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Saw Palmetto for Benign Prostatic Hyperplasia

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ABSTRACT

BACKGROUND

Saw palmetto is used by over 2 million men in the United States for the treatment of benign prostatic hyperplasia and is commonly recommended as an alternative to drugs approved by the Food and Drug Administration.

METHODS

In this double-blind trial, we randomly assigned 225 men over the age of 49 years who had moderate-to-severe symptoms of benign prostatic hyperplasia to one year of treatment with saw palmetto extract (160 mg twice a day) or placebo. The primary outcome measures were changes in the scores on the American Urological Association Symptom Index (AUASI) and the maximal urinary flow rate. Secondary outcome measures included changes in prostate size, residual urinary volume after voiding, quality of life, laboratory values, and the rate of reported adverse effects.

RESULTS

There was no significant difference between the saw palmetto and placebo groups in the change in AUASI scores (mean difference, 0.04 point; 95 percent confidence interval, -0.93 to 1.01), maximal urinary flow rate (mean difference, 0.43 ml per minute; 95 percent confidence interval, -0.52 to 1.38), prostate size, residual volume after voiding, quality of life, or serum prostate-specific antigen levels during the one-year study. The incidence of side effects was similar in the two groups.

CONCLUSIONS

In this study, saw palmetto did not improve symptoms or objective measures of benign prostatic hyperplasia. (ClinicalTrials.gov number, NCT00037154.)

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EXTRACTS OF THE SAW PALMETTO BERRY are widely used for the treatment of benign prostatic hyperplasia, often as an alternative to pharmaceutical agents. In a national survey conducted in 2002, 1.1 percent of the adult population in the United States, or approximately 2.5 million adults, reported using saw palmetto.¹ The herb is widely used in Europe, where half of German urologists prefer prescribing plant-based extracts to synthetic drugs.² Although most prior randomized trials of saw palmetto have reported small improvements in the symptoms of benign prostatic hyperplasia or in urinary flow rates, these studies are limited by the small numbers of subjects enrolled, their short duration, their failure to use standard outcome measures, and the lack of information from participants concerning how effectively the placebo was blinded.³⁻²⁰ Using widely accepted outcome measures and a matched placebo capsule, we conducted a randomized, double-blind trial to determine the efficacy of saw palmetto for the treatment of benign prostatic hyperplasia.

METHODS

PARTICIPANTS

The study protocol and all procedures were approved by the committee on human research at the University of California, San Francisco, and the Kaiser Foundation Research Institute, Oakland, California. The study took place between July 2001 and May 2004. All participants provided written informed consent. Men over the age of 49 years who had moderate-to-severe symptoms of benign prostatic hyperplasia, as defined by a score on the American Urological Association Symptom Index (AUASI) of at least 8 and a peak urinary flow rate of less than 15 ml per second, were recruited from the San Francisco Veterans Affairs Medical Center, Kaiser Permanente Northern California, and the surrounding community by direct mailings to patients, letters to primary care providers, posters, and newspaper and local radio advertisements. All potential participants were screened by means of a telephone interview to identify exclusion criteria. Men who passed the screening interview were asked to come for a clinic visit; those who declined or did not appear at the clinic were classified as having declined to participate. Men were ineligible if they were at

high risk for urinary retention (defined by a peak urinary flow rate of less than 4 ml per second or a residual volume of more than 250 ml after voiding); had a history of prostate cancer, surgery for benign prostatic hyperplasia, urethral stricture, or neurogenic bladder; had a creatinine level of more than 2.0 mg per deciliter (177 μ mol per liter); had a prostate-specific antigen (PSA) level of more than 4.0 ng per deciliter; were using medications known to affect urination; or had a severe concomitant disease. Patients were eligible to participate if they had stopped taking an alpha-blocker at least one month before randomization or discontinued taking saw palmetto or a 5 α -reductase inhibitor six months before randomization. All potentially eligible participants were assigned to a one-month, single-blind, placebo run-in period and were excluded if their rate of adherence was less than 75 percent, as measured by a capsule count.

