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Review

Serenoa Repens (Saw Palmetto) for Lower Urinary Tract Symptoms (LUTS): The Evidence for Efficacy and Safety of Lipidosterolic Extracts. Part III

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Abstract: Parts I and II of this three-part series indicated how a global review of both English-language and non-English language papers, plus a focus on a lipidosterolic extract of Serenoa repens (LSESr) having a standardized fatty acid profile, have together engendered new insights about the biological activity of LSESr vs. LUTS. In this last part, data from the world literature is presented that confirms that LSESr efficacy is the predominant finding in clinical trials. Despite two placebo-controlled clinical trials performed in the U.S. that failed to confirm a benefit of LSESr vs. placebo in LUTS, the global body of the peer-reviewed literature attests not only to efficacy but also to safety. Results will be presented of important trials that compare LSESr to alpha-blockers such as tamsulosin (Flomax®) as well as to 5α-reductase inhibitors such as finasteride (Proscar®) that demonstrate consistent findings of near equivalency between LSESr and these pharmacologic agents. Studies relating data indicative of an additive effect or synergy between LSESr and tamsulosin will also be presented. The heightened effectiveness of LSESr in men with severe LUTS vs. moderate LUTS expands the importance of our scrutiny of the global literature concerning LSESr. Of great consequence are the contributions of non-English language peer-reviewed publications that have consistently provided evidence of LSESr efficacy in treating LUTS/BPH. These peer-reviewed articles have shown that the effect of LSESr is not that of a placebo. Finally, a comparison of the LSESr extraction products used in the treatment of LUTS, and a discussion of the milieu factors that affect the natural history of LUTS and influence the outcome of clinical trials, complete this detailed analysis of LSESr vs. LUTS.

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); ethanolic extract of Serenoa repens (EESr); supercritical carbon dioxide extract of Serenoa repens (sCESr)

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1. LSESr and the Placebo Effect: Is There a Resolution?

How Can We Address the Negative Clinical Trials of LSESr vs. Placebo in Male LUTS?

At least 48 systematic reviews and meta-analyses of Serenoa repens have been analyzed as part of due diligence in scrutinizing 190 studies involved in this report. The Willetts study from Australia and the STEP and CAMUS studies from the U.S. are the three major reports presenting negative findings on LSESr efficacy vs. LUTS. The *S. repens* Treatment for Enlarged Prostates (STEP) [1] and Complementary and Alternative Medicine for Urological Symptoms (CAMUS) trials [2] were randomized, placebo-controlled trials. The findings of STEP and CAMUS contributed to the negative assessment of the efficacy of Serenoa repens, later reported in the Cochrane 2012 meta-analysis [3]. The STEP study randomized a total of 206 men with moderate-to-severe BPH to treatment with placebo (104 patients) or to a supercritical carbon dioxide extract of Serenoa repens (sCESr) (102 patients) using a dose of 160 mg bid [1]. The clinical endpoints of the STEP (Bent) and CAMUS (Barry) trials along with additional information are shown in Table 1.

Table 1. The Bent (STEP) and Barry (CAMUS) studies are the preeminent placebo-controlled trials of LSESr vs. LUTS with negative results.

Author (Lead)	Year	Extraction Process	Pt. #	Study (mos)	IPSS		BPHII		Qmax		Fatty Acids %
					Δ	%	Δ	%	Δ	%	
Bent	2006	CO_2	102	12	−0.7	4	−0.3	10	+0.4	4	92 TFA
		Placebo	104		−0.7	5	−0.1	3	−0.0	0	
Barry	2011	Ethanol	151	18	−2.2	15	−0.8	24	−0.2	−1	54 FFA
		Placebo	155		−3.0	20	−1.0	33	−0.8	−5	

Values for IPSS and BPHII are rounded off to one decimal point; percentages for all are rounded off to the nearest whole number. IPSS, International Prostate Symptom Score; BPHII, BPH impact index; Qmax, peak urinary flow (mL/s); Δ, mean change; mos., months; #, number; Pt., patients; %, percent; TFA, total fatty acids; FFA, free fatty acids.

In STEP, patients were stratified into two groups using the AUA-SI, with moderate LUTS being a score of 8–19 vs. severe LUTS with a score of 20–35. Both the treatment and placebo groups showed a decrease in the AUA-SI of approximately −1.5 during the one-month run-in phase. At 12-months post-randomization there were no significant differences in AUA-SI or urinary flow rate. The AUA-SI decreased −0.68 points from a baseline of 15.7 in patients receiving sCESr vs. a decrease of 0.72 points from a baseline of 15.0 in the placebo group. Similar non-significant changes for sCESr and placebo in the BPHII (BPH Impact Index) were seen from baseline to study end (−0.33) vs. (−0.09), and for Qmax (+0.42 mL/s) vs. (−0.01 mL/s), respectively (Table 1). The sCESr product used in the STEP trial had never been used in a prior study nor assessed in a subsequent study. Perhaps STEP is valid, or perhaps the product used has a lower quality profile than that of other LSESr products that have demonstrated efficacy in the 60 peer-reviewed studies of LSESr vs. LUTS/BPH.

The CAMUS study, published in 2011, was not an investigation of the efficacy of complementary medicine, as per the title, but instead of a particular ethanolic extract of Serenoa repens (EESr) having the brand name Prosta Urgenin® Uno (Rottapharm/Madaus). This was identical to the EESr used 14 years earlier by Derakhshani et al. [4], but surprisingly not discussed by the CAMUS authors [2]. CAMUS randomized 306 men with LUTS to placebo (n = 155) vs. Prosta Urgenin Uno (n = 151) over a study duration of 72 weeks (1.5 years). Eligibility criteria included an AUA-SI of between 8 to 24, and a Qmax $\geq$ 4 mL/s [2]. The daily dose of the EESr was escalated every 24 weeks, from 320 mg to 640 mg and to 960 mg/day. Results showed a decrease in AUA-SI from 14.69 to 11.70 (20% improvement) for placebo vs. 14.42 to 12.22 (15% improvement) for the EESr product (not statistically significant) [2,5] (Table 1). In the Derakhshani 1997 study, there were 1461 patients from 357 practices in Germany that were assessed for IPSS at the end of three months. Therefore, almost ten times the number of patients were assessed in Derakhshani 1997 vs. CAMUS 2011, but with strikingly different results. In Derakhshani 1997, the mean decrease in IPSS after three months was −7.4 points, representing a 40.4% improvement. The QoL improved by 45.9% (n = 1461) and the Qmax by +3.7 mL/s (30.8%) (n = 1277) (Table 2). The change in IPSS of −7.4 in the Derakhshani study far exceeds the threshold of −3 points cited by many authors as defining a significant therapeutic response [6–9]. There is no obvious explanation to reconcile these significant differences in outcomes. In the course of this global analysis of LSESr vs. LUTS, we found a total of 58 peer-reviewed articles that met our criteria for evaluability; these included the CAMUS and the Derakhshani studies. The results of the mean changes in IPSS, QoL and Qmax for the 55 positives of the 58 total reports indicate significant improvements in all parameters. This will be discussed in detail in the sections that follow.

Table 2. The striking difference in the endpoints of IPSS, QoL and Qmax for Barry [2] and Derakhshani [4] using the identical ethanolic extraction product of Serenoa repens (Prosta Urgenin® Uno).

Author (Lead)	Year	Extraction Process	Pt. #	Study (mos)	IPSS *		QoL		Qmax		Fatty Acids %
					Δ	%	Δ	%	Δ	%	
Barry	2011	Ethanol Placebo	151 155	18	−2.2 −3.0	15 20	−0.4 −0.5	11 15	−0.2 −0.8	−1 −5	54 FFA
Derakhshani	1997	Ethanol No Placebo	1461	3	−7.4	40	−1.6	46	+3.7	31	54 FFA

* Values for IPSS, BPHII and Qmax are rounded off to one decimal point and percentages to the nearest whole number. IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, peak urinary flow (mL/s); Δ, mean change; mos, months; #, number; Pt., patient; %, percent; FFA, free fatty acids.

The bottom line is that STEP and CAMUS lessened enthusiasm for the use of Serenoa repens in the United States. Scrutiny of all publications related to both trials does not disclose any obvious shortcomings to account for the lack of efficacy of LSESr in the study participants.

2. Therapeutic Comparator Studies of LSESr vs. LUTS

2.1. HESr and EESr Are Not Inferior to Tamsulosin or to Finasteride

In contrast to STEP and CAMUS finding no evidence of efficacy of LSESr vs. LUTS, a significant benefit has been observed in controlled trials of both HESr and EESr vs. therapeutic comparators. Four trials have compared the therapeutic activity of HESr with that of an alpha-blocker such as tamsulosin, or to a 5α-reductase inhibitor such as finasteride (Table 3).

Table 3. Clinical evaluation of HESr or EESr vs. Tamsulosin (Flomax®) in five studies and HESr vs. Finasteride (Proscar®) in one study.

