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ORIGINAL PAPER

Serenoa repens and its effects on male sexual function. A systematic review and meta-analysis of clinical trials

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Summary

Background: *Serenoa repens (SR) is a plant used to treat benign prostatic hyperplasia and prostatitis. We know that SR act as a 5α-reductase inhibitor, moreover, several studies have proved that SR has anti-inflammatory and antioxidant properties. There is some belief among patients that SR may negatively impact male sexual function. Such belief is circulating in non-medical social networks and is perhaps maintained by patients as a result of incorrect web surfing. However, it is also possible that SR may exert a "nocebo" effect thus negatively impacting on the general well-being of patients.*

Objective: *The aim of this study is to investigate whether SR is causing negative effects on male sexual function.*

Methods: *To ascertain the effect of SR on male sexual function, we conducted a systematic review and meta-analysis, by performing an electronic database search in accordance with the PRISMA guidelines.*

Results: *Out of 20 included papers, 8 papers reported comparisons of SR with placebo, and 7 studies reported comparisons of SR with tamsulosin. The standardized mean difference of changes from baseline scores of sexual function was not significantly different between SR and placebo (SMD: 0.43, 95% CI: 0.18 to 1.05; I^2 = 95%). Similarly, no significant mean differences in the Male Sexual Function-4 (MSF-4) test scores were found between SR and tamsulosin (SMD: -0.31, 95% CI: -0.82 to 0.19; I^2 = 90%).*

Conclusions: *We found no statistically significant differences between negative effects on sexual function in patients treated with SR compared to patients who received placebo. The results of our meta-analysis are similar to those of other systematic reviews. Studies are warranted to ascertain whether any such effects might occur as a result of a nocebo effect.*

KEY WORDS: *Serenoa repens; Adverse effects; Nocebo effect; Male sexual health.*

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INTRODUCTION

Serenoa repens (SR), also known as *Saw palmetto*, *Sabal serrulata*, and *American dwarf palm tree*, is a plant originally used by *Native Americans* (*Seminole* and *Miccosukee tribes*) both as food and to cure urogenital ailments (1). The plant belongs to the *Arecaceae* family and mainly grows in the southern *United States*, particularly in *Florida* and *South Carolina* (2). SR is commonly used throughout the world to treat *benign prostatic hyperplasia* (BPH) and prostatitis. Although its mechanism of action has not fully been demonstrated yet, it is mainly used on the assumption that SR is a 5α-reductase inhibitor, consequently blocking the conversion of testosterone to *dihydrotestosterone* (DHT) a biologically more active hormone (2, 3). In the literature, however, several studies have proved that SR, besides being very selective for the prostate gland, has, above all, pro-apoptotic, anti-inflammatory, and antioxidant properties (4-21). Normally used SR doses vary between 320 and 450 mg/day.

The aim of this study is to clarify whether SR is able to cause negative effects on male sexual function. Such belief is circulating in non-medical social networks and is maintained by patients as a result of web surfing. Not infrequently, even in our clinics, we encounter patients suffering from BPH or prostatitis who underwent treatment of varying length with SR, who claim to have noticed a significant reduction in their erectile potency, and in some cases even in their libido. Many web forums in the world discuss the alleged negative effects of SR, equating them directly to the post-finasteride syndrome; unfortunately, once pseudo-confirmation is found by surfing the net, a belief quickly and easily goes viral.

Is it possible that SR may have a nocebo effect and therefore negatively impact the health of patients, regardless of any real pharmacological adverse effect (22)?

The aim of this work was to assess whether SR can cause negative effects on male sexual function. We therefore carried out an in-depth systematic review and meta-analysis in accordance with the PRISMA guidelines (23).

MATERIALS AND METHODS

This review was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines (23). The review protocol was submitted for registration on the PROSPERO platform (ID 287140). Two electronic databases (*PubMed* and *EMBASE*) were searched for articles published up to 30 September 2021. The search was performed using the following terms: (*Serenoa repens* OR *Saw palmetto* OR *Sabal*

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serrulata) AND (Orgasm OR Ejaculation OR Erectile dysfunction OR sexual dysfunction, physiological). Relevant data were also hand-searched through other sources.

