Medical Management of BPH: Role of Plant Extracts

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Abstract

Objectives: Since decades plant extracts belong to the most popular drugs for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH)/benign prostatic enlargement (BPE). Herein we review biological mechanisms, the placebo effect, results of clinical trials, the role of meta-analyses and guideline recommendations.

Methods: Review of the literature with particular reference to long-term (study period ≥6 months) controlled trials and of BPH-guideline recommendations.

Results: Only few of the large number of available studies meet the criteria defined by the WHO-BPH consensus conference. The few, placebo-controlled, long-term (study period ≥6 months) studies suggest a positive effect of some extracts (saw palmetto, ß-sitosterol, urtica, saw palmetto/urtica combination) on LUTS, an effect on uroflow, post-void residual volume, prostate volume and PSA was not consistently demonstrable. Randomised trials against active comparators (α1-blocker, 5α-reductase inhibitors) are difficult to interpret. Due to the lack of prospective studies, several meta-analyses have been published that can not replace prospective studies according to WHO-BPH recommendations. None of the BPH-guidelines currently recommends plant extracts, yet universally conclude that this is an interesting approach.

Conclusions: Further prospective studies according to WHO-standards are required to reliably determine the role of plant extracts in contemporary LUTS-management.

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1. Introduction

Since decades plant extracts belong to the most popular drugs in the medical management of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia/benign prostatic enlargement (BPE). Market shares of plant extracts reach up to 30–50% in countries with a long tradition of phytotherapy such as Austria, Germany and France [1–3]. Worldwide more than 100 different preparations generated from 30 different plants are in clinical use. The development of α1-blockers and...
5α-reductase-inhibitors (5ARIs) forced producers of plant extracts to present studies meeting the standards to the WHO-consensus conference [4]. To date only five studies with plant extracts meeting these criteria have been published, only three were placebo-controlled.

Herein we review biological mechanisms, placebo effect, results of clinical trials, the role of meta-analyses and guidelines recommendations.

2. Methods

In depth review of the literature with particular reference to long-term (study period ≥6 months) controlled trials, meta-analyses and of guideline recommendations.

3. Standards for medical BPH-trials

The WHO-BPH conference has set standards regarding clinical trials to assess the role of medical therapy [4]: prospective, randomised against placebo or standard therapy (α1-blockers, 5α-reductase inhibitors) and with a study period of 12 months. All major BPH-guidelines respect these recommendations. In the clinical part of this manuscript we therefore concentrate on studies meeting these criteria with the exception that we also considered studies with a follow-up period of 6 months. All other designs (shorter study duration, small sample size, lack of randomisation etc.) allow no reliable conclusions and were not reviewed herein.

Key message: The WHO-BPH conference has defined standards for medical BPH-trials, studies not meeting these criteria allow no valuable conclusions.

4. Placebo effect

One has to be aware that there is a significant and long-lasting placebo effect of any therapy for LUTS [5]. This placebo effect is demonstrable for subjective and objective parameters and underlines the need for placebo-controlled trials to clearly prove clinical efficacy [5]. In a recent review in European Urology we have analysed the placebo effect of all long-term controlled placebo controlled medical trials for LUTS in elderly men [6]. The mean improvement of symptom score after 12 months under placebo was 21.4% (range: 4.8–34%), after 24 months 10.9% (range: 1.5%–24.5%) and after 4.5 years 15.9% (7.9–23.8%) [6]. Qmax improved for a mean of 12.4% after 12 months (0–27%), 5.3% after 24 months (2.6%–14.8%) and 7.5% (1.8%–13.2%) after 4.5 years [6]. The mean decrease of the symptom score in the placebo-controlled trials with plant extracts reviewed herein was 4.7 points (Table 1). The placebo response showed remarkable differences in the various trials most likely caused by different inclusion/exclusion criteria, study designs, dosing etc (Table 1) [6]. The mechanisms leading to this prolonged placebo response remain poorly understood, yet condition-specific factors and self-management, patient-specific factors and trial-specific factors are likely to be involved [6,7]. This prominent placebo effect underlines the need of – ideally placebo – controlled trials to assess clinical efficacy. Although WHO-BPH guidelines suggest randomisation against placebo or standard therapy, others have proposed that at least one placebo controlled trial should be available for each extract.

Key message: The considerable placebo effect underlines the need of placebo controlled trials to document clinical efficacy.