INTERVENTION

Eligible patients were randomly assigned to receive a saw palmetto extract, 160 mg twice daily, or a similar-appearing placebo in soft brown gelatin capsules. This regimen was selected because it had been used in the vast majority of prior clinical trials.²¹ An advisory committee chartered by the National Center for Complementary and Alternative Medicine (NCCAM) conducted a competitive process to select the saw palmetto product to be used in this trial, a proprietary carbon dioxide extract from Indena USA in a soft gelatin capsule furnished by Rexall-Sundown. The extract was manufactured in one batch to optimize product consistency. High-performance gas chromatography of samples of the extract revealed that it contained 92.1 percent total fatty acids just before the initiation of the study; a subsequent analysis at the midpoint of the study revealed that the extract contained 90.7 percent total fatty acids and 0.33 percent total sterols. Placebo capsules contained polyethylene glycol-400, a bitter-tasting liquid with an oily appearance and no free fatty acids, and a brown coloring agent to produce a placebo with the appearance of saw palmetto. Patients were advised to take the study medication twice a day with meals and to bring all unused capsules to each study visit. Patients made eight visits to the study clinic over a period of 14 months, including 12 months of post-randomization follow-up.

OBJECTIVES AND OUTCOMES

The primary objectives of the study were to determine whether the daily use of saw palmetto extract reduces the symptoms of benign prostatic hyperplasia, as measured by the AUASI or objective measures of urinary obstruction (urinary flow rates), as compared with placebo. The AUASI is a validated seven-item, self-administered questionnaire that measures symptoms referable to urinary obstruction, with scores ranging from 0 to 35 according to symptom severity: scores of 0 to 7 indicate mild symptoms; scores of 8 to 19, moderate symptoms; and scores of 20 to 35, severe symptoms.²² Secondary objectives included an examination of changes in the quality of life specific to benign prostatic hyperplasia and overall quality of life (assessed by two self-administered questionnaires, the Benign Prostatic Hyperplasia [BPH] Impact Index²³ and the Medical Outcomes Study 36-Item Short-Form General Health Survey [SF-36²⁴]); prostate size, measured by transrectal ultrasonography; residual volume after voiding, measured by BladderScan (Diagnostic Ultrasound); self-reported side effects; and changes in levels of PSA, creatinine, testosterone, and other laboratory values. The SF-36 consists of 36 items, 35 of which are aggregated to evaluate eight dimensions of health: physical function, pain, general and mental health, vitality, social function, and physical and emotional health.

RANDOMIZATION

Participants who satisfied all eligibility criteria, including completion of the run-in period, underwent randomization in equal proportions to the saw palmetto and placebo groups. Randomization was stratified according to the category of AUASI score (moderate [8 to 19] vs. severe [20 to 35])²² and blocked with the use of randomly chosen even-numbered block sizes of less than 10 according to the `ralloc.ado` procedure in Stata, a software module used to design randomized, controlled trials.²⁵ The randomization list was created by personnel who were not associated with the study. The study medication was dispensed in numbered bottles (provided by the manufacturer), according to the randomization sequence. All study participants and all study personnel who administered interventions, assessed outcomes, or performed data analysis were unaware of the treatment assignment and the randomized sequence list.

STATISTICAL ANALYSIS

The study was designed to have a statistical power of 90 percent to detect a difference between groups of 3.0 in the AUASI score,²⁶ on the basis of a published standard deviation of 6.0 in the AUASI^{27,28} and a two-sided alpha value of 0.04 (set below 0.05 to allow for possible interim analyses). These calculations and values required the enrollment of 178 men, and the number was increased to a target enrollment of 224 to account for a potential dropout rate of up to 20 percent.

The primary efficacy analyses were the comparisons of the change over time in the AUASI scores and the peak urinary flow rate between the saw palmetto and placebo groups. We assessed the significance of these differences in changes in outcomes over time using linear mixed-effects models.²⁹ These models included random intercepts to accommodate the repeated measures gathered from each study participant as well as terms for the fixed effects of time, study group, and the interaction between time and study group, the effects of interest in our analyses. We assessed the functional form of the effect of time within each study group using likelihood-ratio tests and found that for most outcomes, linear time effects fit the data well. However, for the AUASI scores and testosterone levels, a model with quadratic time effects fit the data significantly better, and our models for these outcomes included these nonlinear effects of time. We specified the linear mixed-effects model analytic strategy, including the assessment of the functional form of the effect of time, before analyzing the study data. For each outcome, we present estimated treatment effects, which we calculated as the difference in the predicted change in the response over a period of 12 months between the two study groups. The linear mixed-effects model analyses provide these estimates along with associated standard errors, which were used to construct 95 percent confidence intervals for treatment effects. We fit the linear mixed-effects model using the XTREG procedure in Stata software (version 8.0).³⁰ The overall differences in the total response curves between the two groups were tested with likelihood-ratio tests. The data and safety monitoring board (composed of experts selected by the National Institutes of Health who were not affiliated with the study) elected not to perform interim analyses of efficacy.

