REVIEW

Pygeum africanum for the Treatment of Patients with Benign Prostatic Hyperplasia: A Systematic Review and Quantitative Meta-analysis

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PURPOSE: To conduct a systematic review and quantitative meta-analysis of the therapeutic efficacy and tolerability of *Pygeum africanum* in men with symptomatic benign prostatic hyperplasia.

METHODS: Studies were identified through the search of Medline (1966 to 2000), 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 benign prostatic hyperplasia, the intervention was a preparation of *P. africanum* alone or in combination with other phytotherapeutic agents, a control group received placebo or other pharmacologic therapies for benign prostatic hyperplasia, and treatment duration was at least 30 days. Two investigators independently extracted key data on design features, subject characteristics, and therapy allocation.

RESULTS: A total of 18 randomized controlled trials involving 1,562 men met the inclusion criteria and were analyzed. Many studies did not report results in a method that permitted meta-analysis. Only 1 of the studies reported a method of treatment allocation concealment, although 17 were double-blinded. The mean study duration was 64 days (range 30 to 122). Compared with placebo in 6 studies, *P. 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]). Summary estimates of individual outcomes were also improved by *P. africanum*. Men were more than twice as likely to report an improvement in overall symptoms (risk ratio = 2.1, 95% CI: 1.40 to 3.1). Nocturia was reduced by 19% and residual urine volume by 24%; peak urine flow was increased by 23%. Adverse effects due to *P. africanum* were mild and similar to placebo. The overall dropout rate was 12% and was similar for *P. africanum* (13%), placebo (11%), and other controls (8%; $P = 0.4$ versus placebo and $P = 0.5$ versus other controls).

CONCLUSIONS: The literature on *P. africanum* for the treatment of benign prostatic hyperplasia is limited by the short duration of studies and the variability in study design, the use of phytotherapeutic preparations, and the types of reported outcomes. However, the evidence suggests that *P. africanum* modestly, but significantly, improves urologic symptoms and flow measures. Further research is needed using standardized preparations of *P. africanum* to determine its long-term effectiveness and ability to prevent complications associated with benign prostatic hyperplasia. **Am J Med. 2000;109:654–664.** ©2000 by Excerpta Medica, Inc.

Symptomatic benign prostatic hyperplasia is a common medical problem in older men. As many as 40% of men aged 60 years or older have lower urinary tract symptoms consistent with bladder outlet obstruction (1,2). Treatment goals in the vast majority of men are to relieve bothersome symptoms that reduce quality of life. In the United States, treatment for benign prostatic hyperplasia costs more than $2 billion per year and accounts for 1.7 million physician office visits annually (3,4).

Medicinal herbs, or phytotherapy, have been used extensively for benign prostatic hyperplasia in Europe and are being used more commonly in the United States (5,6). Sales of herbal medicine reached $4 billion in the United States in 1998, and sales of saw palmetto extract for treatment of symptoms attributable to benign prostatic hyperplasia exceeded $20 million, making it the seventh most commonly purchased medicinal herbal preparation (7,8). A recent survey demonstrated that one third of men choosing nonsurgical therapy for benign prostatic hyperplasia were using herbal preparations alone or in combination with prescription medications (9). There is emerging evidence that several plant extracts are well tolerated and provide at least short-term improvement in urologic symptoms and flow (10,11).

Pygeum africanum, an extract from the bark of the African prune tree, has been used in Europe since 1969 to treat men with mild-to-moderate symptoms of benign

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Manuscript submitted April 19, 2000, and accepted in revised form July 31, 2000.

0002-9343/00/$–see front matter
PII S0002-9343(00)00604-5

prostatic hyperplasia. The mechanism of action of *P. africanum* is not known. In animal models, *P. africanum* modulates bladder contractility, has anti-inflammatory activity, decreases production of leukotrienes and other 5-lipoxygenase metabolites, inhibits fibroblast production, affects adrenal androgens, and restores the secretory activity of prostate epithelium (12–16). Despite the widespread use of *P. africanum*, its effectiveness and tolerability are uncertain. A previous qualitative summary did not meet the criteria for a systematic review (17); it included results from open-labeled uncontrolled studies, did not assess study quality or conduct a quantitative meta-analysis to estimate the magnitude or statistical significance of treatment efficacy, and was sponsored by a manufacturer of *P. africanum* extract (18). Furthermore, since its publication, additional randomized controlled trials of *P. africanum* have been reported.

We conducted a systematic review including a quantitative meta-analysis, when possible, of the evidence from randomized controlled trials to determine the therapeutic efficacy and tolerability of *P. africanum* (Tadenan, Laboratories DEBAT, Garches, France; Docosonal, Pigenil, Inverni della Beffa, Milan, Italy), alone or in combination with other herbal agents, for men with symptomatic benign prostatic hyperplasia.

METHODS

Inclusion Criteria

Studies were included if they met the following criteria: men had symptomatic benign prostatic hyperplasia, the intervention contained *P. africanum* alone or in combination with other herbal agents, the control group received either placebo or active pharmacologic therapy, the treatment duration was at least 30 days, and the participants were randomly assigned to treatment or control groups.

