Herbs for Benign Prostatic Hyperplasia

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OBJECTIVE: To review and evaluate the literature relative to the use of herbal therapies in the treatment of benign prostatic hyperplasia.

DATA SOURCES: Literature was identified by MEDLINE, Embase, *International Pharmaceutical Abstracts*, and the International Bibliographic Information on Dietary Supplements searches and through cross-referencing of selected articles.

STUDY SELECTION/DATA EXTRACTION: All articles identified from the data sources were evaluated and all information deemed relevant was included in this review.

DATA SYNTHESIS: A large percentage of men >50 years old begin to experience signs and symptoms of benign prostatic hyperplasia (BPH). Herbs hold promise in the treatment of BPH. *Serenoa repens*, *Pygeum africanum*, *Urtica dioica radix*, and *Cucurbita peponis semen* are some of the botanical therapies used in the treatment of BPH.

CONCLUSIONS: There are many European studies examining efficacy, dose, and adverse effects of these plants in the treatment of BPH. However, numerous questions remain. These include issues concerning long-term beneficial and adverse effects of herbal therapy, prevention of complications, standardization of extracts, and concomitant use with "mainstream" medications. Based on the information available today, these botanical therapies can be used for treatment of a number of objective and subjective symptoms in patients with BPH, stages I and II.

KEY WORDS: alternative medicine, benign prostatic hyperplasia, herbal therapy.

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By age 50, 30% of men begin experiencing difficulties with urination related to benign prostatic hyperplasia (BPH).[1] Problems associated with BPH are usually progressive, with incidence reaching 90% of all men by age 80 years. The cause of this condition is not well understood. BPH is characterized by enlargement secondary to proliferation of both stromal and epithelial cells of the prostate gland. A shift in prostatic androgen metabolism is the underlying factor in BPH.[1,2] During that time, the conversion rate of testosterone to dihydrotestosterone by 5α-reductase increases within the prostate. This increase results in prostatic accumulation of dihydrotestosterone, an active form of testosterone that causes cell proliferation.

During the course of their lives, men produce both testosterone and small amounts of estrogen. As they age, the amount of active testosterone in the blood decreases, leaving a higher proportion of estrogen. Animal research[1] has suggested that BPH may occur because the higher amount of estrogen within the gland increases the activity of substances that promote cell growth. BPH causes characteristic genitourinary signs and symptoms including a decrease in force and caliber of the urine stream, urinary hesitancy (20 to >50% of the time), a sense of urgency (occasional to frequent difficulty in postponing urination), urinary frequency (from 5–7 to 8–12 times/d), dysuria (occasional to frequent burning sensation during urination), and nocturia (1–3 times/night).[1-3] Patients may also experience post-void dribbling and incomplete emptying of the bladder. BPH is staged and conventionally treated based on the severity of signs and symptoms.[1,2]

Treatment goals for BPH are to relieve the irritative and obstructive symptoms. Treatment options include lifestyle modifications, device and surgical therapies, and pharmaceutical interventions. Drugs most commonly used in the treatment of BPH include α_1-adrenergic blockers, the antiandrogen flutamide, the gonadotropin-releasing hormone agonist leuprolide, and finasteride, a 5α-reductase inhibitor.[1,2]

Author information provided at the end of the text.

Over the last few years, the use of complementary and alternative medicine (CAM) has been increasing dramatically. The 1997 follow-up national survey[4] revealed that there were >629 million visits to providers of CAM in 1997, with expenditure associated with CAM amounting to approximately $21.2 billion. In the search for more effective therapies with fewer adverse effects, many patients have turned to herbs and other dietary supplements as alternative treatments for BPH. This article discusses major advantages and disadvantages of using herbs in the treatment of BPH.

Saw Palmetto

HISTORICAL USE

Serenoa repens (saw palmetto), arecaceae/palmaceae family, is one of the most popular herbs used in the US in the treatment of BPH.[5-7] This plant is also called American dwarf palm tree, cabbage palm, ju-zhong, palmier nain, sabal, sabal fructus, and saw palmetto berry. The applicable part of saw palmetto is the ripe fruit.[8]

S. repens was first used by Native Americans in the 18th century for testicular atrophy, erectile dysfunction, prostate gland swelling, improvement of sexual vigor, and also was used as an aphrodisiac.[9-12] Anecdotal reports regarding the efficacy of *S. repens* for relief of prostate gland swelling have existed in medical literature since the 1800s.[11] In the first half of the 20th century, saw palmetto tea was included in the *United States Pharmacopoeia* and the *National Formulary*.[13] The fruit was used as food.

