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A systematic review of herbal medicine in the clinical treatment of benign prostatic hyperplasia

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ABSTRACT

Background: The use of herbal medicine and alternative medicine is reported to be in up to 50% of prescriptions for benign prostate hyperplasia (BPH) in Europe, along with an increased global interest for holistic medicinal approaches. This study aimed to systematically review the published evidence investigating the use of herbal medicines as a treatment for BPH in clinical trials based on PRISMA guidelines.

Methods: A literature search was conducted using PubMed, Cochrane, Medline, and Scopus databases, including English language clinical trials (Jadad score of ≥ 4) that investigated herbal medicine as a sole intervention, reporting at least one of the following outcomes: International Prostate Symptom Score (IPSS); American Urological Association Symptom Index (AUASI); Maximum Urinary Flow Rate (Qmax); Post-void residual volume (PRV); Prostate volume (PV); Serum Prostatic Specific Antigen (PSA); Quality of Life (QoL) Scores.

Results: Following article screening, 28 articles were included. The most frequently studied herbs in isolation or in combination were *Serenoa repens* (54%), *Urtica dioica* (14%), *Cucurbita pepo* (14%), lycopene (14%), *Pygeum africanum* (14%) and *Linum usitatissimum* (7%). These herbal-based formulations mostly improved the symptoms associated with BPH (IPSS/AUASI, Qmax, PSA, QoL scores, PRV and PV). This review further discusses these herbs and the outcomes, with a focus on the potential mechanisms of action.

Conclusions: There are limited high quality clinical trials investigating herbal medicine on BPH, where *S. repens* is significantly more represented than other popular herbs for BPH, such as *C. pepo, U. dioica, P. africanum,* and lycopene. Although the included studies broadly found positive positive results for standardised outcomes for LUTS and urinary flow, there was great variability in the study designs requires caution in interpretation. As these herbs are supported by *in vivo* and *in vitro* studies on potential mechanisms of actions, comparison of efficacy of mono-herbal and poly-herbal approaches, standardized extracts based on identification of active constituents, as well as dosage and long-term safety studies are warrented.

Abbreviations: AUASI, American Urological Association Symptom Index; BPH, Benign Prostate Hyperplasia; CAM, Complementary and Alternative Medicine; DHT, Dihydrotestosterone; IPSS, International Prostate Symptom Score; LUTS, Lower Urinary Tract Syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRV, Post-Voiding Residual Volume; PSA, Prostate Specific Antigen; PV, Prostate Volume; QMax, Maximal Urinary Flow Rate; QoL, Quality of Life; SDG, Secoisolariciresinol Diglycoside; VEGF, Vascular Endothelial Growth Factor (VEGF).

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1. Introduction

Benign prostate hyperplasia (BPH) is a prostate adenoma characterized by the histological proliferation (hyperplasia) of stromal and epithelial cells in the transitional zone of the prostate gland (Chughtai et al., 2016; Foo, 2019). Although BPH is evident in up to 40% of men aged 40 – 50 years, prevalence increases in up to 80% of males beyond 80 years (Madersbacher et al., 2019). In 2016, 14 million men in the United States and 30 million men worldwide presented clinically with BPH (Egan, 2016).

Although the pathophysiology remains poorly understood (Madersbacher et al., 2019), associated mechanisms in the development of BPH includes age-related increase in dihydrotestosterone (DHT) (via 5α-reductase activity on testosterone), estrogen (via aromatase activity on testosterone), and prostatic cellular growth factors (Liao et al., 2012; Madersbacher et al., 2019; Vuichoud and Loughlin, 2015). Further immune and metabolic co-morbidities associated with BPH includes low grade chronic inflammation, insulin resistance, and dyslipidaemia (De Nunzio et al., 2016; Kim et al., 2016; Madersbacher et al., 2019). Clinically, BPH is closely associated with lower urinary tract syndrome (LUTS), characterized by urinary hesitancy, weak urinary flow, urinary intermittency, incomplete bladder emptying and post-terminal dribbling (Chughtai et al., 2016; Lepor, 1998). However, the relationship between LUTS and BPH is complex, and there remains insufficient evidence for a causal relationship (Lepor, 1998).

Clinical assessment of BPH is recommended to include appropriate clinical score sheet evaluation of LUTS, a digital rectal examination, serum prostate specific antigen (PSA), urinary flow parameters, as well as a urinalysis and serum creatinine (Nickel et al., 2018; Santos Dias, 2012). Validated scores sheets (questionnaires) such as the American Urological Association Symptom Index (AUASI) and the International Prostate Symptom Score (IPSS) are recommended to evaluate LUTS (Foo, 2019; Kim et al., 2016; Nakai and Nonomura, 2013). Treatment is determined by the severity of symptoms and any related complications, and includes self-management, medication, and/or surgery (Vuichoud and Loughlin, 2015). Pharmaceutical targets for BPH include 5-α-reductase inhibitors (inhibition of DHT synthesis from testosterone), aromatase inhibitors (inhibition of estrogen synthesis) and α-adrenoreceptor antagonists (muscle relaxation to relieve LUTS) (Madersbacher et al., 2019; Nicholson and Ricke, 2011). In recent years, there is a growing interest in complementary and alternative medicine (CAM) treatments for BPH, particularly the use of herbal medicines.

Herbal medicines have been used extensively through human history and pre-history to treat human disease and improve health. In the modern era, up to 50% of prescription drugs are based on isolates from medical plants (Dhami, 2013; Heinrich and Anagnostou, 2017; Kennedy and Wightman, 2011). Through a variety of secondary metabolites, herbal medicine extractions are complex compounds that work either as isolates or synergistically to modulate (patho)physiological functions (Dhami, 2013; Heinrich and Anagnostou, 2017; Roy Upton, 2015).

