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Serenoa repens for the treatment of lower urinary tract symptoms due to benign prostatic enlargement: A systematic review and meta-analysis

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Purpose: To assess the effects of *Serenoa repens* alone or in combination with other phytotherapy compared to placebo in men with LUTS due to benign prostatic enlargement.

Materials and Methods: Following a registered protocol (CRD42021226655), we searched (December 2020) MEDLINE, CENTRAL, Embase, ClinicalTrials.gov, WHO-ICTRP trials platform and other sources with no restrictions on language, publication date or status. We included randomized controlled trials, and we critically appraised them using the Cochrane Tool for Risk of Bias Assessment (RoB 2). We conducted random-effects meta-analysis when appropriate. The primary outcomes included urinary symptoms score, quality of life, and adverse events. The certainty of the evidence was rated using GRADE.

Results: We included 27 trials with 4,853 participants. *S. repens* results in little to no difference in urinary symptoms, quality of life, and adverse events at short- and long-term follow-up. *S. repens* combined with other phytotherapy may slightly reduce urinary symptoms at short-term follow-up, but the results are uncertain. The results on quality of life and adverse events are also very uncertain.

Conclusions: *S. repens* alone may result in no clinical benefits for men with LUTS. There is greater uncertainty in the effects of *S. repens* in combination with other phytotherapy.

Keywords: Lower urinary tract symptoms; Phytotherapy; Prostatic hyperplasia; Serenoa

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INTRODUCTION

Benign prostatic enlargement (BPE) commonly presents with lower urinary tract symptoms (LUTS), which can be defined as a group of urinary symptoms triggered by an obstruction, abnormality, infection, or irritation of the urethra bladder neck, urinary sphincter or prostate. These symptoms may include voiding or obstructive symptoms such as hesi-

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tancy, poor or intermittent stream, straining, prolonged micturition, feeling of incomplete bladder emptying, dribbling, etc., and storage or irritative symptoms such as frequency, urgency, urge incontinence and nocturia [1]. The prevalence of benign prostatic hyperplasia (BPH) rises with age ranging from 8% to 80% in the 4th to 9th decades of life respectively [2]. The burden of disease attributable to LUTS has been increasing in the past years. From 1990 to 2017, the years lived with disability for males of all ages rose from 1.35 million in 1990 to 2.43 million in 2017 [3]. Diagnosis usually includes patient history, including a formal assessment of symptom severity (using the International Prostate Symptom Score [IPSS] score), physical exam and targeted laboratory testing to assess secondary causes of LUTS [4]. The IPSS questionnaire assesses storage symptoms, voiding symptoms, and an additional quality of life domain [5,6]. Urodynamic assessments and ultrasound may add additional prognostic information [4]. While treatment options may include watchful waiting for those with mild symptoms, medical and surgical therapies are available to those with moderate-to-severe LUTS. Pharmacological treatments for LUTS include: alpha-blockers (ABs) such as tamsulosin reduce smooth-muscle tone in the prostate and bladder neck, improving symptoms measured by IPSS scores [7,8] and are the most commonly prescribed medications [9]; 5-alpha reductase inhibitors (5-ARIs) such as finasteride reduce prostatic volume by inducing epithelial atrophy, improving symptoms measured by IPSS scores [10] and they are mostly reserved for patients with larger prostates, with a latency of onset of action [4]; and combination therapy (using AB+5-ARI or in combination with antimuscarinic drugs). Patients with larger prostates or severe symptoms may be candidates for surgical therapy, including transurethral resection of the prostate or other treatment modalities: laser enucleation of the prostate, convective radiofrequency water vapor therapy (Rezum), ablation (AquaBeam), prostatic urethral lift, prostatic arterial embolization, transurethral microwave thermotherapy, among others [11].

Phytotherapeutic agents are composed of extracts derived from the roots, seeds, bark or fruits of plants. In this review, we will be focusing on the effects due to the use of the extract of the berry of the American dwarf palm (saw palmetto, *Serenoa repens*) in BPE, which is the most popular and widely studied phytotherapeutic agent for the treatment of LUTS. While the purported mechanism of its relief of LUTS secondary to BPE is unknown, some of those proposed are hormonal effects by inhibiting the conversion of testosterone to dihydrotestosterone [12], producing an estrogenic and antiandrogenic effect [13,14]. It may also cause a dependent inhibition of 5-ARI in the stroma and epithelium of the prostate *in vitro* [15], anti-inflammatory effects [14] and the promotion of apoptosis [14,16,17]. Other mechanisms include the relaxation of smooth muscles of the detrusor and the prostate via α1-adrenergic receptors and placebo effect [18].

The most commonly used extracts are hexane, ethanolic, and supercritical CO_2. In this context, the hexane extract of *S. repens* (commercially known as Permixon) has been shown to have higher biologic activity and the lowest variability from batch to batch in free fatty acid content [19,20], possibly suggesting a higher efficacy and fewer adverse events. *S. repens* is usually taken in a daily dose of 320 mg. The most frequently reported adverse events are minor gastrointestinal symptoms, genitourinary problems, musculoskeletal complaints, and upper respiratory tract infections [21].