Identification of Relevant Trials

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 (19). A search of Embase from 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 Extraction and Study Appraisal

Two investigators (AI and RM) independently determined if identified studies met inclusion criteria. The following data were extracted from each included study: study characteristics, demographic characteristics of patients, enrollment criteria, outcomes, adverse effects, and number and reasons for dropout. Missing or additional information was sought from authors and sponsors. Included and excluded studies as well as extracted data were reviewed; discrepancies were resolved by discussion and consensus.

Study quality was assessed on a 1 (worst) to 3 (best) scale (20). A score of 1 was assigned to trials in which concealment was inadequate (eg, alteration or reference to case record numbers or to dates of birth); a score of 2 was assigned to 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 a score of 3 was assigned to trials that were deemed to have adequate measures to conceal allocations (eg, central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes that contained elements convincing of concealment). Additionally, we assessed whether study participants and investigators were blinded to the treatment provided and whether results varied according to exclusion of trials in which more then 20% of patients were lost to follow-up (17).

Statistical Methods

Because no common outcome measure was available from all 18 studies, we used two methods for combining data. One method assessed 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 (21); we used this method when trials reported different outcome measures of effectiveness (eg, symptom scale scores, nocturia, or peak urine flow). In the second method, we calculated a summary measure for individual outcomes including studies that provided similar outcome measures, using standard meta-analytic techniques as described below.

For determining effect size, we used the outcome that was determined a priori to be most clinically important (symptom scale score >nocturia >peak urine flow >residual urine volume). One outcome from each study was then transformed into units of standard deviations, giving a comparable effect size for each study. The study-specific overall effect size was the difference in mean outcome for the *P. africanum* and placebo groups, divided by the pooled standard deviation of the outcome measure. The summary effect size among 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 study using standard meta-analytic methodology

(22). We used the same definition of standardized effect sizes to look at continuous outcomes when available (eg, 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 was used, with 0.8 indicating a large effect, 0.5 indicating a moderate effect, and 0.2 indicating a small effect (23).

Additional meta-analyses considered the difference between *P. africanum* treatment and the control treatment in the mean change from baseline to end of follow-up for each 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 follow-up, based on the correlation between outcomes (24,25). Analyses were conducted for three different assumed values for this correlation (0.25, 0.50, and 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. There were no qualitative differences between the meta-analysis results for the three assumed correlation values; we present the results for the assumed correlation of 0.50. For categorical outcome measures, weighted relative risks (RR) and 95% confidence intervals (CI) were calculated using standard meta-analytic techniques (25).

For individual outcomes, we also calculated a summary measure using studies that provided similar outcome measures. For continuous variables reported in a similar fashion, weighted mean differences and their 95% CI were calculated using RevMan 4.04 software (Update Software, Oxford, England). For categorical variables, weighted risk ratios and 95% CI were calculated.

Chi-square tests were used for analysis of bivariate comparisons (adverse events and dropouts) using simple pooling of data. To assess the proportion of patients having improvement in urologic symptoms, a modified intention-to-treat analysis was performed (ie, men who dropped out or were lost to follow-up were considered to have had worsening symptoms) (26). The denominator for the modified intention-to-treat analysis included the number randomly assigned to treatment at baseline, and the numerator included the number who completed the trial and showed improvement. A test for heterogeneity was calculated according to standard formulas (21,22), and a random effects model was used for all summary estimates.

RESULTS

The combined search strategies identified 31 trials; 18 met inclusion criteria. None were conducted in the United States, and 13 were reported in a non-English language (German [n = 1], Italian [n = 10], French [n = 2]). Fourteen trials were excluded because they did not include a control group (27–40). The majority of studies (n = 11) examined *P. africanum* alone versus placebo alone (41–51). Two trials compared *P. africanum* with an anti-inflammatory drug (52,53). One study that compared *P. africanum* with placebo included an additional treatment arm of *P. africanum* in combination with a corticosteroid (54). Two studies compared *P. africanum* alone with one or more herbal agents and versus placebo (55,56), 1 trial compared *P. africanum* with another herbal agent (57), 1 trial compared different daily dosage forms of *P. africanum* (58), and 1 trial compared two different doses of *P. africanum* in combination with another herbal extract (59) (Table 1). None of the "active comparison" arms have been demonstrated to be effective in treating symptomatic benign prostatic hyperplasia.

A total of 1,562 participants were enrolled in the 18 trials. The mean treatment duration was 61 ± 21 days (range 30 to 122 days). Only 1 of the studies reported a method for concealment of treatment allocation (score = 2), but 17 of the 18 studies were double-blind. The majority of the studies (n = 14, participants = 1,103) used a standardized extract of *P. africanum*. The doses of *P. africanum* ranged between 75 and 200 mg per day. Of the placebo-controlled trials, 1 used a dose of *P. africanum* of 75 mg per day, 7 used a dose of 100 mg per day, 4 used a dose of 200 mg per day, and 1 did not report the dosage (55).

