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[Intervention Review]

Pygeum africanum for benign prostatic hyperplasia

Timothy J Wilt[1], Areef Ishani[2]

[1]General Internal Medicine (111-0), VAMC, Minneapolis, Minnesota, USA. [2]Department of Medicine (111), VA Medical Center, Minneapolis, Minnesota, USA

Contact address: Timothy J Wilt, General Internal Medicine (111-0), VAMC, One Veterans Drive, Minneapolis, Minnesota, 55417, USA. Tim.Wilt@med.va.gov.

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ABSTRACT

Background

Benign prostatic hyperplasia (BPH), nonmalignant enlargement of the prostate, can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH has been growing steadily. The extract of the African prune tree, *Pygeum africanum*, is one of the several phytotherapeutic agents available for the treatment of BPH.

Objectives

To investigate the evidence whether extracts of *Pygeum africanum* (1) are more effective than placebo in the treatment of Benign Prostatic Hyperplasia (BPH), (2) are as effective as standard pharmacologic BPH treatments, and (3) have less side effects compared to standard BPH drugs.

Search methods

Trials were searched in computerized general and specialized databases (MEDLINE (1966 to 2000), EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting relevant manufacturers and researchers.

Selection criteria

Trials were eligible if they (1) were randomized (2) included men with BPH (3) compared preparations of *Pygeum africanum* (alone or in combination) with placebo or other BPH medications (4) included clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements. Eligibility was assessed by at least two independent observers.

Data collection and analysis

Information on patients, interventions, and outcomes were extracted by at least two independent reviewers using a standard form. The main outcome measure for comparing the effectiveness of *Pygeum africanum* with placebo and standard BPH medications was the change in urologic symptoms scale scores. Secondary outcomes included change in urologic symptoms including nocturia and urodynamic measures (peak and mean urine flow, prostate size). The main outcome measure for adverse effects was the number of men reporting adverse effects.

Main results

A total of 18 randomized controlled trials involving 1562 men met inclusion criteria and were analyzed. Only one of the studies reported a method of treatment allocation concealment, though 17 were double blinded. There were no studies comparing *Pygeum africanum* to standard pharmacologic interventions such as alpha-adrenergic blockers or 5-alpha reductase inhibitors. The mean study duration was 64 days (range, 30 to 122 days). Many studies did not report results in a method that permitted meta-analysis. Compared to men receiving placebo, *Pygeum africanum* provided a moderately large improvement in the combined outcome of urologic symptoms and flow measures as assessed by an effect size defined by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome (-0.8 SD [95% confidence interval (CI), -1.4 to -0.3 (n = 6 studies)]). Men using *Pygeum africanum* were more than twice as likely to report an improvement in overall symptoms (RR=2.1, 95% CI = 1.4 to 3.1). Nocturia was reduced by 19%, residual urine volume by 24% and peak urine flow was increased by 23%. Adverse effects due to *Pygeum Africanum* were mild and comparable to placebo. The overall dropout rate was 12% and was similar between *Pygeum Africanum* (13%), placebo (11%) and other controls (8%).

Authors' conclusions

A standardized preparation of *Pygeum africanum* may be a useful treatment option for men with lower urinary symptoms consistent with benign prostatic hyperplasia. However, the reviewed studies were small in size, were of short duration, used varied doses and preparations and rarely reported outcomes using standardized validated measures of efficacy. Additional placebo-controlled trials are needed as well as studies that compare *Pygeum africanum* to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. These trials should be of sufficient size and duration to detect important differences in clinically relevant endpoints and use standardized urologic symptom scale scores.

PLAIN LANGUAGE SUMMARY

Extracts from the African prune tree (*Pygeum africanum*) may be able to help relieve urinary symptoms caused by enlarged prostate (benign prostatic hyperplasia)

Benign prostatic hyperplasia (BPH), enlargement of the prostate gland, is common in older men. An enlarged prostate can interfere with urination, increasing the frequency and urge, or causing problems emptying the bladder. Both surgery and drugs are used to try to treat BPH. However, using herbal medicines to try to relieve the symptoms of BPH is becoming common. *Pygeum africanum* is one of several popular herbal remedies for BPH. The review found that *pygeum africanum* is well tolerated, cheaper than many prescription medicines used for BPH, and provides moderate relief from the urinary problems caused by an enlarged prostate.

BACKGROUND

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate. Symptoms related to BPH are one of the most common problems in older men. Histological evidence of BPH is found in more than 40% of men in their fifties and nearly 90% of men in their eighties (Berry 1984). The majority of men over the age of 60 are considered to have urinary symptoms attributable to BPH. In the United States treatment of BPH accounts for approximately 1.7 million physician office visits (Guess 1992) and results in more than 300,000 prostatectomies annually (McConnell 1994). The proliferative disorder resulting in BPH affects both the stromal and the epithelial portions of the prostate. The enlarging prostate results in the progressive occlusion of the proximal urethra and can result in both obstructive and irritative urinary tract symptoms. The obstructive symptoms of BPH include weak urinary stream, hesitancy, intermittency, incomplete bladder emptying, terminal urine dribbling and abdominal straining (Christensen 1990; Caine 1987). The irritative symptoms include urinary frequency, urgency and nocturia. The treatment goal in the vast majority of patients with BPH is to relieve these bothersome symptoms.