Phytotherapies are widely used in men suffering from urinary symptoms attributable to prostatic conditions, especially *S. repens* in BPE. Despite being widely researched, reviewed and used, these interventions are not officially recommended as a standard treatment for LUTS [4,22]. The last high-quality Cochrane review was published in 2012 [23]. Therefore, it is important to synthesize the available evidence, including a recently published trial [24] using the innovations in methodological standards for systematic review production. We, therefore, aimed to assess the effects of *S. repens* alone or in combination with other phytotherapy compared to placebo in men with LUTS due to BPE.

MATERIALS AND METHODS

1. Inclusion criteria

We followed a predefined protocol covering the full detail of our methods [25] and registered it in PROSPERO (CRD42021226655). Due to the nature of this study, ethical approval was not sought. We included parallel, randomized controlled trials regardless of their publication status or the language of publication as they provide a higher certainty of the effectiveness of interventions. We did not include cross-over or cluster trials. We included trials in men aged 45 years and over with LUTS/BPE with a minimum IPSS score of 8. We excluded trials of men with a known neurogenic bladder due to spinal cord injury, multiple sclerosis, or central nervous system disease and men who have been treated with surgery for BPE already. We included studies in which only a subset of participants are relevant to this review if data was available separately for the relevant subset. We included studies that compared *S. repens* to placebo for the main comparison. For a secondary comparison, we included

phytotherapeutic agents with *S. repens* as a component versus placebo.

2. Outcomes

We did not use the measurement of the outcomes assessed in this review as an eligibility criterion. Our primary outcomes included: urinary symptoms, quality of life, and adverse events. Our secondary outcomes included: peak urinary flow (Qmax), acute urinary retention, and surgical interventions for LUTS. All outcomes were assessed for short-term (<12 months) and long-term (≥12 months). We used clinically important differences to rate the overall quality of the evidence in the 'Summary of findings' table [26,27]. We considered an improvement of the IPSS score of three points as a minimal clinically important difference (MCID) to assess the efficacy and comparative effectiveness [28]. We used different thresholds of MCID based on the severity of IPSS with a threshold of three for men with mild LUTS, five for moderate LUTS, and eight for severe LUTS [28]. We used an MCID of one to assess the efficacy and comparative effectiveness [29].

3. Search methods for identification of studies

We searched the following sources from the inception of each database to the date of search and did not place restrictions on the language of publication.

We will search the following databases and trials registers:

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO; https://www.cochranelibrary.com/) from inception to searched 11 December 2020
- MEDLINE (Ovid MEDLINE ALL 1946 to Daily Update) from inception to searched 11 December 2020
- Embase (https://www.elsevier.com/) from 1974 to searched 11 December 2020
- ClinicalTrials.gov (https://www.clinicaltrials.gov/) from inception to searched 11 December 2020
- World Health Organization International Clinical Trials Registry Platform (ICTRP; https://trialsearch.who.int) from inception to searched 11 December 2020

Details of the search strategies are in the Supplementary File.

4. Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses, and health technology assessment reports. We also contacted the study authors of included trials to identify any further studies that we may have missed. We contacted drug/device manufacturers for ongoing or unpublished trials. We searched for unpublished studies by hand, searching the abstract proceedings of the annual meetings of the American Urological Association, European Association of Urology, and International Continence Society for the last three years (2018–2020).

5. Selection of studies and data extraction

We used Covidence to identify and remove potential duplicate records [30]. Four review authors working in pairs (GAA, LFT, NS, and CF) independently scanned the abstract, title, or both, of remaining records retrieved to determine which studies should be assessed further through Covidence. Four review authors (GAA, LFT, NS, and CF) investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, following the criteria for each provided in the Cochrane Handbook [31]. We resolved all discrepancies through consensus or recourse to a fifth review author (JVAF or JHJ). We presented a PRISMA flow diagram showing the process of study selection [32].

For studies that fulfilled the inclusion criteria, four review authors (GAA, LFT, NS, and CF) independently extracted information on study design, study dates, setting, and country, participant's characteristics, details of the intervention, comparison, and outcomes. We also collected data on funding sources and conflict of interest.

6. Assessment of risk of bias in included studies

We assessed the risk of bias in each study using a recently developed revision of the Cochrane 'Risk of bias' tool (RoB 2: a revised tool to assess the risk of bias in randomized trials) [33]. Four review authors (GAA, LFT, NS, and CF) independently assessed five domains of bias for each outcome considering the effect of assignment to the intervention. When the four authors disagreed, we decided on the final rating by consensus, with the involvement of a fifth author (JVAF). We used the RoB 2.0 Excel tool to manage the data supporting the answers to the signaling questions and risk of bias judgments (available at https://www.riskofbias.info/). The excel file with supporting judgments is available as supplementary material in the Open Science Framework platform [25].

7. Data synthesis

We calculated the mean difference (MD) with a 95% confidence interval (CI) for continuous outcomes and the

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risk ratio (RR) with 95% CI for dichotomous outcomes [34]. We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity in the meta-analysis [35,36]. We interpreted the I^2 statistic following the guidance of the Cochrane Handbook [37]. When we found heterogeneity, we attempted to determine possible reasons for it by examining individual study and subgroup characteristics. Publication bias: when ten or more studies investigating a particular outcome were included, we used funnel plots to assess small study effects. We summarized data using a random-effects model. We used Review Manager 5 software to perform the analysis [38]. We intended to perform subgroup analysis by age, the severity of symptoms and type of preparation, but the heterogeneity across interventions was too low. We performed sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes: restricting the analysis by considering the risk of bias, by excluding studies at an overall 'high risk' of bias. We intended to explore heterogeneity considering the baseline severity of symptoms, age, and type of *S. repens* preparation, but the overall heterogeneity was low. Only for the primary analysis heterogeneity could be explained by a single study (see RESULTS).