Most studies did not provide baseline patient information. There was no information on patient race, comorbid conditions, prostate size, or standardized or validated urologic symptom scale scores. For studies that did provide baseline data, results did not vary between treatment arms and were consistent with moderate benign prostatic hyperplasia. The mean age was 66 ± 7 years (range 42 to 89; 9 studies, n = 845); nocturia = 3.0 ± 0.7 times per evening (4 studies, n = 413); peak urine flow = 12 ± 4 mL/sec (5 studies, n = 416); residual urine volume = 40 ± 26 mL (2 studies, n = 284).

Table 2 shows the outcome data for nocturia, peak urine flow, residual volume, and overall symptoms. Not all studies could be pooled because of differences in reporting methods. Of the 13 trials of *P. africanum* versus placebo, 12 reported a beneficial effect of *P. africanum* on at least one measure of effectiveness (overall symptoms, nocturia, peak urine flow, or residual volume). Only 1 trial found no difference between *P. africanum* and placebo (48). That trial assessed the effect of *P. africanum* on nocturia, peak urine flow, and overall symptom change in 20 men during 12 weeks. None of the trials found that *P. africanum* was worse than placebo or "active control."

Table 1. Description of Randomized Trials of *Pygeum africanum* Extract in Men with Benign Prostatic Hyperplasia

Reference	Drug or Control (mg/d)	Number of Subjects (Number of Dropouts)	Description of Subjects	Study Duration	Double-Blind	Quality of Allocation Concealment*
Barlet (41)	Tadenan 100 mg Placebo	131 (5) 132 (3)	European men with symptomatic BPH. Age range 50–85 years	0 days	yes	unclear
Barth (56)	Docosonal 100 mg vs. Placebo Docosonal 100 mg vs. Sitosterin 30 mg Docosonal 100 mg vs. ERU 300 mg†	50 (27) 46 (16) 37 (10) 34 (8) 24 (1) 24 (5)	European men with symptomatic BPH. Age >50 years.	8 weeks	yes	unclear
Bassi (44)	Pigenil 100 mg Placebo	20 (0) 20 (0)	Italian men with symptomatic BPH. Mean age 67 years.	60 days	yes	unclear
Blitz (45)	Tadenan 100 mg Placebo	30 (0) 27 (0)	French men with symptomatic BPH.	6 weeks	yes	unclear
Bongi (42)	Tadenan 75 mg Placebo	25 (0) 25 (0)	Italian men with symptomatic BPH; residual volume ≤200 mL. Age range 49–84 years.	60 days	yes	block randomization
Chatelain (58)	Tadenan 50 mg bid Tadenan 100 mg	101‡ 108	French men with symptomatic BPH, age >50 years; IPSS ≥10; PUF <15 mL/s; residual volume ≤150 mL. Mean age 66 years.	2 months	yes	unclear
Donkervoort (47)	Tadenan 100 mg Placebo	10 (2) 10 (2)	Dutch men with symptomatic BPH.	12 weeks	yes	unclear
Dufour (46)	Tadenan 100 mg Placebo	60 (28) 60 (28)	French men with symptomatic BPH, not in need of surgery.	6 weeks	yes	unclear
Dutkiewicz (57)	Tadenan 2 tablets BID Cernilton 1 tablet TID	38 (0) 51 (0)	Polish men with symptomatic BPH, Age range 50–68 years.	4 months	no	unclear
Frasseto (48)	Tadenan 200 mg Placebo	10 (0) 10 (0)	Italian men with symptomatic BPH. Age range 51–89 years.	60 days	yes	unclear
Gagliardi (53)	Tadenan 100 mg Anti-inflammatory (not identified)	20 (0) 20 (1)	Italian men with symptomatic BPH. Age range 50–84 years.	30 days	yes	unclear
Giacobini (54)	Tadenan 200 mg Tadenan + Farlutal§ Placebo	7 (0) 7 (0) 7 (0)	Italian men with symptomatic BPH. Age range 48–70 years.	90 days	yes	unclear
Krzeski (59)	Pa 25 mg + Ud 300 mg¶ Half dose	67 (13) 67 (6)	Polish men with symptomatic BPH (≥1 symptom). Age range 53–84 years.	8 weeks	yes	unclear
Mandressi (55)	*Pygeum africanum* Placebo Permixon**	20 (1) 20 (0) 20 (0)	Italian men with symptomatic BPH. Age range 50–80.	30 days	yes	unclear
Maver (51)	Tadenan 100 mg Placebo	30 (0) 30 (0)	Italian men with symptomatic BPH. Age range 55–85 years.	60 days	yes	unclear
Ranno (50)	Tadenan 100 mg Placebo	20 (0) 19 (0)	Italian men with symptomatic BPH. Mean age 70 years.	2 months	yes	unclear
Rigatti (52)	Tadenan 100 mg NSAID	24 (0) 25 (0)	Italian men with symptomatic BPH.	2 months	yes	unclear
Rizzo (49)	Tadenan 200 mg Placebo	20 (0) 20 (0)	Italian men with symptomatic BPH. Age range 42–74 years.	60 days	yes	unclear

* Quality of treatment allocation concealment for randomization scheme.
† Extract of *Rad. urticae.*
‡ Of 235 men who were enrolled, 223 completed the comparative phase but only 209 men had data for a per-protocol analysis.
§ Farlutal = medroxyprogesterone acetate.
¶ *Pygeum africanum* + *Urtica dioica.*
** Permixon = extract of *Serenoa repens.*
BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score; NSAID = nonsteroidal anti-inflammatory drug; PUF = peak urine flow.

