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Rethinking the Role of Saw Palmetto Extract for Men with Lower Urinary Tract Symptoms in North America

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Abstract: Introduction: The effect of the lipidosterolic extract derived from Serenoa repens (commonly known as “saw palmetto extract” or LSESr) berries on benign prostatic hyperplasia (BPH) and male lower urinary tract symptoms (LUTS) has been extensively studied in the global literature. However, a lack of global consensus with regard to its effectiveness remains, resulting in differing recommendations on the role of LSESr in the BPH/LUTS treatment paradigm. Here, we describe the consensus reached by an international panel of urology experts.

Methods: In an independent meeting on 24 April 2021, an international panel of urology experts convened with the goal of developing consensus statements to address the following: the differences between the AUA and EAU guidance regarding the use of LSESr for the treatment of BPH/LUTS, the proposed mechanism of action of LSESr, and data examining the efficacy and safety of LSESrs. These consensus statements were developed over the course of several months after an extensive review of the global literature and a discussion thereof.

Results: A total of seven consensus statements were agreed upon by the panel. These statements addressed the proposed mechanism of action of LSESr, LSESr quality, and the results from clinical trials examining the efficacy and safety of various LSESrs.

Conclusion: Based on the reviewed evidence, the panel recommends that LSESr should be considered as a treatment option for men with mild-to-moderate BPH/LUTS as an alternative to watchful waiting.

Keywords: lower urinary tract symptoms; benign prostate hyperplasia; North America; saw palmetto

1. Introduction

The lipidosterolic extract derived from Serenoa repens (commonly known as “saw palmetto extract” or LSESr) berries has long been investigated for the treatment of lower urinary tract symptoms (LUTS) in men [1,2]. Despite the volume of global literature that has been published on this topic, uncertainty remains in the United States regarding its potential role, if any, in the treatment paradigm for men with LUTS. This could be due to disagreement between the American Urological Association (AUA) and European Association of Urology (EAU) guidelines for its use, as well as a lack of consensus regarding the mechanism of action and findings from the global literature. In this expert consensus document, these topics are summarized with the goal of developing consensus statements related to these topics after a review and discussion of the global literature for the treatment of benign prostatic hyperplasia (BPH)/LUTS.
2. Methods

On 24 April 2021, an international panel of urologists with expertise in the treatment and research of BPH/LUTS met virtually to discuss a potential role for the lipidosterolic extract of *Serenoa repens* (LSESr) in the management of LUTS in men in North America. These urologists practice in various regions of North America and Europe. Panel members were compensated for their preparation for and participation in the discussion by Valensa International, but the discussion was independently designed, moderated and executed, and no further honoraria were awarded for literature review, manuscript development, or the discussion and development of consensus statements. Panel members compared the AUA and EAU guidelines for the use of LSESr and reviewed the available global literature regarding its mechanism of action, its effectiveness, and its safety in men with LUTS. The objective of this review was to determine if the global literature and experience of the urologists supported the use of LSESr for the treatment of BPH/LUTS in North America. After continued discussion, consensus statements were developed over the course of several months following the meeting. The panel unanimously supports each consensus statement listed here.

3. Results

Throughout the meeting and the months thereafter, the global literature examining LSESr use, the proposed mechanism of action, quality, and clinical efficacy and safety was independently evaluated and discussed by the panel experts. Below, each topic is reviewed in detail. Consensus statements were developed where appropriate.

3.1. AUA/EAU Guidelines for Saw Palmetto Extract

The extract from saw palmetto berries (*Serenoa repens*) has been investigated for its medicinal properties in regard to numerous maladies, including those related to the management of LUTS in men [1,2]. Based on several clinical studies that demonstrated its safety and effectiveness, the LSESr known as Permixon® (Pierre Fabre Médicament, Castres, France) was approved for use as a prescription drug for the treatment of mild-to-moderate LUTS in Europe [3,4]. This allowed for the regulation of the quality and dosage of Permixon across Europe. The EAU provides guidance based on regulations decreed by the European Medicines Agency, which applies to all members of the European Union and the United Kingdom. However, Permixon and all other saw palmetto preparations are considered food additives/dietary supplements by the US Food and Drug Administration [5,6]. The FDA regulates hexane in foods and dietary supplements (hexane residue cannot exceed 25 ppm) and, because Permixon is produced by a hexanic extraction methodology, some hexane remains in the final preparation [7–9]. While the recommended prescribed dose of Permixon appears to be entirely safe, as a food, it cannot be guaranteed that men would not be exposed to large enough quantities for extended periods of time to cause toxicity [3,4]. It is believed that Permixon is not available in North America for this reason. LSESr formulations based on ethanolic and supercritical carbon dioxide (SCCO₂) extraction methods are available in the United States and Europe.

Despite its usage in Europe, a disagreement between guidance provided by the AUA and the EAU exists for the use of LSESr. Currently, AUA guidelines state, “[m]any supplements and nutraceuticals containing ingredients such as saw palmetto [ . . . ] and others are popular and have been marketed and studied. Overall the results have been variable, as have study methods and quality, thus positive recommendations regarding their use are not warranted” [10]. Support for this statement from the AUA guidelines comes from the results of the 2006 Saw Palmetto Treatment for Enlarged Prostates (STEP) study, which did not use Permixon as the study drug but found no significant difference in efficacy between the LSESr tested and placebo [10,11]. This is in contrast with EAU guidelines, which state to “offer hexane extracted *Serenoa repens* to men with LUTS who want to avoid any potential adverse events especially related to sexual function”; ethanolic extracts of *Serenoa repens* are supported by the European Medicines Agency Committee on Herbal Medicinal Products.
based on “sufficient safety data and plausible efficacy on the basis of long-standing use and experience” (Table 1) [3,9,12]. It is possible that the difference in guidance between Europe and the United States has greatly contributed to which extracts are used and in what manner in each area of governance. In Europe, hexanic saw palmetto extract is considered for well-established use and is among the most commonly prescribed medications for the treatment of mild-to-moderate LUTS. The EAU defines “well-established use” to mean that the active ingredients of a medicine have been used for more than 10 years and its efficacy and safety have been well established; medicines that meet this standard receive marketing authorization. On the other hand, ethanolic saw palmetto extracts are considered for traditional use as dietary supplements. The EAU defines “traditional use” to mean a herbal medicinal product that does not fulfill the requirements for marketing authorization, but that has sufficient safety data and plausible efficacy on the basis on long-standing use and experience [4]. Conversely, in the United States, saw palmetto products are considered as dietary supplements to be taken at the discretion of the patient and are not generally recommended by healthcare providers for the treatment of LUTS [10]. Additionally, the dietary supplement marketplace is largely unregulated, which can be confusing to consumers with regard to which products are safe or effective [13].

