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Serenoa repens for the Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Enlargement: An Updated Cochrane Review

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Purpose: To assess the effects of *Serenoa repens* in the treatment of men with lower urinary tract symptoms (LUTS) consistent with benign prostatic hyperplasia (BPH).

Materials and Methods: We performed a comprehensive search using multiple databases up to September 2022 with no language or publication status restrictions. We included parallel-group randomized controlled trials of participants with BPH who were treated with *Serenoa repens* or placebo/no treatment. We used standard Cochrane methods, including a GRADE assessment of the certainty of the evidence (CoE).

Results: We included 27 studies involving a total of 4,656 participants. *Serenoa repens* results in little to no difference in urologic symptoms at short-term follow-up (International Prostate Symptom Score [IPSS]: mean difference [MD] −0.90, 95% confidence interval [CI] −1.74 to −0.07; I^2=68%; 9 studies, 1,681 participants; high CoE). *Serenoa repens* results in little to no difference in the quality of life at short-term follow-up (high CoE). *Serenoa repens* probably results in little to no difference in adverse events (moderate CoE). Different phytotherapeutic agents that include *Serenoa repens* may result in little to no difference in urologic symptoms compared to placebo at short-term follow-up (IPSS: MD −2.41, 95% CI −4.54 to −0.29; I^2=67%; 4 studies, 460 participants; low CoE). We are very uncertain about the effects of these agents on quality of life (very low CoE). These agents may result in little to no difference in the occurrence of adverse events (low CoE).

Conclusions: *Serenoa repens* alone provides little to no benefits for men with LUTS due to benign prostatic enlargement. There is more uncertainty about the role of *Serenoa repens* in combination with other phytotherapeutic agents.

Keywords: Meta-analysis; Prostatic hyperplasia; Serenoa; Systematic review

INTRODUCTION

The prostate gland is a walnut-sized organ located below the urinary bladder that surrounds the urethra [1]. Benign prostatic hyperplasia (BPH) is characterized by an increased number of cells in the prostate, leading to enlargement and compression of the urethra [2]. BPH may or may not be accompanied by lower urinary

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tract symptoms (LUTS) in men over 40 years old [3]. The clinical significance of BPH is determined by the presence of bothersome LUTS, which negatively impact the quality of life and prompt treatment seeking. The International Prostate Symptom Score (IPSS) is a self-administered questionnaire used to assess the severity and impact of LUTS [4]. The prevalence of LUTS and BPH increases with age, affecting a significant proportion of men worldwide [5].

The initial evaluation of LUTS suggestive of BPH involves patient history, physical examination, and various tests such as digital rectal examination, urinalysis, prostate-specific antigen (PSA) measurement, and IPSS assessment [6]. PSA is elevated in conditions like BPH, prostate cancer, and prostate inflammation. Additional evaluations may be necessary for differential diagnosis or pre-surgical assessments. Treatment decisions are based on symptom severity and patient bother. Conservative management and medication (alpha-blockers and 5-alpha reductase inhibitors) are the initial treatment options [6]. Surgical interventions are considered for patients who do not respond to conservative and medical treatments or experience complications [6].

Serenoa repens, commonly known as saw palmetto, is a widely used phytotherapeutic compound for BPH treatment. Its extracts, particularly the hexane extract called Permixon, have shown in previous systematic reviews potential benefits with fewer adverse events [7-9]. *Serenoa repens* is usually taken in a daily dose of 320 mg, although some studies have investigated higher doses [10]. The most frequently reported adverse events are minor gastrointestinal symptoms, genitourinary problems, musculoskeletal complaints, and upper respiratory tract infections. The mechanisms of action of *Serenoa repens* include alterations in cholesterol metabolism, antiestrogenic and antiandrogenic effects, anti-inflammatory effects, pro-apoptotic properties, and relaxation of smooth muscles in the prostate and detrusor [11-17].

While BPH and LUTS can have significant consequences, including acute urinary retention and upper urinary tract deterioration, treatment options are available to manage the condition. The use of *Serenoa repens* as a treatment option is not routinely recommended but may be considered for patients who want to avoid adverse side effects of other treatments. Since the last update of this review [18], several new trials have been published. Whereas some newer non-Cochrane reviews have been published, none has included GRADE methods [7-9]. The aim of this review is to assess the effects of *Serenoa repens* in the treatment of men with LUTS consistent with BPH.