Importantly, the use of CAM is reported to be in up to 50% of prescriptions for BPH in Europe (Keehn et al., 2016). This is aligned with the increased global interest and demand for holistic, safe, effective and affordable medicinal approaches (Kennedy and Wightman, 2011). However, the current evidence regarding the use of herbal medicines in BPH treatment remains heterogeneous, making it a challenge to determine the type of herbal extraction or combination that are effective and safe in clinics. Therefore, the aim of this study was to conduct a systematic review to summarize the clinical evidence for the use of herbal medicine as a treatment for BPH.

2. Methods

A systematic literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The PubMed, Cochrane, Medline, and Scopus databases were searched in November 2020 to identify articles investigating the use of herbal medicine in the treatment of BPH. This study protocol was not previously registered.

The following keyword search string and combination of Boolean operators were used with minor variations for the respective databases: (“Pharmacognosy” OR “Pharmacopoeia*” OR “Phytotherap*” OR “Phytomedicine*” OR “Plant Medicine*” OR “Polyherb*” OR “Herbal Medicine*” OR “Traditional Medicine *” OR "Complementary Medicine*" OR "Alternative Medicine*" OR "Andrographis paniculata" OR "Astragalus membranaceus" OR "Camellia sinensis" OR "Centella asiatica" OR "Curcurbita" OR “Pumpkin” OR “Curcuma” OR “Gingko biloba” OR “Nigella sativa” OR "Lepidium meyenii" OR "Ginseng" OR "Panax" OR "Serenoa repens" OR "Sabal serrulata" OR "Saw palmetto" OR "Smilax" OR "Tribulus terrestris" OR “Urtica dioica” OR “Stinging Nettle” OR “Vitis vinifera” OR “Withania somnifera” OR “Ashwaganda” OR "Eurycoma longifolia" OR “Tongkat Ali” OR "Aesculus hippocastanum" OR "Escin" OR "Anthocyanin" OR "Mucuna pruriens" OR “Asparagus racemosus” OR “Chlorophytum borivillianum” OR "Curculigo orchioides" OR "Zingiber officinale" OR “Pygeum” OR “Soy” OR “Secale cereale” OR “Lycopene” OR “Lycopersicon esculentum” OR “Star Grass”) AND (“Benign Prostatic Hyperplasia” OR “BPH”). Retrieved articles were firstly screened based on the title and abstract, while the remaining articles had the full text reviewed for eligibility based on the inclusion and exclusion criteria detailed in Table 1.

Jadad scores are a commonly used tool to assess methodological quality of a trial (Berger and Alperson, 2009), with face validity, content validity, criterion validity construct validity and reproducibility (reliability) (Olivo et al., 2008). A Jadad score was assigned to each of the articles based on the reporting of the critical methodological parameters of randomization, blinding, and accountability of patients (Berger and Alperson, 2009; Jadad et al., 1996). The screening, eligibility and Jadad evaluation of articles for inclusion was conducted by two independent researchers, and any disagreement was settled by an independent researcher. Articles were included with a Jadad score equal or higher than 4 (Table 1).

Information extracted from the included articles were details of the experimental herbal intervention, the dosage and duration of the intervention, the number of participants in the experimental group, and the number of participants in the control group. Outcomes reported as intra- or intergroup statistical evaluation included IPSS or AUASI, Maximal Urinary Flow Rate (QMax), PSA, Quality of Life (QoL), Post-Voiding Residual Volume (PRV) and/or Prostate Volume (PV). These outcomes were tabulated as percentage of change, with an indication of the clinical significance.

3. Results

The literature search resulted in a total of 1561 articles retrieved. Following the removal of 326 duplicates, the remaining 1235 articles were screened based on the titles and abstracts, resulting in the further removal of 1052 non-relevant articles. Subsequently, 183 full text articles were reviewed for eligibility based on the inclusion/exclusion criteria (Table 1). Here, 155 articles were excluded for the following

Table 1
Inclusion and exclusion criteria.

Inclusions	Exclusions
Clinical trials in patients diagnosed with BPH	Prospective, observational and case report studies
Use of internal herbal medicine as intervention (individual or combination)	Animal, *in vitro* and *in silico* studies
Jadad score $\geq$ 4	Meta-analysis, systematic reviews, conference abstracts
Articles reporting at least one clinical outcome of interest: IPSS; AUASI; Qmax; PRV; PV; PSA; QoL	Non-English Studies

reasons: Jadad score < 4 ($n = 112$), inadequate control ($n = 13$), lack of internal herbal medicine or BPH diagnosis ($n = 24$), lack of relevant outcomes reported ($n = 3$), or the full text was not available ($n = 3$). The final number of articles included in the systematic review is 28. This process is summarized in Fig. 1, while the description of the articles is provided in Table 2.

The herbal products used for the interventions in the included articles were classified as registered (46%), polyherbal (29%), and monoherbal (25%). The most frequently studied herbs or herbal components were *Serenoa repens* (54%), followed by *Urtica dioica* (14%), *Cucurbita pepo* (14%), lycopene (14%), *Pygeum africanum* (14%) and *Linum usitatissimum* (7%) (Fig. 2). Although articles reported variable outcomes of interest, 86% of the articles reported IPSS/AUASI, while other outcomes included QMax (75%), PSA (57%), QoL (54%), PRV (50%) and PV (36%).