Lead Author Year, Ref. [#]	Study Duration (mos)	Study Arm	Patients (#) [a]	IPSS *		QoL *		Q_{max} *	
				Δ	%	Δ	%	mL/s	%
Debruyne 2002 [10]	12	HESr Tam	350 354	−4.4 −4.4	28 29	NR NR	NR NR	+1.9 +1.8	17 16
Latil 2015 [11]	3	HESr Tam	83 86	−4.5 −6.5	25 39	−0.9 −1.3	23 34	+1.7 +2.1	15 20
Alcaraz 2020 [12] ‡	6	HESr Tam Combo	222 222 159	−5.6 −5.9 −7.3	30 32 37	−1.3 −1.4 −1.8	34 36 46	+3.3 +2.8 +2.1	25 23 16
Carraro 1996 [13]	6.5	HESr Fin	467 484	−5.8 −6.1	37 39	−1.4 −1.5	38 41	+2.7 +3.2	25 30
Hizli 2007 [14]	6	EESr Tam Combo	20 20 20	−6.1 −4.6 −4.9	34 28 31	−2.6 −2.1 −2.2	62 60 63	+3.2 +3.7 +4.2	34 35 42
Argirovic 2013 [15]	6	EESr Tam Combo	97 87 81	−6.1 −4.6 −4.9	34 28 31	−2.6 −2.1 −2.2	38 40 37	+3.2 +3.7 +4.2	34 35 45

[a] Number of patients at study end. * Values rounded off to one decimal point. Percentages are rounded off to the nearest whole number. ‡ In Alcaraz 2020 the number of patients for Qmax were 43, 33 and 46 for HESr, tamsulosin and the combination, respectively. Data is per protocol (PP) obtained from supplementary material available at https://www.mdpi.com/2077-0383/9/9/2909/s1, accessed on 30 July 2021). Δ, mean change; −, negative change; #, number; %, percent change; +, positive change; AUA, American Urological Association; IPSS, International Prostate Symptom Score; EESr, ethanolic extract of *Serenoa repens*; Fin, finasteride; HESr, hexanic extract of *Serenoa repens*; LUTS, lower urinary tract symptoms; mL/s, milliliters per second; NR, not reported; mos, months; QoL, quality of life; Qmax, peak urinary flow (mL/s); Ref., reference citation; Tam, tamsulosin.

All HESr studies have used Permixon® (Pierre Fabre Medicament S.A.). In fact, all HESr published studies cited in our review have used Permixon, and only the 1987 study of

Ollé Carreras did not specifically identify the HESr product used. An investigation in LUTS therapy involving Permixon vs. the alpha-blocker tamsulosin (Flomax®) was the PERMAL 12-month study reported by Debruyne in 2002 [10]. This large study of over 700 men, with an IPSS eligibility criterion of >10, disclosed a decrease in the IPSS of −4.4 points in both the Permixon and tamsulosin groups, with almost identical percentage improvements of 28% and 29%, respectively (Table 3). The changes in the Qmax for Permixon vs. tamsulosin were +1.8 vs. +1.9 mL/s, respectively. After three months of treatment, 34% of the patients on Permixon had an improvement in Qmax of at least 3 mL/s that persisted at 12 months. Similarly, at three months, 35% of the tamsulosin group improved the Qmax to at least 3 mL/s, and at 12 months 37% of the tamsulosin group had this response. The results of Permixon vs. tamsulosin are almost identical.

Another comparative study was done by Latil et al. in 2015. They performed a randomized, double-blind study comparing HESr at 320 mg/day in 83 patients vs. tamsulosin 0.4 mg/day in 86 patients over three months [11]. The average IPSS score with Permixon decreased from 17.7 at baseline to 13.2 (−4.5) on day 90. In comparison, the respective IPSS decrease for tamsulosin was 16.8 to 10.3 (−6.5) (Table 3).

In 2020, Alcaraz et al. [12] reported their follow-up to the QUALIPROST study of 2016 [16] that compared HESr (Permixon) vs. tamsulosin vs. a combination of the two agents. The combination arm results were statistically superior related to IPSS, QoL, BII at p values of 0.002, 0.001, and 0.007, respectively (supplementary document at https://www.mdpi.com/2077-0383/9/9/2909/s1, accessed on 30 July 2021). The IPSS, QoL, and Qmax results are shown in Table 3. The quality of life as assessed from the bother question of the IPSS is not shown but had similar findings of −2.8 (35.9%), −2.6 (32.9%), and −3.4 (41%) for tamsulosin, Permixon, and the combination, respectively.

A comparison of HESr with the 5-α reductase inhibitor finasteride was done in 1996 by Carraro et al. [13]. This trial evaluated 951 men over 26 weeks to ascertain the efficacy of Permixon (n = 467) vs. finasteride (n = 484) using the IPSS as the primary endpoint. The baseline IPSS was 15.7 ± 5.8 and 15.7 ± 5.7, for Permixon and finasteride, respectively. At 26-weeks, the IPSS decreased by −5.8 and −6.1, representing improvements of 37% vs. 39%, respectively. The onset of action for both Permixon and finasteride was as early as six weeks after initiating treatment and was associated with a similar degree of improvement in the IPSS, with both treatment approaches improving by 22% ($p < 0.001$). However, by 26 weeks there was further improvement, which reached nearly 40% for both treatments. This change in IPSS over time in response to LSESr is important when looking at the results of studies of short duration, (i.e., 4 to 6 weeks), and in hindsight validates our evaluability criterion of at least two or more months study duration to see the full impact of LSESr vs. LUTS on the IPSS. Regarding QoL, 70% of patients reported an improvement at 26-weeks with the QoL measurement (question 8 of the IPSS) dropping from −3.63 to −2.25 with Permixon, and from −3.66 to −2.15 with finasteride. These represent improvements of 38% and 41%, respectively. Qmax at baseline was 10.6 mL/s for Permixon and 10.8 mL/s for finasteride, and at 26-weeks was +2.7 mL/s and +3.2 mL/s, respectively, reflecting 25% improvement for Permixon vs. 30% improvement for finasteride (Table 3). Comparing side effects, patients receiving finasteride experienced a statistically significant deterioration in sexual function vs. those receiving Permixon. This difference was noted from the first follow-up at six weeks and continued to be significant at 26 weeks [13].

Five years after the PERMAL study, Hizli et al. [14] reported the results of a 6 months investigation of EESr vs. tamsulosin. They used Prostagood®, which is licensed to Abdi İbrahim Pharmaceuticals in Turkey and identical to Prostagutt® (Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany) and also known as WS 1473. This study involved three arms: EESr vs. tamsulosin vs. the combination of both agents (combo), with 20 patients in each cohort. In this open-label study, EESr was given as 320 mg/day and tamsulosin 0.4 mg/day, with eligibility criteria of an IPSS ≥ 10, Qmax of <15 mL/s, a gland volume of ≥25 cc, and a PSA of ≤4. At 6-months, the IPSS changes were −6.1, −4.6, and −4.9, for HESr, tamsulosin and the combination, respectively. The percentage

improvements were 34%, 28% and 31%, respectively. Qmax changes were +3.2, +3.7 and +4.2 for percentage improvements of 34%, 35% and 42%, respectively. QoL results showed improvements of −2.6, −2.1 and −2.2, with respective percentage improvements of 62%, 60% and 63% (Table 3).

Argirovic et al. published their 6-month study in 2013 involving a total of 265 patients and compared the EESr Prostamol® Uno (Berlin-Chemie) vs. tamsulosin monotherapy vs. the combination of Prostamol plus tamsulosin. This study found virtually identical results to that of Hizli et al., insofar as both the absolute values and percentage changes from baseline to the end of study [14]. Results comparing baseline with the study-end were statistically significant, but this was not the case when comparing the three regimen's study-end results for IPSS, QoL and Qmax, with p values of 0.1, 0.1, and 0.3, respectively.

These six studies of HESr or EESr vs. a prescription drug comparator show consistent findings relating to the efficacy of LSESr vs. LUTS. Together, they involve a total of 2752 patients and have ample data on the clinical endpoints of IPSS, QoL and Qmax. This represents a comparable degree of improvement in the absolute values and percentage changes between HESr, the alpha-blocker (tamsulosin), and a 5-α reductase inhibitor (finasteride), and a similar degree of efficacy between EESr and the alpha-blocker tamsulosin.

While it is true that these are not placebo-controlled studies, we would have to conclude that LSESr is either an active agent vs. LUTS or that tamsulosin and finasteride are no better than a placebo. After the exhaustive in-depth review of all peer-reviewed studies on LSESr vs. LUTS, the "duck principle" appears applicable (Figure 1).