8. Summary of findings table

We rated the overall quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, which takes into account criteria related only to internal validity: study limitations (overall risk of bias), inconsistency, imprecision, and publication bias; but also to external validity; indirectness of results [39]. For each comparison, each of the authors independently rated the quality of evidence for each outcome as high, moderate, low, or very low. We constructed "Summary of findings" tables and resolved every discrepancy that appeared by consensus or, when needed, via arbitration by other review authors using GRADEpro [40]. These tables provided key information about the best estimate of the magnitude of effect in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome, and the rating of overall confidence in effect estimate for each outcome [41,42].

RESULTS

See Fig. 1 for the PRISMA flow diagram. We identified 6,684 records from databases and, after removing duplicates, we screened 5,520, of which we sought to retrieve 104. We could not retrieve 28 full-text articles, mostly older studies from the 80s and 90s, so 76 were assessed for eligibility. We excluded 49 studies for several reasons (see Supplementary File for a complete list of studies that were excluded, ongoing, or awaiting classification). We included 27 randomized controlled trials performed in an outpatient setting [24,43-68]. Most studies included men in their 60s with moderate LUTS and moderate-sizes prostate (see Table 1 for the characteristics of included studies). These studies included several types of formulation of *S. repens* which were divided into two comparisons: *S. repens* extract vs. placebo (main comparison, 19 studies, 3,630 randomized participants) and *S. repens* extract as a component of combined phytotherapy regimes vs. placebo (secondary comparison, 8 studies, 1,223 randomized participants). One of the studies included two arms of *S. repens*: in standard and high concentration [58]. We only included the standard dose to preserve comparability across studies. Two studies were funded by government agencies [44,46], ten studies were funded by the manufacturers of the product [24,50,51,54,58,59,61,63,65,66], and the other studies did not specify their funding sources.

1. Risk of bias

We here summarize the risk of bias of studies included

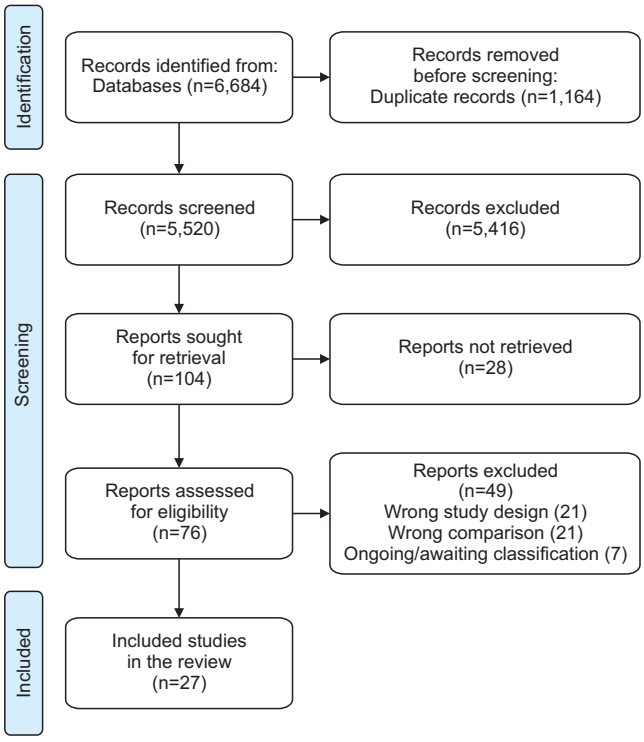

Fig. 1. PRISMA flow diagram.