Baseline variables were compared between

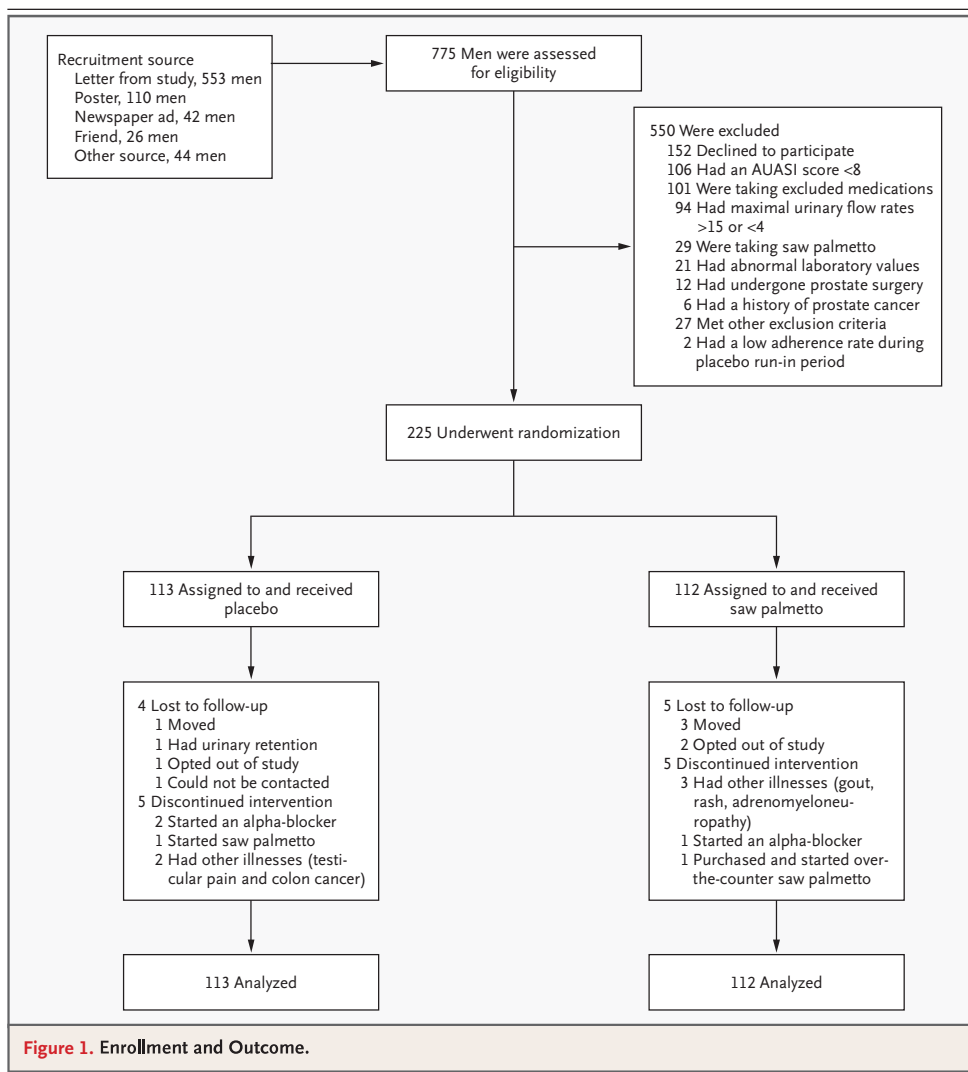


Figure 1. Enrollment and Outcome.

groups with the use of Student's t-test for continuous variables and chi-square tests for categorical variables. All analyses were conducted according to the intention-to-treat principle, so that all data obtained from men who did not complete the study were included in the final analyses. All reported P values are two-sided and have not been adjusted for multiple testing.³¹

Three subgroup analyses were planned a priori on the basis of baseline data: an examination of changes in the primary outcome measures among men with moderate symptoms as compared with men with severe symptoms, men with a high

prostate volume as compared with those with a low prostate volume (dichotomized at 40 ml),³² and men with high PSA levels as compared with men with low levels (dichotomized at 1.4 ng per deciliter).³²

The funding organizations (the National Institute of Diabetes and Digestive and Kidney Diseases and the National Center for Complementary and Alternative Medicine) and the supplier of saw palmetto had no role in the design or conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation, review, and approval of the manuscript.

