
Review

Serenoa repens (saw palmetto) for lower urinary tract symptoms (LUTS): The evidence for efficacy and safety of lipidosterolic extracts. Part I.

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Abstract: Lower urinary tract symptoms (LUTS) are classically characterized as being related to storage (e.g., frequency, urgency, and nocturia) or flow (e.g., weak stream, intermittency, straining, and incomplete emptying). Conventional prescription medications such as α 1-blockers and 5 α -reductase inhibitors are used to treat progressive LUTS in men. Due to the adverse events associated with these prescription drugs, many patients with mild-to-moderate LUTS may decide to initiate treatment with non-prescription medications and/or dietary supplements. The lipidosterolic extract of *Serenoa repens* (LSEsr), at a recommended daily dose of 320 mg/day, has been the focus of numerous peer-reviewed studies and review articles concerning the treatment of LUTS, since the first publication in 1983 by Boccafroschi to the most recent publication in 2021 by Russo. Although it seems improbable that the beneficial effect of LSEsr reflects a placebo effect given the consistent degree of efficacy comparing various studies published in different countries over a span of almost 40 years, this has been the prevailing impression stemming from essentially three publications in the Western medical literature. And despite publications reporting findings of almost identical efficacy using LUTS endpoints such as the International Prostate Symptom Score (IPSS), the quality of life score (QoL), and the peak urinary flow (Qmax) in comparing LSEsr to the α -blocker tamsulosin or the 5 α -reductase inhibitor finasteride, and the recognized acceptance of the hexane lipidosterolic extract product (Permixon®) as an herbal medicine in Europe showing value in the treatment of LUTS, the use of LSEsr remains controversial in the US. Contributing to such an opposing view in the US are the wide variability in quality, composition, and dosage of *Serenoa* products, the commercial prevalence of dried berry powder supplements, and the lack of awareness of a standardized *Serenoa* phytotherapy lipidosterolic profile. Can the controversy over the efficacy LSEsr in the context of LUTS be resolved? By understanding the main literature that has led to clinical practice guidelines for *Serenoa repens* for LUTS in Europe and the US, and an in-depth analysis of the totality of the clinical literature concerning dose, extraction method, and quality of the *Serenoa* product used, it should be possible to answer this question.

Given the extent of this global analysis, this report will be presented in three sections. Part I will introduce LUTS. What are the demographics of LUTS? What symptoms are assessed by LUTS and how do we quantify LUTS? Why would a non-prescription item be a valuable consideration in LUTS treatment versus other treatment options? What is basic information about *Serenoa repens* and what defines a standardized LSEsr product? What are the published trials that have affected the acceptability of *Serenoa repens* in the treatment of LUTS? Finally, a major portion of Part I will discuss the four major reviews of *Serenoa repens* versus LUTS that have influenced how it is accepted in the USA, in Europe, and other parts of the world. Part I, therefore, lays the groundwork and is foundational for the important findings relating to LUTS and *Serenoa repens* that will be presented in Parts II and III.

Keywords: lower urinary tract symptoms; LUTS; benign prostatic hyperplasia; BPH; saw palmetto; *Serenoa repens*; phytotherapy; lipidosterolic extract of *Serenoa repens* (LSEsr); hexanic extract of *Serenoa repens* (HESr)

1. Introduction: LUTS, Symptom Scores, and Treatment Options

The world population is growing. In 30 years, the population will have increased by 29%, from the 2018 estimate of 7.6 billion to 9.9 billion in 2050. With this population growth, the percentage of those who are age 65 and older is projected to increase from 9% to 16%. In more developed countries this increase in the elder population may reach 27%, almost one of every three people! With this change in demographics, lower urinary tract symptoms (LUTS) will emerge as a top priority issue in healthcare and quality of life [1].

LUTS and benign prostatic hyperplasia (BPH) are commonly associated. BPH is a histological finding within the prostate gland found in 50% of men in their 50-60s, and in nearly 90% of men over 80 years of age. But only about 25% of men with BPH develop benign prostatic enlargement that causes obstruction and leads to LUTS. To confuse matters, sometimes small prostates are associated with LUTS and big prostates are not. The conclusion is that LUTS is multifactorial in its etiology and cannot simply be equated with prostate pathology [2]. In this report, we will refer to "LUTS" as lower urinary tract symptoms in men that occur with or without documentation of BPH.

Quantifying LUTS is most commonly done using the International Prostate Symptom Score (IPSS) or the American Urological Association Symptom Index (AUA-SI) [3,4]. Both scoring systems include seven questions relating to urinary symptoms: 1) incomplete emptying; 2) frequency; 3) intermittency; 4) urgency; 5) weak stream; 6) straining, and; 7) nocturia. The IPSS has an additional question concerning the patient's quality of life, while the original AUA-SI did not. In short, LUTS is a collective term used to describe subjective urinary symptoms that typically affect (1) urine storage and (2) flow, with these two categories considered as subsets of the IPSS [5,6]. Storage symptoms can be remembered using the acronym FUN, for Frequency, Urgency, and Nocturia. Storage symptoms are also referred to in many publications as "irritative" or "filling" symptoms. Flow symptoms can be remembered by the acronym WISE, for Weak stream, Intermittency, Straining, and incomplete Emptying. Flow symptoms have also been termed as "obstructive" or "voiding," but detailed urodynamic testing specifically designed for diagnosing outlet obstruction has failed to correlate obstructed from non-obstructed patients using the obstructive (aka flow or voiding) subset score of the IPSS [7]. The terminology is confusing, with "storage," "filling," and "irritative" being synonymous, as are the descriptors "flow," "voiding," and "obstructive." Of key importance is that the storage (aka filling, irritative) subset of the IPSS is associated with a two-fold or greater effect on what bothers patients, compared to the voiding (flow, obstructive) subset. This "bother" is what significantly diminishes the QoL score [8]. In other words, the acronym "FUN" for frequency, urgency, and nocturia, is ironically the opposite case in men with LUTS. This additional data input of the IPSS is termed the "bother question" or BQ and is sometimes designated as IPSS-BQ. Both the IPSS and the AUA-SI use the following to define the degree of LUTS: 1-7 points = mild LUTS; 8-19 = moderate LUTS, and; 20-35 = severe LUTS.

Treatment options are needed for men when they may begin to experience mild-to-moderate LUTS. As symptoms intensify, conventional medications such as α_1 -blockers and 5 α -reductase inhibitors are routinely prescribed [9,10]. However, these drugs are often associated with adverse effects, such as dizziness, fatigue, and sexual dysfunction. In addition, the use of multiple drugs, aka "polypharmacy," increases the risk of drug interactions, a still greater hazard for the elderly population affected by LUTS. Over 20 years ago, examining serious adverse drug reactions (ADRs) and drug-related fatalities in the U.S., Lazarou et al. reported over 2 million serious ADRs and over 100,000 drug-related fatalities [11]. Since that publication in 1998, the number of new drugs in the U.S. has increased by close to 1000. With such high risks for pharmaceutical ADRs, many patients experiencing mild-to-moderate LUTS could significantly benefit by initiating treatment

with medications and/or dietary supplements that have a minimal risk of ADRs, that lack significant drug interactions, and that are unassociated with sexual dysfunction, and surely do not add to the risk of a drug-related fatality. Such agents would then fill an unmet need as an effective option for the management of mild-to-moderate LUTS, and potentially as a means to halt the progression of LUTS/BPH that otherwise could eventually necessitate an invasive procedure. Clinicians should be aware of the clinical data involving the use of such supplements and understand which supplement(s) are efficacious during this early phase of LUTS. But the value of supplements, and in particular phytotherapeutics such as LSESr remains controversial, especially in the United States. In contrast, LSESr products are frequently used in Europe and other parts of the world to treat LUTS and require either a physician's prescription or more intensely regulated non-prescription products. In the United States, Serenoa-derived products are loosely marketed as "saw palmetto," and vary widely in quality, ingredients, and dosage. This situation is a consequence of such products being unregulated or scrutinized by any agency. This has muddled our ability to ascertain the efficacy and safety of Serenoa repens as a phytotherapeutic agent of value in the treatment of LUTS.