The use of plants and herbs for medicinal purposes (phytotherapy) including treatment of BPH symptoms has been growing steadily in most countries. Usage of plant extracts is common in Europe and is increasing in the United States. Phytotherapeutic

agents represent nearly half of the medications dispensed for BPH in Italy, compared with 5% for alpha blockers and 5% for 5-alpha reductase inhibitors (Di Silverio 1993). In Germany and Austria, phytotherapy is the first-line treatment for mild to moderate urinary obstructive symptoms and represents > 90% of all drugs prescribed for the treatment of BPH (Buck 1996). In the United States their use has also markedly increased, they are readily available as nonprescription dietary supplements and are often recommended in "natural health food stores or books" for self treatment of BPH symptoms.

Pygeum africanum, an extract from the bark of the African prune tree, has been utilized in Europe since 1969 for the treatment of mild to moderate symptomatic benign prostatic hyperplasia. The mechanism of action of *Pygeum africanum* remains unclear. In animal models, *Pygeum africanum* has been shown to have pharmacologic properties that may be beneficial in the treatment of benign prostatic hyperplasia. These include modulation of bladder contractility, anti-inflammatory activity, decreased production of leukotrienes and other 5-lipoxygenase metabolites (Sidoti 1993; Paubert-Braquet 1994), inhibition of fibroblast production (Yablonsky 1997; Paubert-Braquet 1993) effects on adrenal androgens (Thieblot 1977), and restoration of secretory activity of prostate epithelium.

Despite the wide-spread use of *Pygeum africanum* uncertainty remains regarding treatment effectiveness and tolerability. A previous qualitative summary did not meet criteria for a systematic review (Andro 1995). This review included results from open-labelled uncontrolled studies, did not assess study quality nor conduct a quantitative meta-analysis to estimate the magnitude or statistical significance of treatment efficacy and was sponsored by a manufacturer of *Pygeum africanum* extract. We conducted a systematic review including a quantitative meta-analysis, where possible, of the evidence from randomized controlled trials to determine the therapeutic efficacy and tolerability of *Pygeum africanum*, alone or in combination with other herbal agents, for men with symptomatic benign prostatic hyperplasia.

OBJECTIVES

The aim of our review was to provide a comprehensive overview including a quantitative meta-analysis of the existing evidence to determine the therapeutic efficacy and the adverse effects of the plant extract *Pygeum africanum*. Specifically, was *Pygeum africanum* more effective than placebo in improving the symptoms and/or urodynamics of BPH and as effective as current medical therapies.

Main comparison

Determine if *Pygeum africanum* was more efficacious than placebo in improving validated and standardized urologic symptom scores in men with symptomatic BPH.

Secondary comparisons

1. Determine if *Pygeum africanum* is more efficacious than placebo in improving urodynamic measurements and urinary symptoms including peak urine flow, mean urine flow, residual urine, prostate size, nocturia, dysuria, and urinary frequency.

2. Determine if *Pygeum africanum* is as efficacious as active controls in improving urologic symptom scores and urodynamic measures.

3. Determine the adverse effects of *Pygeum africanum*.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials.

Types of participants

Men with symptomatic benign prostatic hyperplasia

Types of interventions

Comparison of preparations of *Pygeum africanum* with placebo or medical therapies for BPH with a treatment duration of at least 30 days.

Types of outcome measures

Urologic symptom scores (Boyarsky, American Urologic Association Score, International Prostate Symptom Score:IPSS); Urodynamic measures (defined as change in peak urine flow (PUF), mean urine flow (MUF), residual urine volume; changes in prostate size (measured in cc); urinary frequency, nocturia (times/per evening); quality of life score (QOL); and overall physician/patient health assessment.

Search methods for identification of studies

We searched MEDLINE for 1966 to 2000 using a combination of the March 1996 update of the optimally sensitive search strategy for trials from the Cochrane Collaboration with the MeSH headings "prostatic hyperplasia," "phytotherapy," "plant extracts," "Pygeum africanum," "Tadenan", "Docosonal", and "Pigenil" including all subheadings (Dickersin 1994). A search of EMBASE, years 1974 to 1999 was done by using a similar approach to that for Medline. We also searched the private database Phytodok, Munich Germany, and the Cochrane Library, including the database of the

Cochrane Prostate Diseases and Urologic Malignancies Review Group and the Cochrane Field for Complementary Medicine. Reference lists of all identified trials and previous reviews were searched for additional trials. The manufacturer and authors were contacted for missing data or additional trials. There were no language restrictions.