Table 2. Results of Randomized Trials of *Pygeum africanum* Extract

Reference	Drug/Control(s)	Improvement in Nocturia	Improvement in Peak Urine Flow	Improvement in Residual Volume	Improvement in Overall Symptoms	Effect Size* (95% Confidence Interval)
Barlet (41)	Tadenan	31%	17%	25%	65% (patients/physicians)	−0.18 (−0.32 to −0.04)
	Placebo	19% ($P = 0.007$)	4% ($P = 0.02$)	−4% ($P = 0.02$)	41% pts/31% phys ($P < 0.001$)	
Barth (56)	Docosonal vs.	Both reduced	8%	48%	NA	NA
	Placebo	"almost to normal"	10%	37%		
	Docosonal vs.	Reduced	18%	29%		
	Sitosterin	>control	15%	−17%		
	Docosonal vs.	Reduced	15%	30%		
	ERU†	>control	4%	−14%		
Bassi (44)	Pigenil	75%	Improvement vs.	NA	NA	NA
	Placebo	10% ($P < 0.001$)	placebo ($P < 0.05$)			
Blitz (45)	Tadenan	NA	NA	NA	77%	NA
	Placebo				44% ($P = 0.02$)	
Bongi (42)	Tadenan	59%	NA	29%	88% rating good	−1.65 (−1.92 to −1.38)
	Placebo	17% ($P < 0.01$)		7% ($P < 0.01$)	12% rating good	
Chatelain (58)	Tadenan	NA	16%	No significant	43 (IPSS)	NA
	Tadenan		19%	difference	41%	
Donkervoort (47)	Tadenan	38%	No benefit	NA	No benefit	NA
	Placebo	38%				
Dufour (46)	Tadenan	79%	NA	NA	NA	NA
	Placebo	50% ($P < 0.01$)				
Dutkiewicz (57)	Tadenan	NA	11%	22%	46%(O)/40%(I)	NA
	Cernilton		20%	48%	63%(O)/68%(I)	
Frasseto (48)	Tadenan	57%	NA	NA	NA	NA
	Placebo	19%				
Gagliardi (53)	Tadenan	60%	NA	71%	NA	NA
	Anti-inflammatory	0% ($P < 0.01$)		11% ($P < 0.01$)		
Giacobini (54)	Tadenan	NA	28%	68%	NA	−0.66 (−1.51 to 0.19)
	Tadenan + Farlutal		39%	22%		
	Placebo		16%	0%		
Krzeski (59)	Pa + *Urtica dioica* (full dose)	"Reduced	"Reduced	"Reduced significantly	"No between group	NA
	Pa + *Urtica dioica* (half dose)	significantly in both groups"	significantly in both groups"	in both groups"	differences in efficacy"	

Table 2. Continued

Reference	Drug/Control(s)	Improvement in Nocturia	Improvement in Peak Urine Flow	Improvement in Residual Volume	Improvement in Overall Symptoms	Effect Size* (95% Confidence Interval)
Mandressi (55)	*P. africanum*	38%	NA	−4%	60%	−0.64 (−1.25 to 0.03)
	Placebo	−4%		0%	40% (Per vs. pbo, NS)	
	Permixon	42%		10%	90% (Per vs. Pa, 0.05)	
Maver (51)	Tadenan	47%	NA	23%	NA	−1.34 (−2.23 to −0.45)
	Placebo	10% (P <0.01)		0% (P <0.01)		
Ranno (50)	Tadenan	56%	91%	NA	NA	NA
	Placebo	20%‡	4% (P <0.01)			
Rigatti (52)	Tadenan	NA	NA	75%	NA	NA
	NSAID			56% (P <0.05)		
Rizzo (49)	Tadenan	86%	55%	45%	NA	−1.80 (−2.80 to −1.52)
	Placebo	−7% (P <0.01)	13%‡	−3%‡		

* Effect size defined as difference in mean outcome between *P. africanum* and control group, divided by the pooled SD of the outcome measure.

† Extract of *Rad. urticae*.

‡ Reported as not significant.

I = irritative symptom score; IPSS = International Prostate Symptom Score; NSAID = nonsteroidal anti-inflammatory drug; O = obstructive symptom score; Per = Permixon; Pbo = placebo; Pa = *P. africanum*.