2. The Basics about Serenoa Repens

The fruit (berries) of Serenoa repens contain 10% to 15% lipids. The extracted oil from ripe berries is rich in total fatty acids, free fatty acids, fatty acid esters, fatty alcohols, and sterols. The lipidosterolic extract of Serenoa repens (LSESr) is not pharmacologically equatable with crushed saw palmetto berry powder supplements that are sold in the United States and which have no established efficacy. The chemical profile for a quality LSESr with established clinical efficacy is published in the European Union (EU) monograph [12], and the lipid profile to validate saw palmetto extract identity has been developed by the US Pharmacopeia (USP) and requires a minimum of 80% total fatty acids, with specific fatty acid ratios [13]. The EU monograph for LSESr also established a minimum standard of 80% total fatty acids and additionally mandated the need to use a hexane extraction process. The requirements for free fatty acid content have not been addressed by either organization. The recommended dose of LSESr is 320 mg/day, administered once daily or in two divided doses of 160 mg [12].

Since the majority of OTC saw palmetto products vary widely in quality, composition, and dosage it is not surprising that the use of such non-standardized products along with variations in study design and patient populations has resulted in mixed clinical trial outcomes.

There have been two large US studies that showed no benefit of Serenoa repens (*S. repens*) compared with placebo. One used a supercritical carbon dioxide (the *S. repens* Treatment for Enlarged Prostates [STEP] trial in 2006 [14], and the other an ethanol extraction product of Serenoa repens (Complementary and Alternative Medicine for Urological Symptoms [CAMUS] trial in 2011 [15]. These two negative studies represent a conundrum in assessing LSESr versus LUTS. In contrast, a standardized LSESr product, Permixon®, obtained using hexane extraction, has been studied in at least 35 clinical trials between 1983 and 2015, and has been found to be effective for the treatment of LUTS [16-24]. A possible explanation for such differences in efficacy may relate to the impact of the extraction methodology and product quality. What will be presented in this global review indicates that a standardized lipidosterolic extract is effective in the treatment of LUTS by improving urinary symptoms as measured by the IPSS, patient QoL, and peak urinary flow.

Because such a standardized profile is lacking for many Serenoa products, it is important to educate patients and physicians about selecting high-quality products that comply with recognized composition and dosage. Crucial questions about LSESr remain. Is there any difference in LSESr efficacy when a different extraction process is selected? Does the fatty acid content, free and/or total, play a significant role in efficacy? With all of these issues needing resolution, this investigation was undertaken to perform an in-depth

analytical review of the entire body of peer-reviewed literature relating to the use of LSEsR in the treatment of LUTS. The goals set forth were:

- 1) to critically evaluate the three major LSEsR extraction techniques (hexane, ethanol, CO₂) used in treating LUTS and present information foundational in reading the LUTS literature, (i.e., the European versus the American perspective of LSEsR in LUTS treatment);
- 2) to discuss LSEsR side effects in short studies involving months, and in long-term studies spanning years;
- 3) to better understand the time to onset of action of LSEsR;
- 4) to ascertain the durability of efficacy;
- 5) to investigate whether LSEsR used in long-term studies can prevent the progression of LUTS and BPH; and,
- 6) to conclude whether or not the effects of LSEsR reflect a placebo effect?

Given the scope and depth of this global investigation, findings will be presented in three parts. Part I will discuss the foundational issues enumerated above as 1; Parts II and III will present derivative results involving topics 2-4, and 5-6, respectively.

3. Perspectives on *Serenoa repens* Efficacy vs. LUTS

In the United States, several clinical studies investigating the efficacy of various LSEsR products for the treatment of LUTS have had mixed results. Two large clinical trials failed to show a benefit for LSEsR versus placebo and have led to a generally negative impression about using LSEsR for LUTS [14,15]. Internationally, some reviews and meta-analyses failed to find consistency in the published literature concerning LSEsR efficacy [25,26]. Four publications have been highly influential in the clinical acceptance of LSEsR in LUTS therapy: the European Scientific Cooperative on Phytotherapy (ESCoP) 2003 monograph [27], the 2012 Cochrane meta-analysis [26], the 2014 European Medicines Agency (EMA) monograph [12], and the 2014 guidelines of the American Urology Association (AUAG) [28]. In these four documents, each cited reference was retrieved and reviewed by this author (SBS). Data extraction relating to IPSS, QoL, Q_{max}, and side effects from each publication, and from non-English-language papers translated in full into English using Systrans, Google Translate, and Easy Translator was done by SBS.

Seven criteria were selected as being reasonable to ascertain if a study was evaluable to assess LSEsR efficacy for LUTS. These criteria were: 1) ≥20 patients at study end, 2) a study duration of ≥ 2 months, 3) one or more available LUTS clinical endpoints IPSS or AUA-SI, QoL index, maximum urinary flow (Q_{max}), 4) evaluation of LSEsR monotherapy studies, 5) a 320 mg dose of *S. repens* given once daily or 160 mg twice daily, 6) an identified extraction method for the *Serenoa* product such as ethanol, carbon dioxide or hexane, and therefore an LSEsR, and 7) consistent and interpretable data. Detailed notes were taken during the reading of each citation to understand the relevance of the paper to the body of scientific literature and the conclusions made by the author(s).

3.1. *The European Scientific Cooperative on Phytotherapy (ESCoP 2003)*

The European Scientific Cooperative on Phytotherapy (ESCoP), referred to here as ESCoP 2003, published a monograph on *Serenoa repens*. This is a ten-page report, with four pages related to references [27]. Of the 93 references, 44 were basic science studies that were not relevant to the issue of LSEsR efficacy, and four references could not be obtained. An additional 22 references involved short studies of less than 2 months duration or were patient cohorts of fewer than 20 patients. The remaining 23 studies that met evaluability criteria were analyzed for objective findings of IPSS, QoL, and Q_{max} reported in each paper, or that could be determined by (SBS) from the study findings. Only six studies presented data for all three parameters. Fifteen studies were published either before IPSS scoring or elected not to use IPSS. In these cases, a clinical assessment was made (SBS) on

urinary symptom change from data reported in the cited paper. A summary of the clinical findings in the 23 evaluable studies from ESCOP 2003 is shown in Table 1.

Table 1. Twenty-three studies cited in ESCOP 2003 met eligibility for LSESr efficacy.

Senior Author	Ref. (#)	Year	Extraction Method	Serenoa Patients (#) ^a	Study Duration (mo.)	IPSS		QoL		Q _{max}	
						Δ	%	Δ	%	Δ	%
Cirillo-Marucco	[29]	1983	Hexane	47	4		56 §			+ 4.55	50.4§
Cukier ψ	[30]	1985	Hexane	73	2		33.3 §§				
Pescatore	[31]	1986	Hexane	30	3					+ 2.5	26.9
Authie	[32]	1987	Hexane	500	3		78.1 *				
Ollé Carreras	[33]	1987	Hexane	40	2		67.5 ‡‡				
Orfei	[34]	1988	Hexane	30	3		50.3 ^^	-2.17		+ 0.03	0.2
Mattei ψ	[35]	1990	CO ₂	20	3		55.2 ^				
Dathe	[36]	1991	Hexane	49	6					+5.90	49
Fabricius xx	[37]	1993	CO ₂	176	6		39% and 59%				
Romics	[38]	1993	Ethanol	31	12					+ 4.3	39.0
Vahlensieck	[39]	1993	CO ₂	1,334	4		46.7 §§§				
Vahlensieck	[40]	1993	CO ₂	312	3					+ 5.8	51.8
Braeckman	[41]	1994	CO ₂	305	3	-6.6	34.7	-1.54	41.6	+ 2.41	26.4
Bach	[42]	1996	Ethanol	315	36		73.0			+ 6.1	45.5
Carraro	[17]	1996	Hexane	467	6	-5.8	37.0	-1.38	38.0	+2.7	25.0
Kondas	[43]	1996	Ethanol	38	6					+4.08	39.0
Braeckman	[44]	1997b	CO ₂	125	3		64.0				29.8
Braeckman	[45]	1997a	CO ₂	67	12	-10.2	60.0	-1.5	41.7	+2.6	23.8
Gerber	[46]	1998	Ethanol	46	6	-7.6	37.0			- 0.7	- 5.0
Derakhshani	[47]	1997	Ethanol	1,047	3	-7.4	40.4	-1.61	45.9	+3.7	30.8
Eickenberg	[48]	1997	Ethanol	6,967	6	-8.0	44.4	-1.8	37.5	+ 3.0	23.1
Redecker	[49]	1998	Ethanol	50	3		47.7 ^^			+ 3.4	24.0
Ziegler Ж Ж	[50]	1998	Ethanol	109	3		35.6			+3.72	28.9
Average Changes for All Studies				530	6	-5.3	25%	-1.7	40%	+3.4	27%

Note: Clinical assessment of the change in IPSS, QoL, and Q_{max} presented in the referenced paper, or as determined by SBS.