Out of the 15 articles (54%) investigating *S. repens* as intervention either in isolation ($n = 8$) or in combination with other herbs/components ($n = 7$), 13 articles reported an improvement in IPSS/AUASI (Barry et al., 2011; Bent et al., 2006; Braeckman et al., 1997; Coulson et al., 2013; Giannakopoulos et al., 2002; Hong et al., 2009; Marks et al., 2000; Morgia et al., 2017; Preuss et al., 2001; Shi et al., 2008; Sudeep et al., 2020; Willetts et al., 2003; Ye et al., 2019), although this was not statistically significant in 4 of these articles (Barry et al., 2011; Bent et al., 2006; Marks et al., 2000; Willetts et al., 2003). Similarly, an improvement of Qmax was reported in 12 articles (Barry et al., 2011; Bent et al., 2006; Braeckman et al., 1997; Giannakopoulos et al., 2002; Hong et al., 2009; Marks et al., 2000; Morgia et al., 2017; Preuss et al., 2001; Shi et al., 2008; Sudeep et al., 2020; Willetts et al., 2003; Ye et al., 2019), although it was not significant in 6 of these articles (Barry et al., 2011; Bent et al., 2006; Marks et al., 2000; Morgia et al., 2017; Preuss et al., 2001; Willetts et al., 2003). PSA, analyzed in 10 articles, was reportedly improved: $P<0.05$ ($n = 3$); $P>0.05$ ($n = 6$); no p-value provided ($n = 1$,), along with 6 articles reporting improvement in QoL scores: $P<0.05$ ($n = 3$); $P>0.05$ ($n = 2$); no p-value provided ($n = 1$) (Barry et al., 2011; Bent et al., 2006; Braeckman et al., 1997; Coulson et al., 2013; Giannakopoulos et al., 2002; Hong et al., 2009; Marks et al., 2000; Morgia et al., 2017; Preuss et al., 2001; Shi et al., 2008; Sudeep et al., 2020; Willetts et al., 2003; Ye et al., 2019). Improvement was reported for PRV in 3 articles: $P<0.05$ ($n = 1$); $P>0.05$ ($n = 1$); no p-value provided ($n = 1$) (Bent et al., 2006; Braeckman et al., 1997; Sudeep et al., 2020) and PV in 5 articles: $P<0.05$ ($n = 1$); $P>0.05$ ($n = 3$) no p-value provided ($n = 1$) (Bent et al., 2006; Braeckman et al., 1997; Hong et al., 2009; Marks et al., 2000; Ye et al., 2019).

Out of 4 articles (14%) investigating *U. dioica* as intervention either

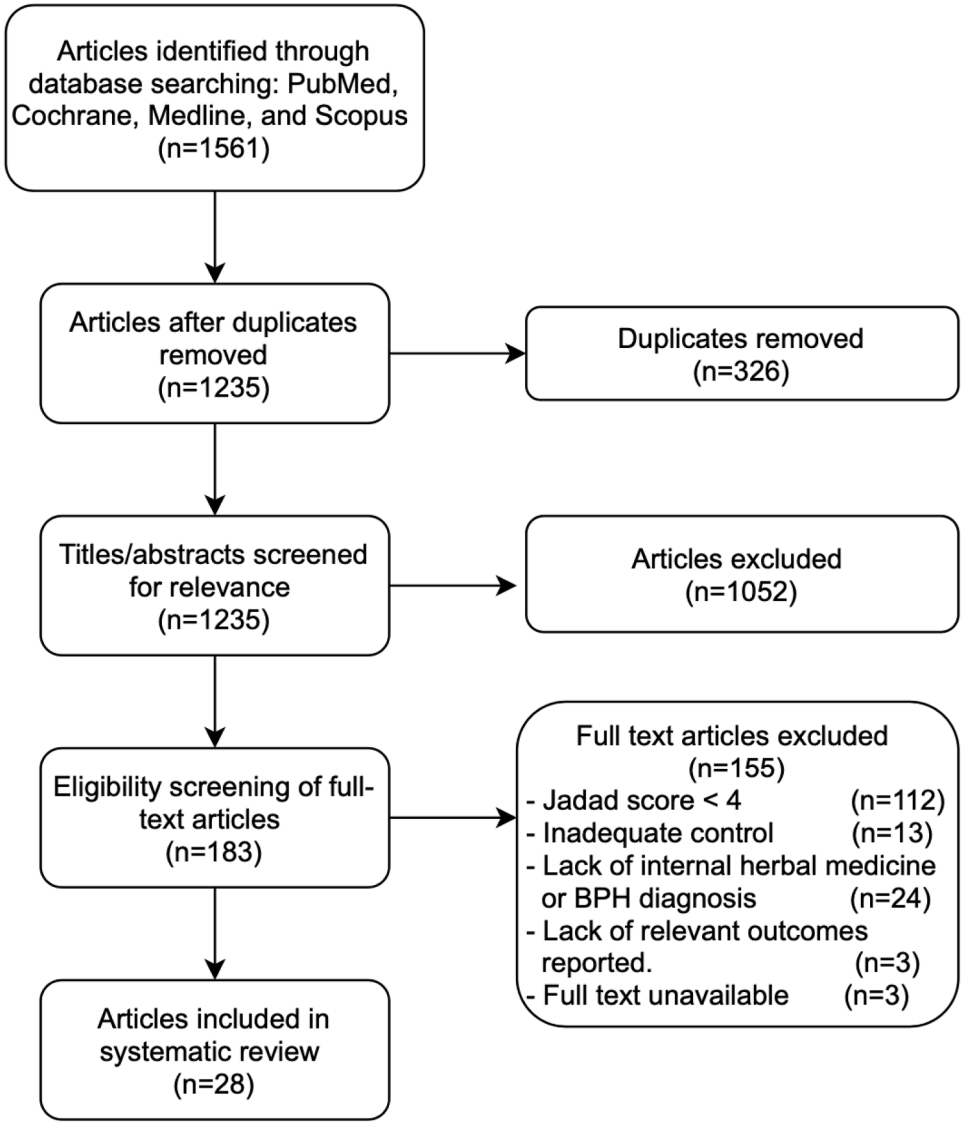

Fig. 1. Flow diagram of literature search and selection of articles that were included in the systematic review.