Saw palmetto has many traditional uses other than relief of BPH symptoms including treatment of urogenital tract infection, asthma, bronchitis, colds, sore throat, diabetes, migraines, underdeveloped breasts,[14] and stimulation of hair growth.[15] *S. repens* has also been used as a mild diuretic,[11] a sedative, an antiinflammatory,[16] and an antiseptic agent. The powdered fruit has been used as a uterine and vaginal tonic suppository.[17] Finally, saw palmetto is used in combination with 7 other herbs (PC-SPES) to treat prostate cancer.[18]

MECHANISM OF ACTION

The exact mechanism of action of saw palmetto is unknown, although several theories exist. Dihydrotestosterone has been the major androgen implicated in the pathogenesis of BPH, male pattern baldness, acne, and female hirsutism.[19] The mechanisms most likely involve inhibition of 5α-reductase[8,10,20] and/or inhibitory effects on androgen and estrogen receptors.[8,10,17,21-25] Inhibition of 5α-reductase results in a decrease in the conversion of testosterone to dihydrotestosterone.

Studies[7,21,26] have shown that the antiestrogenic effect may be due to competitive blocking of the translocation of cytosolic estrogen receptors to the nucleus. A similar mechanism has been proposed for the effect on androgen receptors. In regard to *S. repens'* antiestrogenic effects, Di Silverio et al.[17] postulated that inactivation of androgen and progesterone receptors as well as 5α-reductase activity may be secondary to estrogen receptor blockade; the inhibition of estrogen may actually potentiate the effects of antiandrogens.[17,27,28] In addition to these more likely mechanisms, other possibilities include antiinflammatory effects,[8,21,23,29] decreased availability of sex hormone–binding globulin (SHBG),[3,6] inhibition of prolactin and growth factor–induced prostatic cell proliferation,[8,21] and stimulation of apoptosis.[8,22-24] *S. repens* extract inhibits testosterone-stimulated prostate enlargement in rats.[29]

DOSAGE

The daily dose used in most studies was 320 mg of lipidosterolic serenoa extract, usually administered as 160 mg twice daily of a lipophilic extract containing 80–90% fatty acids.[5,30] A 6-month dose-ranging study[21] of Permixon found no difference in efficacy between twice-daily dosing with 160 mg or 480 mg. It is important to remember that, due to the differences in manufacturing and extraction processes, the results of this study cannot be strictly applied to use of other brands. Many saw palmetto products are standardized based on the fatty acid content. The dosage form used in most trials[11,31] was a liposterolic extract of *S. repens* containing 80–95% fatty acids and sterols.

Standardized extracts are needed to conduct reliable clinical trials. The standardization of an extract includes not only a series of analytical controls, but also a thorough description of the starting drug and the entire extraction process, both basic items for the constancy of the quality of an extract. Another important aspect in the standardization of an extract is its nomenclature, which must include all the necessary data for a clear definition (drug, physical state, solvent of extraction, composition) of the extract itself. Every patient needs to be taught that not every standardized product possesses high quality. It is also important to remember that results of a single trial cannot be applied to the use of other extracts.

In addition to extracts, other dosage forms of saw palmetto exist. According to the *Natural Medicine Comprehensive Database*,[8] the recommended daily doses for the treatment of BPH for other formulations of this herb are 1–2 g of whole berries and 0.6–1.5 mL of liquid extract.[7] The most effective saw palmetto products seem to be whole-berry extracts prepared with lipophilic nonpolar solvents.

A tea can also be made by simmering 0.5–1 g of dried berry in 150 mL of boiling water over 5–10 minutes, then strained and taken 3 times daily.[7] However, brewed teas or other hydrophilic preparations may not contain adequate amounts of active constituents due to the lipophilicity of the active ingredients.[30]

CLINICAL STUDIES

Many studies have examined the efficacy of *S. repens*, providing sufficient justification for its use in the treatment

of BPH. In clinical studies[6,21,32] lasting up to 48 weeks and meta-analyses, *S. repens* significantly alleviated the signs and symptoms of this disorder in comparison with placebo. Saw palmetto has also significantly improved outcomes such as International Prostate Symptom scores (I-PSS) (measurements of urgency, hesitancy, frequency), quality-of-life (QOL) scores, peak and mean urinary flow rates, residual urinary volumes, pain during urination, perineal heaviness, nocturia, and dysuria.[6,10,21,32] It also seems to lower residual urine volume in patients with BPH. Increased prostate size and/or volume, another sign of BPH, was not significantly alleviated by saw palmetto in the majority of studies. One trial[21] reported greater improvements in peak urinary flow rate, nocturia, and dysuria in subjects with baseline residual urine volumes of <100 mL. *S. repens* has been investigated in comparative trials[6,25,32-39] with other treatments for BPH.