Table 1. Comparison of AUA and EAU guidelines with regard to LSESr.

| Guidance                                                                 | Reasoning                                                                 |
|-------------------------------------------------------------------------|--------------------------------------------------------------------------|
| American Urological Association                                         | “Previous reviews suggested that saw palmetto may have a modest efficacy. More rigorous studies showed no effects.” [14] |
| “No dietary supplement, combination phytotherapeutic agent or other nonconventional therapy is recommended for the management of LUTS secondary to BPH.” [14] | “Overall the results have been variable, as have study methods and quality . . . ” [10] |
| “At this time, the available data do not suggest that saw palmetto has a clinically meaningful effect on LUTS secondary to BPH.” [14] |                                                                 |
| “[ . . . ] positive recommendations regarding [the use of supplements and nutraceuticals containing ingredients such as saw palmetto, Pygeum africanum, stinging nettle, zinc, selenium, and others] are not warranted.” [10] |                                                                 |
| European Association of Urology                                          | “A review of recent extraction techniques and their impact on the composition/biological activity of available Serenoa repens-based products showed that results from different clinical trials must be compared strictly according to the same validated extraction technique and/or content of active compounds, as the pharmacokinetic properties of the different preparations can vary significantly.” [12] |
| “European Union monographs are divided into two sections: (a) Well-established use (marketing authorisation): when an active ingredient of a medicine has been used for more than ten years and its efficacy and safety have been well established (including a review of the relevant literature); and (b) Traditional use (simplified registration): for herbal medicinal products which do not fulfil the requirements for a marketing authorisation, but there is sufficient safety data and plausible efficacy on the basis of long-standing use and experience.” [12] |                                                                 |
| “Only hexane extracted Serenoa repens has been recommended for well-established use.” [12] |                                                                 |
| “Offer hexane extracted Serenoa repens to men with LUTS who want to avoid any potential adverse events especially related to sexual function.” [12] |                                                                 |

AUA—American Urological Association; BPH—benign prostate hyperplasia; EAU—European Association of Urology; HESr—hexane extract of Serenoa repens; LSESr—lipidosterolic extract of Serenoa repens; LUTS—lower urinary tract symptoms; Qmax—maximum flow rate; RCT—randomized controlled trial.
3.2. MOA of LSESr for the Treatment of LUTS

Currently, there are a few theories on the prostate function and physiology that lead to BPH and LUTS. [15,16] One theory is that a disruption in androgen receptor signaling homeostasis that is associated with the conversion of testosterone to dihydrotestosterone (DHT) by the nuclear membrane protein 5α-reductase (5-AR) within prostate cells results in greater downstream prostate cell proliferation relative to prostate cell apoptosis [15,17]. DHT acts as a potent androgen signaling molecule and can contribute to an increase in cellular proliferation (e.g., enlarged prostate causing bladder outlet obstruction) and the production of pro-inflammatory mediators [15,16,18]. These mediators can result in chronic prostate inflammation and worsen the symptoms of male LUTS [18,19].

Beyond the effects of androgen signaling on prostate cellular processes, chronic prostate inflammation driven by additional stimuli (e.g., bacterial/viral infection, autoimmune disease, diet, aging, metabolic factors such as metabolic syndrome, etc.) can play a large role in the development and worsening of male LUTS [19,20]. Research to determine which pro-inflammatory mediators might cause these histologic changes within the prostate and whether those changes directly result in BPH/LUTS is ongoing. Often, chronic inflammation within the prostate involves the increased presence of lymphocytes and macrophages that can release pro-inflammatory cytokines, which in turn increase the production of several growth factors (e.g., IL-15, IL-17, fibroblast growth factor, etc.) [20,21]. These increased growth factors can instigate abnormal growth in prostate stroma and epithelial cells, increasing local oxygen demand and generating low levels of reactive oxygen species, which can maintain lymphocyte and macrophage presence [20]. This process may ultimately result in histologic changes in the surrounding prostate cell tissue that results in the exacerbation of BPH and the symptoms associated with male LUTS [20,21].

The potential mechanisms by which LSESr affects these cellular processes and mitigates LUTS continue to be studied [22]. Studies have provided evidence that prostate cells preferentially take up free fatty acids, including those contained within LSESr [23–25]. Once fatty acids are incorporated into the nuclear membrane, they can alter membrane fluidity, inducing temporary conformational changes to the 5-AR protein structure that can disrupt the conversion of testosterone to DHT [22,23,26–29]. This form of non-competitive, reversible inhibition is hypothesized to reduce DHT-dependent androgen signaling, resulting in increased prostate cell apoptosis and decreased prostate cell proliferation and, subsequently, slowed prostate growth [15,22,26,27,29]. These effects have been observed in in vitro experiments using rat liver cells, pig prostate cells, biopsied human prostate cells, and PC3 prostate cancer cells [22,26–29].

Consensus Statement

Reliable and reproducible evidence points to the mechanism of action of LSESr involving the inhibition of 5-AR and the reduction in prostate inflammation by altering prostate cell nuclear membrane fluidity and reducing the presence of inflammatory cells in prostate tissue. However, it is not known to what degree this or any other mechanism associated with the observed effects of LSESr impacts BPH/LUTS.

