Phytotherapy for benign prostatic hyperplasia

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Abstract

Objective: To systematically review the existing evidence regarding the efficacy and safety of phytotherapeutic compounds used to treat men with symptomatic benign prostatic hyperplasia (BPH).

Design: Randomized trials were identified searching MEDLINE (1966–1997), EMBASE, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. The studies were included if men had symptomatic benign prostatic hyperplasia, the intervention was a phytotherapeutic preparation alone or combined, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Key data were extracted independently by two investigators.

Results: A total of 44 studies of six phytotherapeutic agents (*Serenoa repens*, *Hypoxis rooperi*, *Secale cereale*, *Pygeum africanum*, *Urtica dioica*, *Curcubita pepo*) met inclusion criteria and were reviewed. Many studies did not report results in a method allowing meta-analysis. *Serenoa repens*, extracted from the saw palmetto, is the most widely used phytotherapeutic agent for BPH. A total of 18 trials involving 2939 men were reviewed. Compared with men receiving placebo, men taking *Serenoa repens* reported greater improvement of urinary tract symptoms and flow measures. *Serenoa repens* decreased nocturia (weighted mean difference (WMD) = −0.76 times per evening; 95% CI = −1.22 to −0.32; $n = 10$ studies) and improved peak urine flow (WMD = 1.93 ml s^{-1}; 95% CI = 0.72 to 3.14, $n = 8$ studies). Men treated with *Serenoa repens* rated greater improvement of their urinary tract symptoms versus men taking placebo (risk ratio of improvement = 1.72; 95% CI = 1.21 to 2.44, $n = 8$ studies). Improvement in symptoms of BPH was comparable to men receiving the finasteride. *Hypoxis rooperi* ($n = 4$ studies, 519 men) was also demonstrated to be effective in improving symptom scores and flow measures compared with placebo. For the two studies reporting the International Prostate Symptom Score, the WMD was −4.9 IPSS points (95% CI = −6.3 to −3.5, $n = 2$ studies) and the WMD for peak urine flow was 3.91 ml s^{-1} (95% CI = 0.91 to 6.90, $n = 4$ studies). *Secale cereale* ($n = 4$ studies, 444 men) was found to modestly improve overall urological symptoms. *Pygeum africanum* ($n = 17$ studies, 900 men) may be a useful treatment option for BPH. However, review of the literature has found inadequate reporting of outcomes which currently limit the ability to estimate its safety and efficacy. The studies involving *Urtica dioica* and *Curcubita pepo* are limited although these agents may be effective combined with other plant extracts such as *Serenoa* and *Pygeum*. Adverse events due to phytotherapies were reported to be generally mild and infrequent.

Conclusions: Randomized studies of *Serenoa repens*, alone or in combination with other plant extracts, have provided the strongest evidence for efficacy and tolerability in treatment of BPH in comparison with other phytotherapies. *Serenoa repens* appears to be a useful option for improving lower urinary tract symptoms and flow measures. *Hypoxis rooperi* and *Secale cereale* also appear to improve BPH symptoms although the evidence is less strong for these products. *Pygeum africanum* has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no convincing evidence supporting the use of *Urtica dioica* or *Curcubita pepo* alone for treatment of BPH. Overall, phytotherapies are less costly, well tolerated and adverse events are generally mild and infrequent. Future randomized controlled trials using standardized preparations of phytotherapeutic agents with longer study durations are needed to determine their long-term effectiveness in the treatment of BPH.

Keywords
Phytotherapy
Benign prostatic hyperplasia
Randomized controlled trials
Systematic reviews
Meta-analysis

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Table 1 Plant extracts commonly used for BPH

Scientific name	Common name
Curcubita pepo	Pumpkin seed
Hypoxis rooperi	South African star grass
Pygeum africanum	African plum tree
Serenoa repens [*Sabal serrulata*]	Saw palmetto berry
Urtica dioica	Stinging nettle root
Secale cereale	Rye pollen

Phytotherapy or the use of plant extracts for treatment of lower urinary tract symptoms (LUTS) consistent with benign prostatic hyperplasia (BPH) was first described in Egypt in the 15th century BC[1]. Phytotherapy is common in Europe and is increasing in the Western Hemisphere. In 1998, the sale of botanical medications in the United States was $1.5 billion per year and the use of phytotherapeutic compounds increased nearly 70% among US adults[2,3].

About 30 phytotherapeutic compounds are used for the treatment of BPH (Table 1). Phytotherapeutic agents represent nearly half the medications dispensed for treatment of BPH in Italy, compared with 5% for alpha-blockers and 5% for 5α-reductase inhibitors[4]. In Germany and Austria, phytotherapy is the first-line treatment for mild to moderate lower urinary tract symptoms and represents more than 90% of drugs prescribed for treatment of BPH. In the United States, phytotherapies for BPH are available as nonprescription dietary supplements. Nearly a quarter of men attending a United States urology clinic who had previously treated BPH indicated they had used phytotherapeutic agents for self-treatment of urinary tract symptoms[5].

Phytotherapies are often promoted to 'maintain a healthy prostate' and as natural and harmless treatment of BPH symptoms. Despite their popularity with the public there has been reluctance among many practitioners to routinely recommend these products. This is because of uncertainty regarding their efficacy and safety[6,7]. Most phytotherapeutic compounds are unlicensed and do not require evidence of efficacy, safety or purity.

There have been over 40 published randomized controlled trials evaluating the efficacy of phytotherapy for symptomatic BPH in approximately 5000 men. Many more trials are in progress and should provide needed evidence regarding the role of phytotherapeutic products.

Systematic reviews of the existing literature provide a systematic assembly of the results of primary investigations using strategies that limit bias and random error[8]. Systematic reviews efficiently integrate unmanageable amounts of information and provide results that allow for rational decision making. They can establish whether findings are consistent and generalized or whether findings vary by subsets. If clinically and statistically appropriate, a quantitative summary (meta-analysis) can be performed resulting in statistical pooling of results and enhancement of the estimates of therapeutic effects and risk estimates. This is especially helpful when a large number of small trials have been conducted or when results from comparable studies provide differing results. Systematic reviews also identify gaps in existing evidence and make recommendations for future research to close these scientific and clinical gaps.