MATERIALS AND METHODS

1. Inclusion criteria

We updated the methods of this Cochrane review since its last version in 2012 to the latest standards [19,20]. We defined the eligible participant population as men over the age of 40 years with a prostate volume of 20 mL or greater (as assessed by ultrasound or cross-sectional imaging), with LUTS as determined by IPSS of eight or over, and a maximum flow rate (Qmax) of less than 15 mL/second, as measured by non-invasive uroflowmetry, invasive pressure flow studies, or both. We excluded studies of men with active urinary tract infection, bacterial prostatitis, chronic renal failure, untreated bladder calculi or large diverticula, prostate cancer, and urethral stricture disease, as well as those who had undergone prior prostate, bladder neck, or urethral surgery. We also excluded studies of people with other conditions that affect urologic symptoms, such as neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease.

We included two comparisons: 1) *Serenoa repens versus* placebo or no intervention; 2) *Serenoa repens* in combination with other phytotherapy *versus* placebo or no intervention.

Our primary outcomes were: urologic symptom scores, quality of life, and adverse events. We considered outcomes measured up to and including 12 months after randomization as short-term and later than 12 months as long term. For adverse events, the timing of outcome assessment was not well-defined across studies, and outcome data were not disaggregated by follow-up, so we did not divide them into short and long term.

2. Search methods

We searched the following sources in September 2022 from the inception of each database to the date of search with no restrictions on the language of publication: CENTRAL, MEDLINE, Embase, Scopus, Science Citation Index Expanded, Latin American and Caribbean Literature in Health Sciences; ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP).

3. Data collection and analysis

We used Covidence software (Veritas Health Innovation) to identify and remove potential duplicate records. Two review authors (out of LT, NJS, GAA, and CF) independently screened articles for eligibility and independently extracted data [19]. We presented a PRISMA 2020 flow diagram showing the process of study selection [21]. Two review authors (out of LT, NJS, GAA, and CF) authors independently extracted data and assessed the risk of bias in the included studies using the revised version of the Cochrane risk of bias tool for randomized trials (ROB 2) [22,23]. We summarized data using a random-effects model. We planned to assess heterogeneity statistically, with the I^2 statistic >50% considered to indicate substantial heterogeneity. We tested for publication bias by assessing funnel plot asymmetry, but the number of trials per comparison was insufficient. We used RevMan Web (Cochrane) to perform the statistical analyses. When possible, we explored the effect of bias in the effect estimates and performed pre-defined subgroup analyses. We intended to explore the effect of bias in the results, but all studies were at a high or unclear risk of bias. We included a 'Summary of findings' table reporting the primary outcomes using the GRADE approach.

The full methods of this review, including the full search strategy, can be found in the published version at the Cochrane Library [24].

