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Review

Dietary supplements for benign prostatic hyperplasia: An overview of systematic reviews

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a common chronic condition in older men. The aim of this overview of systematic reviews (SRs) is to summarise the current evidence on the efficacy and adverse effects of dietary supplements for treating BPH with lower urinary tract symptoms. We searched 5 electronic databases and relevant overviews without limitations on language or publication status. Six SRs of 195 articles were included in this overview. Serenoa repens was reviewed in 3 studies and no specific effect on BPH symptoms and urinary flow measures was observed. However, β-sitosterol, Pygeum africannum and Cernilton were reviewed in one study each, and significant improvement was observed for all three. All the included compounds have mild and infrequent adverse effects. SRs on β-sitosterol, Pygeum africannum and Cernilton have not been updated since 2000, thus an update of reviews on these compounds will be necessary in the future.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a relatively common condition characterised by abnormal but non-malignant enlargement of the prostate gland and a strong predictor of spontaneous acute urinary retention (AUR) in men with lower urinary tract symptoms (LUTS) [1]. Epidemiological evidence suggests that BPH is related to the male ageing process: from histological diagnoses, the prevalence of BPH is approximately 50% of men in their fifties, increasing to 90% of the male population in their eighties [2,3]. BPH is diagnosed based on a patient's history and comprehensive symptom and test results. Men with LUTS and benign prostate enlargement may be diagnosed with BPH after other pathologies are ruled out [4].

Alpha-blockers and 5-alpha-reductase inhibitors are the most commonly used pharmacological treatments for BPH in conventional medicine, but adverse events related to these drugs, including intraoperative floppy iris syndrome during cataract

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surgery by tamsulosin and treatment of male breast cancer by finasteride, cannot be easily ignored [5]. BPH is a disease of long duration in older men, and it sometimes induces complications including frequent recurrent urinary retention, urinary tract infections, and rare post-renal renal failure [6]. Therefore patients and clinicians need a long-term, effective and safe strategy for managing BPH.

According to the US Dietary Supplement Health and Education Act, the definition of a dietary supplement is a product for oral administration that is intended to supplement the diet and that contains dietary ingredients such as vitamins, minerals, botanicals, and amino acids [7]. Dietary supplements have played an important role in the treatment of BPH in many countries. Phytotherapeutics, which are key dietary supplements for BPH, are used as the first-line therapy in Germany and Austria, and in the US, they are easy to access without a doctor's prescription [8]. Considering the current broad usage of dietary supplements for BPH, efforts to critically assess the clinical evidence on these treatments seem warranted.

The purpose of this overview of systematic reviews (SRs) is to summarise the current evidence on the benefits and drawbacks of dietary supplements for treating BPH with LUTS. With this review, we aim to provide information on dietary supplements for patients and clinicians to aid in the clinical decision-making process.

2. Methods

Only systematic reviews of randomised, controlled trials of dietary supplements for BPH were included in this review. Patients included men with lower urinary tract symptoms (LUTS) secondary to BPH, and the interventions included phytotherapeutic agents (Serenoa repens extracts, Pygeum africanum extracts, beta-sitosterols, etc.), vitamins (vitamin E) and trace minerals (selenium, carotenoids, zinc, etc.) [9]. Electronic databases including The Cochrane library 2012 (Issue 5), Databases of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Medline and EMBASE were searched through June 2012 without limitations on language or publication status. Important previous overviews of systematic reviews were hand-searched. The search term was as follows:

(Benign prostatic hyperplasia) and (dietary supplement or phytotherapeutic agent or Serenoa repens or *P. africanum* or beta-sitosterol or vitamin or trace mineral or selenium or carotenoid or zinc) and (systematic review).

Two independent authors participated in the process of study selection, data extraction and assessments of the quality of the individual reviews, and all disagreements were resolved through discussion. Urologic symptom scores including the American Urologic Association Symptom Index (AUA), the international prostate symptom score (IPSS), urodynamic study results, post-void residual urine (PVR), nocturia and changes in prostate size were the main outcomes of the efficacy evaluation, and withdrawal due to adverse events was assessed as a safety outcome. The primary purpose of this review was to evaluate the specific effects of individual dietary supplements; thus, only information on the comparison between the supplement and placebo were extracted. The quality of the included reviews was assessed by two authors using the "assessment of multiple systematic reviews (AMSTAR)" instrument [10], and the quality of each review was decided by the number of appropriate criteria in the AMSTAR instrument: the highest quality (if all 11 criteria were met), high quality (if 8–11 were met), medium quality (if 4–7 were met) or low quality (if 0–3 were met) [11].