We considered *randomized controlled trials* (RCTs) with an open-label or single/double blinded design published in English without time constraints.

We included studies involving male subjects taking Serenoa repens extracts to treat a prostatic condition, compared with placebo, or with various drugs prescribed for *benign prostatic hyperplasia* (BPH) (e.g., alpha adrenoceptor blockers, alpha-reductase inhibitors).

The following outcomes were considered: (i) the rate of sexual dysfunction (erectile dysfunction, ejaculatory dysfunction, dysorgasmia, loss of libido), and/or the changes of scores of questionnaires measuring sexual function. The *Brief Male Sexual Function Inventory* (BMSFI) is a questionnaire to measure male sexual function covering sexual drive (two items), erection (three items), ejaculation (two items), perceptions of problems in each area (three items), and overall satisfaction (one item) (24).

The *International Index of Erectile Function* (IIEF) is a 15-item questionnaire addressing five relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) (25). An abridged, five-item version of the IIEF-5 can also be administered for the evaluation of erectile dysfunction (26).

Increasing severity of sexual function is associated with lower scores of BMSFI and IIEF. The *Male Sexual Function-4* item (MSF-4) questionnaire is a concise survey evaluating four items (interest in sex, quality of erection, achievement of ejaculation, and achievement of orgasm). Lower scores of this instrument are associated with better preserved sexual function (27).

Two independent authors performed title and abstract screening of all retrieved records to delete duplicates and to exclude reports that did not meet the inclusion criteria. A second round of full-text screening to confirm/exclude the inclusion of retrieved studies and to extract relevant information was performed by 2 authors using a standardized form.

The publication bias was assessed in the presence of at least 5 trials. It was analyzed by visually inspecting funnel plots and by performing the Egger's and Begg's tests using the MetaEssentials 1 software (*Rotterdam School of Management, Erasmus University, The Netherlands*).

Statistical analysis was performed using the RevMan5 software. Meta-analysis was performed using a random effects model. Dichotomous data (presence/absence of sexual dysfunction) or continuous data reporting changes of mean values of sexual function scores and number of per-protocol or intent-to-treat patients were extracted.

For dichotomous data we calculated *odds ratios* (OR), for continuous data presented as pre-vs. post-therapy mean differences, we calculated inverse variance weighted standardized mean differences. For all analyses we calculated 95% *confidence intervals* (CI). Heterogeneity was assessed by calculating the I^2 value with 95% CIs, and interpreted as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity.

A summary of findings table was generated, and the quality of the evidence emerging from meta-analyses including at least 3 studies was rated according to GRADE criteria.