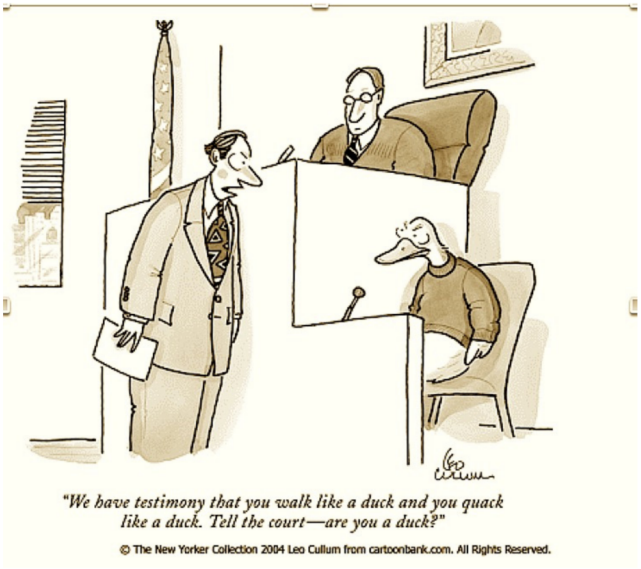

Figure 1. The Duck Principle: "But when I see a bird that quacks like a duck, walks like a duck, has feathers and webbed feet and associates with ducks, I'm certainly going to assume that he IS a duck."—Emil Mazey Secretary-Treasurer UAW Labor leader 1946.

2.2. LSESr Efficacy Is Greater in Severe vs. Moderate LUTS

The greatest improvement in IPSS using a hexanic extract of Serenoa repens (HESr) was observed in those patients with severe lower urinary tract symptoms (LUTS), defined as an IPSS of 20 to 35. In a follow-up to the 2002 PERMAL study [17], a subset of patients with a baseline IPSS of >19 had a decrease of −7.8 points in the Permixon group (65 patients) vs. a −5.8 decrease in the tamsulosin group (49 patients). The corresponding mean percentage decrease in the total IPSS was 35.2% vs. 25.0%, respectively [17]. Further analysis showed that patients with the higher baseline IPSS (>21) had still greater improvement with Permixon and tamsulosin with average IPSS of −9.3 and −6.0 compared to −6.9 and −5.5 found in patients with a baseline IPSS of 20–21, respectively. Flow symptoms (aka

obstructive, voiding) symptoms improved more than storage symptoms (aka irritative, filling) symptoms for groups having an IPSS of 20–21 as well as an IPSS >21 with a similar pattern of response for Permixon and tamsulosin. These findings have been extracted from the text and graphs in the Debruyne 2002 and 2004 papers and are shown in Table 4.

Table 4. Comparative changes in IPSS with Permixon vs. tamsulosin from PERMAL (adapted after Debruyne 2002 [10] and Debruyne 2004 [17]).

IPSS Value	PERMAL 2002		PERMAL 2004	
	Δ (%) IPSS		Δ (%) IPSS	
	Permixon	Tamsulosin	Permixon	Tamsulosin
>10	−4.4 (28%)	−4.4 (29%)		
>19 [a]			−7.8 (35%)	−5.8 (25%)
=20–21 (all)			−6.9	−5.5
=20–21 irritative			−2.5	−2.0
=20–21 obstructive			−4.4	−3.5
>21 (all)			−9.3	−6.0
>21 irritative			−3.5	−1.9
>21 obstructive			−5.8	−4.1

[a] For patients with a baseline IPSS > 19, Permixon was superior to tamsulosin ($p = 0.051$). The greatest change in IPSS (e.g., ≥9 points) was seen in patients receiving Permixon vs. tamsulosin (41.5% vs. 25.4%), respectively. Δ, mean change in IPSS from baseline to study end; −, decrease in IPSS from baseline; %, percent improvement in IPSS from baseline; IPSS, International Prostate Symptom Score.

Brown and Emberton endorsed the findings of the Debruyne 2004 paper with the following editorial comments. "There is no reason not to take this study seriously. It was part of a European multi-center large-scale study that was well designed and thought out". "Overall, it appears that phytotherapy is as valid a pharmacotherapy as α-blockers and 5α-reductase inhibitors in the management of men with BPH/LUTS. Indeed, it may have less adverse effects, be better tolerated, and cheaper". Emberton noted that in the UK phytotherapy cannot be prescribed and that urologists should be aware and informed about phytotherapy as it will inevitably become part of the standard medical therapy for men with BPH/LUTS. "The previous lack of standardization of herbal remedies that once prevented doctors from recommending these products is now much improved" [17].

The Breza study in 2005 from Slovakia evaluated 596 patients who received Prostamol® Uno, an EESr, at a dose of 320 mg/day [18]. In the total population, the change in IPSS over one year was −5.89 (35.9%), with 84% of patients experiencing more than a 3-point drop. In a subgroup of 150 patients with a mean baseline IPSS of 23.3 (range 20–33), the mean IPSS decreased to a post-treatment value of 15.5 or −7.8 points reflecting a 33.5% improvement. However, as Barry et al. pointed out, the change in absolute values in the IPSS may not be as valid as the percentage change in measurements of the IPSS [19]. This appears to be a logical criticism, and if true the percentage changes seen in the Breza study are possibly not of statistical significance. In the Debruyne 2004 study, percentage changes could not be calculated for the IPSS subgroups 20–21 and >21, while they could for the IPSS subgroups >10 vs. >19. Therefore, for Debruyne 2004, only in these subgroups (>10 vs. >19) can it be concluded that the greatest changes in IPSS percentage and absolute values occur in those patients with the more severe baseline values.

The 2020 follow-up to the QUALIPROST study was mentioned earlier. An analysis of response to Permixon vs. tamsulosin vs. the combination of the two in men presenting with IPSS baseline values of >12 indicated a significant improvement in the combination arm over either monotherapy arms in men with an IPSS of >19. In the per protocol (PP) cohort of these severe LUTS patients, the absolute change in IPPS was −7.8 for HESr, −8.2 for tamsulosin, and −10.5 for the combo. The percentage improvements could not be calculated because data for the baseline values in the severe group (IPSS > 19) were not provided. For all PP patients (an IPSS > 12), the PP results were −5.6, −5.9, and −7.3, with

percentage improvements of 29.9%, 31.5%, and 37.2% for HESr, tamsulosin and the combo, respectively. In this study and others, it would be important to compare the changes in IPPS in the cohort of patients with severe LUTS (20–35 IPSS) vs. those with moderate LUTS (8–19 IPSS), instead of comparing the severe cohort with all patients. Using the mean IPSS of all pa-tients diminishes the differential results in contrast to the results found when comparing the IPSS changes between the moderate and severe cohorts.

The study performed by Eickenberg et al. in 1997 performed a comparison between men with a baseline IPSS of $\leq$18 vs. $\geq$19. In that study, 6967 patients were treated with an EESr (Sita®) at a dose of 320 mg/day for 6 months. At the study end, the IPSS was −8.0. A subgroup analysis based on the IPSS categories $\leq$18 vs. $\geq$19 revealed the same mean percentage improvement of 41% at study end [20]. This issue of degree of efficacy of LSESr based on the severity of the baseline IPSS warrants further scrutiny and, perhaps in a follow-up study, the authors of QUALIPROST will clarify this issue by comparing IPSS changes in the severe with the moderate LUTS cohorts. Notwithstanding, the 2020 QUALIPROST publication [12] and its supplement (URL provided earlier) are valuable contributions and raise the possibility of a synergistic effect of LSESr with the alpha-blocker tamsulosin.

3. Peer-Reviewed Evaluable Studies of LSESr vs. LUTS

3.1. Fifty-five out of Fifty-Eight Evaluable Studies Indicate Efficacy

31 English-language and 27 non-English-language peer-reviewed publications were identified and were evaluable. Considering only peer-reviewed evaluable English-language papers on LSESr vs. the endpoints of IPSS, QoL, and Qmax, data was extracted (SBS) from 31 publications for analysis. Not all studies reported all three endpoints. Of the 31 studies, Bent 2006 (STEP) [1], Barry 2011 (CAMUS) [2], and Willetts 2003 [21] represent the three publications reporting no effect of LSESr vs. LUTS. The remaining 28 studies (90%) show results that for the most part are not consistent with a placebo effect (Table 5).

An English-language trial conducted in Egypt by El-Demiry and published in 2004 as an abstract in the British Journal of Urology International was identified late in our exhaustive search of the Serenoa literature [22]. El-Demiry evaluated 200 patients over 6 months using Permixon 160 mg bid after a 2-week washout period. IPSS, QoL, Qmax, residual volume, prostate volume, and PSA assessments were made after 1, 3, and 6 months of treatment. A total of 190 patients completed the study. Significant improvement was seen in the IPSS (−6.6, 30%) at 1 month, and further improvement at 6 months (−11.4, 51%, $p < 0.0001$). QoL improved by a mean value of 73% at 6 months, and Qmax increased significantly, by +2.8 mL/s at 1 month, up to +3.7 mL/s at 3 months, and further improvement by +4.4 mL/s (45.4%) at 6 months ($p < 0.0001$; Table 5) [22].