Effect estimates for individual outcomes were extracted from the original reviews and presented as relative risk (RR) for dichotomous data and mean differences (MD) for continuous outcomes.

Table 1
Characteristics of excluded studies.

Study (first author, year published)	Reason for exclusion
Agbabiaka (2009) [12]	Invalid outcome assessment
Dedhia (2008) [13]	Overview of systematic reviews
Dvorkin (2002) [14]	Overview
Fong (2005) [15]	Overview of systematic reviews
Gaynor (2003) [16]	Narrative review
Gerber (2004) [17]	Narrative review
Ilic (2012) [18]	Invalid outcome assessment
Ishani (2000) [19]	Duplication
Lowe (2009) [20]	Overview of systematic reviews
Macdonald (2012) [21]	Duplication
Madersbacher (2007) [22]	Narrative review
McNicholas (2011) [5]	Overview of systematic reviews
Sosnowska (2009) [23]	Invalid outcome assessment
Strong (2004) [24]	Narrative review
Ulbricht (2006) [25]	Overview of systematic reviews
Webber (2006) [26]	Updated review
Wilt (2002) [27]	Updated review
Wilt (1999) [28]	Duplication

3. Results

A total of 195 articles were located from electronic databases and by hand searching. Among them, hard copies of 24 studies were reviewed. The characteristics of the reviewed and excluded studies are presented in Table 1 [5,12–28]. Of 24 studies, 6 SRs were included in this overview (Fig. 1, Table 2) [2,8,29–32].

The intervention agents for all included studies were phytotherapeutic compounds, and SRs of other types of dietary supplements were not included. Among the 6 SRs included, Serenoa repens was reviewed in 3 studies [2,8,29] and β-sitosterol [30], Pygeum africannum [31] and Secale cereal [32] were reviewed in one study each. The total number of included SRs ranged from 4 to 18 among the studies. However, a small number of the studies (from 1 to 11) were used for a meta-analysis of individual outcomes. AUA [2], IPSS [2,30] and improvement as reported by patients [8] or by physicians [31] and nocturia [2,8,29,31,32] were assessed for the evaluation of urologic symptoms. Peak urinary flow (Q_{max}) [2,8,29–32] and PVR [8,30–32] were assessed for urodynamic evaluation, and prostate size [30] was assessed for ultrasound diagnosis in these reviews. In 1 study, meta-analysis data on withdrawals from treatment were evaluated for the safety assessment [2].

According to the quality assessment of the SRs by the AMSTAR instruments, 3 studies [8,30,31] were of high quality, and the highest [2], medium [32] and low quality [29] ratings were found for 1 study each. Within the AMSTAR 11 checklist, the assessment of publication bias was not met in any study except 1 [31]. All the Cochrane reviews were of good quality [2,30,31], but the others were not (Table 3) [29,32].

3.1. Serenoa repens

Serenoa repens is an extract of the berry of the American saw palmetto or dwarf palm plant that has been widely used for relieving symptoms related to BPH [2]. Three reviews assessed the benefits and drawbacks of this phytotherapeutic compound [2,8,29]. Boyle et al. evaluated one type of Serenoa repens product, Permixon, which is a lipido-sterolic extract [29], and the authors reported positive effects of Permixon in improving peak urine flow rate and reducing nocturia compared with placebo. Wilt et al. assessed all types of Serenoa repens preparations including S serrulata, Sabalis serrulata, Serenoa serrulata, Permixon, PA 109, Serendar, Talso, Curbicin, Prostagutt, Prostaselect, Prostagalen, Prostavigol, Strogen forte and SPRO 160/120 and reported positive effects on urinary tract symptoms and flow measurements [8]. On the other hand, a relatively recent high-quality review by Tacklind

Table 2
Summary of included systematic reviews.[a]