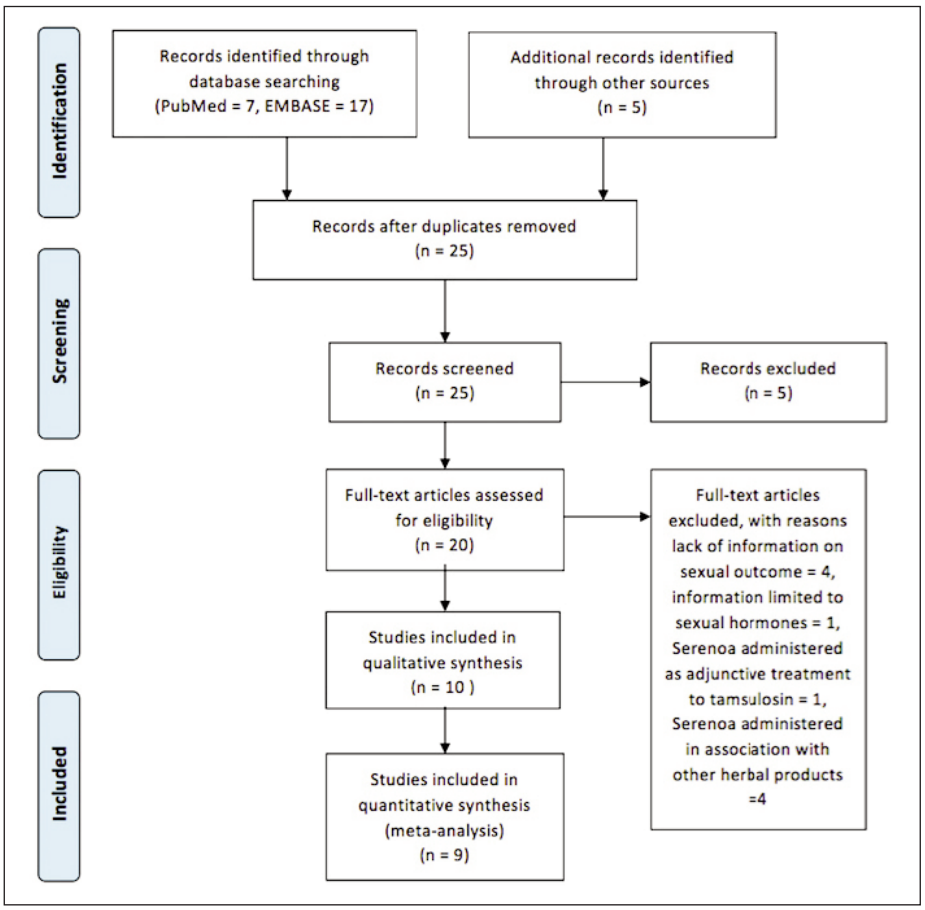

Figure 1.
A PRISMA flow diagram.

Results

A PRISMA flow diagram illustrates the results of the study selection process (see Figure 1). We retrieved 29 papers: 7 papers from PubMed, 17 papers from EMBASE and 5 from other sources (hand-searching). Four duplicate papers were removed, and 5 papers were excluded as they were found to be not related to this review.

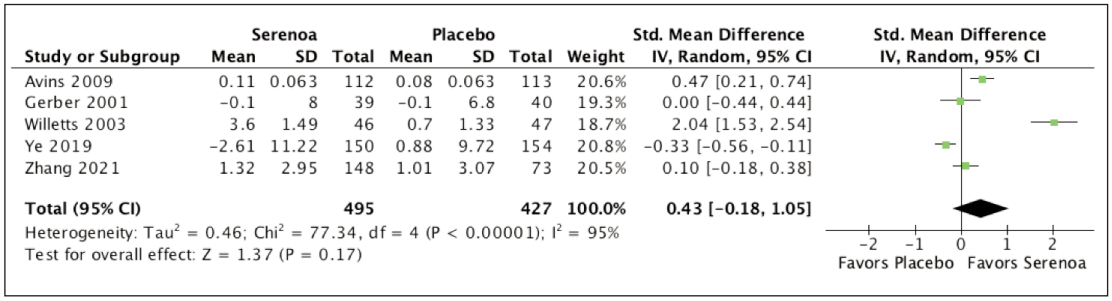

Figure 2.
Statistical analysis: differences in sexual dysfunction between treatment with Serenoa repens and placebo.

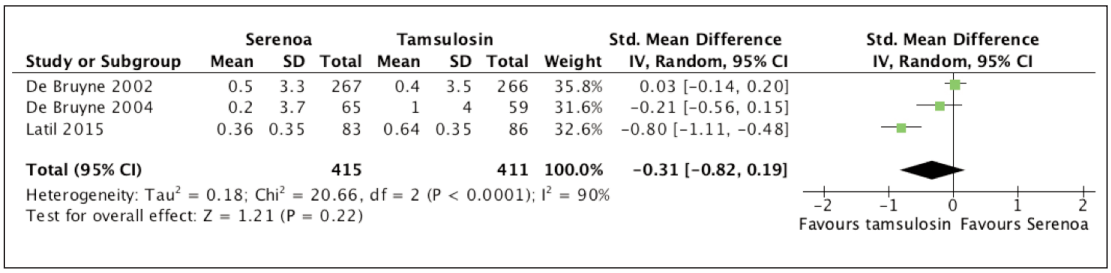

Figure 3.
Statistical analysis: differences in the MSF-4 test scores between treatment with Serenoa repens and Tamsulosin.

