Review

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

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Abstract: Part I of this 3-part series provided the groundwork for understanding the role of a standardized lipidosterolic extract of Serenoa repens (LSESr) in the treatment of LUTS. It documented that a treatment having a high therapeutic index (i.e., a ratio of benefit to adverse reactions) is a critical need in the demographic context of a rapidly growing elder population. Part I described the clinical symptomatology of LUTS and how it is quantified. A critique of the reports from four authoritative bodies: the European Scientific Cooperative on Phytotherapy (ESCOP), Cochrane 2012, the European Medicines Agency (EMA), and the AUA (American Urological Association) was presented. The foundation above then fine-tuned our search to require (a) consistent evaluability criteria, (b) the quantification of clinical findings, (c) the need to focus on studies employing a standardized LSESr product meeting the fatty acid profile set forth by the European Medicines Agency (EMA) and the US Pharmacopeia and (d) a global assessment of scientific investigations published in all languages and not limited to only English. With the above four constraints, "new" findings about LSESr vs. LUTS are presented. How did the search strategy and selection criteria lead to new understandings about the role of LSESr vs. LUTS? How safe is LSESr in contrast to its counterpart prescription drugs? Of the proposed major mechanisms of action of LSESr (e.g., 5-alpha reductase inhibition and anti-inflammatory activity), what are the key points? After initiating treatment with LSESr, when is clinical improvement seen? How durable is LSESr in ameliorating LUTS? Can LSESr prevent the progression of BPH?

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); hypercritical CO_2 extract of Serenoa repens (hCESr); supercritical carbon dioxide extraction of Serenoa repens (sCESr)

1. Search Strategy and Selection Criteria Were Pivotal to Perspective on LSESr vs. LUTS

At the beginning of this analysis of Serenoa repens in the treatment of LUTS it seemed most appropriate to first lay the groundwork and define the importance, the nature, and the vocabulary of LUTS, and then follow this with an analysis of the four key reviews (ESCOP 2003, Cochrane 2012, AUAG 2014 and EMA 2014) that have impacted the acceptability of Serenoa repens in LUTS treatment. It quickly became clear that a global review of the peer-reviewed literature would be needed in light of the plethora of non-English publications, many of which had never been translated and referenced, and thus ignored in analyzing the efficacy of Serenoa repens in LUTS. Given how important the above modus operandi has been to fully appreciate the role of Serenoa repens in LUTS, and that such an approach would likely have relevance to other scientific investigations, the details concerning search strategy and selection criteria are presented below.

The initial approach to gain a general understanding of the therapeutic index of LSESr in the treatment of male LUTS involved a standard search of peer-reviewed literature

using PubMed and Google Scholar with the main focus being on clinical research papers. Citations from within these retrieved papers were then used to identify additional relevant publications. We excluded from review any studies that included men with stage III/IV BPH because they are at high risk for acute urinary retention and not reasonable candidates for LSESr monotherapy. Such studies used the Alken or Vahlensieck staging classifications for BPH which urologists rarely use today [1–3]. Also important to note, in this 3-part review, papers dating back to 1983 were considered, and our exclusion criteria recognized both the merits and/or limitations of those two staging approaches. Case reports were also excluded.
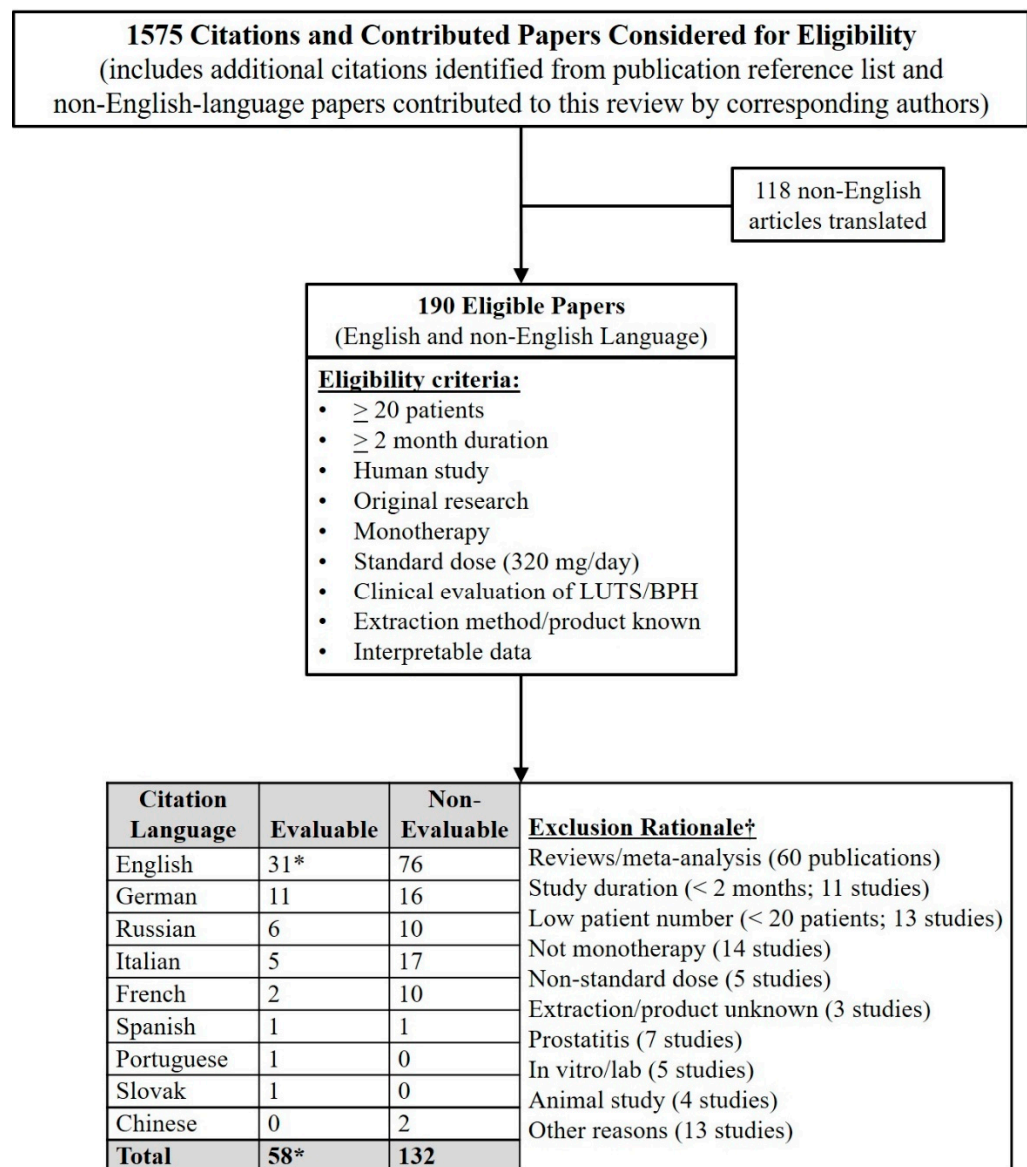
In all, 1575 citations relating to LSESr were identified. Publications related to animal studies, pharmacologic investigations, or pathology findings were read, but were not considered relevant to the immediate focus on the clinical issues relating to LSESr vs. LUTS. Of the 1575 articles, 190 were considered relevant and therefore possibly eligible for inclusion, with 118 of these (62%) not being English-language publications and requiring translation into English. Within those 190 eligible publications, there were differences in study design (open, comparative, blinded, placebo-controlled); dose (mg per day); dosing (once a day vs. twice a day); study duration; the active ingredient profile of the LSESr product, and the rigor of statistical analysis. Any of these factors could result in clinical results that could impact our understanding of the efficacy of LSESr vs. LUTS. Some studies involved small sample sizes and were of short duration. If the number of patients at the end of the study was less than twenty, that publication was arbitrarily excluded from this author's analysis. It was similarly decided that studies with durations of less than two months would also be considered non-evaluable to assess LSESr efficacy vs. LUTS. If the dose of LSESr was not stated, or the extraction method was not identified, or the LSESr product had not been previously verified as meeting EMA or USP standards for quality, then those studies were also excluded.