^a Number of patients at study end, or as reported.

ψ Placebo-controlled study.

*Study prior to IPSS; nocturia, frequency, and urgency improvements of 82%, 67%, and 85.3%, respectively (average improvement 78.1%); average complete resolution of these symptoms was 43.5%.

§ Study done prior to IPSS; raw data on nocturia; study also included Q_{max} results.

§§ Study done prior to IPSS; raw data on nocturia.

§§§ IPSS not used. Number shown based on change in frequency and nocturia (urinations) pre- versus post-*S. repens*.

^ Using scores from frequency, nocturia, and incomplete emptying.

^^ Using scores from frequency, nocturia, urgency, weak stream, and straining at beginning and end of study.

^^^ Only able to evaluate nocturia with before and after scores.

‡‡ IPSS not used. Number shown based on change in frequency with complete resolution in 27/40 patients.

xx Fabricius's study did not use IPSS and reported on frequency and nocturia (39% decrease in frequency and 59% decrease in nocturia). Maximum average nocturia events dropped from 10 to 3.

Ж Ж Ziegler did not use IPSS, so his reported symptoms were based on percent improvement involving weak stream, hesitancy, incomplete emptying, frequency, and nocturia.

Δ, mean change; -, negative change; #, number; %, percent change; +, positive change; CO₂, carbon dioxide; IPSS, International Prostate Symptom Score; mo., month; QoL, quality of life; Q_{max}, peak urinary flow (ml/s); Ref., reference citation.

A thorough investigation of the fifteen reports that assessed LUTS but did not use the IPSS revealed significant findings often not referred to in other publications. Cirillo-

Marucco presented raw data on nocturia (56% improvement), and their study also assessed Q_{\max} (+4.55 ml/s, 50% improvement) [29]. Cukier presented raw data on nocturia from a placebo-controlled trial, which related to a 33% clinical improvement [30]. Pescatore evaluated urinary flow and post-void volume. After 90 days, Q_{\max} improved by 27% (+2.5 ml/s) [31]. Authie reported improvements in nocturia, frequency, and urgency by 82%, 67%, and 85%, respectively [32]. The Ollé Carreras study reported changes in frequency symptomatology with complete resolution in 67.5% (27/40) of patients [33]. Calculated values (SBS) of IPSS, QoL, and Q_{\max} , reporting 50.3% change for IPSS, a -2.17 improvement in QoL, and a +0.03 ml/s (0.2% change) in Q_{\max} from the study data, as presented in Table 1. Clinical data from Orfei were determined from reported scores for frequency, nocturia, urgency, weak stream, and straining at the beginning and end of the study [34]. Mattei's placebo-controlled trial with Serenoa repens presented clinical outcomes for frequency, nocturia, and incomplete emptying [35]. A 55% improvement in symptom score was calculated from the study data (SBS). Dathe [36] and Romics [38] both reported improvements in urine flow (Q_{\max} +5.9 ml/s, 49% improvement and +4.3 ml/s, 39% improvement, respectively). Fabricius did not use IPSS but reported a 39% decrease in frequency and a 58% decrease in nocturia; these findings are presented in Table 1. The study found maximum average nocturia events dropped from 10 to 3 [37]. Vahlensieck published two papers in 1993 in ESCOP 2003. For the 1,334-patient study, the data reflect changes in frequency and nocturia before and after Serenoa repens therapy [39]. In this large study, IPSS was calculated and indicated an improvement of 46% (SBS). The second Vahlensieck study evaluated 312 patients and used a 4-point scale to assess flow and post-void volume [40]. The use of Serenoa repens led to a Q_{\max} improvement of +5.8 ml/s (51%). Kondas, et al. only reported data on urinary flow (Q_{\max} +4.08, 39%) [43]. For Redecker, multiple graphs within the publication were analyzed (SBS) to objectify the clinical endpoints of nocturia and peak urinary flow, with the finding of a 47.7% decrease in nocturia, and an improvement in peak urinary flow by +3.4 ml/s (24% improvement). Figure 1 is adapted from Redecker and Funk's publication in German [49].

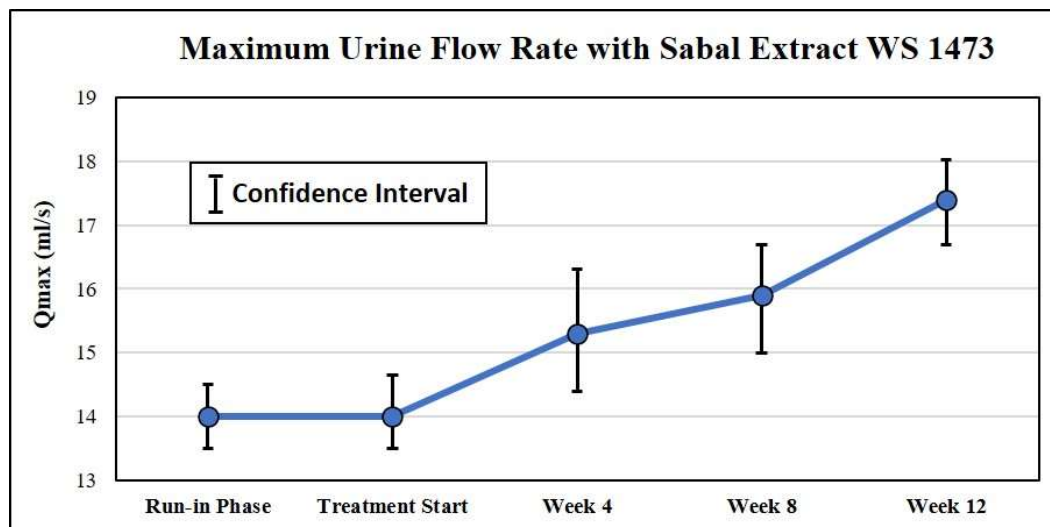


Figure 1. Data on maximum urine flow rate with Serenoa extract over a 12-wk study. Peak urinary flow rate (Q_{\max} , ml/s) mean value curve with a 95% confidence interval reported. Modified based on Redecker, et al [49].

Ziegler used a visual analog scale instead of the IPSS to record changes concerning weakness of the urinary stream, hesitancy, incomplete emptying, frequency, and nocturia. Improvements ranged from 20% to 50%, with an overall improvement of 35.6%. Peak urinary flow data assessment (SBS) showed an improvement of 28.9%, with a change from a

baseline value of 12.83 to 16.56 (+3.73) ml/s by week 12 [50]. The IPSS data from the remaining eight citations considered by ESCOP 2003 are detailed in Table 1. As per the last row of this table, the mean values of the 23 evaluable ESCOP studies for IPSS, QoL, and Q_{max} were -5.3 points (25% improvement), -1.7 (40% improvement), +3.4 ml/s (27% improvement), respectively. No differences in the results were related to hexane, ethanol, or carbon dioxide extraction methodology. The mean patient numbers and study duration (months) were 530 and 6, respectively. Clinically, there was clear efficacy of LSEsr in LUTS in the evaluable citations considered by ESCOP 2003. Surprisingly, this was not the official position taken by the ESCOP authors. My conclusion is that ESCOP 2003 authors did not perform a detailed assessment of evaluable studies.

3.2. The Cochrane Meta-Analysis (Cochrane 2012)

The first Cochrane meta-analysis of *S. repens* was published in 2000 [51], updated in 2002 [52] and 2009 [53], and last revised in 2012 [26]. Cochrane 2012 included 32 randomized controlled trials and listed a total of 36 primary references that were considered conclusive as to the efficacy and toxicity of LSEsr versus LUTS. Three distinct studies by Braeckman were referenced, but Braeckman 1994, a multicenter open study [41], and Braeckman 1997, a dosing regimen study [45], were not counted in the 32 controlled trials considered in Cochrane 2012. Also, Debruyne 2002 [19], a one-year randomized trial was included, but not the Debruyne 2004 subset analysis [18], despite the latter relating important independent findings on patient outcome. Finally, two papers by Sökeland from 1997 and 2000 are listed references, although only Sökeland 1997 [54] is considered in Cochrane 2012. The Sökeland 2000 publication is the same cohort as the 1997 publication with a subset analysis of prostate volume and therapeutic outcome [55]. The authors of the 87-page Cochrane 2012 review concluded that Serenoa repens did not improve urinary flow measures or prostate size versus placebo in men with LUTS/BPH [25,26].