Data collection and analysis

Eligibility:
Two investigators (AI and RM) independently determined if identified studies met inclusion criteria.
Extraction:
The following data were extracted from each included study: study characteristics, demographics of patients, enrollment criteria, outcomes, adverse effects, and number and reasons for dropout. Missing or additional information was sought from authors/sponsors. Included and excluded studies as well as extracted data were reviewed and discrepancies resolved by discussion and consensus.
Assessment of methodological quality:
Study quality was assessed using the method outlined by Schulz and colleagues (Schulz 1995) assigning 1 to poorest quality and 3 to best quality: 1 = trials in which concealment was inadequate (e.g. alteration or reference to case record numbers or to dates of birth); 2 = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories; and 3 = trials deemed to have adequate measures to conceal allocations (e.g. central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes etc. that contained elements convincing of concealment).
Summarizing results of primary studies:
Outcomes:
The mean urologic symptom score (points), peak and mean urine flow (mL/sec), residual urine volume (mL), prostate size (cc), frequency (% men reporting), urgency (% men reporting), dysuria (% men reporting) and nocturia (# times). The number and percent of men reporting specific side effects and/or withdrawing from the study.
Meta-analysis:
Because no common outcome measure was available from all eighteen studies we utilized two methods for combining data. One method, reported by Saint 1995, assesses treatment effect size for continuous variables by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome when trials report different outcome measures of effectiveness (e.g. symptom scale scores, nocturia, peak urine flow rate). The second method calculates a summary measure for individual outcomes using studies that provide similar outcome measures and utilizes standard meta-analytic techniques described below.
For determining effect size we utilized the outcome that was determined a priori to be most clinically significant (order of clinical importance: symptom scale score > nocturia > peak urine flow > residual urine volume). One outcome from each study was then transformed into units of standard deviations (SD), giving a comparable effect size for each study. The study-specific overall effect size was the difference in mean outcome for the *Pygeum africanum* and placebo groups, divided by the pooled SD of the outcome measure. The summary effect size across studies was calculated as the weighted average of the study-specific effect size, with weights equal to the inverse of the estimated variance of each using standard meta-analytic methodology as developed by DerSimonian and Laird (DerSimonian 1986; Laird 1990). We used the same definition of standardized effect sizes to look at individual and comparable continuous outcomes when available (nocturia and peak urine flow). The statistical significance of the summary effect size was assessed by comparing it with the standard normal distribution. A scale for effect size suggested by Cohen 1988 was used with 0.8 reflecting a large effect, 0.5 a moderate effect, and 0.2 a small effect.
Additional meta-analyses considered the difference between *Pygeum africanum* treatment and the control treatment in the mean change from baseline to end of follow-up for each separate continuous outcome. For those studies not reporting mean change scores and the corresponding standard errors, the standard errors for the mean change scores were approximated using the standard errors of the outcomes at baseline and followup. The approximation used the methodology reported by Laird 1990 and Lau 1996 based on the correlation between outcomes. Analyses were conducted for three different assumed values for this correlation (0.25, 0.50, 0.75). This approach was taken to examine the sensitivity of the results to the value of this unknown parameter. Weighted mean differences were calculated using the methodology outlined above. There were no qualitative differences between the meta-analysis results for the three assumed correlation values; we present here the results for the assumed correlation of 0.50. For categorical outcome measures weighted relative risks and 95% CI were calculated using standard meta-analytic techniques.
Chi squared tests were used for analysis of bivariate comparisons (adverse events and dropouts) using simple pooling of data. To assess the percentage of patients having improvement in urologic symptoms, a modified intention-to-treat analysis was performed (i.e., men who dropped out or were lost to follow-up were considered to have had worsening symptoms) (Lavori 1992). The denominator for the modified intention-to-treat analysis included the number randomized to treatment at baseline, and the numerator included the number completing the trial and showing improvement. A test for heterogeneity was calculated according to standard formulas (DerSimonian 1986; Saint 1995) and a random effects model utilized for all summary estimates.

RESULTS

Description of studies

The combined search strategies identified 31 trials; 18 met inclusion criteria. None were conducted in the United States and 12 were reported in a non-English language [German (1), Italian (10), French (2)]. Fourteen trials were excluded because they did not include a control group (Anonymous 1973; Breza 1998; Diz 1973; Grasset 1974; Greiner 1970; Grévy 1970; Guilland-Vallée 1970; Guillemin 1970; Huet 1970; Lange 1970; Lhez 1970; Martínez-Piñeiro '73; Robineau 1976; Rometti 1970). The majority of studies examined *Pygeum Africanum* alone versus placebo alone (n = 11) (Barlet 1990; Bassi 1987; Blitz 1985; Bongi 1972; Donkervoort 1977; Dufour 1984; Frasseto 1986; Maver 1972; Ranno 1986; Rizzo 1985). Two trials comparing *Pygeum africanum* against an anti-inflammatory drug (Gagliardi 1983; Rigatti 1983). One study comparing *Pygeum Africanum* to placebo included an additional treatment arm of *Pygeum africanum* in combination with a steroid (Giacobini 1986). Two studies compared *Pygeum africanum* alone to one or more herbal agents and versus placebo (Barth 1981; Mandressi 1983), one trial compared *Pygeum africanum* to another herbal agent (Dutkiewicz 1996), one trial compared different daily dosage forms of *Pygeum africanum* (Chatelain 1999), and one trial compared two different doses of *Pygeum africanum* in combination with another herbal extract (Krzeski 1993). None of the "active comparison" arms have been conclusively demonstrated to be effective in treating symptomatic benign prostatic hyperplasia.

