Clinical Efficacy of *Serenoa repens* Versus Placebo Versus Alpha-blockers for the Treatment of Lower Urinary Tract Symptoms/Benign Prostatic Enlargement: A Systematic Review and Network Meta-analysis of Randomized Placebo-controlled Clinical Trials

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**Abstract**

**Context:** International guidelines do not make any specific recommendations on *Serenoa repens* (SeR) for the treatment of male lower urinary tract symptoms (LUTS) secondary to benign prostatic enlargement (BPE), due to product heterogeneity and methodological limitations of the published trials and meta-analyses.

**Objective:** We aimed to compare the clinical efficacy of hexanic extract of *SeR* (HESr) versus non-HESr (nHESr) versus placebo versus alpha-blockers (ABs) in patients affected by LUTS secondary to BPE through a network meta-analysis method.

**Evidence acquisition:** The search was conducted until December 31, 2018 using Medline, Scopus, and Web of Science databases without restriction. We included randomized controlled trials (RCTs) with at least one comparison between SeR, ABs, or placebo for the treatment of LUTS/BPE. Outcomes of the study were the mean change in the International Prostate Symptom Score (IPSS) and peak flow (PF). This systematic review has been registered on PROSPERO (CRD42018084360).

**Evidence synthesis:** In total, 2115 articles were identified. After the global assessment, 22 RCTs matched with the inclusion criteria, including 8564 patients. For IPSS, the mean efficacies against placebo were +0.48 and −1.69 for HESr and nHESr, respectively, at 3 mo; 0.59 for nHESr at 6 mo; and −1.31 and −3.30 for HESr and nHESr, respectively, at 12 mo. For PF, the mean efficacies against placebo were +0.53 and +2.82 for HESr and nHESr, respectively, at 3 mo; +1.85 for nHESr at 6 mo; and +4.05 and +5.52 for HESr and nHESr, respectively, at 12 mo.

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1. Introduction

Medical treatment for lower urinary tract symptoms (LUTS) secondary to benign prostatic enlargement (BPE) has consistently changed in recent years, with new indications and drugs. Medical therapy may be tailored with alpha-blockers (ABs), 5α-reductase inhibitors, phosphodiesterase type 5 inhibitors, antimuscarnic drugs and beta-3 agonists, and phytotherapy on the basis of their different mechanisms of action [1].

Many different extracts are available, but the hexanic lipidosterolic extract of Serenoa repens (HESr) has extensively been studied in both basic and clinical research. The proposed mechanisms of action of HESr include anti-inflammatory properties, antianogenic activity, and anti-proliferative actions [2].

Two recent systematic reviews assessed the efficacy and safety of HESr [3,4]. Both reviews analyzed data from randomized controlled trials (RCTs), while the latter also analyzed data from observational studies. Both studies found that HESr was effective for increasing urinary flow in men with prostatic enlargement compared with placebo, while urinary symptoms and nocturia were also improved. They also confirmed that HESr was comparable with tamsulosin and short-term finasteride in symptom improvement. However, in these meta-analyses, authors did not perform a subset analysis based on the extraction of S. repens (SeR), such as nonhexanic versus hexanic, or the duration of therapy based on the treatment.

In fact, we would like to point out that statistical power in meta-analysis is conceptually similar to statistical power in primary studies. In both cases, statistical power is a function of the estimated population effect size, type I error rate, and sample size [5].

In accordance with this, the European Association of Urology Guideline Panel has not made any specific recommendations on phytotherapy for the treatment of male LUTS due to product heterogeneity, a limited regulatory framework, and methodological limitations of the published trials and meta-analyses.

The hypothesis of the present study was that previous systematic reviews with meta-analysis failed to investigate the potential role of SeR compared with other standard treatments such as ABs. Taking into consideration that RCTs are no longer performed due to their costs and complexity, a network meta-analysis (NMA) approach could be beneficial in order to fulfill our aims.

In fact, NMA may be helpful in synthesizing data from a network of trials involving more than two competing healthcare interventions. The integration of direct evidence (from studies directly comparing interventions) with indirect evidence (information about two treatments derived via a common comparator) increases the precision in the estimates and produces a relative ranking of all treatments for the studied outcome [6]. The aim of our NMA was to investigate the clinical efficacy of SeR (HESr and nHESr) against placebo and ABs in patients affected by LUTS/BPE, taking into consideration only randomized clinical trials.

2. Evidence acquisition

The current systematic review has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [7]. A PICO review protocol has been created by the authors, and the study was registered at PROSPERO (CRD42018084360).