To assess the validity of the conclusions of Cochrane 2012, an independent analysis and review of all 36 studies [26] referenced were undertaken (SBS). The Sökeland 2000 paper on prostate volume was excluded because it was not relevant. Of the remaining 35 citations, LUTS efficacy was determined using the previously mentioned criteria for evaluability: ≥ 20 patients at study end, study duration of ≥ 2 months, a standardized 320 mg dose of Serenoa repens, and LSEsr monotherapy only. A flow chart to analyze the Cochrane 2012 citations is presented in Figure 2.

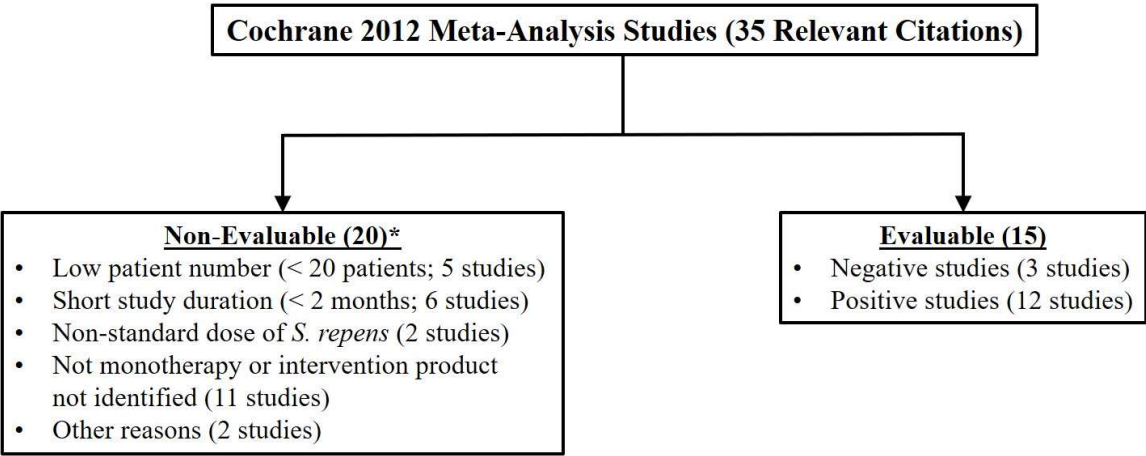


Figure 2. Cochrane 2012 patient evaluability. Of the 35 citations, only 15 were evaluable. Of those 15, only three were negative studies. *Some studies failed to meet evaluable criteria for more than one reason. Low patient numbers were identified in five studies, and a study duration of fewer than two months was found in six studies. Non-standard doses of Serenoa repens were noted in three studies, and nine studies did not involve monotherapy. In two studies, the intervention product and/or extraction technology could not be determined. Finally, one study had data that were not interpretable, and another article (Mohanty) did not specify the extraction technology.

In Figure 2, when applying the established evaluability criteria to Cochrane 2012, 20 of the 35 (57%) were excluded as non-evaluable for LUTS efficacy. In five studies, the number of patients evaluated was less than 20. In six studies, the study duration was less than 2 months. In two citations, the dose of Serenoa was either unspecified or was less than 320 mg/day. A combination of Serenoa with other phytonutrients, vitamins, or prescription drugs occurred in nine studies, and the intervention product was not identified in two further studies for a total of 11 non-evaluable citations. The study by Mohanty [56], a 73-patient placebo-controlled study, used an LSESr product and fulfilled all the evaluability criteria with the exception that it did not specify the extraction method. It did show significant benefit for the LSESr arm but lacking all required acceptability issues had to be moved to the non-evaluable group. The Reece Smith study [57] had data inconsistencies that made the interpretation of efficacy questionable. For the 15 studies meeting requirements for evaluability, detailed notes for each citation on endpoints such as IPSS, QoL, and Q_{\max} were created (SBS) as shown in Table 2.

Table 2. Evaluable studies in Cochrane 2012. Of the 15 out of 35 studies considered evaluable, only 3 (shaded in gray) presented negative findings of LSESr efficacy. Patient numbers were active patients at study end.

Senior Author	Ref. [#]	Year	Serenoa Therapy	Serenoa Patients (#) ^a	Study Duration (mo.)	Comments on Study Data
Cukier	[30]	1985	Permixon Hexane	73	2	Frequency and nocturia significantly improved with Permixon
Pannunzio	[58]	1986	Permixon Hexane	30	2	Q_{\max} ↑ + 5.1 (74%) versus +2.2 (28%); no IPSS or QoL data
Mattei	[35]	1990	Talso CO ₂	20	3	Frequency 43.8% improved vs. 7.1% for placebo; nocturia 68.9% improved vs. 4.8% for placebo; incomplete emptying 68.8% improved vs. 7.7% for placebo
Braeckman	[41]	1994	Prostaserene CO ₂	305	3	IPSS Δ -6.6 (34.7%); QoL Δ -1.54 (41.6%); Q_{\max} Δ +2.41 (26.4%)
Carraro	[17]	1996	Permixon Hexane	467	6	Permixon vs. finasteride; ↓ IPSS by 37% vs. 39%; ↑ QoL by 38% vs. 41%; Q_{\max} + 2.7 vs. +3.2 ml/s
Braeckman	[45]	1997a	Prostaserene CO ₂	67	12	IPSS -6.8, QoL -1.5, Q_{\max} + 2.6 ml/s
Braeckman	[44]	1997b	Prostaserene CO ₂	125	3	“IPSS” Δ -4.0 (51.3%) (authors scoring system); Q_{\max} Δ +3.1 (29.8%) vs. placebo “IPSS” Δ -1.7 (25.4%) and Q_{\max} Δ + 1.1 (10%)
Bauer	[59]	1999	Talso CO ₂	101	6	IPSS ↓ 37% at study end; no hard numbers, only %
Gerber	[60]	2001	Solaray Ethanol	39	6	IPSS -4.4 (26%) vs. -2.2 (14%); QoL -0.7 (21%) vs. -0.3 (10%); Q_{\max} +1.0 vs. + 1.4
Debruyne	[19]	2002	Permixon Hexane	350	12	Permixon vs. tamsulosin with IPSS improvement of 28% vs. 29%; Q_{\max} ↑ 1.8 vs. 1.9 ml/s
Willettts	[61]	2003	Serenoa CO ₂	46	3	QoL -0.49 (13%) vs. placebo -0.69 (17%); Q_{\max} no significant difference, IPSS calculated from graphs -1.1 (7.8%) vs. -3.9 (21.8%) for placebo; negative study
Debruyne	[18]	2004	Permixon Hexane	124	12	Permixon vs. tamsulosin: IPSS Δ -7.8 (35%) vs. -5.8 (25%); QoL -1.2 (29%) vs.

						Δ -0.9 (23%); Qmax Δ + 1.2 (11%) vs. Δ +1.7 (17%)
Bent	[14]	2006	Indena USA CO ₂	112	12	No significant difference between Serenoa vs. placebo; negative study
Hizli	[22]	2007	Prostagood Hexane*	20	6	Serenoa vs. tamsulosin vs. Serenoa plus tamsulosin; Serenoa \approx tamsulosin; no benefit with combination
Barry	[15]	2011	Prosta-Urgenin Ethanol	164	18	AUA-SI with no significant difference between <i>S. repens</i> vs. placebo; negative study

Note: ^a Number of patients at study end, or as reported.
* Prostagood is Permixon brand name in Turkey
 \approx , approximately equivalent; Δ , mean change; \downarrow , decreased; \uparrow , increased; -, negative change; #, number; +, positive change; AUA-SI, American Urological Association Symptom Index; CO₂, carbon dioxide; IPSS, International Prostate Symptom Score; ml/s, milliliters per second; mo., month; QoL, quality of life; Q_{max}, peak urinary flow (ml/s); Ref., reference citation; vs., versus.