A total of 1562 participants were randomized in the 18 trials. The mean treatment duration was 64 ± 21.1 days and ranged from 30 to 122 days. The majority of the studies (n = 14; participants = 1103) utilized a standardized extract of *Pygeum africanum*. The doses of *Pygeum africanum* ranged between 75 to 200 mg per day. Of the placebo controlled trials 1 utilized a dose of *Pygeum africanum* equal to 75 mg per day, 7 utilized a dose of 100 mg per day, 4 utilized a dose of 200 mg/day and one did not report the dosage (Dutkiewicz 1996). For studies that provided baseline data, results did not vary between treatment arms and were consistent with men typically presenting with moderate benign prostatic hyperplasia. The mean age was 66.± 6.9 years (9 studies, n = 845, range 42 to 89); nocturia = 3 ± 0.7 times per evening (4 studies, n = 413); peak urine flow = 12 ± 3.6 mL/sec (5 studies, n = 416); residual urine volume = 40 ± 25.6 mL (2 studies, n = 284). Not all studies could be pooled because of differences in reporting methods. Of the 13 trials of *Pygeum africanum* versus placebo identified, 12 reported a beneficial effect of *Pygeum africanum* on at least one measure of effectiveness: overall symptoms, nocturia, peak urine flow or residual volume. Only one trial demonstrated no difference between *Pygeum africanum* and placebo (Rizzo 1985). This trial assessed the effect of *Pygeum africanum* on nocturia, peak urine flow and overall symptom change in 20 men over 12 weeks. None of the trials showed an effect of *Pygeum africanum* worse then placebo or "active control."

Risk of bias in included studies

Only one of the studies reported a method for concealment of treatment allocation (score = 2) but 17 of the 18 studies were double-blinded. Most studies did not provide baseline patient information nor provide clinically relevant baseline or outcomes data in a standardized fashion. No placebo-controlled studies utilized standardized, validated symptom scales (the outcome measure of greatest clinical significance). There was no information on patient race, comorbid conditions, prostate size or standardized/validated urologic symptom scale scores. All studies were of short treatment duration with none having a follow up greater than four months.

Effects of interventions

Summary Effect Sizes:

Six studies involving 474 participants (54% of all participants enrolled in placebo controlled trials) could be pooled to provide a weighted estimate of effectiveness (Barlet 1990; Bongi 1972; Giacobini 1986; Mandressi 1983; Maver 1972; Rizzo 1985). All involved *Pygeum africanum* alone versus placebo, and five utilized a standardized preparation of *Pygeum africanum*. The overall summary effect size was -0.8 SD (95% CI -1.4 to -0.3) indicating a statistically significant large improvement with *Pygeum africanum*. The summary effect size from three studies that provided data on nocturia was -0.8 SD (95% CI -1.4 to -0.1) (Barlet 1990; Bongi 1972; Mandressi 1983). This indicates that *Pygeum africanum* resulted in a statistically significant moderate to large improvement in nocturia. Summary results from the four studies providing data on peak urine flow demonstrated a mean effect size of 0.7 SD (95% CI 1.3 to 0.0) indicating a moderate effect on peak urine flow (Barlet 1990; Giacobini 1986; Maver 1972; Rizzo 1985).

Urinary symptoms and flow measures:

Consistent with the results seen in the summary effect sizes, *Pygeum africanum* improved specific urinary symptoms and flow measures. In 5 double-blind trials involving 430 participants, men receiving *Pygeum africanum* were more than twice as likely to be rated by their physician as having overall improvement in symptoms compared to men taking placebo (65% vs. 30%; RR = 2.1; 95% CI = 1.4 to 3.1) (Barlet 1990; Blitz 1985; Bongi 1972; Donkervoort 1977; Mandressi 1983). *Pygeum africanum* reduced nocturia compared to placebo by 19% (weighted mean difference (WMD) = - 0.9 times per evening; 95% CI = -2.0 to 0.1) though this did not reach statistical significance (Barlet 1990; Bongi 1972; Mandressi 1983). *Pygeum africanum* also increased peak urine flow compared to placebo by 23%, WMD = 2.5 mL/sec (95% CI = 0.3 to 4.7) (Barlet 1990; Giacobini 1986; Maver 1972; Rizzo 1985). *Pygeum africanum* reduced residual urine volume by 24% (WMD = -13 mL; 95% CI = -23.3 to -3.0) (Barlet 1990; Giacobini 1986).