The accumulation of LSESr fatty acids has also demonstrated an ability to down-regulate pro-inflammatory genes and reduce other histologic hallmarks of inflammation, though it remains unclear if this is also accomplished by increasing nuclear membrane fluidity or by some additional mechanism [28,30–33]. Furthermore, LSESr has demonstrated the ability to reduce the number of CD45+ cell clusters present, inhibit the early steps of leukocyte infiltration by impeding monocyte and T-cell attraction/adherence, and inhibit prostaglandin synthesis and 5-lipoxygenase metabolites from the arachidonic acid cascade [30–32]. These downstream changes may result in reduced prostate inflammation [32].
This proposed mechanism is reliant on the presence of a high concentration of free fatty acids. Studies have demonstrated that lauric acid, oleic acid, myristic acid, and linoleic acid—each a major constituent of LSESr—are more potent inhibitors of 5-AR than many other types of fatty acids [26,34]. Furthermore, current evidence seems to indicate the ratio of these fatty acids relative to lauric acid—or fingerprint—contained within the LSESr appears important to activity, as the Permixon fingerprint has demonstrated consistent clinical efficacy whereas others have yielded inconsistent results [1,5,34,35].

Studies show that the major constituents of LSESr—lauric acid, oleic acid, myristic acid, and linoleic acid—have more potent inhibitory properties to 5-AR than many other types of fatty acids and are considered among the most therapeutically relevant fatty acids to the proposed mechanism of action of LSESr [26,34]. It has been reported that an intracellular concentration of 10 to 100 µg/mL of the fatty acids with inhibitory properties must be reached in order for any therapeutic effect to be observed [26,34]. Therefore, the United States Pharmacopeia (USP), an independent and non-profit organization whose goal is to improve global health through public standards, has defined that an effective LSESr must contain ≥80% total fatty acids in a ratio range that is similar to that which is present in Permixon, the fingerprint that has demonstrated the most consistent clinical efficacy (Table 2) [5].

Table 2. Fatty Acid Ratios Relative to Lauric Acid for LSESrs Listed by the USP [5].

| Fatty Acid | Extracted with Hexane or Hydroalcohol | Extracted with SCCO2 |
|------------|--------------------------------------|----------------------|
|            | Minimum Ratio | Maximum Ratio | Minimum Ratio | Maximum Ratio |
| Capric     | 9.0          | 16.0          | 9.0          | 16.0          |
| Caproic    | 8.5          | 24            | 9.0          | 40            |
| Caprylic   | 8.5          | 17.5          | 8.5          | 17.5          |
| Linoleic   | 5.0          | 16.0          | 4.0          | 8.0           |
| Linolenic  | 31.5         | 55.0          | 35           | 60            |
| Myristic   | 2.2          | 2.8           | 2.2          | 2.8           |
| Oleic      | 0.6          | 1.15          | 0.6          | 1.15          |
| Palmitic   | 2.8          | 3.9           | 2.8          | 3.9           |
| Stearic    | 14.0         | 26.0          | 13.0         | 20.0          |

LSESr—lipidosterolic extract of Serenoa repens; SCCO2—supercritical carbon dioxide; USP—United States Pharmacopeia. The ranges for ratios of the concentration of lauric acid to the concentration of the respective fatty acid. The USP defines an effective LSESr as having ≥80% free fatty acid content [5].

Currently, wide variability exists between various saw palmetto products with regard to their total fatty acid content and ratio of fatty acids [1,36,37]. For example, an analysis of the composition of 14 different brands of Serenoa repens revealed the mean percentage of free fatty acids ranged from 80.7% (Permixon) to 40.7% (Soloray®; Nutraceutical Corporation, Park City, UT, USA) [37]. This variability can arise from different extraction procedures, the use of saw palmetto berries of different ripeness, and/or the use of an ineffective solvent for the extraction of the fatty acids [1,36,37]. However, the most common method to achieve the USP-recommended fatty acid profile is via a standardized lipidosterolic extraction process of ripe saw palmetto berries yielding LSESr.

**Consensus Statement**

Current evidence suggests that a lipidosterolic extraction process that produces the lipid fingerprint defined by the USP, which is similar to the fingerprint found in Permixon, is likely the key to clinical effectiveness.

### 3.3. Efficacy of LSESr in the Global Literature

For decades, LSESr has been evaluated in numerous clinical trials around the world [35]. The most successful formulation of LSESr in clinical trials has been Permixon, which has
demonstrated statistically significant improvements to urinary symptoms when compared to placebo in randomized clinical trials and in observational studies relative to watchful waiting [35]. Permixon has also demonstrated comparable efficacy to prescription α1-blockers and 5-AR inhibitors (5-ARIs) in comparison studies [35]. These findings were recently published in a 2018 meta-analysis that showed that Permixon was associated with clinically significant improvement in the International Prostate Symptom Score (I-PSS), an increase in maximum urine flow (Q\text{\textsubscript{max}}), and an improvement in patient-reported quality of life [35].

When examining the global literature, a positive effect on LUTS has also been observed with other LSESr formulations. At this meeting, 58 original clinical research studies (25 where Permixon was the LSESr tested and 33 where a LSESr formulation other than Permixon was tested), published in English or another language, were evaluated and summarized for general trends (Tables 3 and 4) [35]. Of these 58 studies, only 1 study utilizing an ethanol-extracted LSESr and 2 studies utilizing an SCCO\textsubscript{2}-extracted LSESr failed to demonstrate benefit in alleviating LUTS [11,38–40]. To date, the STEP and Complementary and Alternative Medicine for Urological Symptoms (CAMUS) trials represent some of the largest and most robust clinical trials of LSESr for the treatment of LUTS. Despite the volume of positive reports of LSESr that demonstrate the symptomatic improvement of LUTS, these two large, US-based, randomized controlled trials were not able to demonstrate statistical significance over placebo [11,39]. The reason for the lack of efficacy between the placebo and treatment groups in these two trials, as opposed to the global evidence, is still up for debate. However, it is unclear if either trial used an LSESr product that would have met the standard outlined by the USP [11,39].