Twelve of the 15 evaluable studies showed efficacy for Serenoa repens. Only three studies Willetts 2003, Bent 2006, and Barry 2011, are negative studies insofar as disclosing no benefit from Serenoa repens [14,15,61]. The product used in the Willetts study was ProserenTM manufactured by Blackmores in Australia. Per communication with their web-site support team, this was a 1600 mg Serenoa capsule derived from a 10:1 CO₂ extraction process with a dose equivalent to 320 mg/day. This product has not been used in another LUTS/BPH study. The Serenoa repens used in the Bent study and manufactured by Indena also has not been used in another published LUTS study. The Barry study selected an ethanol extract of Serenoa called Prosta-Urgenin UnoTM with results indicating it to be no better than placebo using the AUA-SI as the objective endpoint [15]. In an earlier large 3-month intervention study by Derakhshani, et al. [47], but not discussed by Barry et al., Prosta-Urgenin Uno was used in 1047 patients from 357 urologic practices. At study end, Derakhshani reported an overall mean change in IPSS of -7.4 points representing a 40% improvement, a QoL change of -1.61 representing a 45.9% improvement, and a Q_{max} increase after 3 months of + 3.7 ml/s for a 30.8% improvement. This striking difference in clinical outcomes with Prosta-Urgenin Uno between Derakhshani 1997 and Barry 2011 has never been addressed by any author, until this current report.

Only half of the studies considered by Cochrane 2012 used consistent symptom scoring (i.e., IPSS, AUA-SI). Therefore, clinical data from the Cochrane meta-analysis drew from inconsistent symptom assessment methodology. Moreover, Cochrane 2012 included some studies involving saw palmetto products of inconsistent and/or indeterminant quality. The authors of the updated Cochrane 2012 meta-analysis acknowledged that their conclusions might not be generalizable to products containing a standardized extract of *S. repens* with an established chemical composition [25,26]. Six of the 35 (17%) citations in Cochrane 2012, upon detailed review (SBS), indicated negative findings. The three evaluable studies were discussed above. The other three studies with a lack of benefit from the LSESr arm were non-evaluable because they used Serenoa in combination with additional herbal products (Englemann, Lopatkin)[62,63] or the study was only of six weeks duration (Löbelenz) [63].

As to the extraction process used, six evaluable studies in Cochrane 2012 used the standardized hexanic lipidosterolic extract of Serenoa repens with the brand name of PermixonTM (aka ProstagoodTM in Turkey), and all showed efficacy (Table 2) [17,19,22,30,58,64]. There were also non-evaluable studies in Cochrane 2012 that had used a standardized hexanic lipidosterolic extract of Serenoa repens versus placebo or comparator. Of these six studies, four had <20 patients (Boccafoschi, Emili, Mandressi, Tasca)[65-68] and four had a study duration of <2 months (Champault, Descotes, Emili, Mandressi) [64,66,67,69]. Emili and Mandressi had both <20 patients and <2 months study duration. Table 3 presents an assessment of the clinical findings in these six studies. As an aside, all six studies, although non-evaluable per criteria, reported a significant benefit in clinical

outcome for *Serenoa repens* in LUTS vs. placebo or comparator. The mean outcomes across these six studies are: Q_{max} +3.4 ml/s (5 studies), decreased nocturia by 55% (3 studies), and decreased urgency by 65% (2 studies).

Table 3. Efficacy of the hexane extract of *S. repens* vs. placebo. Six of 20 non-evaluable studies in Cochrane 2012 used a standardized hexanic lipidosterolic extract and reported clinical improvement in symptoms vs. placebo.

Senior Author	Year	Ref. (#)	Serenoa Patients (#) ^a	Study Duration (mo.)	Key Results for Serenoa vs. Placebo or Comparator
Boccafoschi	1983	[65]	11	2	Q_{max} + 4.2 (42%) vs. placebo + 2.1 (20.6%)
Emili	1983	[66]	15	1	Q_{max} +3.56 (34.5%) vs. placebo + 0.20 (2.2%)
Mandressi	1983	[67]	19	1	Serenoa vs. Pygeum vs. placebo; ↓ urgency 70% vs. 62% vs. 24%; ↓ frequency 30% vs. 22% vs. 10%; ↓ nocturia 42% vs. 38% vs. -4%
Champault	1984	[69]	50	1	Q_{max} +2.7 (50.5%) vs. placebo +0.25 (5%); nocturia -1.53 (49%) vs. placebo -0.48 (15%)
Tasca	1985	[68]	14	2	Q_{max} +3.3 (25.6%) vs. placebo -0.6 (-5%); nocturia 74.3% vs. 38.7%; urgency 60% vs. 20%; weak stream 50% vs. 16.6%
Descotes	1995	[64]	82	1	Q_{max} +3.4 (28.9%) vs. placebo + 1.1 (8.9%)
Average Changes in Q_{max} , Nocturia and Urgency					Q_{max} +3.4; ↓ nocturia 55%; ↓ urgency 65%

Note: ^a Number of patients at study end, or as reported.
↓, decreased; ↑, increased; -, negative change; #, number; +, positive change; mo., month; Q_{max} , peak urinary flow (ml/s); Ref., reference citation; vs., versus.

A critique of 2012 Cochrane, published in 2015 by Bachmann, detailed many of the previously mentioned issues [70]. It also mentioned that some studies in Cochrane 2012 used doses lower than 320 mg/day. The lack of consistent criteria for evaluability is a significant criticism in this meta-analysis, and it is even more the case when considering the number of evaluable studies that were never assessed by Cochrane 2012. Bachmann’s major criticism was the lack of logic in conclusions reached by Cochrane 2012 when contrasting the efficacy of *Serenoa repens* with established comparison prescription products such as finasteride, tamsulosin, and gestonorone caproate. Paraphrasing Bachmann, if *Serenoa repens* has the same effect as placebo, as well as the same effect as the comparison products, then the three established prescription drugs are also ineffective and logically should be considered no better than placebo [70].

Additional thoughts can be offered for Cochrane 2012. A decline in IPSS by ≥ 3 points has been considered to be an indicator of efficacy of any agent in the treatment of LUTS [71-73]. Eight studies involving *Serenoa repens* in Cochrane 2012 had clinically meaningful IPSS improvement with an average drop of -6.14, and a range from -4.4 to -9 as shown in Table 2. Some of these LSESr preparations were combination products involving either phytonutrients and vitamins or α-blockers and were studies tagged as non-evaluable by our established criteria, and not included in our results. Why the authors of Cochrane 2012 selected so many studies with such clear-cut deficiencies is difficult to understand. Yet, despite such obvious laxity involving study selection in Cochrane 2012, the reported results within Cochrane 2012 do not justify the official stated conclusions.

3.3. The American Urological Association Guidelines (AUAG 2014)

The American Urological Association guidelines (AUAG) for the management of BPH were revised in 2014 [28]. The guideline authors considered literature from January 1, 1999, to February 28, 2008. Studies on *Serenoa repens* that were non-English full-text studies, or that had an English abstract but not the full paper, were excluded. The AUAG 2014 key findings can be summarized as: “At this time, the available data do not suggest

that saw palmetto has a clinically meaningful effect on LUTS secondary to BPH. Further clinical trials are in progress and the results of these studies will elucidate the potential value of saw palmetto extracts in the management of patients with BPH." The two references cited by McVary, et al., are Bent 2006 and Shi 2008 [14,74]. The Shi paper used a combination product containing lyophilized prostate, Serenoa extract, zinc, flower pollen, Pygeum, pumpkin seed, and more [74]. Certainly, the Shi study is not evaluable and should not have been cited. The Bent 2006 publication is one of the two major articles relating to the lack of efficacy of Serenoa repens in treating LUTS [14]. As mentioned previously, the Bent trial used a CO₂ Serenoa extract manufactured by Indena. Although no peer-reviewed studies using the Indena product to confirm or refute the Bent results have been published to date, the Bent study is routinely cited concerning the lack of efficacy of LSESr for reducing LUTS.

Statements in AUAG 2014 about the use of dietary supplements are worthy of further comment. "...most patients who use dietary supplements self-medicate with these products and often do not inform their physicians about this use." This statement reflects how uncomfortable most patients feel about reporting their supplement use to their physician. The reality is that most physicians disparage any non-prescription use, and from the patient's point of view, physicians in general regard supplement use as taboo and not open for discussion. If the physician asks the patient about what dietary supplement(s) he may be using, then this information is freely exchanged between the patient and the physician and/or his staff. "Furthermore, the quality and purity of these OTC supplements are not rigorously monitored, adding further uncertainty about the value and safety of these products," is indeed a major problem in countries like the US. Regulation of supplement quality and/or use is not nearly as strict as in other parts of the world. In Germany, for example, the hexane extraction product Permixon is a prescription item.