RESULTS

We conducted a de novo search for this update and

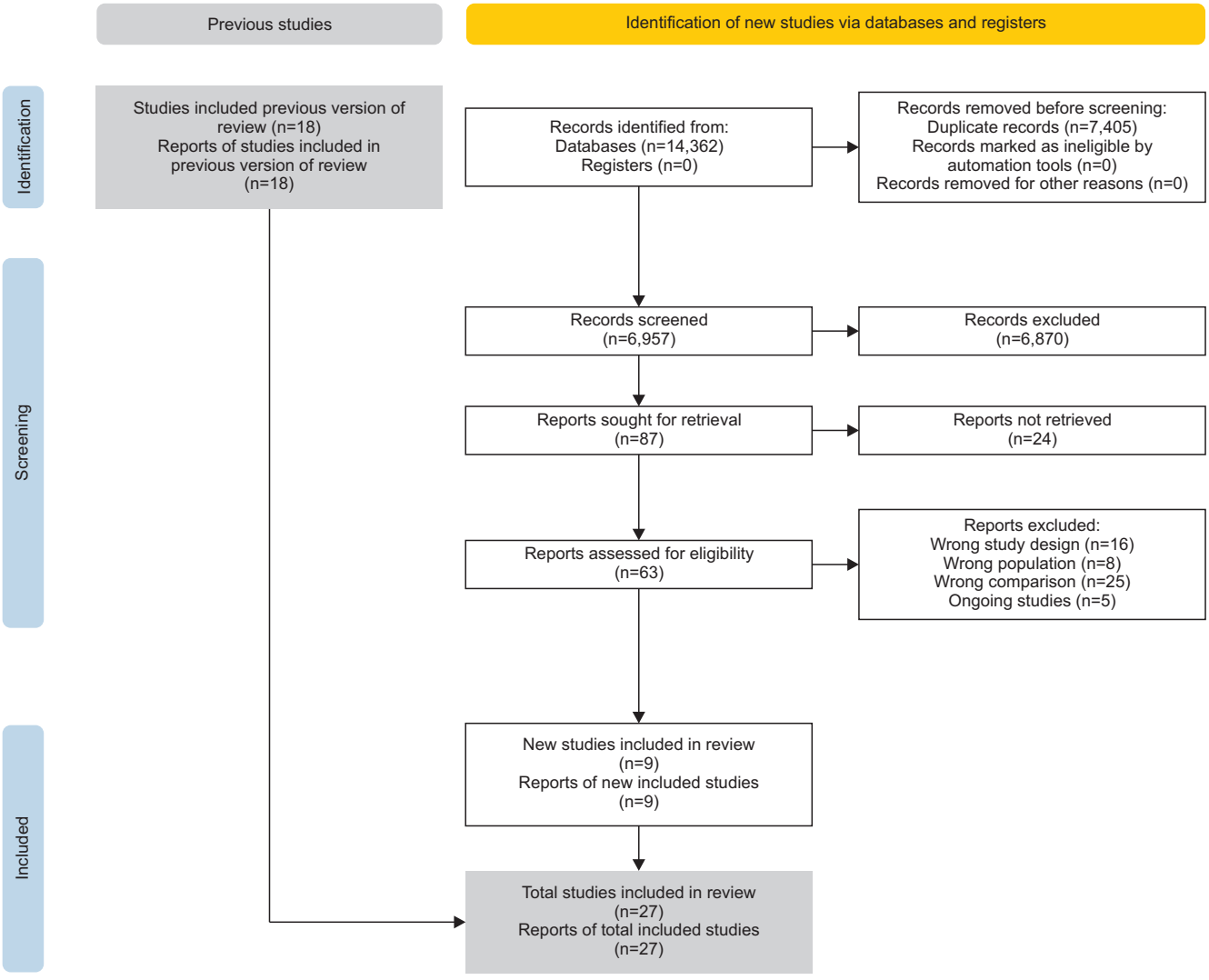

Fig. 1. PRISMA flow diagram.

identified 14,362 records from electronic databases. We found no relevant records in additional sources. After removing duplicates, we screened the titles and abstracts of the remaining 6,957 records, of which 6,870 were excluded. We assessed 87 full-text articles and excluded 49 records for various reasons. Considering the 18 relevant studies from the previous version of the review, we included 27 studies with 4,656 participants in this update. A PRISMA flow diagram illustrating the flow of literature through the assessment process is presented in Fig. 1. The list of excluded studies is available in the full version of this review. See Table 1 for a summary of the studies' characteristics [10,25-50]. Ten studies were funded by the pharmaceutical industry [25-34]; two studies were funded by government agencies [10,35]; and the remaining studies did not specify funding sources. The risk of bias of outcomes across all results and domains was mostly 'some concerns' due to a lack of pre-specification of outcomes and analysis plans. We assessed three studies as an overall low risk of bias [10,29,35]. We assessed three studies as at high risk of bias due to missing outcome data or bias in the measurement of the outcome (due to lack of blinding), in addition to some concerns regarding selective reporting [36-38]. In the following sections, we summarized the main findings.

1. *Serenoa repens* versus placebo or no intervention (short term)

Results for this comparison are based on pre-defined sensitivity analyses limited to studies at low risk of bias (Table 2).

1) Urologic symptoms

Serenoa repens results in little to no difference in urologic symptoms at short-term follow-up (3 to 6 months; mean difference [MD] −0.90; 95% confidence interval [CI] −1.74 to −0.07; I^2=68%; 9 studies, 1,681 participants; high-certainty evidence). All heterogeneity was explained by a single study of 304 participants that compared *Serenoa repens* to placebo and showed a difference in IPSS scores of −2.77 (95% CI −3.71 to −1.83) [31], which is statistically significant but clinically unimportant.

