximately three to seven new leaves appear in the plant each year and survive for two years before being replaced.

During spring, one to three clusters of small, white, insect pollinated flowers and berries emerge, with the berries ripening in summer. Some plants may flower throughout the year but their berries seldom ripen out of season. The berries themselves contain one seed surrounded by a fleshy pulp, and are light green when young and bluish-black when fully ripe.

HISTORY:

Saw Palmetto has been used medicinally and as a food for thousands of years. Native Americans used extracts of Saw Palmetto for the treatment of genitourinary problems, abdominal disorders and dysentery and the fruit was used extensively as a food staple. [xxix] The dried leaves of the plant were also employed to make thatching, mattresses and straw hats. [xxx]

One of the first encounters Westerner's had with Saw Palmetto was documented in a book by Thomas Dickinson in 1796. [xxxi] According to his book a group of Quaker's were shipwrecked in 1696 on the coast of Florida and were captured by the indigenous Indians of the area. They were presented to the tribe's chief who ate Saw Palmetto berries. During their time with the tribe they were only offered Saw Palmetto berries and fish to eat. They described the taste of the berries.

"The Indians offered us some of their berries, which we endeavoured to eat, but could not;the taste was so irksome and ready to take our breath from us when we tried to eat them."

"We tasted them, but not one among us could suffer them to stay in our mouths, for we could compare the taste of them to nothing else but rotten cheese steeped in tobacco juice." [xxxii]

Despite their negative reaction to the fruit, it no doubt saved them from death by starvation as the indigenous Indians relied on them as a food staple.

According to the Chicago physician Dr Edwin M. Hale in 1897, the first recorded medical use of Saw Palmetto was by Dr Read of Savannah, Georgia and Dr A.A. Solomons. They were credited with introducing its use to the Materia Medica during an address to the Georgia Pharmaceutical Association in the late 1800s. [xxxiii]

Dr Hale went into great detail about his personal experiments using the herb and discussed the use of various preparations, including the use of suppositories made from the oil extracted from the berry, which he recommended;

"They are indicated in rectal catarrah or intestinal haemorrhoids, especially when there is discharge of irritating, offensive mucous." He also recommended the suppositories for;

"Leucorrhoea from the cervix and mucous lining of the uterus; the volatile oil may find its way into the interior of that organ; in vaginal leucorrhoea of a catarrhal or gonorrhoeal nature, especially if there is soreness and pain in the ovaries." [xxxiv]

Its various uses were detailed in King's American Dispensatory in 1898;

"Saw Palmetto appears, from clinical reports, to be a nutritive tonic. It is also an expectorant, and controls irritation of mucous tissues. It has proved useful in irritative cough, chronic bronchial coughs, whooping-cough, laryngitis, (acute and chronic) acute catarrh, asthma, tubercular laryngitis, and in the cough of phthisis pulmonalis. Upon the digestive organs it acts kindly, improving the appetite, digestion, and assimilation. However, its most pronounced effects appear to be those exerted upon the urogenital tracts of both male and female, and upon all the organs concerned in reproduction. It is said to enlarge wasted organs, as the breasts, ovaries, and testicles, while the paradoxical claim is also made that it reduces hypertrophy of the prostate." [xxxv]

They go on to describe it as being a specific remedy for prostatic irritation, known as the *"old man's friend"*, giving relief from the symptoms of an enlarged prostate, increasing the tone of the bladder and relieving pain. They also recommended it as a treatment for gonorrhoea, orchitis, ovaritis and epididymitis, and reported its reputation as a tonic to restore sexual activity after exhaustive excesses in men and strengthen sexual appetite in 'feeble' women. [xxxvi]

The crude extract has been used for centuries to improve breast size, sperm production and as an aphrodisiac. [xxxvii]

Grieve listed the actions of Saw Palmetto as diuretic, sedative and tonic in her book "A Modern Herbal" (1931) and recommends its tissue building properties and beneficial effects on the respiratory mucous membranes. She also stated;

"It has been claimed that sabal is capable of increasing the nutrition of the testicles and mamae in functional atony of these organs. It probably acts by reducing catarrhal irritation and relaxed condition of the bladder and urethra.' [xxxviii]

Researchers investigated the use of Saw Palmetto in various conditions in the late 19th century, including; ovarian dysfunction, dysmenorrhoea, prostatitis, gonorrhoea, as a galactagogue and to stimulate the appetite. [xxxix]

Saw Palmetto was listed in the US Pharmacopoeia as an official drug in the US National Formulary from 1926-1950. [xl]

Its use continues to grow at an exponential rate. The World Health Organisation estimated that sales of Saw Palmetto in the United States grossed $131,000,000 in the year 2000, up from $86,000,000 in 1997.[xli] In 2002 it was rated as the fifth top selling natural medicine product in the United States in a survey of herbal and dietary supplements, above Ginseng, St John's Wort, Valerian and St Mary's Thistle. [xlii]

USE AS A FOOD:

Despite its apparent lack of palatability, Saw Palmetto berries have been used as a food by the indigenous Americans for thousands of years.

FOLKLORE:

Saw Palmetto has a long history of being considered an aphrodisiac herb. Its potential in this area was documented thoroughly in personal experiments By Dr Edward M Hale in 1897 who used drop doses and reported its success in great detail. He stated that;

"The second week I changed to 2 drops of the tincture three times daily. This aroused up some amorous feeling; good firm erections, but the feelings fully under control of moral will power." He goes on to state that; *"The embracing was very satisfactory, and my partner wanted to know what made me so fierce; the work was good.... but gave full enjoyment to both sides, as it used to be with me thirty or forty years ago."* [xliii]

Despite his reports of amorous success a recent study has found that there is no evidence of a beneficial effect on sexual performance. A randomised clinical trial investigated the effects of Saw Palmetto (160mg twice daily over one year) compared to placebo in a group of 225 men with moderate to severe symptoms of benign prostatic hyperplasia. Researchers assessed the sexual function of trial participants and found no benefit, however it was found to provide a small, but significant, improvement in the perception of sexual problems.[xliv]

Baseline and 12 month closeout scores for the domains of the O'Leary Brief Sexual Function Inventory [xlv]

