HERBAL THERAPEUTICS

(6) BENIGN PROSTATIC HYPERPLASIA

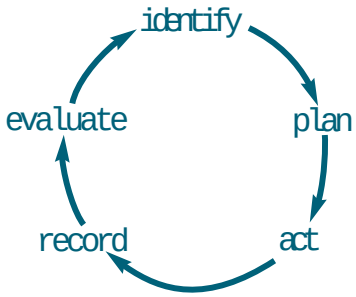
By Jo Barnes, PhD, MRPharmS

This article considers evidence for the efficacy and safety of herbal medicines used to improve symptoms associated with benign prostatic hyperplasia

identify gaps in your knowledge

1. List three lower urinary tract symptoms associated with benign prostatic hyperplasia.
2. Name a herb commonly used to treat benign prostatic hyperplasia.
3. Do you know how this herb is thought to work?

This article relates to the Royal Pharmaceutical Society's core competencies of "medicinal products" and "evidence-based practice" (see "Medicines, ethics and practice — a guide for pharmacists", number 26, July 2002, pp105–6). You should consider how it will be of value to your practice.



Benign prostatic hyperplasia (BPH) is one of the most common problems occurring among older men. Prevalence figures vary, but a conservative estimate is that up to 40 per cent of men aged over 70 years experience lower urinary tract symptoms (LUTS), such as urinary frequency, urgency, nocturia, reduced urine flow and urinary retention associated with BPH.[1]

Research into herbal products used for BPH has focused mainly on the effects of saw palmetto (*Serenoa serrulata* Hook. F., *S repens*, *Sabal serrulata*), nettle (*Urtica dioica* L.)[2] and pygeum (African prune tree, *Pygeum africanum* Hook. F., *Prunus africana* Hook. F.), although like saw palmetto, other herbs, such as *Panax ginseng* (also known as Korean ginseng or panax) have a history of traditional use as "male tonics" and are still used by herbalists to treat prostatic enlargement.[3]

It is beyond the scope of this article to consider the aetiology, classification, diagnosis and treatment of BPH; pharmacists are advised to consult standard reference sources for this information. Pharmacists are encouraged, where possible, discreetly to probe individuals' reasons for purchasing products containing saw palmetto or other herbs used for BPH. If the intended use is to relieve LUTS, apply usual protocols to establish the possible cause, duration and type of symptoms, treatments already tried or being used, other action taken, and so on.

BPH should not be self-diagnosed and self-treated, and individuals experiencing symptoms associated with BPH should be referred to a general practitioner for diagnosis, and particularly, the exclusion of other disorders, such as prostate cancer. If BPH has been diagnosed, over-the-counter treatment with saw palmetto or other herbal medicines should be under medical, pharmaceutical or other appropriate supervision.

Information on the use of saw palmetto fruit, nettle root and pygeum bark extracts in conjunction with conventional medicines for BPH (eg, finasteride and alpha-blocking agents, such as tamsulosin) is lacking. It has been suggested that saw palmetto fruit and nettle root extracts may have anti-androgenic activity, so the potential for interaction with other substances with similar effects cannot be ruled out. In any case, patients taking saw palmetto and so on concomitantly with conventional medicines for BPH should be advised to inform their GP and other individuals responsible for their care of this fact, since it is important that the effects of such herbs are considered when treatment outcomes for conventional medicines are assessed.

BACKGROUND

Saw palmetto, also known as the dwarf palm, is a small palm-like shrub which is native to parts of North America.[3] The fruit (berries) are used pharmaceutically. Some marketed products contain liposterolic (containing lipids and sterols) extracts.

Nettle, also known as stinging nettle, is usually considered to be a weed and grows throughout the United Kingdom and other temperate regions.[3] Both the leaf and the root are used pharmaceutically, although use in BPH is limited to the root. Pygeum originates from Central Africa. The bark is used pharmaceutically. Other herbs used in BPH include pumpkin seed (*Cucurbita pepo* L.), which is native to America but is now grown around the world.