The selection of a minimum of 20 patients at the end of the study, and a study duration of at least two months was arbitrary. It was decided that a subset analysis of studies of less than 20 patients at the study end, or less than two months duration could be done to see if they altered the conclusions reached in this global review. Studies were also eliminated from analysis if other phytotherapeutic agents were given in combination with LSESr. Studies of LSESr involving patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) Types I-IV were considered not evaluable for study. After the review of the selected papers was completed, it became evident that some of the arbitrary decisions (e.g., patient number and study duration) would not have impacted the conclusions reached in our analysis. As mentioned later in discussing the anti-inflammatory effect of LSESr, the cohort of patients with CP/CPPS Types III and IV would have been a reasonable subset for analysis given this important mechanism of action of LSESr. This may well be the subject of a future analysis. Sixty review articles or meta-analyses did not present original data on LSESr efficacy, or the lack thereof. The process for identifying evaluable studies and the reason for exclusion as non-evaluable are provided in Figure 1.

The retrieval of full-text articles was immeasurably enhanced by using either the PubMed ID (PMID) or Digital Object Identifier (DOI) information when using the services of the reprint desk at Oregon Health Sciences University (OHSU), and EurekaMag.com. These resources were a necessity in the retrieval of PDFs of many articles not available via PubMed, Google Scholar, or the journal in which the study was published. On several occasions, the corresponding author was emailed and asked to clarify items such as the extraction process or the dose of the LSESr product. More often than not, the author's responses to such emails were received. Some authors volunteered additional publications that had been missed by all of the above search techniques. This was especially the case regarding publications from Spain, Italy, and Russia.

Non-English-language articles were initially sent for formal translation into English, but due to the high expense of commercial translation services incurred after the first four such translations, this author successfully translated articles from German, Italian,

Spanish, Chinese, Russian, Portuguese, and Slovak to English using Mac OS X apps such as Easy Translator 14 (www.acetools.net (accessed on 17 January 2019)) in association with an editing app called TextSoap version 8 (www.unmarked.com/textsoap/ (accessed on 17 September 2017)). The non-English text within graphics was similarly translated, and when images were modified and reproduced for this review, they were edited using a Mac OS X screen capture app called Voila (www.globaldelight.com (accessed on 30 June 2016)). These translated articles were saved as Word documents and exported to PDF format. Using this approach, a total of 118 non-English-language peer-reviewed publications were scrutinized. If it was apparent after the initial translation of the first few pages that the publication was not relevant to this project, then a full translation to English was aborted. Of the 118 non-English-language articles, 83 (70%) appeared evaluable, and they were fully translated to English.

1575 Citations and Contributed Papers Considered for Eligibility
(includes additional citations identified from publication reference list and non-English-language papers contributed to this review by corresponding authors)

118 non-English articles translated

190 Eligible Papers
(English and non-English Language)

Eligibility criteria:
- ≥ 20 patients
- ≥ 2 month duration
- Human study
- Original research
- Monotherapy
- Standard dose (320 mg/day)
- Clinical evaluation of LUTS/BPH
- Extraction method/product known
- Interpretable data

Citation Language	Evaluable	Non-Evaluable	Exclusion Rationale†
English	31*	76	Reviews/meta-analysis (60 publications)
German	11	16	Study duration (< 2 months; 11 studies)
Russian	6	10	Low patient number (< 20 patients; 13 studies)
Italian	5	17	Not monotherapy (14 studies)
French	2	10	Non-standard dose (5 studies)
Spanish	1	1	Extraction/product unknown (3 studies)
Portuguese	1	0	Prostatitis (7 studies)
Slovak	1	0	In vitro/lab (5 studies)
Chinese	0	2	Animal study (4 studies)
			Other reasons (13 studies)
Total	**58***	**132**	

Figure 1. Disposition of 190 eligible papers. * Sixty evaluable studies (31%) with one duplication. Since Robert 2015 [4] and Latil 2015 [5] were separate papers but reported the same data they were counted as one study. † May contain more than one reason for exclusion.