AUAG 2014 references Cochrane 2012 in saying: "*Serenoa repens* was not more effective than placebo for the treatment of urinary symptoms consistent with BPH," However, this again refers to the publication of Bent 2006 [14], and also to reports by Barry 2011[15] and Willetts 2003 [61]. Willetts, like Bent, used a product that has never been used in any other peer-reviewed publication. Willetts compared a CO₂ extraction product in fifty patients versus 50 receiving a placebo in a study period of 3 months. Note that in ESCOP and EMA such study durations were criticized as being too short for accurate assessment. Willetts 2003 reported no significant differences in Q_{max} or QoL between Serenoa repens extract and placebo. IPSS data, extracted from a graph (SBS) indicated the IPSS for the Serenoa extract group went from a baseline of ≈ 14.1 to 13, while paradoxically, that of placebo went from ≈ 17.9 to 14, a drop of 3.9 points. Improvement in the IPSS of ≥ 3 points is cited as a criterion of product efficacy [71-73,75-77]. Of additional interest is that Q_{max} improved for both the Serenoa extract and placebo groups by 2.35 ml/s. Details on the profile of the Blackmores product could not be confirmed. Thus, Barry 2011 remains the most valid negative study that impugns the value of LSESr in LUTS [15]. This will be discussed in more detail later in the context of the many evaluable studies showing favorable responses with LSESr that were not considered by the EMA and the AUA.

AUAG 2014 was significantly critical of the studies by Debruyne 2002 and Hizli 2007 [19,22]. "One of the two trials that compared saw palmetto with tamsulosin in 704 men reported a decline in AUA-SI scores of 4.4 points in both treatment groups [Debruyne 2002]; the other also reported no significant difference in the change in symptom scores among 40 randomized men when comparing LSESr to tamsulosin [Hizli 2007]." AUAG 2014 concluded: "In the two comparisons of saw palmetto with the alpha-blocker tamsulosin, there was no significant difference in changes in LUTS-related QoL between the treatment arms." In addition, "The active-controlled studies comparing saw palmetto with tamsulosin also found no significant difference in urinary flow rates at closeout." Such statements could be misconstrued that Serenoa lacked efficacy, but instead, the emphasis should have been that tamsulosin was no better than Serenoa repens. In other words, the two were equivalent in efficacy insofar as IPSS, QoL, and Q_{max} endpoints. If we

look at the two referenced studies[19,22] and extract the data related to the endpoints above, it is clear that there is significant value in the use of Serenoa repens in LUTS as seen in Table 4. Note also that this criticism of AUAG 2014 is essentially identical to that made by Bachmann[70] of Cochrane 2012.

For all reports, the clinical value of Serenoa is with the lipidosterolic extract of Serenoa repens (LSEsr), and this ought to be routinely distinguished from the unacceptable naming of the study product as “saw palmetto” or “Serenoa repens.” Such distinction must be emphasized in all scientific publications and presentations to the lay public. Saw palmetto, Serenoa, Serenoa repens, and *S. repens*, do not equate, per se, with the lipidosterolic extract of Serenoa repens (LSEsr), or specifically with a hexane, ethanol, or carbon dioxide lipidosterolic extraction product at the accepted daily dose of 320 milligrams per day, and meeting the fatty acid profile standards of the EMA and US Pharmacopeia.

Table 4. Debruyne 2002 and Hizli 2007 clinical evaluation of LSEsr vs. tamsulosin (Flomax®) at study end. These two clinical trials were cited by AUA 2014 as broadly indicative of the lack of value of “saw palmetto” to ameliorate LUTS despite essentially identical results with tamsulosin.

Senior Author Year, Ref. (#)	Study Duration (mo.)	Study Arm	Patients (#) ^a	IPSS		QoL		Q _{max}	
				Δ	%	Δ	%	ml/s	%
Debruyne 2002 [19]	12	LSEsr	350	-4.5	29%	NR	NR	+1.8	17%
		Tam	354	-4.4	29%	NR	NR	+1.8	16%
Hizli 2007 [22]	6	LSEsr	20	-6.1	34%	-2.6	62%	+3.2	34%
		Tam	20	-4.6	28%	-2.1	60%	+3.7	35%

^aNumber of patients at study end
Δ, mean change; -, negative change; #, number; %, percent change; +, positive change; AUA, American Urological Association; IPSS, International Prostate Symptom Score; LSEsr, lipidosterolic extract of *Serenoa repens*; LUTS, lower urinary tract symptoms; ml/s, milliliters per second; NR, not reported; mo., month; QoL, quality of life; Q_{max}, peak urinary flow (ml/s); Ref., reference citation; Tam, tamsulosin.

In Table 4, the IPSS improvement with Serenoa repens was comparable to that of tamsulosin (Debruyne 2002, Hizli 2007). The improvements as a percentage in IPSS, QoL, and Q_{max} are essentially equivalent. Debruyne 2002 involved eleven European countries enrolling 811 patients with a baseline IPSS of ≥11 [19]. This double-blinded, randomized study also included a 4-week run-in phase to exclude patients who were non-compliant in taking the placebo. At study end, the per-protocol patient numbers were 350 in the LSEsr group (Permixon) and 354 in the tamsulosin group. If the findings quoted above represent a placebo effect, then tamsulosin must also be considered a placebo. As stated in Debruyne 2002, “In each group, more than 80% of the patients exhibited a decrease in IPSS. A decrease in IPSS by at least 3 points was observed in two-thirds (67%) of the patients and by at least 5 points in half of them (49%). The greatest improvement in IPSS total score was observed in those patients with the greatest severity of disease. For the severe patients (with a baseline IPSS >19; n =94), the mean changes from baseline were greater in the Permixon group than in the tamsulosin group (8.0 and 6.8, respectively). As for side effects, ejaculation disorders were significantly more frequent with tamsulosin (15, or 4.2%) than with Permixon (2, or 0.6%; p= 0.001.) [19].”

Hizli 2007 randomized patients into three groups of 20 patients: HESr monotherapy, tamsulosin monotherapy, and HESr combined with tamsulosin [22]. No additive or synergistic effect was seen in the combination arm. QoL in Hizli showed similar improvements with changes from baseline to six months of 4.2 to 1.6 (62% improvement), and 3.5 to 1.4 (60% improvement) for HESr and tamsulosin, respectively. If any conclusion were to be stated by AUAG 2014, it should have been that LSEsr monotherapy, using the com-

mercial product Prostagood (Permixon product), was comparable to tamsulosin monotherapy in lessening LUTS using the endpoints of IPSS, QoL, and Q_{\max} . AUAG 2014 further criticizes the same two studies for not using the BPH Impact Index (BPHII or BII). “The BPHII was not assessed in either of the other two placebo-controlled studies nor in the studies comparing saw palmetto with an alpha-blocker.” This criticism could be directed at virtually every study involving conventional medical therapy for LUTS since almost all studies do not include BPHII data. Moreover, the QoL (aka IPSS-BQ) has been shown to be a reliable index correlating with the severity of LUTS, and also highly correlated with the bother question in the BPHII [78].

AUAG 2014 discussed the Carraro study, which compared the standardized hexanic LSESr, Permixon, versus finasteride for 6 months [17]. Results of that study showed Permixon improved IPSS by 37%, improved QoL by 38%, and improved Q_{\max} by +2.7 ml/s (25%) vs. 39%, 41% and +3.2 ml/s for finasteride (Table 2). Yet, AUAG 2014 only mentions Carraro with “saw palmetto does not affect serum PSA (prostate-specific antigen) levels.” Lastly, AUAG 2014 remarked that there were no significant differences in adverse events between the two arms of all Serenoa versus placebo-controlled trials, and that “only” the Bent 2006 study conducted thorough lab testing for potential toxicity [14]. The topic of safety will be discussed in detail in Part II, but scores of peer-reviewed clinical publications and meta-analyses on LSESr have consistently reported on the safety and tolerability of LSESr. A thorough evaluation of adverse effects is therefore not unique to Bent 2006 [12,42,45,64,79,80]. What appears commonplace in orthodox medicine are criticisms routinely directed to natural products, but less so when referencing prescription drugs. I would aver that double standards have no place in medicine. Additionally, there may be a conflict of interests noting that two panel members of AUAG 2014 were also authors in the Bent 2006 and Barry 2011 studies.