Table 3. Summary of Global Literature Examining the Efficacy of Non-Permixon LSESr [38].

| Author (Year)       | Extraction Solvent | Patients (N) | Duration (Months) | Mean (% Change in I-PSS from Baseline) | Mean (% Change in QoL Measurement from Baseline) | Mean (% Change in Q\text{max} from Baseline) |
|---------------------|--------------------|--------------|-------------------|---------------------------------------|-------------------------------------------------|-------------------------------------------|
| Derakhshani (1997) *| Ethanol            | 1047         | 3                 | −7.4 (40)                             | −1.6 (46)                                       | +3.7 (31)                                  |
| Eickenberg (1997) *| Ethanol            | 6967         | 6                 | −8.0 (44)                             | −1.8 (38)                                       | +3.0 (23)                                  |
| Gerber (1998)       | Ethanol            | 46           | 6                 | −7.6 (37)                             | −                                             | −0.7 (−5)                                  |
| Redeker (1998) *    | Ethanol            | 50           | 3                 | − (48)                                | −                                             | +3.4 (24)                                  |
| Ziegler (1998) *    | Ethanol            | 109          | 3                 | − (36)                                | −                                             | +3.7 (29)                                  |
| Hizli (2007)        | Ethanol            | 20           | 6                 | −6.1 (34)                             | −2.6 (62)                                       | +3.2 (34)                                  |
| Barry (2011)        | Ethanol            | 151          | 18                | −2.2 (15)                             | −                                             | −                                         |
| Gerber (2001)       | Ethanol            | 39           | 6                 | −4.4 (26)                             | −0.7 (21)                                       | +1.0 (10)                                  |
| Breza (2005) *      | Ethanol            | 596          | 12                | −5.9 (36)                             | −1.7 (54)                                       | +2.3 (19)                                  |
| Aliaev (2007) *     | Ethanol            | 50           | 6                 | −3.0 (26)                             | −1.8 (43)                                       | +1.7 (14)                                  |
| Razumov (2007) *    | Ethanol            | 30           | 6                 | −6.9 (43)                             | −2.7 (68)                                       | +2.8 (23)                                  |
| Aliaev (2009) *     | Ethanol            | 50           | 24                | −4.2 (37)                             | −2.2 (52)                                       | +2.7 (21)                                  |
| Vinarov (2010) *    | Ethanol            | 50           | 36                | −6.0 (50)                             | −2.0 (50)                                       | +4.5 (39)                                  |
| Sinescu (2011)      | Ethanol            | 120          | 24                | −5.5 (40)                             | −1.8 (50)                                       | +5.6 (54)                                  |
| Aliaev (2013) *     | Ethanol            | 38           | 120               | −1.3 (12)                             | −1.1 (35)                                       | +3.3 (26)                                  |
| Argirovic (2013)    | Ethanol            | 97           | 6                 | −6.1 (34)                             | −2.6 (38)                                       | +3.2 (34)                                  |
| Cai (2013)          | Ethanol            | 46           | 3                 | −3.1 (18)                             | −                                             | +0.5 (4)                                   |
| Suter (2013)        | Ethanol            | 69           | 2                 | −7.5 (52)                             | −                                             | −                                         |
| Saidi (2019)        | Ethanol            | 40           | 12                | −2.1 (18)                             | −                                             | +0.8 (6)                                   |
Table 3. Cont.

| Author (Year) | Extraction Solvent | Patients (N) | Duration (Months) | Mean (%) Change in I-PSS from Baseline | Mean (%) Change in QoL Measurement from Baseline | Mean (%) Change in $Q_{\text{max}}$ from Baseline |
|---------------|--------------------|--------------|-------------------|----------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Vinarov (2019) | Ethanol            | 30           | 180               | −6.0 (50)                              | −3.0 (60)                                       | +5.0 (45)                                     |
| Ye (2019)     | Ethanol            | 159          | 6                 | −4.4 (29)                              | −1.2 (26)                                       | +4.1 (36)                                     |
| Romics (1993)  | SCCO$_2$           | 31           | 12                | −                        | −                                    | +4.3 (39)                                     |
| Bach (1996)   | SCCO$_2$           | 315          | 36                | − (73)                                | −                                    | +6.1 (46)                                     |
| Mattei (1990) * | SCCO$_2$        | 20           | 3                 | − (55)                                | −                                    | −                                             |
| Fabricius (1993) * | SCCO$_2$   | 1334         | 4                 | − (39; 55)                            | −                                    | −                                             |
| Vahlensieck (1993) * | SCCO$_2$ | 400          | 3                 | − (94)                                | −                                    | +5.8 (52)                                     |
| Kondas (1996)  | SCCO$_2$           | 38           | 6                 | −                                    | −                                    | +4.1 (39)                                     |
| Braeckman (1994) | SCCO$_2$      | 305          | 3                 | −6.6 (35)                             | −1.5 (42)                                       | +2.1 (26)                                     |
| Braeckman (1997) | SCCO$_2$      | 67           | 12                | −10.2 (60)                            | −1.5 (42)                                       | +2.6 (24)                                     |
| Braeckman (1997) | SCCO$_2$      | 125          | 3                 | − (64)                                | −                                    | − (30)                                        |
| Bauer (1999) *  | SCCO$_2$           | 101          | 6                 | − (37)                                | −                                    | − (16)                                        |
| Willets (2003) * | SCCO$_2$       | 46           | 3                 | −1.1 (8)                              | −0.5 (13)                                       | −                                             |
| Bent (2006)   | SCCO$_2$           | 102          | 12                | −0.7 (4)                              | −                                    | +0.4 (4)                                      |

