

## REVIEW

### Alternative medications for benign prostatic hyperplasia available on the Internet: a review of the evidence for their use

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#### Introduction

The number of people seeking alternative medications to treat disease is increasing; indeed, this was the subject of a study conducted by Eisenberg et al. in 1993 [1] who reported that there were 425 million visits to providers of alternative treatment during 1992 in the USA. This number has probably increased since then. These alternative therapies are sold as nutritional supplements for numerous illnesses, ranging from treatments for the common cold to those for depression. As with other specialities, there is now an abundance of alternative therapies for urological conditions. It is estimated that in the USA 30–90% of patients seen by urologists for putative BPH may be taking some form of alternative therapy for the condition [2–4]. Access to these agents has become easier with the expansion of health-food shops, but more so with the increased use of the Internet by these patients. An Internet search using the words ‘alternative treatments for BPH’ as a search term revealed >1000 sites offering help and advice about BPH. On reviewing these sites there were several available alternative therapies, available via the Internet, for treating BPH:

· *Serenoa repens* (Saw palmetto berry extract); · *Hypoxis rooperi* (South African star grass); · *Pygeum africanum* (African plum); · *Cucurbita pepo* (pumpkin seeds); · *Urtica dioica* (Stinging nettle); · *Secale cereale* (Rye pollen); Flaxseed oil; · Lycopene; · zinc; · *b*-sitosterol; · selenium.

Each of these substances can be bought singly but much more common are the various combined ‘prostate health’ products. Some combination products list numerous ingredients, but the amount of each ingredient varies among products, and therefore if a combination product is selected the patient is required to undertake much painstaking reading of the labels. Despite the increased use of these products both in Europe and the USA, most urologists have little understanding or knowledge of them. There is also limited evidence of their efficacy [4]. In this article we review the evidence which supports their widespread use by current urological patients.

#### *Serenoa repens* (Saw palmetto berry extract)

This agent is derived from the olive-sized berries of the saw palmetto tree and is the most popular phytotherapeutic agent used in the treatment of BPH. The exact mechanism of its action has not been confirmed, although numerous mechanisms have been proposed. These include an anti-inflammatory effect, anti-androgenic activity, inhibitory effect on type 1 and 2 isoenzymes of 5 $\alpha$  reductase, and inhibition of prolactin and growth factor-induced cell proliferation. The in vitro studies to determine its mechanism of action mainly used supraphysiological dosages, leaving the significance of these studies open to debate [4–6]. Lowe et al. [7] conducted a meta-analysis which set out to review all placebo-controlled trials using the ‘Permixon’ brand of saw palmetto. There were seven such studies, each of short duration, i.e. <3 months, reporting an improvement in symptoms, although the only symptom common to all of the studies was nocturia. There was also an improvement in urine flow when compared with placebo, although this was apparently limited.

The most widely quoted study of ‘Permixon’ saw Accepted for publication 9 February 2002 palmetto was a comparison with finasteride, a 5 $\alpha$  reductase inhibitor, and involved 1098 patients in a 6-month double-blind, randomized controlled study. Both symptom scores and urinary peak flow rate were improved to a similar extent in both groups. The differences were significant when compared with baseline for both drugs. However, there was no placebo group in this trial and therefore the improvements reported might simply have been the result of a placebo effect.

### Pygeum africanum (African plum)

In traditional African medicine a tea made from the powdered bark of this tall evergreen tree is drunk to control urinary disorders in men. Today, this supplement is commonly used in France, known more commonly under its trade name of Tadenan. It is frequently sold in combination with saw palmetto and other agents as part of pills for 'male health'. Tadenan has been shown to have several effects, including inhibition of fibroblast growth factors, antiestrogenic effects, inhibition of chemotactic leukotrienes and other 5 lipo-oxygenase metabolites [4,8]. Breza et al. [9] evaluated this agent in a recent 2-month open-label trial using a daily dosage of 100 mg. Using the IPSS they reported a 40% reduction in scores and an improvement in mean peak urinary flow rates (10.97 mL/s at baseline to 13.07 mL/s at the end of the study). This was an uncontrolled study, only suggesting a benefit from Tadenan, and obviously no other conclusions can be made. Unfortunately, there are no recent placebo-controlled clinical studies using Tadenan.

