

Benign prostatic hyperplasia treated with saw palmetto: a literature search and an experimental case study

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European physicians treat benign prostatic hyperplasia (BPH) with saw palmetto extract (SPE), while American physicians generally disregard SPE because “research is lacking.” The authors investigated this discrepancy with a literature search and a clinical trial. The literature search began with MEDLINE, then expanded to “alternative” databases, including AGRICOLA, EMBASE, IBIS, and Cochrane, plus a manual search of unindexed herbal journals. The clinical trial was an experimental case study in which a 67-year-old man with symptomatic BPH was randomly administered SPE (160 mg standardized extract twice daily) or placebo. Outcome measures included the American Urological Association Symptom Index (AUASI), serum prostate-specific antigen, and prostate volume. Our expanded literature search revealed 58 clinical trials, whereas MEDLINE yielded only 19 clinical trials, or 33% of the total. Our clinical trial measured a baseline AUASI score of 20, which improved to 7 after unblinded administration of SPE. Subsequent double-blinded placebo produced a score of 14, and final single-blinded allotment of SPE produced a score of 11. Prostate-specific antigen was 10.3 ng/mL at baseline and 10.7 ng/mL at trial’s conclusion. Baseline prostatic volume was 92 mL, and end volume was 75 mL. In conclusion, MEDLINE proved inadequate as a stand-alone search engine for locating information about an herbal medicine. Our experimental case study, similar to N=1 research methodology, proved suitable for clinical evaluation of an herbal medicine in a rural private practice. SPE improved the patient’s BPH. Unstandardized look-alike herbs may act as nontherapeutic placebos and may undermine consumer confidence in herbal medicine.

(Key words: hyperplasia, benign prostatic; saw palmetto; databases, medical literature; herbal medicine)

Symptoms of benign prostatic hyperplasia (BPH) are caused by two obstructive mechanisms: *mechanical* obstruction of the urethra, from an overgrowth of epithelial tissue in the transitional zone of the prostate, and *dynamic* obstruction due to excess sympathetic

tone in the prostate and bladder neck.¹ The pharmaceutical treatment of BPH consists of two choices—5 α -reductase inhibitors and α_1 -adrenergic antagonists. 5 α -Reductase inhibitors (eg, finasteride) block the reduction of testosterone to 5 α -dihydrotestosterone (DHT). DHT

stimulates prostatic hyperplasia, so 5 α -reductase inhibitors relieve mechanical obstruction. α_1 -Adrenergic antagonists (e.g., terazosin hydrochloride, doxazosin mesylate, prazosin hydrochloride) relax smooth muscle in the prostate and thus relieve dynamic obstruction.

European physicians rarely prescribe these pharmaceutical remedies. Instead, over 90% of prescriptions for BPH are herbal medicines, especially saw palmetto extract (SPE; extracted from berries of *Serenoa repens*, formerly called *Sabal serrulata*).² The use of SPE is discouraged by American academicians because “evidence is inconclusive.”³ Similarly, the Food and Drug Administration (FDA) rejected SPE for the treatment of BPH because of “inadequate evidence.”⁴ These academicians and FDA decision analysts searched for evidence using MEDLINE, a database generated by the National Library of Medicine, considered the gold standard in allopathic medicine. We hypothesized that much of the literature regarding herbal medicine, like the literature regarding osteopathic manipulation, is not indexed by MEDLINE. We compiled this scattered bibliography by expanding the search beyond MEDLINE, to include “alternative” databases and unindexed herbal journals.

The literature search was followed by a clinical trial of SPE, utilizing an experimental case study design, similar to the N=1 methodology espoused by epidemiologists and statisticians.⁵⁻⁸ The method consists of a systematic but random administration of multiple courses of either active or placebo treatments to one patient. It is simple, inexpensive, patient-focused, and relevant to the patient’s individual condition. Experimental case studies are a pragmatic way for office-based physicians to evaluate herbal medicines and other alternative modes of therapy in their clinical practices⁸ and are especially useful for osteopathic physicians, who utilize alternative modes of therapy more frequently than allopathic physicians.⁹ We hypothesized that SPE treatment would improve the patient’s BPH sufficiently to obviate the need to prescribe α_1 -adrenergic

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antagonists (the patient was borderline hypotensive) or 5 α -reductase inhibitors (the patient feared the possibility of finasteride-induced sexual dysfunction).