Most importantly, data extraction relating to changes in IPSS, QoL, and Qmax from the 107 English-language and 83 non-English-language eligible studies was performed. When such data were not provided in the text of the publication, data were obtained from graphics

within the paper when possible. Specifically, when graphs were presented but no absolute numerical values were presented in the text, an estimation of the numerical values relating to IPSS, QoL, and Qmax was determined (SBS). After full translation and data extraction, 27 of the 83 non-English-language papers (32%) met the criteria for evaluability. These non-English-language publications and basic information compiled from these studies are shown in Table 1.

Table 1. Evaluable non-English-language papers (27 studies) were categorized by the extraction method, the average number of patients, the study duration, and the clinical endpoints IPSS, QoL, and Qmax.

First Author	Ref #	Year	Extraction Method	Serenoa Patients (#) [a]	Study Duration (mos)	IPSS		QoL		Qmax	
						Δ	%	Δ	%	Δ	%
Cirillo-Marucco ε	[6]	1983	Hexane	47	4		56			+4.6	50
Cukier ψ λ	[7]	1985	Hexane	73	2		33				
Tosto Ω	[8]	1985	Hexane	20	3	−5.0	28				
Pannunzio	[9]	1986	Hexane	30	2					+5.0	74
Pescatore	[10]	1986	Hexane	30	3					+2.5	27
Authie π	[11]	1987	Hexane	500	3		78				
Ollé Carreras φ	[12]	1987	Hexane	40	2		68				
Orfei χ	[13]	1988	Hexane	30	3		50	−2.2		+0.0	0.2
Mattei ψ ω	[14]	1990	CO_2	20	3		55				
Dathe	[15]	1991	Hexane	49	6					+5.9	49
Vahlensieck Þ	[16]	1993	CO_2	1334	4		47				
Vahlensieck	[17]	1993	CO_2	312	3					+5.8	52
Fabricius δ	[18]	1993	CO_2	176	6		39;59				
Derakhshani	[19]	1997	Ethanol	1047	3	−7.4	40	−1.6	46	+3.7	31
Eickenberg	[20]	1997	Ethanol 96%	6967	6	−8.0	44	−1.8	38	+3.0	23
Foroutan	[21]	1997	Hexane	592	3	−6.5	38	−1.5	45	+5.9	66
Redecker ν	[22]	1998	Ethanol 90%	50	3		48			+3.4	24
Ziegler Θ	[23]	1998	Ethanol 90%	109	3				36	+3.7	29
Bauer γ ψ	[24]	1999	CO_2	101	6		37				16
Medeiros †	[25]	2000	Hexane	130	3	−6.5	37	−1.4	39	+2.0	22
Aliaev	[26]	2002	Hexane	26	60	−8.8	76	−1.3	53	+4.3	35
Breza	[27]	2005	Ethanol	596	12	−5.9	36	−1.7	54	+ 2.3	19
Aliaev	[28]	2007	Ethanol	50	6	−2.9	26	−1.8	43	+ 1.7	14
Razumov	[29]	2007	Ethanol	30	6	−6.9	43	−2.7	68	+2.8	23
Aliaev∞	[30]	2009	Ethanol	50	24	−4.2	37	−2.2	52	+ 2.7	21
Vinarov	[31]	2010	Ethanol	50	36	−6.0	50	−2.0	50	+ 4.5	39
Aliaev	[32]	2013	Ethanol	38	120	−1.3	12	−1.1	35	+ 3.3	26
Mean Across All 27 Studies				**463**	**12**	**−5.8**	**40–41** [b]	**−1.8**	**47**	**+3.5**	**31**
Hexane extraction n = 12											
Ethanol extraction n = 10											
Carbon dioxide extraction n = 5											

Values for IPSS, QoL, and Qmax rounded off to one decimal point. Percentages rounded off to nearest whole number. [a] number of patients at study end, or as reported. ε Cirillo-Marucco study done prior to IPSS; raw data on nocturia. ψ placebo-controlled studies. λ Cukier study done prior to IPSS; raw data on nocturia. Ω Tosto study done prior to IPSS; authors used a unique point scoring to evaluate frequency, nocturia, incomplete emptying, weak stream. π Authie done prior to 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 IPSS not used. The number shown is based on the changes in frequency with complete resolution in 27 out of 40 patients. χ Orfei used scores from frequency, nocturia, urgency, weak stream, and straining at study beginning vs. end. ω Mattei used scores from frequency, nocturia, and incomplete emptying. Þ Vahlensieck did not use IPSS. The data is based on the change in frequency and nocturia before and after LSESr. Frequency improved by 39% and nocturia by 55%; average improvement for both was 47%. δ Fabricius study did not use IPSS; [b] the Fabricius 1993 study 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). ν Redecker data evaluated nocturia before and after LSESr. Θ Ziegler did not use IPSS; he reported symptoms based on % improvement involving weak stream, hesitancy, incomplete emptying, frequency, and nocturia. γ Bauer only indicated percentage improvement. Talso® Uno with 37% vs. 13% for placebo. † Medeiros study used a QoL scale 6 (worst) to 1 (best) rather than 6 (worst) and 0 (best). ∞ Aliaev 2009 is a 2-year extension of the 6-month 2007 paper. 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.