To assess for publication bias we constructed funnel plots from published trials providing data for calculation of summary effect size, overall symptom improvement, nocturia and peak urine

flown. The few studies available for funnel plot analysis make assessment difficult and do not provide clear evidence for or against publication bias.

Adverse Events:

All studies provided information on the percentage of men who dropped-out or were lost to follow up, potentially the most reliable indicator of tolerability. The mean percentage of participants who dropped out was 12% (n = 179), ranged from 0% to 45% and did not differ between *Pygeum africanum* (13%), placebo (11%) and other controls (8%) (P = 0.4 vs placebo and P=0.5 vs other control). Three studies (two placebo controlled) had drop out rates > 20%. The reason for the high drop out rate was not reported but two of the trials (Barth 1981; Chatelain 1999) indicated that adverse effects were "infrequent and mild" in participants completing the trial. None of these three trials reported outcome data in a method suitable for incorporation into the effect size analyses. Thirteen of the eighteen studies provided information on specific adverse events. Adverse events due to *Pygeum africanum* were generally mild in nature and comparable in frequency to placebo. The most frequently reported adverse events were gastrointestinal and occurred among seven men in five trials.

DISCUSSION

This systematic review summarizes the available evidence from randomized controlled trials regarding the efficacy and tolerability of *Pygeum africanum* for the treatment of lower urinary tract symptoms attributable to benign prostatic hyperplasia. Our results suggest that *Pygeum africanum* improves urinary symptoms and flow measures and that the point estimate for the effect size is moderate in magnitude. Because of the diversity of outcome measures, a summary estimate of the effect of *Pygeum africanum* was based on units of SD available from 6 studies involving 474 participants. This method is useful for determining if an overall benefit exists but only indicates whether the overall effect is of small, moderate or large magnitude. Our analyses of individual effect sizes for nocturia and peak urinary flow indicate that improvement of comparable magnitude occurred in both urinary symptoms and flow measures.

Summary risk ratios and weighted mean differences comparing *Pygeum africanum* to placebo for overall symptoms, peak urine flow, and residual urine volume demonstrated a statistically significant improvement as well as a trend towards improvement for nocturia. These findings are considered clinically significant, comparable to other widely used treatment options and consistent with the results obtained utilizing effect sizes. The results from individual trials demonstrated that all but one study noted an improvement with *Pygeum africanum* for symptoms attributable to benign prostatic hyperplasia. Additionally, *Pygeum africanum* was well tolerated with the drop out rate for men receiving *Pygeum africanum* not different than for men receiving placebo.

While studies utilized different quantities, dosing intervals and preparations of *Pygeum africanum* the majority of studies utilized a standardized extract of *Pygeum africanum* at a dose of 100 to 200 mg per day. Five of the six studies providing data for summary estimates of effect size utilized the standardized extract of *Pygeum africanum*. All summary efficacy data were derived from placebo-controlled, double blind studies utilizing a "noncombination" source of *Pygeum africanum*. This suggests that a standardized preparation of *Pygeum africanum* is associated with the observed improvement in symptoms and flow measures.

No study was conducted in the United States and many studies did not report means and standard deviations making completion of a quantitative review difficult. There was no information provided to determine if *Pygeum africanum* prevented long-term complications of benign prostatic hyperplasia such as acute urinary retention, renal insufficiency or the need for surgical intervention. No studies compared *Pygeum africanum* with medical interventions of demonstrated effectiveness including alpha adrenergic blockers and 5-alpha reductase inhibitors. The "active controls" used in the studies have not been convincingly demonstrated to have beneficial effects.

A possible source of bias is that outcomes included in the effect size calculation could have been selected to favor *Pygeum africanum*. However, we ranked outcome measures for inclusion in the effect size calculation prior to data abstraction and analysis. Furthermore, effectiveness was consistently observed in all but one of the studies and regardless of whether the results were reported as physician rating of patient's global symptom improvement (n = 6 trials; 430 patients); nocturia (n = 3 trials; 325 participants); peak urine flow (n = 4 trials; 363 participants); or residual volume (n = 4 trials; 264 participants). An additional source of bias could result from failure to publish small negative studies (publication bias) or outcomes that were not favorably affected. This would enhance the summary effect size estimates and could contribute to our finding that only one out of seventeen reported studies was negative. Funnel plots were constructed to assess for publication bias, however few studies could be included in the plot construction.

AUTHORS' CONCLUSIONS

Implications for practice

The overall standardized effect size and the summary improvement in global symptoms, nocturia, peak urine flow and residual urine volume suggests that *Pygeum africanum* is effective in men with symptomatic benign prostatic hyperplasia. This benefit is of modest size and appears to be clinically significant. *Pygeum africanum* is well tolerated and costs less than most prescription medications.