Table 1. Characteristics of the included studies

Study	Trial period	Country	n	Follow-up	Brand (when available)	Age (y)		IPSS		Prostate volume	
						I	C	I	C	I	C
Studies comparing *Serenoa repens* with placebo											
Argirović et al. 2013 [43]	2008–2010	Serbia	199	6 months	Prostamol Uno	59.2±7.8	56.8±7.7	18.0±4.9	16.2±4.7	35.2±10.3	38.6±11.6
Barry et al. 2011 [44]	2008–2010	USA	369	72 weeks	Prosta-Urgenin Uno	61.25±8.72	60.7±8.08	14.42±4.29	14.69±4.75	N/A	N/A
Bauer et al. 1999 [45]	N/A	Germany	101	6 months	Talso uno	N/A	N/A	N/A	N/A	N/A	N/A
Bent et al. 2006 [46]	2001–2004	USA	225	14 months	Carbon dioxide extract	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 and Annoscia 1983 [47]	N/A	Italy	22	60 days	Permixon	68 (55–80)	68 (54–78)	N/A	N/A	N/A	N/A
Champault et al. 1984 [48]	N/A	France	110	30 days	Permixon	N/A	N/A	N/A	N/A	N/A	N/A
Descotes et al. 1995 [49]	1995	France	176	30 days	Permixon	65.6±8.4	67±7.6	N/A	N/A	N/A	N/A
BASTA 2006 [50]	N/A	International	1,011	12 months	Permixon	N/A	N/A	N/A	N/A	N/A	N/A
Gerber et al. 2001 [51]	1999–2000	USA	85	6 month	*Serenoa repens*	64.6±9.9	65.3±9.7	16.7±4.9	15.8±4.8	N/A	N/A
Glemain et al. 2002 [52]	N/A	France	329	52 weeks	Permixon	65.2±7.9	64.4±7.7	16.2±5.2	16.3±5.6	40.8±16.5	38.6±15
Hizli and Uygur 2007 [53]	2005	Turkey	60	6 months	Permixon	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. 2009 [68]	N/A	Korea	62	12 months	*Serenoa repens*	52.0	53.1	18.3	15.4	26.1	23.2
Marks et al. 2000 [54]	1997–1998	USA	44	6 months	Lipoidal extract	65.1±8.1	62.9±9.3	18.1±7.2	16.6±5.3	58.5±29.8	55.6±26.7
Reece Smith et al. 1986 [55]	N/A	UK	70	12 weeks	Permixon	66.15±5.86	67.03±6.03	N/A	N/A	N/A	N/A
Ryu et al. 2015 [56]	2012–2013	Korea	120	12 months	Permixon	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. 2008 [57]	N/A	China	94	3 months	Prostataplex	65.91	64.04	16.85	14.46	47.72	48.38
Sudeep et al. 2020 [58]	N/A	India	99	12 weeks	SPO	57.76±7.25	55.18±8.56	20.00±4.41	20.00±3.74	N/A	N/A
Willetts et al. 2003 [59]	1999–2000	Australia	100	12 weeks	Carbon dioxide extract	62.1±1.2	63.9±1.3	N/A	N/A	N/A	N/A
Ye et al. 2019 [24]	2014–2016	China	354	24 weeks	*Serenoa repens*	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 *S. repens* with placebo											
Carbin et al. 1990 [60]	1990	Sweden	55	3 month	Curbicin	62.0±6.7	61.2±5.8	N/A	N/A	N/A	N/A
Coulson et al. 2013 [61]	N/A	Australia	60	3 months	ProstateEZE Max	63±10.1	64.9±9.6	19.5	18	N/A	N/A
Iacono et al. 2015 [62]	N/A	Italy	185	6 months	+Tradamixina	N/A	N/A	20.6±5.4	N/A	N/A	N/A
Lopatkin et al. 2005 [63]	1997–2000	Russia	257	24 weeks	PRO 160/120	67±7	68±6	17.4±3.3	17.8±3.3	43.5±17.6	44.8±17.6
Metzker et al. 1996 [64]	N/A	Germany	40	12 months	Prostagutt forte	66.0	65.1	18.6	19.0	N/A	N/A
Morgia et al. 2014 [65]	2011–2012	Italy	225	12 months	Profluss	65	66	20	19	45	45
Preuss et al. 2001 [66]	N/A	USA	144	3 months	Cernitin AF	N/A	N/A	18.9	17.1	N/A	N/A
Schulz 2006 [67]	N/A	Germany	257	24 weeks	Verum	N/A	N/A	18	18	N/A	N/A

Values are presented as mean±standard deviation, median (interquartile range), or mean only.
IPSS, International Prostate Symptom Score; I, intervention; C, control; N/A, not available.

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in our analysis and summary of findings table. Only four studies were found to be at an overall low risk of bias [44,46,57,58]. Three studies were considered at an overall high risk of bias considering that they were open-label and outcome assessors were not blinded or due to problems with missing outcome data [53,56,68]. We rated the rest of the studies with 'some concerns' due to lack of detail of the randomization process and a lack of a protocol or analysis plan, which precluded an assessment of selective outcome reporting. See the Supplementary File to summarize the risk of bias assessment in each analysis and the supplementary file (excel spreadsheet) at the Open Science Framework [25].

2. Effect of interventions

1) Main comparison: *Serenoa repens* versus placebo

We included 19 studies with 3,630 participants in this comparison; however, not all studies reported the outcomes relevant to this review. The majority of studies did not specify the proprietary name of the intervention; however, some were identified: Permixon (8 studies), Prostamol Uno (1 study), Prosta-Urgenin Uno (1 study), Talso uno (1 study), Prostataplex (1 study), and SPO (1 study). See Table 2 for a summary of the main results and the Supplementary File for the supporting analysis.

(1) Urinary symptoms

S. repens results in little to no difference in urinary symptoms at short-term follow-up (2 to 6 months, MD -0.84, 95% CI -1.65 to -0.03; 1,725 participants; 10 studies; I^2=63%, high certainty of the evidence). All of the heterogeneity is explained by a single study of 304 participants that compared *S. repens* to placebo and showed a difference in IPSS scores of -2.77 (95% CI -3.71 to -1.83) [24], which is statistically significant but clinically unimportant compared to the minimal important difference of three points [6]; therefore we did not downgrade due to inconsistency considering a minimally contextualized approach [69]. We also did not downgrade for risk of bias since our main analysis is based on the sensitivity analysis, excluding studies at high risk of bias [53,56,68]. Some studies could not be included in the meta-analysis since they only reported p-values for each comparison. One study with 101 participants found that *S. repens* results in a reduction of urinary symptoms (p<0.01) [45]. Another study with 1,011 participants found a decrease in urinary symptoms with *S. repens* compared to placebo at 12 months follow-up (p=0.04) [50]. *S. repens* results in little to no difference in urinary symptoms at a long-term follow-up (12 to 17 months, MD 0.01, 95% CI -0.58 to 0.59; 1,018 participants; 5 studies; I^2=0%).