The mean number of patients in the evaluable non-English-language studies for LSESr for efficacy in LUTS was 460, influenced by the Vahlensieck 1993 study with 1334 patients [16], the Derakhshani 1997 study with 1047 patients at the study end [19] and the Eickenberg 1997 study with 6967 patients [20]. The mean study duration across the 27 evaluable non-English-language papers was 12 months, influenced by Aliaev 2002 (60 months) [26], Breza 2005 (12 months) [33], Aliaev 2009 (24 months) [30], Vinarov 2010 (36 months) [31], and especially Aliaev 2013 (120 months) [32]. The contributions of non-English peer-reviewed articles were invaluable to gain a broader perspective on Serenoa repens vs. LUTS. For five decades, the noted American news broadcaster Paul Harvey would conclude each episode with "The rest of the story." Our scientific research should do just that (i.e., review the full scope of the literature and tell the full story).

2. LSESr Has a High Safety Profile in Contrast to Counterpart Prescription Drugs

In the extensive review of peer-reviewed literature on LSESr, a safety profile of high tolerability and low side effects has been a consistent finding. A collection of 50 articles focused on the safety and tolerability of LSESr, with eight having study durations ranging from two to fifteen years [26,30,32,34–38]. Safety and tolerability of LSESr were never issues of concern per the Cochrane reviews, multiple meta-analyses, and the EMA monograph. Despite these sources questioning the therapeutic value of LSESr, they all concurred that LSESr was associated with minimal side effects and a highly acceptable safety profile [39–46]. The Cochrane 2012 meta-analysis, for example, reported that adverse effects associated with LSESr were not statistically significant [44]. In the STEP trial, there was no evidence of toxicity compared with placebo using escalating daily doses of LSESr (carbon dioxide extraction) up to 960 mg per day; this included the risk of serious adverse events or non-serious symptomatic adverse events [47]. Of additional relevance is that the long-term studies (2 to 15 years duration) cited earlier have used all three major extraction processes, specifically, hexane, ethanol, and carbon dioxide, and no significant side effects were reported.

The two-year study by Pytel et al. [36] reported an incidence of side effects of 5.8% for Permixon[®], whereas the three-year study by Schulman et al. [48], using tamsulosin reported side effects in 26% of patients. Ye et al. evaluated LSESr in 354 patients over six months and reported side effects in 1.18% of patients, which was almost identical to the 1.89% rate in the placebo arm [49]. In the placebo-controlled CAMUS trial, there were no significant differences in the incidence of adverse events between LSESr (ethanol extraction) and placebo [50]. The adverse sexual side effects of α-blockers and 5α-reductase inhibitors, which include decreased libido, retrograde ejaculation, and a decrease in ejaculate volume [51], are non-issues in men using LSESr [36,37,52,53]. In a 2007 study using a 320 mg ethanolic extract of Serenoa repens (EESr), Prostamol[®] Uno (Berlin Chemie), a combination of tamsulosin with Prostamol Uno was used in the first 3 months of treatment followed by ongoing treatment for another six months with half the study population receiving either the combination vs. Prostamol Uno monotherapy. At nine months, 10.6% reported retrograde ejaculation and 11% hypotensive episodes in the combination arm vs. no side effects in the Prostamol Uno arm [54]. In the context of treating LUTS, it is apparent that the adverse effects of LSESr are negligible in contrast to the counterpart prescription drugs currently in use.

3. An Anti-Inflammatory Effect Appears to Be the Major Mechanism of Action of LSESr

Many proposed mechanisms of action have been postulated to explain the effects of LSESr vs. LUTS. These include anti-androgenic, anti-proliferative, anti-α1-adrenergic, and anti-inflammatory activity [55–58]. Each of these possible mechanisms influences urinary tract symptoms through a different pathway [56]. An in-depth critical analysis of all proposed mechanisms of action of LSESr is not addressed here, but two postulated mechanisms, 5α-reductase inhibition and an anti-inflammatory effect are discussed further.

3.1. 5α-Reductase Inhibition

LSESr has been shown to inhibit the reduction of testosterone to dihydrotestosterone (DHT) by inhibiting the activity of the 5α-reductase enzyme, of which there are three major isoforms (Types 1, 2 and 3) [56,59,60]. In epithelial and fibroblast cell cultures, the hexane-sterolic extract of Serenoa repens (HSESr), commercially available as Permixon (Pierre Fabre Medicament S.A., Paris, France), has demonstrated the highest inhibitory activity and lowest variability in effect among seven commercial LSESr products available in Europe [61]. Two of the long-chain fatty acids, linoleic and oleic acids account for one-third of the lipidosterolic profile and are active inhibitors of 5α-reductase Type 1 and to a lesser extent, 5α-reductase Type 2. LSESr has been shown to decrease DHT predominantly in the tissue of the periurethral zone of the prostate, an area primarily responsible for urinary obstruction caused by BPH [62]. However, LSESr does not reduce serum levels of DHT, PSA, testosterone, or intra-prostatic testosterone levels [63–65]. In contrast, the two major 5-alpha reductase inhibitors finasteride (Proscar®) and dutasteride (Avodart®) significantly lower serum DHT levels [66,67]. It does not appear that a decrease in tissue DHT in the periurethral zone accounts for the major impact of LSESr, especially when compared to the reliable effects of Avodart and Proscar in serum DHT reduction and associated decreases in PSA and prostate gland volume.

3.2. Anti-Inflammatory Effect

An important etiologic factor in the development of BPH, which typically clinically manifests as LUTS, is the finding of chronic histologic inflammation detected with prostate biopsies [68–71]. The publication by Song et al. is a landmark article that focuses on the many factors involved with LUTS, from the prostate to the lower and upper urinary tracts and various body systems [72]. Other factors such as age, hormone levels, lifestyle choices such as diet, smoking, alcohol consumption, and stress are additionally important [73–77]. Adverse lifestyle factors appear to contribute to an increase in inflammatory cells infiltrating the prostate [57,73]. The inflammatory cells cause damage to both epithelial and stromal cells, stimulating cytokine release and increasing the concentration of growth factors, such as fibroblast growth factor (FGF) [78]. These inflammatory processes within the prostate lead to a progressive increase in prostate volume. The presence of chronic prostatic inflammation is correlated with urinary tract symptoms [5,69,79], and for this reason, inflammation is an area of intense research in the treatment of BPH [56].