Overall, studies[14,40,41] comparing *S. repens* 320 mg/d with finasteride 5 mg/d resulted in similar improvements in subjective urinary symptoms, I-PSS, QOL, and peak urinary flow rates, although prostate size was reduced 18% by finasteride and 6% by serenoa. Finasteride also reduces serum dihydrotestosterone by 65%, while no effect is found for serenoa extract or placebo.[42] Several studies[32,43-45] showed that, despite all of the positive urinary findings associated with serenoa extract, patients had no change in peak flow, prostate-specific antigen (PSA) or concentrations of testosterone, follicle-stimulating hormone, and luteinizing hormone.

S. repens has also been compared with α_1-receptor antagonists, alfuzosin, and prazosin. One study[46] examined *S. repens* 160 mg twice daily and alfuzosin 2.5 mg 3 times daily over 3 weeks. Peak flow improved by 48% with serenoa and 72% with alfuzosin in this double-blind trial of 63 patients with BPH. In a 3-month trial[47] with 45 BPH patients, serenoa was nearly as beneficial as prazosin for irritative symptoms. Doses used for this study could not be determined since the information was not included in the English abstract of the article, which was published in Spanish. Treatments in both of these trials[46,47] improved overall symptoms, decreased urinary frequency and residual urine volume, and increased urinary flow rate. In general, although α_1-antagonists had greater clinical efficacy, there were few statistically significant differences between treatment groups. Treatment for 1–2 months with saw palmetto is usually necessary before significant symptomatic improvement occurs.[6,32,39]

S. repens offers several advantages over more conventional therapies for BPH. The herb is better tolerated than both finasteride and α_1-antagonists.[21,40] Studies[6] revealed significantly lower rates of erectile dysfunction with saw palmetto than with finasteride. Patients treated with *S. repens* actually reported[40] modest improvement in sexual function score in comparison with deterioration reported with finasteride. Unlike 5α-reductase inhibitors, *S. repens* did not interfere with the ability of prostate cells to secrete PSA and did not modify serum PSA concentrations; finasteride, however, significantly decreased PSA concentrations.[10,40] Economically, *S. repens* is less costly than other pharmacologic therapies for BPH.[5] On average, a monthly supply of finasteride costs the patient nearly $60; a monthly supply of saw palmetto could be purchased for $7–20.

Despite the advantages, there are many limitations of the clinical studies involving *S. repens*. There are limited published data; many of the available studies were of short duration and varied in study design. In addition, most trials with this herb were conducted before development of validated urologic symptom scale scores for outcome evaluation.[6] The meta-analysis[6] included studies of short duration (mean 9 wk) and therefore was unable to determine whether *S. repens* prevented long-term complications of BPH (e.g., acute urinary retention, need for surgical intervention). In the same meta-analysis, finasteride was determined to be effective in decreasing the development of these complications. Despite these limitations, *S. repens* appears to be a viable alternative for the treatment of mild to moderate BPH.

TOXICITY

Saw palmetto appears to be well tolerated, causing only mild and infrequent adverse effects.[6,8,10,44,46,48] The most commonly reported adverse effects were minor gastrointestinal problems (nausea, vomiting, constipation, diarrhea) that resolved when the herb was taken with meals.[10,34,35] Uncommonly reported adverse effects included mild pruritus,[46] headache, hypertension, erectile dysfunction, ejaculatory disturbance, and decreased libido. These adverse reactions are probably linked to the effects of 5α-reductase inhibition. However, clinical studies indicate that the occurrence of impotence in men taking saw palmetto is similar to that with placebo and significantly less than with finasteride.[6,35,40]

Saw palmetto has been safely used in clinical studies[5-7,49] lasting up to 48 weeks. As a result, the long-term safety and efficacy of this herb are unknown. Laboratory fertility studies indicate that saw palmetto has no effect on oocytes or sperm motility, but it might induce metabolic changes in sperm.[50,51]

There is an insufficient amount of reliable information available regarding interactions between *S. repens* and other herbs, supplements, and food products. Concomitant use of saw palmetto can interfere with oral contraceptives and hormone therapy.[7] Contrary to earlier concerns, saw palmetto extract appears to have no significant effect on serum PSA concentrations.[44]

Saw palmetto has antiandrogen and estrogenic activity[7,11,12] and is contraindicated during pregnancy and lactation.[8]