Domain (range)	Saw palmetto		Placebo		Difference	95% CI	p-Value[a]
	Baseline	12 months	Baseline	12 months			
Sexual drive (0–8)	4.79 ± 0.17	4.78 ± 0.18	4.76 ± 0.17	4.77 ± 0.18	0.03	0.35 to 0.41	0.89
Erectile function (0–12)	5.43 ± 0.16	5.71 ± 0.16	5.42 ± 0.16	5.61 ± 0.16	0.08	0.31 to 0.45	0.49
Ejaculation (0–8)	1.60 ± 0.22	1.55 ± 0.22	1.80 ± 0.22	1.90 ± 0.22	0.16	0.67 to 0.36	0.75
Perception of problems (0–12)	8.84 ± 0.33	8.79 ± 0.33	8.78 ± 0.33	8.38 ± 0.33	0.35	0.31 to 1.01	0.04
Overall satisfaction (0–4)	2.18 ± 0.10	2.12 ± 0.11	2.01 ± 0.10	2.08 ± 0.10	0.13	0.40 to 0.14	0.40

Mean values at baseline and the 12-month closeout visit and between-group differences (calculated as the change in the placebo group subtracted from the change in the saw palmetto group). Mean values are derived from the mixed effects regression models. The p-values for the between-group differences are derived from the hypothesis test on the group-by-time interaction term from the linear mixed-effects model which tests for overall differences between groups at any time point; the confidence interval for the between-group differences are obtained from the difference between the estimated baseline and closeout values and does not consider interim time points. CI: confidence interval.

[a] p-Value for between-group differences in change in variable.

Undoubtedly it has beneficial effects on the genitourinary tract, but perhaps its reputed efficacy as an aphrodisiac can be put into the realm of folklore at this stage.

TRADITIONAL USES OF SAW PALMETTO

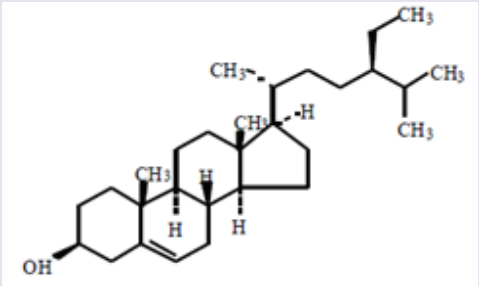
Part of the Body	Historical Use
Digestive System	Dysentery,[xlvi] to improve appetite, digestion, and assimilation [xlvii]
Immune System	Common cold, sore throat [xlviii]
Reproductive System	Aphrodisiac, epididymitis, galactogogue, gonorrhoea, leucorrhoea, orchitis, ovaritis and to enlarge breasts, ovaries, and testicles [l][li]
Respiratory System	Acute catarrh, asthma, chronic bronchial coughs, expectorant, irritative cough, laryngitis, tubercular laryngitis, phthisis pulmonalis, whooping-cough [xlix]
Urinary System	Difficulty passing urine,* hypertrophy of the prostate gland,* prostatitis [lii]
General	Nutritive tonic [liii]

* Uses verified by current research

CONSTITUENTS:

The major constituents of Saw Palmetto are free fatty acids, which make up about 90% of the berry extract. [liv] However, it is the phytosterols, in particular β-sitosterol, that are thought to be the main active phytochemicals.

β-sitosterol is also found in other herbs such as Licorice, Withania, Sage and Evening Primrose. [lv] Many therapeutic properties have been attributed to β-sitosterol, including; androgenic, anorexic, anti-adenomic, anti-androgenic, anti-oestrogenic, anti-fertility, anti-gonadotropic, anti-inflammatory, anti-leukaemic, anti-mutagenic, antiophidic (inhibits effect of snake bite), anti-progestational, anti-prostatadenomic, antiprostatitic, anti-tumour, cancer preventative, candidicide, oestrogenic, gonadotropic, hepatoprotective, hypocholesterolaemic, hypoglycaemic, hypolipidaemic, pesticide, spermicide, and viricide,[lvi] not all of which are found in Saw Palmetto.

Constituent	Chemical Structure
Sterols:	
β-sitosterol [lvii]	
β-sitosterol-D-glucoside [lviii]	

Campesterol [lix]	
Cycloartenol [lx]	
Daucosterol [lxi]	
Stigmasterol [lxii]	
Flavonoids:	
Quercetin [lxiii]	
Kaempferol [lxiv]	
Uronic Acid [lxv]	
Fatty acids: (The total fatty acid content is not less than 9.0%) [lxvi]	
Oleic (3.0%) [lxvii]	
Lauric (2.0%) [lxviii]	
Myristic (1.2%) [lxix]	
Palmitic (1.1%) [lxx]	

Linoleic (0.4%) [lxxi]	
Caphoic (0.2%) [lxxii]	
Caprylic (0.2%) [lxxiii]	
Capric (0.2%) [lxxiv]	
Palmitoleic (0.1%) [lxxv]	
Stearic (0.1%) [lxxvi]	
Linolenic acids (0.1%) [lxxvii]	
Vaccenic [lxxviii]	
Arachidic [lxxix]	
Gondoic [lxxx]	
Behenic [lxxxi]	
Linoceric [lxxxii]	

Monoacylglycerides:	
1-monolaurin [lxxxiii]	
1-monomyristin	
Other Constituents:	
Mannitol [lxxxiv]	

PHARMACOKINETICS:

While no specific pharmacokinetic studies have been performed using Saw Palmetto, information is available on phytosterols and β-sitosterol in particular. Phytosterols are poorly absorbed in the human digestive tract, with usually less than 5% entering the system and 95% of dietary phytosterols being excreted in the bile and passed into the colon. In mammalian systems cholesterol is absorbed in the intestine preferentially over β-sitosterol. Absorption of β-sitosterol in animals is greater than that of the plant sterols campesterol and stigmasterol.[lxxxv]

Early studies showed that the absolute bioavailability of β-sitosterol in dogs after oral administration was 9%, with a three hour half-life and terminal distribution half-life of 129 hours; [lxxxvi] although original data is difficult to access.

ACTIONS

Endocrine System

- Anti-androgenic
- Polycystic Ovarian Syndrome

Genitourinary System

- Prostate
  - Benign Prostatic Hyperplasia
  - Prostatitis

Immune System

- Anti-cancer
- Anti-parasitic

Integumentary System

- Anti-alopecia
- Anti-acne

Systemic

- Anti-inflammatory
- Antioxidant

USES

- Acne
- Alopecia
- Benign prostatic hyperplasia
- Hirsutism
- Leucorrhoea
- Nocturia
- Polycystic ovarian syndrome
- Prostatitis

RESEARCH

Research into Saw Palmetto has focused on its effects in benign prostatic hyperplasia (BPH) and other conditions of the prostate. Several commercial preparations have been used in clinical trials, these include;

Common Formulations used in Research

Permixon (also known as Capistan, Libeprosta and Seroprostat) [lxxxvii]
Prostasan [lxxxviii]
Prostadyn [lxxxix]

Unlike many other herbs that have research based on individual constituents, most research on Saw Palmetto is based on whole extracts of the berries.