Table 1. Baseline Characteristics of 225 Men with Benign Prostatic Hyperplasia.*

Characteristic	All Men (N=225)	Saw Palmetto (N=112)	Placebo (N=113)
Age — yr	63.0±7.7	62.9±8.0	63.0±7.4
Race or ethnic group — no. (%)			
White	183 (82)	94 (84)	89 (79)
Black	12 (5)	4 (4)	8 (7)
Asian or Pacific Islander	15 (7)	7 (6)	8 (7)
Hispanic	11 (5)	6 (5)	5 (4)
Other	3 (1)	1 (1)	2 (2)
Education — yr	16.5±3.5	16.5±3.3	16.6±3.6
AUASI score†	15.4±5.5	15.7±5.7	15.0±5.3
BPH Impact Index score‡	3.1±2.1	3.4±2.2	2.8±2.1
SF-36 score§			
Physical subscale	49.5±8.5	49.0±8.2	50.0±8.9
Mental subscale	52.9±7.9	52.5±7.8	53.3±8.0
Sexual function (O'Leary scale)¶	2.1±1.0	2.2±1.1	2.0±1.0
Prostate volume — ml	34.2±14.5	34.7±13.9	33.9±15.2
Prostate transitional-zone volume — ml	12.9±10.7	13.2±10.4	12.5±11.0
Maximal urinary flow rate — ml/sec	11.5±3.9	11.4±3.5	11.6±4.3
Residual volume after voiding — ml	82.3±58.2	80.0±51.9	84.5±63.8
PSA — ng/dl	1.7±1.4	1.8±1.4	1.6±1.4
Creatinine — mg/dl	1.0±0.17	1.0±0.16	1.0±0.18
Testosterone — ng/dl	374±135	375±128	373±142

* Plus-minus values are means ±SD. There were no significant differences in baseline characteristics between the groups except in the BPH Impact Index ($P=0.02$ by Wilcoxon's test). To convert creatinine values to micromoles per liter, multiply by 88.4. PSA denotes prostate-specific antigen. Race and ethnic group were self-reported.

† Scores on the AUASI can range from 0 (no symptoms) to 35 (severe symptoms).

‡ Scores on the BPH Impact Index can range from 0 (no symptoms) to 13 (severe symptoms).

§ Scores on the SF-36 can range from 0 to 100; higher scores indicate a better quality of life.

¶ Overall scores on the O'Leary Scale of Sexual Function can range from 0 to 4, with higher scores indicating better function.

|| Prostate volume was measured by transrectal ultrasonography.

RESULTS

Of 775 men who were screened for eligibility, 225 satisfied all eligibility criteria and underwent randomization, 112 to saw palmetto and 113 to placebo, between July 2001 and May 2003. Figure 1 shows the source of recruitment for potential participants and reasons for exclusion. Five men in the saw palmetto group and four men in the placebo group were lost to follow-up, for a completion rate of 96 percent. An additional five men in each group discontinued the study medication but completed all outcome assessments. The adherence rate was high, with 92 percent of all

study medicine consumed and no significant difference in adherence between groups. The baseline characteristics of the treatment groups were similar, with the exception of the scores on the BPH Impact Index ($P=0.02$) (Table 1).

There was a small but significant decrease (improvement) in the AUASI score during the single-blind, placebo run-in period in both groups (mean change among all participants, -1.49 ; 95 percent confidence interval, -0.96 to -2.02) (Fig. 2). Both groups also had a small decrease in the AUASI score during the one-year study: the score decreased by 0.68 in the saw palmetto group (95 percent confidence interval, -1.37 to 0.01) and by