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. All involved *P. africanum* alone versus placebo, and 5 used a standardized preparation of *P. africanum*. The overall summary effect size was −0.8 SD (95% CI: −1.4 to −0.3), indicating a large and statistically significant improvement with *P. africanum* (Figure 1). The summary effect size from 3 studies that provided data on nocturia was −0.8 SD (95% CI: −1.4 to −0.1). This indicates that *P. africanum* resulted in a moderate-to-large improvement in nocturia that was statistically significant. Summary results from the 4 studies providing data on peak urine flow demonstrated a mean effect size of 0.7 SD (95% CI: 0.0 to 1.3), indicating a moderate effect on peak urine flow.

Urinary Symptoms and Flow Measures

Consistent with the results seen in the summary effect sizes, *P. africanum* improved specific urinary symptoms and flow measures. In 6 double-blind trials involving 430 participants, men receiving *P. africanum* were more than twice as likely to be rated by their physician as having overall improvement in symptoms compared with men taking placebo (65% versus 30%, RR = 2.1, 95% CI: 1.4 to 3.1; Figure 2). *P. africanum* reduced nocturia compared with placebo by 19% (weighted mean difference = −0.9 times per evening, 3 studies, n = 325), although this did not reach statistical significance (95% CI: −2.0 to 0.1; Figure 3). *P. africanum* also increased peak urine flow compared with placebo by 23% (weighted mean difference = 2 mL/sec, 95% CI: 0.3 to 4.7, 4 studies, n = 363; Figure 4). Additionally, *P. africanum* reduced residual urine volume by 24% (weighted mean difference = −13 mL, 95% CI: −23 to 3, 2 studies, n = 264).

To assess for publication bias, we constructed funnel plots from published trials providing data for calculation of summary effect size (Figure 5), overall symptom improvement (n = 5), nocturia, and peak urine flow. 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 among *P. africanum* (13%), placebo (11%), and other controls (8%; P = 0.4 versus placebo and P = 0.5 versus other controls). Three studies (2 placebo-controlled) had dropout rates >20%. The reasons for the high dropout rate were not reported, but 2 of the trials (57,59) indicated that adverse effects were "infrequent and mild" in

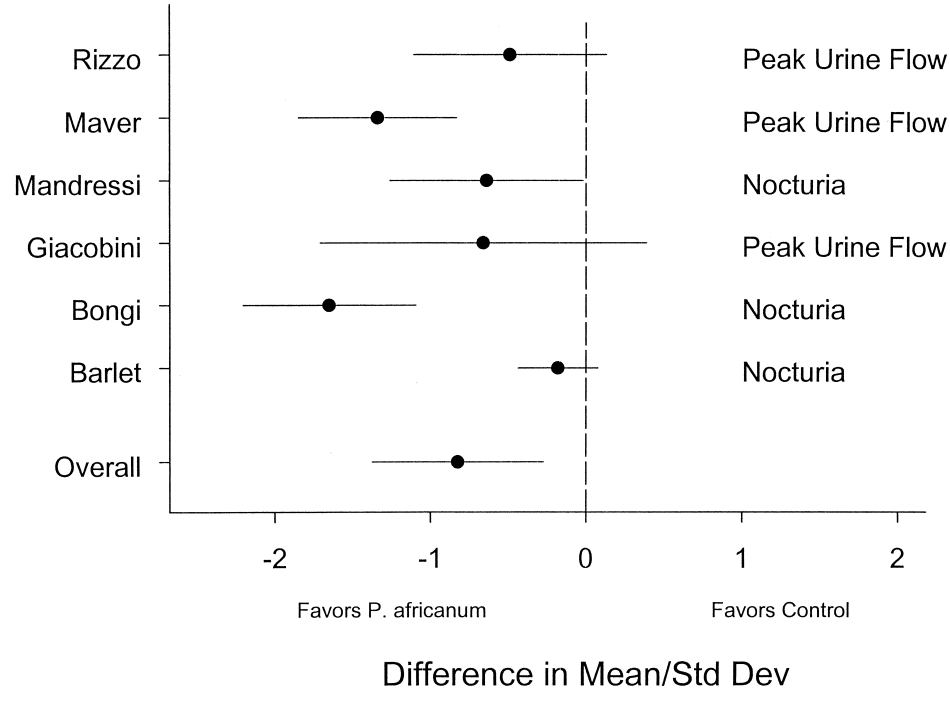

Figure 1. Efficacy of *Pygeum africanum* on overall summary effect size. Overall effect size is the difference between the mean outcome in *P. africanum* and placebo groups divided by the pooled SD. **Dots** represent point estimates. **Horizontal lines** denote 95% confidence intervals. The outcomes used to calculate the study specific and overall effect size are included. Effect sizes <0 favor *P. africanum*.