MECHANISM OF ACTION

Much of what is known of the mechanism of action of Saw Palmetto hinges around its actions on the endocrine system and the prostate. Studies have shown that Saw Palmetto has multiple mechanisms of action including;

- Inhibition of 5-α reductase [xc xci]
- Competitive inhibition of dihydroxytestosterone (DHT) binding to androgen receptors [xcii xciii]
- Inhibition of cyclooxygenase, lipoxygenase and Bcl-2 (an apoptosis regulating protein). [xciv xcv]
- Competitive inhibition of epithelial growth factor at receptor sites [xcvi]
- Partly displaces epithelial growth factor (EGF) from its receptor and fully blocks EGF -induced cell proliferation in prostate tissue [xcvii]
- Inhibits lipopolysaccharide-induced proliferation of prostate cells via interference with Toll-like receptor-4 signaling pathways [xcviii]
- Inhibits the secretion of monocyte chemotactic protein-1 and granulocyte-macrophage colony stimulating factor (GM-CSF) in the presence of lipopolysaccharide [xcix]
- Reduces lipopolysaccharide-induced secretion of interleukin-12 [c]
- Inhibition of fibroblast growth factor-induced prostate proliferation [ci]
- Inhibition of insulin-like growth factor-1 (IGF-1) which may mediate anti-proliferative and pro-apoptotic effects on prostatic epithelia [cii]
- Increase prostate epithelial cell apoptosis (in vivo) [ciii]
- Competitive inhibition of oestrogen at receptor sites [civ]
- Has a specific affinity to autonomic receptors in the urinary tract, binding to α1-adrenergic and muscarinic (acetylcholine) receptors [cv]
- Inhibition of calcium ion inward flow by acting on plasma membranes which is thought to contribute in part to its ability to relax smooth muscle [cvi]

ENDOCRINE SYSTEM

ANTI-ANDROGENIC

POLYCYSTIC OVARIAN SYNDROME

Polycystic ovarian syndrome (PCOS) is a systemic disorder affecting the hypothalamus-pituitary-ovarian axis, pancreas, adrenals and thyroid. It typically causes disruption to the menstrual cycle, infertility, acne, hirsutism and hyperinsulinaemia.

In PCOS the ovaries produce excess testosterone and the levels of sex hormone binding globulin, which is responsible for binding testosterone, is decreased. Consequently, more testosterone is biologically available which can lead to the development of acne, hirsutism and in some cases male pattern baldness.

Despite the lack of clinical trials investigating it effects in this area, Saw Palmetto is used widely in the herbal treatment of PCOS due to its ability to inhibit 5-α reductase conversion of testosterone to the more potent androgen DHT. It may be useful in the treatment of androgen excess conditions associated with PCOS such as acne, hirsutism and male pattern baldness. (See integumentary section)

Reproductive Effects of Saw Palmetto and β-Sitosterol [cvii]