MAJOR CONSTITUENTS

The constituents of saw palmetto are well-documented, although it has not yet been established definitively which are responsible for activity. Important constituents include free fatty acids and their glycerides, and steroids, such as b-sitosterol, campesterol and stig-

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masterol. Other constituents include flavonoids and carbohydrates.[2] Many clinical trials have tested the effects of liposterolic extracts of saw palmetto, containing 85 to 95 per cent fatty acids and 0.2 to 0.4 per cent total sterols (including 0.1 to 0.3 per cent b-sitosterol).[2]

Nettle root also contains sterols, including b-sitosterol, as well as a lectin, the coumarin scopoletin, phenylpropane derivatives and lignans.[2] Several of these constituents may be important for activity. Pygeum contains phytosterols, pentacyclic triterpenes and ferulic acid esters.[4] The constituents of pumpkin seed include linoleic acid, steroids and sterol glucosides, but which of these are the active principles is not yet known.

EVIDENCE OF EFFICACY

The issue of variation between manufactured products, and the suggestion that evidence for efficacy and safety should be considered to be extract- or product-specific, were raised in the first article in this series (*PJ*, 8 June, pp804–6).

Saw palmetto Most clinical trials of saw palmetto have investigated the effects of hexane liposterolic extracts of saw palmetto fruit (eg, Permixon), whereas some studies have tested ethanolic liposterolic extracts (eg, IDS-89) or extracts of saw palmetto fruit prepared by supercritical fluid extraction with carbon dioxide. Studies have focused on exploring the effects of saw palmetto extracts in treating LUTS associated with BPH.

Evidence from controlled clinical trials indicates that extracts of saw palmetto are more effective than placebo, and possibly as effective as the 5-a-reductase inhibitor finasteride, in relieving LUTS associated with BPH.

A Cochrane systematic review and meta-analysis included 18 randomised controlled trials (16 of which were also double-blind) of extracts of saw palmetto involving a total of almost 3,000 men with symptomatic BPH.[5] Fourteen trials compared saw palmetto extracts with placebo (three tested saw palmetto extracts in combination with other herbs), and three trials compared saw palmetto extracts (one of which was combined with other herbs) with active control. The remaining study compared the effects of an oral and a rectal formulation of saw palmetto extract. Dosages of liposterolic extracts of saw palmetto used were usually 160mg twice daily, and the mean duration of the studies was nine weeks (range four to 48 weeks). A criticism of many of the included studies is that few used standardised and validated urologic symptom scales, such as the international prostate symptom score (IPSS, see Panel 1).

PANEL 1: GLOSSARY

IPSS The international prostrate symptom score is a system developed by the World Health Organization to allow the assessment of the severity of BPH symptoms. The patient is asked seven questions about the frequency of symptoms over the past month:

- How often have you had the sensation of not completely emptying your bladder after urinating?
- How often have you needed to urinate within two hours of last urinating?
- How often have you stopped and started again several times while urinating?
- How often have you had to get up in the night to urinate?
- How often have you found it difficult to postpone urinating?
- How often have you had a weak urinary stream?
- How often have you had to push or strain to start urinating?

The patient's answers are given a score from 0 to 5, where 0 indicates "not at all", 3 indicates "about half the time" and 5 "almost always".

The scores are then totalled to indicate the severity of symptoms, where a total of 0 to 7 indicates mild symptoms, 8 to 19 moderate symptoms and 20 to 35 indicates severe symptoms.

Compared with placebo, saw palmetto extracts were associated with statistically significant reductions in urinary symptom scores and nocturia, and statistically significant improvements in peak urine flow and self-rating of urinary symptoms (eg, nocturia; weighted mean difference [WMD], 95 per cent confidence interval [CI] : –0.76 times per evening, –1.22 to –0.32; n = 10 studies).[5] The review also found that saw palmetto extracts achieved improvements in urinary symptom scores (WMD of 0.37 points on IPSS, 95 per cent CI, –0.45 to 1.19; n = 2 trials) and peak urine flow (WMD –0.74ml, 95 per cent CI, –1.66 to 0.18; n = 2 studies) that were similar to those with finasteride.