If non-English-language peer-reviewed papers are considered, 27 evaluable publications can be identified (Table 6). All but two studies indicated the efficacy of LSESr vs. LUTS using an IPSS threshold of ≥ -3. One additional study by Tosto did not meet the threshold of clinical significance when using the criteria of an IPSS percentage improvement of less than 35% [23]. The majority of these non-English-language studies were not cited by authors of the major English-language literature on LSESr. The publication dates of these non-English-language publications range from 1983 to 2013. It would seem improbable for the beneficial effects of LSESr to be the result of a placebo effect given the (a) consistency regarding efficacy across so many studies published in different countries over close to 40 years (1983 to 2021), and (b) the average improvement of the IPSS of −6.7, and −5.3 for hexane, and ethanol extraction methods, respectively, given the cited threshold of changes in IPSS of more than −3 or −4 as being able to differentiate placebo from active agents [6–9].

Table 5. Thirty-one LSESr vs. LUTS English-language studies meeting evaluability criteria. The three negative studies are shown in red font.

Author (Lead)	Year	Extraction (Method)	Pt. #	Duration (mos)	IPSS		QoL		Qmax		Fatty Acids%
					Δ	%	Δ	%	Δ	%	
Carraro α	1996	Hexane	467	6	−5.8	37	−1.4	38	+2.7	25	81
Stepanov β	1999	Hexane	92	3	−6.4	33	−1.0	26	+1.6	18	81
Al-Shukri	2000	Hexane	57	2	−2.2	27	−0.6	18	+0.7	6	81
Debruyne γ	2002	Hexane	350	12	−4.4	28			+1.9	17	81
Giannakopoulos δ	2002	Hexane	100	6	−8.0	40	−0.6	17	+3.7	40	81
Pytel ε	2002	Hexane	116	24	−5.3	42	−1.3	40	+1.2	10	81
Debruyne θ	2004	Hexane	124	12	−7.8	35	−1.2	29	+1.2	11	81
El-Demiry ι	2004	Hexane	190	6	−11.4	51			+4.4	45	81
Djavan Ω	2005	Hexane	88	24	−1.0	17	−0.4	19	+1.8	15	81
Giulianelli	2012	Hexane	591	6	-5.6	32			+3.0	28	81
Latil κ	2015	Hexane	83	3	−4.5	25	−0.9	23	+1.7	15	81
Robert	2015	Hexane	102	2	−4.5	25					81
Alcaraz	2020	Hexane	222	6	−5.6	30	−1.3	34	+3.3	25	81
Hexane Averages		***n* = 12**	**207**	**9**	**−5.5**	**33**	**−0.9**	**26**	**+2.2**	**21**	**81**
Gerber λ	1998	Ethanol	46	6	−7.6	37			−0.7	−5	40
Hizli μ	2007	Ethanol	20	6	−6.1	34	−2.6	62	+3.2	34	81
Barry Þ	2011	Ethanol	151	18	−2.2	15					54
Gerber ν	2001	Ethanol	39	6	−4.4	26	−0.7	21	+1.0	10	41
Sinescu π	2011	Ethanol	120	24	−5.5	40	−1.8	50	+5.6	54	59
Argirovic ρ	2013	Ethanol	97	6	−6.1	34	−2.6	38	+3.2	34	59
Cai	2013	Ethanol	46	3	−3.1	18			+0.5	4	–
Suter	2013	Ethanol	69	2	−7.5	52					95
Saidi	2019	Ethanol	40	12	−2.1	18			+0.8	6	59
Vinarov	2019	Ethanol	30	180	−6.0	50	−3.0	60	+5.0	45	59
Ye	2019	Ethanol	159	6	−4.4	29	−1.2	26	+4.1	36	68

Table 5. *Cont.*

Author (Lead)	Year	Extraction (Method)	Pt. #	Duration (mos)	IPSS		QoL		Qmax		Fatty Acids%
					Δ	%	Δ	%	Δ	%	
ETOH Averages		***n* = 11**	**74**	**25**	**−5.0**	**32**	**−1.8**	**43**	**+2.5**	**27**	**62**
Romics	1993	CO_2	31	12					+4.3	39	55
Bach φ	1996	CO_2	315	36		73			+6.1	46	55
Kondas χ	1996	CO_2	38	6					+4.1	39	55
Braeckman	1994	CO_2	305	3	−6.6	35	−1.5	42	+2.1	26	74
Braeckman ω	1997	CO_2	67	12	−10.2	60	−1.5	42	+2.6	24	74
Braeckman ψ	1997	CO_2	125	3		64				30	74
Willetts	2003	CO_2	46	3	−1.1	8	−0.5	13.0	+2.4	–	–
Bent	2006	CO_2	102	12	−0.7	4			+0.4	4	92
CO_2 Averages		***n* = 8**	**129**	**10.9**	**−4.7**	**41**	**−1.2**	**32**	**+3.2**	**30**	**68**
Averages All			**194**	**15.0**	**−5.1**	**35**	**−1.3**	**34**	**+2.6**	**26**	**70**

IPSS, QoL & Qmax values are rounded off to one decimal point. Percentages are rounded off to the nearest whole number. The Hutchison 2007 study was not shown because it was a group analysis, but it is a valuable study. Since Latil 2015 and Robert 2015 contain identical content that was reported in two different journals, Robert 2015 was arbitrarily excluded from the table.
α Carraro study of Permixon vs. finasteride. HESr showed equivalent efficacy to 5ARI with fewer side effects.
β Stepanov study comparing Permixon at 160 mg bid vs. 160 mg ×2 once a day. Average results used.
γ Debruyne 2002 study of Permixon vs. tamsulosin study with 4-week run-in phase. No significant differences in the effect of Permixon vs. tamsulosin 0.4 mg/day.
δ Giannakopoulos study compared 160 mg bid vs. 160 tid. The results shown are the average of both findings. Qmax with 480 mg/day +4.54 vs. +2.8 for 320 mg/day.
ε Pytel reported that 46–69% of patients reported improvement in obstructive and irritative symptoms from month-6 to the study's end at 2 years.
θ Debruyne 2004 subset analysis of high >19 IPSS patients with randomization between Permixon vs. tamsulosin.
ι El-Demiry is an abstract but with solid data. Ω Djavan study on prevention of progression of LUTS from mild to greater than mild; Permixon vs. WW.
K Latil study comparing Permixon vs. tamsulosin and correlations with inflammation.
λ Gerber 1998 noted improvement at 2 months. At 6 months, 46% of patients with ≥50% (21/46) improvement.
μ Hizli 2007 study comparing Prostagood® (ethanol extraction) vs. tamsulosin vs. Prostagood + tamsulosin. All groups with no significant differences in efficacy; Prostagood + tamsulosin did not increase efficacy.
Þ Barry study is a negative study and the placebo group had Δ in IPSS of −2.99 or 20% improvement.
ν Gerber 2001 study a with one-month placebo run-in for all patients.
π Sinescu used Prostamol Uno.
ρ Argirovic study compared Prostamol Uno 320 mg/day vs. tamsulosin vs. tamsulosin + Prostamol uno; percentage improvements were 33.9% vs. 28.4% vs. 31.4%, respectively for IPSS. Results were 38% vs. 40% vs. 37% for QoL; and for Qmax they were 34% vs. 35% vs. 44.5%, respectively.
φ Bach 1996 3-year study quantitated nocturia, frequency, and incomplete emptying. Nocturia improved 73%, and no nocturia or nocturia ×1 increased from 33% to 85%. Improvements in frequency and incomplete emptying of 54% and 76%, respectively.
χ Kondas used Strogen® Forte, aka Sabal IDS 89, (Strathmann GmbH & Co. KG, Hamburg, Germany). The authors stated they measured IPSS but did not report results.
ω Braeckman 1997 study #1 used Prostaserene® as LSESr. QoL is not from IPSS but only a rating scale. Only 67 patients completed the study, with 34 patients receiving LSESr at 160 mg bid and 33 patients receiving 320 mg/day.
ψ Braeckman 1997 study with calculations done by SBS. For placebo, IPSS improved 25% and Qmax improved 10%.

Table 6. Evaluable non-English-language papers (27 studies) categorized by extraction method. The mean number of patients, duration of the study, and the key clinical outcome assessments are detailed. The extensive footnotes report key findings of individual studies.