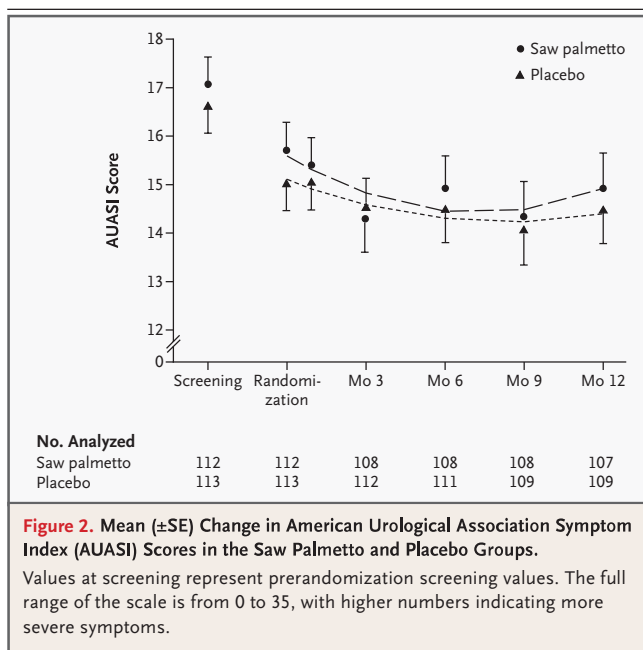


Figure 2. Mean (\pm SE) Change in American Urological Association Symptom Index (AUASI) Scores in the Saw Palmetto and Placebo Groups.

Values at screening represent prerandomization screening values. The full range of the scale is from 0 to 35, with higher numbers indicating more severe symptoms.

0.72 in the placebo group (95 percent confidence interval, -1.40 to -0.04) (Table 2). There was, however, no significant difference between groups in the mean change in AUASI scores over time (difference in mean change, 0.04 point; 95 percent confidence interval, -0.93 to 1.01). Figure 2 shows that the fitted curves for the saw palmetto and placebo groups nearly coincide, indicating similar changes in AUASI scores over time in the two groups (likelihood-ratio chi-square test, 0.62 with 2 degrees of freedom; $P=0.73$).

Similarly, there was no significant difference between groups in the change in the peak urinary flow rate during the one-year study period. The peak urinary flow rate changed by 0.42 ml per minute (95 percent confidence interval, -0.25 to 1.10) in the saw palmetto group and by -0.01 ml per minute (95 percent confidence interval, -0.68 to 0.66) in the placebo group (mean difference, 0.43 ml per minute; 95 percent confidence interval, -0.52 to 1.38). Figure 3 shows that the fitted curves for the saw palmetto and placebo groups nearly coincide, indicating similar changes in the

Table 2. Changes in Primary and Secondary Outcome Measures.*

Measure	Saw Palmetto (N=112)	Placebo (N=113)	Difference between Groups (95% CI)
<i>mean (\pmSE) change</i>			
Primary outcomes			
AUASI score [†]	-0.68 ± 0.35	-0.72 ± 0.35	0.04 (-0.93 to 1.01)
Peak urinary flow rate (ml/sec)	0.42 ± 0.34	-0.01 ± 0.34	0.43 (-0.52 to 1.38)
Secondary outcomes			
Prostate volume (ml)	3.76 ± 0.98	4.98 ± 0.96	-1.22 (-3.90 to 1.47)
Prostate transitional-zone volume (ml)	3.26 ± 1.03	2.01 ± 1.01	1.25 (-1.57 to 4.07)
Residual volume after voiding (ml)	14.10 ± 7.24	18.62 ± 7.14	-4.51 (-24.44 to 15.42)
BPH Impact Index score [‡]	-0.33 ± 0.13	-0.09 ± 0.13	-0.24 (-0.60 to 0.13)
SF-36 score [§]			
Mental subscale	-0.72 ± 0.72	0.47 ± 0.71	-1.18 (-3.16 to 0.79)
Physical subscale	0.10 ± 0.67	-0.51 ± 0.66	0.61 (-1.24 to 2.45)
Sexual function (O'Leary scale) [¶]	-0.06 ± 0.10	0.07 ± 0.10	-0.13 (-0.40 to 0.14)
Laboratory values			
Creatinine (mg/dl)	0.002 ± 0.01	-0.004 ± 0.01	0.006 (-0.02 to 0.03)
Testosterone (ng/dl)	-16.82 ± 8.74	-1.42 ± 8.64	-15.40 (-39.49 to 8.69)
PSA (ng/dl)	-0.005 ± 0.07	0.15 ± 0.07	-0.16 (-0.36 to 0.04)

* Plus-minus values are means \pm SE. To convert creatinine values to micromoles per liter, multiply by 88.4. CI denotes confidence interval, and PSA prostate-specific antigen.

[†] Scores on the AUASI can range from 0 (no symptoms) to 35 (severe symptoms).