A standardized preparation of *Pygeum africanum*, may be a useful treatment option, at least in the short term, for men with lower urinary symptoms consistent with benign prostatic hyperplasia.

Implications for research

Additional placebo-controlled trials are needed as well as studies that compare *Pygeum africanum* to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. Future trials should be of sufficient size and duration (e.g. > 6 months) to detect important differences in clinically relevant endpoints and use standardized urologic symptom scale scores.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barlet 1990

Methods	Multicentre study. Double blinded: yes.
Participants	N=263 European men with symptomatic BPH, age > 50. Age range 50-85, mean 67. Lost to follow-up: 8 (3%).
Interventions	Control: placebo (n=132). Treatment: P. africanum extract (Tadenan) 100 mg twice daily (n=131). Treatment duration: 60 days.
Outcomes	Overall improvement in symptoms (MD/subject - rating); Nocturia; peak urine flow; residual volume. Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Barth 1981

Methods	Double blinded: yes.
Participants	N=215 European men with symptomatic BPH, age > 50. Lost to follow-up: 67 (31%).
Interventions	Control 1: placebo (n=46). Treatment 2: P. africanum extract (Docosanol) 100 mg daily (n=50). Control 2: Sitosterin 30 mg (n=34). Treatment 2: P. africanum extract (Docosanol) 100 mg daily (n=37). Control 3: ERU* 300 mg (n=24). Treatment 3: P. africanum extract (Docosanol) 100 mg daily (n=24). Treatment duration: 8 weeks.
Outcomes	Nocturia; peak urine flow; residual volume. Adverse events.
Notes	

Risk of bias

Barth 1981 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bassi 1987

Methods	Double blinded: yes.
Participants	N=40 Italian men with symptomatic BPH. Mean age: 67 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=20). Treatment: P. africanum extract (Pigenil) 100 mg daily (n=20). Treatment duration: 60 days.
Outcomes	Nocturia; peak urine flow. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Blitz 1985

Methods	Double blinded: yes.
Participants	N=57 French men with symptomatic BPH. Lost to follow-up: 0.
Interventions	Control: placebo Treatment: P. africanum extract (Tadenan) 100 mg daily Treatment duration: 60 days.
Outcomes	Overall improvement in symptoms.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Blitz 1985 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bongi 1972

Methods	Double blinded: yes.	
Participants	N=50 Italian men with symptomatic BPH, residual volume < 200 ml. Age range: 49-84. Lost to follow-up: 0.	
Interventions	Control: placebo Treatment: P. africanum extract (Tadenan) 75 mg daily Treatment duration: 60 days	
Outcomes	Nocturia; residual volume.	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Chatelain 1999

Methods	Double blinded: yes.	
Participants	N=209 French men with symptomatic BPH, age > 50, IPSS 10 or >, PUF < 15 ml/s, residual volume < 150 ml. Mean age: 66 years. Lost to follow-up: 26 (11.1%).	
Interventions	Treatment 1: P. africanum extract (Tadenan) 50 mg x 2 daily (n=101). Treatment 2: P. africanum extract (Tadenan) 100 mg daily (n=108). Treatment duration: 60 days.	
Outcomes	Symptom score (IPSS); peak urine flow. Adverse events.	
Notes	235 men were randomized, 223 completed the comparative phase, but only 209 men were valid for per-protocol analysis	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Chatelain 1999 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	B - Unclear

Donkervoort 1977

Methods	Double blinded: yes.
Participants	N=20 Dutch men with symptomatic BPH. Lost to follow-up: 4 (20%).
Interventions	Control: placebo Treatment: P. africanum extract (Tadenan) 75 mg daily Treatment duration: 12 weeks.
Outcomes	Overall improvement in symptoms; Nocturia; peak urine flow.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dufour 1984

Methods	Double blinded: yes.
Participants	N=120 French men with symptomatic BPH not in need of surgery. Lost to follow-up: 56 (47%).
Interventions	Control: placebo (n=60). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=60). Treatment duration: 6 weeks.
Outcomes	Nocturia.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dutkiewicz 1996

Methods	Single-site study. Double blinded: no. Randomization: unclear Patients not blinded: Providers not blinded: Lost to follow-up: none
Participants	N=89 Polish men with symptomatic BPH. Age range: 50-68. Lost to follow-up: 0.
Interventions	Control: Cernilton 2 tablets three times daily x 2 weeks followed by 1 tablet three times daily up to 4 months (n=51). Treatment: Tadenan 2 tablets twice daily (38). Treatment duration: 24 weeks.
Outcomes	Obstructive symptom score Irritative symptom score; peak urine flow; residual volume; prostate volume. Adverse events.
Notes	Exclusions: No details provided.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Frasseto 1986

Methods	Double blinded: yes.
Participants	N=20 Italian men with symptomatic BPH. Age range: 50-84, mean 67 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=10). Treatment: P. africanum extract (Tadenan) 75 mg daily (n=10). Treatment duration: 60 days
Outcomes	"Dysuric symptoms" (nocturia, pollachiuria, reduced strenght of flux). Adverse events.
Notes	Prostate size evaluated by ultrasonography.