BPH—benign prostate hyperplasia; I-PSS—International Prostate Symptom Score; LSES$_r$—lipidosterolic extract of *Serenoa repens*; LUTS—lower urinary tract symptoms; $Q_{\text{max}}$—maximum flow rate; QoL—quality of life; SCCO$_2$—supercritical carbon dioxide. * Published in a language other than English. † Fabricius 1993 reported decreases in urinary frequency and nocturia of 39% and 58%, respectively. ‡ These data reflect the change in frequency and nocturia before and after treatment with LSES$_r$; frequency improved by 39% and nocturia improved by 55%. Analysis of studies from the global literature that analyzed the efficacy of a non-Permixon LSES$_r$. Inclusion criteria included: >20 patients, >2-month duration, human study, original research, monotherapy, standard dose (320 mg/d), clinical evaluation of LUTS/BPH, extraction method/product known, and interpretable data [41]. Percent +/– indicate either the percent change of improvement (+) or worsening (–) from baseline measurement. Studies highlighted in orange indicate placebo-controlled studies in which the LSES$_r$ in use failed to improve LUTS as compared with placebo. Studies highlighted in blue indicate placebo-controlled studies in which the LSES$_r$ in use improved LUTS as compared with placebo. Not all fatty acid percentages were reported. Adapted with permission from Strum SB. Uro 2022, 1, 155–179. Copyright year: 2021. Copyright owner: Stephen B. Strum.

Table 4. Summary of global literature examining the efficacy of Permixon [38].

| Author (Year) | Patients (N) | Duration (Months) | Mean (%) Change in I-PSS from Baseline | Mean (%) Change in QoL Measurement from Baseline | Mean (%) Change in $Q_{\text{max}}$ from Baseline |
|---------------|--------------|-------------------|----------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Cirillo-Marucco (1983) * | 47           | 4                 | (56)                                   | −                                  | + 4.6 (50)                                     |
| Tosto (1985) * | 20           | 3                 | −5.0 (28)                              | −                                  | −                                             |
| Pescatore (1986) * | 30           | 3                 | −                                    | −                                  | +2.5 (27)                                     |
| Ollé Carerras (1987) * | 40           | 2                 | − (68)                                | −                                  | −                                             |
| Orfei (1988) *  | 30           | 3                 | 50                                    | −2.2 (−)                                | 0.0 (0.2)                                     |
| Aliav (2002) *  | 26           | 60                | −8.8 (76)                              | −1.3 (53)                              | +4.1 (35)                                     |
| Carraro (1996)  | 467          | 6                 | −5.8 (37)                              | −1.4 (38)                              | +2.7 (25)                                     |
| Stepanov (1999) | 92           | 3                 | −6.4 (33)                              | −1.0 (26)                              | +1.6 (18)                                     |
| Al-Shukri (2000) | 57           | 2                 | −2.2 (27)                              | −0.6 (18)                              | +0.7 (6)                                      |
| Debruyne (2002) | 350          | 12                | −4.4 (28)                              | −                                  | +1.9 (17)                                     |
| Giannakopulos (2002) | 100         | 6                 | −8.0 (40)                              | −0.6 (17)                              | +3.7 (40)                                     |
| Pytel (2002) | 116          | 24                | −5.3 (42)                              | −1.3 (40)                              | +1.2 (10)                                     |
Table 4. Cont.

| Author (Year)       | Patients (N) | Duration (Months) | Mean (%) Change in I-PSS from Baseline | Mean (%) Change in QoL Measurement from Baseline | Mean (%) Change in $Q_{\text{max}}$ from Baseline |
|---------------------|--------------|-------------------|----------------------------------------|------------------------------------------------|-------------------------------------------------|
| Debruyne (2004)     | 124          | 12                | −7.8 (35)                              | −1.2 (29)                                        | +1.2 (11)                                        |
| El-Demiry (2004)    | 190          | 6                 | −11.4 (51)                             | −0.4 (19)                                        | +1.8 (15)                                        |
| Djavan (2005)       | 88           | 24                | −1.0 (17)                              | −0.4 (19)                                        | +0.8 (15)                                        |
| Giulianelli (2012)  | 591          | 6                 | −5.6 (32)                              | −0.9 (23)                                        | +1.7 (15)                                        |
| Latil (2015)        | 83           | 3                 | −4.5 (25)                              | −0.9 (23)                                        | +1.7 (15)                                        |
| Robert (2015)       | 102          | 2                 | −4.5 (25)                              | −0.9 (23)                                        | +1.7 (15)                                        |
| Alcaraz (2020)      | 222          | 6                 | −5.6 (30)                              | −1.3 (34)                                        | +3.3 (25)                                        |
| Cukier (1985) *     | 73           | 2                 | −(33)                                  | −(33)                                            | −(33)                                            |
| Pannunzio (1986) *  | 30           | 2                 | −(33)                                  | −(33)                                            | −(33)                                            |
| Authie (1987) *     | 500          | 3                 | −(78)                                  | −(78)                                            | −(78)                                            |
| Dathe (1991) *      | 49           | 6                 | −(33)                                  | −(33)                                            | −(33)                                            |
| Foroutan (1997) *   | 592          | 3                 | −6.5 (38)                              | −1.5 (45)                                        | +5.9 (66)                                        |
| Medeiros (2000) *   | 130          | 3                 | −6.5 (37)                              | −1.4 (39)                                        | +2.0 (22)                                        |

BPH—benign prostate hyperplasia; I-PSS—International Prostate Symptom Score; LUTS—lower urinary tract symptoms; $Q_{\text{max}}$—maximum flow rate; QoL—quality of life. * Published in a language other than English.

Analysis of studies from the global literature that analyzed the efficacy of Permixon. Inclusion criteria included: >20 patients, >2-month duration, human study, original research, monotherapy, standard dose (320 mg/d), clinical evaluation of LUTS/BPH, extraction method/product known, and interpretable data [41]. Percent +/-- indicate either the percent change of improvement (+) or worsening (−) from baseline measurement. Studies highlighted in blue indicate placebo-controlled studies in which the LSESr in use improved LUTS as compared with placebo. The fatty acid % of Permixon is 81%. Adapted with permission from Strum SB. Uro 2021, 1, 155–179. Copyright year: 2021. Copyright owner: Stephen B. Strum.