2) Quality of life

Serenoa repens results in little to no difference in quality of life at short-term follow-up (3 to 6 months,

Table 1. Characteristics of the included studies

Study	Trial period	Country	Number	Follow-up	Brand and daily dosage (when available)	Co-intervention	Mean age (SD), y		Mean IPSS (SD)		Mean prostate volume (SD)	
							I	C	I	C	I	C
Studies comparing SR with placebo												
Argirović and Argirović [44] (2013)	2008–2010	Serbia	199	6 months	Prostamol Uno 320 mg	Tamsulosin	65.9 (7.4)	56.8 (7.7)	15.6 (3.2)	16.2 (4.9)	31.2 (4.2)	38.6 (11.6)
BASTA [25] (2010)	2006–2008	International	1,011	12 months	Permixon[a] 320 mg daily Prostamol Uno 320 mg	None	64.61 (7.69) 65.14 (7.67)	64.14 (7.69)	N/A	N/A	N/A	N/A
Barry et al [10] (2011)	2008–2010	USA	369	72 weeks	Prosta Urgenin Uno 320 mg	None	61.25 (8.72)	60.7 (8.08)	14.42 (4.29)	14.69 (4.75)	N/A	N/A
Bauer et al [40] (1999)	N/A	Germany/ Italy	101	6 months	Talso Uno 320 mg daily	None		66.1	9.6	8.9	34.5	31.7
Bent et al [35] (2006)	2001–2004	USA	225	14 months	Carbon dioxide extract 320 mg	None	62.9 (8.0)	63.0 (7.4)	15.7 (5.7)	15.0 (5.3)	34.7 (13.9)	33.9 (15.2)
Boccafoschi et al [41] (1983)	N/A	Italy	22	60 days	Permixon[a] 320 mg	None	68 (55–80)	68 (54–78)	N/A	N/A	N/A	N/A

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Table 1. Continued 1

Study	Trial period	Country	Number	Follow-up	Brand and daily dosage (when available)	Co-intervention	Mean age (SD), yr		Mean IPSS (SD)		Mean prostate volume (SD)	
							I	C	I	C	I	C
Champault et al [42] (1984)	N/A	France	110	30 days	Permixon[a] 320 mg	None	N/A	N/A	N/A	N/A	N/A	N/A
Descotes et al [43] (1995)	1995	France	176	30 days	Permixon[a] 320 mg	None	65.6 (8.4)	67 (7.6)	N/A	N/A	N/A	N/A
Gerber et al [27] (2001)	1999–2000	USA	85	6 months	SR 320 mg	None	64.6±9.9	65.3±9.7	16.7±4.9	15.8±4.8	N/A	N/A
Glémain et al [45] (2002)	N/A	France	329	52 weeks	Permixon[a] 320 mg	Tamsulosin	65.2 (7.9)	64.4 (7.7)	16.2 (5.2)	16.3 (5.6)	40.8 (16.5)	38.6 (15)
Hizli et al [36] (2007)	2005	Turkey	60	6 months	Permixon[a] 320 mg	Tamsulosin	60.2 (6.3)	58.9 (5.7)	15.6 (3.2)	16.2 (4.7)	31.2 (4.2)	38.6 (11.6)
Hong et al [37] (2009)	N/A	Korea	62	12 months	SR 320 mg	None	52.0	53.1	18.3	15.4	26.1	23.2
Mandressi et al [46] (1983)	N/A	Italy	60	1 month	Permixon[a] 320 mg	None	N/A	N/A	N/A	N/A	N/A	N/A
Reece Smith et al [47] (1986)	N/A	UK	70	12 weeks	Permixon[a] 320 mg	None	66.15 (5.86)	67.03 (6.03)	N/A	N/A	N/A	N/A
Ryu et al [38] (2015)	2012–2013	Korea	120	12 months	Permixon[a] 320 mg	Tamsulosin	62.5 (1.21)	63.4 (1.44)	19.6 (0.73)	20 (0.85)	30.1 (0.93)	30.2 (0.67)
Shi et al [48] (2008)	N/A	China	94	3 months	Prostataplex (dosing not reported)	None	65.91	64.04	16.85	14.46	47.72	48.38
Sudeep et al [29] (2020)	N/A	India	99	12 weeks	VISPO/SPO 400 mg	None	57.76 (7.25)	55.18 (8.56)	20.00 (4.41)	20.00 (3.74)	N/A	N/A
Willetts et al [30] (2003)	1999–2000	Australia	100	12 weeks	Carbon dioxide extract 320 mg	None	62.1 (1.2)	63.9 (1.3)	N/A	N/A	N/A	N/A
Ye et al [31] (2019)	2014–2016	China	354	24 weeks	SR 320 mg	None	61.47 (5.20)	60.32 (5.96)	14.42 (3.88)	14.34 (4.08)	37.0 (19.7)	37.3 (25.4)
Studies comparing phytotherapy containing SR with placebo												
Carbin et al [49] (1990)	1990	Sweden/ Denmark	55	3 months	Curbicin (PSO 480 mg+SR 480 mg)	None	62.0 (6.7)	61.2 (5.8)	N/A	N/A	N/A	N/A
Coulson et al [26] (2013)	N/A	Australia	60	3 months	ProstateEZE Max (PSO 160 mg, epilobium 500 mg, lycopene 2.1 mg, pygeum 15 g+SR 660 mg)	None	63 (10.1)	64.9 (9.6)	19.5	18	N/A	N/A
Iacono et al [50] (2015)	N/A	Italy	185	6 months	Tradamixina (Eisenia 80 mg, Tribulus 100 mg, chitosan oligosaccharide [Biovis] 100 mg+SR 320 mg)	None	64.2 (8.6)		20.6 (5.4)	N/A	N/A	N/A
Lopatkin et al [28] (2005)	1997–2000	Russia	257	24 weeks	PRO 160/120 (Sabal-Urtica 240 mg+SR 320 mg)	None	67 (7)	68 (6)	17.4 (3.3)	17.8 (3.3)	43.5 (17.6)	44.8 (17.6)