### Hypoxis rooperi (South African star grass)

This agent contains mainly b-sitosterol, which is thought to be the major active component, with other sterols being detected in lesser amounts [4,5]. The extract of star grass is marketed as Harzol. In vitro studies with Harzol show that it enhances the production and secretion of plasminogen activators in isolated epithelial cells. In prostate stromal cell cultures there are also increased levels of TGF-b1 when conditioned with b-sitosterol. TGF-b1 is a differentiation factor and induces apoptosis. These in vitro studies have not been verified in vivo and they have not been shown to be clinically relevant [4]. This drug has been studied in a double-blind placebocontrolled trial [10]; 200 patients were randomized to receive a placebo or a preparation of phytosterol. In both groups there were symptomatic improvements over baseline measurements and the difference was greater in the phytosterol group. These authors also reported a larger improvement (by 4.1 mL/s) in the peak urinary flow rate in those treated with Harzol than in the placebo group. At the 18-month follow-up the group initially given the placebo were given Harzol; they then had improvements which were comparable with the group initially treated with Harzol. Interestingly, the beneficial effect of Harzol continued over the next 12 months regardless of whether the patient stopped Harzol or was given the placebo [11].

### Urtica dioica (stinging nettle)

There are at least 16 different preparations of this extract taken from the roots of the stinging nettle. The roots contain a mixture of lectins, phenols, sterols and lignins. Despite its widespread use in Germany for treating BPH there are limited clinical data about its efficacy for this condition. Two double-blind placebo-controlled studies were conducted >10 years ago, but with few patients and in trials of <3 months, the data produced were of little value.

### Secale cereale (rye pollen)

The commercial preparation 'Cernilton' is a pollen prepared from several plants found growing in countries such as Sweden and Switzerland. This drug is available across Europe and is manufactured by microbial digestion of the pollen. As with many alternative medications the mechanism of action remains unclear. Several mechanisms have been proposed, including an improvement in detrusor activity, inhibition of 5a reductase activity, and an influence on androgen metabolism in the prostate [5]. A study reported in 1996 [4] compared Cernilton with Tadenan over a 4-month period; there was no placebo group in the study. No conclusions can be drawn from this study as the efficacy of Tadenan has, as yet, not been confirmed. Despite this, the authors [4] reported a better response, in terms of symptom scores, residual volumes and peak flow rates, with Cernilton. Clearly, a double-blind placebo-controlled trial is required.

### Soy

Environmental factors such as diet are thought to influence the causes of BPH. The underlying rationale for this comes from epidemiological data showing that the incidence of BPH is much lower in the Orient than in the Western world. This difference is not solely caused by genetic differences, as the incidence of BPH increases in those who migrate from the Orient to the USA [12]. When Western and Oriental diets are compared a major difference is the high intake of soybean products in the latter. Genistein is derived from soybean and is a major ingredient of tofu; it is also an active oestrogen, with a high affinity for the oestrogen receptor. Geller et al. [13] studied the effects of genistein on human BPH tissue in vitro, showing a dose-dependent decrease in the growth of this tissue. These promising results support a possible role for soy products in managing BPH, although further study is required.

## Trace elements

Trace elements such as zinc and selenium are often marketed for their beneficial effects in the management of BPH. Although there is no evidence to support the efficacy of such trace elements they are still widely taken by patients.

## Combination pills

Many of the above extracts are sold as combination pills. One such combination is 'Prostagutt forte', which is a combination of *Serenoa repens* and *Urtica dioica*; it is widely used although there are no data to support increased efficacy with combination products. This combination pill was compared with finasteride in 489 randomized patients in a 48-week trial; there were no statistically significant differences in the IPSS and peak urinary flow rates between the groups. Unfortunately, because there was no placebo group, no valid conclusions can be made from this study. Combination pills remain popular, although in many the amount of saw palmetto varies considerably, with some actually containing very little. Despite the lack of evidence for them, there is still widespread use of these products.

## What advice should be given to patients?

Lowe et al. [4] reported that should a patient wish to try an alternative medication for BPH, then their advice would be for the patient to select the least expensive one available and trial it for 1 month. If the agent 'does not work', then they should try another brand for a month, even trying a third. Lowe et al. felt that if there was no change after 3 months then the patient would be best advised to take conventional medication. We concur with this advice and also suggest that the patient should be made aware that the alternative medications that they might be taking have not been subjected to the same rigorous clinical trials that 'conventional' drugs are, and that several of these alternative drugs remain 'unknown quantities'.

In summary, patients are now resorting to alternative medications for BPH with increasing frequency. One of the main reasons for this is the increasing public awareness of these previously 'unknown' products, through the expansion of health-food shops but particularly through the increasing use of the Internet by patients. From this review it is apparent that although the use of these medications is increasing, understanding about them and the mechanisms of action are not increasing at the same rate. Although some of the studies cited here have shown promising results, randomized controlled trials containing many patients followed for long periods are needed. This will allow the initial results reported with these alternative medications to be validated or refuted. Only then will urologists be able to confidently and safely recommend these products to patients.

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