Phytotherapeutic compounds

Serenoa repens (saw palmetto)

Background

The most widely used phytotherapeutic agent for BPH is the extract of the dried ripe fruit from the American dwarf palm plant, saw palmetto, *Serenoa repens* (also known by its botanical name as *Sabal serrulata*). *Serenoa repens* has been approved in France and Germany for treatment of BPH. Berries from saw palmetto were first used by the American Indians in the southeast United States in the early 1700s to treat testicular atrophy, erectile dysfunction, and prostate gland swelling or inflammation[1]. The medicinal value of *Serenoa repens* for relief of prostate gland swelling has been reported since the 1800s. The mechanism of action of *Serenoa repens* has been investigated in several *in vitro* or indirect *in vivo* studies and has not been definitively defined. The mechanism may include alteration of cholesterol metabolism, anti-oestrogenic, anti-androgenic (including 5α-reductase inhibitor activity), anti-inflammatory effects, and a decrease in available sex hormone binding globulin[9–12].

Results of studies

A systematic review and meta-analysis of randomized trials assessed the existing evidence regarding efficacy and safety of *Serenoa repens* in men with symptomatic BPH[13]. Studies were identified through a search of MEDLINE (1966–1997), EMBASE, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. Randomized trials were included if participants had symptomatic BPH, the intervention was a preparation of *Serenoa repens* alone or in combination with other phytotherapeutic agents, a control group received placebo or other pharmacologic therapies for BPH, and the treatment duration was at least 30 days. Two investigators independently extracted key data on design features, subject characteristics, therapy allocation and outcomes of the studies.

A total of 18 studies involving almost 3000 men were identified and analysed[14–31] (Tables 2–5). Many studies did not report results in a method that permitted quantitative meta-analysis. Sixteen trials were double blinded, 14 were placebo controlled and four involved *Serenoa repens* in combination with other phytotherapeutic agents. The average study duration was 9 weeks (range 4–48 weeks) and the average age of enrollees was 65 years. Baseline characteristics regarding prostate volume, urine flow rates

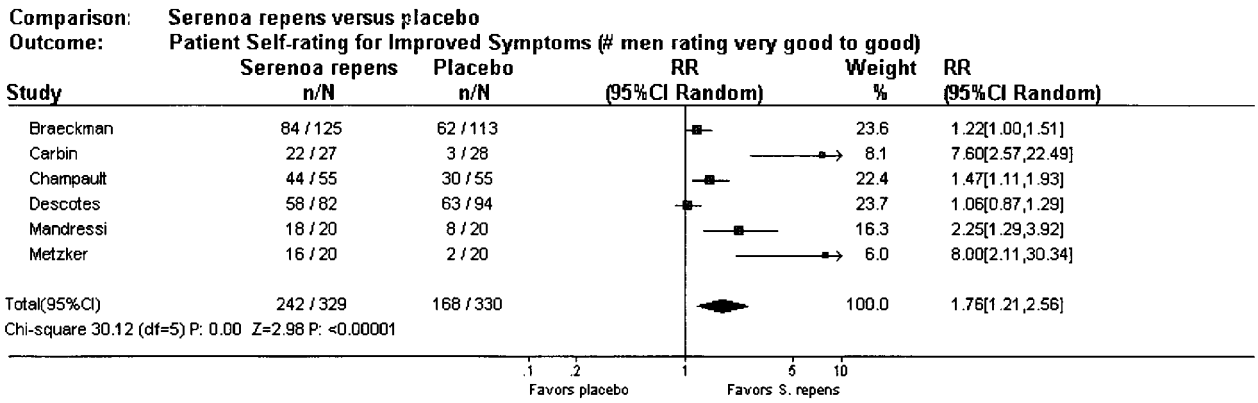

Fig. 1 Effect of *Serenoa repens* on self-rating of improvement in urinary tract symptoms for men treated with *Serenoa repens* vs. placebo

and symptom scale scores were comparable with previous trials evaluating pharmacologic management of BPH.

The available data indicate that *Serenoa repens* (alone or in combination with other phytotherapeutic agents) improves urinary symptoms and flow measures (Figs 1–3). Compared with placebo, saw palmetto improved urinary symptom scores by 28% and nocturia by 25% (the weighted mean difference (WMD) = −0.76 times per evening; 95% CI = −1.22 to −0.32; $n = 10$ studies). Peak urine flow was improved by 24% (WMD = 1.93 ml s^{-1}; 95% CI = 0.72 to 3.14, $n = 8$ studies), mean urine flow by 28% (2.22 ml s^{-1}; data not shown), and residual urine volume by 43% (−22.05 ml; data not shown). Men taking *Serenoa repens* were more likely to report improvement in urinary symptoms than men taking placebo (73.6% vs. 50.9%; risk ratio = 1.76). Adverse effects were generally mild and comparable with placebo.

Compared with finasteride[17,30], saw palmetto provided similar responses in urologic symptom scores (0.37 International Prostate Symptom Score (IPSS) points), nocturia (−0.20 times per evening) and flow measures. Saw palmetto was associated with a lower rate of erectile dysfunction than finasteride (1.1% vs. 4.9%; $P < 0.001$) and reduced neither prostate size nor prostate specific antigen (PSA) levels. Critics have stated that comparing saw palmetto with finasteride might be showing equivalency to placebo. However, previous trials and meta-analyses have demonstrated that finasteride provides symptomatic improvement in men with prostate glands >40 g, a size comparable to those enrolled in this study[32,33].