Frasseto 1986 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gagliardi 1983

Methods	Double blinded: yes.
Participants	N=40 Italian men with symptomatic BPH. Age range: 50-84, mean 67 years. Lost to follow-up: 1 (2.5%)
Interventions	Control: Anti-inflammatory (not identified) (n=20) Treatment: P. africanum extract (Tadenan) 100 mg daily (n=20). Treatment duration: 30 days.
Outcomes	Nocturia; residual volume. Adverse events.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Giacobini 1986

Methods	Double blinded: yes.
Participants	N=21 Italian men with symptomatic BPH. Age range: 48-70. Lost to follow-up: 0
Interventions	Control: placebo (n=7). Treatment 1: P. africanum extract (Tadenan) 200 mg daily (n=7). Treatment 1: P. africanum extract (Tadenan) 200 mg daily + medroxyprogesterone acetate (Farlutal) (n=7). Treatment duration: 90 days.
Outcomes	Peak flow rate; residual volume. Adverse events.
Notes	

Giacobini 1986 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Krzeski 1993

Methods	Double blinded: yes.
Participants	N=134 Polish men with symptomatic BPH (> 1 symptom). Age range: 53-84, mean 64 years. Lost to follow-up: 14.2%.
Interventions	Treatment 1: P. africanum 25 mg + Urtica dioica 300 mg (n=67). Treatment 2: half dose of above (n=67). Treatment duration: 8 weeks.
Outcomes	Overall improvement in symptoms; nocturia; peak flow rate; residual volume. Adverse events
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Mandressi 1983

Methods	Double blinded: yes. Randomization: Identical packaging
Participants	N=60 Italian men with symptomatic BPH. Age range: 50-80.
Interventions	Control 1: placebo (n=20). Control 2: Permixon 320mg daily (n=20). Treatment: Pygeum africanum extract Average (n=20). Treatment duration: 30 days. Lost to follow-up: unclear

Mandressi 1983 (*Continued*)

Outcomes	Patient self-rating of "Dysuric symptoms" (pain on voiding) Nocturia. Adverse events. Dropouts due to side effects: none
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Maver 1972

Methods	Double blinded: yes.
Participants	N=60 Italian men with symptomatic BPH. Age range: 55-85, mean 66 years
Interventions	Control: placebo (n=30). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=30). Treatment duration: 60 days.
Outcomes	Nocturia; residual volume. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ranno 1986

Methods	Double blinded: yes.
Participants	N=39 Italian men with symptomatic BPH. Mean age: 70 years. Lost to follow-up: 0
Interventions	Control: placebo (n=19). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=20). Treatment duration: 2 months.
Outcomes	Nocturia; peak urine flow. Adverse events.

Ranno 1986 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rigatti 1983

Methods	Double blinded: yes.
Participants	N=49 Italian men with symptomatic BPH. Lost to follow-up: 0.
Interventions	Control: NSAID (n=25). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=24). Treatment duration: 60 days.
Outcomes	Residual volume. Adverse events.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rizzo 1985

Methods	Double blinded: yes.
Participants	N=40 Italian men with symptomatic BPH. Age range: 42-74, mean 62 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=20). Treatment: P. africanum extract (Tadenan) 100 mg twice daily (n=20). Treatment duration: 60 days.
Outcomes	Nocturia; peak urine flow; residual volume. Adverse events.
Notes	

Risk of bias

Rizzo 1985 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

* Extract of Rad. urticae

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anonymous 1973	No control group.
Breza 1998	No control group.
Diz 1973	No control group.
Grasset 1974	No control group.
Greiner 1970	No control group.
Grévy 1970	No control group.
Guilland-Vallée 1970	No control group.
Guillemin 1970	No control group.
Huet 1970	No control group.
Lange 1970	No control group.
Lhez 1970	No control group.
Martínez-Piñeiro '73	No control group.
Robineau 1976	No control group.
Rometti 1970	No control group.

DATA AND ANALYSES

Comparison 1. Pygeum africanum vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptoms improvement: Overall improvement/Global assessment/MD rating	5	430	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.40, 3.06]
2 Nocturia (times per evening)	3	325	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.95, 0.14]
3 Peak urine flow (mL/sec)	4	363	Mean Difference (IV, Random, 95% CI)	2.50 [0.29, 4.71]
4 Residual volume (mL)	2	264	Mean Difference (IV, Random, 95% CI)	-13.17 [-23.34, -2.99]

Analysis 1.1. Comparison 1 Pygeum africanum vs. placebo, Outcome 1 Symptoms improvement: Overall improvement/Global assessment/MD rating.