5. Origin, components and suggested mechanisms of plant extracts

A large number of different plants have been used for the preparation of plant extracts (Table 2). Some of these stem from roots, seeds, bark or fruits of a single plant only (monopreparations); others are combination preparations of two or more plants [8,9]. The origin of plant extracts currently used is listed in Table 2. The number of components identified in plant extracts is constantly increasing; the most important ones are phytosterols, β-sitosterols, fatty acids and lectins (Table 2). In parallel, numerous biological mechanisms of plant extracts such as 5α-reductase inhibition, aromatase activity, androgen blockade, α1-blockade, inhibition of prostaglandin synthesis, anti-inflammatory activity etc. have been proposed based on in vitro data (Table 2). The majority of experimental studies used supraphysiologic doses thus hindering an extrapolation to the in vivo situation; moreover data on pharmacodynamics and bioavailability are scant [8]. Although these mechanisms have been documented in vitro, there is no convincing evidence that any of these mechanisms acts also in vivo. For instance, a reduction of prostate volume or serum PSA has not been shown in any clinical trial; these observations suggest that a 5α-reduction or anti-androgenic activity is not demonstrable in vivo. The marginal effect on bladder outlet obstruction
Table 1 – Changes of IPSS and Qmax of all prospective, randomized trials with plant extracts and a study period of ≥6 months

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study-arm</th>
<th>Dosing</th>
<th>Study length</th>
<th>Patients</th>
<th>IPSS mean (SD)</th>
<th>Qmax [ml/sec] mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Study end</td>
</tr>
<tr>
<td>10</td>
<td>Saw palmetto</td>
<td>320 mg/die</td>
<td>6 mo</td>
<td>553</td>
<td>15.7 (5.9)</td>
<td>9.9 (5.4)</td>
</tr>
<tr>
<td></td>
<td>Finasteride</td>
<td>5 mg/die</td>
<td>6 mo</td>
<td>545</td>
<td>15.7 (5.7)</td>
<td>9.5 (5.5)</td>
</tr>
<tr>
<td>11</td>
<td>Saw palmetto</td>
<td>320 mg/die</td>
<td>12 mo</td>
<td>350</td>
<td>15.3 (4.3)</td>
<td>10.8 (5.5)</td>
</tr>
<tr>
<td></td>
<td>Tamsulosin</td>
<td>0.4 mg/die</td>
<td>12 mo</td>
<td>354</td>
<td>15.4 (5.2)</td>
<td>11.0 (6.0)</td>
</tr>
<tr>
<td>13</td>
<td>Saw palmetto</td>
<td>160 mg/bid</td>
<td>12 mo</td>
<td>112</td>
<td>15.7 (5.7)</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>12 mo</td>
<td>113</td>
<td>15.0 (5.3)</td>
<td>14.3</td>
<td>–0.7</td>
</tr>
<tr>
<td>16</td>
<td>β-Sitosterol</td>
<td>20 mg/tid</td>
<td>6 mo</td>
<td>100</td>
<td>14.9 (4.7)</td>
<td>7.5 (4.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6 mo</td>
<td>100</td>
<td>15.1 (4.2)</td>
<td>12.8 (4.5)</td>
<td>–2.3</td>
</tr>
<tr>
<td>17</td>
<td>β-Sitosterol</td>
<td>130 mg/die</td>
<td>6 mo</td>
<td>88</td>
<td>16.0 (4.6)</td>
<td>7.8 (4.9)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6 mo</td>
<td>89</td>
<td>14.9 (5.2)</td>
<td>12.1 (5.6)</td>
<td>–2.8</td>
</tr>
<tr>
<td>19</td>
<td>Stinging root</td>
<td>459 mg/die</td>
<td>12 mo</td>
<td>114</td>
<td>18.7 (0.3)*</td>
<td>13.0 (0.5)*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>12 mo</td>
<td>112</td>
<td>18.5 (0.3)*</td>
<td>13.8 (0.5)*</td>
<td>–4.7</td>
</tr>
<tr>
<td>20</td>
<td>Pumpkin seed</td>
<td>500 mg/bid</td>
<td>12 mo</td>
<td>233</td>
<td>17.6 (3.7)</td>
<td>10.9 (4.5)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>12 mo</td>
<td>243</td>
<td>17.7 (3.8)</td>
<td>12.2 (5.1)</td>
<td>–5.5</td>
</tr>
<tr>
<td>21</td>
<td>Rye Pollen</td>
<td>6 mo</td>
<td>30</td>
<td>no validated questionnaire</td>
<td>–69%</td>
<td>10.3 (5.2)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>6 mo</td>
<td>30</td>
<td>no validated questionnaire</td>
<td>–29%</td>
<td>11.8 (6.4)</td>
</tr>
<tr>
<td>24</td>
<td>Saw palmetto/Urtica</td>
<td>160/120/die</td>
<td>12 mo</td>
<td>245</td>
<td>11.3 (6.5)</td>
<td>6.5 (5.8)</td>
</tr>
<tr>
<td></td>
<td>Finasteride</td>
<td>5 mg/die</td>
<td>12 mo</td>
<td>244</td>
<td>11.8 (6.6)</td>
<td>6.2 (5.2)</td>
</tr>
<tr>
<td>25</td>
<td>Saw palmetto/Urtica</td>
<td>160/120/die</td>
<td>12 mo</td>
<td>71</td>
<td>20.4 (4)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Tamsulosin</td>
<td>0.4 mg/die</td>
<td>12 mo</td>
<td>69</td>
<td>21.0 (4)</td>
<td>10</td>
</tr>
</tbody>
</table>