The treatment effect sizes noted with saw palmetto were comparable to effects reported with other pharmacologic agents, such as finasteride. However, the results should be viewed cautiously. Studies utilized different doses and preparations of *Serenoa repens* (including combination preparations). The most extensively investigated preparation of *Serenoa repens* is manufactured in France and sold as Permixon. The most commonly reported dosage was 160 mg twice per day. Many studies did not report outcome data in a consistent fashion. Only three studies reported validated urologic symptom scales. Trials were of short duration with only two studies having follow-up of at least

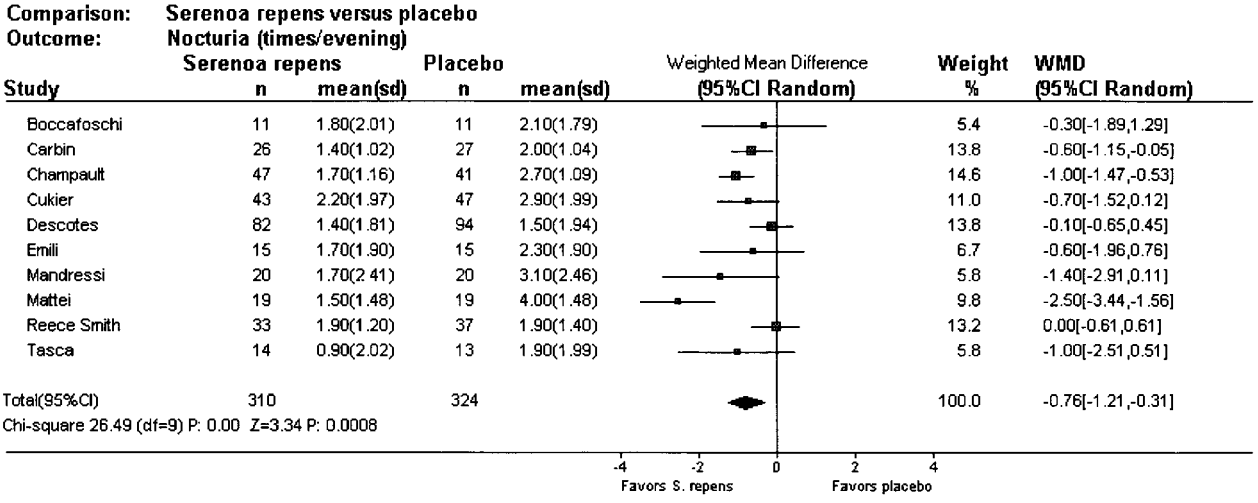

Fig. 2 Effect of *Serenoa repens* on nocturia for men treated with *Serenoa repens* vs. placebo

Table 2 Clinical trials of saw palmetto extracts (*Serenoa repens*/*Sabal serrulata*): trials of efficacy

First author	Year	Design	Sample size*	Dose per day	Main outcome measures	Results
Boccafoschi	1983	Randomized controlled trial (RCT); double-blind (DB); placebo-controlled (PC). Study duration (SD): 8.5 wks	22 (0)	320 mg	Nocturia (times/evening); peak urine flow rate (ml/s); mean urine flow rate (ml/s); residual volume (ml)	Significant improvements vs. placebo in nocturia, peak and mean urine flow rates ($P < 0.05$)
Braeckman	1997	RCT; DB; PC. SD: 12 wks	238 (12)	320 mg	Symptom scale score (not identified); patient self-rating of improvement; peak urine flow; mean urine flow; residual volume	Significant improvement vs. placebo in symptoms improvement (symptom score)
Carbin	1990	*Sabal* combined with *C. pepo* L.). RCT; DB; PC. SD: 12 wks	55 (2)	320 mg	Patient self-rating of improvement; nocturia; residual volume	Significant improvements vs. placebo in self-rating of improvement ($P < 0.001$), nocturia ($P < 0.01$), residual volume ($P < 0.001$)
Carraro	1996	RCT; DB; Active-controlled (AC) (Finasteride 5 mg) SD: 26 wks	1098 (147)	320 mg	International Prostate Symptom Score (IPSS); peak urine flow; mean urine flow; prostate volume	Similar improvements in IPSS and peak urine flow. Significant decrease in prostate volume ($P < 0.001$) with finasteride. Fewer adverse events associated with phytotherapy
Champault	1984	RCT; DB; PC. SD: 4 wks	110 (16)	160 mg	Patient self-rating and physician-rating of improvement; nocturia; mean urine low	Significant improvements vs. placebo in all outcomes ($P < 0.001$)
Cukier	1985	RCT; DB; PC. SD: 10 wks	168 (22)	320 mg	Nocturia; residual volume	Significant improvements vs. placebo in nocturia ($P < 0.001$), residual volume ($P < 0.05$)
Descotes	1995	RCT; DB; PC. SD: 4 wks	215 (39)	320 mg	Patient self-rating and physician-rating of improvement; nocturia; peak urine flow	Significant improvements vs. placebo in nocturia, peak urine flow ($P < 0.05$)
Emili	1983	RCT; DB; PC. SD: 4 wks	30 (0)	320 mg	Nocturia; peak urine flow; residual volume	Significant improvements vs. placebo in all outcomes ($P < 0.05$, 0.001 for peak urine flow)
Gabric	1987	*Sabal* combined with *Urtica* extracts. RCT; DB; PC. SD: 6 wks	30 (0)	20 drops × 3 daily	Physician-rating of improvement; peak urine flow; residual volume	Significant improvements vs. placebo in all outcomes ($P < 0.05$)
Löbelenz	1992	RCT; DB; PC. SD: 6 wks	60 (0)	100 mg	Peak urine flow	No significant improvement vs. placebo
Mandressi	1983	3-arm study (vs. placebo, vs. *Pygeum* extracts). RCT; DB SD: 4 wks	60 (0)	320 mg	Patient self-rating of improvement; nocturia; residual volume	Improvements: patient self-rating of improvement *Serenoa* 90%, *Pygeum* 60%, placebo 40%, ($P < 0.05$, $P < 0.001$); nocturia *Serenoa* 42%, *Pygeum* 38%, placebo −4%; residual volume *Serenoa* 10%, *Pygeum* −4%, placebo 0%

(*continues*)

Table 2. (*continued*)

