

# Herbal medicines for benign prostatic hyperplasia

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**Is there enough evidence to recommend the use of herbal medications to men with benign prostatic hyperplasia?**

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**D**ietary supplements and herbal medications have become increasingly popular in the treatment of men with benign prostatic hyperplasia (BPH). Many patients referred to urologists will have trialed a form of complementary herbal medicine, usually a phytotherapeutic agent; studies show that this rate ranges from 30 to 90% of referred patients.<sup>1-3</sup>

The increase in use of phytotherapeutic agents is due to a number of factors. These include increased advertising in multiple media platforms and greater availability of these agents in local health food stores and on the Internet. Also, these agents are cheaper and easier to access than established formulary pharmaceutical medications.

It is important to have a good understanding of the existing evidence for phytotherapeutics because both urologists and GPs are often asked about the efficacy of these substances. The variability of doses and different formulations makes it difficult for patients to choose between them. There is a lack of well-designed comparative studies for the multitude of formulations.

This article reviews the commonly available phytotherapeutic agents for BPH and evaluates the level of evidence supporting the use of these agents. It also reviews the natural history of BPH and considers the evaluation of the clinical trials considered, including the placebo effect.

**TABLE. COMMON PHYTOTHERAPEUTIC AGENTS FOR BENIGN PROSTATIC HYPERPLASIA**

Agent	Also known as
<i>Serenoa repens</i>	<i>Sabal serrulata</i> Saw palmetto
<i>Prunus africana</i>	Pygeum
<i>Urtica dioica</i>	Stinging nettle
<i>Epilobium parviflorum</i>	Hoary willowherb Epilobium

### PHYTOTHERAPEUTIC AGENTS FOR BPH

The most common agents for the treatment of men with BPH are listed in the Table. Combination herbal supplements are available in many different forms.

#### Serenoa repens

*Serenoa repens* (saw palmetto) is the most commonly used phytotherapeutic agent for BPH. Its mechanisms of action may include inhibition of 5-alpha-reductase enzymes, inhibition of growth factors, anti-inflammatory effects and an antioestrogen effect.<sup>4</sup> There have been studies comparing *Serenoa repens* with placebo and other agents, such as 5-alpha-reductase inhibitors. The outcomes were variable, with some showing improvement in one or more parameters and some showing no difference.<sup>5,6</sup>

A meta-analysis in 2002 by Boyle and colleagues of published trials of a specific brand of *Serenoa repens* demonstrated reduction in symptoms of nocturia and increased urinary flow compared with placebo.<sup>7</sup> It is important to note that although this improvement was shown to be statistically significant, the clinical significance of these benefits is negligible.

A Cochrane review conducted in 2012 analysed all randomised trials involving *Serenoa repens*.<sup>8</sup> Evaluating only high-quality, long-term trials, no significant improvement in symptoms was seen when comparing *Serenoa repens* with placebo, even at double and triple doses. The conclusion of this Cochrane review was that *Serenoa repens* does not improve urinary flow measures or prostate size in men with BPH.<sup>8</sup>

#### Prunus africana

*Prunus africana* (pygeum) is a commonly used phytotherapeutic agent extracted from the bark of the African plum tree. Its effects may include inhibition of fibroblast growth, an antioestrogen effect, inhibition of some chemotactic agents and protective effects on the bladder.<sup>4</sup> The exact mechanisms of action remain uncertain.

Multiple trials comparing *Prunus africana* with placebo groups have been performed but there are no randomised trials

comparing the effects of this agent with standard agents such as alpha-blockers or 5-alpha-reductase inhibitors. A Cochrane review analysed the pooled data from 12 randomised controlled trials involving more than 1500 patients.<sup>9</sup> Results showed a significant improvement in symptom scores and flow measures when compared with placebo. Nocturia was reduced by 19%, residual urine volume was reduced by 24% and peak urine flow was increased by 23%. Adverse effects due to *Prunus africana* were mild and comparable with placebo. The main issue with these trials was their short to medium duration, small sample sizes, and the use of various doses and preparations of the agent. The Cochrane review recommended that further studies be carried out to compare *Prunus africana* with placebo as well as active controls for sufficient time periods.<sup>9</sup>

#### Urtica dioica

*Urtica dioica* (stinging nettle) is another common phytotherapeutic agent but has been less extensively researched than others. There are many different preparations of this product available. Two double-blind placebo-controlled trials conducted more than 15 years ago are of limited usefulness because of small sample sizes and short durations of treatment (three months).<sup>4</sup> More recently, a randomised, double-blind placebo-controlled trial showed significant improvement in symptom score and urinary flow rate as well as a decrease in postvoid residual.<sup>10</sup> The study length was of short duration (six months) and further trials are required to evaluate this agent.