Lead Author	Ref. [#]	Year	Extraction Method	Serenoa Patients (#) [a]	Study Duration(mos)	IPSS		QoL		Qmax	
						Δ	% [b]	Δ	%	Δ	%
Cirillo-Marucco	[24]	1983	Hexane	47	4		56 ε			+4.6	50 ε
Cukier ψ	[25]	1985	Hexane	73	2		33 λ				
Tosto	[26]	1985	Hexane	20	3	−5.0	28 Ω				
Pannunzio	[27]	1986	Hexane	30	2					+5.1	74
Pescatore	[28]	1986	Hexane	30	3					+2.5	27
Authie	[29]	1987	Hexane	500	3		78 π				
Ollé Carreras	[30]	1987	Hexane	40	2		68 φ				
Orfei	[31]	1988	Hexane	30	3		50 χ	−2.2		+0.0	0.2
Dathe	[32]	1991	Hexane	49	6					+5.9	49
Aliaev	[33]	2002	Hexane	26	60	−8.8	76	−1.3	53	+4.1	35
Foroutan	[34]	1997	Hexane	592	3	−6.5	38	−1.5	45	+5.9	66
Medeiros α	[35]	2000	Hexane	130	3	−6.5	37	−1.4	39	+2.0	22
Totals Hexane (12)			**Averages**	**131**	**7.8**	**−6.7**	**52**	**−1.6**	**46**	**+3.8**	**40**
Derakhshani	[4]	1997	Ethanol	1047	3	−7.4	40	−1.6	46	+3.7	31
Eickenberg *	[20]	1997	Ethanol	6967	6	−8.0	44	−1.8	38	+3.0	23
Redecker **	[36]	1998	Ethanol	50	3		48 ν			+3.4	24
Ziegler ** β	[37]	1998	Ethanol	109	3				36	+3.7	29
Breza	[18]	2005	Ethanol	596	12	−5.9	36	−1.7	54	+2.3	19
Aliaev	[38]	2007	Ethanol	50	6	−3.0	26	−1.8	43	+1.7	14
Razumov	[39]	2007	Ethanol	30	6	−6.9	43	−2.7	68	+2.8	23
Aliaev γ	[40]	2009	Ethanol	50	24	−4.2	37	−2.2	52	+2.7	21
Vinarov	[41]	2010	Ethanol	50	36	−6.0	50	−2.0	50	+4.5	39
Aliaev	[42]	2013	Ethanol	38	120	−1.3	12	−1.1	35	+3.3	26
Totals Ethanol (10)			**Averages**	**899**	**22**	**−5.3**	**37**	**−1.9**	**47**	**+3.1**	**25**

Table 6. *Cont.*

Lead Author	Ref. [#]	Year	Extraction Method	Serenoa Patients (#) [a]	Study Duration(mos)	IPSS		QoL		Qmax	
						Δ	% [b]	Δ	%	Δ	%
Mattei ψ	[43]	1990	CO_2	20	3		55 ω				
Vahlensieck	[44]	1993	CO_2	1334	4		39;55 Þ				
Vahlensieck	[45]	1993	CO_2	400	3		94 θ			+5.8	52
Fabricius δ	[46]	1993	CO_2	153	6		39;58 δ				
Bauer ψ	[47]	1999	CO_2	101	6		37 ρ				16
Totals CO_2 (5)			Averages	402	4.4						34
Mean Across All Studies (n = 27) Hexane extraction (n = 12) Ethanol extraction (n = 10) Carbon dioxide extraction (n = 5)				477	12	−6.0	45%	−1.7	47%	+3.5	33%

The clinical endpoints of IPSS, QoL and Qmax are rounded off to two significant digits. Percentages are rounded off to the nearest whole number.
≈, approximately; Δ, mean change; −, negative change; #, number; %, percent change; +, positive change; CO_2, carbon dioxide; IPSS, International Prostate Symptom Score; mos, months; QoL, quality of life; Qmax, peak urinary flow (mL/s); Ref., citation reference.
[a] The number of patients at study end, or as reported.
ψ Placebo-controlled study. The study by Bauer was also double-blinded and randomized.
α Medeiros study used a QoL scale 6 (worst) to 1 (best) rather than 6 (worst) and 0 (best).
* Eickenberg used a 96% EESr.
** Redecker & Ziegler used a 90% EESr.
β Ziegler did not use IPSS, so his reported symptoms were based on % improvement involving weak stream, hesitancy, incomplete emptying, frequency, and nocturia.
γ Aliaev 2009 is a 2-year extension of the 6-month 2007 paper.
δ Fabricius 1993 reported decreases in frequency and nocturia of 39%, and 58%, respectively. Nocturia ≤ 1 in 16% pre-LSESr vs. 79% at end of study (n = 153).
ε Cirillo-Marucco study done before IPSS; raw data on nocturia; the study also included Qmax results.
λ Cukier study done before IPSS; only raw data on nocturia.
Ω Tosto study done before IPSS; authors used a unique point scoring to evaluate frequency, nocturia, incomplete emptying, weak stream.
π Authie study before IPSS use; nocturia, frequency, and urgency improvements were 82%, 67%, and 85.3%, respectively (average improvement 78.1%); average complete resolution of these symptoms was 43.5%.
φ Ollé Carreras did not use IPSS. The number shown is based on the change in frequency with complete resolution in 27 out of 40 patients.
χ Orfei used scores from frequency, nocturia, urgency, weak stream, and straining at the beginning and end of the study
ν Redecker data evaluated nocturia before and after LSESr.
ω Mattei used scores from frequency, nocturia, and incomplete emptying. For these three endpoints, average improvement 55% vs. placebo average improvement of 1.4%.
Þ Vahlensieck did not use IPSS. The data reflects the change in frequency and nocturia before and after LSESr. Frequency improved by 39% and nocturia by 55%.
Θ Vahlensieck 2nd study reported an average decrease in frequency episodes of 94%. For nocturia, 59.5% of patients had ≤ 1 episode at end of the study vs. 9.7% at the start of the study.
P Bauer only indicated percentage improvement. Talso® Uno with 37% vs. 13% for placebo.

In addition, head-to-head studies, placebo-controlled and non-placebo-controlled studies of LSESr, showed similar, if not superior, efficacy when compared with the 5α-reductase inhibitor finasteride or with the α-blocker tamsulosin as shown earlier in Table 3. If LSESr is a placebo, then so too are finasteride and tamsulosin. This is what Frater-Schröder concluded in the 2009 editorial entitled "when a = b and a = c, then b = c" [48]. This editorial was directed at the Cochrane 2012 meta-analysis [3] and its criticism of the Carraro 2006 [13] and Debruyne 2002 [10] studies. In Frater-Schröder's opinion, "Quasi-scientifically-based reports like this Cochrane review weaken the importance and value of phytotherapy in the awareness of experts and the general public" [48]. At the time this editorial was published, Frater-Schröder was the co-secretary and an active member of the scientific committee of ESCOP, an organization that described the results of some Serenoa studies, but whose committee report never came to conclusions about the efficacy of LSESr [49].

3.2. Previous Key Assessments of the Literature (Novara and Vela-Navarrete)

Two key meta-analyses reviewed the efficacy and safety of the HESr (Permixon) in the treatment of LUTS [50,51]. The Novara 2016 meta-analysis identified seven randomized and controlled clinical trials each conducted with Permixon and concluded that Permixon improved peak urinary flow rate (Qmax) and decreased nocturia compared with placebo. However, 6 of 7 studies cited by Novara were considered (SBS) non-evaluable for the following reasons. Three studies had less than 20 patients at study end [52–54], two studies had a duration of only four weeks [55,56], and one study presented unclear data [57]. Two additional studies reviewed by Novara concluded that Permixon relieved LUTS comparably to tamsulosin [10,11]. These latter two studies did meet the requirements for evaluability (Debruyne 2002 and Latil 2015, Table 3). Finally, in two other studies reviewed by Novara, Permixon and tamsulosin were used as therapy in combination, but Permixon was not evaluated as monotherapy, so efficacy could not be concluded [58,59]. In contrast to tamsulosin and finasteride, Permixon had little impact on sexual function and the safety profile of HESr was comparable to placebo [50].

Similar to the Novara meta-analysis, Vela-Navarrete reviewed 27 studies using HESr as monotherapy in patients with LUTS at the standard dose of 320 mg/day [51]. This 2018 meta-analysis included 15 randomized and controlled studies and 12 observational studies conducted under conditions of routine clinical practice. The authors concluded that the standardized HESr was well-tolerated and effective for the long-term treatment of LUTS/BPH and that HESr reduced nocturia and improved peak urinary flow rate vs. placebo. Moreover, patients receiving the standardized HESr had a statistically significant mean improvement in the IPSS, decreasing from baseline by −5.73 points ($p < 0.0001$), and well above the minimum 3-point improvement cited by Barry 1995 as a threshold for clinical significance [6]. The mean IPSS per Vela-Navarrete above is very close in value to the mean IPSS of −5.1 and −6.0 shown in the 31 English-language and the 27 evaluable non-English studies shown in Tables 5 and 6, respectively. Vela-Navarrete's review included 27 studies, vs. the 58 studies employing all extraction methods in this review. The Vela-Navarrete 2018 review included the 1997 open-label study by Foroutan et al. [34] conducted in Austria, with 592 patients evaluated over 3 months. This study showed an improvement in IPSS (−6.48; 38%), in QoL (−1.49; 45%), and in Qmax (+5.85 mL/s; 66%). This study was initially missed in this author's (SBS) search of the Serenoa literature; it is an important evaluable study (see Table 6). Of note with these results, and results presented in Parts I–III, is that Roehrborn et al. found an improvement in symptom score of ≥35% to be "clinically significant" [23].