As was the case in the STEP and CAMUS trials, the heterogeneity between LSESr products makes it difficult to compare efficacy results across studies [35–37,39]. Furthermore, many LSESr products experience batch-to-batch variability [1,35–37]. As previously discussed, the fatty acid concentration and fingerprint are important for LSESr biologic activity and are dependent on the saw palmetto berry extraction process [1,34,35]. Therefore, we would expect inconsistencies in the extraction/formulation process to yield different products, despite being an LSESr extract by definition. It is here that we find one of the biggest limitations to the 2012 Cochrane review, which concluded that LSESr was no better than placebo at alleviating LUTS [35,42]. Though 32 robust studies of saw palmetto extracts were included for analysis, 12 studies analyzed the effectiveness of Permixon, 5 studies analyzed the effectiveness of Prostagutt® Forte (another commercialized LSESr product; Dr. Willmar Schwabe GmbH and Co. KG, Karlsruhe, Germany), and 14 studies analyzed the effectiveness of “generic” formulations of *Serenoa repens* extracts [42]. When drawing conclusions about the results of their analysis, the authors of this Cochrane review claim, “[w]e believe the [STEP] and [CAMUS] trials have shown *Serenoa repens*, if not necessarily Permixon’s, non-superiority to placebo” [42]. It is clear that the AUA’s (as well as the 2012 Cochrane review article) lack of an endorsement for LSESr is based on the pooling of results across many different saw palmetto products. As was previously described, Permixon demonstrated comparable efficacy to prescription $\alpha_1$-blockers and 5-AR inhibitors (5-ARIs) in comparison studies and statistically significant improvements to urinary symptoms in a 2018 meta-analysis [35]. This analysis included 14 of the 15 Permixon studies included in the 2012 Cochrane review, indicating that a determination on the efficacy of LSESr should not be made by pooling the results of different products [35,42].
### 3.4. Safety of LSESr in the Global Literature

While there has been some debate in the literature over the true efficacy of a high-quality LSESr for the treatment of LUTS, there has been no such controversy over the safety of LSESr among men using it for LUTS. LSESr has demonstrated a large window of activity without reaching a maximum tolerated dose and has been associated with a low rate of adverse events, even when taken daily for 15 years, as demonstrated by one long-term study [35,39,43]. A recent meta-analysis of 27 studies noted a low incidence of adverse events with good tolerability and no adverse events considered to be associated with LSESr [35]. This meta-analysis also determined four adverse events that had a mean incidence of >1%: gastrointestinal disorders (3.8%; 95% CI: 2.2–6.5), nausea/vomiting (2.6%; 95% CI: 0.8–8.6), hypertension (1.2%; 95% CI: 0.2–8.0), and tinnitus (1.2%; 95% CI: 0.2–8.0) [35]. LSESr has also been well-tolerated up to 960 mg/day, three times what is considered the therapeutic dosage of 320 mg/day [39,44]. When compared with placebo, adverse event rates with LSESr were similar (odds ratio, 1.12 [95% CI, 0.13–9.75]; \( p = 0.92 \)) and withdrawal rates were also similar (odds ratio, 1.52 [95% CI, 0.32–7.33]; \( p = 0.60 \)) [45]. In clinical trials, only rare instances of sexual side effects were noted in patients receiving LSESr [35,45]. Of note, the use of LSESr does not interfere with the detection of prostate-specific antigen levels, which is an important biomarker for the detection of prostate cancer [35]. Lastly, there are no known drug interactions with LSESr [46]. This safety profile has remained consistent across all formulations of LSESr that have undergone a clinical trial [42].

### Consensus Statement

LSESr is safe to use in men with mild-to-moderate BPH/LUTS and has a low incidence of adverse events when used at the recommended dose.

### Discussion

An international panel of urology experts convened to discuss the current AUA and EAU recommendations for the use of LSESr in treating male LUTS, a possible mechanism of action for its therapeutic effects, and the evidence supporting its safe use and efficacy. After this discussion, several areas of future research for the optimal use of high-quality LSESr for the treatment of LUTS became apparent. To our knowledge, there has been no study that has utilized real-world evidence to evaluate the therapeutic benefit of multiple LSESrs in men with LUTS. The benefits of conducting such a study today include the opportunity to evaluate a large population via electronic diary records and the ability to analyze the effectiveness of several high-quality, standardized LSESr products at the same time. However, the disadvantages of such a study would be the lack of placebo control and poor follow-up. Nevertheless, the opportunity to compare LSESr products...
within the same trial while also measuring for a clinically meaningful benefit is one we feel should be explored. Additionally, experiments and clinical trials that examine the USP-recommended fatty acid concentrations that define LSESr extract could be performed. Currently, there is no single study that compares the efficacy of various LSESr mixtures by adjusting the fatty acid ratios. Determining the fatty acid activity relationship could provide valuable information to support the mechanism of action of LSESr as well as identify efficacious products.

Throughout our discussion and evaluation of the global evidence, it is clear that a certain threshold of LSESr quality must be met in order for there to be a distinguishable therapeutic benefit. However, a large number of low-quality products are commercially available, which creates confusion for consumers and raises questions about the effectiveness of any LSESr product [1,35]. Therefore, an additional area of future research is to further define the components of a therapeutic LSESr and to identify those products in a crowded and unregulated marketplace. Currently, the literature and USP have indicated that a high-quality LSESr must contain—at minimum—80% total fatty acid content and contain a mixture of fatty acids that meets the specified ratios [1,5,34,35]. We feel that current products that meet this rigorous threshold should be identified by some means to better aid consumer choice and future LSESr research.