[‡] Scores on the BPH Impact Index can range from 0 (no symptoms) to 13 (severe symptoms).

[§] Scores on the SF-36 can range from 0 to 100; higher scores indicate a better quality of life.

[¶] Overall scores on the O'Leary Scale of Sexual Function can range from 0 to 4, with higher scores indicating better function.

peak urinary flow rate over time in the two groups (likelihood-ratio chi-square test, 0.87 with 2 degrees of freedom; $P=0.65$).

Examination of the secondary outcome measures also revealed no significant difference between treatment groups (Table 2). Changes in prostate size, residual volume after voiding, the BPH Impact Index, the overall quality of life as measured by the SF-36, and serum PSA, creatinine, and testosterone levels did not differ significantly between the two groups. The preplanned subgroup analyses also showed no benefit for any of the subgroups: for the AUASI outcome, there were no significant differences in response between the groups when stratified according to the baseline AUASI score ($P=0.32$), prostate size ($P=0.23$), or PSA level ($P=0.86$). Similarly, for the peak urinary flow rate, there were no interactions with the baseline AUASI score ($P=0.13$), prostate size ($P=0.63$), or PSA level ($P=0.87$).

A total of 26 serious adverse events occurred in 17 participants during the study: 8 in men assigned to saw palmetto and 18 in men assigned to placebo (Table 3). The risk of at least one serious adverse event did not differ significantly between the two groups ($P=0.31$ by Fisher's exact test). There were also no significant differences in the mean number of nonserious adverse events per participant in the saw palmetto and placebo groups (0.51 vs. 0.47, $P=0.72$ by Student's t-test) (Table 4) or in the change in laboratory values, including testosterone, PSA, and creatinine levels (Table 2).

The adequacy of blinding was assessed by asking participants whether they believed they were taking saw palmetto or placebo capsules. At 12 months, 40 percent of men in the saw palmetto group believed they were taking the herbal extract, as compared with 46 percent of men in the placebo group ($P=0.38$).

DISCUSSION

In this year-long randomized trial, we found that saw palmetto was not superior to placebo for improving urinary symptoms and objective measures of benign prostatic hyperplasia. The confidence intervals around the finding of no effect were narrow, excluding clinically important effects. For example, the 95 percent confidence interval for the difference in the change in the AUASI score between groups (-0.93 to 1.01) is

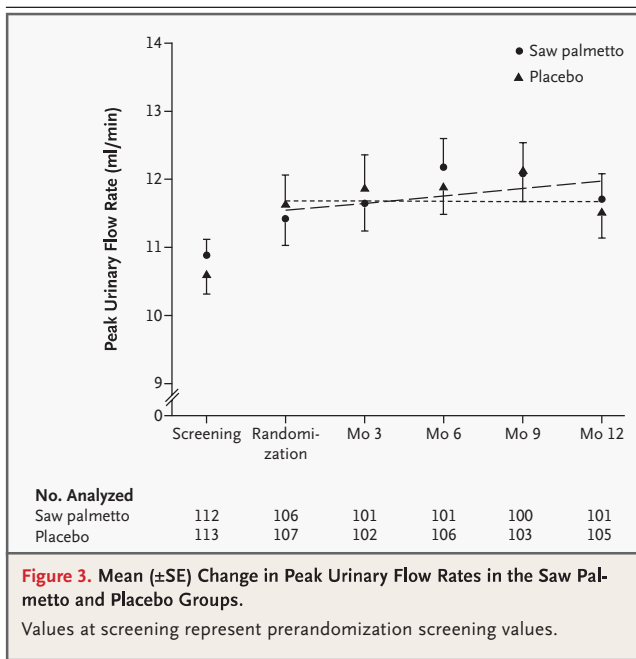


Figure 3. Mean (\pm SE) Change in Peak Urinary Flow Rates in the Saw Palmetto and Placebo Groups.

Values at screening represent prerandomization screening values.

Table 3. Serious Adverse Events.

Variable	Saw Palmetto (N=112)	Placebo (N=113)
	<i>number</i>	
Events		
Cardiovascular event	2	7
Elective orthopedic surgery	3	3
Gastrointestinal bleeding	2	1
Bladder cancer	0	1
Colon cancer	0	1
Elective hernia repair	0	1
Hematoma	0	1
Melanoma	1	0
Prostate cancer	0	1
Shortness of breath	0	1
Rhabdomyolysis	0	1
Total	8	18
Patients with ≥ 1 event	6	11

consistent with only a 1-point improvement in the AUASI score. Previous research has suggested that a clinically meaningful change in symptoms of benign prostatic hyperplasia requires a change in the AUASI score of at least 3 points.²⁶ Also, all symptomatic measures (including the AUASI and

Table 4. The 10 Most Commonly Reported Nonserious Adverse Events.