Study (first author, year published)	Data search (or updated)	Total no. of primary studies	Comparison	Outcome	No. of included studies	Effect size	Conclusion (quote)
Serenoa repens							
Boyle (2004) [29]	n.r.	17	Permixon vs. placebo	Q_{max} (mL/s)	4	MD 1.0 [0.1 to 2.0]	. . .showed a significant improvement in peak flow rate and reduction in nocturia above placebo. . .
				Nocturia (times)	4	MD −0.37 [−0.23 to −0.51]	
Tacklind (2009) [2]	January 2012	17	Serenoa repens vs. placebo	AUA	2	MD 0.25 [−0.58 to 1.07]	Serenoa repens, at double and triple doses, did not improve urinary flow measures or prostate size in men with lower urinary tract symptoms consistent with BPH.
				IPSS	1	MD 1.74 [−0.54 to 4.03]	
				Q_{max}	3	MD 0.40 [−0.30 to 1.09]	
				Nocturia (times)	9	MD −0.79 [−1.28 to −0.29]	
				Prostate size (cm^3)	2	MD −2.20 [−8.98 to 4.58]	
				Study withdrawals	11	RR 0.95 [0.69 to 1.30]	
Wilt (1998) [8]	1997	18	Serona repens vs. placebo	Self-rating improvement by patients	6	RR 1.72 [1.21 to 2.44]	. . .the available evidence suggests that *S. repens* improves urinary tract symptoms and flow measures
				Nocturia	10	MD −0.76 [−1.21 to −0.32]	
				Q_{max}	8	MD 1.93 [0.72 to 3.14]	
				PVR (mL)	6	MD −22.05 [−40.78 to −3.32]	
β-Sitosterol							
Wilt (2000) [30]	1998	4	β-Sitosterol vs. placebo	IPSS (point)	2	MD −4.9 [−6.3 to −3.5]	β-Sitosterols improve urological symptoms and flow measures. . .
				Q_{max} (mL/s)	4	MD 3.91 [0.91 to 6.90]	
				PVR (mL)	4	MD −28.62 [−41.42 to −21.66]	
				Prostate size (cm^3)	2	MD −6.19 [−15.29 to 2.92]	
Pygeum africannum							
Wilt (2002) [31]	2000	18	Pygeum africannum vs. placebo	Patient self-reporting improvement	6	RR 2.1 [1.4 to 3.1]	Pygeum africannum improves urinary symptoms and flow measures and the point estimate for the effect size is moderate in magnitude. . .
				Nocturia (times)	3	MD −0.9 [−2.0 to 0.1]	
				Q_{max} (mL/s)	4	MD 2.5 [0.3 to 4.7]	
				PVR (mL)	2	MD −13 [−23.3 to −3]	
Cernilton							
MacDonald (2000) [32]	1998	4	Cernilton vs. placebo	Nocturia (self-rating improvement)	2	RR 2.05 [1.41 to 3.99]	Cernilton improved subjective symptoms and nocturia compared with placebo. . .did not significantly improve objective measures such as peak and mean urinary flow rates. . .
				Q_{max}	2	MD 1.60 [−5.77 to 2.59]	
				PVR	2	MD −14.35 [−30.35 to 1.66]	

[a] Calculated from review data Q_{max}: peak urinary flow; AUA: American Urologic Association Symptom Index; IPSS: International Prostate Symptom Score; PVR: post-void residual urine.