5. Conclusions

In closing, after careful consideration and discussion, it was concluded from this meeting that LSESr has been well-tolerated over extended periods of daily use. Additionally, we feel the current evidence links the fatty acid fingerprint of LSESr to increased effectiveness in LUTS. The evaluation of the global literature suggests that LSESr should demonstrate effectiveness in the treatment of LUTS when composed of a standardized extraction and composition that meet the current USP standards for LSESr. Notably, the LSESr prescribed under the brand name Permixon in Europe meets these conditions and consistently demonstrates the ability to reduce LUTS with minimal side effects [5,35,47]. Therefore, it is the opinion of this panel that LSESrs that meet these criteria should be more broadly utilized in the United States for the treatment of LUTS. Furthermore, it is likely that the efficacy of any LSESr is highly dependent on the fatty acid quantity and fingerprint contained within. However, more evidence is needed in the global literature to support that LSESr products can produce the same biologic effects as Permixon in a consistent manner.

Despite our confidence in the therapeutic benefits of high-quality LSESr products for men with LUTS, we feel that the confusion surrounding the existence of this benefit has been born from unrealistically high initial expectations of the capabilities of these products that may have led to disappointment and skepticism after the results of STEP and CAMUS. Therefore, we feel the expectations for the capabilities of high-quality LSESr products should be readjusted from the lofty ones prior to STEP and CAMUS. Though Permixon and other LSESr have demonstrated similar efficacy compared to certain α1-blockers and 5-ARIs in reducing LUTS in several global clinical trials, it is evident that there exists a larger range of therapeutic outcomes when taking LSESr than initially expected [35,43]. Therefore, at this time, we believe that patients and healthcare professionals can expect a modest symptomatic improvement in some men with LUTS. Additionally, though there has been evidence of symptomatic improvement in men with moderate-to-severe BPH/LUTS, we believe, at this time, the best results for LSESr use will be achieved in men with mild-to-moderate BPH/LUTS who are interested in a proactive approach to the management of their symptoms, are interested in slowing symptom progression, and/or are interested in the modest symptomatic improvement of LUTS without the risk of possible sexual side effects observed in α1-blockers and 5-ARIs [48–50]. Patients with moderate-to-severe BPH/LUTS that has a significant impact on quality of life should continue to seek pharmacologic and/or surgical options for symptom relief.
**Consensus Statement**

LSESr should be considered as a treatment option for men with mild-to-moderate BPH/LUTS as an alternative to watchful waiting.

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**Abbreviations**

5-AR, 5α-reductase; 5-ARI, 5α-reductase inhibitor; AUA, American Urological Association; BPH, benign prostatic hyperplasia; CAMUS, Complementary and Alternative Medicine for Urological Symptoms; CI, confidence interval; DHT, dihydrotestosterone; EAU, European Association of Urology; FFA, free fatty acid; HESr, hexane extract of Serenoa repens; I-PSS, International Prostate Symptom Score; LSESr, lipidosterolic extract of Serenoa repens; LUTS, lower urinary tract symptoms; MOA, mechanism of action; Qmax, maximum urine flow; QoL, quality of life; RCT, randomized controlled trial; SCCO₂, supercritical carbon dioxide; STEP, Saw Palmetto Treatment for Enlarged Prostates; USP, United States Pharmacopeia.

**References**

1. Booker, A.; Suter, A.; Krmjic, A.; Strassel, B.; Zloh, M.; Said, M.; Heinrich, M. A phytochemical comparison of saw palmetto products using gas chromatography and (1) H nuclear magnetic resonance spectroscopy metabolomic profiling. *J. Pharm. Pharmacol.* **2014**, *66*, 811–822. [CrossRef] [PubMed]

2. Hale, E.M. Saw Palmetto: Its History, Botany, Chemistry, Pharmacology, Proveris, Clinical Experience and Therapeutic Applications; Boericke & Tafel: Philadelphia, PA, USA, 1898.
27. Palin, M.F.; Faguy, M.; LeHoux, J.G.; Pelletier, G. Inhibitory effects of *Serenoa repens* on the kinetic of pig prostatic microsomal Salpa-reductase activity. *Endocrine* 1998, 9, 65–69. [CrossRef]

28. Petrangeli, E.; Lenti, L.; Buchetti, B.; Chinzari, P.; Sale, P.; Salvatori, L.; Ravenna, L.; Lococo, E.; Morgante, E.; Russo, A.; et al. Lipido-sterolic extract of *Serenoa repens* (LSESr, Permixon) treatment affects human prostate cancer cell membrane organization. *J. Cell. Physiol.* 2009, 219, 69–76. [CrossRef] [PubMed]

29. Bayne, C.W.; Ross, M.; Donnelly, F.; Habib, F.K. The selectivity and specificity of the actions of the lipido-sterolic extract of *Serenoa repens* (Permixon) on the prostate. *J. Urol.* 2000, 164, 876–881. [CrossRef]

30. de la Taille, A. Therapeutic approach: The importance of controlling prostate inflammation. *Eur. Urol.* Suppl. 2013, 12, 116–122. [CrossRef]

31. Latil, A.; Libon, C.; Templier, M.; Junquero, D.; Lantoine-Adam, F.; Nguyen, T. Hexanic lipidosterolic extract of *Serenoa repens* inhibits the expression of two key inflammatory mediators, MCP-1/CCL2 and VCAM-1, in vitro. *BJU Int.* 2012, 110, E301–E307. [CrossRef] [PubMed]

32. Bernichtein, S.; Pigat, N.; Camparo, P.; Latil, A.; Viltard, M.; Friedlander, G.; Goffin, V. Anti-inflammatory properties of Lipidosterolic extract of *Serenoa repens* (Permixon®) in a mouse model of prostate hyperplasia. *Prostate* 2015, 75, 706–722. [CrossRef]

33. Robert, G.Y. Comparison of the effects of hexanic extract of *Serenoa repens* (Permixon) and tamsulosin on inflammatory biomarkers in the treatment of benign prostatic hyperplasia-related lower urinary tract symptoms. *Eur. Urol. Suppl.* 2015, 14, e1470–e1474. [CrossRef]