We found no difference based on the type of extract (Hexanic versus non-hexanic) (p-value= 0.27, see Analysis 1.1.4. in the Supplementary File).

(2) Quality of life

S. repens results in little to no difference in the quality of life at short-term follow-up (2 to 6 months, MD -0.15, 95% CI -0.30 to -0.01; 1,001 participants; 5 studies; I^2=0%, high certainty of the evidence). Moreover, *S. repens* results in little to no difference in quality of life at long-term follow-up (12 to 17 months, MD -0.12, 95% CI -0.37 to 0.13; 1,002 participants; 5 studies; I^2=39%). We did not downgrade for risk of bias since our main analysis is based on the sensitivity analysis, excluding studies at high risk of bias [53,56,68].

(3) Adverse events

S. repens does not increase the risk of adverse events (2 to 17 months, RR 1.04, 95% CI 0.80 to 1.34; 2,443 participants; 13 studies; I^2=16%, high certainty of the evidence). We did not downgrade for risk of bias since our main analysis is based on the sensitivity analysis, randomized excluding studies at high risk of bias [53,56]. Three studies were not included in the meta-analysis since they reported no adverse events [45,57,58]. The most commonly reported adverse events were: headache, gastrointestinal disorders (e.g., diarrhea, nausea and vomiting, stomach upset), upper respiratory (e.g., rhinitis), ejaculation disorders, musculoskeletal (e.g., arthralgia in the knees and muscular arm pain), and dizziness.

Two studies classified adverse events as severe and non-severe [50,52]. In one study, the severe adverse events described were dizziness in the placebo group and hypotension in the intervention group [52], whereas in the other study those described in the intervention group included colon cancer, gastrointestinal hemorrhage, urinary retention, and myocardial ischemia [50].

(4) Peak urinary flow (Qmax)

S. repens may result in an increase in Qmax compared to placebo at 2 to 6 months follow-up (MD 1.16, 95% CI 0.47 to 1.84; 1,833 participants; 13 studies; I^2=75%), however this effect dissolve at 12 to 17 month follow-up (MD 0.26, 95% CI -0.22 to 0.74; n=1,019; 5 studies; I^2=0%). See Fig. 2 for further details.

(5) Acute urinary retention

Two studies found little to no difference in the incidence of acute urinary retention between *S. repens* and placebo; however, the CIs included substantial benefits and harms (2 to 17 months, RR 3.30, 95% CI 0.52 to 21.05; 409 participants; 2

Table 2. Summary of findings for the main comparison: *Serenoa repens* compared to placebo/no treatment for lower urinary symptoms due to benign prostatic hyperplasia

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE[a])	Relative effect (95% CI)[b]	Anticipated absolute effects	
				Risk with placebo/no treatment	Risk difference with *S. repens*
Urologic symptom score Measured by IPSS scores (range 0–35) Higher scores indicate worse symptoms Follow-up: 2 to 6 months	1,725 (10 RCTs)	⊕⊕⊕⊕ HIGH	-	The mean urologic symptom score was 14.23	MD 0.84 lower (1.65 lower to 0.03 lower)
Quality of life Measured by IPSS-QoL score (range 0–6) Follow-up: 2 to 6 months	1,001 (5 RCTs)	⊕⊕⊕⊕ HIGH	-	The mean quality of life was 3.10	MD 0.15 lower (0.30 lower to 0.01 lower)
Adverse events Cumulative incidence Follow-up: 2 to 17 months	2,443 (13 RCTs)	⊕⊕⊕⊕ HIGH	RR 1.04 (0.80 to 1.34)	179 per 1000	7 more per 1000 (36 fewer to 61 more)

Patient or population: lower urinary symptoms due to benign prostatic hyperplasia. Setting: Australia, China, France, Germany, India, Italy, Korea, Serbia, Turkey, United Kingdom, and United States of America. Intervention: *S. repens*. Comparison: placebo/no treatment.

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; CI, confidence interval; IPSS, International Prostate Symptom Score; -, not available; MD, mean difference; QoL, quality of life; RR, risk ratio.

[a]:GRADE Working Group grades of evidence: (1) High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. (2) 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. (3) Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. (4) 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.

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

We did not downgrade the certainty of the evidence due to the risk of bias because these results are based on the sensitivity analysis excluding studies with high risk of bias. Moreover, we found no other concerns to further downgrade the certainty of the evidence.