Table 2
Herbal medicines clinically investigated in the treatment of benign prostatic hyperplasia reporting at least one outcome: IPSS/AUASI, Qmax, PSA, QoL, PRV or PV. Intragroup comparison was performed between baseline and end-point of treatment, and is reported as percentage. Intergroup comparison was performed between the experimental and control groups end-point of treatment.

Reference	*Experimental Exposure*	*Dosage and Duration*	*Control*	*Outcomes (Intragroup Percentages and Intergroup P-Value)* IPSS/AUASI	Qmax	PSA	QOL	PRV	PV
Coulson, 2013	**ProstateEZE MAX** *C. pepo* seed oil (160 mg); *E. parviflorum* (500 mg); Lycopene (2.1 mg); *P. Africanum* (15 g); *S. repens* (660 mg)	Daily for 12 weeks (n = 32)	Placebo (n = 25)	Experimental: 36% ↓* Placebo: 8% ↓ ***P* < 0.05**	–	Experimental: 3.6% ↓ Placebo: 21.2% ↑ **NA**	–	–	–
Carbin, 1990	**Curbicin** *C.pepo* seeds (80 mg); *S. repens* (80 mg)	Daily for 12 weeks (n = 26)	Placebo (n = 27)	–	Experimental: 44.8% ↑* Placebo: 4.5% ↑ ***P* < 0.001**	–	–	Experimental: 31.5% ↓* Placebo: 5.96% ↓ ***P* < 0.01**	–
Vahlensieck, 2014	**Granu Fink (A)** *C. pepo* seed extract **Pumpkin Seeds (B)** *C. pepo* seeds	A. 1000 mg daily for 52 weeks (n = 481) B. 10 g daily for 52 weeks (n = 475)	Placebo (n = 475)	Experimental: A. 28.8% ↓ ***P* < 0.72 NS** B. 36.3% ↓* ***P* < 0.02** Placebo: 27.3% ↓	Experimental: A. 45.1% ↑ B. 49.1% ↑ Placebo: 41.7% ↑ **NA**	Experimental: A. 5.8% ↑ B. 11.1% ↑ Placebo: 10.5% ↑ **NA**	Experimental: A. 33.4% ↓ B. 36.0% ↓ Placebo: 29.2%% ↓ **NA**	Experimental: A. 5.3% ↓ B. 7.3% ↓ Placebo: 3.4% ↑ **NA**	Experimental: A. 7.9% ↑ B. 9.4% ↑ Placebo: 8.9% ↑ **NA**
Hong, 2009	***S. repens* Oil (SPO) *C. pepo* Oil (PSO)**	A, B, C /daily for 52 weeks A. SPO 320 mg (n = 13) B. PSO 320 mg (n = 16) C. 320 mg SPO + 320 mg PSO (n = 11)	Placebo (n = 7)	Experimental: A. 58.0% ↓* B. 50.3% ↓* C. 75.3% ↓* Placebo: No Change ***P* < 0.05**	Experimental: A. 51.4% ↑* B. 14.9% ↑* C. 5.5% ↑ Placebo: 22.1% ↓ ***P* < 0.05**	Experimental: A. 12.5% ↑ B. 8.3% ↓ C. 41.7% ↓* Placebo: 10.0% ↑ ***P* < 0.05**	Experimental: A. 38.9% ↓* B. 40.5% ↓* C. 57.9% ↓* Placebo: 12.5% ↓ ***P* < 0.05**	–	Experimental: A. 5.0% ↓ B. 14.7% ↓ C. 8.4% ↓ Placebo: 0.9% ↑ **NA**
Sudeep, 2020	**β-sitosterol Enriched *S.repens* Oil (VISPO) *S.repens* Oil (SPO)**	1000 mg daily for 12 weeks A. VISPO (n = 33) B. SPO (n = 33)	Placebo (n = 33)	Experimental: A. 15.9% ↓* B. 4.92% ↓ Placebo: 3.65% ↑ ***P* < 0.001**	Experimental: A. 20.4% ↑* B. 3.9% ↑ Placebo: 3.9% ↓ ***P* < 0.001**	Experimental: A. 2.5% ↓* B. 6.8% ↑ Placebo: 6.4% ↑ ***P* < 0.0008**	–	Experimental: A. 11.3% ↓* B. 1.71 ↓ Placebo: 0.97% ↑ ***P* < 0.001**	–
Marks, 2000	**Saw palmetto HB** *S. repens* lipoidal extract (160 mg); *U.dioica* (80 mg); Lemon bioflavonoid extract (160 mg); β-carotene (190 mg)	Daily for 48 weeks (n = 21)	Placebo (n = 23)	Experimental: 30.3% ↓ Placebo 18.7% ↓ **NS**	Experimental 25.3%↑ Placebo: 5.2% ↑ **NS**	Experimental 4.9% ↑ Placebo: 2.7% ↑ **NS**	–	–	Experimental: 5.8%↑ Placebo: 0.4%↑ **NS**
Preuss, 2001	**Cernitin, saw palmetto, β-sitosterol, vitamin E** Cernitin (378 mg); *S. repens* (286 mg); Vitamin E (100 IU)	Daily for 12 weeks (n = 70)	Placebo (n = 69)	Experimental: 32.7% ↓* Placebo: 18.3% ↓ ***P* = 0.009**	Experimental: 5.4%↑ Placebo: 8.3%↑ **NS**	Experimental: No change Placebo: 36.8% ↑ **NS**	–	–	–
Vidlar, 2016	**Flowens** *V. oxycoccus*	A. 500 mg daily (n = 40) B. 250 mg daily (n = 43)	Placebo (n = 41)	Experimental: A. 43.6% ↓* ***P* < 0.001** B 32.0% ↓* ***P* = 0.05** Placebo: 16.5% ↓	Experimental: A. 11.3% ↑ B. 4.4% ↑ Placebo: 0.45% ↓	–	Experimental: A. 9.5% ↓ B. 13.0% ↓ Placebo: 16.7% ↓	Experimental: A. 44.4% ↓* ***P* = 0.027** B 14.5% ↓Placebo: 4.0% ↓	–
Zegarra, 2007	***B. orellana***	750 mg daily for 52 weeks (n = 68)	Placebo (n = 68)	–	Experimental: 29.2%↑ Placebo: 34.4%↑ ***P* = 0.07**	–	–	Experimental: 24.4%↑ Placebo: 55.4% ↑ ***P* = 0.33 NS**	–
Rao, 2019	**Testofen** *T. foenum-graceum*	2 × 300 mg daily for 12 weeks (n = 42)	Placebo (n = 42)	Experimental: 22.0% ↓ Placebo: 25.4% ↓ `**NS**	–	Experimental: 1.8% ↓ Placebo: 1.8% ↑ **NS**	Experimental: 20.5% ↓ Placebo: 10.5% ↓ **NS**	–	–
Braeckman, 1997	**Prostaserene** *S. repens*	320 mg Prostaserene daily for 52 weeks (n = 65)	160 mg Prostaserene daily for 12 months (n = 67)	Experimental: 61.2% ↓* Control: 59.5% ↓* ***P* < 0.0001**	Experimental: 21.4% ↑* Control: 23.8% ↑* ***P* < 0.0001**	–	Experimental: 72.0% ↓ Control: 68.0% ↓ **NS**	Experimental: 24.8% ↓* Control: 6.2% ↓* ***P* < 0.0001**	Experimental: 15.2% ↓* Control: 10.8% ↓* ***P* < 0.0001**
Shi, 2008	**Prostaplex** *S. repens* (300 mg); Curcumin (100 mg); Pollen (100 mg); β-Carotene (25,000 IU);	Two capsules daily for 12 weeks (n = 46)	Placebo (n = 48)	Experimental: 12.0% ↓* Placebo: 2.3% ↓ ***P* < 0.001**	Experimental: 13.5% ↑* Placebo: 8.92% ↓ ***P* < 0.001**	Experimental: 0.44% ↑ Placebo: 12.5% ↓ **NS**	–	–	–