The effect of the hexanic extract of Serenoa repens (HESr) on measures of inflammation was evaluated in two controlled studies [5,80]. In the Giulianelli 2012 open-label multicenter study, men with prostate diseases with associated inflammation showed significant improvement after six months in urinary flow rate, IPSS, and chronic prostatitis symptoms [80]. In Latil 2015 [5], men with moderate-to-severe LUTS were evaluated with biomarkers of chronic prostatic inflammation in an international, randomized, double-blind study comparing HESr at 320 mg/day vs. tamsulosin at 0.4 mg/day. Gene and protein expression biomarkers of inflammation were quantitated after three months of treatment. This revealed that two proteins involved in the recruitment and trafficking of inflammatory cells, monocyte chemoattractant protein-1(MCP-1), and interferon γ inducible protein 10 were decreased with HESr but slightly raised after tamsulosin. After a comprehensive gene expression analysis, a favorable anti-inflammatory effect on gene expression was observed in 73.3% of HESr patients vs. only 26.6% in patients receiving tamsulosin. In this study, a subset of patients with overexpression of macrophage migration inhibitory factor (MIF) had an average IPSS decline of 6.4 points for HESr vs. 6.5 for tamsulosin. MIF is a T-cell inflammatory cytokine, and its expression appears to be activated by a higher inflammatory microenvironment [81].

Additional studies using histologic and immunohistochemical criteria have demonstrated that LSESr reduces prostatic inflammation [5,57,79,82–85]. LSESr decreases B-cell infiltrates and serum levels of key cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) [79]. LSESr has been found to differentially affect proliferation

and apoptosis in BPH by upregulating anti-inflammatory genes and downregulating pro-inflammatory genes [56]. In the process of inflammation, interleukins will upregulate androgen receptor (AR) activity and lessen the efficacy of 5α-reductase inhibitors like finasteride or dutasteride. 5α-reductase inhibitors decrease DHT, which is a ligand for the AR. The result is a decrease in DHT-AR binding and amelioration of BPH. Therefore, LSESr may prove to be a valuable adjunct to 5α-reductase inhibitors in the context of inflammation by inhibiting interleukin-stimulated up-regulation of the AR [57].

As noted previously, our study criteria excluded publications involving LSESr vs. LUTS in the context of non-bacterial prostatitis. Upon reflection, this may have been in error given the extremely high presence of histologically documented chronic inflammation in prostate biopsies of men with LUTS [42,68,70,86–90]. In fact, a brief search of the literature reveals several articles on the effectiveness of LSESr vs. chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [91–99]. Given that LSESr lowers IL-1β, TNF-α, MCP-1, and other pro-inflammatory cytokines, the use of LSESr may be of paramount importance vs. other inflammatory conditions, age-related degenerative diseases, and neoplasia. In such contexts, biomarkers of inflammation are routinely abnormal and signal transduction pathway aberrancies are commonly found. In fact, peer-reviewed studies indicate cancer cell death resulting from the downregulation of tumor-associated growth factors such as IL-6 [100,101], COX-2 [102,103], akt [103,104], LTB4 [103], STAT 3 [105,106], urokinase-type plasminogen activator [107], basic fibroblast growth factor (bFGF, FGF-β, FGF2) [108], and proinflammatory cytokines [103] occurring with the use of Serenoa repens, and specifically LSESr. This warrants clinical investigation in light of the high therapeutic index evidenced in patients receiving LSESr in the treatment of LUTS.

4. The Onset of LUTS Response to LSESr Occurs as Early as 4 Weeks

In multiple publications, three months is the most commonly reported time for the onset of action of LSESr vs. LUTS, but a few studies have documented a significant response as early as six weeks. There is difficulty in knowing the earliest time to therapeutic action, because patients are typically not followed at close intervals, such as every two weeks. A small number of studies have evaluated patients at 4-to-6-week intervals. Debruyne et al. studied a total of 811 patients with an IPSS of >10 in a 12-month, double-blind, randomized study with a 1-month run-in period to exclude patients non-compliant in taking placebo [109]. The study compared Permixon at 320 mg/day with tamsulosin at 0.4 mg/day. At 6 weeks, the IPSS for Permixon dropped approximately 4.7 points, and for tamsulosin 5.2 points, with a further drop at 3 months by 0.7 and 0.8 points for Permixon and tamsulosin, respectively. This decrease was maintained for the 12-month duration of the study, with Permixon showing a total IPSS decrease of −5.9 points vs. a tamsulosin drop of 6.0 points. In the Derakhshani et al. 1997 study of 1047 patients from 357 practices, Prosta-Urgenin Uno, an EESr, was given at a dose of 320 mg/day for 3 months [19]. At baseline, 15% of patients reported no nocturia, but after 6 weeks, the percentage of patients without nocturia increased to 38% and was absent in 54% at 3 months. Forty-seven percent of patients had three episodes of nocturia per night at baseline, but after 3 months of Prosta-Urgenin Uno, this was reduced to 10%. The changes in the IPSS, QoL, and Qmax from baseline to 3 months were: −7.4 (40.4%), −1.61 (45.9%), and +3.7 mL/s (30.8%), respectively. Specifically, for Qmax, 16% of patients went from a baseline of 12.0 mL/s to above 18 mL/s [19]. Recall that in the Barry 2011 study [110], the use of Prosta-Urgenin Uno was no better than placebo. In the Braeckman 1994 study, 305 men were treated over 3 months with a hCESr, (Prostaserene®), at a dose of 160 mg bid [111]. At approximately 6 weeks (day 45), 83% of patients reported that the drug was effective, and this percentage increased to 88% after 3 months. IPSS, QoL and Qmax absolute change and percentage improvement from baseline to 3 months were: −6.6 points (34.7%); −1.54 (41.6%); and Qmax +2.41 mL/s (26.4%), respectively [111]. In one of the first studies of LSESr published in 1983, Cirillo-Marucco reported positive effects of Permixon after 2 months [6], and Dathe in 1991 presented graphs of Qmax showing improvement with Permixon starting