Methods

The expanded literature search, as described previously,¹⁰ began with MEDLINE (1966-1998, MeSH key words: medicinal plants, plant extracts; text words: saw palmetto, *Serenoa repens*, *Sabal serrulata*, Permixon, Prostagutt, Prostaselect, Strogon Forte). The same key words were used to search AGRICOLA (1990-1998, National Agriculture Library, Beltsville, Md), EMBASE (1974-1998, Excerpta Medica, Amsterdam, The Netherlands), IBIS (Interactive BodyMind Information System, AMR'TA, Portland, Ore), and the Cochrane CD Library (Cochrane Collaboration, Oxford, England). We hand-searched three reference texts on herbal medicine¹¹⁻¹³ and five unindexed "alternative" journals (*Alternative Therapies in Clinical Practice*, *HerbalGram*, *Journal of Naturopathic Medicine*, *Medical Herbalism*, *Protocol Journal of Botanical Medicine*). Data were extracted from all published clinical reports of SPE, irrespective of trial methodology. Procured reports were scanned for supporting citations; antecedent sources were also obtained. Reports were acquired at the local medical library or via interlibrary loan.

The experimental case subject was a 67-year-old Caucasian male with symptomatic BPH. Exclusion criteria included infection, carcinoma, and bladder instability; the subject was free of these conditions as determined by urinalysis, urodynamic studies, ultrasound, and ultrasound-guided prostatic biopsy. Prostatic biopsy provided a tissue diagnosis of benign adenomatous hyperplasia. The subject received information about SPE, our methods of outcome measurement, and stopping rules if SPE caused side effects. His wife agreed to serve as executor of assignment (dispense SPE capsules), and the subject provided informed consent. Our experiment began as an unblinded clinical trial of a new medical treatment, a routine familiar to clin-

icians, termed a "trial of therapy." Dosage consisted of one capsule containing 160 mg of standardized 12:1 SPE (Murdock Madaus Schwabe, Karlsruhe, Germany), taken twice a day, with morning and evening meals.

Subjective outcome measures were assessed using the American Urological Association Symptom Index (AUASI), which is the English version of the International Prostate Symptoms Score (IPSS), a measure often reported in European studies. The AUASI has been shown to have greater reliability than more objective measures such as uroflowmetry.¹⁴ It is a self-administered instrument consisting of seven questions (Table). The first six questions are scored on a scale from 0 to 5, based on the following responses: no symptoms at all = 0; less than one time in five = 1; less than half the time = 2; about half the time = 3; more than half the time = 4; almost all the time = 5. The seventh question is quantitative, asking the subject how many times he had to urinate during the night (0, 1, 2, 3, 4, or 5 times or more). The sum of the seven questions' scores reflects the overall severity of the patient's BPH (0 to 7, mild; 8 to 19, moderate; 20 to 35, severe). Two objective measures were obtained — prostate-specific antigen (PSA) and prostate volume. PSA is a glycoprotein found in serum and serves as a semi-quantitative indicator of prostatic cancer, but PSA levels also may become elevated in BPH. Prostate volume was measured via transrectal ultrasound.

The AUASI was administered before treatment and 12 weeks after treatment began. After 12 weeks, the subject's initial supply of standardized SPE was depleted. His wife inadvertently replaced the standardized SPE with an unstandardized, ineffective product (saw palmetto berries, 580 mg, Solaray Inc, Utah). The subject did not detect the substitution. After taking the ersatz product for approximately 12 weeks, the subject complained to his physician (JM), "the saw palmetto doesn't seem to be working anymore." The AUASI was readministered.

A separate discussion with his wife revealed her inadvertent substitution. At

that point, the standardized SPE was immediately resumed under the conditions originally agreed upon by the subject, but without the subject's knowledge that the original conditions were inadvertently interrupted for 12 weeks. In the absence of an institutional review board, this decision was reached after reviewing principles outlined in the Declaration of Helsinki guide to research ethics.¹⁵ After 12 weeks on the resumed SPE, outcome measures were obtained a final time. At the trial's conclusion, effects of treatments were interpreted by charting numeric data under each regimen.

Results

Literature search

The expanded search of the literature yielded 58 reports of clinical trials. This count excludes preliminary reports (eg, Weisfer and Kreig¹⁶), duplicate publications of previous clinical trials,¹⁷⁻²² and reports published in obscure publications that proved impossible to locate through interlibrary loan (eg, Pisani²³ and Tenaglia et al²⁴ cited in Paoletti²⁵). In contrast, the MEDLINE search yielded only 19 clinical trials, or 33% of our expanded search.