First author	Year	Design	Sample size*	Dose per day	Main outcome measures	Results
Mattei	1990	RCT; DB; PC SD: 13 wks	40 (2)	320 mg	Nocturia; residual volume	Significant improvements vs. placebo in nocturia ($P < 0.05$), residual volume ($P < 0.01$)
Metzker	1996	*Sabal* combined with *Urtica* extracts (120 mg). RCT; DB; PC. SD: 48 wks	40 (3)	320 mg	International Prostate Symptom Score (IPSS); peak urine flow; residual volume	Significant improvements vs. placebo in IPSS ($P < 0.01$), peak urine flow ($P < 0.05$)
Pannunzio	1986	RCT; AC (Gestonorone caproate 200 mg) SD: 8 wks	60 (0)	320 mg	Nocturia; peak urine flow	Significant improvement vs. control in peak urine flow ($P < 0.05$)
Reece Smith	1986	RCT; DC. SD: 12 wks	80 (10)	320 mg	Patient self-rating and physician-rating of improvement; nocturia; peak urine flow; residual volume	No significant differences in outcomes improvement versus placebo
Roveda	1994	RCT; Comparison study (oral vs. rectal capsules) SD: 4 wks	30 (0)	640 mg for both	Overall effect of treatment; residual volume	No significant differences between two groups demonstrating bioequivalence
Sokeland	1997	*Sabal* combined with *Urtica* extracts (120 mg). RCT; DB; AC (Finasteride 5 mg) Study duration: 12 wks	543 (54)	320 mg	International Prostate Symptom Score (IPSS); peak urine flow; residual volume; prostate size	No significant differences in outcomes improvement vs. finasteride. Fewer adverse events associated with phytotherapy
Tasca	1985	RCT; DB; PC Study duration: 8 wks	30 (3)	320 mg	Nocturia; peak urine flow	Significant improvement vs. placebo in peak urine flow ($P < 0.05$)

* (), not available to follow-up.

Table 3 Clinical trials of South African star grass extracts (*Hypoxis rooperi*/β-sitosterols): trials of efficacy

First author	Year	Design	Sample size*	Dose per day	Main outcome measures	Results
Berges	1995	RCT; DB; PC. SD: 26 wks	200 (10)	60 mg	International Prostate Symptom Score (IPSS); Boyarsky Symptom Score; peak urine flow; residual volume; prostate volume	Significant improvements vs. placebo in all outcomes ($P < 0.01$) except prostate volume
Fischer	1993	RCT; DB; PC. SD: 4 wks	80 (0)	195 mg	Patient self-rating and physician-rating of improvement; nocturia; peak urine flow; residual volume	Significant improvements vs. placebo in all outcomes ($P < 0.001$)
Kadow	1986	RCT; DB; PC. SD: 24 wks	62 (9)	0.30 mg†	Peak urine flow; residual volume; prostate volume	No significant differences in outcomes improvement vs. placebo
Klippel	1997	RCT; DB; PC. SD: 26 wks	177 (22)	195 mg	International Prostate Symptom Score (IPSS); peak urine flow; residual volume	Significant improvements vs. placebo in all outcomes ($P < 0.01$)

* (), not available to follow-up.
† Study used pure β-sitosterol-β-D-glucoside. In the other three trials the quantity of this derivative was <5% of the daily dose of β-sitosterol.

6 months' duration. Therefore, it is not known whether *Serenoa repens* prevents long-term complications of BPH such as acute urinary retention or the need for surgical intervention. The only trial comparing *Serenoa repens* with alpha-blockers lasted less than 3 weeks, making a comparison impossible. Finally, it is possible that study results were not reported if there were no improvements in symptoms or flow measures (publication bias). There are two placebo-controlled studies involving 298 men that were scheduled for completion in 1998. However, their results have not yet been reported.

Summary

Extracts from the saw palmetto plant, *Serenoa repens*, provide modest improvement in urinary symptoms and flow measures. Compared with finasteride *Serenoa repens* produces similar improvements in symptoms and flow measures, has fewer adverse treatment effects and costs less. The long-term safety and efficacy of *Serenoa repens* and its ability to prevent complications from BPH are not known. Standardized preparations are often not available. Publication of ongoing trials is encouraged and initiation of long term studies compared with alpha-blockers would be useful.

Hypoxis rooperi (South African star grass, β-sitosterol)

Background

Phytosterol extracts derived from the South African star grass, *Hypoxis rooperi*, are popular. The presumed active constituent is β-sitosterol. Beta-sitosterol contains a mixture of phytosterols, with smaller amounts of other sterols, bonded with glucosides[1]. Additionally, the quantity of β-sitosterol-βD-glucoside is often reported. The product is sold under the trade names Harzol or Azuprostat. Although the mechanism of action of β-sitosterols is not known it may be related to cholesterol metabolism or anti-inflammatory effects (via interference with prostaglandin metabolism)[1].

Results of studies

Four randomized controlled trials evaluated β-sitosterol in 519 men with symptomatic BPH[34–37] (Table 3). All were