Several other clinical studies of saw palmetto extracts in BPH have been published since the Cochrane review. A six-month, randomised, double-blind placebo-controlled trial involving 85 men with LUTS (IPSS score of 8 or higher) reported a statistically significant reduction in the mean IPSS score but no improvement in urinary flow rates in saw palmetto recipients compared with placebo recipients (P=0.038).[6] Another study compared a liposterolic extract of saw palmetto 320mg daily with the a_1-receptor blocker tamsulosin 0.4mg daily in a 12-month randomised, double-blind, multicentre trial involving 704 men with symptomatic BPH (IPSS score of 10 or higher).[7] Reductions in IPSS scores were similar in both groups.

Several other studies have provided some supporting evidence for saw palmetto, but generally did not use a rigorous study design capable of testing efficacy, eg, no random allocation to treatment, compared outcomes (eg, symptom scores) for saw palmetto recipients with baseline values rather than with those of the control group, or lacked a placebo or active control group.[2]

Other herbs Clinical evidence to support the effects of nettle root extract in improving symptoms of BPH is less substantial. Two placebo-controlled trials which assessed the effects of nettle root extract 600mg daily for up to nine weeks have reported improvements in peak urine flow, urine volume and residual urine volume.[3] Improvements in urological symptoms have also been reported from several uncontrolled trials of nettle root extracts in men with BPH although, because of the design of these studies, the effects cannot be definitively attributed to the use of nettle root extract.

There is some evidence from randomised controlled trials (RCTs) to support the use of pygeum preparations in treating LUTS associated with BPH. A Cochrane systematic review of 18 RCTs reported that, based on pooled data from six studies, pygeum preparations improved urological symptoms (such as self-reported nocturia) and urinary flow measures.[8] However, since most of the studies involved only small numbers of patients, did not use validated outcome measures and had other methodological limitations, further investigation was deemed necessary.

Pumpkin seed has been subject to little formal clinical investigation. A post-marketing surveillance-type study involving 2,245 men with BPH stage 1 or 2 who received pumpkin seed extract for 12 weeks reported marked improvements in IPSS scores compared with baseline values.[9] However, this type of study is not designed to test efficacy, and observed improvements cannot be definitely attributed to treatment with pumpkin seed extract.

Herbal combinations Several trials have compared combinations of the herbal preparations mentioned above with placebo or finasteride or both. In some cases, these studies have provided conflicting results. For example, in a six-month, randomised, double-blind trial, 44 men with BPH received a herbal combination preparation (which included saw palmetto extract, nettle root extract and pumpkin seed oil) or placebo. Symptom scores and urinary flow improved in both groups with no statistically significant difference between the herbal treatment and placebo. Another randomised, double-blind trial involving men with BPH compared the effects of a combination of saw palmetto extract and nettle root extract with those of finasteride. At the end of the 48-week study, improvements in peak urine flow and IPSS scores were similar in both groups.[2]

Other studies have compared different doses of a combination preparation of nettle root extract and pygeum bark extract, or compared the combination preparation with pygeum bark extract alone. The studies found both higher and lower doses of the combination to be effective, and the combination to be more effective than pygeum alone.[3] However, neither study included a placebo or active

action : practice points

1. Read the information on or in the packaging of any saw palmetto products sold in your pharmacy. How does the dosage compare to those tested in trials and in Martindale?
2. Visit the Bandolier website www.jr2.ox.ac.uk/bandolier/ to look at some of the evidence for using herbal products for BPH.
3. Many men are too embarrassed to discuss BPH symptoms. Consider how you could help a person overcome this.

evaluate

How could your learning have been more effective?
What will you do now and how will this be achieved?

control group, so the possibility that the studies simply compared one "placebo" with another cannot be excluded.