The efficacy of SPE has been demonstrated by a hierarchy of research designs, the least rigorous designs being uncontrolled, open clinical trials.²⁵⁻⁵⁶ Most uncontrolled studies lasted less than 3 months, but some studies continued up to 1 year⁴⁴ and 3 years.⁴⁸ The potency of SPE over placebo has been proven in double-blind, randomized studies.⁵⁷⁻⁷⁶ One dissenting study showed SPE was no better than placebo.⁷⁷ SPE has been compared to pharmaceutical drugs. It worked better than gestonorone caproate, an antiandrogen agent,⁷⁸ but was less effective than two α_1 -adrenergic antagonists, prazosin hydrochloride⁷⁹ and alfuzosin.⁸⁰ A large, 6-month trial compared SPE to finasteride; the drugs produced comparable symptomatic improvements, although SPE caused less sexual dysfunction than finasteride.⁸¹ A recent study reported similar findings—no significant differences between SPE and finasteride in resolving symptoms of BPH, but SPE had fewer side effects.⁸²

Table
Measurements Correlating the Severity of Benign Prostatic Hypertrophy at
Baseline and at the End of Three Treatment Protocols of 12 Weeks Each

Measurement	Baseline	Standardized saw palmetto extract	Placebo (unstandardized extract)	Standardized saw palmetto extract
Serum prostate-specific antigen (ng/mL)	10.3	6.5		10.7
Prostate volume, estimated by transrectal ultrasound (mL)	91.6			74.5
American Urological Association Symptom Index (seven items)*				
1. During the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?		0		
2. During the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	4	2	2	2
3. During the past month or so, how often have you found you stopped and started again several times when you urinated?	3		2	2
4. During the past month or so, how often have you found it difficult to postpone urination?	5		3	2
5. During the past month or so, how often have you had a weak urinary stream?	4		3	2
6. During the past month or so, how often have you had to push or strain to begin urination?	0	0	0	0
7. During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	3	2	3	2
8. Sum of index items 1 to 7	20	7	4	
*The index items are scored on a scale from 0 to 5, as described in the Methods section.				

Side effects from SPE occur in approximately 2% of subjects in clinical trials, primarily gastrointestinal complaints (nausea, diarrhea, constipation, abdominal discomfort) and, rarely, headache, back pain, hypertension, and urinary retention. Cholestatic hepatitis developed in a 65-year-old man 2 weeks after taking Prostate, a combination remedy that contains unextracted, unstandardized saw palmetto.⁸³

The literature search identified three types of SPE extracts utilized in clinical trials: hexane extract (e.g., Permixon) is considered the “gold standard.”⁸⁴ The extract is a complex mixture of free fatty acids and their esters, β -sitosterol and its glucoside, long-chain aliphatic alcohols, and various flavonoids and other polyphenolic compounds. The ethanol extract (e.g., Prostagutt) also has a high concentration of lipophilic compounds, especially esterified fatty acids. The carbon dioxide extract (e.g., Prostaserene) reportedly contains the greatest concentration of fatty acids (range, 85% to 95%). The commonly prescribed daily dosage of SPE—320 mg—equals 10 g of whole, dried *Serenoa repens* berries.⁸⁵

The literature search also revealed many pharmacologic studies that support the use of SPE. SPE works by a variety of mechanisms, befitting its polypharmaceutical nature:

- SPE inhibits 5α -reductase.⁸⁶⁻⁹⁶
- SPE inhibits binding of DHT to androgen receptors.^{86-89,97,98}
- SPE down-regulates nuclear androgen receptors⁹⁹ and cytosol androgen receptors.¹⁰⁰⁻¹⁰³
- SPE inhibits 17β -hydroxysteroid dehydrogenase (17β -HD), also called 17β -hydroxysteroid oxidoreductase, a reversible oxidator of testosterone.^{93,104,105} This inhibition may be mediated by β -sitosterol in SPE; β -sitosterol is a known inhibitor of 17β -HD,¹⁰⁶ and β -sitosterol by itself has successfully treated BPH.^{107,108}
- SPE is antiestrogenic^{99,109}; estrogen contributes to BPH by inhibiting the hydroxylation and elimination of DHT.
- SPE inhibits growth factor–induced prostatic proliferation.^{110,111}
- SPE inhibits prolactin-induced prostatic growth.^{112,113}

■ SPE acts as an anti-inflammatory agent.¹¹⁴⁻¹¹⁸ The fatty acid component of SPE provides this effect, not the sterol fraction.¹⁰⁷

■ SPE has a spasmolytic effect on smooth muscle.^{119,120}

■ SPE is antiemetic.^{64,121}

SPE has no effect on PSA levels, according to uncontrolled studies^{47,56} and a randomized, double-blind study.⁸⁰ Decreasing PSA would not be desired in a BPH medication, because it may mask or delay the detection of prostatic carcinoma. Paradoxically, SPE may decrease prostate volume—three uncontrolled studies show a reduction of 10% to 11%,^{44,47,54} while controlled studies show no change,^{63,74} a 6% to 8% reduction,^{66,80} and a 30% reduction.⁷⁷

Experimental case study

At baseline, the subject’s AUASI summed to 20 points, a score suggesting severe BPH (Table). His baseline PSA was elevated at 10.3 ng/mL (age-weighted normal, 4.8 ng/mL), and prostate volume was enlarged at 91.8 mL (non-age-weighted normal, 25 mL, SD \pm 19 mL¹²²). After receiving SPE for 12 weeks, the subject’s AUASI decreased to 7 points, a score suggesting mild BPH. His PSA level decreased to 8.5 ng/mL.