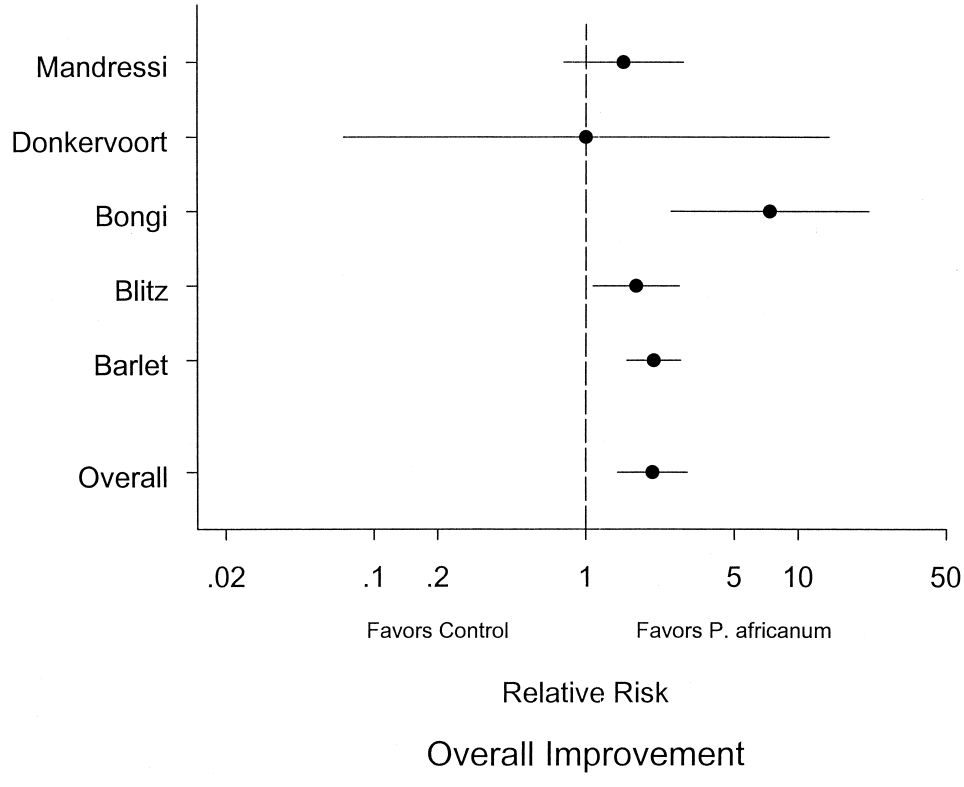

Figure 2. Effect of *Pygeum africanum* on overall urinary symptoms as assessed by the physician. **Dots** represent point estimates. **Horizontal lines** denote 95% confidence intervals. A relative risk >1 indicates greater likelihood of having improved urinary symptoms and favors *P. africanum*.

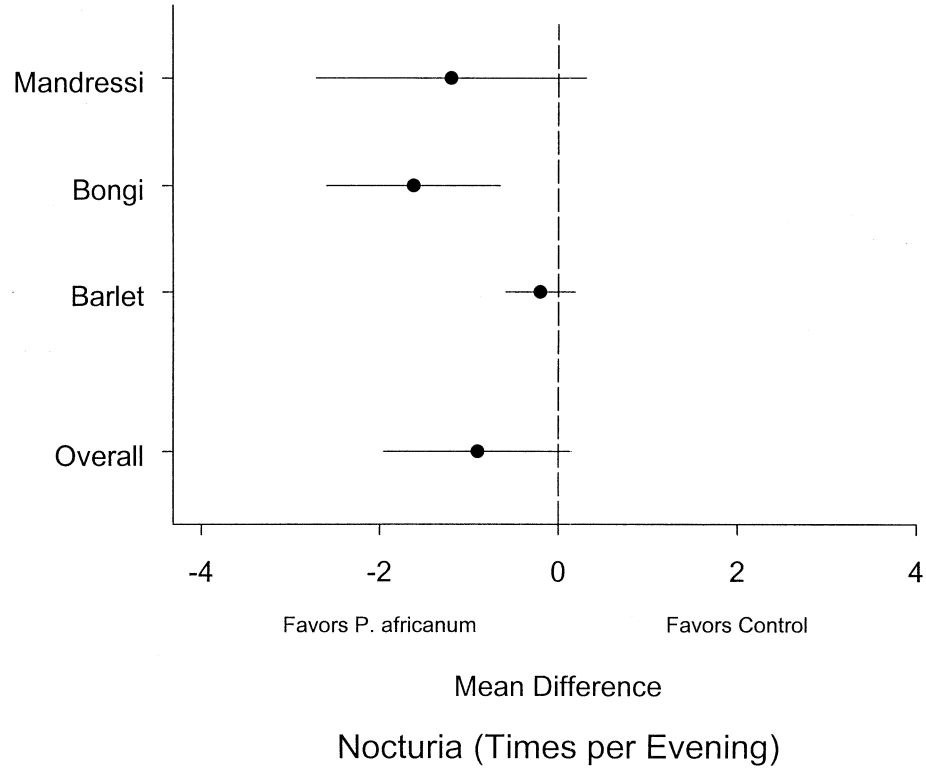

Figure 3. Effect of *Pygeum africanum* on nocturia. **Dots** represent point estimates. **Horizontal lines** denote 95% confidence intervals. A mean difference <0 indicates reduced nocturia and favors *P. africanum*.

participants who completed the trial. None of these 3 trials reported outcome data in a method suitable for incorporation into the effect size analyses. Thirteen of the 18 studies provided information on specific adverse events. Adverse events due to *P. africanum* were generally mild in nature and similar in frequency to placebo. The most frequently reported adverse events were gastrointestinal and occurred among 7 men in 5 trials.