Review: Pygeum africanum for benign prostatic hyperplasia

Comparison: 1 Pygeum africanum vs. placebo

Outcome: 1 Symptoms improvement: Overall improvement/Global assessment/MD rating

Study or subgroup	P. africanum n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Barlet 1990	83/131	40/132		38.2 %	2.09 [1.57, 2.79]
Blitz 1985	23/30	12/27		28.6 %	1.73 [1.08, 2.75]
Bongi 1972	22/25	3/25		10.4 %	7.33 [2.51, 21.41]
Donkervoort 1977	1/10	1/10		2.1 %	1.00 [0.07, 13.87]
Mandressi 1983	12/20	8/20		20.8 %	1.50 [0.79, 2.86]
Total (95% CI)	**216**	**214**		**100.0 %**	**2.07 [1.40, 3.06]**

Total events: 141 (P. africanum), 64 (Placebo)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 7.57$, df = 4 (P = 0.11); $I^2 = 47\%$

Test for overall effect: Z = 3.67 (P = 0.00024)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Pygeum africanum vs. placebo, Outcome 2 Nocturia (times per evening).

Review: Pygeum africanum for benign prostatic hyperplasia

Comparison: 1 Pygeum africanum vs. placebo

Outcome: 2 Nocturia (times per evening)

Study or subgroup	P. africanum N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Barlet 1990	116	2 (1.51)	119	2.2 (1.53)		43.3 %	-0.20 [-0.59, 0.19]
Bongi 1972	25	1.38 (1.75)	25	3 (1.75)		33.1 %	-1.62 [-2.59, -0.65]
Mandressi 1983	20	1.9 (2.41)	20	3.1 (2.46)		23.6 %	-1.20 [-2.71, 0.31]
Total (95% CI)	**161**		**164**			**100.0 %**	**-0.91 [-1.95, 0.14]**

Heterogeneity: $Tau^2 = 0.62$; $Chi^2 = 8.12$, df = 2 (P = 0.02); $I^2 = 75\%$

Test for overall effect: Z = 1.69 (P = 0.091)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Pygeum africanum vs. placebo, Outcome 3 Peak urine flow (mL/sec).

Review: Pygeum africanum for benign prostatic hyperplasia

Comparison: 1 Pygeum africanum vs. placebo

Outcome: 3 Peak urine flow (mL/sec)

Study or subgroup	P. africanum N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Barlet 1990	126	15.7 (8.87)	123	14.6 (8.76)		33.6 %	1.10 [-1.09, 3.29]
Giacobini 1986	7	12.07 (2.73)	7	11 (2.73)		27.2 %	1.07 [-1.79, 3.93]
Maver 1972	30	10.46 (4.38)	30	5.76 (4.38)		33.3 %	4.70 [2.48, 6.92]
Rizzo 1985	20	23.92 (13.82)	20	19.24 (13.82)		5.9 %	4.68 [-3.89, 13.25]
Total (95% CI)	**183**		**180**			**100.0 %**	**2.50 [0.29, 4.71]**

Heterogeneity: $Tau^2 = 2.54$; $Chi^2 = 6.56$, df = 3 (P = 0.09); $I^2 = 54\%$

Test for overall effect: Z = 2.22 (P = 0.027)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Pygeum africanum vs. placebo, Outcome 4 Residual volume (mL).

Review: Pygeum africanum for benign prostatic hyperplasia

Comparison: 1 Pygeum africanum vs. placebo

Outcome: 4 Residual volume (mL)

Study or subgroup	P. africanum N	Mean(SD)	placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Barlet 1990	126	28.7 (42.88)	124	41.3 (42.54)		92.4 %	-12.60 [-23.19, -2.01]
Giacobini 1986	7	15.71 (35.13)	7	35.71 (35.13)		7.6 %	-20.00 [-56.80, 16.80]
Total (95% CI)	**133**		**131**			**100.0 %**	**-13.17 [-23.34, -2.99]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.14$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 2.54 (P = 0.011)

Test for subgroup differences: Not applicable

WHAT'S NEW

Last assessed as up-to-date: 25 November 1997.

Date	Event	Description
28 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 2, 2002

Date	Event	Description
26 November 1997	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Veterans Affairs Health Services Research and Development (HSRD) Office, USA.
- Minneapolis/VISN-13 Center for Chronic Diseases Outcomes Research (CCDOR), USA.

External sources

- No sources of support supplied

NOTES

This review is out of date and has been withdrawn.

INDEX TERMS

Medical Subject Headings (MeSH)

*Phytotherapy; Plant Bark [chemistry]; Plant Extracts [therapeutic use]; Prostatic Hyperplasia [*drug therapy]; Randomized Controlled Trials as Topic; Urination Disorders [drug therapy]

MeSH check words

Humans; Male