Table 1. Continued 2

Study	Trial period	Country	Number	Follow-up	Brand and daily dosage (when available)	Co-intervention	Mean age (SD), yr		Mean IPSS (SD)		Mean prostate volume (SD)	
							I	C	I	C	I	C
Marks et al [32] (2000)	1997–1998	USA	44	6 months	Nettle root 240 mg, PSO 480 mg, lemon 99 mg, vitamin A 570 IU+SR 318 mg	None	65.1 (8.1)	62.9 (9.3)	18.1 (7.2)	16.6 (5.3)	58.5 (29.8)	55.6 (26.7)
Metzker et al [39] (1996)	N/A	Germany	40	12 months	Prostagutt forte (Sabal-Urtica 240 mg+SR 320 mg)	None	66.0	65.1	18.6	19.0	N/A	N/A
Morgia et al [33] (2014)	2011–2012	Italy	225	12 months	Profluss (selenium and lycopene+SR 320 mg)	Tamsulosin	65	66	20	19	45	45
Preuss et al [34] (2001)	N/A	USA	144	3 months	Cernitin AF (Cernitin 378 mg, vitamin E 100 IU+SR with beta-sitosterol 286 mg)	None	N/A	N/A	18.9	17.1	N/A	N/A

C: control, I: intervention, IPSS: International Prostate Symptom Score, IU: international units, N/A: not available (not described), PSO: pumpkin seed oil, SR: *Serenoa repens*, SD: standard deviation.
[a]Hexanic extract of *Serenoa repens*.

MD −0.20, 95% CI −0.40 to −0.00; I^2=39%; 5 studies, 1,001 participants; high-certainty evidence).

3) Adverse events

Serenoa repens probably results in little to no difference in adverse events (1 to 17 months, risk ratio [RR] 1.01, 95% CI: 0.77–1.31; I^2=18%; 12 studies, 2,399 participants; moderate-certainty evidence). Based on 164 cases per 1,000 men in the placebo group, this corresponds to 2 more (38 fewer to 51 more) per 1,000 men in the *Serenoa repens* group.

The most commonly reported adverse events were headache, gastrointestinal disorders (e.g. diarrhea, nausea and vomiting, stomach upset), upper respiratory symptoms (e.g. rhinitis), ejaculation disorders, musculoskeletal symptoms (e.g. arthralgia in the knees and muscular arm pain), and dizziness. Many of these symptoms may be attributable to co-interventions (alpha-blockers).

4) Subgroup and sensitivity analysis

We were unable to detect differences in urologic symptoms when comparing the effects of hexanic *versus* non-hexanic extract (p=0.23). Few studies in each category precluded subgroup analyses according to age, symptom severity, and prostate size. We conducted a sensitivity analysis excluding studies at an overall high risk of bias. Given that these analyses provided moderate- to high-certainty evidence, we incorporated them into the main results and Table 2.