3.4. The European Medicines Agency Monograph (EMA 2014)

The EMA 85-page monograph reported by Laekeman in 2014 [12] based its conclusions mainly on the review of 15 clinical articles cited by ESCOP 2003 [27], and 20 clinical articles cited by Cochrane 2012 [25,26]. Seven publications are unique to EMA 2014 and appear to have been obtained from a PubMed search. Of these seven papers, three were non-evaluable per prior criteria established for this review. The complete EMA report presents information on the use of Serenoa repens in various countries in the EU, basic science information on possible mechanisms of action of Serenoa, and studies involving analyses of efficacy and toxicity. EMA 2014 found that only “one well conducted controlled clinical trial with the supercritical CO₂ extract has been published” (Braeckman, et al. 1997a) [45], but the provided information is not sufficient to support its use as “a well-established medicinal product” (i.e., recognized efficacy and acceptable safety). EMA 2014 further affirms, “The requirement for 30 years of experience on the market is not fulfilled for the supercritical CO₂ extract.” A similar conclusion is reached concerning the ethanolic extraction products of Serenoa repens. “Although ethanolic extracts are widely used in EU member states, the clinical data available are limited.” EMA 2014 concluded that “only the hexane extract of the fruit of *Serenoa repens* is considered to be supported by sufficient evidence to grant a well-established use as a medicinal product with recognised efficacy and acceptable safety.”

EMA 2014 is challenging in its mixed messages, since it also states, “The use of the ethanolic extracts is considered plausible on the basis of clinical studies with related extracts and the long-standing use and experience. The benefit-risk balance of commercialized ethanolic extracts is positive and a traditional use can be granted.” And, further stated by the monograph authors, “Other double-blind, randomised, placebo-controlled studies have been carried out with extracts that were not sufficiently documented and (not) registered in EU member states. Despite the fact that the studies were generally well conducted, the results cannot be used to elaborate the monograph.” It therefore appears that if a commercial product is not registered by the EU it is rejected. Many readers may

misconstrue such a report as a valid scientific analysis of the body of clinical literature. Of additional concern in EMA 2014 are the assessor’s comments, which are essentially a “verdict” as to the acceptability of a study. However, a blank area is present where the assessor’s identity would be shown. The monograph is replete with criticisms about various studies, yet the individual’s identity who has made these remarks is not provided. If transparency and possible conflict of interests is important in evaluations of scientific merit, then this principle should apply to all.

3.5. What Can Be Learned from ESCOP 2003, Cochrane 2012, AUAG 2014, and EMA 2014?

These four authoritative reports have influenced the perception of many urologists concerning the efficacy of LSEsr versus LUTS. Figure 3 depicts the evaluable versus non-evaluable assessment of the 69 citations that relate to LSEsr efficacy in LUTS that are discussed in ESCOP 2003, Cochrane 2012, and EMA2014. Since there were no unique citations presented in AUAG, these 69 published studies represent the evidence considered by these four authoritative bodies. Of these 69 studies, approximately half (36 studies, 52%) were considered evaluable for an assessment of efficacy. AUAG 2014 did cite six citations that were considered to be evaluable, and all six were been cited by at least two of the three other authoritative publications [14,17,19,22,60,61]. As stated earlier, the Carraro 1996 reference was cited concerning LSEsr not having an effect on PSA levels, but lacked any discussion of clinical endpoints affecting LSEsr versus LUTS [17].

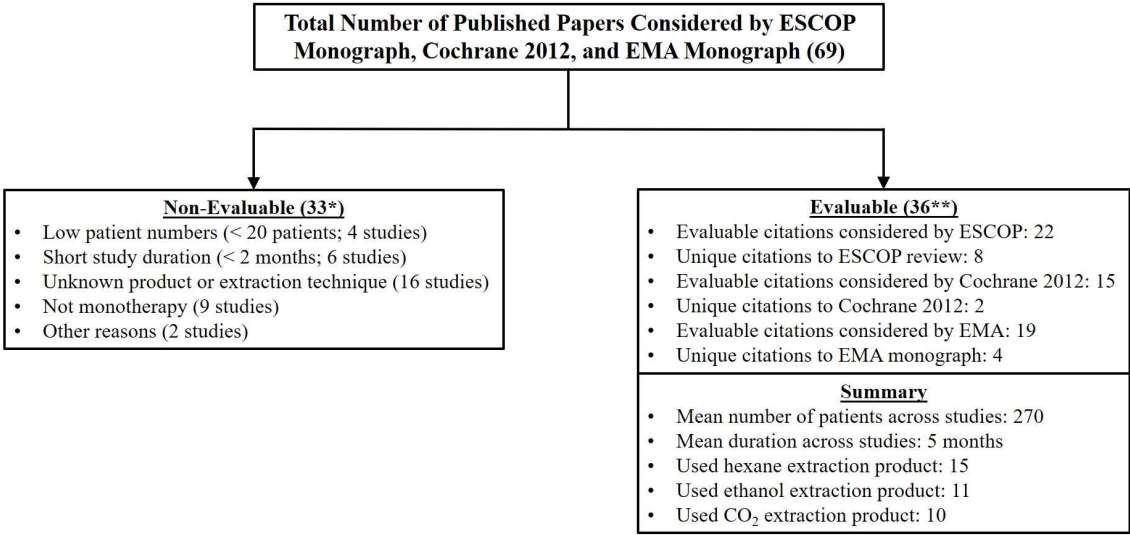


Figure 3. Categorization of 69 evaluable citations in ESCOP 2003, Cochrane 2012, and EMA 2014. *Studies could have more than one reason for exclusion. **Of the 36 evaluable citations, 22 were considered by ESCOP (61%), 15 by Cochrane (42%), and 19 by EMA (53%). There were eight studies unique to ESCOP, two studies unique to Cochrane. EMA cited four studies not found in either of the other two reviews. CO₂, carbon dioxide; EMA, European Medicines Agency; ESCOP, European Scientific Cooperative on Phytotherapy.

Using the detailed notes compiled during the critical review and analysis (SBS), a summary of the body of literature (69 published studies) considered across ESCOP 2003, Cochrane 2012, AUAG 2014, and the EMA 2014 was created. Table 5 notes which studies were considered by each authoritative body, and includes data on Serenoa product/extract method, study patient numbers, and study duration for 56 of the 69 cited papers. The evaluable studies (36 of 69 or 52%) are indicated with the senior author’s name bolded. The remaining non-evaluable studies (33 of 69 or 48%), show the senior author in normal

font. Fourteen of 36 trials were unique to either ESCOP, Cochrane, or EMA, whereas 22 studies were cited in two or more of these reports. AUAG 2014 did not contain any unique publications. When comparing ESCOP, Cochrane, AUAG, and EMA there were 58%, 43%, 54%, and 58% evaluable papers, respectively. In other words, approximately 50% of the studies considered by these authoritative publications failed to meet the criteria for evaluability in our investigation of the utility of Serenoa in the treatment of LUTS.

A total of 38 non-English-language papers were cited by ESCOP, Cochrane 2012, and the EMA authors, with the majority in German (19) or Italian (13). Fifty-two percent of the German language papers were evaluable, but only 31% of the Italian language papers were evaluable due to small patient numbers (<20 patients in the Serenoa arm) and short study duration (<2 months). Of the 31 English-language papers considered by ESCOP, Cochrane, and EMA, 61% were evaluable, including the three negative studies by Willetts 2003, Bent 2006, and Barry 2011 [14,15,61]. In considering the extraction products used in those remaining 36 evaluable studies in ESCOP, Cochrane 2012 and EMA, 15 studies (42%) used a hexane-extracted product, 11 (30%) used an ethanol-extracted product, and 10 (28%) used a CO₂ extraction product.

For the 56 studies that have information summarized in Table 5 for product, patient number, and study duration, the mean number of patients across the studies was 270, and the mean study duration was 5 months, indicating a robust set of clinical trials of Serenoa repens for efficacy in treating LUTS. If a larger percentage of evaluable studies and non-English-language papers had been considered by the four authoritative bodies, the efficacy of LSESr for LUTS would have been affirmed.

Table 5. Summary of all citations from ESCOP, Cochrane 2012, AUAG, and EMA.