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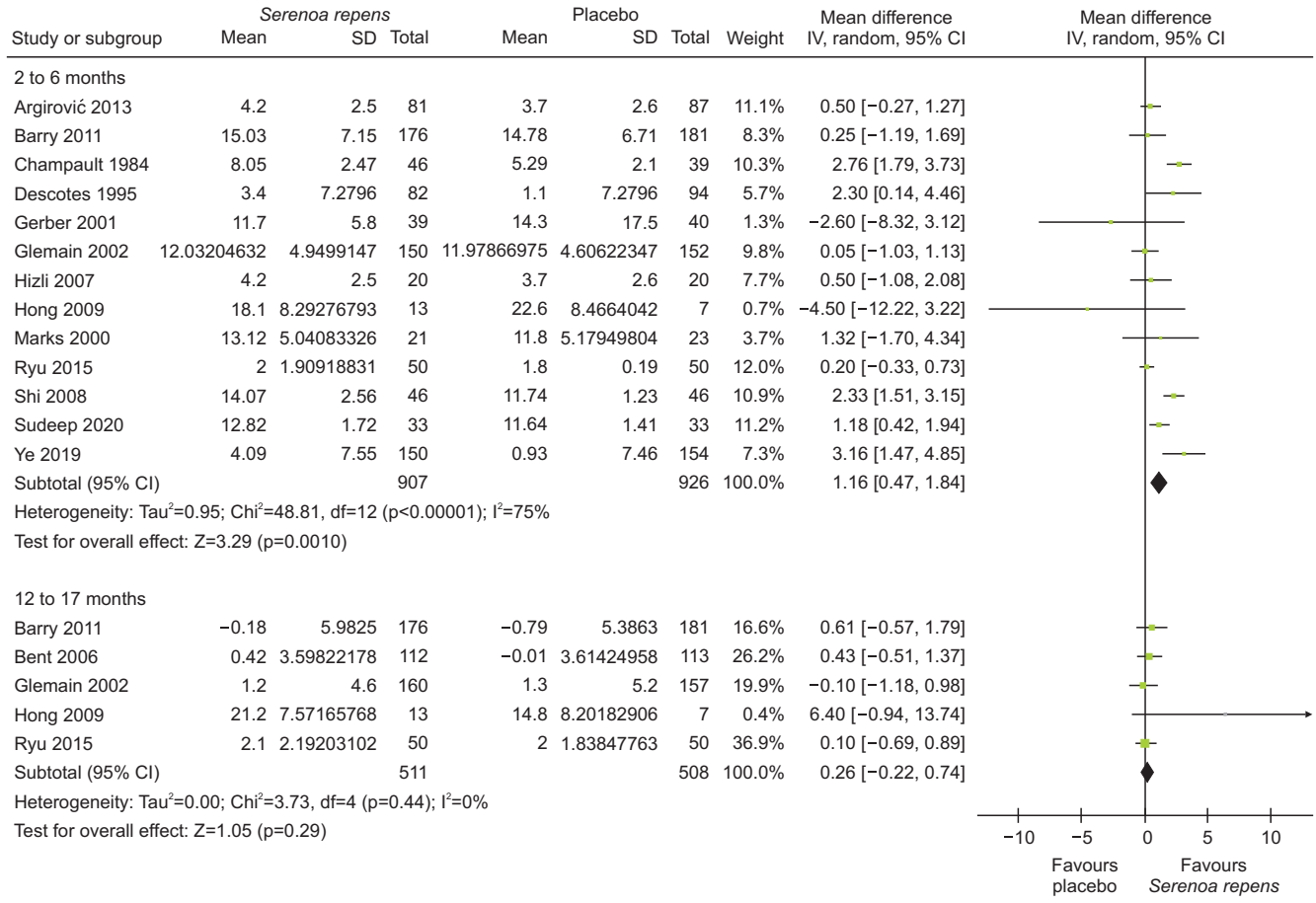

Fig. 2. Effects of *Serenoa repens* on peak urinary flow (Qmax). SD, standard deviation; CI, confidence interval.

studies; I^2=0%, see analysis in Supplementary File). Another study with 1,011 participants reported no difference in the incidence of acute urinary retention between participants who received *S. repens* and placebo (p-value not available) [50]. Moreover, two studies reported no cases of acute urinary retention [55,56].

None of the included studies reported the effects of *S. repens* on surgical interventions for LUTS.

2) Secondary comparison: phytotherapeutic agents with various agents including *Serenoa repens* versus placebo

We included eight studies with 1,223 participants in this comparison. These studies compared the effects of the following agents containing *S. repens* as a component: Curbicin, ProstateEZE Max, Serenoa Repens plus Tradamixine, PRO 160/120, Prostagutt forte, Profluss, Cernitin AF, and Verum. See Table 3 for a summary of the main results and the Supplementary File for the supporting analysis.

(1) Urinary symptoms

Phytotherapeutic agents with various agents, including *S. repens*, may reduce urinary symptoms compared to placebo at short-term follow-up but the evidence is very uncertain (12 to 48 weeks, MD -2.94, 95% CI -5.55 to -0.32; 416 participant; 3 studies; I^2=77%, very low certainty of the evidence). Three studies could not be included in the meta-analysis since they only reported p-values for each comparison: one study with 60 participants found a 36% reduction in the total IPSS median score in the active group (*S. repens*, lycopene, *Prunus Africana*, *Epilobium parviflorum*, and *Cucurbita pepo*) compared to 8% in the placebo group at three months follow-up (p<0.05) [61]. Another study with 225 participants found a greater decrease in IPSS scores for combination therapy (*S. repens*, lycopene, and selenium) compared to control at 12-month follow-up (median change 2.0, range -3 to -1, p<0.01) [65]. Finally, a study with 257 participants found a mean decrease in the intervention group of 6 points in the IPSS score in comparison with 4 points in the placebo group at 24 weeks follow-up (p<0.01) [67]. One study reported as an abstract did not provide comparative data (only a decrease in IPSS in the intervention group) [62].