2. *Serenoa repens* versus placebo or no intervention (long term)

1) Urologic symptoms

Serenoa repens results in little to no difference in urologic symptoms at long-term follow-up (12 to 17 months; MD 0.07; 95% CI −0.75 to 0.88; I^2=34%; 3 studies, 898 participants; high-certainty evidence).

2) Quality of life

Serenoa repens results in little to no difference in quality of life at long-term follow-up (12 to 17 months; MD −0.11, 95% CI −0.41 to 0.19; I^2=65%; 3 studies, 882 participants; high-certainty evidence).

3) Adverse events

None of the included studies reported this outcome.

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Table 2. Summary of findings for the comparison of *Serenoa repens vs* placebo or no intervention

Outcome	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[a]	
				Risk with placebo/no treatment	Risk difference with *Serenoa repens*
Urologic symptom score Measured by IPSS scores (range 0–35); higher scores indicate worse symptoms; follow-up: 3 to 6 months; MCID: 3 points	1,681 (9 RCTs)	⨁⨁⨁⨁ High[b]	MD −0.90 (−1.74 to −0.07)	The mean score was 14.33	MD 0.90 lower (1.74 lower to 0.07 lower)
Quality of life Measured by IPSS-QoL score (range 0–6); follow-up: 3–6 months; MCID: 0.5 points	1,001 (5 RCTs)	⨁⨁⨁⨁ High[b]	MD −0.20 (−0.40 to 0.00)	The mean score was 3.11	MD 0.20 lower (0.40 lower to 0.00 lower)
Adverse events Cumulative incidence; follow-up: 1–17 months; MCID: relative risk reduction/increase of 0.25	2,399 (12 RCTs)	⨁⨁⨁⊖ Moderate[c]	RR 1.01 (0.77 to 1.31)	164 per 1,000	2 more per 1,000 (38 fewer to 51 more)

Patient or population: lower urinary tract symptoms due to benign prostatic hyperplasia. Setting: outpatient (Australia, Asia, Europe, and the USA). Intervention: *Serenoa repens*. Comparison: placebo/no treatment.

CI: confidence interval, IPSS: International Prostate Symptom Score, MCID: minimal clinically important difference, MD: mean difference, QoL: quality of life, RCT: randomized controlled trial, RR: risk ratio.

GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]We did not downgrade the certainty of the evidence for risk of bias as these results were robust following sensitivity analysis excluding studies at high risk of bias.

[c]We did not downgrade the certainty of the evidence for risk of bias as these results were robust following sensitivity analysis excluding studies at high risk of bias. We downgraded one level due to imprecision as the CI included little to no benefit and also harms (based on a 25% relative risk reduction).

4) Subgroup analysis and sensitivity analysis

Few studies in each category precluded these subgroup analyses. We conducted a sensitivity analysis excluding studies at an overall high risk of bias. Given that these analyses provided high-certainty evidence, we incorporated them into the main results.

3. *Serenoa repens* in combination with other phytotherapy versus placebo or no intervention

1) Urologic symptoms

Different phytotherapeutic agents that include *Serenoa repens* may result in little to no difference in urologic symptoms compared to placebo at short-term follow-up (12 to 24 weeks; MD −2.41, 95% CI −4.54 to −0.29; I^2=67%; 4 studies, 460 participants; low-certainty evidence).

2) Quality of life

We are very uncertain about the effects of these agents on quality of life (very low-certainty evidence). In one study with 40 participants, 84.2% of participants in the intervention group had improvements in their quality of life after six months of treatment compared to 11.1% of participants in the placebo group (p<0.001) [39]. Another study with 225 participants found little to no difference in quality of life scores (median change 0, range −0.1 to 1) [33].