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Table 2 (*continued*)

Reference	*Experimental Exposure*	*Dosage and Duration*	*Control*	*Outcomes (Intragroup Percentages and Intergroup P-Value)* IPSS/AUASI	Qmax	PSA	QOL	PRV	PV
	Vitamin C (1000 mg); Vitamin D (4000 IU); Zinc (15 mg); Alfalfa Leaf Concentrate (250 mg); Buchu leaf (150 mg); Corn silk (150 mg)								
Morgia, 2014	**Profluss** *S.repens* (320 mg); Lycopene (5 mg); Selenium (50 mcg)	Daily for 26 weeks (n = 54)	Placebo (n = 54)	–	–	Experimental: 53.2% ↓* Placebo: 52.2% ↓ ***P* < 0.001**	–	–	–
Morgia, 2017	**Profluss** *S.repens* (320 mg); Lycopene (5 mg); Selenium (50 mcg)	Daily for 12 weeks (n = 45)	Placebo (n = 45)	Experimental: 10.0% ↓* Placebo: No significant decrease ***P* < 0.05**	Experimental: 12.5% ↑ Placebo: No significant increase **NS**	–	–	–	–
Giannakopoulos, 2002	**Liberprosta** *S. repens* lipidosterolic extract	Daily for 26 weeks (n = 50)	320 mg daily for 26 weeks (n = 50)	Experimental: 43.13% ↓* Control: 37.5% ↓* ***P* < 0.001**	Experimental: 49.8% ↑* Control: 30.1% ↑* ***P* < 0.05**	–	Experimental: 18.5% ↓* Control: 15.2% ↓* ***P* < 0.05**	Experimental: 50.1% ↓* Control: 38.9% ↓* ***P* < 0.05**	–
Barry, 2011	***S.repens* extract**	320 mg daily for 24 weeks, 640 mg daily for 24 weeks, then 960 mg for 24 weeks for a total of 72 weeks (n = 183)	Placebo (n = 186)	Experimental: 15.3% ↓ Placebo: 20.4% ↓ **NS**	Experimental: 1.3% ↓ Placebo: 5.3% ↓ **NS**	Experimental: 9.5% ↑ Control: 7.3% ↑ **NS**	Experimental: 18.9% ↓ Placebo: 23.6% ↓ **NA**	Experimental: 18.7% ↑ Control: 2.3% ↑ **NS**	–
Bent, 2006	***S.repens* extract**	320 mg daily for 14 months + 12 months of follow-up (n = 112)	Placebo (n = 113)	Experimental: 4.3% ↓ Placebo: 4.8% ↓ **NS**	Experimental: 3.7% ↑ Placebo: 0.09% ↓ **NS**	Experimental: 0.28% ↓ Placebo: 9.4% ↑ **NS**	–	Experimental: 17.6% ↑ Placebo: 22.0% ↑ **NA**	Experimental: 10.8% ↑ Placebo: 14.7% ↑ **NS**
Willetts, 2003	***S.repens* extract**	320 mg daily for 12 weeks (n = 50)	Placebo (n = 50)	**NS**	Experimental: 13.5% ↑ Control: 39.3% ↑ **NS**	–	Experimental: 3.7% ↓ Placebo: 17.3% ↓ **NS**	–	–
Ye, 2019	***S.repens* extract**	320 mg daily for 24 weeks (n = 159)	Placebo (n = 166)	Experimental: 30.4% ↓* Placebo: 11.3% ↓ ***P* < 0.0001**	Experimental: 36.3% ↑* Placebo: 6.86%↑ ***P* = 0.0008**	Experimental: 9.95% ↓ Placebo: 0.47% ↑ **NS**	Experimental: 28.3% ↑* Placebo: 16.2% ↑ ***P* = 0.001**	–	Experimental: 2.08% ↑ Placebo: 0.83% ↑ **NS**
Melo, 2002	***P. africanum* and *U.dioica*** *P. africanum* (25 mg), *U. dioica* (300 mg)	325 mg daily for 48 weeks (n = 27)	Placebo (n = 22)	Experimental: 21.6% ↓ Placebo: 19.7% ↓ **NS**	Experimental: 17.2% ↑ Placebo: 13.3% ↑ **NS**	–	Experimental: 12.5% ↓ Placebo: 5.7% ↑ **NS**	–	–
Krzeski, 1993	***U. dioica* root and *P. africanum* bark extract** *U. dioica* (300 mg); *P. africanum* (25 mg)	Full Dose: 650 mg daily for 8 weeks (n = 72)	Control: Half Dose (n = 72)	–	Experimental: 22.2% ↑ **NS** Half-Dose: 20.0% ↑ **NS**	–	–	Experimental: 66.0% ↓ **NS** Half-Dose: 69.8% ↓* ***P* = 0.0004**	–