Table 3. Summary of findings for the secondary comparison: phytotherapy with *Serenoa repens* versus placebo

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE[a])	Relative effect (95% CI)[b]	Anticipated absolute effects	
				Risk with placebo/no treatment	Risk difference with phytotherapy with *S. repens*
Urologic symptom score Measured by IPSS scores (range 0–35) Higher scores indicate worse symptoms Follow-up: 12 to 48 weeks	416 (3 RCTs)	⊕◯◯◯ VERY LOW[c,d,e]	-	The mean urologic symptom score was 11.1	MD 2.94 lower (5.55 lower to 0.32 lower)
Quality of life Measured by IPSS-QoL score (range 0–6) Follow-up: 6 to 12 months	265 (2 RCTs)	⊕◯◯◯ VERY LOW[c,f,g]		One study reported improvements ($p<0.05$) while the other did not.	
Adverse events Cumulative incidence Follow-up: 12 to 48 weeks	437 (3 RCTs)	⊕⊕◯◯ LOW[c,e]	RR 0.87 (0.56–1.36)	158 per 1,000	21 fewer per 1,000 (70 fewer to 57 more)

Patient or population: lower urinary symptoms due to benign prostatic hyperplasia. Setting: Sweden, Australia, Italy, Russia, Germany, USA. Intervention: *S. repens* with other phytotherapy. Comparison: placebo/no treatment.

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; CI, confidence interval; IPSS, International Prostate Symptom Score; -, not available; MD, mean difference; QoL, quality of life; RR, risk ratio.

[a]:GRADE Working Group grades of evidence: (1) High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. (2) 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. (3) Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. (4) 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.

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

[c]:Downgraded one level due to concerns about bias: all studies did not have a pre-specified analysis plan or protocol (some concerns of selective outcome reporting).

[d]:Downgraded one level due to concerns about inconsistency: high statistical inconsistency (I^2=77%).

[e]:Downgraded one level due to imprecision: wide confidence interval.

[f]:Downgraded one levels due to imprecision: the included studies reported p-values and we are uncertain about effect sizes.

[g]:Downgraded one level due to inconsistency: the included studies reported different effects.

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(2) Quality of life

We are very uncertain on the effects of these agents on quality of life (very low certainty of the evidence). One study with 40 participants found that 84.2% of the participants in the intervention group had improvements in their quality of life after six months of treatment in comparison with 11.1% of improvement in the placebo group (p<0.001) [64]. Another study with 225 participants found little to no difference in the quality of life scores (median change 0, range -0.1 to 1) [65].

(3) Adverse events

Phytotherapeutic agents with various agents, including *S. 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 0.87, 95% CI 0.56 to 1.36; 437 participants; 3 studies; I^2=0%, low certainty of evidence). Two studies reported that there were no adverse events [60,61]. Another study with 225 participants reported no significant differences in treatment-related adverse events (p=0.67) [65]. The most commonly reported adverse events were: headache, gastrointestinal disorders (e.g. diarrhoea, nausea and vomiting, stomach upset), upper respiratory (e.g. rhinitis), ejaculation disorders, musculoskeletal (e.g. arthralgia in the knees and pain), and dizziness.

(4) Peak urinary flow (Qmax)

The effects of these phytotherapeutics agents on this parameter were inconsistent (MD 1.46, 95% CI -0.53 to 3.45; 220 participants; 3 studies; I^2=76%). Another study with 152 participants found little to no difference in the change of Qmax in the intervention group compared with placebo (median change 0.8, range 0.1 to 1.7) [65].

None of the included studies in this comparison reported the effects of these treatments on acute urinary retention and surgical interventions.

DISCUSSION

We conducted a systematic review including 27 randomized controlled trials assessing the effects of *S. repens* alone or in combination with other phytotherapy. For *S. repens* alone, high certainty evidence indicates that there is little to no clinical benefits for patients with LUTS. For *S. repens* in combination with phytotherapy, we found similar results but with greater uncertainty.

A recent systematic review and network meta-analysis on the same topic included 22 randomized clinical trials with multiple comparisons of hexanic and non-hexanic extract of *S. repens* (HESr and nHESr) with alpha-adrenergic agonists and placebo [70]. The authors concluded that there were clinically insignificant improvements in IPSS for HESr and nHESr at 12 weeks; however, their CIs included little to no difference (placebo vs. HESr: MD -0.47, 95% IC -2.69 to 1.74; nHESr vs. placebo: MD -1.69, 95% CI -4.36 to 0.98). Moreover, the authors reported improvements in IPSS using HESr compared to nHESr; however, their reported CI includes little to no difference (nHESr vs. HESr: MD -2.16, 95% CI -5.64 to 1.30), similar to our findings in our subgroup analysis. Regarding Qmax, their results were similar to ours, with an increase of peak urinary flow of 1 to 2 points compared with placebo (nHESr +2.4 and HESr +1.04). Finally, the review was limited due to fewer studies comparing *S. repens* with placebo (7 in that review compared to 15 in ours) with a substantial imprecision in their results. Another systematic review included seven randomized clinical trials comparing HESr (restricted to Permixon) with placebo for the outcomes of nocturia, Qmax and adverse events but did not assess IPSS [71]. The peak urinary flow analysis reported an increase of Qmax (MD 3.37 points) compared to the increase we found (MD 1.16 points). They also found a decrease in the episodes of nocturia that may be clinically insignificant (MD -0.31, range -0.59 to -0.03); however, the findings on adverse events were similar to ours. Finally, a systematic review including 15 randomized clinical trials and 12 observational studies comparing Permixon with placebo assessed nocturia, Qmax and adverse events but did not assess IPSS [72]. This review also found a small reduction in nocturia that may be clinically insignificant (MD -0.64, range -0.98 to -0.31) and similar results regarding adverse events. This systematic review showed a peak urinary flow improvement of 2.75 mL/s which is slightly higher than our findings. While the overall clinical important effects of *S. repens* remain unproven, higher concentrations may result in small but positive improvements in LUTS symptoms as described in a single study [58].