SD: standard deviation.
* Statistical significant difference.
# Standard error of the mean (SEM) instead of standard deviation.
** No detailed information, yet no difference between plant extract and placebo.
(see below) casts doubts on the proposed α-blockade. Finally it is unknown which component of plant extracts is responsible for the proposed mechanisms.

Key message: The in vivo mechanism of any plant extract remains to be identified.

6. Clinical results

6.1. Saw palmetto

Saw palmetto is derived from olive-sited berries of the saw palmetto tree and is the most popular phytotherapeutic agent in BPH-management. In Germany, for instance, more than 30 different preparations are on the market. The by far most intensively studied product of this group is a n-hexan-liposterol-extract (Permixon®) which is very popular in France [10,11]. This product is a complex mixture of free fatty acids and their esters, phytosterols, aliphatic alcohols and various polymeric compounds that has been tested in two large scale prospective randomised trials against standard therapy (Table 1, Figs. 1 and 2) [10,11]. Carraro et al randomised 1.098 patients into a Permixon®- and a finasteride-arm [10]. The study period was 6 months. At study end, improvements of the IPSS (Permixon®: −6.2 points; finasteride: −6.6 points) and quality of life were identical in both arms [10]. The rise in Qmax was slightly higher under finasteride (finasteride: +2.8 ml/sec; Permixon®: +2.1 ml/sec;
Reduction of PSA and prostate volume were demonstrable for finasteride only. This study has been criticised for the short study period of 6 months particularly regarding the fact that finasteride exerts its full clinical efficacy after 3–6 months and the lack of a placebo arm [10]. It is therefore unknown whether results of this trial exceeded the putative placebo effect. In another large-scale trial Permixon® has been tested in a 12 months study randomised against tamsulosin. A total of 704 patients entered this trial. Results regarding Qmax and IPSS were identical in both arms [11]. Both products were well tolerated, yet ejaculatory disorders were more frequent under tamsulosin [11]. The authors concluded that both products are equal effective regarding the medical management of LUTS. Also this study has been criticised for the lack of a placebo arm [11]. There exists one large-scale placebo controlled 12-months trial with Harzol® that has randomised 198 patients into each arm. This trial was only briefly described in a recent meta-analysis [12]. Unfortunately, this key trial has never been published [12]. At least regarding Qmax and nocturia there was no difference to placebo after 12 months [12]. The only 12 months, placebo controlled trial with a saw palmetto product published in the peer-reviewed literature has been recently reported by Bent et al in the New England Journal of Medicine [13]. In this highly published, industry-independent and probable best designed phytotherapy trial 225 patients were followed for 12 months [13]. In this trial, changes of the AUA-symptom score (saw palmetto: −0.7; placebo: −0.7), the Qmax (saw palmetto: +0.4 ml/sec; placebo: +0.0 ml/sec), prostate volume (saw palmetto: +3.8 ml; placebo: +5.0 ml), PVR (saw palmetto: +14 ml; placebo: +19 ml) were identical between saw palmetto and placebo. The authors provided several explanations for the discrepancy of this negative study to the summary of prior evidence [13]. The authors, for instance, argued that blinding was effective. Since saw palmetto has a strong, pungent odour, the authors speculated that many previous studies might not have achieved adequate blinding [13]. Inadequate blinding has the potential to reduce response in men who are given placebo (who may be aware they are taking placebo), artificially increasing the comparative efficacy of saw palmetto [13].