as early as 6 weeks [15]. Additional publications have noted significant improvement in one or more endpoints as early as 6 weeks [22,52,112,113]. Of note are the findings of a placebo-controlled study by Zhang et al. in 2021 comparing a supercritical CO_2 LSESr at 160 mg bid vs. placebo. The authors found a significantly greater improvement in LUTS in the LSESr arm of 148 patients compared to the placebo group of 73 patients at two weeks from the start of the study and across the entire treatment period ($p = 0.0044$) [99]. This was a study of patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and therefore not evaluable based on our study criteria. The study is mentioned for two reasons. First, it points out that the onset of action of a standardized LSESr may occur in as little as two weeks, and second, it reinforces the probability that a major mechanism of action of LSESr involves anti-inflammation. However, in the majority of studies concerning LSESr vs. LUTS, an evaluation of response was often done at 3 months and relatively few studies formally evaluated patients at earlier times.

5. The Response to LSESr vs. LUTS Is Durable

There are 17 peer-reviewed studies of LSESr in which patients were treated for a minimum of 12 months to a maximum of 180 months (15 years). Of these 17 studies, 7 are 12 months in duration, with the remainder having durations of 18 months (1 study), 24 months (4), 36 months (2), 60 months (1), 120 months (1), and 180 months (1). The total number of patients involved in all 17 studies was 1976. Two studies used a hCESr [114,115], 5 studies employed a HESr [26,35,36,116] and 10 studies evaluated an EESr [27,30–32,34,37,38,110,117,118]. The average change in IPSS, QoL, and Qmax across all studies was −4.8, −1.6, and +3.0 mL/s, respectively. Of the two hCESr studies, the averages for IPSS, QoL, and Qmax were −5.5, −1.5, and +1.5 mL/s, respectively [114,115]. Of the five HESr studies, the averages for IPSS, QoL, and Qmax were −5.5, −1.1, and +2.0 mL/s, respectively [35,109,116]. Of the 10 EESr studies, the averages were −4.1, −2.0 and +3.8 mL/s, respectively [27,30–32,34,37,38,110,117,118]. Note that of the two carbon dioxide extraction studies that lasted more than 12 months, one was the negative study by Bent [114], and, in the 10 ethanol extraction studies, one was the negative study by Barry [110]. The data extracted from these long-term studies are shown in Table 2. The data from these 17 studies using LSESr for one year or longer show that one extraction process had no apparent benefit over another. The total number of studies summarized in Table 2 did not allow for an appropriate statistical analysis.

Table 2. Long-term (≥12 months) studies using LSESr. Seventeen studies of ≥ 12 months involving all extraction technologies (CO_2, ethanol, hexane) with calculated average values across all studies. Nine studies of ≥ 2 years show the first author in bolded font. The two negative studies by Bent 2006 and Barry 2001 are shaded in green.

Senior Author	Ref. (#)	Year	Extraction	Serenoa Patients (#) [a]	Study Duration (mos)	IPSS * Δ	%	QoL Δ	%	Qmax Δ	%
Bent	[114]	2006	CO_2	102	12	−0.7	4			+0.4	4
Braeckman π	[115]	1997	CO_2	67	12	−10.2	60	−1.5	42	+2.6	24
Aliaev Ω	[30]	2009	Ethanol	50	24	−4.2	37	−2.2	52	+2.7	21
Aliaev	[32]	2013	Ethanol	38	120	−1.3	12	−1.1	35	+3.3	26
Bach	[34]	1996	Ethanol	315	36		73			+6.1	46
Barry π	[110]	2011	Ethanol	151	18	−2.2	15				
Breza	[27]	2005	Ethanol	596	12	−5.9	36	−1.7	54	+2.3	19
Romics	[117]	1993	Ethanol	31	12					+4.3	39
Saidi	[118]	2019	Ethanol	40	12	−2.1	18			+0.8	6
Sinescu	[37]	2011	Ethanol	120	24	−5.5	40	−1.8	50	+5.6	54
Vinarov	[31]	2010	Ethanol	50	36	−6.0	50	−2.0	50	+4.5	39

Table 2. *Cont.*

Senior Author	Ref. (#)	Year	Extraction	Serenoa Patients (#) [a]	Study Duration (mos)	IPSS * Δ	IPSS * %	QoL Δ	QoL %	Qmax Δ	Qmax %
Vinarov	[38]	2019	Ethanol	30	180	−6.0	50	−3.0	60	+5.0	45
Aliaev	[26]	2002	Hexane	26	60	−8.8	76	−1.3	53	+4.1	35
Debruyne	[109]	2002	Hexane	350	12	−4.4	28			+1.9	17
Debruyne	[116]	2004	Hexane	124	12	−7.8	35	−1.2	29	+1.2	11
Djavan δ	[35]	2005	Hexane	88	24	−1.0	17	−0.4	19	+1.8	15
Pytel	[36]	2002	Hexane	116	24	−5.3	42	−1.3	40	+1.2	10
Averages of 17 Studies **15 positive studies** **2 negative studies**			Ethanol (10) Hexane (5) CO_2 (2)	135	37	−4.8	37	−1.6	44	+3.0	26

[a] number of patients at study end, or as reported. * values for IPSS, QoL, and Qmax rounded off to one decimal point; percentages rounded off to nearest whole number. π placebo-controlled and double-blinded, randomized study. Ω 2-year extension of the 6-month Aliaev 2007 study. δ Permixon vs. watchful waiting. Δ, mean change; −, negative change; #, number; %, percent change; +, positive change; CO_2, carbon dioxide; IPSS, International Prostate Symptom Score; mos, months; n.s., not significant; QoL, quality of life; Qmax, peak urinary flow (mL/s); Ref, reference citation.