Chatelain, 1999	***P.africanum* Extract**	100 mg daily for 8 weeks (n = 108)	50 mg twice daily for 8 weeks (n = 101)	Experimental: 37.6% ↓* Control: 34.6% ↓ ***P* = 0.004**	Experimental: 18.5% ↑ Control: 16.0% ↑ **NA**	–	Experimental: 27.7% ↓ Control: 27.5% ↓ **NA**	Experimental: 6.25% ↑ Control: 0.60% ↑ **NA**	–
Karami, 2020	**Urtidin** *U. dioica* extract; Polysaccharides; Phytosterols; Flavonoids; Triterpenic acids	450 mg daily for 12 weeks +12 weeks follow-up (n = 28)	Placebo (n = 28)	Experimental: 25.4% ↓* Placebo: 7.8% ↓ ***P* < 0.001**	–	Experimental: 17.5% ↓ Placebo: 12.5% ↓ ***P* = 0.091 NS**	–	–	–
Simons, 2015	**LinumLife EXTRA** L. *usitatissimum* extract with 100 mg active component secoisolariciresinol diglucoside (SDG)	Low Dose Active (LDA):100 mg SDG /daily + 1 placebo capsule for 8 weeks (n = 24) High Dose Active (HDA): 200 mg SDG /daily for 8 weeks (n = 25)	Placebo (n = 26)	Experimental: LDA 56.3% ↓* ***P* < 0.001** HDA 56.1% ↓* ***P* < 0.01** Placebo: 56.0% ↓* ***P* < 0.001**	–	–	–	Experimental: LDA 16.1% ↑ HDA 12.96% ↓* ***P* < 0.001** Placebo: 27.4% ↓* ***P* < 0.05**	Experimental: LDA 9.08% ↑ HDA 12.96% ↓* ***P* < 0.05** Placebo: 3.43% ↓

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Table 2 (*continued*)

Reference	*Experimental Exposure*	*Dosage and Duration*	*Control*	*Outcomes (Intragroup Percentages and Intergroup P-Value)* IPSS/AUASI	Qmax	PSA	QOL	PRV	PV
Zhang, 2008	**Beneflax** L.usitatissimum lignan extract with either 0, 75 or 150 mg SDG per tablet	A. 300 mg SDG /daily for 16 weeks (n = 29) B. 600 mg SDG /daily for 16 weeks (n = 29)	Placebo (n = 29)	Experimental: A. 38.1% ↓* B. 35.8% ↓* Placebo: 20.1% ↓ ***P* < 0.01**	Experimental: A. 16.1% ↑ B.25.0% ↑* ***P* < 0.01** Placebo: 3.8% ↑	–	Experimental: A. 36.4% ↓* B. 43.8% ↓* Placebo: 18.7% ↓ ***P* < 0.001**	Experimental: A. 13.6% ↓ B. 27.4% ↓ Placebo: 19.1% ↓ **NS**	Experimental: A. 15.1% ↓* B. 14.1% ↓* Placebo: 13.1% ↓* ***P* < 0.01**
Schwarz, 2008	**Lycopene**	15 mg for 48 weeks (n = 19)	Placebo (n = 18)	Experimental: 14.2% ↓* ***P* < 0.01** Placebo: 18.5% ↓ * ***P* < 0.05**	–	Experimental: 11.3% ↓* ***P* < 0.05** Placebo: 0.58% ↓	Experimental: No change Placebo: 22.2% ↑ **NS**	–	–
Vostalova, 2013	**Selenium-Silymarin** L-selenomethionin (80 mcg); Silymarin (190 mg)	Daily for 48 weeks (n = 26)	Placebo (n = 29)	Experimental: 41.3% ↓* Placebo: 0.49% ↑ ***P* < 0.05**	Experimental: 22.9%↑* Placebo: 5.3%↓ ***P* < 0.05**	Experimental: 1.28 ↑ Placebo: 12.5% ↑ **NS**	Experimental: 7.7% ↑* Placebo: 10% ↑ ***P* < 0.05**	–	Experimental: 6.3% ↑* Placebo: 20.4% ↓ ***P* < 0.05**
Beiraghdar, 2017	**P. alke-kengi, E.amoenum V. odorata extracts hydro-alcoholic solution** *P. alke-kengi* 1.5% *E. amoenum* 1% *V. odorata* 1.5%	2 mL /daily for 2 weeks (n = 57)	Placebo (n = 29)	Experimental: 50.8% ↓* Placebo: 25.2% ↓ ***P* = 0.001**	–	–	Experimental: 34.2% ↓* Placebo: 21.5% ↓ ***P* = 0.001**	Experimental: 28.1% ↓* Placebo: 35.2% ↓ ***P* = 0.001**	Experimental: 16.9% ↓* Placebo: 2.9% ↓ ***P* = 0.001**