Several meta-analyses for saw palmetto have been published [12,14,15]. In 2004 Boyle et al presented the most recent meta-analysis. In total 14 randomized and open trials with 4.280 patients were analysed, only three randomized trials had a study period of 6 months or longer [12]. In this meta-analysis the IPSS decreased by 4.8 points and the Qmax by 2.2 ml/sec under Permixon®; the respective changes under placebo were 4.5 IPSS-points and for the Qmax 1.2 ml/sec [12]. Wilt et al investigated saw palmetto extracts in another meta-analysis based on 18 randomized trials with a total of 2.939 men [14]. The mean symptom-improvement was 1.4 points, the Qmax by 1.9 ml/sec and nocturia-episodes decreased by 0.8 [14]. The conclusion of this meta-analysis is hampered by the fact that 11 different extracts in different concentrations and different extraction techniques were included [14]. Only two trials fulfilled the WHO-BPH criteria. The authors concluded that there is evidence that saw palmetto extracts improve symptoms and Qmax yet also stated that further controlled trials according to BPH-criteria are required before definitive conclusions can be drawn.

Key message: Despite the fact that saw palmetto is the most intensively studied and used plant extract, no definitive conclusion can be made at this time point. Further placebo-controlled trials according to WHO-criteria are necessary.

6.2. *Hypoxis rooperi* (South African star grass)

This extract contains mainly β-sitosterol, which is thought to be the major active component, with other sterols being detected in the lesser extent. The most widely used extract of star grass is Harzol®. This product has been investigated on one placebo-controlled trial with 200 patients (Table 1, Figs. 1 and 2) [16]. After 6 months the IPSS decreased by 2.3 points under placebo and by 7.4 points under Harzol®, the difference of Qmax against placebo was quite high, 4 ml/sec [16]. Klippel et al investigated another β-Sitosterol extract (Azuprostas®; 65 mg bid) in a placebo-controlled trial for 6 months. (Table 1, Figs. 1 and 2) [17]. Also in this study the plant extract was clearly superior to placebo: the IPSS improved by 8.2 points under the plant extract in comparison to only 2.8 points under placebo (p < 0.01) [17]. The absolute increase of the Qmax in this trial was 8.8 ml/sec (!) with the plant extract. This “dramatic” improvement is far higher than that of α1-blockers and 5α-reductase inhibitors, indicating that these data have to be interpreted with caution. The increase of the Qmax in the placebo arm (+4.4 ml/sec) was also unusually high. One meta-analysis is available that has analysed pooled data of 5 prospective studies with a total of 516 patients; the study period was 4–26 weeks [18]. The mean difference of the IPSS between placebo
and β-sitosterol was 4.9 points, the Qmax increased by 34% and the post void residual volume by 24%. The authors of this meta-analysis were unable to provide a valid conclusion because in these four trials three different extracts were used [18].

Key message: The two 6-months placebo-controlled trials provide encouraging data that need to be confirmed by studies according to WHO-BPH criteria.

6.3. Stinging nettle (Urtica dioica)

The roots of the stinging nettle contain a mixture of water- and alcohol-soluble compounds including lectins, phenols, sterols and lignins. There are at least 16 different preparations of this extract available that is particularly popular in Germany. Recently a 12-months placebo controlled trial with one stinging root extract (Bazoton-uno®; 459 mg/die) has been reported. (Table 1, Figs. 1 and 2) [19]. A total of 226 patients were randomized 1:1 into a placebo and plant extract arm. After 12 months, the IPSS decreased by 5.7 points with the plant extract and by 4.7 points under placebo, this one point difference reached statistical significance (p = 0.02) [19]. Changes of Qmax, post void residual volume and quality of life were identical under placebo and the plant extract [19]. The plant extract was well tolerated. In summary the only difference in this well-designed trial was a one-point difference of the IPSS after 12 months, yet no effect on Qmax, post void residual volume and quality of life. The clinical relevance of this finding is questionable. All other trials with stinging nettle extracts do not fullfill current quality criteria; meta-analyses are not available.

Key message: One placebo-controlled study meeting the WHO-BPH criteria demonstrates a slight effect on LUTS yet no impact on objective parameters. Further studies according to WHO-BPH criteria are required.