6. The Early Use of LSESr Delays the Progression of LUTS/BPH

In the evolution of BPH, an increase in LUTS is characteristic of progressive disease. If there is indeed a significant effect of high-quality LSESr on LUTS endpoints and the safety profile of that LSESr is better than the available prescription drugs for LUTS, then early and sustained use of an LSESr could conceivably halt or delay the progression of BPH. A pro-active approach to LUTS/BPH therapy would therefore involve not only achieving relief in the patient's subjective complaints but also stopping the progression of the disease.

Studies on the natural progression of BPH have been performed and have revealed a marked deterioration of between 24% and 58% in the clinical status of symptomatic BPH patients over a period of 2.4 to 5 years, as reported by Ball, Birkhoff, and Craigen [119–121]. In Bach's 3-year LSESr study involving 315 patients, the deterioration rate in LUTS symptomatology was only 13.6% and the need for surgical intervention occurred in 9.4% of patients [34]. Bach interpreted such data as a possible expression of pharmacodynamic action and that LSESr had influenced the pathogenetic or pathophysiological factors connected to BPH progression. In the Djavan 2005 study comparing watchful waiting with Permixon, 247 men were tracked over 2 years to determine if there was a difference in the progression of mild LUTS [35]. At study end, the incidence of progression was 24% in the watchful waiting group vs. 16% in men receiving Permixon ($p = 0.03$). With additional follow-up at 3 years, the rate of progression, defined as change from mild IPSS to moderate or severe IPSS or the occurrence of acute urinary retention or need for any surgical intervention, was 31% for watchful waiting vs. 19% for Permixon. At 3 years, IPSS, QoL, and Qmax had improved by 22%, 24%, and 14%, respectively, in Permixon-treated patients vs. 5%, 10%, and 9%, respectively, in the watchful waiting group (Table 3). This difference in progression rates between Permixon vs. watchful waiting was more pronounced in patients at high risk of progression as ascertained by a PSA of >1.5 ng/mL and a transition zone volume of >25 cc per transrectal ultrasound [35]. Although the progression rates showed statistically significant differences, the degree of change in IPSS, QoL, and Qmax was disappointingly low. The differences in both absolute and percentage changes in these endpoints with LSESr are far greater in the long-term studies focused on the delay in LUTS associated BPH progression discussed below.

Emphasizing the importance of accessing the non-English-language peer-reviewed literature, the 1988 article by Orfei [13], published in Italian, concluded what other investigators confirmed 17 years later: "It is our belief that using one of the available pharmacological treatments and including Permixon, and above all starting with the appearance of the first signs of BPH, that at least the progression of BPH could have been stopped, if not

the regression of the signs of hypertrophy at a decidedly earlier stage. In such a context, the therapeutic efficacy of pharmacological treatments can be better achieved".

Table 3. Delay in the progression of LUTS/BPH with Permixon vs. Watchful Waiting (adapted from Djavan [35]. Permixon showed a statistically significant delay in progression at 2 and 3 years. Progression was defined as change from mild IPSS (1–7) to moderate (8–18) or severe IPSS (>18), or to the occurrence of surgical intervention. The "net" benefits of Permixon over Watchful Waiting were IPSS improvement of 27%, QoL improvement of 34%, and Qmax improvement of 23%.

Study Group	Cumulative Progression	Changes * in IPSS, QoL, Qmax at 2-Years (%)	*p* Value	Changes ** in IPSS, QoL, Qmax at 3-Years	*p* Value
Watchful Waiting					
At 6 months	6%				
At 12 months	13%	IPSS: −0.3 (+5%)		IPSS: +5%	
At 18 months	15%	QoL: −0.2 (−9%)		QoL: −10%	
At 24 months	24%	Qmax: 0.10 (−8%)		Qmax: −9%	
At 36 months	31%		*p* = 0.03 at 2-years		*p* = 0.001 at 3-years
Permixon					
At 6 months	1%				
At 12 months	7%	IPSS: −1.0 (−17%)		IPSS: −22%	
At 18 months	9%	QoL: −0.4 (−19%)		QoL: −24%	
At 24 months	16%	Qmax: +1.8 (+15%)		Qmax: +14%	
At 36 months	19%				

* Negative percentages for IPSS and QoL are improvements, while for Qmax represent deterioration. ** No absolute values and only percentage change provided by study authors at 3 years. −, negative change; +, positive change; BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; QoL, quality of life; Qmax, peak urinary flow (mL/s).

Major findings related to the use of an LSESr in halting or delaying the progression of LUTS are documented in multiple Russian publications led by Aliaev, Vinarov, Pytel, Sivkov, Apolikhin, Lopatkin, and others [26,30–32,36,38]. In Aliaev 2013, the safety and efficacy of Prostamol Uno in 38 men over a period of 10 years were evaluated [32]. The following issues were emphasized by Aliaev:

1. The patient's subjective evaluation of the aggravation of their condition, as determined by the IPSS, is a relevant sign of BPH progression since it helps a doctor choose the most appropriate treatment.
2. When an active supervision method is applied, the medicinal preparations are prescribed as soon as BPH symptoms start impacting the patient's quality of life. Therefore, the study of long-term pharmacological therapy of patients with minimal subjective manifestations of BPH and the risk of its progression is of utmost relevance.
3. Serenoa's complex pathogenetic effects are aimed at both inhibiting the process of BPH development and eliminating the symptoms of chronic prostatitis.
4. Because Serenoa does not decrease the PSA level it does not conceal the development of prostate cancer.
5. The presence of the risk of BPH progression was a necessary criterion for admission of patients into the observation group. The reason for this is that the presence of men not subject to the risk of BPH progression would have complicated our ability to prove efficacy using a multi-year continuous administration of the extract of Serenoa repens to prevent BPH progression.