3) Adverse events

Different phytotherapeutic agents that include *Serenoa repens* may result in little to no difference in the occurrence of adverse events; however, the CIs included substantial benefits and harms (12 to 48 weeks; RR 0.91, 95% CI 0.58–1.41; I^2=0%; 4 studies, 481 participants; low-certainty evidence). Based on 132 cases per 1,000 men in the placebo group, this corresponds to 12 fewer (55

Table 3. Summary of findings for the comparison *Serenoa repens* in combination with other phytotherapy *vs* placebo or no intervention

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)[a]	
				Risk with placebo/no treatment	Risk difference with *Serenoa repens*
Urologic symptom score Measured by IPSS scores (range 0–35); higher scores indicate worse symptoms; follow-up: 12–24 weeks; MCID: 3 points	460 (4 RCTs)	⨁⨁◯◯ Low[b,c]	MD −2.41 (−4.54 to −0.29)	The mean score was 12	MD 2.41 lower (4.54 lower to 0.29 lower)
Quality of life Measured by IPSS-QoL score (range 0–6); follow-up: 2–6 months; MCID: 0.5 points	265 (2 RCTs)	⨁◯◯◯ Very low[d,e,f]	1 study reported improvements (p<0.05), while the other did not		
Adverse events Cumulative incidence; follow-up: 12–48 weeks; MCID: relative risk reduction/ increase of 0.25	481 (4 RCTs)	⨁⨁◯◯ Low[g]	RR 0.91 (0.58 to 1.41)	132 per 1,000	12 fewer per 1,000 (55 fewer to 54 more)

Patient or population: lower urinary tract symptoms due to benign prostatic hyperplasia. Setting: outpatient (Europe/USA). Intervention: *Serenoa repens* with other phytotherapy. Comparison: placebo/no intervention.
CI: confidence interval, IPSS: International Prostate Symptom Score, MCID: minimal clinically important difference, MD: mean difference, QoL: quality of life, RCT: randomized controlled trial, RR: risk ratio.
GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b]Downgraded one level due to concerns about inconsistency: high statistical inconsistency (I^2=67%).
[c]Downgraded one level due to imprecision: wide CI including substantial benefit and little to no effect.
[d]Downgraded one level due to risk of bias: high risk of bias in included studies.
[e]Downgraded one level due to inconsistency: the included studies reported different effects.
[f]Downgraded one level due to imprecision: the included studies reported P values, and we are uncertain about effect sizes.
[g]Downgraded two levels due to imprecision: CI includes substantial benefits and harms.

fewer to 54 more) per 1,000 men in the combined phytotherapeutic agents with *Serenoa repens* group.

The most commonly reported adverse events were headache, gastrointestinal disorders (e.g. diarrhea, nausea and vomiting, dyspepsia), upper respiratory symptoms (e.g. rhinitis), ejaculation disorders, musculoskeletal symptoms (e.g. arthralgia in the knees and pain), and dizziness. Many of these symptoms may be attributable to co-interventions (alpha-blockers).

Few studies in each category precluded these subgroup analyses. We were unable to conduct a sensitivity analysis because the meta-analyses did not include studies at an overall high risk of bias (Table 3).

DISCUSSION

For this update, we narrowed the review question. We included 27 studies (of which 9 were new studies) with 4,656 participants, 19 studies comparing *Serenoa repens* with placebo, and eight studies comparing *Serenoa repens* in combination with other phytotherapeutic agents *versus* placebo. Based on pre-defined sensitivity analyses limited to studies at low risk of bias, *Serenoa repens* results in little to no difference in urologic symptoms and quality of life at short-term follow-up, and probably results in little to no difference in adverse events. *Serenoa repens* results in little to no difference in urologic symptoms and quality of life at long-term follow-up. There were no data on long-term adverse events for this comparison. Moreover, *Serenoa repens* in combination with other phytotherapy *versus* placebo or no intervention phytotherapeutic agents with various agents, including *Serenoa repens*, may result in little to no difference in urologic symptoms compared to placebo at short-term follow-up. We are very uncertain about the effects of these agents on quality

of life. These agents may result in little to no difference in the occurrence of adverse events; however, the CIs included substantial benefits and harms.

Despite the expanding body of research subsequent to the last review update in 2012, our conclusions remain unaltered. Current clinical practice guidelines have shifted their focus away from incorporating *Serenoa repens* into treatment protocols. Notably, the 2021 Guideline established by the American Urological Association concentrates on managing LUTS stemming from BPH through conventional surgical techniques and minimally invasive options. This emphasis has resulted in limited exploration of various medical interventions, including the utilization of *Serenoa repens* [6]. An earlier iteration of the guideline dating back to 2010 already indicated that existing data do not strongly support the notion that *Serenoa repens* significantly impacts LUTS stemming from BPH [51]. Furthermore, it asserted that due to the scarcity of high-quality trials, there's a lack of endorsement for dietary supplements, combined herbal treatments, or other unconventional therapies in managing such LUTS [51]. Conversely, the European Association of Urology guidelines for handling non-neurogenic male LUTS put forth several therapeutic and surgical options for BPH-affected men [52]. Within these guidelines, it is suggested to provide men with LUTS the hexane extract of *Serenoa repens* if they wish to avert potential adverse effects, particularly those tied to sexual function (with a weak recommendation). However, patients should be informed that the effectiveness might be modest (with a strong recommendation) [52]. Our review adds a note of caution regarding the use of *Serenoa repens*. Lastly, the Korean Urological Association's evidence-based directives for diagnosing and treating BPH offer fundamental insights into diagnostic procedures, pharmaceutical approaches, and surgical remedies, yet the mention of *Serenoa repens* as a management choice is absent from these recommendations [53].