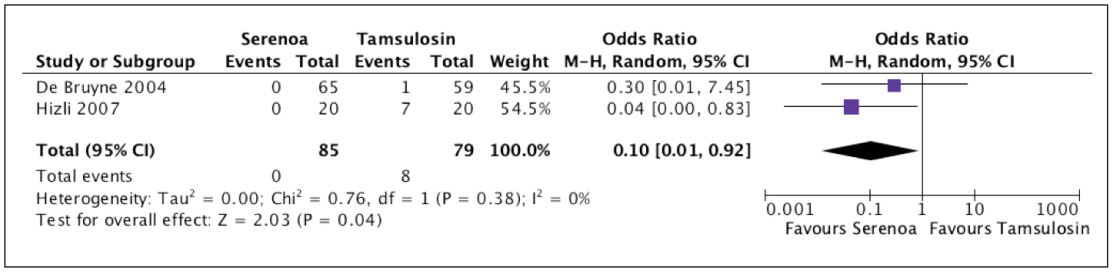

Figure 4.
Statistical analysis: ejaculatory disorders after treatment with Serenoa repens and Tamsulosin.

Out of the 20 remaining papers, we selected 8 papers reporting comparisons of SR with placebo. Three records were discarded after full-text reading (two were lacking information on sexual outcomes and one reported only information on sexual hormones).

Other 7 studies reported comparisons of SR with tamsulosin. Two studies were excluded because Serenoa repens was administered in association with other herbal products and one because SR was administered in combination with tamsulosin versus tamsulosin alone.

Two studies compared SR with finasteride; one was excluded because SR was administered in combination with other herbal products.

Three studies compared a SR extract with other herbal products. Two were discarded because of lack of information on sexual function and one because SR was administered in a formulation containing other herbal products.

The characteristics of the 10 studies finally included in this systematic review, and the evaluation of risk of bias are presented in the "***Supplementary Materials***".

Quantitative analysis was limited to five studies comparing therapy with a SR extract with placebo, and to four studies comparing a SR extract with tamsulosin (28-36).

A study comparing a SR extract with finasteride was only qualitatively evaluated (37).

To evaluate differences in sexual dysfunction between treatment arms we calculated standardized mean differences, as included trials used different sexual function scales. The standardized mean difference of changes from baseline scores was not significantly different between SR and placebo (SMD: 0.43, 95% CI: -0.18 to 1.05; 5 trials, 922 patients; Z = 1.37, P = 0.17; Egger's P = 0.16; Begg's P = 0.32). This analysis was characterized by considerable heterogeneity (I^2 = 95%) (Figure 2).

No significant mean differences in the MSF-4 test scores were found between SR and tamsulosin (SMD: -0.31, 95% CI: -0.82 to 0.19; 3 trials, 826 patients; Z = 1.21, P = 0.22; I^2 = 90%) (Figure 3).

However, random-effects meta-analysis revealed that treatment with SR is associated with significantly lower odds of ejaculatory disorders compared to tamsulosin (odds ratio = 0.10, 95% CI: 0.01 to 0.92; 2 trials, 164 participants, Z = 2.03, P = 0.04, I^2 = 0%), compared to placebo (see Figure 4) (34,35).

Final results are reported in Table 1.

Discussion

Although the quality of evidence grade of our meta-analysis is low (see Table 1), we found no statistically significant differences between negative effects on sexual function in patients treated with SR compared to patients who received placebo or tamsulosin.

This suggests that SR does not appear produce negative

Table 1.
Summary of findings.