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.2.1 Humans						
Humans (age n.p.)	M, number n.p.	saw palmetto extract, 80-90% purity	320 mg/day	n.p.	Saw palmetto exhibited an antiestrogenic effect and blocked progesterone and androgenic receptors.	Tavalle (1995)
Humans with BPH (age n.p.)	Control: 12 M Treatment: 18M	saw palmetto extract (Permixon®)	480 mg/day orally	3 mo. exposure	Subjects were not treated previously for BPH. ..718 was positive for estrogen receptors in the nucleus fraction of prostatic cells compared to 1/11 for controls. 12 subjects in both treatment and control groups were positive for estrogen receptors in the cytosolic fraction. The author noted that the antiestrogenic action of the extract, in addition to an antiandrogenic action, may be competatively blocking translocation of cytosolic estrogen receptors to the nucleus	Di Silverio et al (1992)
Humans with BPH (age n.p.)	M, number n.p.	saw palmetto extract	saw palmetto extract, CPA or E2/A plus saw palmetto extract dose n.p.)	n.p.	A multicenter double blind study. A statistically significant difference in positive volume reduction in the saw palmetto extract plus CPA treatment group compared to either of the monotherapies. The combination of saw palmetto extract plus CPA is thought to be effective due to its antiandrogenic action on the epithelial component) and antiestrogenic (active on the stromal component) properties.	Di Silverio et al (1993)
9.2.2 Mice						
Mice (immature)	Number n.p.	saw palmetto extract or pure β sitosterol	injected, dose n.p.	n.p.	Both treatments exhibited estrogenic properties. Saw palmetto was 1/1,000 as potent as β sitosterol.	Tyler (1990, cited by Mendoza, 1997)
Pregnant mice (strain and age n.p.)	n.p.	7 hydroxysitosterol, 7 ketositosterol, or sitosterol, purity n.p.	50 mg/kg/day (0.07 mmol/kg/day), orally, at day 1 or day 6-7 of pregnancy	n.p.	7 hydroxysitosterol was the most effective at inducing abortion; ketositosterol and sitosterol were only slightly effective	Pakrashi and Basak (1976; cited by Finocchiaro and Richardson, 1983)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	References
9.2.3 Rats						
Rats (albino Wistar strain, 3-4 month-old)	[illegible] per group	Beta-sitosterol, purity n.p.	0.5, 1.5, or 2.5 mg/kg/d (0.001, 0.004 or 0.006 mmol/kg/day), s.c.	30 day exposure. Sacrificed 24 h after last injection	At 1.5 mg, beta-sitosterol induced a stress oestrous cycle in 60% of the animals. At 2.5 mg, beta-sitosterol induced a constant estrus cycle that was prolonged so long as treatment continued and caused a marked increase in uterine, uterine, and pituitary weights. Estrogenic properties of beta-sitosterol were noted.	Malini and Vanithakumari (1988)
Rats (albino Wistar, adult)	10 M per group	Beta-sitosterol, purity n.p.	0.5 or 5 mg/kg/day (0.001 or 0.012 mmol/kg/day), s.c.	Low and high dose group administered for 16, 32, and 48 days, respectively. Withdrawal group administered for 16, 32, and 48 days and then treatment was withdrawn for 30 days	Antifertility effect was observed at the high dose level and was most pronounced after 32 to 48 days of exposure. A significant decrease in serum concentrations was observed after 48 days of treatment with the low dose and at all 3 periods of treatment with the high dose. After a 30-day withdrawal from treatment, serum concentrations remained lower. After 32 and 48 days of treatment with the low dose, testicular weight was significantly reduced, respectively. The high dose group showed a significant time-dependent decrease in testicular weight at all 3 lengths of exposure.	Malini and Vanithakumari (1991)
Rats (albino Wistar, 3-4 month-old)	10 ovariectomized F per group	Beta-sitosterol, purity n.p.	0.5, 2.5, or 5.0 mg/kg/day (0.001, 0.006, or 0.012 mmol/kg/day), s.c.	Administered for 10 days. Killed 24 h after last treatment.	At all dose levels, beta-sitosterol caused a dose-dependent increase in glycogen concentration and total lactate dehydrogenase (LDH) activity. At the 2.5 and 5.0 mg/kg/day doses, beta-sitosterol significantly elevated glucose 6 phosphate dehydrogenase (G6PDH) and phosphohexose isomerase (PHI) enzyme activity.	Malini and Vanithakumari (1992)
Rats (albino Wistar 3-4 month-old)	10 ovariectomized F per group	β sitosterol, purity n.p.	0, 5, 2.5, or 5.0 mg/kg/day (0.001, 0.006, or 0.012 mmol/kg/day), s.c. in olive oil	Administered for 10 days.	β Sitosterol caused a dose dependent increase in uterine weight. DNA, RNA and protein concentrations were significantly increased following β sitosterol administration at the 0.25 and 0.5 mg/100g body weight/day dose levels.	Malini and Vanithakumari (1993)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	References
Rats (strain n.p., neonatal)	M and F number n.p.	β-sitosterol, purity n.p.	0.003 or 0.03 mg (0.0000007 or 0.000007 mmol); injections	10-day exposure; 45-day observation period	Both classical β-sitosterol steroid estrogenic responses (increased basal levels of luteinizing hormone in males and females) and classical β-sitosterol antiestrogenic responses (altered postpubertal pituitary response to GnRH in females)	Register et al. (1995)
9.2.4 Rabbits						
Rabbits (strain n.p., immature)	M, number n.p.	β-sitosterol, purity n.p.	s.c. (dose n.p.)	n.p.	Classical estrogenicity in spermatogenesis	Ghannudi et al. (1978) cited by Jones et al., (1995)
9.2.5 Sheep						
sheep (25-wk-old lambs)	6 F per group	β-sitosterol, purity n.p.	0.5, 1.0, 5.0, 10.0, 15.0, or 20.0 mg/day (0.001, 0.002, 0.012, 0.024, 0.036, or 0.048 mmol/day); s.c. in olive oil	2, 4, and 6 wk exposure	Ovarian weight was decreased at all doses for all lengths of exposure, except at 1.0 mg, for 2 wks, where ovarian weight was increased. With increasing doses of β-sitosterol, follicular growth was inhibited and follicular distribution did not extend past the 6 and 7 granulosal size layers. The Graafian follicle exhibited signs of atresia or induced ovulation. In the uterus, there was a significant decrease in alkaline phosphatase distribution at a dose of 20 mg.	El-Semmanoudy et al. (1979)
9.2.6 Fish						
mosquitofish (Gambusia affinis; age n.p.)	F (number n.p.)	kraft pulp mill effluent	n.p.	n.p.	Exposed females possessed a modified anal fin resembling a gonopodium (the intromittent organ of males) and exhibited male reproductive behaviors such as mating attempts.	Howell et al. (1980; cited by LeBlanc and Dam, 1994)
white sucker fish (Catostomus commersoni; age n.p.)	n.p.				Exposed fish had lower serum 17β-estradiol, testosterone, 17α,20β-dihydroprogesterone, and 11-ketotestosterone compared to fish collected from reference sites.	McMaster et al. (1991); Munkittrick et al. (1991; both cited by LeBlanc and Dam, 1994)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
lake whitefish (*Coregonus clupeaformis*, age n.p.)						Munkittrick et al. (1992; cited by Lehtinen and Dahl, 1997)
rainbow trout (*Oncorhynchus mykiss*, age n.p.)					Exposed fish had a 50% reduction of plasma testosterone levels.	Lindstrom Seppa et al. (1988; cited by Lehtinen and Dahl, 1997)
fish of the Great Lakes region	n.p.	pulp mill effluent	n.p.	n.p.	Exposed fish show a seven- year delay of time to sexual maturation. The investigators indicate that β-sitosterol found in high concentrations in the effluent, may be the primary agent responsible for the endocrine effects	McMaster et al. (1991; cited by Cooper and Kaulock, 1997)
goldfish (presumably *Carassius auratus*), age n.p.	M, F (number n.p.)	β-sitosterol, purity n.p.	β-sitosterol, i.p. (dose n.p.)	n.p.	Plasma testosterone levels were significantly reduced in both castrated females. 17β-estradiol was significantly reduced in females. Findings suggest that β-sitosterol may be contributing factors to the reproductive dysfunction observed in fish exposed to bleached kraft pulp mill effluent	MacLatchy and Van der Kraak (1995)
trout (age n.p.)	n.p.	β-sitosterol	n.p.	n.p.	β-Sitosterol lowered gonadal steroid production by possibly altering cholesterol availability or inhibiting cytochrome P450 activity	McMaster et al. (1996; cited by Cooper and Kaulock, 1997)

GENITOURINARY SYSTEM

PROSTATE

BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is a benign enlargement of the prostate gland commonly affecting men as they age. BPH is a result of hyperplasia of epithelial and stromal cells which form nodules in the periurethral region of the prostate. As the prostate enlarges it puts pressure on the urethral lumen, which causes compression and partial obstruction of the urethra and interferes with the flow of urine. Although the symptoms of BPH can significantly affect quality of life it is not considered to be a premalignant condition.

Common symptoms of Benign Prostatic Hyperplasia

Abdominal straining	Nocturia
Dysuria	Terminal urine dribbling
Frequent urination	Urinary hesitancy
Incomplete bladder emptying	Urinary retention
Increased risk of urinary tract infections	Weak urinary stream
Urinary intermittency	

The prevalence of one or more of these symptoms in Australian men is around 26.4% in all ages and 48.3% in those aged over 65 years. [cviii] In a biopsy and cadaver study performed in America in the 1980s it was shown that BPH was found in more than 40% of men in their 50s and in 90% of men in their 80s, demonstrating the age related increase in occurrence. [cix]

Diagnosis is based on symptoms and is confirmed by digital rectal examination and an elevation of prostate specific antigen (PSA) levels, which is attributed to increased organ volume and inflammation.