34. Raynaud, J.P.; Cousse, H.; Martin, P.M. Inhibition of type 1 and type 2 Salpha-reductase activity by free fatty acids, active ingredients of Permixon. *J. Steroid Biochem. Mol. Biol.* 2002, 82, 233–239. [CrossRef]

35. Vela-Navarrete, R.; Alcaraz, A.; Rodriguez-Antolin, A.; Minana Lopez, B.; Fernandez-Gomez, J.M.; Angulo, J.C.; Castro Diaz, D.; Romero-Otero, J.; Brenes, F.J.; Carballido, J.; et al. Efficacy and safety of a hexanic extract of *Serenoa repens* (Permixon®) for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (ULTS/BPH): Systematic review and meta-analysis of randomised controlled trials and observational studies. *BJU Int.* 2018, 122, 1049–1065. [CrossRef]

36. Scaglione, F. How to choose the right *Serenoa repens* extract. *Eur. Urol. Suppl.* 2015, 14, e1464–e1469. [CrossRef]

37. Habib, F.K.; Wyllie, M.G. Not all brands are created equal: A comparison of selected components of different brands of *Serenoa repens* extract. *Prost. Cancer Prost. Dis.* 2004, 7, 195–200. [CrossRef]

38. Strum, S.B. *Serenoa repens* (Saw Palmetto) for lower urinary tract symptoms (LUTS): The evidence for efficacy and safety of lipidosteroidal extracts. Part III. *Uro* 2021, 1, 155–179. [CrossRef]

39. Barry, M.J.; Meleth, S.; Lee, J.Y.; Kreder, K.J.; Avins, A.L.; Nickel, J.C.; Roehrborn, C.G.; Crawford, E.D.; Foster, H.E., Jr.; Kaplan, S.A.; et al. Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: A randomized trial. *JAMA* 2011, 306, 1344–1351. [CrossRef] [PubMed]

40. Willetts, K.E.; Clements, M.S.; Champion, S.; Ehsman, S.; Eden, J.A. *Serenoa repens* extract for benign prostate hyperplasia: A randomized controlled trial. *BJU Int.* 2003, 92, 267–270. [CrossRef] [PubMed]

41. Strum, S.B. *Serenoa repens* (Saw Palmetto) for Lower Urinary Tract Symptoms (LUTS): The Evidence for Efficacy and Safety of Lipidosteroidal Extracts. Part II. *Uro* 2021, 1, 139–154. [CrossRef]

42. Tackilnd, J.; Macdonald, R.; Rutks, I.; Stanke, J.U.; Wilt, T.J. *Serenoa repens* for benign prostatic hyperplasia. *Cochrane Database Syst. Rev.* 2012, 12, CD001423. [CrossRef]

43. Vinarov, A.Z.; Spivak, L.G.; Platonova, D.V.; Raportop, L.M.; Korolev, D.O. 15 years’ survey of safety and efficacy of *Serenoa repens* extract in benign prostatic hyperplasia patients with risk of progression. *Urologia* 2019, 86, 17–22. [CrossRef]

44. Dathe, G.; Schmid, H. Phytotherapy of Benign Prostatic Hyperplasia (BPH) with Extract of *Serenoa repens* (Permixon®). *Urol. Augs.* 1991, 31, 223–330.

45. Novara, G.; Giannarini, G.; Alcaraz, A.; Cozar-Olmo, J.M.; Descazeaud, A.; Montorsi, F.; Ficarra, V. Efficacy and safety of hexanic lipidosterolic extract of *Serenoa repens* (Permixon) in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: Systematic review and meta-analysis of randomized controlled trials. *Eur. Urol. Focus* 2016, 2, 553–561. [CrossRef]

46. Markowitz, J.S.; Donovan, J.L.; Devane, C.L.; Taylor, R.M.; Ruan, Y.; Wang, J.S.; Chavin, K.D. Multiple doses of saw palmetto (*Serenoa repens*) did not alter cytoktheme P450 2D6 and 3A4 activity in normal volunteers. *Clin. Pharmacol. Ther.* 2003, 74, 536–542. [CrossRef]

47. Pennugonda, K.; Lindshield, B.L. Fatty acid and phytosterol content of commercial saw palmetto supplements. *Nutrients* 2013, 5, 3617–3633. [CrossRef]

48. Alcaraz, A.; Rodriguez-Antolin, A.; Carballido-Rodriguez, J.; Castro-Diaz, D.; Esteban-Fuertes, M.; Cozar-Olmo, J.M.; Ficarra, V.; Medina-Lopez, R.; Fernandez-Gomez, J.M.; Angulo, J.C.; et al. Clinical benefit of tamsulosin and the hexanic extract of *Serenoa repens*, in combination or as monotherapy, in patients with moderate/severe LUTS-BPH: A subset analysis of the QUALIPROST study. *J. Clin. Med.* 2020, 9, 2909. [CrossRef] [PubMed]
49. Latil, A.; Petrissans, M.T.; Rouquet, J.; Robert, G.; de la Taille, A. Effects of hexanic extract of *Serenoa repens* (Permixon(R) 160 mg) on inflammation biomarkers in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. *Prostate* 2015, 75, 1857–1867. [CrossRef] [PubMed]

50. Alcaraz, A.; Carballido-Rodriguez, J.; Unda-Urzain, M.; Medina-Lopez, R.; Ruiz-Cerda, J.L.; Rodriguez-Rubio, F.; Garcia-Rojo, D.; Brenes-Bermudez, F.J.; Cozar-Olmo, J.M.; Baena-Gonzalez, V.; et al. Quality of life in patients with lower urinary tract symptoms associated with BPH: Change over time in real-life practice according to treatment—the QUALIPROST study. *Int. Urol. Nephrol.* 2016, 48, 645–656. [CrossRef] [PubMed]