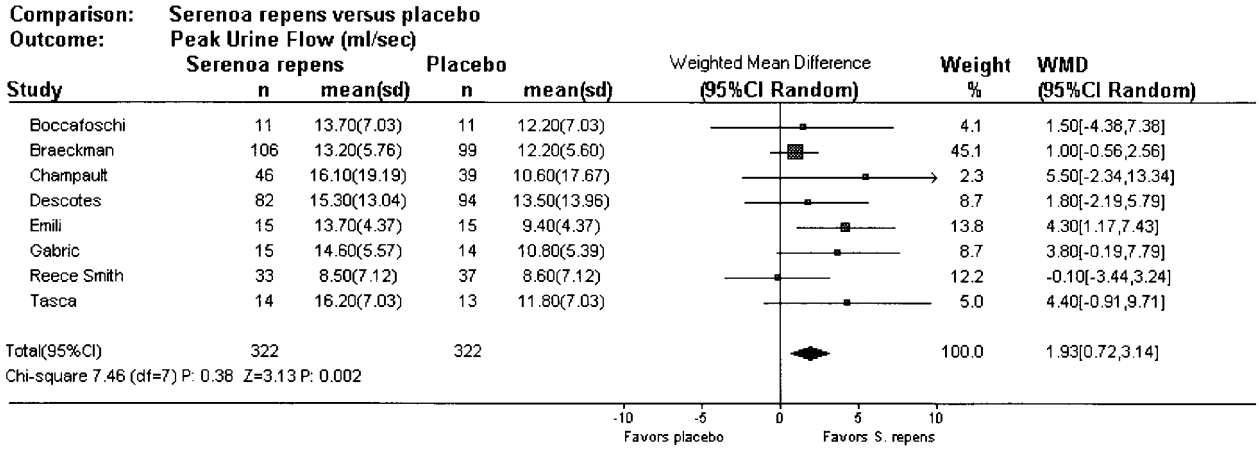

Fig. 3 Effect of *Serenoa repens* on peak urine flow for men treated with *Serenoa repens* vs. placebo

Table 4 Clinical trials of rye grass pollen extracts (*Secale cereale*): trials of efficacy

First author	Year	Design	Sample size*	Dose	Main outcome measures	Results
Becker	1988	RCT; DB; PC. SD: 12 wks	103 (7)	NA†	Nocturia; peak urine flow; residual volume	Significant improvements vs. placebo in nocturia ($P < 0.01$), residual volume ($P < 0.05$)
Buck	1990	RCT; DB; PC. SD: 24 wks	60 (7)	NA	'Overall improvement in symptoms'; nocturia; peak urine flow; residual volume	Significant improvements vs. placebo in overall improvement in symptoms ($P < 0.01$), residual volume ($P < 0.05$)
Dutkiewicz	1996	Controlled clinical trial (CCT); AC (*Pygeum* extracts 'Tadenan') SD: 16 wks	89 (0)	NA	Obstructive and Irritative symptom scores; peak urine flow; residual volume	Improvements: obstructive symptom score *Secale* 63%, *Pygeum* 46%; irritative symptom score *Secale* 68%, *Pygeum* 40%; peak urine flow *Secale* 20%, *Pygeum* 11%; residual volume *Secale* 48%, *Pygeum* 22%
Maekawa	1981	RCT; DB; AC. (Paraprost 6 g). SD 12 wks	192 (14)	252 mg	International Prostate Symptom Score (IPSS); nocturia; peak urine flow; residual volume; prostate size	No significant differences in outcomes improvement vs. control

* (), not available to follow-up.
† NA, not available.

double-blinded and lasted between 4 and 26 weeks. Three trials used non-glucosidic β-sitosterols in doses ranging from 30 mg to greater than 120 mg per day[34,35,37]. The other trial utilized a preparation that contained 100% β-sitosteryl-β-D-glucoside (0.15 mg twice a day)[36]. The average age of participants was 65 years. Men had moderately severe BPH (mean baseline IPSS score = 15.2; peak urine flow = 10.2 ml s^{-1}; prostate size = 49 cc).

Beta-sitosterol provided statistically significant improvements in urinary symptom scores and flow measures (Figs 4 and 5). In the two studies reporting the IPSS score, the WMD compared with placebo was −4.9 points (95% CI = −6.3 to −3.5, $n = 2$ studies) (35% improvement). The WMD for peak urine flow was 3.91 ml s^{-1} (45% improvement) and for residual volume the WMD = −28.62 ml (95% CI = 0.91–6.90, $n = 4$ studies) (29% improvement). Beta-sitosterol did not reduce prostate size and the trial using 100% β-sitosteryl-β-D-glucoside (WA184) did not show improvement in urinary flow rates. Adverse events were infrequent and mild. Withdrawal rates were less than 10% and did not differ from placebo.

Summary

An extract from South African star grass, β-sitosterol, improved urologic symptoms and flow measures. However, the existing evidence is limited to trials of short duration, relatively few patients studied and lack of standardized β-sitosterol preparations. Their long term effectiveness, safety and ability to prevent BPH complications are not known.

Secale cereale (rye-grass pollen)

Background

Rye pollen extract is prepared from the rye-grass, *Secale cereale*. It is used by millions of men worldwide and is a registered pharmaceutical throughout Western Europe, Japan, Korea and Argentina[38]. In the United States, Cernilton is used as a nutritional supplement by approximately 5000 men[39]. One dose contains 60 mg of Cernitin T60, a water-soluble pollen extract fraction, and 3 mg of Cernitin GBX, an acetone-soluble pollen extract fraction[38]. The acetone-soluble fraction was found to contain β-sterols[40]. *In vitro* studies suggest that Cernilton may have anti-androgenic effects, relax urethral smooth muscle tone and increase bladder muscle contraction, or may act on the alpha-adrenergic receptors and relax the internal and external sphincter muscles[41–43].

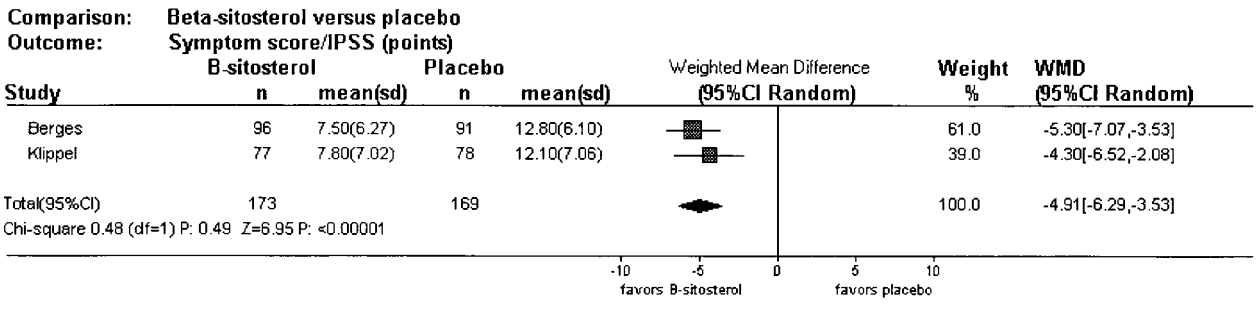

Fig. 4 Effect of β-sitosterol on urinary symptom scores vs. placebo

Table 5 Clinical trials of African plum tree extracts (*Pygeum africanum*): trials of efficacy