* = intergroup change is statistically significant ($P < 0.05$) between the experimental and control groups with p-value provided.
NS = Not statistically significant between the experimental and control groups.
NA = p-value is not calculated and provided.
IPSS = International Prostate Symptom Score; AUASI = American Urological Association Symptom Index; LUTS = lower urinary tract symptoms; Qmax = maximum urinary flow rate; PRV = post-void residual volume; PV = prostate volume; PSA = Serum Prostatic Specific Antigen; QoL = quality of life scores.

in isolation ($n = 1$) or in combination with other herbs/components ($n = 3$), IPPS/AUASI was improved in 3 articles: $P<0.05$ ($n = 1$); $P>0.05$ ($n = 2$) (Karami et al., 2020; Marks et al., 2000; Melo et al., 2002), and Qmax non-significantly improved in 3 articles: $P>0.05$ (Krzeski et al., 1993; Marks et al., 2000; Melo et al., 2002). PSA was non-significantly improved in 2 articles: $P>0.05$ (Karami et al., 2020; Marks et al., 2000), PVR significantly improved in 1 article: $P<0.05$ (Krzeski et al., 1993), and QoL non-significantly improved in 1 article; $P>0.05$ (Melo et al., 2002).

Of the 4 articles (14%) investigating *C. pepo* as intervention either in isolation ($n = 2$) or in combination with other herbs/components ($n = 2$), IPSS/AUASI was significantly improved in 3 articles; $P<0.05$ (Coulson et al., 2013; Hong et al., 2009; Vahlensieck et al., 2015), and Qmax improved in 3 articles: $P<0.05$ ($n = 2$); p-value not provided ($n = 1$) (Carbin et al., 1990; Hong et al., 2009; Vahlensieck et al., 2015). PSA improved in 2 articles: $P<0.05$ ($n = 1$); p-value not provided ($n = 1$) (Coulson et al., 2013; Hong et al., 2009). QoL scores improved: $P<0.05$ ($n = 1$); p-value not provided ($n = 1$), PRV improved $P<0.05$ ($n = 1$); p-value not provided ($n = 1$), and PV improved: p-value not provided ($n = 2$) (Carbin et al., 1990; Coulson et al., 2013; Vahlensieck et al., 2015).

A total of 4 articles (14%) investigating the plant derived antioxidant Lycopene as an intervention were included, from which one study was with Lycopene in isolation ($n = 1$) and three others were in combination with other herbs/components ($n = 3$) (Coulson et al., 2013; Morgia et al., 2017, 2014; Schwarz et al., 2008). When used as the sole treatment, lycopene significantly improved IPSS ($P<0.01$) and Qmax ($P<0.005$) (Schwarz et al., 2008). Profluss (containing lycopene in combination with *S. repens*), was used as treatment in 2 articles, which alternatively reported an improvement of either IPSS/AUASI: $P<0.05$ ($n = 1$), Qmax; $P>0.05$ ($n = 1$) or PSA; $P<0.05$ ($n = 1$) (Morgia et al., 2017, 2014). ProstateEZE MAX (containing lycopene in combination with *C. pepo, P. africana, and S. repens*), was used as treatment in 1 article, reporting improved IPSS/AUASI ($P<0.05$) and PSA (p-value not provided) (Coulson et al., 2013).

P. africanum was used as an intervention in 4 out of the 28 (14%) included articles, either individually ($n = 1$) and in combination with other herbs ($n = 3$) (Chatelain et al., 1999; Coulson et al., 2013; Krzeski et al., 1993; Melo et al., 2002). As a sole intervention, improved outcomes included IPSS/AUASI; $P = 0.004$ ($n = 1$), Qmax; p-value not provided ($n = 1$), QoL; p-value not provided ($n = 1$), and PRV; p-value not provided ($n = 1$) (Chatelain et al., 1999). The combination treatment of *P. africanum* with *U. dioica* improved PRV; $P = 0.004$ ($n = 1$), IPSS (p-value not provided), Qmax (p-value not provided), and QoL (p-value not provided) (Krzeski et al., 1993; Melo et al., 2002). ProstateEZE MAX (containing *P. africana* in combination with *C. pepo, S. repens*, and lycopene) showed a significant improvement of IPSS/AUASI ($P<0.05$) and PSA (p-value not provided) (Coulson et al., 2013).

In the 2 articles (7%) investigating L.*usitatissmum* as registered products (*i.e.* LinumLife EXTRA and Beneflax), significant improvements of IPSS ($n = 2$; $P<0.001$, $P<0.01$, respectively) and PV ($n = 2$; $P<0.05$, $P<0.01$, respectively) were reported in both articles (Simons et al., 2015; Zhang et al., 2008). Additional outcomes that improved were Qmax; $P<0.01$ ($n = 1$), QoL; $P<0.001$ ($n = 1$), and PRV; $P<0.001$ ($n = 1$); NS ($n = 1$).