An additional non-English-language study not easily discoverable with standard search approaches is the open, multicenter study by Medeiros et al., published in 2000 in Portuguese [35]. They evaluated 130 patients from 17 urology centers over 3 months. The IPSS was significantly improved (−6.54, 37.5%, $p < 0.0001$), as was QoL (−1.37, 38.6%, $p < 0.0001$) and Qmax (+1.95 mL/s, 22%, $p < 0.0001$; Table 6). Medeiros et al. used a

different scale for QoL assessment, scoring 6 (worst) to 1 (best), rather than the established scoring of 6 (worst) and 0 (best).

4. In the Final Analysis, the Effect of LSESr vs. LUTS Is Not a Placebo Effect

There is no question that the lack of efficacy of LSESr per the STEP and CAMUS double-blind placebo-controlled trials resulted in diminishing physician acceptance of LSESr in the US. This negative impact has been and continues to be compounded by the absence of tight regulations concerning quality requirements and the commercial prevalence of non-standardized Serenoa products in the United States. In other words, the marketplace in the US is flooded with saw palmetto products that range from good to inferior quality. In contrast, LSESr products from hexane, ethanol, or carbon dioxide extraction processes that meet a standardized profile are widely used in Europe, and accordingly physician perception of LSESr vs. LUTS is of a significantly higher degree in Europe, Asia, and South America than in the US.

Adding to the complexity of the above issue concerning the quality of Serenoa repens products is that the carbon dioxide LSESr product used in STEP was never evaluated in another trial, which would have confirmed or refuted the conclusions reached in STEP. Did the results of STEP represent an outlier study, in contrast with the results of many other published studies? With the evaluability criteria detailed in Part I, a total of 58 evaluable peer-reviewed studies of LSESr were found (SBS) using the three different extraction methodologies. Thirteen of these 58 used a lipidosterolic product from carbon dioxide extraction as did STEP. The mean clinical endpoints of IPSS, QoL, and Qmax in these 13 studies were −4.6, −1.2, and +3.5, respectively. It is important to note that these results include both negative studies using carbon dioxide extraction (STEP [1], and Willetts [21]). If these two negative studies are eliminated from analysis, the mean results are −8.4 for IPSS, −1.5 for QoL, and +4.2 mL/s for Qmax, with percentage improvements of 53%, 42%, and 34%, respectively (see Table 7). Once again, per Roehrborn et al.: "A clinically significant improvement in lower urinary tract symptoms was prospectively defined as a 35% or better improvement in the AUA Symptom Index (AUASI) compared to baseline."

Table 7. Summary of mean outcome for evaluable studies grouped by extraction technology for IPSS, QoL, and Qmax. Data are shown for all studies, and also for only the positive studies. All 24 HESr studies were positive. The three negative studies were Willetts 2003 (CO_2) [21], Bent 2006 (CO_2) [1], and Barry 2019 (Ethanol) [2].

Extraction Technology	Mean Patients #	Mean Study Duration (mos)	Included Studies	IPSS		QoL		Qmax		Typical FFA %
				Δ	%	Δ	%	mL/s	%	
Hexane n = 24	245	8.5	All positive	−5.8	41	−1.1	32	+2.9	29	Min ≈ 80
Ethanol n = 21 (1 negative)	477	23	All studies †	−5.1	34	−1.8	45	+2.8	25	Min ≈ 70
			Positive only	−5.3	36					
CO_2 n = 13 (2 negative)	228	8.4	All studies	−4.6	43	−1.2	32	+3.5	31	Min ≈ 65–70
			Positive only	−8.4	53	−1.5	42	+4.2	34	

† The one negative ethanol study (Barry) did not significantly alter the IPSS outcome. The free fatty acid (FFA) minimums are typical values for lipidosterolic products (data on file 2021, Valensa International). The clinical endpoints of IPSS, QoL and Qmax are rounded off to two significant digits. Percentages are rounded off to the nearest whole number. ≈, approximately; Δ, mean change; −, negative change; %, percent; +, positive change; CO_2, carbon dioxide; FFA, free fatty acid; IPSS, International Prostate Symptom Score; mL/s, milliliters per second; mos, months; QoL, quality of life; Qmax, peak urinary flow (mL/s).

The CAMUS 2011 study publication used Prosta Urgenin Uno, an EESr. An earlier paper by Derakhshani in 1997 involving 1047 men evaluated the identical product over a treatment period of three months. Findings showed a mean change in IPSS of −7.4, QoL improvement by 46%, and Qmax increase of 3.7 mL/s [4]. Of the 58 evaluable studies reviewed by this author (SBS), 21 (36%) used an ethanol extract product and all showed positive results except for the CAMUS study. The mean clinical endpoints of IPSS, QoL, and Qmax, including the negative CAMUS study, were −5.1, −1.8, and +2.8, respectively. The percentages of mean improvement were 34%, 45% and 25%, respectively. If the CAMUS

data for IPSS are removed, the IPSS mean results further improve from −5.1 to −5.3 (see Table 7). After examining all extraction processes, including the outcome from negative studies, and including all evaluable peer-reviewed articles published in every language, it would appear that the benefit of LSESr vs. LUTS is undeniable.

Cochrane 2012 presented results from studies comparing Serenoa repens vs. placebo [3]. Some of these references were considered non-evaluable (SBS) because the patient number at the end of the study was less than 20, and/or the study duration was less than 2 months. Contrary to the position taken by the authors of Cochrane 2012, those non-evaluable studies (SBS) did indicate efficacy of Serenoa repens vs. LUTS. Data from these studies considered negative by Cochrane 2012 included a Qmax +3.4 mL/s, a decrease in nocturia with 55% improvement, and a decrease in urgency of 65%. In contrast to the Cochrane 2012 assessment, the 2018 Vela-Navarrete meta-analysis confirmed the efficacy of the HESr product Permixon vs. placebo (or comparator) in randomized clinical trials. Of the 15 trials considered by Vela-Navarrete 2018, seven are placebo-controlled [51]. Vela-Navarrete 2018 used a random effect model and considered publication bias. The outcome of their review determined that HESr compared to placebo was associated with 0.64 fewer voids/night (95% confidence interval (CI) −0.98 to 0.31, $p < 0.001$) and an increase in Qmax of +2.75 mL/s (95% CI 0.57 to 4.93; $p = 0.01$). Figure 2 in the Vela-Navarrete 2018 paper [51] showed a forest plot for Qmax from four studies (Boccafoschi 1983 [52], Emili 1983 [53], Tasca 1985 [54], and Descotes 1995 [55]) comparing HESr ($n = 122$) to placebo ($n = 133$). The studies that supported efficacy for a decrease in nocturia and improvement in Qmax were not impacted by study heterogeneity, and no publication bias could be found in the 2018 review and meta-analysis by Vela-Navarrete et al. [51].

A table of the 17 English and non-English-language placebo-controlled studies for Serenoa repens vs. LUTS/BPH is presented in Table 8. For the HESr studies, Vela-Navarrete 2018 did not cite the Mandressi 1983 study [56], which also included a separate Pygeum intervention arm. Boccafoschi 1983, Emili 1983, Mandressi 1983, Champault 1984 [60], Tasca 1985, and Descotes 1995 were all considered by Cochrane 2012 [61]. Including clinical studies of LSESr using hexane, ethanol, and CO_2 extraction processes, a robust set of literature for placebo-controlled trials for Serenoa repens exists and confirms that the body of evidence for the efficacy of Serenoa repens does not represent a placebo effect.

The Boyle 2004 meta-analysis analyzed eight randomized clinical trials and presented findings consistent with the data presented above in (Table 8). Boyle et al. found that HESr vs. LUTS was associated with a 5-point reduction in IPSS and significant improvements in Qmax and nocturia compared to placebo [62]. As mentioned earlier, of these 17 placebo-controlled studies, eight were categorized as non-evaluable due to a short study duration in five (Champault, Descotes, Emili, Mandressi, Löbelenz) [53,55,56,63], too few patient numbers in two (Boccafoschi, Tasca), [52,54] or unclear data in one (Reece Smith) [57]. Excluding these arbitrarily defined non-evaluable studies did not alter the results from our analysis of the evaluable studies in supporting the efficacy of LSESr vs. the key study endpoints such as IPSS, QoL, and Qmax. Moreover, of the seven studies considered non-evaluable due to low patient number (<20 patients) or short duration (<2 months), clinical endpoints such as urgency decreased by 65%, nocturia decreased by 55%, and Qmax improved by 3.0 mL/s (Table 9). These findings further support to the body of literature attesting to LSESr efficacy vs. LUTS.