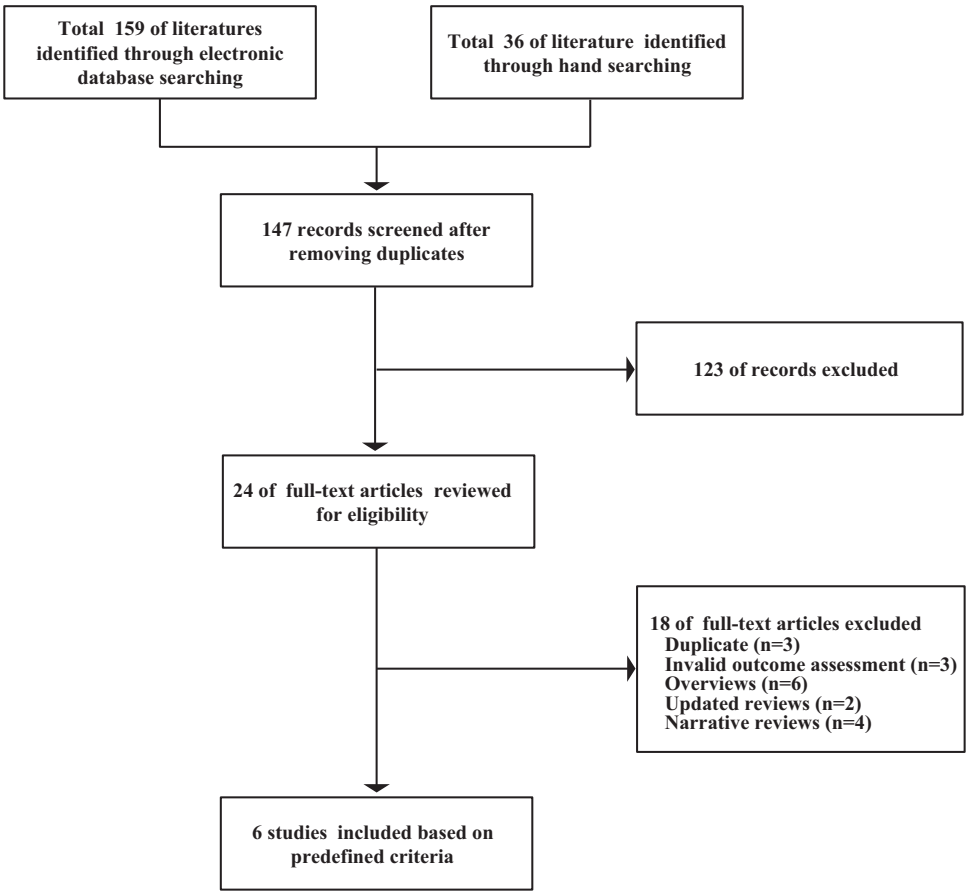

Fig. 1. Flowchart for selection of included systematic reviews.

et al. concluded that Serenoa repens did not improve urinary flow or prostate size [2]. The difference may originate from the negative results of 2 recent high-quality, large-scale, long-term follow-up clinical trials that Tacklind et al. discussed in their review [2]. However, withdrawal rates were not significantly different between Serenoa repens and the placebo group, which suggests that adverse events related to this phytotherapeutic compound are not serious (Table 1).

3.2. β-Sitosterol

β-Sitosterol is a phytotherapeutic extract mainly originating from South African star grass, which consists of phytosterols bonded with glucosides [30]. Wilt et al. reviewed the specific effects of β-sitosterol and concluded that it improved urological symptom scores (IPSS) and urodynamic measurement including Qmax and PVR [30]. In addition, the authors suggested that the adverse effects of β-sitosterol were generally mild and there was no difference in adverse event rates compared with placebo (β-sitosterol 7.8% and placebo 8.0% withdrawal rate, Table 1) [30].

3.3. Pygeum africannum

Pygeum africannum is an extract from the bark of the African prune tree [31]. Wilt et al. assessed the effects of Pygeum africannum for BPH and suggested that it improved self-rated symptoms, nocturia and PVR compared with placebo [31] (Table 1). Additionally, they reported that adverse events were generally minor in nature, i.e., infrequent gastrointestinal problems (Pygeum africannum 13% and placebo 11% withdrawal rate, Table 1) [31].

3.4. Cernilton

Cernilton is a phytotherapeutic product whose extract originates from rye grass pollen. It is composed of a water-soluble pollen fraction as well as an acetone-soluble extract fraction that contains β-sterols [32]. MacDonald et al. reviewed the specific effects of Cernilton and suggested that it improved subjective symptoms including nocturia, but no significant improvement in urodynamic measures was observed when compared with placebo [32] (Table 1). It was also reported that withdrawal rates were not significantly higher with Cernilton (4.8%) than with placebo (2.7%, $p = 0.26$, Table 1) [32].

4. Discussion

From the extensive search results, only 4 types of phytotherapeutic products were located in 6 SRs [2,8,29–32]. Serenoa repens was evaluated in 3 SRs, and the most recent review concluded that it did not deliver significant improvements in urinary tract symptoms, urinary flow or prostate size, [2] which is the opposite conclusion of the other 2 reviews [8,29]. However, β-sitosterol, Pygeum africannum and Cernilton showed significant improvements [30–32]. All of these extracts had mild and infrequent adverse events.

This overview has several strong points. First, we have summarised the scattered SRs of dietary supplements, which provides a comprehensive picture of the clinical evidence for these products. Although direct comparisons of dietary supplements were impossible, summary effect estimates suggested in this review may offer some information for the effect size of each compound. Second, we assessed the quality of the included SRs through AMSTAR

Table 3
AMSTAR checklist assessment.