BPH is thought to be driven by dihydroxytestosterone (DHT), a potent androgen which is converted from testosterone by the enzyme 5-α reductase.[cx] Medical treatment for BPH includes therapy with pharmacological agents such as 5-α reductase inhibitors (e.g. finasteride) and α-adrenergic drugs for mild to moderate symptoms. Treatment for more severe cases may include transurethral surgical resection of the prostate (TURP), transurethral incision, laser prostatectomy, prostatic stents or microwave therapy for more severe symptoms.

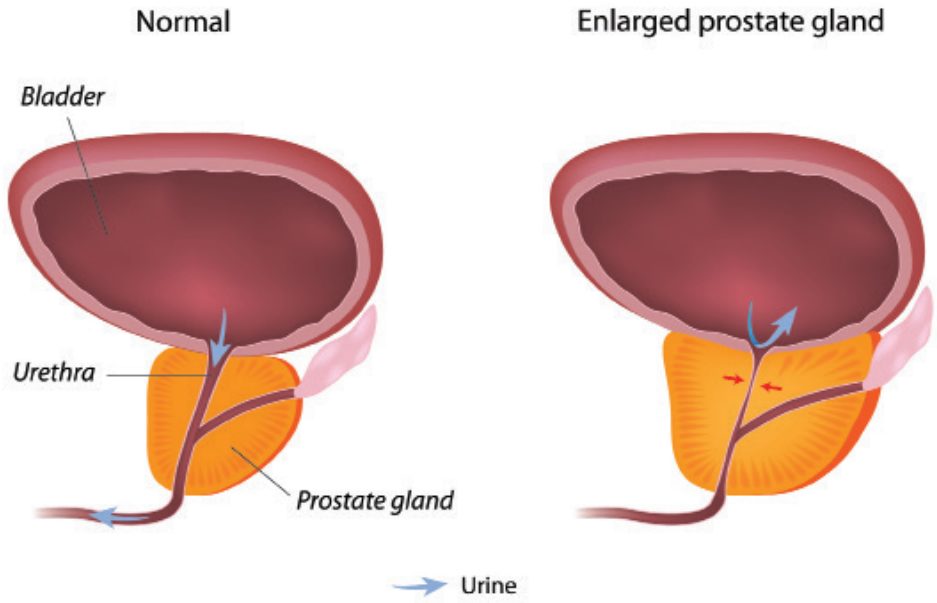


Fig 1: Benign Prostatic Hyperplasia

SAW PALMETTO FOR BENIGN PROSTATIC ENLARGEMENT

Saw Palmetto has a long history of use in prostate disorders. It was traditionally used by indigenous American Indians for problems associated with urination, and was described as "the old man's friend" in King's American Dispensatory in 1898.[cxi] It is currently the leading natural medicine product for the treatment of BPH and is one of the top five natural medicine supplements used by men in America. [cxii]

MECHANISM OF ACTION

In vitro research into the action of Saw Palmetto in the 1980s discovered its ability to competitively inhibit 5-α reductase, the enzymes responsible for the conversion of testosterone into the more potent dihydroxytestosterone (DHT) which is considered a major driver of BPH. It was also found to competitively inhibit DHT binding to androgen receptor sites in the prostate.[xciii cxiv] Later in vitro studies confirmed its inhibitory action on both type I [cxv] and II 5-α reductase enzymes. [cxvi]

This effect on androgens and androgen receptors was demonstrated in a double-blind, placebo-controlled clinical trial of men with BPH. The treatment group received 480mg of Saw Palmetto for three months before undergoing a prostatectomy. It was found that DHT and growth factor levels were significantly decreased in the prostate tissue of men receiving Saw Palmetto compared to controls. Testosterone levels were increased, thereby indicating the inhibition of 5-α reductase. [cxviii]

Six years later, the same research group performed a similar trial on a larger group of men using 320mg of Saw Palmetto per day for three months. Results were similar to that seen with finasteride (a medication used to treat BPH). Saw Palmetto caused a significant decrease of DHT and epidermal growth factor particularly in the periurethral region of the prostate (enlargement of this area is responsible for the obstructive symptoms of BPH). [cxviii]

Despite the fact that Saw Palmetto has been shown to inhibit 5-α reductase activity in vitro and in vivo, it has not been shown in clinical trials to significantly decrease the size of the prostate or plasma levels of prostate specific antigen (PSA). A large clinical trial comparing Saw Palmetto to finasteride found that while both treatments provided significant symptomatic relief only finasteride decreased prostate volume and PSA levels. [cxix]

The prostate is also a target tissue for oestrogen and although poorly understood, oestrogen and selective oestrogen receptor modulators (SERMs) have been shown to promote or inhibit prostate proliferation, the latter indicating a role in prostate health and BPH. Testosterone can be metabolised via CYP19/aromatase into the potent oestrogen, oestradiol-17β.[cxx]

The potential role of oestrogen in the pathogenesis of BPH was identified in the 1970s in canine studies. The prostate is reliant on androgens to maintain its size and secretory function, when castrated dogs were administered exogenous androgens the prostate showed regrowth and a resumption of normal function. When exogenous oestrogens were added to the treatment protocol the dogs developed glandular hyperplastic prostates, including an increase in total number of prostate cells. [cxxi]

Human studies on a small group of men who had undergone medical castration in the treatment of BPH in the early 1990s found that when the men were given oestrogen in the absence of testosterone it induced squamous metaplasia of the prostate. [cxxii]

Di Silverio and colleagues (1992) found that Saw Palmetto administered to BPH patients prior to prostatectomy significantly decreased progesterone and oestrogen receptor sites in the prostate and therefore could be considered anti-oestrogenic as well as anti-androgenic in prostate tissue. [cxxiii]

While Saw Palmetto has certain specificity for steroid hormone receptors in prostate tissue and other hormonally sensitive tissues, it has not been shown to effect plasma levels of testosterone, luteinising hormone or follicular stimulating hormone in human clinical trials. [cxxiv]

Despite what we know about Saw Palmetto there is some conjecture amongst the scientific community regarding the exact mechanism of action in BPH. It does not reduce the volume of the prostate or PSA levels as seen with finasteride and other 5-α reductase inhibitors, nor does it cause the side effects commonly associated with these drugs, such as gynecomastia and ejaculation disorders. It has been suggested that mechanisms other than its hormonal effects are responsible for its efficacy in BPH.