Pygeum

HISTORY

Another herb that is used for the treatment of BPH is *Pygeum africanum* (or *Prunus africana*). The plant is known as African plum tree or African prune and belongs to the Rosaceae family. This herb has been employed to

treat mild to moderate symptomatic BPH in France since 1969.[52] Some of the symptoms alleviated by *P. africanum* include nocturia, dysuria, pollakiuria micturitional disorders, and bladder fullness.[11,52-56] Other illnesses that pygeum has been used for historically are inflammation, kidney disease, urinary problems, malaria, stomach ache, fever, difficult urination, fever, "madness," and prostate gland inflammation. There are reports[15] suggesting use of pygeum as an aphrodisiac. In the US, products containing pygeum or its combinations with other herbs are now widely marketed.[52]

MECHANISM OF ACTION

Pygeum bark contains a number of different ingredients, some of which have demonstrated benefit in the treatment of BPH. These constituents include long-chain fatty alcohols (n-docosanol, n-tetracosanol, and their *trans*-ferulic acid esters),[57] β-sitosterol, and its 3-O-glucoside, β-sitosterone, oleanolic, ursolic, crataegolic, and fatty acids.[58,59] Ferulic acid esters of fatty acids reduce prostatic cholesterol concentrations, limiting synthesis of testosterone.[11,52]

Theoretically the phytosterols, including β-sitosterol, β-sitosterone, and campesterol,[11,52] compete with androgen precursors and inhibit prostaglandin biosynthesis.[52] There are reports[11,52] stating that triterpenes such as oleanolic, crataegolic, and ursolic acid have antiinflammatory activity in prostate connective tissue. Docosanol reduces plasma testosterone and luteinizing hormone and increases adrenal steroid secretion in rats.[60]

This extract is postulated to possess several mechanisms of action. Studies[53] in rats have shown a beneficial effect on age-related bladder contractility, while pygeum extract appears to reduce contractile dysfunction in rabbits in doses of 100 mg/kg/d for 3 weeks.[61]

Additional research[44,62] revealed that inflammatory cell infiltration, as well as fibroblast proliferation, may play a key role in development of BPH. *P. africanum* exhibited antiinflammatory activity and inhibited fibroblast proliferation, specifically fibroblasts induced by prostatic growth factors, basic fibroblast growth factor, and epidermal growth factor.[53,62]

Although it appears unlikely that *P. africanum* inhibits either androgens or 5α-reductase,[63] it may have direct protective effects by restoring structural and functional characteristics in the aging prostate.[53] Pygeum is possibly effective for the treatment of functional symptoms of prostatic adenoma.[64]

P. africanum improves prostate histologic architecture, restores normal secretory patterns,[11] inhibits pathologic fibroblast proliferation, decreases hypersensitivity of the detrusor muscle, and has antiinflammatory effects and even some estrogenic action.[65,66] This variety of mechanisms enables this herb to provide a combined pharmacologic approach to the treatment of BPH.

DOSAGE

P. africanum is typically dosed at 100 mg in divided doses in the treatment of functional symptoms of BPH[53] in 6- to 8-week cycles.[11,52] Standardized extract of *P. africanum* is available.[67] A dose regimen study[68] comparing Tadenan 50 mg twice daily with 100 mg once daily did not reveal any clinically significant differences in efficacy between regimens. The regimens appeared to be equally safe and effective for functional symptoms of BPH. One trial[67] involving 100 mg/d over 12 months revealed that this dose significantly improves signs and symptoms of BPH after 2 months in comparison with the results of other studies involving placebo ($p < 0.05$), and that this improvement is maintained after 12 months of treatment.

CLINICAL STUDIES

Open-label, noncomparative studies[53] showed overall improvement in signs and symptoms of BPH including mean maximum urinary flow rate, nocturia, daytime frequency, hesitancy, urgency, weak stream, and dysuria. A high proportion of patients with symptomatic BPH in these studies showed prolonged improvement during long-term treatment. Double-blind, placebo-controlled trials yielded more variable results.

Donkervoort et al.[69] reported no evidence of beneficial urodynamic effects (e.g., maximum urinary flow rate) with *P. africanum* extract, whereas more recent studies[53] showed a statistically significant advantage of the extract over placebo. Regarding nocturia,[55,70] daytime frequency, and other symptoms, the majority of trials showed statistically significant benefit for *P. africanum* over placebo. The extract also significantly improved I-PSS symptoms including nocturia, QOL, peak urinary flow rate, micturition,[52,70] and other urinary parameters, with >40% reduction in I-PSS from baseline in symptomatic BPH patients.[55,68]

Prostatic volume, another important parameter in BPH, was slightly but statistically significantly decreased by *P. africanum* after a treatment period of 12 months ($p < 0.05$). *P. africanum* has also been studied[68] in comparison with other active treatments for BPH. Symptomatic response with *P. africanum* was superior to that observed in randomized trials with α-antagonists and 5α-reductase inhibitors. *P. africanum* extract was compared with *Urticae urtae radix* (nettle root) in a small study.[53] The results of the trial favored the pygeum prepraration. However, the power of this study is questionable since small numbers of patients were involved. Other studies[53] comparing *P. africanum* with antiinfective and/or antiinflammatory treatments, such as nonsteroidal antiinflammatory drugs, have found statistically significant advantages for the extract.