6.4. Pumpking seed extracts

One study meeting the WHO-criteria is available. In this placebo-controlled trial 476 patients were included and followed for 12 months [20]. At study end, the IPSS declined by 6.7 point under the plant extract (Prosta Fink forte®, 500 mg/die) and by 5.5 points under placebo [20]. This one point difference was statistical significant. Changes of Qmax, quality of life, prostate volume and post void residual volume were identical under placebo and the plant extract (Table 1, Figs. 1 and 2) [20].

Key message: One study meeting the WHO-BPH criteria showed a slight effect on LUTS yet no impact on objective parameters. Further studies according to WHO-BPH criteria are required.

6.5. Rye pollen (Secale cereale)

The commercial preparation “Cernilton®” is a pollen extract prepared from several plants found growing in countries such as Sweden. This drug is available across Europe and is manufactured by microbial digestion of the pollen. There is only one placebo controlled trial with a study duration of 6 months available that has included only 60 patients [21]. The improvement of LUTS (no validated questionnaire, just one question) was 69% for Cernilton® and 29% for placebo, changes of Qmax were identical under Cernilton® and plabebo [21]. One meta-analysis that has included only 4 studies is available; three of these studies had a very short duration (12–16 weeks) only one study had a duration of 24 weeks [22]. The authors concluded that due to the limited number of studies, small sample sizes and short study period no viable conclusions can be made [22].

Key message: No study meeting the WHO-BPH criteria is available; therefore no conclusion can be drawn. Further placebo-controlled trials are mandatory.

6.6. African plum (Pygeum africanum)

In traditional African medicine a tea made from the powdered bark of this tall evergreen tree is drunk to control urinary disorders in men. Today, this supplement is commonly used in France, Germany and Austria (Tadenan®). None of the studies fulfilled WHO-criteria, there is even no 6-months controlled trial available [23].

Key message: No study meeting the WHO-BPH criteria is available; therefore no conclusion can be drawn.

6.7. Combination products

Many manufacturers of plant extract produce not only mono- but also combination extracts although there is no scientific evidence for an additive or even
potentising effect. One combination product of (saw palmetto/stinging nettle; Prostagutt® forte) has been tested against finasteride in a large scale (489 patients) prospective, randomized 12-months trial (Table 1, Figs. 1 and 2) [24]. The IPSS decreased by 4.8 points under placebo and by 5.6 points under finasteride; there was no difference between the two study arms [24]. Also regarding Qmax, both study arms yielded comparable improvements (plant extract: 2.2 ml/sec; finasteride: 2.6 ml/sec) [24]. The combination product had no effect on prostate volume; finasteride reduced prostate volume by 15% [24]. Both products were well tolerated, erectile dysfunction (2.8%) and reduced ejaculate volume (2%), however, were more frequent under finasteride [24]. The same combination (Prostagutt® forte) has been compared to tamsulosin in a 12-month prospective, randomized trial [25]. The IPSS improved in both study arms by 9 points. Detailed data on Qmax, post void residual volume and prostate volume were not presented [25].

Key messages: Two studies meeting the WHO-BPH criteria suggest a similar efficacy as standard therapy. Further studies with a placebo arm are required to clearly document the clinical efficacy.

7. The role of meta-analyses

As shown above, a number of meta-analyses have been published for various plant extracts [12,15,18,22,23]. The major problem of all meta-analyses is the fact that their quality strongly depends on the quality of studies entering the meta-analysis. It is therefore not surprising that the authors of almost all meta-analyses concluded that further prospective trials are needed before definitive conclusions can be drawn. Meta-analyses can not supplement prospective trials according to WHO-BPH-criteria.

8. Recommendations of BPH-guidelines

All major BPH-guidelines, such as those of the EAU, the AUA or of the German Urologists make statements regarding the role of plant extracts in contemporary management of elderly men with LUTS [26–28]. In general, these guidelines are quite sceptical regarding the role of plant extracts. The guidelines of the German Urologists state “For some plant extracts there is evidence of clinical efficacy based on the results of randomised controlled trials that all require confirmation” [26]. The most recent published update of the EAU-guidelines states: “The mode of action of phytotherapeutic agents is unknown. The biological effects are unclear although a few RCTs show encouraging data. These drugs are not recommended for the treatment of elderly men with LUTS suggestive of benign prostatic obstruction” [27]. Finally, the AUA-guidelines conclude that “Phytotherapeutic agents cannot be recommended for treatment of BPH at this time. . . mechanisms of action, effectiveness, and safety of these agents have not been well documented in multicenter, clinical trials with independent data monitoring” [28].