Table 8. Summary of 17 placebo-controlled LSESr clinical trials. Eight studies (bolded) did not meet our criteria for evaluability for LSESr vs. LUTS/BPH.

Lead Author	Year	Study	Extraction	Product	Serenoa Patients δ	Placebo Patients δ	Study Duration (mos)
Boccafoschi	1983	D, P	Hexane	Permixon	11	11	2
Emili	1983	D, P	Hexane	Permixon	15	15	1
Mandressi	1983	D, P	Hexane	Permixon	19	15	1
Champault	1984	D, P	Hexane	Permixon	50	44	1
Tasca	1985	D, P	Hexane	Permixon	14	13	2
Reece Smith	1986	D, P	Hexane	Permixon	33	37	3
Löbelenz ‡	1992	P	Ethanol	Sabal Extract	30	30	1.5
Descotes	1995	D, P	Hexane	Permixon	82	94	1
Cukier	1985	D, P	Hexane	Permixon	71	76	2.5
Mattei	1990	D, P	CO_2	Talso®	20	20	3
Braeckman	1997	D, R, P	CO_2	Prostaserene	125	113	3
Bauer *	1999	D, R	CO_2	Talso® Uno	101		6
Gerber	2001	D, R	Ethanol	Solaray®	39	40	6
Willetts	2003	R, C	CO_2	Proseren®	46	47	3
Bent	2006	D, P	CO_2	Not stated	102	104	12
Barry	2011	D, P	Ethanol	Prosta Urgenin Uno	151	170	18
Ye	2019	D, P	Ethanol	Prostess® Uno	159	169	6

IPSS, QoL & Qmax values are rounded off to one decimal point. Percentages are rounded off to the nearest whole number. δ The number of patients at study end, or as reported. ‡ Löbelenz study was only six weeks in duration. * Bauer study presented the sum of the Talso Uno and placebo patients. mos, months; D, double-blind; R, randomized; P, placebo-controlled; CO2, carbon dioxide.

Table 9. Efficacy of HESr (Permixon) vs. placebo in seven arbitrarily defined "non-evaluable" studies in Cochrane 2012. All seven studies reported clinical improvement in symptoms vs. placebo.

Author (Lead)	Year	Ref. [#]	Serenoa Patients (#) δ	Study Duration (mos)	Key Results for Serenoa vs. Placebo or Comparator
Boccafoschi	1983	[52]	11	2	Qmax +4.2 (42%) vs. placebo +2.1 (20.6%)
Emili	1983	[53]	15	1	Qmax +3.56 (34.5%) vs. placebo +0.20 (2.2%)
Mandressi	1983	[56]	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	[63]	50	1	Qmax +2.7 (50.5%) vs. placebo +0.25 (5%); nocturia −1.53 (49%) vs. placebo −0.48 (15%)
Tasca	1985	[54]	14	2	Qmax +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%
Löbelenz	1992	[64]	30	1.5	Qmax +1.2 (9.8%) vs. placebo +0.6 (4.6%)
Descotes	1995	[55]	82	1	Qmax +3.4 (28.9%) vs. placebo +1.1 (8.9%)
Mean Across All Studies for Clinical Outcome					Qmax +3.0 (32%); ↓ nocturia 55%; ↓ urgency 65%

δ The number of patients at study end, or as reported. Löbelenz study did not specify how many patients in LSESr cohort at the end of the study. ↓, decreased; −, negative change; #, number; +, positive change; mos, months; Qmax, peak urinary flow (mL/s); Ref., reference citation; vs., versus.

5. Extract Quality May Affect LSESr Efficacy

Major differences between extraction technology and composition of finished Serenoa products have been identified, and which have been stated to significantly impact the ability of the supplement to ameliorate LUTS [65–68]. Research suggests that there is a "fingerprint" of saw palmetto that represents a quality standardized profile. A key element of this quality standardized profile is the ratio and content of fatty acids, which can vary dramatically across products [67]. Both the EU monograph and USP standards established the minimum level of total fatty acids (TFA) that are needed for a quality Serenoa repens extract. The USP also established ratios of the key fatty acids compared with lauric acid that are required to meet the established chemical profile [69]. The USP stated the chemical profile for a quality Serenoa repens extract would have a minimum of 80% total fatty acids and have a fatty acid composition of oleic acid (30–35%), lauric acid (26–32%), myristic acid (10–12%), palmitic acid (8.5–9.2%), and linoleic acid (4.3–6.0%) [69]. This fatty acid profile distinguishes quality saw palmetto extracts from vegetable oils, adulterated products, and dried saw palmetto berry powders that are deficient in fatty acid amount and/or composition. Key issues remain whether or not the content of total vs. free fatty acids (FFA) of LSESr correlates with efficacy in treating LUTS or does a particular fatty acid account for LSESr activity, and also, whether or not one extraction process is better than another.

6. The Extraction Process Does Not Correlate with the Efficacy of LSESr Products vs. LUTS

An analysis of 20 commercially available Serenoa repens products using a gas chromatography-flame identification detector (GC-FID) and gas chromatography-mass spectrometry (GC-MS) showed considerable variability in TFA and phytosterol content among preparations [68]. In another gas chromatography study involving 19 different Serenoa repens mono-preparations, the fatty acid content varied from one-tenth to greater than 4.6-times the fatty acid mg/day dose stated on the supplement product package insert [65]. The mean FFA content in 14 different Serenoa repens products available in Europe has ranged from as high as 80.7% to as low as 40.7% [67]. Additionally, only 9 of the 19 mono-preparations evaluated contained the recommended daily dosage of 320 mg LSESr per day, consisting of 70% to 95% fatty acids (range, 224–304 mg) [65]. With consideration of this huge variability in the quality of Serenoa repens products, the hexanic lipidosterolic extract Permixon has been found to have the highest percentage of FFA, and this finding has been attributed to the therapeutic efficacy of this LSESr.

Studies suggest that hexane, supercritical CO_2, and ethanol extraction technologies lead to different fatty acid and phytonutrient profiles. However, commercial Serenoa repens extract-containing products made from any of the extraction technologies are said to have demonstrated activity against 5α-reductase and/or to have an impact on symptoms of LUTS/BPH [50,70]. At a biological level, the pharmacologic activity of 10 lipidosterolic extracts of Serenoa repens differed in the degree to which they inhibited fibroblast proliferation as well as 5α-reductase Types 1 and 2 [71]. It was the hexanic lipidosterolic extract that most actively inhibited enzyme activity and fibroblast-induced cell proliferation. Data on supercritical CO_2 extracts are more limited, but it is reported that LSESr extracts using ultrahigh-pressure supercritical CO_2 have a fatty acid profile similar to hexanic lipidosterolic extracts (Valensa International. 2021. Comparable fatty acid profile of LSESr products. Data on file). Because ethanol has a different polarity than hexane, this may contribute to the differences in the extract profiles of hexane vs. ethanol lipidosterolic products. Do such differences in fatty acid profiles or biochemical actions translate to marked differences in the clinical efficacy of LSESr vs. LUTS? Our review of the peer-reviewed Serenoa repens literature, with evaluability requirements for LSESr monotherapies, and known extraction modality yielded findings that failed to show any obvious relationships between extract type and the degree of clinical effect. The pooled results of the IPSS, QoL, and Qmax for 24, 21, and 13 evaluable studies using hexane, ethanol, and CO_2 extraction, respectively, show very similar results. These findings were

presented previously (Table 7). Neither FFA content nor extraction modality have any bearing on clinical efficacy.

Unfortunately, none of the clinical studies of LSESr products have involved head-to-head comparisons of one extraction process vs. another [72]. Although it would seem apparent that every peer-reviewed study should detail the extraction process and the details of dosing, it is disappointing that some publications omitted such crucial information. Concerning the clinical endpoints of IPSS, QoL and Qmax, when the extraction method is one of the standard LSESr processes, be it hexane, ethanol, or carbon dioxide, there is no evidence of the superiority of one process over another. The biological differences seen in non-clinical studies dealing with various pharmacologic actions in vitro seem to have minimal relevance to what is seen in vivo in human clinical studies. The major challenge is to educate both physicians and the lay public that products labeled as "saw palmetto" or "*Serenoa repens*" are not equivalent to a standardized lipidosterolic extract of Serenoa repens (LSESr) with a product profile that meets an established definition, and that only the use of the latter is acceptable.