First author	Year	Design	Sample size*	Dose per day	Main outcome measures	Results
Barlet	1990	RCT; DB; PC SD: 8 wks	263 (8)	100 mg	Patient self-rating and physician-rating of improvement; nocturia; peak urine flow; residual volume	Significant improvements vs. placebo in all outcomes ($P < 0.01$)
Barth	1981	3 combined studies: *Pygeum* vs. (1) Placebo, (2) Sitosterin, and (3) *Urtica* extracts. RCT; DB; PC; AC SD: 8 wks	96 (43) 71 (18) 48 (6)	100 mg	Nocturia; peak urine flow; residual volume	Improvements: Nocturia *Pygeum* and placebo 'reduced almost to normal'; peak urine flow *Pygeum* 8%, placebo 10%; residual volume *Pygeum* 48%, placebo 37%. *Pygeum* reduced nocturia, peak urine flow, and residual volume>controls
Bassi	1987	RCT; DB; PC SD: 8 wks	40 (0)	100 mg	Nocturia; peak urine flow	Significant improvements vs. placebo in nocturia ($P < 0.001$), peak urine flow ($P < 0.05$)
Blitz	1985	RCT; DB; PC SD: 6 wks	57 (0)	100 mg	'Overall improvement in symptoms'	Significant improvements vs. placebo in overall improvement in symptoms ($P < 0.05$)
Bongi	1972	RCT; DB; PC SD: 8 wks	50 (0)	75 mg	'Overall improvement in symptoms'; nocturia; residual volume	Significant improvements vs. placebo in all outcomes ($P < 0.01$)
Chatelain	1999	Comparison study of 2 doses. RCT; DB SD: 8 wks	235 (26)	50 mg ×2 vs. 100 mg	International Prostate Symptom Score (IPSS); peak urine flow	No significant differences between two groups
Donkervoort	1977	RCT; DB; PC SD: 12 wks	20 (4)	100 mg	'Overall improvement in symptoms'; nocturia; peak urine flow	No significant differences in outcomes improvement versus placebo
Dufour	1984	RCT; DB; PC SD: 6 wks	120 (54)	100 mg	Nocturia	Significant improvements vs. placebo in nocturia ($P < 0.01$)
Dutkiewicz	1996	Controlled clinical trial (CCT); AC (*Secale* extracts 'Cernilton') SD: 16 wks	89 (0)	NA†	Obstructive and irritative symptom scores; peak urine flow; residual volume	Improvements: obstructive symptom score *Pygeum* 46%, *Secale* 63%; irritative symptom score *Pygeum* 40%, *Secale* 68%; peak urine flow *Pygeum* 11%, *Secale* 20%; residual volume *Pygeum* 22%, *Secale* 48%
Frasseto	1986	RCT; DB; PC SD: 8 wks	20 (0)	200 mg	Nocturia	Improvement: nocturia *Pygeum* 57%, placebo 19%
Gagliardi		RCT; DB; AC (control not identified). SD: 4 wks	40 (0)	100 mg	Nocturia; residual volume	Improvements: nocturia *Pygeum* 60%, control 0%; residual volume *Pygeum* 71%, control 11%
Giacobini	1986	3-arm study (vs. *Pygeum* combined with medroxy-progesterone acetate [Falutal] vs. placebo) RCT; DB; PC. SD: 13 wks	21 (0)	200 mg	Peak urine flow; residual volume	Improvements: peak urine flow *Pygeum* 28%, *Pygeum*+Farlutal 39%, placebo 16%; residual volume *Pygeum* 67%, *Pygeum*+Farlutal 22%, placebo 0%

continues

Table 5. (*continued*)

First author	Year	Design	Sample size*	Dose per day	Main outcome measures	Results
Krzeski	1993	*Pygeum* combined with *Urtica* extracts (600 mg & 300 mg). Comparison study of 2 doses. RCT; DB SD: 8 wks	144 (19)	50 mg vs. 25 mg	'Overall improvement in symptoms'; nocturia; peak urine flow; residual volume	No significant differences between two groups
Mandressi	1983	3-arm study (vs. placebo, vs. *Serenoa* extracts). RCT; DB, PC. SD: 4 wks	60 (0)	NA†	Patient self-rating of improvement; nocturia; residual volume	Improvements: patient self-rating of improvement *Pygeum* 60%, *Serenoa* 90%, placebo 40% (*Serenoa* vs. *Pygeum* $P < 0.05$, *Serenoa* vs. placebo $P < 0.001$); nocturia *Pygeum* 38%; *Serenoa* 42%, placebo −4%; residual volume *Serenoa* 10%, *Pygeum* −4%, placebo 0%;
Maver	1972	RCT; DB; PC SD: 8 wks	60 (0)	100 mg	Nocturia; residual volume	Significant improvements vs. placebo both outcomes ($P < 0.01$)
Ranno	1986	RCT; DB; PC SD: 8 wks	39 (0)	200 mg	Nocturia; peak urine flow	Significant improvement vs. placebo in peak urine flow ($P < 0.01$)
Rigatti	1983	RCT; DB; AC (NSAID). SD: 8 wks	49 (0)	100 mg	Residual volume	Significant improvement vs. control in residual volume ($P < 0.05$)
Rizzo	1985	RCT; DB; PC SD: 8 wks	40 (0)	200 mg	Nocturia; peak urine flow; residual volume	Significant improvement vs. placebo in nocturia ($P < 0.01$)

* (), not available to follow-up.
† NA, not available.