Iglesias and colleagues (2011) investigated the androgen independent effects of Saw Palmetto and found that it blocks epithelial growth factor (EGF)-induced cell proliferation in prostate tissue in vitro and partially displaces EGF from its receptor site. It also inhibits a range of pro-inflammatory responses in prostate epithelial cells, including; inhibition of lipopolysaccharide-induced proliferation of prostate cells via interference with Toll-like receptor-4 signaling pathways; and inhibition of the secretion of monocyte chemotactic protein-1 and granulocyte-macrophage colony stimulating factor (GM-CSF) in the presence of lipopolysaccharide. [cxxv]

There is thought to be a link between inflammation and the pathogenesis of various prostate conditions including BPH, where elevated cyclooxygenase-2 (COX-2) expression has been linked to an increase in proliferation of prostatic epithelium.[cxxvi] Saw Palmetto has been shown to inhibit COX-2 enzymes[cxxvii cxxviii] in vitro.

As BPH is essentially an obstructive process, Saw Palmetto's ability to provide relief from the urinary symptoms of BPH without significantly changing prostate volume has led to further research into its effects on the urinary tract. Saw Palmetto has been found to have specific effects on the autonomic nervous system that would partially explain its ability to relieve urinary symptoms.

Studies have demonstrated that Saw Palmetto potently and non-competitively inhibits human α 1-adrenergic receptors in vitro. In vivo experiments on rats with induced BPH found that oral doses of Saw Palmetto as low as 0.6 to 60mg/kg per day reduced detrusor contractility (inner bladder wall contractility) and prolonged micturition intervals. [cxxix] Similar results have been replicated in other in vivo studies using 60mg/kg per day. [cxxx]

This reduction in urinary symptoms was found to be due to Saw Palmetto's direct action on the autonomic nervous system via the non-competitive binding to α 1-adrenergic and muscarinic (acetylcholine) receptors in various tissues, including the bladder, prostate spleen and heart. It was also found to significantly reduce the number of binding sites in the bladder even at the lowest dose tested. [cxxxi]

Despite these promising results a small placebo-controlled, double-blind clinical trial has found that Saw Palmetto given at 320mg per day for eight days failed to alter plasma catecholamines, and the α 1-adrenergic receptor antagonism seen in in vitro and in vivo studies was not replicated at the recommended therapeutic dose. [cxxxii]

Saw Palmetto has also been shown to have spasmolytic effects in various animal tissues in vitro, including uterus, aorta and bladder, which occurred via its effects on plasma membranes causing an inhibition of calcium ion inward flow.[cxxxiii] This, combined with Saw Palmetto's effect on neurotransmitters, would contribute to the symptomatic relief demonstrated in clinical trials; however further studies may identify other mechanisms.

CLINICAL TRIALS

Numerous clinical trials have demonstrated the efficacy of Saw Palmetto in BPH and the weight of evidence supports its use in this condition. A recent Cochrane review of Saw Palmetto for the treatment of lower urinary tract symptoms of BPH examined the data from 21 randomised, controlled, clinical trials, lasting between four to 48 weeks. The studies included 3,139 men with a mean age of 65 years.

Saw Palmetto was found to reduce nocturia by 25% compared with placebo and was equivalent to finasteride. It was found that Saw Palmetto provided improvement in urinary symptoms and flow measures, similar to that of finasteride and was associated with fewer adverse events. [cxxxiv]

Another meta-analysis conducted in 2004 found similar results. This compared data from 14 randomised trials and three open-label trials involving 4,280 men. All trials investigated the efficacy of the Saw Palmetto preparation Permixon in BPH. Overall, it was found that Saw Palmetto provided a statistically significant reduction in nocturia over placebo and was associated with a mean reduction in the International Prostate Symptom Score of 4.78. [cxxxv]

It is well accepted that Saw Palmetto provides relief from the symptoms of BPH; however future studies will help to refine our knowledge of its mechanism of action.

PROSTATITIS

Saw Palmetto has traditionally been used to treat a range of urinary problems, including prostatitis. The term prostatitis refers to inflammation of the prostate gland which is generally an immune response to bacterial infection; however non-bacterial prostatitis, known as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), can also occur, the aetiology of which is poorly understood.

Saw Palmetto has garnered much attention in urology due to its proven ability to mitigate the urinary symptoms of BPH and its ability to inhibit a range of pro-inflammatory responses in prostate tissue in vitro. Several studies have investigated the efficacy of Saw Palmetto in prostatitis.

In 2004 a long term randomised, open-label, clinical trial compared the efficacy of finasteride to Saw Palmetto in 64 men diagnosed with chronic prostatitis or chronic pelvic pain syndrome. Men received either 5mg of finasteride or 325mg of Saw Palmetto daily over one year. While finasteride treatment resulted in a decrease in pain scores and other symptoms, Saw Palmetto had little effect in all measured outcomes.[cxxxvi] It is interesting to note that despite the negligible improvements provided by Saw Palmetto 41% of trial participants chose to continue with Saw Palmetto treatment after completion of the trial.

Another larger clinical trial performed in the same year investigated the effects of the Saw Palmetto preparation, Prostadyn, in chronic prostatitis at a dose of 320mg twice daily. All participants (125) reported a positive outcome and improvement in the National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI) measures. Unfortunately, the full study is only available in Chinese and information on the length of the trial is not available. [cxxxvii]

Most recently an Italian multicentre, randomised, controlled trial compared Saw Palmetto alone to a combination formula (Profluss®) of Saw Palmetto, selenium and lycopene in the treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Endpoints measured were maximal peak flow rate, PSA levels, white blood cell count, International Prostate Symptom Score (IPSS) and NIH-CPSI score. It was found that both groups had a significant reduction in the IPSS score with a stronger effect for the combination formula. The mean NIH-CPSI score was also significantly improved with a 26.06% reduction for Saw Palmetto alone and 51.64% reduction in the Profluss® group. PSA levels and white blood cell count were also significantly decreased in the Profluss® group. [cxxxviii]

Despite the mixed results reported from clinical trials there is some evidence that Saw Palmetto may have application in prostatitis. No doubt future studies will help to address its use in this condition.

IMMUNE SYSTEM

CANCER

Prostate cancer is the most common cancer in men and second only to lung cancer as a leading cause of cancer deaths among men in the Western world.[cxxxix] Whilst generally considered a slow growing cancer affecting older men, more aggressive forms of prostate cancer do occur and can affect younger men.