DISCUSSION

This systematic review summarizes the available evidence from randomized controlled trials about the efficacy and tolerability of *P. africanum* for the treatment of lower-urinary-tract symptoms attributable to benign prostatic hyperplasia. Our results suggest that *P. africanum* improves urinary symptoms and flow, 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 *P. africanum* was based on units of SD available from 6 studies involving 474 participants. This method is useful for determining if there is an overall benefit, 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.

Summary risk ratios and weighted mean differences comparing *P. africanum* with placebo for overall symptoms, peak urine flow, and residual urine volume demonstrated a statistically significant improvement as well as a trend toward improvement for nocturia. These findings are considered clinically meaningful, similar to other widely used treatment options, and consistent with the results obtained using effect sizes. Furthermore, the results from individual trials demonstrated that all but one study noted that *P. africanum* improved symptoms attributable to benign prostatic hyperplasia. Additionally, *P. africanum* was well tolerated.

Our results should be viewed with caution. Most of the 18 trials did not provide clinically relevant baseline and outcome data in a standardized fashion. None were conducted in the United States, and many studies did not report means and standard deviations, making completion of a quantitative review difficult. No placebo-controlled studies used standardized, validated symptom scales, the outcome measure of greatest clinical significance. All studies were of short duration, with none having a follow-up longer than 4 months. There was no information provided to determine if *P. africanum* prevented long-term complications of benign prostatic hyperplasia, such as acute urinary retention, renal insufficiency, or the need for surgical intervention. Finally, no studies compared *P. africanum* with medical interven-

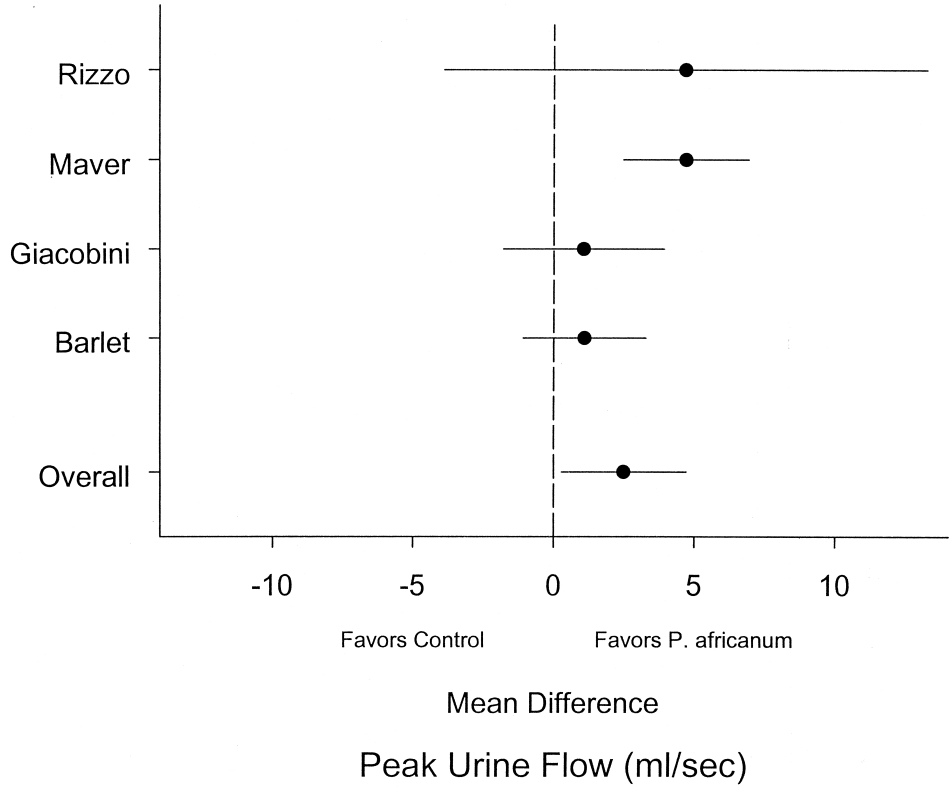

Figure 4. Effect of *Pygeum africanum* on peak urine flow. **Dots** represent point estimates. **Horizontal lines** denote 95% confidence intervals. A mean difference >0 indicates increased peak urine flow and favors *P. africanum*.

tions of demonstrated effectiveness, such as alpha-adrenergic blockers and 5-alpha-reductase inhibitors. The "active controls" used in the studies have not been demonstrated to have beneficial effects.

Although the studies used different quantities, dosing intervals, and preparations of *P. africanum*, the majority of studies used a standardized extract of *P. africanum* at a dose of 100 to 200 mg per day. Five of the 6 studies providing data for summary estimates of effect size used the standardized extract of *P. africanum*. All summary efficacy data were derived from placebo-controlled, double-blind studies utilizing a "noncombination" source of *P. africanum*. This suggests that a standardized preparation of *P. africanum* is associated with the observed improvement in symptoms and flow measures.

