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
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.

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masterol. Other constituents include flavonoids and carbohydrates. 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 t-sitosterol). Nettle root also contains sterols, including t-sitosterol, as well as a lectin, the coumarin scopoletin, phenylpropane derivatives and lignans. Several of these constituents may be important for activity. Pygeum contains phytosterols, pentacyclic triterpenes and ferulic acid esters. 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 (PF, 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 and nocturia, and statistically significant 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=0.018). Another study compared a liposterolic extract of saw palmetto 320mg daily with the a1-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). 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.

**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. 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 definitely 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. 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. However, this type of study is not designed to test efficacy, and observed improvements cannot be definitely attributed to treatment with pumpkin seed extract.

**IPSS** The international prostate 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:

1. How often have you had the sensation of not completely emptying your bladder after urinating?
2. How often have you needed to urinate within two hours of last urinating?
3. How often have you stopped and started again several times while urinating?
4. How often have you had to get up in the night to urinate?
5. How often have you found it difficult to postpone urinating?
6. How often have you had a weak urinary stream?
7. 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”. These 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). 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.

**PANEL 1: GLOSSARY**

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MECHANISM OF ACTION

The precise mechanism(s) by which saw palmetto extracts improve symptoms of BPH is unclear. Several *in vitro* studies have demonstrated that liposterolic extracts of saw palmetto inhibit 5α-reductase activity. 5α-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 5α-reductase activity.

- 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 α1-adrenoceptors as determined by a radio-receptor assay.

*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 prostate volume), but without clinical signs (eg, decreased urinary flow), found that saw palmetto had no effect on prostatic weight and prostate volume.

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

1. Nettle root extract is only a weak inhibitor of 5α-reductase
2. 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
3. Nettle root extract inhibits the interaction between SHBG and its receptor on human prostatic membranes in a dose-dependent manner

*In vitro*, pygeum bark extract inhibits 5α-reductase and aromatase, the enzyme which converts testosterone into oestradiol.

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. 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. 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. 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.

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.

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.

REFERENCES