TOXICITY

Clinical studies and postmarketing safety data have shown that *P. africanum* is well tolerated with only mild to moderate adverse effects, mostly gastrointestinal in nature (diarrhea, constipation, gastric pain, nausea).[11,51,52,68] Additional adverse effects observed in patients taking pygeum include dizziness, visual disturbance, restlessness, head-

ache, and difficulty falling asleep. Most serious adverse effects that were noted affect a urogenital system (dysuria, urinary retention).

Dosing regimens of 100 mg once daily or 50 mg twice daily did not reveal significant differences in adverse effect profiles. After 2 or 12 months of treatment, no significant changes in sexual activity, blood test data (i.e., PSA concentrations), or urinalysis were reported.[68] In comparison with *S. repens*, patients treated with *P. africanum* had significantly less improvement in subjective self-assessment of symptoms and objective clinical results.[8]

There are no known interactions with herbs, supplements, drugs, foods, and laboratory tests with this plant.[8] Reliable information on the use of pygeum in pregnancy and lactation is not available; therefore, these women should avoid using the plant.[8]

Nettle Root

HISTORY

The root of *Urtica dioica radix* (or *Urtica urens*) is known as common nettle, great stinging nettle, nettle, nettles, small nettle, urtica, and urticae radix. The plant belongs to the Urticaceae family. Nettle root is used for urination disorders associated with BPH.[5,11,52,71-74] Traditionally, stinging nettle root has been used as a diuretic,[11,52,73] an astringent,[73] and for treatment of joint abnormalities. Additional uses include hypertention[75] and treatment of salmonella infection.[76] Nettle root is also Commission E–approved for the treatment of difficulty in urination due to BPH stages I and II.[5,71]

In this article, the root of stinging nettle is primarily described because this part of the plant is used for urinary disorders such as BPH. It should not be confused with the above-ground parts of stinging nettle and white dead nettle. The above-ground parts of stinging nettle are usually used for the treatment of allergies, arthritis, conjunctivitis, and a number of other disorders. White dead nettle herb is used for gastrointestinal complaints, inflammation of the mucous membranes of the upper respiratory tract, and vaginal discharge.[8]

MECHANISM OF ACTION

The mechanism of action of this herb in BPH is unclear; however, several theories exist. β-sitosterol, a component of stinging nettle extract, may promote improvement in symptoms and urinary flow in patients with BPH.[77] The effects of androgens on proliferation, metabolism, biosynthesis, and secretion of the prostate are partially mediated through binding of the steroid-receptor complex to various plasma membrane receptors, one being membrane Na^+-K^+-ATPase. An in vitro study[78] involving prostate tissue homogenate and organic-solvent extracts of *U. dioica* showed significant inhibition of prostate Na^+-K^+-ATPase activity, resulting in a decreased number of signs and symptoms of BPH.

The aqueous extract of urtica has also been found to bind SHBG[5,52,71,73,77,79] and might suppress prostatic cell metabolism.[52,71] Polysaccharides and lectins also play a role in the action of urtica extract. Polysaccharides are anti-inflammatory in nature and lectins intervene in immunologic,[71,74] endocrine, and weak antiinflammatory[52,71] processes. *U. dioica* agglutinin, a lectin from stinging nettle roots, may directly inhibit cell proliferation and block the binding of epidermal growth factor to its receptor, which inhibits prostate growth.[77]

DOSAGE

According to Commission E monographs,[5] the approved dose of the dried herb is 4–6 g. The recommended daily doses of other formulations of the nettle root for the symptomatic treatment of BPH are dried hydroalcoholic extract (5:1, extracted with methanol 20%) 600–1200 mg/d, liquid extract (1:1 in alcohol 45%) 1.5–7.5 mL 3 times per day, and ethanolic extract (1:5 in alcohol 40%) 5 mL/d. For tea, the dose is 1 cup (steep 1.5 g dried, powdered root in 150 mL of boiling water for 5–10 minutes, strain) up to 4–6 g/d.[8,13]

CLINICAL STUDIES

Few researchers have performed placebo-controlled, double-blind trials evaluating the therapeutic efficacy of nettle root extract. One of the trials[80] showed a significant increase in urinary output compared with placebo ($p < 0.001$). Other subjective symptoms such as urine flow and residual urine volume did not show significant difference.