A possible source of bias is that outcomes included in the effect size calculation could have been selected to favor *P. africanum*. However, we ranked outcome measures for inclusion in the effect size calculation before data abstraction and analysis. Furthermore, effectiveness was observed in all but 1 of the studies, regardless of whether the results were reported as physicians' rating of patient's global symptom improvement (n = 6 trials, 430 participants); 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. We constructed funnel plots to assess for publication bias but only a few studies could be included in this plot.

The cost of *P. africanum* is similar to that of other pharmacologic therapies. A 90-day supply of *P. africanum* (100 mg per day) costs approximately $90. The pharmacy charges for a 90-day supply of finasteride (5 mg per day) is approximately $200; for terazosin (5 mg per day), the charge is approximately $200 and $120. According to the *2000 Red Book of Average Wholesale Prices*, the cost for generic prazosin (5 mg) is about $54. Additional studies comparing standardized preparations of *P. africanum* with both placebo and standard medical therapy are required before its use in treating benign prostatic hyperplasia is determined. Future trials should be of sufficient duration and size to detect clinically important differences in urinary symptoms using validated symptom scale scores. Large trials will also be able to delineate adverse affects associated with *P. africanum*.

The Committee on Other Medical Therapies of the Fourth International Consultation on benign prostatic hyperplasia concluded that most plant extract preparations have different components, that it is not known what mechanisms of action demonstrated in vitro might

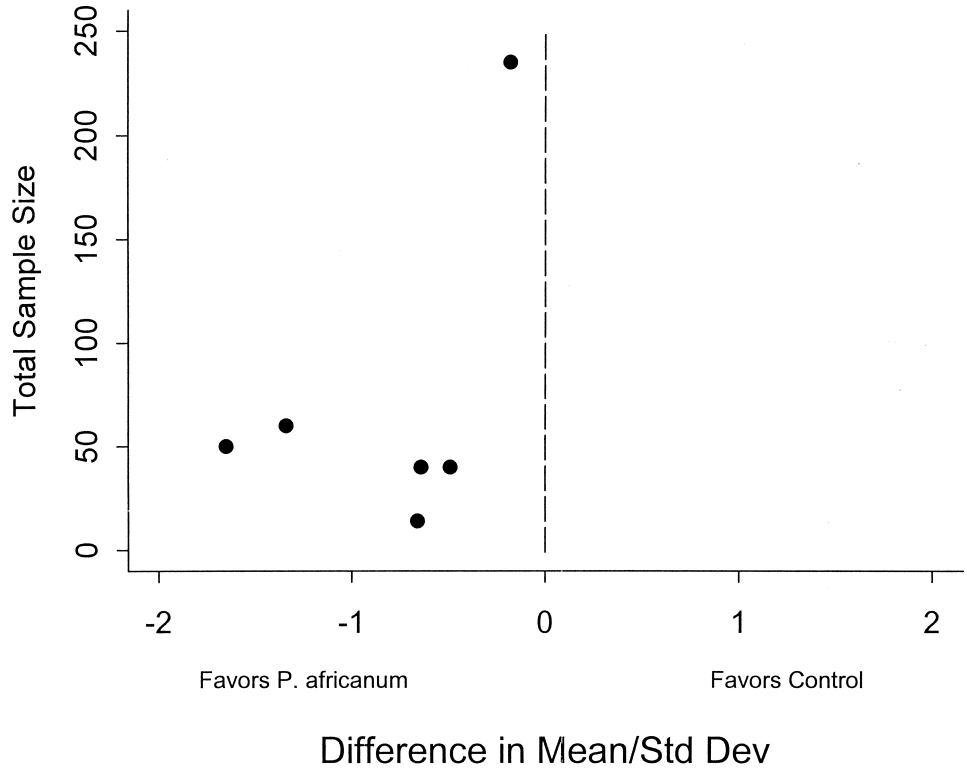

Figure 5. Funnel plot of the 6 randomized controlled trials used to calculate the summary effect size plotted against sample size. Effect size is the difference between the mean outcome in *Pygeum africanum* and placebo groups divided by the pooled SD.

be responsible for clinical effects, that short-term randomized studies suggest clinical efficacy for some preparations, and that studies were usually inadequate due to their methodology, small numbers, and short duration. They recommended the completion of additional high-quality studies of long duration to evaluate the efficacy and safety of phytotherapeutic products for the treatment of benign prostatic hyperplasia (60). Until completion of additional high-quality trials, this systematic review suggests that *P. africanum* is effective in men with symptomatic benign prostatic hyperplasia. This benefit is of modest size and appears to be clinically meaningful. *P. africanum* is well tolerated and costs less than most prescription medications. A standardized preparation of *P. africanum* may be a useful treatment option, at least in the short term, for men with urinary symptoms consistent with benign prostatic hyperplasia.

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