2.1. Search strategy and selection criteria

The search was conducted using studies in Medline, Scopus, and Web of Science databases published until December 31, 2018, without restriction on year of publication and using the following search terms for each database: (“Serenoa Repens” OR “Saw Palmetto”) OR (“alpha-blockers” OR “placebo”) AND (“LUTS” OR “prostate” OR “benign prostatic hyperplasia” OR “lower urinary tract symptoms” OR “benign prostatic enlargement”) OR (“medical therapy” OR “treatment” OR “drug” OR “management”) AND (“clinical trial” OR “randomized clinical trial”) for each database. Additional relevant studies were also searched from reference lists of retrieved articles and reviews selected.

Randomized controlled clinical trials were included if they compared at least one therapy against placebo or another drug in the treatment of LUTS/BPE. Any crossover trials, case-series studies, single-arm studies, open-label studies, and studies without sufficient data (mean, standard deviation [SD], and sample size) were excluded to construct the NMA. All ABs have been considered: alfuzosin, doxazosin, tamsulosin, silodosin, and terazosin. No restriction has been applied regarding SeR formulation, but only studies including 320 mg of dosage were included.

Concerning the follow-up of the studies, we included those with 3, 6, or 12 mo of follow-up.
In case of overlapping data on the same study protocol, the most complete report was chosen.

2.2. Outcome measures and data extraction

Data were extracted in duplicate by two researchers (G.I.R. and A.C.), and a third reviewer (G.C.) resolved any disagreements. Continuous data, including summary estimates per group (mean, changes in means) with measures of variability (SD and 95% confidence interval) were extracted as available.

The primary efficacy outcome of the study was represented by the change in the International Prostate Symptom Score (IPSS) from baseline to final follow-up. The secondary efficacy outcome was represented by the change from baseline to study end in peak flow (PF).

Fig. 1 – PRISMA flowchart of included studies. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT = randomized controlled trial.
Table 1 – List of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>n</th>
<th>Follow-up</th>
<th>Mean age (yr) at baseline</th>
<th>SD at baseline</th>
<th>Qmax at baseline</th>
<th>SD at baseline</th>
<th>Mean IPSS at baseline</th>
<th>SD at baseline</th>
<th>Mean PVR at baseline</th>
<th>SD at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordling et al (2005)</td>
<td>Randomized</td>
<td>Alfuzosin</td>
<td>154</td>
<td>12 wk</td>
<td>65.00</td>
<td>9.20</td>
<td>18.00</td>
<td>5.40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lepor et al (1996)</td>
<td>Randomized</td>
<td>Terazosin</td>
<td>305</td>
<td>12 mo</td>
<td>65.00</td>
<td>7.10</td>
<td>18.00</td>
<td>5.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roehrborn and Siegel (1996)</td>
<td>Randomized</td>
<td>Terazosin</td>
<td>1053</td>
<td>12 mo</td>
<td>65.70</td>
<td>0.22</td>
<td>10.50</td>
<td>2.60</td>
<td>80.00</td>
<td>51.90</td>
<td>15.00</td>
<td>3.80</td>
</tr>
<tr>
<td>Arcioglio and Arcioglio (2013)</td>
<td>Randomized</td>
<td>Terazosin</td>
<td>1053</td>
<td>12 mo</td>
<td>65.70</td>
<td>0.22</td>
<td>10.50</td>
<td>2.60</td>
<td>80.00</td>
<td>51.90</td>
<td>15.00</td>
<td>3.80</td>
</tr>
<tr>
<td>Lepor et al (1998)</td>
<td>Randomized</td>
<td>Tamsulosin</td>
<td>254</td>
<td>13 wk</td>
<td>65.00</td>
<td>9.75</td>
<td>18.00</td>
<td>4.90</td>
<td>34.00</td>
<td>32.80</td>
<td>34.00</td>
<td>32.80</td>
</tr>
<tr>
<td>Morgia et al (2014)</td>
<td>Randomized</td>
<td>Tamsulosin</td>
<td>78</td>
<td>12 mo</td>
<td>66.00</td>
<td>5679.00</td>
<td>11.80</td>
<td>4.15</td>
<td>19.00</td>
<td>12.33</td>
<td>50.00</td>
<td>140.00</td>
</tr>
<tr>
<td>Van Kerrebroeck et al (2013)</td>
<td>Randomized</td>
<td>Tamsulosin</td>
<td>179</td>
<td>12 wk</td>
<td>65.00</td>
<td>8.30</td>
<td>18.00</td>
<td>3.80</td>
<td>35.70</td>
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<td>35.70</td>
<td>38.20</td>
</tr>
<tr>
<td>Yokoyama et al (2013)</td>
<td>Randomized</td>
<td>Tamsulosin</td>
<td>152</td>
<td>12 wk</td>
<td>79.00</td>
<td>12.20</td>
<td>16.60</td>
<td>6.40</td>
<td>32.70</td>
<td>37.10</td>
<td>32.70</td>
<td>37.10</td>
</tr>
</tbody>
</table>