In another double-blind study,[81] 79 patients receiving 600 mg/d of extract for 4–6 weeks showed a significant increase in urine flow ($p < 0.02$).

Effectiveness of β-sitosterol was tested in 2 separate randomized, double-blind, placebo-controlled trials[82,83] in patients with symptomatic BPH. Efficacy of the substance was assessed based on outcomes in patients' I-PSS, as well as their QOL, peak urinary flow rate, and post-void residual urinary volume. Both trials concluded that β-sitosterol was effective in improvement of the symptoms. A follow-up[84] of 1 of those studies[83] concluded that the beneficial effects of the treatment recorded during the trials were maintained for 18 months.

TOXICITY

Adverse effects of stinging nettle root include occasional mild gastrointestinal upset,[5,52,71,74] sweating,[52] and allergic skin reactions.[52,71] Allergic reactions occur due to stinging qualities of the hairs on the plant and can be reduced by drying the plant or eliminated by brief heating. According to an open prospective study[48] using a combination of sabal extract and urtica extract, only 0.7% of all patients (15 of 2080) experienced mild adverse effects.

There is no sufficient reliable information available regarding interactions between nettle root and other herbs, supplements, drugs, foods, and laboratory tests. There are

also no known reasons to suspect any clinically significant interactions with these substances or diverse diseases and conditions.[8] Sufficient reliable information on the use of nettle root in pregnancy is not available; therefore, pregnant women or those who are breast-feeding should avoid use of the herb in these conditions.[8]

Pumpkin Seed

HISTORY

Pumpkin seed is also known as *Cucurbita peponis semen*, field pumpkin, and pepo. It belongs to the Cucurbitaceae family. For many years, *C. peponis* seed has been used in folk remedies, particularly in Europe, for bladder irritation,[5,54,72,74] pyelonephritis,[74] treatment of intestinal worms,[15] and micturition problems caused by the prostate.[85] Pumpkin seed oil extract has been effectively employed in the treatment of BPH symptoms (stages I and II) in combination with other extracts.[86] Roasted pumpkin seeds are considered a snack food in many countries.[13] Seeds of several other members of the Cucurbitaceae family (autumn squash [*Cucurbita maxima*]) and Canadian pumpkin (crooked neck squash [*Cucurbita moschata*]) have characteristics similar to those of pumpkin seeds.[15]

MECHANISM OF ACTION

Although the exact mechanism of action of *C. peponis* is not clear, several possible theories have been documented, one being that the herb may decrease the binding capacity of the androgen receptor to testosterone.[85] Pumpkin seeds contain phytosterols, which are structurally similar to androgens and estrogens. Due to this similarity, phytosterols may competitively bind to androgen receptors, resulting in decreased testosterone binding. Pumpkin seeds also contain carotenoids (lutein, carotene, β-carotene).[5,15] In addition to these constituents, pumpkin seeds are also rich in linoleic and oleic unsaturated fatty acids.[5] The diuretic properties of pumpkin seed oil enhance the relief of bladder discomfort. The phytosterol constituents are also believed to affect urine flow. *C. peponis* may also exert a chemoprotective effect through its relatively high concentrations of zinc.[87]

DOSAGE

The average daily dose for dysuria secondary to BPH and bladder irritation is 5 g of seed twice daily.[5,52,74] Doses of 20–167 g of seeds have been used 3 times daily for the anthelmintic properties.[15]

CLINICAL STUDIES

Clinical trials are needed to address questions of therapeutic efficacy of this product. There are several European trials describing use of *Cucurbita pepo* for treatment of stages I and II of BPH. It appears that, in 2245 patients taking pumpkin seeds for 12 weeks, the I-PSS decreased by 41% and QOL improved by 46%.[88]

TOXICITY

One of the adverse effects postulated[13] with pumpkin seed therapy is potential electrolyte loss secondary to its diuretic properties. There are no reported interactions with herbs, supplements, drugs, foods, or laboratory tests.[8] This plant should be avoided in amounts greater than found in food during pregnancy and lactation.

Combination Herbal Remedies

Several herbal combinations are used in the treatment of BPH; one of these is *U. dioica* and *P. africanum*. The principal effects of this combination result from inhibition of the enzymes 5α-reductase and aromatase.[9] *P. africanum* is the more potent inhibitor of 5α-reductase, with *U. dioica* being a somewhat weaker inhibitor. A study[9] of a combination product examining 134 subjects with BPH found that 1 capsule twice daily was as effective as 2 capsules twice daily (each capsule contained 300 mg of *U. dioica* root extract and 25 mg of *P. africanum* bark extract) in improving urinary flow, nocturia, and residual volume as assessed by physicians and patients.