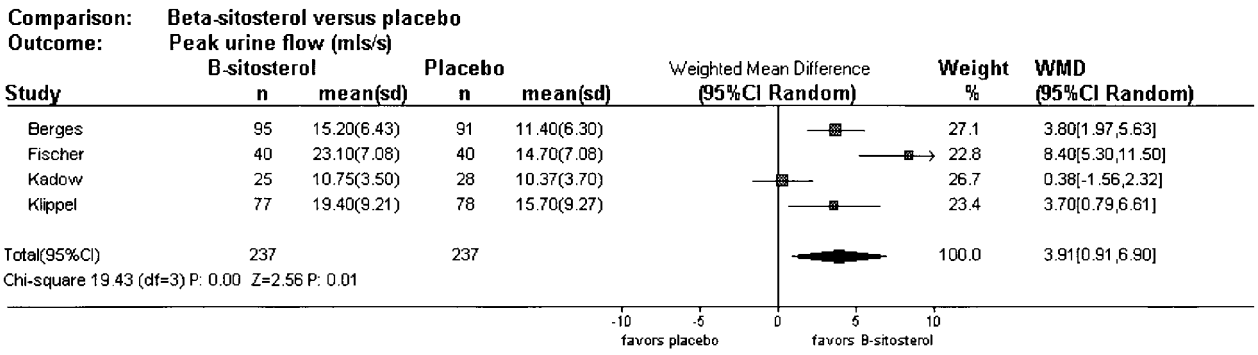

Fig. 5 Effect of β-sitosterol on peak urine flow vs. placebo

Results of studies

A total of 444 men have been enrolled in two placebo-controlled ($n = 163$) and two comparative trials lasting from 12 to 24 weeks[44–47] (Table 4). Three studies were double-blinded[44,45,47]. The mean age of participants was 69 years. Differences in the control agents and methods of reporting results did not permit all studies to be combined in a meta-analysis. However, three studies reported symptom scores or measured symptom improvement[45–47]. Nocturia was reported in three studies[44,45,47] and all studies reported peak urine flow and residual urine volume. Data from all studies were consistent with improvement in symptoms and urinary flow.

Cernilton improved 'self-rated urinary symptoms' versus placebo and Tadenan, an extract from *Pygeum africanum*[46]. Almost 70% men taking Cernilton reported symptom improvement compared with 29% taking placebo. Obstructive and irritative symptom scores improved from baseline by 60% in men taking Cernilton compared with 40% with Tadenan.

Cernilton reduced nocturia compared with placebo and Paraprost, a pharmacologic treatment used primarily in Japan containing 265 mg of L-glutamic acid, 100 mg of L-alanine and 45 mg of aminoacetic acid[47]. Versus placebo, there was a two-fold improvement in the percentage of men reporting improvement in nocturia (63% vs. 31%)[44,45]. Compared with Paraprost, Cernilton reduced nocturia by 0.40 times per evening. The only adverse event reported was mild nausea.

Although the results suggest that Cernilton provided modest benefit there are limitations to the evidence. The longest treatment duration was 24 weeks. Only one study reported results from a standardized and validated urologic symptom scale. While the manufacturer suggests two to four tablets or capsules daily, the dosages and standardization of preparation were not usually reported. The most frequently reported amount was two Cernilton capsules three times per day.

Summary

The evidence suggests that an extract from rye-grass pollen, Cernilton, is well tolerated and modestly improves urologic symptoms. However, trials were of short duration, enrolled relatively few patients, and lacked standard product preparation. Additionally, there was infrequent use of validated symptom scale scores. It does not improve urinary flow measures and the long-term safety and effectiveness is not known.

Pygeum africanum (African plum)

Background

Traditionally, the bark of the African plum tree (*Pygeum africanum*) was collected and powdered, then drunk as a tea to improve genito-urinary symptoms. Purified bark extracts have been used throughout Europe for the past 30 years. The postulated active components include phytosterols, especially β-sitosterols, pentacyclic triterpenoids and esters of long-chain fatty alcohols. *Pygeum africanum* extract may suppress LUTS by reducing bladder hyperreactivity, decreasing inflammation, and protecting against abnormal prostate growth[48].

A 1995 review identified 12 double-blind, placebo controlled studies involving 717 men with BPH[46,49–63] (Table 5). Most studies used a *Pygeum* extract under the trade name Tadenan with doses ranging from 75 to 200 mg day^{-1}. All studies were at least 16 weeks in duration. More than half the studies measured peak urinary flow and all but one measured urinary frequency. Standardized and validated symptom scores were not utilized and there was no pooled estimate of treatment effect size or adverse events. The majority of studies noted an improvement in nocturia compared with placebo. An ongoing double-blind placebo-controlled study is evaluating Tadenan (100 mg and 400 mg) in 750 men with symptomatic BPH. The primary endpoint is a mean reduction in the IPSS score between baseline and 6 months. However, the results have not been reported.

In five small-scale studies involving 183 men, *P. africanum* was compared with active drug or therapy[50,57,63]. Two studies involved plant extracts (sitosterin and extract of *Radix urticae urtae*)[50]. The results

indicate that *Pygeum* reduced nocturia more than comparators in the 3 studies reporting this endpoint. However, in two of these studies there were no statistical comparisons. Since the publication of this review there have been two additional trials utilizing *Pygeum*. One was a study utilizing a combination of *Pygeum* with *Urtica* and is discussed in the section on *Urtica*[59]. The other trial demonstrated that *Pygeum* was less effective than Cernilton in improving 'self-rated urinary symptoms'[46]. Obstructive and irritative symptom scores improved from baseline by 60% in men taking Cernilton compared with 40% in men taking Tadenan.

Summary
Extracts from the African plum tree, *Pygeum africanum*, may be a useful treatment option for BPH. However, inadequacies in the reporting of outcomes limit the ability to estimate its safety and efficacy. An ongoing trial should provide much needed information on the short-term effectiveness and tolerability of *Pygeum africanum*.

Urtica dioica (stinging nettle)

Background
Extracts from roots of the stinging nettle are often used in Germany for the treatment of BPH. The extracts contain a mixture of water- and alcohol-soluble compounds with extraction procedures varying from company to company. Proposed mechanisms of action include inhibition of prostatic growth factor including blocking the conversion of testosterone to dihydrostersterone[1].