#### Epilobium parviflorum

*Epilobium parviflorum* (epilobium) has been described in folklore as providing benefit to men who suffered the effects of BPH. Little is known about this phytotherapeutic agent. Studies suggest that in vitro epilobium may have an antiproliferative effect on human prostate cells and may possess antioxidant and anti-inflammatory effects.<sup>11,12</sup> There are no randomised trials comparing this agent with placebo or an accepted formulary agent.

### NATURAL HISTORY OF BPH

Lower urinary tract symptoms (LUTS) such as voiding difficulty or frequency and urgency have many causes. Bladder outflow obstruction due to BPH is only one of these. It is important when evaluating men with LUTS to obtain an accurate history and perform a thorough examination before arriving at a diagnosis.

Histological changes in the prostate with proliferation of glandular and stromal elements is a progressive phenomenon termed BPH. These changes in the prostate may have a functional effect giving rise to LUTS, but this is not predictable. In most cases, LUTS may impact on quality of life but have no significance in relation to an increased risk of significant complications.



Longitudinal studies have shown that most patients either improve or remain stable in relation to symptoms. In men with moderate LUTS, 46% had no worsening of symptoms and 13% had improvement in their symptoms at four years. Similarly in men with severe symptoms of LUTS, 38% had no change and 23% had improvement in their symptoms. Overall, men with more severe symptoms are more likely to undergo treatment failure and subsequent definitive therapy via surgery.<sup>13</sup>

### PLACEBO EFFECT AND OTHER CONSIDERATIONS IN TRIAL EVALUATION

The placebo effect is a real effect that should be anticipated in all studies measuring subjective outcomes such as symptom scores. McConnell and colleagues analysed data from control groups treated with placebo in randomised controlled trials of BPH treatment.<sup>14</sup> A total of 1417 men from 45 randomised controlled trials were included. Overall, 40% of patients showed some improvement. More specifically, the probability of improvement in urine flow and decrease in residual urine were 36% and 38%, respectively.<sup>14</sup> The placebo effect has been shown to drift back to baseline after a period of time. Data from the placebo arm of the Proscar Long-term Efficacy and Safety Study (PLESS) revealed reversal of the initial placebo effect towards the end of the four-year study period.<sup>15</sup> Hence trials that have more objective ways of measuring the end-point can lower this effect and be of higher quality. It is important to account for the lead time bias when assessing patients with BPH. Trials should be of sufficient duration to measure the long-term efficacy of these agents. Due to these important factors most herbal medication trials are of limited value.

Another factor to consider in the evaluation of trials of these phytotherapeutic agents is the clinical importance and efficacy of the agents. Quite often studies have shown statistically significant differences between drug and placebo but the magnitude of the difference has been quite small. Barry and colleagues assessed the relation between decrease in BPH symptom scores and patient ratings of improvement in more than 1000 patients.<sup>13</sup> An average of 3.1 points on the International Prostate Symptom Score was required for patients to perceive subjectively a slight improvement in symptoms. This improvement had to be of higher value if the symptoms were more severe. Hence, when evaluating trials of alternative medications, even though statistically significant differences may be observed, one should look for the magnitude of improvement to draw a conclusion regarding the usefulness of a drug.

### CONCLUSION

We recommend that if symptoms of LUTS are mild and not significantly bothersome and in the absence of more sinister pathology, herbal medications may be an option for certain groups of patients with BPH. However, with the existing levels of evidence

of efficacies we are unable to scientifically recommend most of these agents, and this information should be disclosed to all patients considering such agents. **MT**

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