During this study, the remedies administered for 8 weeks significantly improved nocturia, residual urine, and urine flow after 28 days of treatment ($p < 0.05$). Further significant decreases in symptoms were seen on day 56 of treatment. Although it is difficult to compare the results of different studies, the combination of both extracts exhibited greater inhibitory effect on aromatase in this trial than in other studies where the 2 extracts were administered alone. The combination of these 2 herbs did not appear to cause adverse effects significant enough to lead to discontinuation of therapy. Adverse effects occurred in only 5 patients and included gastrointestinal pain, fatigue, and intermittent headaches.[9]

Saw palmetto and stinging nettle root (PRO 160/120) is another herbal combination that has been evaluated in the treatment of early stages of BPH. In a double-blind comparison of PRO 160/120 with finasteride,[87] 543 patients were treated for 48 weeks. Results were comparable for urine flow increase and symptom decrease. The safety analysis showed that patients taking the herbal combination experienced fewer adverse effects than those receiving finasteride.

Curbicin is a third combination product that has been used for treatment of BPH. It contains 160 mg of standardized extract from *C. peponis* (80 mg) and *S. repens* (80 mg).[85] The beneficial effects of this combination are mediated through competitive binding of phytosterols to androgen receptors. Curbicin has been studied using a dose of 2 tablets 3 times daily for 3 months. The treatment population included patients experiencing mild symptoms of BPH while awaiting surgery and patients unfit for surgery because of coexisting disease. Curbicin provided significant

improvement in subjective and objective parameters in comparison with placebo. Subjective variables included dysuria, diurnal frequency, nocturia, and subjective symptom rating (descriptive scale). Objective variables included urinary flow rate, voiding time, and residual volume. Overall, the authors of the study believed that this combination is appropriate for the treatment of mild symptoms of outflow tract obstruction secondary to prostatic hyperplasia.

Adverse effects associated with combination products include a report[86] of decreased ejaculatory volume with a product containing nettle root extract, saw palmetto extract, pumpkin seed oil extract, lemon bioflavonoid extract, and vitamin A, and report[89] of cholestatic hepatitis associated with use of a multiingredient product containing saw palmetto (Prostata).

Finally, it is important to remember that there is a discrepancy between the doses of the herbs sold separately and the same herbs sold as ingredients of combination products.

Summary

Botanical supplements hold great promise in the treatment of BPH (Table 1). Many European studies are examining the efficacy, dose, and adverse effects of these treatments. We believe that many questions regarding use of the supplements remain. These issues concern beneficial and adverse effects, prevention of complications, standardization of extracts, and concomitant use with "mainstream" medications such as finasteride and α-antagonists. However, based on the information available, use of these supplements (especially saw palmetto and pygeum) can improve QOL and a number of objective symptoms in patients with stage I or II BPH.

Table 1. General Comparison of Herbs Used for the Treatment of BPH

Herb	Mechanisms	BPH Symptoms Addressed	Common Doses and Dosage Forms	Effects	Products on the Market
Saw palmetto (*Serenoa repens*)	5_{α}-reductase inhibition, antiandrogenic, antiestrogenic, antiinflammatory, competitive inhibition of androgen binding, decreased availability of SHBG, inhibition of growth factor–induced prostatic cell proliferation, inhibition of prolactin, stimulation of apoptosis	dysuria, frequency, hesitancy, nocturia, peak and mean urinary flow rates, perineal heaviness, QOL scores, residual urinary volume, urgency	extract: 160 mg bid dried whole berries: 1–2 g liquid extract: 0.6–1.5 mL tea: 0.5–1 g of berries in 150 mL of water tid	constipation, diarrhea, decreased libido, ejaculatory disturbance, erectile dysfunction, headache, hypertension, mild pruritus, nausea, vomiting	Quanterra Prostate (Warner-Lambert), ProstaPro (Phytopharmica), Saw palmetto (Centrum), standardized saw palmetto extract (Nature's Way), Super Saw Palmetto (Enzymatic Therapy)
Pygeum (*Pygeum africanum*)	antiinflammatory activity, competition with androgen precursors, decreased hypersensitivity of detrusor muscle, inhibition of fibroblast proliferation, reduction of prostatic cholesterol concentrations, reduction of plasma testosterone, restoration of structural and functional characteristics of aging gland	daytime frequency, dysuria, hesitancy, mean maximum urinary flow, micturition, nocturia, prostate volume, urgency	50 mg bid or 100 mg qd	constipation, diarrhea, dizziness, gastric pain, headache, insomnia, nausea, restlessness, visual disturbance	one daily pygeum (Solaray), pygeum (African) (12–13% Phytos.) (Nature's Plus), pygeum 13% standardized extract (Nature's Way), pygeum power (Nature's Herb)
Nettle root (*Urtica dioica radix*)	antiinflammatory effects, binding to SHBG, inhibition of cell proliferation, Na^+-K^+-ATPase inhibition	nocturia, peak urinary flow, urinary frequency, urinary output, urinary volume	dried herb: 4–6 g hydroalcoholic extract: 600–1200 mg/d liquid extract: 1.5–7.5 mL tid ethanolic extract: 5 mL/d tea: 1.5 root per 150 mL water	allergic skin reactions, mild gastric upset, sweating	nettle root power (Nature's Herb), saw palmetto and nettle root (Nature's Way)
Pumpkin seeds (*Cucurbita peponis semen*)	antihelmintic properties, competitive binding to androgen receptors, decreased binding capacity of the androgen receptor to testosterone, diuretic properties	bladder irritation, frequency, hesitancy, pyelonephritis, QOL scores, urgency	5 g bid for dysuria 20–167 g in 3 divided doses for antihelmintic properties whole or ground seeds expressed oils and dry extracts	potential electrolyte loss	Hain pumpkin seed oil caps, pumpkin seed (Nature's Answer)