The 2020 Guideline of the American Urological Association focuses on the treatment of LUTS attributed to BPH using common surgical techniques and minimally invasive surgical therapies; thus, the information on the different types of medical interventions is not deepened, much less the use of *S. repens* [11]. Despite this, we found a previous version of this guideline from 2010, where it is mentioned that the available data do not suggest that *S. repens* has a clinically significant effect on LUTS secondary to BPH [73]. Furthermore, it adds that no dietary supplement, combined herbal medicine or other unconventional therapy is recommended to manage LUTS secondary to BPH due to the

paucity of high-quality published trials [73]. The European Association of Urology guidelines on the management of non-neurogenic male LUTS makes recommendations on therapeutic and surgical interventions in patients with BPH [4]. In addition, a comprehensive and exhaustive bibliographic search was carried out on herbal medicine, especially on *S. repens*. This guide recommends offering the hexane extract of *S. repens* to men with LUTS who want to avoid possible adverse events, especially those related to sexual function (weak recommendation), informing the patient that the magnitude of efficacy may be modest (strong recommendation) [4]. The guidelines by the Korean Urological Association for the evidence-based diagnosis and treatment of BPH and basic information on diagnostic testing, drug therapy, and surgical treatment [74]. This guide recommends drug therapy as the primary treatment in patients with moderate or severe symptoms, reserving surgical interventions to those with moderate to severe LUTS and for patients who develop acute urinary retention or other complications related to BPH [74]. However, this guideline does not mention phytotherapy or *S. repens* in managing urological symptoms in BPH.

The overall certainty of the evidence was high for the main comparison considering minor concerns due to inconsistency and focusing on our main sensitivity analysis excluding studies at high risk of bias. For the secondary comparison, however, we could not perform sensitivity analysis since all studies were found to have limitations in their report. This highlights the importance of researchers and journal editors adhering to CONSORT [75]. Moreover, the CIs were wide, and we found substantial heterogeneity, which could be partially explained by the differences in components across combined agents. Not all studies the full details of critical outcomes such as urinary symptoms, quality of life, and adverse events, which would be desirable considering patient's values and preferences [76].

Our study has several limitations. First, we initially aimed to assess the effects of *S. repens* compared to placebo or other treatments; however, based on the emerging evidence from other reviews, we considered that if *S. repens* was not more effective than placebo, comparisons to other treatments may be misleading; therefore we focused on its effects alone or in combination with other phytotherapy. Second, we could not retrieve some full-text articles; however, based on our inspection of other systematic reviews, we estimate that many of these studies might be observational or might not provide sufficient data relevant to our main outcomes [23]. This is because older studies focus on nocturia and not IPSS scores, which is currently the mainstay outcome for this condition. Third, we could not incorporate several studies in meta-analysis due to missing data (missing standard deviation or standard error), but we reported these results separately. Finally, we could not perform many predefined funnel plots, subgroup, and sensitivity analysis due to the scarcity of data, low heterogeneity across comparisons, and few trials included in each comparison. Nevertheless, our systematic review has several strengths. It is the most up-to-date comprehensive review on this topic, including the greatest number of studies per comparison due to a thorough bibliographic search and incorporating new review methods (such as Risk of Bias 2). Moreover, it is the most up-to-date review using GRADE, which allows for the seamless incorporation of evidence into recommendations, and it is the preferred approach for guideline development [77,78].

CONCLUSIONS

S. repens alone results in no clinical benefits for men with LUTS. There is greater uncertainty in the effects of *S. repens* in combination with other phytotherapy. While others reviews on this subject found small effect sizes for some formulations, their CI indicated no important effects. Our review incorporating GRADE includes a comprehensive interpretation of these effect estimates. Future studies need to fully report their methods (including randomization and allocation concealment together with their prospectively registered protocols) and funding sources.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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This protocol predominantly used a template structure (background and methods) from a previous protocol by one of the authors on a different topic [8] and the latest Cochrane review [23].

AUTHORS' CONTRIBUTIONS

Research conception and design: Juan Víctor Ariel Franco and Jae Hung Jung. Data acquisition: Camila Micaela Escobar Liquitay, Leonel Fabrizio Trivisonno, Cecilia Fieiras, Nadia Sgarbossa, and Gustavo Ariel Alvez. Statistical analysis: Juan Víctor Ariel Franco and Jae Hung Jung. Data analysis and interpretation: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript:

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20210254.

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