HESr = hexanic extract of S. repens; IPSS = International Prostate Symptom Score; nHESr: non-hexanic extract of S. repens; PVR = postvoid residual; SD = standard deviation.
Clinically meaningful improvement (CMI) has been considered as an improvement of IPSS of ≥3 points [8] and an increase of PF of ≥3 ml/s [9].

2.3. Quality of evidence

The quality of the evidence from direct evidence and NMA was assessed by using risk, which is the recommended approach for assessing risk of bias in studies included in GRADE Working Group reviews [10].

2.4. Statistical analysis

The statistical analysis approach has been published previously [11]. The pooled data were analyzed using Stata software, version 14 (StataCorp 2015. Stata Statistical Software: Release 14, 2015; StataCorp LP, College Station, TX, USA). Summary effect sizes were calculated as weighted mean difference (WMD) for IPSS, PF, and postvoid residual with 95% prediction intervals [12]. The surface under the cumulative ranking curve (SUCRA) was also calculated for different treatments [6]. This tool ranges from 0% to 100%, where 100% reflects the best treatment with no uncertainty and 0% reflects the worst treatment with no uncertainty [6]. Publication bias was examined through visual inspection of the funnel plot.

3. Evidence synthesis

Figure 1 shows the flowchart of the search according to the PRISMA statement.

In total, 2117 articles were identified after the electronic search. After the global assessment, 22 studies matched with the inclusion criteria, including 8564 patients (Fig. 1) [13–34].

Table 1 lists the characteristics of included studies, and Figure 2 shows the geometric plot and the contribution plot of the comparison NMA for the included studies.

3.1. Data synthesis and analysis

The mean age range of patients was 64.27 yr (SD 8.01), the mean IPSS was 18.23 (SD 4.64), the mean Qmax was 10.29 ml/s (SD 3.21), and the mean postvoid residual was 68.99 ml (SD 49.58). Figures 3A and 3B show the risk of bias according to the included studies (Table 2).

3.2. Primary endpoint (IPSS)

Overall, the mean changes in IPSS against placebo were the following: tamsulosin −1.50, silodosin −2.16, terazosin −4.29, alfuzosin −1.75, nHESr −1.60, and HESr −1.24 (Supplementary Table 1).

For IPSS at 3 mo, the mean efficacies against placebo were as follows: tamsulosin −1.80, silodosin −2.23, alfuzosin −1.81, HESr +0.48, and nHESr −1.69. The contrast between nHESr and tamsulosin was −2.27, and the contrast between

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Table 2 - Network meta-analysis between all treatments for Qmax at 12 wk.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effect size</th>
<th>Standard error</th>
<th>Lower confidence interval</th>
<th>Upper confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>HESr vs alfuzosin</td>
<td>−2.95</td>
<td>3.48</td>
<td>−9.78</td>
<td>3.86</td>
</tr>
<tr>
<td>Placebo vs alfuzosin</td>
<td>−1.49</td>
<td>1.43</td>
<td>−6.30</td>
<td>−6.68</td>
</tr>
<tr>
<td>Tamsulosin vs alfuzosin</td>
<td>−2.63</td>
<td>1.74</td>
<td>−6.05</td>
<td>0.77</td>
</tr>
<tr>
<td>Silodosin vs alfuzosin</td>
<td>−2.95</td>
<td>2.15</td>
<td>−7.18</td>
<td>1.27</td>
</tr>
<tr>
<td>nHESr vs alfuzosin</td>
<td>−0.66</td>
<td>3.30</td>
<td>−7.13</td>
<td>5.80</td>
</tr>
<tr>
<td>Placebo vs HESr</td>
<td>−0.33</td>
<td>3.24</td>
<td>−6.08</td>
<td>5.81</td>
</tr>
<tr>
<td>Tamsulosin vs HESr</td>
<td>0.31</td>
<td>3.01</td>
<td>−5.58</td>
<td>6.22</td>
</tr>
<tr>
<td>Silodosin vs HESr</td>
<td>0.00</td>
<td>3.49</td>
<td>−6.84</td>
<td>6.85</td>
</tr>
<tr>
<td>nHESr vs HESr</td>
<td>2.28</td>
<td>4.39</td>
<td>−6.33</td>
<td>10.90</td>
</tr>
<tr>
<td>Tamsulosin vs placebo</td>
<td>0.85</td>
<td>1.19</td>
<td>−1.48</td>
<td>3.18</td>
</tr>
<tr>
<td>Silodosin vs placebo</td>
<td>0.53</td>
<td>1.66</td>
<td>−2.72</td>
<td>3.80</td>
</tr>
<tr>
<td>nHESr vs placebo</td>
<td>2.82</td>
<td>2.97</td>
<td>−3.00</td>
<td>8.65</td>
</tr>
<tr>
<td>Silodosin vs tamsulosin</td>
<td>−0.31</td>
<td>1.77</td>
<td>−3.78</td>
<td>3.16</td>
</tr>
<tr>
<td>nHESr vs tamsulosin</td>
<td>1.96</td>
<td>3.20</td>
<td>−4.30</td>
<td>8.24</td>
</tr>
<tr>
<td>nHESr vs silodosin</td>
<td>2.28</td>
<td>3.40</td>
<td>−4.39</td>
<td>8.96</td>
</tr>
</tbody>
</table>