Anti-androgen medication is an important therapy in prostate cancer as androgens not only promote the growth of normal prostate tissue but promote the growth of neoplastic cells in prostate cancer. Most prostate cancers are thought to be androgen dependent in the

early stages with some cancers becoming 'hormone refractory' in the later stages (i.e. non-respondent to hormone suppression therapy).

Oestrogen also plays a role in prostate cancer. Human studies on a small group of men who had undergone medical castration in the treatment of BPH in the early 1990's found that when the men were given oestrogen in the absence of testosterone it induced squamous metaplasia of the prostate. [cxl]

A pharmaceutical 5-α reductase inhibitor, finasteride, has been shown to reduce the risk of the emergence of prostate cancer in a long term (seven year), placebo-controlled study of 18,882 men over the age of 55 years.[cxli] Despite this, little research has investigated the effects of Saw Palmetto which has also been shown to inhibit 5-α reductase.

Interestingly, an epidemiological study involving 35,171 men investigated if there was an increased risk of developing cancer when using Saw Palmetto. Ten percent of the men surveyed (aged between 50-75 years of age) reported that they had used Saw Palmetto at least once per week, for at least one year in the ten year period prior to baseline and it was found that of these men only 530 developed prostate cancer. Researchers found that at the reported levels used, Saw Palmetto was not associated with an increased risk of prostate cancer. [cxlii]

Saw Palmetto is commonly used by men with prostate cancer despite little being known about its effects in this area. In a multicentre study assessing the use of complementary therapies in 2,582 men with prostate cancer, 6% reported using Saw Palmetto. [cxliii]

IN VITRO RESEARCH

In vitro research has shown that Saw Palmetto may inhibit cancer growth via two possible mechanisms. It has been shown to inhibit cell growth in several prostate cancer cell lines which may partly be due to changes observed in the expression of Bcl-2, an apoptosis regulator protein. It may also be due to its ability to inhibit COX-2 expression as demonstrated in vitro, since increased COX-2 expression is associated with an increased incidence of prostate cancer. [cxliv]

Despite earlier in vitro studies which used the Saw Palmetto extract, Permixon, showing that it had little effect on apoptosis or cell cycle progression,[cxlv] more recent studies using a different extract have found that it does have an effect on cancer cells. In 2009, in vitro studies found that Saw Palmetto and β-sitosterol demonstrated anti-cancer properties via an effect on certain genes which control cell cycle progression. It was shown to increase the activity of P53 (a tumour suppression protein) while decreasing the activity of P21 and P27, two proteins responsible for regulating cell cycle progression. [cxlvi]

IN VIVO RESEARCH

Despite conflicting in vitro evidence, Saw Palmetto has been shown to inhibit tumour growth in an animal model of prostate cancer. Animals were fed a customised diet providing either 50mg/kg per day or 300mg/kg per day over 12 or 24 weeks. At the end of the trial several measurements were examined including toxicity, androgen levels, 5-α reductase activity and prostate cell changes. It was found that Saw Palmetto treatment at 300mg/kg daily greatly reduced the concentration of DHT in the prostate and caused significant increases in apoptosis and a decrease in tumour grade and frank tumour incidence.[cxlvii]

There are no clinical trials investigating the potential of Saw Palmetto in prostate cancer at this stage, hopefully future results from in vitro and in vivo trials may support a move to further research in a clinical setting.

COMBINATION FORMULAS

Between 1997 and 2002 a herbal medicine product containing Saw Palmetto, known as PC-SPES which was based on a Traditional Chinese Medicine formula, was used in the treatment of hormone refractory prostate cancer. At the time it was considered one of the most promising herbal treatments for prostate cancer. The formula was shown to inhibit growth in androgen-sensitive and androgen-independent prostate cancer cells,[cxlviii] and several small clinical trials demonstrated significant efficacy with one study of 23 patients showing a median drop in PSA levels of 40%.[cxlix] It was withdrawn from the market in 2002 after

contamination of the formula with synthetic oestrogens was discovered. It was also shown to cause several thromboembolic events during the trial, which may be related to oestrogen contaminants.[cl]

PC-SPES (1997-2002) [cli]
Dendranthema morifolium
Ganoderma lucidum
Glycyrrhiza uralensis (Licorice root)
Isatis indigotica
Rabdosia rubescens
Scutellaria baicalensis
Seronoa repens (Saw Palmetto)
Panax pseudoginseng

A new standardised version of the formula, known as PC-SPES2, is now being investigated in clinical studies and despite a high dropout rate due to gastrointestinal side effects it has demonstrated an ability to decrease PSA levels.

ANTI-PARASITIC

Although not thought of as an anti-parasitic herb, Saw Palmetto was used traditionally in the treatment of dysentery. In vitro research has identified its ability to completely inhibit the growth of *Histomonas meleagridis, Tetratrichomonas gallinarum*, and *Blastocystis* spp. These results led researchers to investigate the anti-parasitic activity of Saw Palmetto in vivo against *Histomonas meleagridis*, which is a deadly parasitic infection in birds. Results showed that an ethanolic extract of Saw Palmetto added to the drinking water of turkeys failed to exert an anti-parasitic action against *Histomonas meleagridis*. [clii]

INTEGUMENTARY SYSTEM

ALOPECIA

Alopecia, particularly androgenic alopecia (known as male pattern baldness), may potentially benefit from treatment with Saw Palmetto. Androgenic alopecia is thought to be caused by a genetic sensitivity of receptors in hair follicles to DHT, which is converted from testosterone via 5-α reductase. High concentrations of DHT are thought to 'shut down' the activity of sensitive hair follicles causing minimisation of the hair follicle and ultimately alopecia.

It is recognised that Saw Palmetto inhibits 5-α reductase[cliii] [cliv] thereby decreasing levels of DHT, as well as competitively inhibiting DHT binding to androgen receptor sites.[clv] [clvi] The skin is a target tissue for androgens with androgen receptors present in both hair follicles and sebaceous glands. Dehydroepiandrosterone (DHEA) may also play a role as it is a steroid hormone that is produced by the adrenal glands and is a weak but prolific precursor to androgens including testosterone and DHT. DHEA is converted to testosterone and DHT via enzymatic conversion by P450 aromatase and 3β-hydroxysteroid dehydrogenase (3β-HSD) enzymes, both of which are found in the terminal follicle and external root sheath of hair.[clvii]

CLINICAL STUDY

One small randomised, double-blind, placebo-controlled clinical trial has investigated the effects of Saw Palmetto treatment in androgenic alopecia. Males in the study were aged between 23 and 64 years of age with mild to moderate androgenic alopecia. It was found that treatment with Saw Palmetto provided a significant improvement in 60% of trial participants. Researchers concluded that these results were due to its 5-α reductase activity and recommended that the study be repeated in a larger clinical trial.[clviii]

ACNE

Much like its effects on alopecia, Saw Palmetto is used for acne caused by hormonal dysregulation, particularly in women with polycystic ovarian syndrome (PCOS). PCOS is characterised by androgen excess, cystic acne, weight gain and excess male pattern hair growth in women.