MECHANISM OF ACTION

The precise mechanism(s) by which saw palmetto extracts improve symptoms of BPH is unclear.[2,3] Several *in vitro* studies have demonstrated that liposterolic extracts of saw palmetto inhibit 5-a-reductase activity. 5-a-reductase is the enzyme that catalyses the conversion of testosterone to dihydrotestosterone (DHT, a more potent androgen on which prostate growth depends) in androgen target tissues, including the prostate. Theoretically this would lead to growth inhibition. However, the clinical significance of these findings is uncertain, because studies involving men with BPH have reported conflicting results for the inhibitory effects of saw palmetto extracts on 5-a-reductase activity.[2]

a-Adrenoceptor blocking activity (theoretically blocking sympathetic activity and leading to relaxation of smooth muscle) has been documented for saw palmetto extract following *in vitro* studies, but this was not borne out by a small placebo-controlled, cross-over study involving healthy volunteers who received three different preparations of saw palmetto extract, none of which showed binding to a_1-adrenoceptors as determined by a radio-receptor assay.[2]

In vitro, anti-androgenic activity (eg, inhibition of the binding of DHT to androgen receptor sites) has been documented for liposterolic extracts of saw palmetto.

Experimental studies involving rat models of BPH have provided supporting evidence for the effects of liposterolic extracts of saw palmetto described above, although a study involving 20 dogs with BPH (determined by raised prostatic volume), but without clinical signs (eg, decreased urinary flow), found that saw palmetto extract had no effect on prostatic weight and prostatic volume.[2]

In vitro studies with nettle root extract and its isolated constituents have shown that:

- Nettle root extract is only a weak inhibitor of 5-a-reductase
- Lignans, such as secoisolariciresinol, and their metabolites reduce the binding activity of human sex hormone binding globulin (SHBG; most circulating testosterone is bound to SHBG). It is thought that SHBG binds to or enters androgen target tissues and, thus, binding activity of SHBG may play a role in the action of testosterone
- Nettle root extract inhibits the interaction between SHBG and its receptor on human prostatic membranes in a dose-dependent manner[3]

In vitro, pygeum bark extract inhibits 5-a-reductase and aromatase, the enzyme which converts testosterone into oestradiol.[4]

SAFETY ASPECTS

Data from RCTs indicate that extracts of saw palmetto are generally well-tolerated when used at recommended doses for up to 48 weeks.[5] A Cochrane systematic review found that the adverse effects associated with treatment with saw palmetto extracts were generally mild, and comparable in type and frequency to those occurring with placebo administration, and that saw palmetto extracts were associated with fewer adverse effects than finasteride.[5] For example, unwanted gastrointestinal effects were reported in 0.9, 1.3 and 1.5 per cent of men who received placebo, saw palmetto extract and finasteride, respectively. Similarly, withdrawal rates from the studies were 7.0, 9.1 and 11.2 per cent, respectively.

Another Cochrane systematic review of RCTs reported that adverse effects associated with pygeum during up to 12 weeks' treatment were mild and comparable to those with placebo.[8] However, clinical trials are usually only able to detect common, acute adverse effects, and long-term studies involving larger numbers of patients are required to identify less common adverse reactions, delayed effects and adverse effects that occur with chronic administration.

Several post-marketing surveillance-type studies (which were open and uncontrolled) involving men with BPH who received saw palmetto extracts 160mg twice daily for periods ranging from 12 weeks to three years have reported that for a large majority of participants, tolerability of saw palmetto was "good" or "very good/excellent". The most common non-serious adverse effects reported were mainly gastrointestinal effects (such as gastralgia, diarrhoea, constipation), nausea and anorexia.

Mild gastrointestinal effects may also occur following ingestion of nettle root. A post-marketing surveillance-type study involving over 4,000 men with BPH reported that the proportion of men experiencing such effects was less than 1 per cent.[3]

No specific interactions with conventional drugs have been reported for the herbal preparations described. However, for patients receiving treatment with sex hormones, it would be prudent to consider the hormonal effects of saw palmetto.[2]

Clearly, BPH occurs only in men, although pharmacists should be aware that some women may use saw palmetto for its anti-androgen effects. There is a lack of information on the use of saw palmetto (as well as nettle root, pumpkin seed and pygeum bark) preparations by pregnant or lactating women. In view of this, and the lack of toxicity data, the use of these herbs during pregnancy and lactation should be avoided.[2]

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