Results of studies
There have been five randomized trials evaluating stinging nettle. Three of these involved combinations with other phytotherapeutic agents (*Pygeum* and *Sabal*), making it difficult to evaluate the efficacy of stinging nettle alone[26,30,59]. Furthermore, one of these studies merely compared two different doses of a combined extract of *Urtica* and *Pygeum*[59]. The report by Sokeland compared a combination of *Sabal* and *Urtica* (PRO 160/120) extract with finasteride and placebo[30]. This trial lasted 12 weeks and evaluated 543 men. Compared with finasteride there were no differences in IPSS scores (−4.8 vs. −5.8 IPSS points), peak urine flow or residual urine volume. More adverse events were associated with finasteride, including more cases of erectile dysfunction, diminished ejaculation volume, and headaches. Compared with placebo, the combination of *Sabal–Urtica* (Prostagutt) improved IPSS scores by 17% (−3.5 IPSS points)[26].

One placebo-controlled study lasting 3 months compared a liquid preparation of stinging nettle with placebo in 41 men with BPH[64]. An improvement in IPSS scores was noted in men taking stinging nettle. However, because of unacceptable taste this preparation has been removed from the market. Another placebo-controlled trial examined the effectiveness of Urticae extract capsules[65]. Although improvements in peak urine flow and total voided volume were reported, there was no difference in urologic symptoms. Additionally, 24% of men (6/25) taking Urticae withdrew from the study; half of them due to unspecified side effects.

Summary
Evidence from randomized trials suggests combination preparations of Urticae appear to provide some benefit for treatment of lower urinary tract symptoms, although stinging nettle extracts alone do not appear to be beneficial. Additional randomized controlled trials need to be conducted before Urticae can be recommended as an effective option for the treatment of LUTS.

Curcubita pepo (pumpkin seed)

Results of studies
There has been only one small-scale randomized trial of short duration that has evaluated the efficacy of pumpkin seed extracts[16]. This study evaluated 55 men, lasted for 12 weeks and utilized a preparation that included pumpkin seed, *Curcubita pepo*, and *Sabal serrulata* (Curbicin 160 mg three times a day). Compared with placebo, Curbicin improved self-rating of urinary symptoms (85% noted improvement vs. 11% taking placebo) and nocturia. Residual urine volume was reduced by 31% (42.5 cc) compared with only 6.5% (7.6 cc) with placebo. Because the study utilized a combination preparation the reported improvement in urologic symptoms and flow measures cannot be clearly attributed to pumpkin seeds.

Summary
There is no convincing evidence that extracts of pumpkin seed alone improve urologic symptoms or flow measures. They may provide improvement in urinary symptoms and flow measures when used in combination with *Sabal serrulata*. Randomized controlled trials need to be conducted.

Recommendations and conclusions

Should physicians recommend plant extracts for treatment of BPH? Despite their popularity and the existence of over 40 randomized controlled trials involving nearly 5000 men, the available data do not yet provide clear evidence of efficacy for most phytotherapeutic products. Extracts of saw palmetto (*Serenoa repens*) (alone or in combination with other phytotherapeutic products) have the strongest evidence for efficacy and tolerability. They appear to be a useful option for improving lower urinary tract symptoms and flow measures.

Rye-grass pollen (*Secale cereale*) and South African star grass (*Hypoxis rooperi*, β-sitosterol) also appear to improve symptoms and are well tolerated. However, the evidence is

less strong for these products. African plum tree bark (*Pygeum africanum*) has been studied extensively but inadequate reporting of outcomes limits the ability to conclusively recommend it. There is no convincing evidence supporting the use of pumpkin seed (*Curcubita pepo*) or stinging nettle (*Urtica dioica*) extracts alone for treatment of BPH. They may be effective in combination with other phytotherapeutic products.

The widespread use of phytotherapy attests to the popularity of plant extracts for treatment of BPH symptoms. They cost less and are better tolerated, at least in the short-term, than either alpha-blockers or finasteride. However, if the primary goal is to reduce symptoms, alpha-blockers such as doxazosin, tamsulosin, alfuzosin or terazosin seem to be a better choice than finasteride and probably phytotherapy. Additionally, plant extracts have not yet been demonstrated to reduce complications from BPH or the need for surgical intervention in comparison with interventions such as finasteride[33].

The Committee on Other Medical Therapies of the Fourth International Consultation on BPH concluded that: most plant extract preparations have different components; it is not known what mechanisms of action demonstrated *in vitro* might be responsible for clinical effects; short-term randomized studies suggest clinical efficacy for some preparations; and studies were usually inadequate due to the methodology utilized, small numbers and short duration of study. Of greatest importance is the completion of additional high quality studies of long duration to fully evaluate the efficacy and safety of phytotherapeutic products for treatment of BPH[6].

Until completion of these studies and/or regulation of these products the lack of universal definitions, practices, and standards within the supplement industry place the onus on the physician to judge product quality and efficacy. Manufacturers/companies of plant extracts often use different extraction processes. There is no evidence that the extract from one manufacturer is equivalent to that of another. Additionally, since the active ingredient(s) are not known, it is possible that one product might have clinical efficacy while another does not. Each company's product must be tested to evaluate clinical efficacy and bioactivity.

The following recommendations have been made for assessing quality measures (these do not directly address clinical efficacy or safety) in selecting high-quality and reliable preparations of phytotherapeutic products manufactured in the United States[66].

1. The manufacturer tests raw ingredients for purity and potency prior to inclusion in a product.
2. The product is manufactured in a pharmaceutically licensed facility registered with the Food and Drug Administration.
3. The product's ingredients meet the applicable United States Pharmacopoeia (USP) standards.
4. All finished products are analysed for purity and potency following production by an independent laboratory using established methods to ensure that the product meets label claims and is of good quality.

In some cases, this information can be found on product labelling. All reputable manufacturers will keep certificates of laboratory results for each finished batch of product on file. These should be available to physicians and pharmacists on request.

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