In light of prostate size categories defined at 40 mL and 80 mL for small, medium, and large prostates, all the studies encompassed individuals with small to moderately-sized prostates and moderate urologic symptoms. Notably, no studies catered to men with large prostates, and only a handful addressed individuals with more severe urologic symptoms (Table 1).

Only a few investigations encompassed supplementary interventions like tamsulosin [33,36,38,44,45], but this didn't introduce noteworthy statistical diversity when evaluating adverse event outcomes. Nevertheless, many of these narratively described adverse events, such as dizziness and ejaculatory disorders, are typically linked to alpha-blockers [54]. For the primary comparison, the overall certainty in the evidence was high, except for adverse events where imprecision was identified. Our approach mirrored that of prior reviews, excluding studies with high bias risk from the primary analysis. However, concerns also arose regarding precision and inconsistency for the second comparison. A number of studies lacked comprehensive details on critical outcomes, including urologic symptoms, quality of life, and adverse events, elements vital for considering men's preferences [55].

A recent systematic review and network meta-analysis of the same theme encompassed 22 randomized clinical trials comparing hexanic and non-hexanic *Serenoa repens* extracts with alpha-adrenergic agonists and placebo [8]. Their conclusion highlighted clinically insignificant IPSS improvements at 12 weeks, with CIs that covered little to no difference from placebo (MD −0.47, 95% CI −2.69 to 1.74 for hexanic extract; MD −1.69, 95% CI −4.36 to 0.98 for non-hexanic extract). While hexanic extracts showed greater improvements than non-hexanic extracts, subgroup estimates demonstrated minimal disparity, aligning with our review (MD −2.16, 95% CI −5.64 to 1.30). This review was limited due to fewer placebo comparisons (7 *vs* our 15), contributing to substantial imprecision in their findings.

Several limitations characterize our review. Seven original study texts couldn't be located for re-analysis using updated methods. Despite efforts, neither the original authors nor external sources held copies of these studies. A Cochrane TaskExchange inquiry yielded no resolution. These studies appeared to primarily focus on non-validated outcome measures and Qmax, which wouldn't substantially affect our primary analyses. Additionally, 17 additional references were pending classification due to inaccessibility, mostly from the 1980s and 1990s, likely unsuitable for main analyses incorporation.

Although recent reports have improved adverse event timing disclosure, our assessment couldn't ascertain their occurrence timing in line with CONSORT-Harms guidelines [56,57]. Consequently, we couldn't disaggregate data by follow-up length since most events correlated with treatment initiation or co-intervention

effects, implying short-term occurrence.

Finally, five studies' outcomes were excluded from our meta-analyses due to data gaps, but these were documented separately. Pre-defined funnel plots, subgroups and sensitivity analyses were challenging due to sparse data, minimal heterogeneity, and few trials in each comparison.

CONCLUSIONS

Serenoa repens alone provides little to no benefits for men with LUTS due to benign prostatic enlargement. There is more uncertainty about the role of *Serenoa repens* in combination with other phytotherapeutic agents. Considering the uncertainties about the effects of *Serenoa repens* in higher doses or combined with other herbal treatments, future high-quality, placebo-controlled randomized controlled trials are needed in this area that focus on patient-important outcomes, including urologic symptoms, quality of life, and adverse events.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Research conception and design: JVAF, JHJ. Data acquisition: CMEL, LFT, CF, NS, GAA. Statistical analysis: JVAF, JHJ. Data analysis and interpretation: all authors. Administrative, technical or material support: JVAF. Supervision: JVAF. Writing – original draft: all authors. Writing – review & editing: all authors. Approval of the final manuscript: all authors.

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