Saw Palmetto may work in two ways to reduce androgen-induced acne. As a 5-α reductase inhibitor Saw Palmetto may help to decrease the conversion of androgens to more potent forms and lessen their effect on the skin. In vitro research has also identified a specific enzyme, 3β--HSD, located in the sebaceous glands, that converts weak androgen precursors to potent androgens.[clix] This process stimulates lipogenesis, and increases sebum production, forming the comedones that are typical of cystic acne.

One clinical trial of a topical formula using a combination of Saw Palmetto with other herbal ingredients for the treatment of acne and oily skin has reported positive results,[clx] however clinical trials using Saw Palmetto internally or topically as an individual treatment are lacking at this stage.

SYSTEMIC

ANTI-INFLAMMATORY

While not specifically known as an anti-inflammatory herb, Saw Palmetto has been shown to inhibit inflammation in vitro via its effects on COX-2 enzymes.[clxi clxii] This anti-inflammatory effect may partially explain its ability to mitigate the symptoms of BPH, as inflammatory processes, particularly an elevation of COX-2, have been linked to its pathogenesis.[clxiii]

Other in vitro studies have investigated the anti-inflammatory activity of Saw Palmetto in lipopolysaccharide-stimulated rat macrophages and found that it inhibited the inflammatory cascade in all areas measured, including; inducible COX-2, 5-lipoxygenase (5-LOX), inducible nitric oxide synthase (iNOS), and inhibitor kBa (IkB-a) as well NF-κB binding activity and TNF-α gene expression.

These in vitro results were increased when Saw Palmetto, lycopene and selenium were tested in combination and were also found to have significant anti-inflammatory effects in vivo in a mouse model of partial bladder obstruction.[clxiv]

ANTIOXIDANT

There is some evidence[clxv] that oxidative stress plays a role in the pathogenesis of BPH and prostate cancer and it is thought that a natural increase in oxidative damage over time may partially explain the age related increase in the occurrence of BPH.

In vivo studies using the Permixon preparation of Saw Palmetto has shown a dose of 100mg/kg prevents an increase in lipid peroxidation and glutathione peroxidase activity in prostate tissue as well as effectively reducing prostate mass and volume.[clxvi]

SAFETY

The general safety profile of Saw Palmetto is good when taken at the approved dose. It is considered to be superior to that of Finasteride (a drug commonly used to treat BPH); sexual dysfunction is less common compared to Finasteride and has not been associated with erectile dysfunction, altered libido or ejaculatory disturbance.[clxvii]

A Cochrane review of 21 trials involving 3,139 BPH patients found that adverse effects were generally mild and comparable to that of placebo. Specific adverse events were reported in 11 of the 21 trials.[clxviii]

Adverse Event	Saw Palmetto	Placebo	Finasteride
Gastrointestinal Symptoms	1.3%	0.9%	1.5%
Impotence	1.1%	0.7%	4.9%

A detailed safety assessment was performed during the STEP trial (Saw Palmetto for Treatment of Enlarged Prostates). This placebo-controlled, randomised clinical trial conducted over a one year period reported that a daily dose of 320mg of Saw Palmetto was well tolerated with a safety profile equivalent to that of placebo.[clxix]

In a review of the literature conducted in 2000 which included 40 clinical trials, Saw Palmetto was again found to have a safety profile similar to that of placebo. The most frequently reported adverse events were abdominal pain, diarrhoea, nausea, fatigue, headache, decreased libido and rhinitis, all of which were considered mild, infrequent and reversible.[clxx]

Isolated case reports of more serious adverse events such as haemorrhage[clxxi] and acute pancreatitis[clxxii] have been reported, however causality is questionable.

SAFETY IN PREGNANCY AND LACTATION

PREGNANCY

Saw Palmetto is not recommended for use by pregnant women or by women planning a pregnancy due to its effects on 5-α reductase. Not only may it interfere with hormonal metabolism during pregnancy, there is some in vivo evidence that in utero exposure to the pharmacological 5-α reductase inhibitor, finasteride, may interfere with the formation of the genitourinary tract of male foetuses.[clxxiii]

BREASTFEEDING

No safety data exists on the use of Saw Palmetto in breastfeeding, however it has been shown to interact with prolactin receptors. In vitro research has indicated that Saw Palmetto may inhibit several steps of PRL receptor signal transduction,[clxxiv] therefore Saw Palmetto should be avoided during breastfeeding until further information can clarify its effects.

DRUG INTERACTIONS

In vitro studies have shown that Saw Palmetto has no significant effect on CYP1A2, CYP2D6, CYP2E1, or CYP3A4 activity, therefore researchers concluded that Saw Palmetto appears to pose a minimal risk for CYP-mediated herb-drug interactions in humans.[clxxv]

DOSE:

- Saw Palmetto 1:2 15-30ml per week

The British Herbal Pharmacopoeia (1983) dosage guidelines state the liquid extract of the berries to be taken three times per day at a dose of 0.6ml to 1.5ml.

GLOSSARY

ATCH	Adrenocorticotropic hormone
3β-HSD	3β-hydroxysteroid dehydrogenase
BPH	Benign prostatic hyperplasia
COX-2	Cyclooxygenase-2
CP/CPPS	Chronic prostatitis/chronic pelvic pain syndrome
DHT	Dihydroxytestosterone
EGF	Epithelial growth factor
GSH	Glutathione
GM-CSF	Monocyte chemotactic protein-1 and granulocyte-macrophage colony stimulating factor
GSHPx	Glutathione peroxidase
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IPSS	International Prostate Symptom Score
NIH-CPSI	National Institute of Health Chronic Prostatitis Symptom Index
NF-κB	Nuclear factor-kappa B
NO	Nitric oxide
PSA	Prostate specific antigen
SERMS	Selective oestrogen receptor modulators
SOD	Superoxide dismutase
TGF-B1	Transforming growth factor-beta-1
TNF-α	Tumour necrosis factor-α
TURP	Transurethral surgical resection of the prostate
VEGF	Vascular endothelial growth factor

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