AMSTAR checklist	1	2	3	4	5	6	7	8	9	10	11	Overall quality assessment
	A priori design	Duplicate extraction	Literature search comprehensive	Status of publication used criteria	Included and excluded list provided	Studies' characteristics provided	Quality assessed and documented	Quality impacted conclusions	Methods for combining appropriate	Publication bias assessed	Conflicts of interest stated	
Boyle (2004) [29]	U	U	N	U	N	Y	N	N	N	N	N	Low
Tacklind (2009) [2]	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	High
Wilt (1998) [8]	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	High
Wilt (2000) [30]	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	High
Wilt (2002) [31]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	The Highest
MacDonald (2000) [32]	U	U	Y	N	N	Y	Y	N	Y	N	Y	Medium

AMSTAR, assessment of multiple systematic reviews; Y, yes; N, no; U, unclear; AMSTAR quality assessment – the highest quality, if all 11 criteria were met; high quality, if 8–11 were met; medium quality, if 4–7 were met; low quality, 0–3 were met.

instruments, which reflect the methodological rigour of each SR. Through this qualitative evaluation method, health care providers can estimate the clinical relevance and methodological stringency of the included SRs [33].

However, there are several limitations to this overview. First, the effect size we suggested in the table cannot provide information for direct comparisons between the different compounds. As comparisons between the supplement and conventional drug therapy were also presented in the SRs, clinical trials in which different dietary supplements are evaluated together will be necessary for direct comparisons. Second, the quality of the evidence could not be assessed in this overview. Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a well-established approach for evaluating the quality of the evidence on the synthesised results [34]. Among the included SRs, only 1 review presented quality of evidence (GRADE) on each outcome in the summary of findings table [2], thus we could not assess the GRADE of all studies. Third, we excluded several reviews on the safety of dietary supplements alone [12,35]. We only extracted data on safety issues from the included SRs, which provided limited information. Another review is warranted for the evaluation of the safety of dietary supplements for BPH.

After an extensive search for SRs, only phytotherapeutic compounds were identified that met our inclusion criteria. There may be evidence of the use of other dietary supplements including vitamins, minerals, etc. that are not used as frequently as phytotherapeutics. However, as zinc has the potential risk of increasing prostate carcinoma as reported in a recent epidemiological study [35], other dietary supplements also need to be evaluated with regard to efficacy and safety through rigorous clinical studies. Second, SRs on Serenoa repens have been updated recently, and evidence of their specific effects on symptoms and urodynamic measures were not provided due to a lack of sufficiently large clinical trials [2]. However, SRs on β-sitosterol, Pygeum africannum and Cernilton have not been updated since 2000. Therefore, the efficacy data on these compounds are currently inconclusive, and updated reviews on these compounds are necessary.

In conclusion, several phytotherapeutic compounds, including β-sitosterol, Pygeum africannum and Cernilton, showed specific effects on the symptoms and urinary flow measures related to BPH, but Serenoa repens did not. In terms of safety, all included compounds had mild and infrequent adverse effects. Reviews of β-sitosterol, Pygeum africannum and Cernilton will need to be updated in the future.

Contributors

Tae-Hun Kim and Myeong Soo Lee designed the review, performed searches, appraised and selected trials, extracted data, contacted authors for additional data, carried out analysis and interpretation of the data, and drafted this report.

Hyun-Ja Lim and Myung-Sunny Kim reviewed and critiqued on the review protocol and this report, assisted in designing of the review.

Competing interest

None declared.

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References

[1] Roehrborn CG, Malice M, Cook TJ, Girman CJ. Clinical predictors of spontaneous acute urinary retention in men with luts and clinical bph: a comprehensive analysis of the pooled placebo groups of several large clinical trials. Urology 2001;58:210–6.

[2] Tacklind J, MacDonald R, Rutks I, Stanke Judith U, Wilt Timothy J. Serenoa repens for benign prostatic hyperplasia. Cochrane Database of Systematic Reviews 2009. http://dx.doi.org/10.1002/14651858.CD001423.pub2.

[3] Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. Journal of Urology 1984;132:474–9.

[4] Homma Y, Gotoh M, Yokoyama O, et al. Outline of jua clinical guidelines for benign prostatic hyperplasia. International Journal of Urology: Official Journal of the Japanese Urological Association 2011;18:741–56.

[5] McNicholas T, Kirby R. Benign prostatic hyperplasia and male lower urinary tract symptoms (luts). Clinical Evidence 2011;08:1801.

[6] Homma Y, Gotoh M, Yokoyama O, et al. Jua clinical guidelines for benign prostatic hyperplasia. International Journal of Urology 2011;18:e1–33.

[7] Office of Dietary Supplements. Dietary supplements. http://ods.Od.Nih.Gov/factsheets/dietarysupplements-healthprofessional/ [last assessed 14.06.12].

[8] Wilt TJ, Ishani A, Stark G, MacDonald R, Lau J, Mulrow C. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. Journal of the American Medical Association 1998;280:1604–9.