Variable	Saw Palmetto (N=112)	Placebo (N=113)
	<i>number</i>	
10 Most common events		
Upper respiratory tract infection	12	10
Back pain	4	4
Rash	1	3
Diarrhea	2	2
Gout	2	2
Gastroesophageal reflux disease	0	3
Abdominal pain	2	1
Joint pain or swelling	2	1
Trauma	2	1
Cough	1	2
Patients with any adverse event	39	34

the BPH Impact Index) and all objective measures (including urinary flow rates, residual volume after voiding, and prostate size) were consistent in showing no evidence of an effect. The subgroup analyses indicated that there was no benefit among patients with either more or less severe symptoms or among patients with either small or large prostate glands.

In 2001, a systematic review identified 21 randomized, placebo-controlled trials of saw palmetto, of which 18 were double-blind and 13 compared saw palmetto alone with placebo. Only one of the studies of saw palmetto alone used a symptom scale equivalent to the AUASI (the International Prostate Symptom Scale); it found that saw palmetto improved symptom scores by 2.2 points, as compared with placebo (95 percent confidence interval, 0.3 to 4.4).¹³ In nine of the studies that compared saw palmetto with placebo, the summary estimate showed that saw palmetto increased the peak urinary flow rate by 1.86 ml per second more than placebo (95 percent confidence interval, 0.60 to 3.12).²¹ The studies included in this review had a number of methodologic limitations, including a mean duration of 13 weeks, a failure to use validated symptom scores, and inadequate concealment of treatment assignment in 10 of the 21 studies.²¹ Nonetheless, the weight of the prior evidence suggested that saw palmetto may induce mild-to-moderate improvements in urinary symptoms and flow measures.

Several factors can explain the discrepancy between our negative study and the summary of prior evidence. We measured the adequacy of blinding, and we found that blinding was effective, with a similar percentage of men in the saw palmetto and placebo groups reporting that they believed they were taking the active extract. Since other studies did not assess the adequacy of blinding, and since saw palmetto has such a strong, pungent odor, many prior studies may not have achieved adequate blinding. Inadequate blinding has the potential to reduce the response in men who are given placebo (who may be aware they are taking placebo), artificially increasing the comparative efficacy of saw palmetto.

It is also possible that the participants in this study had attributes that made them less likely to have a response to saw palmetto. However, the baseline characteristics of participants in our trial with regard to age, symptom scores, prostate volume, and peak urinary flow rate were similar to those of men in previous trials of herbs or pharmaceutical agents for benign prostatic hyperplasia.^{21,28,32-34}

The level of active ingredient in the extract may not have been sufficient to produce a measurable effect. We cannot completely address this possibility, because the active ingredient in saw palmetto, if one exists, is not known. However, prior *in vitro* studies suggest that the active ingredient is contained within the fatty-acid fraction.³⁵ Although there are no widely accepted guidelines on the contents of saw palmetto extract, authorities have recommended that the extract contain either 80 to 95 percent combined fatty acids and sterols³⁶⁻³⁸ or 85 to 95 percent fatty acids and greater than 0.2 percent sterols.³⁹ The U.S. Pharmacopeia states that the product should contain 70 to 95 percent fatty acids and 0.2 to 0.5 percent sterols.⁴⁰ The extract we used (which, on separate measurements, had 90.7 to 92.1 percent fatty acids and 0.33 percent sterols) meets all the criteria proposed by the various authorities and was selected by an expert advisory committee chartered by the NCCAM.

The saw palmetto extract we used also had characteristics similar to those of other commonly used products in the United States. A reference laboratory that provides Web-based information tested the majority of saw palmetto products available in the United States and found that 17 of 22 tested products had fatty acid levels of 85

to 95 percent and sterol levels of more than 0.2 percent.³⁹ The saw palmetto extract in our study had the same range of values for these ingredients and is therefore similar to the majority of currently available products. In summary, we found that 160 mg of saw palmetto given twice daily for one year does not improve lower urinary tract symptoms caused by benign prostatic hyperplasia.

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