Serenoa repens compared with placebo or active drug (Tamsulosin)

Patient or population: Patients with Benign Prostatic Hyperplasia
Settings: Outpatient
Intervention: Serenoa repens extract
Comparators: Placebo or active comparator (alpha adrenoceptor blocker)

Outcomes	Intervention vs. comparator results	Number of participants (studies)	Quality of the evidence (grade)
Sexual (dys)function, SD units [assessed using different sexual function scales]	The sexual function score in the Serenoa repens groups was on average 0.43 SDs (95% CI: -0.18 to 1.05) higher than in the placebo groups.	922 (5)	⊕⊕⊝⊝ low Reasons for downgrading: - Inconsistency (considerable heterogeneity) - Indirectness (subjectiveness) of evidences
Sexual (dys)function, SD units [assessed using the Male Sexual Function 4-items test]	The score of the MSF-4 test in the tamsulosin groups was on average 0.31 SDs (95% CI: -0.82 to 0.19) lower than in the Serenoa repens groups.	826 (3)	⊕⊕⊝⊝ low Reasons for downgrading: - Inconsistency (considerable heterogeneity) - Indirectness (subjectiveness) of evidence

SD: Standard deviation; CI: Confidence interval; MSF-4: Male Sexual Function 4-items test.
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

effects on male sexual function. Such view is supported by two studies (*Marks et al.*, 2000; *Pytel et al.*, 2002) which did not detect a reduction in the serum levels of male sex hormones (testosterone, dihydrotestosterone) after treatment with SR (38, 39).
The results of our meta-analysis are similar to those of other authoritative systematic reviews, where SR was proved to have no negative impact on male sexual function (40-42).
It should furthermore be evaluated whether the negative effect of SR on male sexuality reported by a number of patients both in our clinics and on Internet forums may be generated by neuropsychological mechanisms. This is where the concept of nocebo comes in. A nocebo effect is generated when a patient's beliefs and negative expectations cause a worsening of the individual's health status (22). The psychological mechanisms underlying this pesky effect seem to include negative expectations concerning treatment, high levels of anxiety, and classic conditioning (43). A study by *Mondaini et al.* (2007) provides a very interesting analysis of the causal role of "*negative expectations*" on the nocebo effect, after patient have been informed of the possible side effects of a therapeutic substance (44). In this study, which included 107 patients suffering from BPH, two treatment groups were created, with finasteride 5 mg/day and a treatment length of 12 months. Patients of Group 1 (52 patients) were also not informed of the risk of side effects on their sexuality; patients of Group 2, instead, were told of the possible – albeit rare – onset of sexual problems such as erectile dysfunction (ED), decreased libido, and ejaculation disorders. The results, after treatment with finasteride 5 mg/day for 12 months, were the following: Group 1, adverse sexual side effects 15.3 % (ED 9.6%, decreased libido 7.7%, ejaculation disorders 5.7%); Group 2, adverse sexual side effects 43.6% (ED 30.9%, decreased libido 23.6%, ejaculation disorders 16.3%). The significantly higher rate of sexual dysfunctions in Group 2 compared to Group 1 clearly proves that the nocebo effect had a significant impact on the greater number of occurrences of sexual problems in the patients of Group 2 (44). It is possible that SR may also have a "*nocebo*" effect and therefore negatively impact the health of patients.

Conclusions

Based on the results of our review, SR does not appear to cause negative effects on male sexuality; should any such effects occur, they may be ascribed to a nocebo effect.
Adequately powered studies are needed to confirm this hypothesis. In such a case to reduce the likelihood of a nocebo effect, when mentioning possible side effects during the informed consent process prior to treatment, it may be necessary to structure the information to patients by avoiding the classic "*negative*" narrative frame (percentage of possibility of having a specific side effect), employing instead a "*positive*" approach, providing information about the percentage of patients who are likely not to experience any side effects.
A more in-depth knowledge of the mechanisms that cause the nocebo effect, will help to minimize its impact in the clinical activity of general practitioners and specialists alike.

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