[9] Dreikorn K. Complementary and alternative medicine in urology. BJU International 2005;96:1177–84.

[10] Shea BJ, Grimshaw JM, Wells GA, et al. Development of amstar: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology 2007;7:10.

[11] Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the alcohol withdrawal syndrome. Cochrane Database of Systematic Reviews (Online) 2011:CD008537.

[12] Agbabiaka TB, Pittler MH, Wider B, Ernst E. Serenoa repens (saw palmetto): a systematic review of adverse events. Drug Safety: An International Journal of Medical Toxicology and Drug Experience 2009;32:637–47.

[13] Dedhia RC, McVary KT. Phytotherapy for lower urinary tract symptoms secondary to benign prostatic hyperplasia. Journal of Urology 2008;179:2119–25.

[14] Dvorkin L, Song KY. Herbs for benign prostatic hyperplasia. Annals of Pharmacotherapy 2002;36:1443–52.

[15] Fong YK, Milani S, Djavan B. Role of phytotherapy in men with lower urinary tract symptoms. Current Opinion in Urology 2005;15:45–8.

[16] Gaynor ML. Isoflavones and the prevention and treatment of prostate disease: is there a role? Cleveland Clinic Journal of Medicine 2003;70, 203–204, 206, 208–209 passim.

[17] Gerber GS, Fitzpatrick JM. The role of a lipido-sterolic extract of Serenoa repens in the management of lower urinary tract symptoms associated with benign prostatic hyperplasia. BJU International 2004;94:338–44.

[18] Ilic D, Misso M. Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: a systematic review. Maturitas 2012;72:269–76.

[19] Ishani A, MacDonald R, Nelson D, Rutks I, Wilt TJ. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. American Journal of Medicine 2000;109:654–64.

[20] Lowe FC. The role of Serenoa repens in the clinical management of lower urinary tract symptoms due to benign prostatic hyperplasia. BJU International 2004;94:338–44.

[21] Macdonald R, Tacklind JW, Rutks I, Wilt TJ. Serenoa repens monotherapy for benign prostatic hyperplasia (bph): an updated cochrane systematic review. BJU International 2012;109:1756–61.

[22] Madersbacher S, Ponholzer A, Berger I, Marszalek M. Medical management of bph: role of plant extracts. EAU-EBU Update Series 2007;51:1522–33.

[23] Sosnowska J, Balslev H. American palm ethnomedicine: a meta-analysis. Journal of Ethnobiology and Ethnomedicine 2009;5:43.

[24] Strong KM. African plum and benign prostatic hypertrophy. Journal of Herbal Pharmacotherapy 2004;4:41–6.

[25] Ulbricht C, Basch E, Bent S, et al. Evidence-based systematic review of saw palmetto by the natural standard research collaboration. Journal of the Society for Integrative Oncology 2006;4:170–86.

[26] Webber R. Benign prostatic hyperplasia. Clin Evid 2006:1213–26.

[27] Wilt T, Ishani A, Mac Donald R. Serenoa repens for benign prostatic hyperplasia. Cochrane Database of Systematic Reviews (Online) 2002:CD001423.

[28] Wilt TJ, MacDonald R, Ishani A. Beta-sitosterol for the treatment of benign prostatic hyperplasia: a systematic review. BJU International 1999;83:976–83.

[29] Boyle P, Robertson C, Lowe F, Roehrborn C. Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. BJU International 2004;93:751–6.

[30] Wilt T, Ishani A, MacDonald R, Stark G, Mulrow C, Lau J. Beta-sitosterols for benign prostatic hyperplasia. Cochrane Database of Systematic Reviews (Online) 2000:CD001043.

[31] Wilt T, Ishani A, Mac Donald R, Rutks I, Stark G. Pygeum africanum for benign prostatic hyperplasia. Cochrane Database of Systematic Reviews (Online) 2002:CD001044.

[32] MacDonald R, Ishani A, Rutks I, Wilt TJ. A systematic review of cernilton for the treatment of benign prostatic hyperplasia. BJU International 2000;85:836–41.

[33] Kung J, Chiappelli F, Cajulis OO, et al. From systematic reviews to clinical recommendations for evidence-based health care: validation of revised assessment of multiple systematic reviews (r-amstar) for grading of clinical relevance. Open Dentistry Journal 2010;4:84–91.

[34] Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.

[35] Moyad MA. Zinc for prostate disease and other conditions: a little evidence, a lot of hype, and a significant potential problem. Urologic Nursing 2004;24:49–52.