Senior Author	Year	Product	Serenoa Patients (#) ^a	Study Duration (mo.)	ESCOP	Cochrane	AUAG	EMA
Authie ‡	1987	Hexane	500	3	*			
Bach †	1995	Ethanol	315	36	*			
Barry †	2011	Prosta-Urgenin Ethanol	151	18		+		+
Bauer ‡	1999	Talso CO ₂	101	6		*		
Bent †	2006	Indena USA CO ₂	112	12		+	+	+
Boccafroschi ‡	1983	Permixon	11	2	+	+		+
Braeckman †	1994	Prostaserene CO ₂	505	3	+	+		+
Braeckman1 †	1997	Prostaserene CO ₂	67	12	+	+		+
Braeckman2 †	1997	Prostaserene CO ₂	125	3		+		+
Breu ‡	1992				+			+
Carbin †	1990	Serenoa + Curbicin	26	3		*		
Carraro †	1996	Permixon	467	6	+	+	+	+
Champault ‡	1984	Permixon	50	1	+	+		+
Cirillo-Marucco ‡	1983	Hexane	47	4	*			
Cukier ‡	1985	Permixon	73	2	+	+		+
Dathe ‡	1991	Hexane	49	6	+			+
Debruyne †	2002	Permixon	350	12		+	+	+
Debruyne†	2004	Hexane	124	12		+		+

Derakhshani ‡	1997	Prosta-Urgenin Ethanol	1047	3	*			
Descotes †	1995	Permixon	82	1	+	+		+
Eickenberg ‡	1997	Ethanol	6967	6	*			
Emili ‡	1983	Permixon	15	1	+	+		+
Engelmann †	2006	Pro 160/120	56	15		+	+	
Fabricius ‡	1993	CO ₂	176	6	+			+
Gabric ‡	1987	Prostagutt	15	1.5		*		
Gerber †	1998	Ethanol	46	6	*			
Gerber †	2001	Solaray Ethanol	39	6		+	+	+
Giannakopoulos †	2002	Hexane	100	6				*
Giulianelli †	2012	Hexane	591	6				*
Glémain ‡	2002	Not given	159	12		+		+
Grasso †	1995				+			+
Hagenlocher ‡	1993				*			
Helfand †	2012							*
Hizli †	2007	Prostagood Hexane	20	6		+	+	+
Kaplan †	2004							*
Koch ‡	1994				*			
Koch ‡	1995				*			
Kondas †	1996	Ethanol	38	6	*			
Löbelenz ‡	1992	Sabal Ethanol	30	1.5		+		+
Lopatkin †	2005	Pro 160/120	129	6		+	+	
Mancuso ‡	1986				*			
Mandressi ‡	1983	Permixon	19	1		*		
Marks †	2000	Nutrilite Blend	20	6		+	+	
Martorana ‡	1986				*			
Mattei ‡	1988	Talso CO ₂	20	3	+	+		+
Metzker ‡	1996	Pro 160/120	37	12		*		
Mohanty †	1999		36	2		*		
Ollé Carreras ‡	1987	Hexane	40	2	*			
Orfei ‡	1988	Hexane	30	3	*			
Pannunzio ‡	1986	Permixon	30	2		*		
Paoletti ‡	1986				*			
Pescatore ‡	1986	Hexane	30	3	*			
Preuss †	2001	Blend Herbs/Vitamin				+	+	
Pytel †	2002	Hexane	116	24				*
Pytel ‡	2004							*
Redecker ‡	1998	Ethanol	50	3	*			
Reece Smith †	1986	Permixon	33	3	+	+		+

Romics †	1993	Ethanol	31	12	*			
Roveda ‡	1994	“Serenoa”	30	1		*		
Schneider ‡	1994				+			+
Shi †	2008	Prostataplex	46	3		+	+	+
Sökeland ‡	1997	Pro 160/120	245	12		*		
Stepanov †	1999	Hexane	92	3				*
Tasca ‡	1985	Permixon	14	2	+	+		+
Vahlensieck ‡	1993	CO ₂	1,334	4	+			+
Vahlensieck ‡	1993	CO ₂	312	3	+			+
Vespasiani ‡	1987		15	9	*			
Willetts †	2003	Serenoa CO ₂	46	3		+	+	+
Ziegler ‡	1998	Ethanol	109	3	*			
Averages Across All Studies with Data Tabulated			270	5	Evaluable/ Total Citations (%)	Evaluable/ Total Citations (%)	Evaluable/ Total Citations (%)	Evaluable/ Total Citations (%)
69 Total Citations/36 Evaluable Citations								
● No unique citations to AUAG								
● 20 citations considered only by ESCOP								
● 9 unique citations considered only by Cochrane					22 of 38 (58%)	15 of 35 (43%)	6 of 11 (54%)	19 of 33 (58%)
● 7 citations unique to the EMA monograph								

Bold typeface for the first author reflects an evaluable study. Of the 69 citations across the reports, 33 citations (48%) were not evaluable for determinations on the efficacy of LSESr for LUTS. Only one citation, Carraro [17] was considered by all four reports. Of the evaluable studies, 15 used a standardized hexane extract, 11 used an ethanol extract, and 10 used a supercritical carbon dioxide extract of *Serenoa repens*.

^a Number of patients at study end, or as reported.

† Publications in English; ‡ non-English publications; * Unique to that report; + Cited by that report; AUAG, American Urological Association Guidelines; CO₂, carbon dioxide; EMA, European Medicines Agency; ESCOP, European Scientific Cooperative on Phytotherapy; LSESr, lipidosterolic extract of *Serenoa repens*; LUTS, lower urinary tract symptoms; mo., month; #, number.

4. What Information Is Not Controversial?

The suggested target population for supplement use in LUTS involves men in the watchful waiting phase with mild-to-moderate symptoms who are not yet “particularly bothered [81].” During this early treatment period, and for that matter during any phase of the treatment of LUTS, it is crucial to select a *Serenoa* extract product that can achieve an optimal outcome insofar as a decrease in symptoms and a lack of progression and/or resolution of the underlying pathophysiology that has caused LUTS. Crushed dried saw palmetto berry powder is not relevant to LUTS nor comparable to a lipidosterolic extract, but unfortunately, this has not been recognized by most urologists. Definitions for a standardized *Serenoa* extract product are suggested by US Pharmacopeia [13] and EMA[12], and would have a lipid profile with a minimum of 80% total fatty acids; would have a specific ratio of fatty acids and be rich in free fatty acids; and, would have a minimum amount of phytosterols and fatty alcohols. Unfortunately, the specific makeup of *Serenoa* and the percentage of components that determine efficacy in treating LUTS have not been ascertained. The hexanoic extract product, Permixon, which does meet the above standard, has shown established benefit in LUTS. It will be detailed later in Part II of this review that lipidosterolic products using any of the three extraction methods have efficacy in the treatment of LUTS. As for dosing, efficacy has been established at the recommended dose of 320 mg/day of the lipidosterolic extract, and higher doses do not offer further benefit [21,36]. It is not established if a lower dose can be efficacious. Also, the safety of LSESr has been repeatedly cited in the literature and also is not controversial. The technical role of

extraction in regard to outcome in LUTS will be discussed in Part II of this review and has been a topic of debate [12].

With these fundamental principles (target population and standardized extract) in mind, it is clear that the clinical evaluation of LSESr has been negatively impacted by the following: 1) variability in the composition and quality of LSESr; 2) a primary focus on LUTS progression being related to prostate enlargement rather than the more clinically relevant outcome of storage (irritative) and flow (obstructive) symptoms, and; 3) a need for long-term studies of LSESr focused on delay in progression and perhaps resolution of LUTS, and, in the best-case scenario, inhibition of the histologic development and clinical progression of BPH. Therefore, it does have great importance to critically evaluate the scientific evidence related to the use of LSESr for LUTS, with a particular focus on 1) standardized extraction products of known quality, 2) standardized dosing, 3) efficacy using measurable endpoints like IPSS, QoL, and Q_{max} , 4) durability of response, 5) safety and 6) the ability to delay the progression of LUTS that relates to the pathobiology of LUTS associated with BPH and/or inflammation.

5. Conclusion to Part I.

In Part I of this series of three articles, we have focused on re-exploring the use of the herbal product *Serenoa repens* in the treatment of male LUTS. We have described what LUTS is, why it is an increasingly important concern in the changing demographics of our world, and some basic information valuable to understanding clinical studies of LUTS. But most importantly, we have addressed the four major reports or meta-analyses of *Serenoa* use in LUTS and elaborated with detailed findings on issues that have negatively influenced the use of standardized *Serenoa* products in the clinical context of male LUTS. These findings were brought to the forefront because of a more complete analysis of the English-language peer-reviewed articles, and also because of the far broader scope of this analysis that resulted from including translated non-English language publications with an in-depth analysis of their data. Part I, therefore, lays the foundation for Parts II and III of this global analysis in which important derivative findings relating to LUTS and LSESr will be presented.

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