BPH = benign prostatic hyperplasia; Na^+–K^+–ATPase = sodium–potassium-adenosine triphosphatase; QOL = quality of life; SHBG = sex organ–binding globulin.

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EXTRACTO

OBJETIVO: Revisar y evaluar la literatura referente al uso de terapias botánicas en el tratamiento de hipertrofia benigna de la próstata (BPH).

FUENTES DE INFORMACIÓN: Se identificó la literatura clínica usando los sistemas de búsqueda de información MEDLINE, Embase,

International Pharmaceutical Abstracts, y la International Bibliographic Information en el tema supplementos nutricionales. Además se utilizaron referencias de artículos selectos.

EXTRACCIÓN DE DATOS: Todos los artículos identificados de las fuentes de información fueron evaluados, y toda la información relevante se incluyó en este artículo de revisión.

SÍNTESIS: Un gran número de hombres sobre los cincuenta años de edad comienzan a padecer de signos y síntomas de BPH. La evidencia de la literatura sostiene que varias plantas tienen suficiente actividad como para considerarse prometedoras en el tratamiento de BPH. *Serenoa repens*, *Pygeum africanum*, *Urticae dioica*, y *Cucurbitae peponis* son algunos de los tratamientos botánicos usados para BPH.

CONCLUSIONES: Existen muchos estudios europeos examinando la eficacia, dosis, y efectos adversos de estas plantas en BPH. Sin embargo, existen muchas preguntas que quedan por contestar. Algunas de las preguntas incluyen el beneficio a largo plazo, los efectos adversos, como prevenir complicaciones, asuntos sobre la estandarización de los extractos, y el uso concomitante con fármacos. Basándonos en la información actual disponible, estas terapias botánicas pueden usarse para el tratamiento de los síntomas subjetivos de los pacientes con BPH en estadíos I y II.

Jorge R Miranda Massari

RÉSUMÉ

OBJECTIF: Réviser et évaluer la littérature relative à l'utilisation des thérapies à base d'herbes dans le traitement de l'hyperplasie bénigne de la prostate (HBP).

REVUE DE LITTÉRATURE: La littérature fut identifiée par une recherche informatisée sur "MEDLINE," "Embase," "*International Pharmaceutical Abstracts,*" et sur "International Bibliographic Information on Dietary Supplements" ainsi que via les bibliographies d'articles obtenus.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Tous les articles identifiés dans la revue de littérature furent évalués et toute information pertinente fut inclue dans cet article.

RÉSUMÉ: Un large pourcentage d'hommes âgés de plus de 50 ans démontre des signes et symptômes d'HBP. Certaines herbes telles *Serenoa repens*, *Pygeum africanum*, *Urticae dioica*, et *Cucurbitae peponis* sont utilisées avec succès dans le soulagement d'HBP.

CONCLUSIONS: Il existe plusieurs études européennes évaluant l'efficacité et l'innocuité de ces herbes pour soulager l'HBP. Cependant, plusieurs questions sont sans réponses. Les effets bénéfiques et indésirables à long terme, la prévention des complications, la standardisation des extraits, et l'utilisation concomitante des médicaments traditionnels en sont des exemples en fonction de la littérature disponible aujourd'hui, les thérapies à base d'herbes peuvent être utilisées pour traiter plusieurs symptômes objectifs et subjectifs des patients avec HBP de stade I et II.

Marc M Perreault