Despite these critical conclusions all BPH-guidelines underline that phyotherapy is an interesting approach that deserves further evaluation, in particular more studies meeting the WHO-criteria (placebo arm). The EAU and German BPH-guidelines are currently updated, yet it is unlikely that different recommendations regarding the role of plant extracts will be made.

9. Conclusions

As repeatedly emphasised a definitive conclusion regarding the role of plant extracts in the current management of LUTS in elderly men can not be made to date. Although a handful studies meeting the WHO-BPH criteria are available, convincing evidence for their clinical efficacy is still lacking. None of the three 12 months placebo-controlled trials available to date has demonstrated an effect on prostate volume, PSA, Qmax or post void residual volume. Interestingly, the two trials against an active comparator revealed identical efficacy as tamsulosin and finasteride. One attractive aspect of plant extracts is their good tolerability that renders this approach particularly attractive for sexually active men who want to avoid sexual side effects of α1-blockers and 5ARIs.

In parallel to α1-blockers or 5α-reductase inhibitors, there should be at least one 12-months placebo controlled trial available. It is worth to note that clinical efficacy of α1-blockers and 5ARIs has been convincingly demonstrated in a number of placebo-controlled trials [6]. However, these studies are very expensive and it is very unlikely that the producers of plant extracts will make these investments, particularly facing the fact that reimbursement, e.g. in Germany, is no more granted. Furthermore plant extracts can not be patented. Finally, the data of e.g. one saw palmetto extract can not be extrapolated to another one due to different origins, extraction techniques and compositions.
Hence, each extract needs to be analysed separately.

The data of the prospective trials and meta-analyses presented above suggest a slight positive effect on LUTS; an effect on urodynamic parameters such as Qmax or post void residual volume is less convincing. An impact of PSA or prostate volume has not been demonstrated, data on the impact of the natural history (risk of acute urinary retention, surgery) are lacking. Due to these data plant extracts should only be offered to patients with bothersome LUTS without significant benign prostatic obstruction and a low risk of progression. Patients, however, should be instructed that the definitive proof of their efficacy is still lacking and that they are currently not recommended by BPH-guidelines.

Conflict of interest

The authors have nothing to disclose.

References

CME questions

Please visit www.eu-acme.org/europeanurology to answer these CME questions on-line. The CME credits will then be attributed automatically.

1. Which statement regarding plant extracts is correct?
   A. Plant extracts induce a reduction of prostate volume by about 20%.
   B. Plant extracts lower serum prostate-specific antigen by 15%.
   C. Plant extracts are recommended by the AUA and EAU guidelines.
   D. None of the above.

2. Which statement regarding the mechanism of plant extracts is correct?
   A. Plant extracts have a 5α-reductase activity in vivo.
   B. The exact mechanism of plant extracts in vivo is unknown.
   C. Plant extracts inhibit the aromatase in vivo.
   D. Plant extracts have no in vitro efficacy.

3. The role of meta-analyses in the assessment of plant extracts:
   A. Meta-analyses provide no relevant conclusions.
   B. Meta-analyses can supplement prospective trials according to WHO-BPH criteria.
   C. Meta-analyses cannot supplement prospective trials according to WHO-BPH criteria.
   D. Meta-analyses have convincingly documented the clinical efficacy of plant extracts.

4. The clinical efficacy of plant extracts:
   A. Plant extracts increase the maximum flow rate by >7 ml/s in the majority of studies.
   B. Plant extracts reduce the postvoid residual volume by 50%.
   C. Plant extracts reduce the risk of prostate surgery by 50%.
   D. The majority of plant extracts have a slight positive effect on lower urinary tract symptoms (LUTS).

5. Which group of patients will most likely benefit from plant extracts?
   A. Patients with severe LUTS and a high risk of progression.
   B. Patients with mild/moderate LUTS and no relevant benign prostatic obstruction.
   C. Patients with high postvoid residual volume and large prostates.
   D. Patients with bladder stones and upper urinary tract dilatation.

6. Which statement of the EAU-BPH guidelines regarding plant extracts is correct?
   A. Strong recommendation of the use of plant extracts as a primary treatment.
   B. Plant extracts are indicated in men at a high risk of disease progression.
   C. Plant extracts are clearly indicated in men with minimal symptoms and no impairment of quality of life.
   D. No clear recommendation for plant extracts.