HESr = hexanic extract of S. repens; nHESr = nonhexanic extract of S. repens.

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nHESr and silodosin was $-2.70$. The corresponding numbers for HESr were 0.11 and 0.53, respectively (Fig. 4A and Table 3).

At 6 mo, the mean IPSS changes compared with placebo were as follows: tamsulosin $-0.90$ and nHESr $0.59$. Further, the contrast between nHESr and tamsulosin was $1.5$ (Table 4).

At 12 mo, the mean IPSS changes against placebo were the following: tamsulosin $-1.30$, terazosin $-4.29$, nHESr $-1.31$, and HESr $-3.30$. Moreover, the contrast between nHESr and tamsulosin was 0.0, and the contrast between nHESr and terazosin was $2.98$. For HESr, the differences were $-1.99$ and $0.98$, respectively. Finally, the comparison of nHESr over HESr was 1.99 (Table 5).

### 3.3. Secondary endpoints

Overall, the mean changes in PF (expressed in ml/s) against placebo were as follows: tamsulosin $+1.45$, silodosin $+0.76$, terazosin $+1.35$, alfuzosin $+3.57$, nHESr $+2.4$, and HESr $+1.04$ (Supplementary Table 2).

At 3 mo, the mean changes in PF against placebo were as follows: tamsulosin $+0.85$, silodosin $+0.54$, alfuzosin $+3.49$, HESr $+0.53$, and nHESr $+2.82$ (Fig. 4B).

At 6 mo, the mean changes in PF were the following: tamsulosin $+2.35$ and nHESr $+1.85$. Further, the contrast between nHESr and tamsulosin was $0.5$ (Table 4). Concerning postvoid residual (ml), the contrast against placebo was $-9.67$ for tamsulosin and $+14.17$ for nHESr. Further, the difference between nHESr and tamsulosin was $+4.5$ (Table 4).

At 12 mo, changes in PF versus placebo were as follows: tamsulosin $+5.03$, terazosin $+1.47$, nHESr $+5.52$, and HESr $+4.05$. Moreover, the difference between nHESr and tamsulosin was $+0.48$, and the difference between nHESr and terazosin was $+4.05$. For HESr, the differences were $-0.98$ and $+2.56$, respectively. Finally, the difference between nHESr and HESr was $1.46$ (Table 6).

Based on the SUCRA rankograms, terazosin showed the highest score (99.6%), while alfuzosin, tamsulosin, silodosin, HESr, and nHESr showed scores of 53.7%, 42.3%, 68.5%, 36.7%, and 47.3%, respectively (Fig. 5).

Finally, Figure 6 shows the net funnel plot for all included studies, demonstrating diffused heterogeneity between comparisons.

### 3.4. Discussion

In this NMA, we have provided, for the first time, comparisons between two different extracts of SeR, ABs, and placebo for the treatment of LUTS/BPE.

In general, the magnitude of effects of HESr and nHESr in terms of CMI were similar to placebo for both IPSS and PF. Interestingly, we found similar CMI for tamsulosin in the studies at 6 mo of follow-up. In this regard, however, studies were designed comparing tamsulosin versus nHESr, while studies directly comparing tamsulosin versus placebo were lacking.