7. Milieu Factors Are Important When Assessing LSESr vs. LUTS

The demographics of the population under study cannot be ignored when evaluating clinical trial results. Strong epidemiologic data demonstrate that lifestyle factors such as obesity, diet, alcohol intake, stress, and physical activity, play a role in LUTS etiology and progression [73–77]. In fact, such lifestyle issues interact with each other and are consequential in the processes of inflammation, aging, and cancer. The patient's medical history, the presence of co-existent chronic inflammation, the proper assessment of diabetes, metabolic syndrome, and details about medications and supplements and possible drug interactions need to be taken into account when determining the clinical efficacy of LSESr vs. LUTS [78–85]. Study design should stratify patients into subsets of those who may have lingering pharmacologic effects of alpha-blockers vs. those who were never on them. Inflammation is of such paramount importance that a more substantive assessment of the patient's inflammatory status must be routine in any analysis of LUTS. Despite significant technological advances in the biological sciences, the current testing of inflammation remains inadequate and should be addressed in future trials of LSESr given the widely recognized role of inflammation in the development of LUTS [86–93]. The anti-inflammatory properties of Serenoa repens are detailed in many reports [11,93–98]. Lifestyle modifications aimed at reducing inflammation should help modulate LUTS symptoms and possibly prevent progression [73]. Investigators should consider stratifying the patient population using an "inflammation index", and further interpreting clinical data by comparing an "inflammation index" with a quality of life indicator such as the bother question of the AUASI [99,100] or the BPHII [16].

Simple measures such as restricting fluid intake 4 h before bedtime, routinely attempting to void prior to sleep, limiting or omitting caffeinated beverages, and avoiding salt in the diet can significantly affect a key symptom such as nocturia [101–104]. Principal investigators should evaluate study participants based on these lifestyle factors to clarify the potential beneficial effects of LSESr relative to the possible lifestyle modifications known to affect LUTS. In an article published 25 years ago [55], Descotes et al. referred to an article written by Castro still 23 years earlier. In that publication from nearly a half-century ago, Castro remarked on the challenges faced when evaluating patients undergoing treatment for LUTS. "The clinical symptoms of BPH are also labile, and can vary with time, seasons, stress, medication, changes in sympathetic activity, bladder training, sedentary activity, and irregular voiding. Spontaneous variation in disease symptoms and the degree of dynamic obstruction, coupled with a pronounced placebo effect, clearly complicate any assessment of drug efficacy in BPH" [55,105]. Forty-two years after the 1972 publication by Castro, Vaughan shared his views about the clinical lability of LUTS. "To this, I would add my 47 years in frankly discussing LUTS with thousands of patients. Not only is there variability in nocturia, but also in symptoms of hesitancy, weak stream, incomplete

emptying, urgency, and terminal dribbling" [106]. At age 78 years (SBS), and despite being a non-smoker, non-drinker, following a low sodium diet, and not having sleep apnea or obesity as problems, I too echo these observations about the day-to-day variations in LUTS. Such variable symptomatology, combined with issues such as the quality of the Serenoa repens product, and patient compliance with medications, contribute to the difficulty in our understanding of LUTS and its optimal approach to prevention and treatment.

8. Clinical Perspective

A review and network meta-analysis (NMA) of randomized placebo-controlled trials on Serenoa repens vs. placebo vs. alpha-blockers in the treatment of LUTS was reported by Russo et al. [107]. Twenty-two trials were identified by the authors for data investigation using this NMA methodology. The outcomes of IPSS and peak flow were considered across the 22 studies, including 10 randomized trials comparing LSESr to a placebo (five studies), or an alpha-blocker (five studies). For the LSESr studies, two used a HESr product that was compared to tamsulosin, and eight other studies used a non-hexane Serenoa product, with five being placebo-controlled and three studies using a prescription drug as a comparator. From the NMA, Russo concluded that HESr and non-HESr did not demonstrate clinically meaningful improvement in LUTS and peak flow over placebo. De Nunzio et al. [108] published a response to Russo, criticizing the NMA methodology for being inappropriate to ascertain clinical efficacy, and that patient cohorts were unbalanced and affected the validity of the conclusions reached. De Nunzio et al. also noted that a large number of randomized clinical trials were either not identified or were excluded. They concluded that these shortcomings could lead to false conclusions [108]. Many criticisms similar to those voiced by De Nunzio et al. of the Russo review are to be found in our global review presented herein. This includes failure to retrieve all eligible publications for analysis, including early science that represents the body of literature relevant to modern medicine, and failure to establish strict evaluability criteria for the studies to be reviewed as opposed to relying on methodology for analysis at the expense of clinical relevance. In fact, of the 22 studies cited by Russo, four did not indicate the extraction process, and three of those four were combinations of Serenoa repens with other products, and one study involved only 13 patients. If clinical data are used to present an opinion only, rather than to enhance medical practice, then the data do not have value. The same could be said for the methodology for both reviews and meta-analyses, and the failure to consider non-native language publications. Dated science that is well done builds a foundation for clinical practice and allows patient care to be improved.

The clinical literature on Serenoa repens for the treatment of LUTS is extensive. In some studies, important variables are often inadequately controlled. This has resulted in inconsistent findings and controversy concerning what benefit may result from the use of commercially available Serenoa products. The most important variable repeatedly presented in this multi-part report is whether the product is a lipidosterolic extract of Serenoa repens (LSESr) vs. a crude product such as crushed dried saw palmetto berry powder. In addition to the use of a high-quality standardized LSESr, other factors to consider when evaluating the Serenoa clinical literature are the dosage of LSESr, the criteria used to select patients, the exclusion of products combining Serenoa with other agents, and the clinical study design. Based on the evidence presented, a standardized LSESr, given as monotherapy, and that has an established profile defined by the EMA or USP, at a dosage of 320 mg/day, either in divided doses or as a single daily dose, may contribute to the alleviation of LUTS. The clinically significant endpoints include a decrease in the IPSS score, an improvement in the QoL score, and an increase in peak urinary flow (Qmax), with all parameters achieved in association with a high therapeutic index. LSESr's very favorable safety profile includes a negligible impact on sexual function [50,51,109–115]. Despite achieving the desired endpoints mentioned, the American Urological Association (AUA) and the European Association of Urology (EAU) treatment guidelines have downplayed

the efficacy of LSESr therapy [116,117]. In contrast, meta-analyses published in 2016 and 2018 support the use of LSESr in men with mild-to-moderate LUTS/BPH [50,51].

In this clinician's perspective, based upon nearly 40 years of clinical data, some conclusions are clear. First, LSESr has a definite role in the treatment of LUTS. It has a high safety profile with relatively few adverse side effects. It does not cause sexual dysfunction such as ejaculatory disorders seen with 5α-reductase inhibitors, nor hypotension with some α-blockers such as tamsulosin (Flomax®). LSESr does not alter PSA expression and therefore, does not interfere with the monitoring of men at risk of developing prostate cancer. LSESr using hexane, ethanol, or carbon dioxide extraction have all shown efficacy in published studies. The onset of action may be as early as two weeks but is clearly established by 3 months. Of importance is the durability of efficacy seen with long-term treatment of LUTS with LSESr. Of greater significance is the finding of slowing and even halting the progression of LUTS/BPH during prolonged studies using LSESr, with some trials extending 10 to 15 years. Such studies may indicate that LSESr is affecting the pathological processes i.e., pathobiology or etiopathogenesis, that lead to LUTS/BPH. Patient selection is important, and those patients with severe LUTS, and at high risk for acute urinary retention are not optimal candidates and warrant careful observation relating to the need for surgical intervention. The most critical issue in the use of Serenoa repens in treating LUTS is the need to educate physicians that crude herbal products are never to be equated with standardized LSESr products that have a profile established by the EMA or USP and that the former products have no role to play in LUTS treatment. An unresolved issue in the use of LSESr relates to the lack of head-to-head studies to ascertain any difference in the hexane vs. ethanol vs. carbon dioxide extracts, but the results presented in this report would indicate that no particular extraction process is superior to another. An additional issue relates to regulatory agencies and their role in monitoring the quality of products such as LSESr. Why is LSESr available by prescription in some countries, OTC in others, and is inadequately regulated concerning product quality in others, the latter especially in the United States? We should never confuse the business of medicine with the practice of principled medicine. The former has led to the deterioration of medicine as a profession and has diminished the quality of care to patients while increasing the risk of adverse events.

In summary, LSESr (lipidosterolic extract formulations of Serenoa repens) show efficacy in treating LUTS ± BPH, and the results discussed herein provide a rationale for conducting larger, better-controlled studies using such formulations in men with mild-to-moderate LUTS. These studies should quantitate change in IPSS, QoL, Qmax. An evaluation of the inflammatory status of the patient and the effect of long-term use of LSESr on halting the progression of LUTS/BPH should provide further confirmation that LSESr alters the natural history of this affliction of great "bother" in the adult male.

9. Addendum

During the review process of Part III, the response to a discussion of the ethanolic lipidosterolic product Prostagood led to the finding of an additional peer-reviewed paper by Akbulut et al. that had been overlooked during the initial search [118]. In their study of 106 patients, ages 45 years or older and with a baseline IPSS greater than 10, the use of Prostagood for three months resulted in an IPSS decrease of −6.4 (35% improvement). This result is consistent with the findings of our global review.

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