The work of these Russian investigators and their collaboration and collegiality made it possible to analyze some publications that were impossible to translate due to the poor quality of pdf files obtained from the National Library of Medicine and the near impossibility to perform optical character recognition. The findings of these authors

concerning the use of LSESr in preventing the progression of LUTS/BPH mandates further attention. The Vinarov 2010 study involved 100 men, of which 50 were randomized to either Prostamol Uno at 320 mg/day and 50 to the control group [31]. Baseline eligibility requirements were an IPSS of 8 to 15 and a Qmax of 10–15 mL/s. At the end of 3 years, the changes in the Prostamol Uno group for IPSS, QoL, and Qmax were: −6 (50%), −2 (50%), and +4.5 mL/s (39%), respectively. The control group results of +4 (36%), +1 (25%) and −2.6 mL/s (21%) indicated deterioration in all parameters. The figures within the Vinarov 2019 publication [38], originating from data in the earlier Vinarov 2010 study [31] and presented during a workshop organized by Berlin-Chemie/Menarini at the 26th Annual EAU Congress in 2011 [122], demonstrate the changes in those endpoints (Figure 2 below).
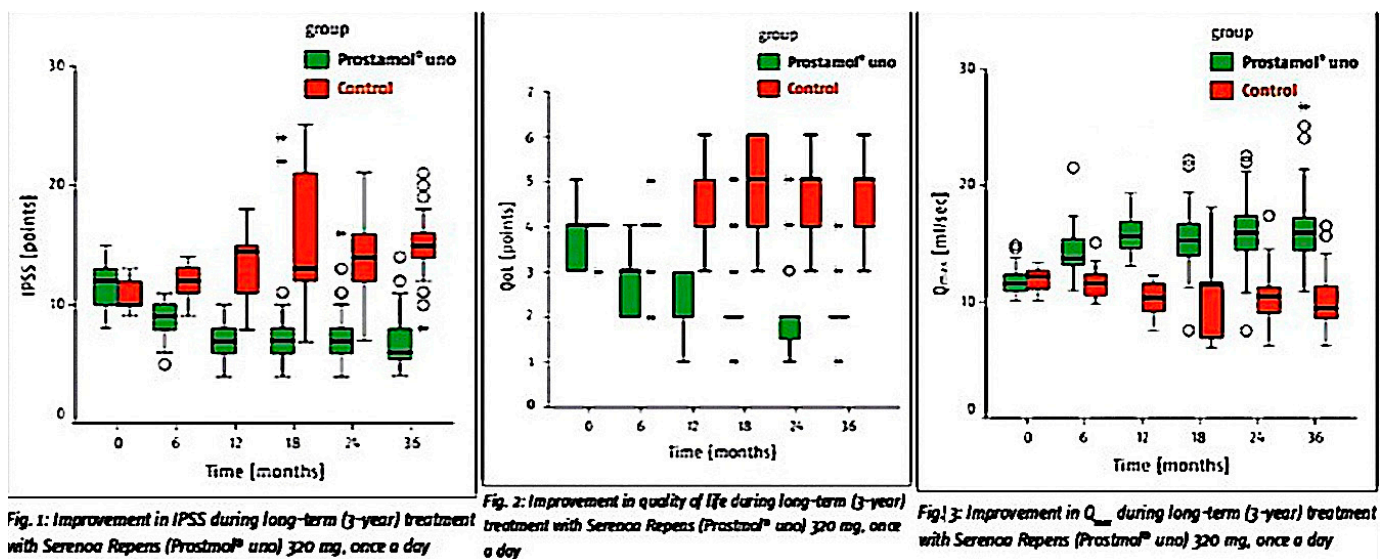

Fig. 1: Improvement in IPSS during long-term (3-year) treatment with Serenoa Repens (Prostmol® uno) 320 mg, once a day

Fig. 2: Improvement in quality of life during long-term (3-year) treatment with Serenoa Repens (Prostmol® uno) 320 mg, once a day

Fig. 3: Improvement in Q__ during long-term (3-year) treatment with Serenoa Repens (Prostmol® uno) 320 mg, once a day

Figure 2. Changes in IPSS, QoL, and Qmax for LSESr vs. control in a 3-year intervention study. Modified after Vinarov [122].

The Vinarov 2019 study involved 30 patients with LUTS observed over 15 years [38]. These men had baseline IPSS scores of 8 to 15, symptoms for more than 3 months, and a Qmax of less than 15 mL/s. All received Prostamol Uno as a single 320 mg/day dose. The mean baseline values for the IPSS, QoL, and Qmax were 12, 5, and 11, respectively. At the study end, the absolute changes and (percentage changes) were −6 (50%), −3 (60%), and +5 mL/s (45%), respectively. Also, at the study end, no significant prostatic enlargement due to BPH was observed. The authors concluded that "this type of therapy can stop the progression of BPH growth and improve bladder function . . . " The PSA values remained stable in all patients, no patients were diagnosed with acute urinary retention, and there were no adverse effects due to LSESr [38].

7. Conclusions

We used stringent criteria to assess the value of Serenoa repens in the treatment of male LUTS. This involved reviewing only studies that used a lipidosterolic extract of Serenoa repens (LSESr) meeting either EMA or USP standards. At the same time, the scope of our peer-reviewed literature search included not only English-language articles but also studies of LSESr published in non-English languages and fully translated into English with data extraction that included the clinical endpoints of IPSS, QoL, and Qmax. The totality of this approach has revealed new information about LSESr vs. LUTS that indicates rapid onset of action, durability of effectiveness, and the ability of LSESr to prevent the progression of benign prostatic hyperplasia (BPH).

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Ethical Approval/Patient Consent: This is a review of the literature and did not require ethical board approval.

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