Moreover, at 12 mo HESr was demonstrated to reduce IPSS by $-3.30$. In addition, both HESr and nHESr demonstrated a CMI in PF over placebo of $+4.05$ and $+5.52$, respectively.

In this regard, we have applied the definition of clinically meaningful symptom improvement in men with lower urinary tract as an increase of at least $\geq3$ IPSS points [8].

Whether a two-point change is clinically significant or easily perceived by men is uncertain since this definition is arbitrary, but these results are similar to the response to AB treatment in the meta-analysis performed by the American Urological Association Benign Prostatic Hyperplasia (BPH) Guideline Panel [35].

Similarly, a systematic review with meta-analysis by Novara et al [3,27] demonstrated that Qmax was significantly higher in patients treated with HESr (WMD 3.37; $p < 0.001$) than in those treated with placebo.

In this regard, it is important that previous data from RCTs assessing drugs for LUTS consistently report high placebo responses [36]. This has led some to debate about the efficacy of pharmacological treatment of LUTS [37].

Others claim the placebo effect to be largely illusory and suggest that it is due to the natural history of the disease, concomitant treatments, methodological flaws, polite patient answers, misquotations, and lack of clarity of the placebo concept [38].

In order to assess this aspect, Barry et al [39] aimed to determine the effect of a saw palmetto extract at up to three times the standard dose on LUTS attributed to BPH. Authors demonstrated that increasing doses of a saw palmetto fruit extract did not reduce LUTS more than placebo.

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**Fig. 3** – (A) Risk of bias graph. (B) Risk of bias summary. Review authors’ judgments about each risk of bias item are presented as percentages across all included studies.
A recent Cochrane Collaboration meta-analysis pooled all available RCTs evaluating all the different extracts of SeR and demonstrated that they were not more effective than placebo in relieving male LUTS/BPH [40]. However, quality of plant extracts is strictly related to the quality of the botanical source as well as to the method of preparation and drug extraction. In fact, some preclinical studies confirmed that major differences exist among different brands of SeR [3].
Table 5 – Network meta-analysis between all treatments for IPSS at 12 mo.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effect size</th>
<th>Standard error</th>
<th>Lower confidence interval</th>
<th>Upper confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo vs HESr</td>
<td>3.30</td>
<td>2.65</td>
<td>-1.90</td>
<td>8.51</td>
</tr>
<tr>
<td>Tamsulosin vs HESr</td>
<td>1.99</td>
<td>1.65</td>
<td>-1.25</td>
<td>5.24</td>
</tr>
<tr>
<td>Terazosin vs HESr</td>
<td>-0.98</td>
<td>2.83</td>
<td>-6.65</td>
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<td>nHESr vs HESr</td>
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<td>-2.71</td>
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<td>Tamsulosin vs placebo</td>
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<td>2.08</td>
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<td>Terazosin vs placebo</td>
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<td>0.99</td>
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</tr>
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<td>nHESr vs tamsulosin</td>
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<td>nHESr vs terazosin</td>
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<td>1.51</td>
<td>0.011</td>
<td>5.95</td>
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</table>

HESr = hexanic extract of S. repens; IPSS = International Prostate Symptom Score; nHESr = nonhexanic extract of S. repens.

Table 6 – Network meta-analysis between all treatments for peak flow at 12 mo.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Effect size</th>
<th>Standard error</th>
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<th>Upper confidence interval</th>
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</thead>
<tbody>
<tr>
<td>Placebo vs HESr</td>
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<td>6.77</td>
<td>-17.33</td>
<td>9.22</td>
</tr>
<tr>
<td>Tamsulosin vs HESr</td>
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<td>4.73</td>
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<td>10.24</td>
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<td>Terazosin vs HESr</td>
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<td>7.41</td>
<td>-17.11</td>
<td>11.93</td>
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<tr>
<td>nHESr vs HESr</td>
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<td>6.28</td>
<td>-10.83</td>
<td>13.76</td>
</tr>
<tr>
<td>Tamsulosin vs placebo</td>
<td>5.03</td>
<td>5.62</td>
<td>-5.99</td>
<td>16.06</td>
</tr>
<tr>
<td>Terazosin vs placebo</td>
<td>1.47</td>
<td>3.49</td>
<td>-5.34</td>
<td>8.30</td>
</tr>
<tr>
<td>nHESr vs placebo</td>
<td>5.52</td>
<td>3.43</td>
<td>-1.23</td>
<td>12.29</td>
</tr>
<tr>
<td>Terazosin vs tamsulosin</td>
<td>-3.57</td>
<td>6.47</td>
<td>-16.25</td>
<td>9.11</td>
</tr>
<tr>
<td>nHESr vs tamsulosin</td>
<td>0.48</td>
<td>4.73</td>
<td>-8.79</td>
<td>9.75</td>
</tr>
<tr>
<td>nHESr vs terazosin</td>
<td>4.05</td>
<td>4.83</td>
<td>-5.42</td>
<td>13.53</td>
</tr>
</tbody>
</table>

HESr = hexanic extract of S. repens; nHESr = nonhexanic extract of S. repens.