When the subject switched to an unstandardized “placebo” product, his BPH symptoms worsened to a moderate level (AUASI 14). After resuming standardized SPE, the subject’s symptoms again improved (AUASI 11). His PSA level obtained at that time was 10.7 ng/mL, and his prostate volume equaled 74.5 mL.

Discussion

MEDLINE is the largest and most comprehensive database in medicine, with more than 9 million citations extracted from 3700 journals.¹²³ Nevertheless, MEDLINE only located 33% of our total citations, which demonstrates its inadequacy as a stand-alone search engine for locating information about herbal medicine. Previously, Knipschild¹²⁴ determined that MEDLINE yielded only 36% of reports of studies of vitamin C for the common cold, and a mere 17% of the

homeopathic literature. Clinicians researching “alternative” medical topics, including osteopathic manipulation, should not rely solely on MEDLINE for retrieving literature. Similarly, decision analysts and policymakers in government agencies and insurance corporations must expand their literature search beyond MEDLINE before dismissing alternative therapies “because evidence is lacking.”

Several literature reviews of SPE have recently been published. Three reviews did not describe their search methodology, but they likely relied on MEDLINE plus citation tracking; they located 9 clinical studies,² 12 clinical studies,³ and 26 clinical trials.¹²⁵ The most recent literature survey, a systematic review, was performed by Wilt and associates.¹²⁶ Systematic reviews, like meta-analyses, make strenuous efforts to locate all studies, published and unpublished, that meet inclusion criteria. Thus Wilt et al searched well beyond MEDLINE, but because they limited their inclusion criteria to randomized controlled clinical trials, they only located 24 studies. Limiting a review to randomized trials will eliminate various types of bias and support robust statistical analysis,¹²⁷ but at a loss of analytical diversity and data points. For instance, Wilt et al could not report the results of any studies that compared SPE to α_1 -adrenergic antagonists (we report two studies herein), nor could they determine the effect of SPE on PSA levels (we report three studies).

Only part of our experimental case study was prospective,¹²⁸ so it does not qualify as an N = 1 study. As described previously, we did not recognize we were performing a randomized trial until partially into it. Thus, the trial began unblinded, became double-blinded, and finished single-blinded. Basically our trial began by accident, an indirect result of the poorly regulated state of herbal medicines in the United States.

The subject’s AUASI score deteriorated after switching from a standardized German SPE product to an unstandardized American product. The ingredients in the American product cannot be determined. Unstandardized products may contain little of what they claim

to consist.¹²⁹⁻¹³¹ Until the regulation of herbs improves in the United States, the authors will continue to prescribe SPE produced by regulated German corporations.

Experimental case studies and N=1 trials are easy to conduct by office-based clinicians who wish to determine the most effective treatments for their individual patients. Thus, these methods avoid some of the ethical pitfalls associated with multipatient clinical trials.^{5,6} We believe that N=1 trials are excellent for practitioners who wish to introduce research into their practices. N=1 trials work best for disease symptoms that are chronic and consistent. The treatments must be short acting, because prolonged washouts compromise any clinical trial with a crossover design, and N=1 trials utilize multiple crossovers between active and placebo treatments. N=1 trials typically cycle through 4 to 10 courses of randomly allocated treatments, but even two treatments may be sufficient.⁶ Outcome measures, such as signs, symptoms, or laboratory measurements, are recorded throughout the trial. At the trial conclusion, the effects of treatment can be interpreted by simply charting numeric data.⁷ Formal statistical analysis can also be performed, but often produces disappointing results. In an N=1 trial with six treatments, the smallest possible one-sided P value is .016 (1/26) when treatments are randomized independently.⁶ Thus, the standard P<.05 of statistical certainty is difficult to achieve in an N=1 trial. Preparing and performing an N=1 trial takes an average of 16.5 hours⁶; specific guidelines are available.⁷

The experimental case study measured the results of SPE treatment after 12 weeks. Improvement from SPE should be expected in 6 to 8 weeks.^{8,4} A long-term study showed continued improvement for up to 12 months before benefits from SPE reached a plateau.⁸ Our subject's PSA level initially decreased, then returned to a level near baseline. Other SPE studies show no effect on PSA levels.^{3,4,7,56,80} The subject's prostate volume decreased 19%, which is within the range of other studies.^{4,4,47,54,77,80}

SPE is considerably less expensive than currently available pharmaceuticals, and causes fewer side effects. After our trial, the subject chose to continue taking SPE. Currently, a dozen patients in our small, rural clinic are undergoing N=1 trials that evaluate herbal remedies. We are also conducting N=1 trials that evaluate osteopathic manipulation, but these trials are not blinded; osteopathic manipulation is difficult to blind.¹³²

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