Fig. 5 – Plots of the surface under the cumulative ranking probability for all treatments in the network. The area under the curve represents the cumulative rank probability of each treatment (the larger the better). HESr: hexanic extract of S. repens; nHESr: nonhexanic extract of S. repens.
Together with all these considerations, it is plausible that the more subjective outcomes used in LUTS treatment, including the (self-reported) number of incontinence episodes and symptom scores, yield much higher placebo responses than objective measurements (Qmax and voided volume) [36].

However, taking into account all these considerations, both nHESr and HESr showed only similar CMI of symptoms or PF to placebo after short terms; on the contrary, in the long term, they showed effects. We may speculate that the mechanism of action of SeR needs much more time (>1 yr) in order to be effective, and studies with longer follow-up (>2 yr) have not yet been published.

In fact, we found that SeR showed a clinical benefit after a long period of treatment. Although we were not able to perform the analysis of side effects, this compound could be chosen in patients who want to preserve their ejaculation function and need only minimal improvement over a longer period. Furthermore, we should point out that a minimal difference between extraction of SeR has been noticed, with HESr showing advantages in terms of IPSS (−1.99) but disadvantage in terms of PF (+1.46). Unfortunately, we do not have previous clinical data about this comparison, but these data can reflect the difference in extraction.

On the contrary, we should note that based on the SUCRA rankograms, extracts of SeR showed lower level of efficacy.

Before concluding, we would like to underline some limitations. First, although we selected only RCTs, thereby reducing the source of bias, baseline characteristics of the studies may influence the CMI. Second, we did not assess the risk of progression of LUTS/BPE since these data were not present in the included studies. Likewise, the drug treatment–related side effects were not analyzed in the present work because of different side effects among different kinds of drugs and the limited data provided in the original studies. Third, some studies discussing other uncommon regimens were excluded from our NMA.

Finally, we observed a different degree of mean changes of IPSS among all ABs investigated. However, considering all the ABs, a certain degree of efficacy may be observed. In fact, Jin Qiu Yuan et al (2015) reported in a recent NMA that when compared with placebo, the ABs such as doxazosin (IPSS: mean difference [MD], −3.67 [−4.33 to −3.02]; PF: MD, 1.95 [1.61−2.30]) and terazosin (IPSS: MD, −3.37 [−4.24 to −2.50]; PF: MD, 1.21 [0.74−1.66]), showed the greatest improvement among all ABs.

4. Conclusions

In this NMA, we demonstrated that in a short-term follow-up, no CMI in IPSS or PF of SeR has been demonstrated over placebo or ABs. On the contrary, we could only demonstrate a long-term (12 mo) benefit of SeR in the treatment of men with LUTS/BPE. In particular, HESr showed a greater improvement than nHES in terms of IPSS. Overall, both HESr and nHESr extracts showed a lower value of rank compared with all ABs. Based on the current results, patients should be counseled about the limited scientific evidence of meaningful efficacy of both HESr and nHESr. On the contrary, for patients who want to avoid side effects of
ABs and do not need rapid efficacy, SeR compounds could have a rationale.

**Author contributions:** Giorgio I. Russo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Russo.

**Acquisition of data:** Scandura, Cacciamani, Cocci, Di Mauro.

**Analysis and interpretation of data:** Russo, Scandura.

**Drafting of the manuscript:** Russo, Albersen, Hatzichristodoulou, Fode, Capogrosso, Cimino, Marcelissen, Minervini.

**Critical revision of the manuscript for important intellectual content:** Russo, Albersen, Hatzichristodoulou, Fode, Capogrosso, Cimino, Marcelissen, Minervini, Gacci, Cornu.

**Statistical analysis:** Russo.

**Obtaining funding:** None.

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**Supervision:** None.

**Other:** None.

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**Appendix A. Supplementary data**

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.euf.2020.01.002.

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