4. Discussion

BPH is considered a chronic pathology that requires long-term treatment, where common pharmaceutical interventions such as 5α-reductase inhibitors and alpha-blockers are associated with adverse events (Kim et al., 2012). Therefore, effective, safe and affordable herbal medicines for long term management required investigation and development (Kim et al., 2012). Although the intervention used in the included articles are heterogenous, the result of this review suggests that herbal preparations from plants such as *S. repens, P. africanum, C. pepo, U. dioica,* L. *usitatissmum* and the plant extract lycopene can be promising

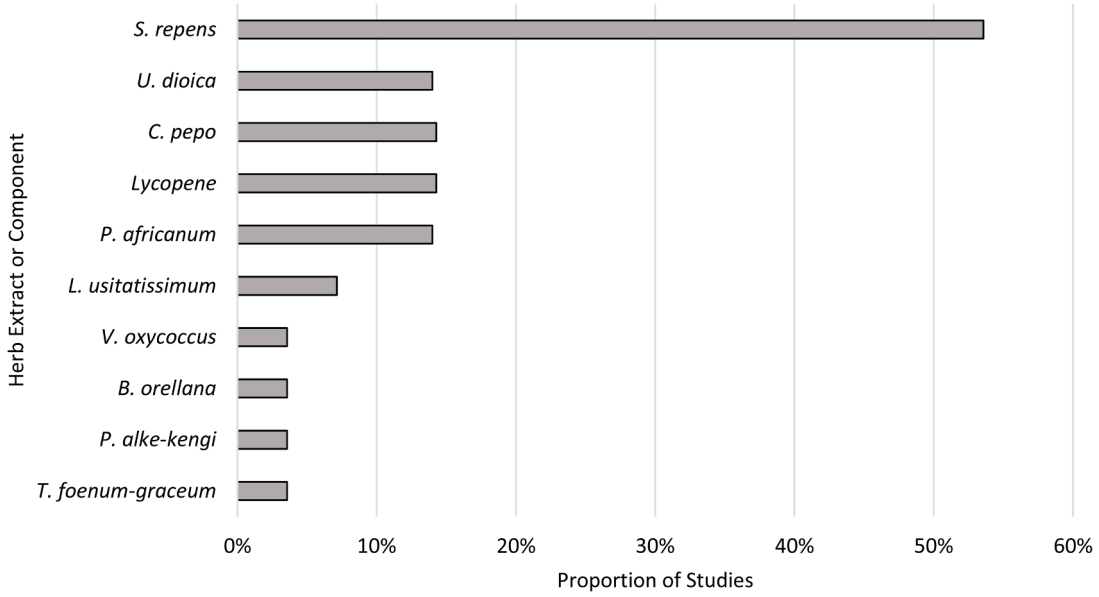

Fig. 2. Proportion of studies ($n = 28$) representing different herb extracts used as therapeutic intervention either alone or in combination.

treatments for BPH as a single herb or in combination. This agrees with the findings of previous reviews, where plant extractions from *S. repens, P. africanum, C. pepo* and *U. dioica* were used for BPH in clinical and pre-clinical articles (Azimi et al., 2012; Cicero et al., 2019; Dedhia and McVary, 2008; Kim et al., 2012).

4.1. *Serenoa repens*

S. repens, commonly known as saw palmetto, is part of the Arecaceae palm family and native to the southern regions of North America (Chua et al., 2014). In agreement with previous reports (Azimi et al., 2012; Cicero et al., 2019; Dedhia and McVary, 2008; Kim et al., 2012), *S. repens* was found to be the most widely used plant for BPH in this review. The efficacy of *S. repens* as the sole intervention for BPH was investigated in 8 articles (Barry et al., 2011; Bent et al., 2006; Braeckman et al., 1997; Giannakopoulos et al., 2002; Hong et al., 2009; Sudeep et al., 2020; Willetts et al., 2003; Ye et al., 2019), which mostly reported an improvement of IPSS/AUASI and Qmax (Braeckman et al., 1997; Giannakopoulos et al., 2002; Hong et al., 2009; Sudeep et al., 2020; Ye et al., 2019), along with PSA (Hong et al., 2009; Sudeep et al., 2020), QoL scores (Giannakopoulos et al., 2002; Hong et al., 2009; Ye et al., 2019), PRV (Braeckman et al., 1997; Giannakopoulos et al., 2002; Sudeep et al., 2020) and PV (Braeckman et al., 1997; Ye et al., 2019). This is further supported by positive outcomes in studies where *S. repens* was used as a polyherbal formulae (Carbin et al., 1990; Coulson et al., 2013; Hong et al., 2009; Marks et al., 2000; Morgia et al., 2017, 2014; Preuss et al., 2001; Shi et al., 2008).

These findings suggest that *S. repens* may be of benefit in BPH. This agrees with Cochrane reviews published in 2002 that reported *S. repens* improved mild-to-moderate LUTS and urinary flow parameters in a manner that was comparable to finasteride, a 5-alpha reductase inhibitor (preventing the conversion of testosterone to DHT), that is used in the treatment of BPH (Wilt et al., 2002). Furthermore, a 2004 meta-analysis on Permoxion (*S. Repens*) reported a significant improvement in IPSS, peak flow rate and nocturia compared to placebo (Boyle et al., 2004). However, updated reviews in 2009 (Tacklind et al., 2009) and 2012 (MacDonald et al., 2012; Nilsen et al., 2012) suggested that the herb did not significantly improve LUTS, urinary flow, nocturia or reduce prostate size compared to placebo. Although MacDonald (2012) reported that *S. repens* does not improve LUTS or Qmax compared with placebo in men with BPH at double and triple the usual dose, this was based on a meta-analysis including only 3 RCTs (MacDonald et al., 2012). This excluded studies included in this systematic review, and more recent RCTs, suggesting a positive impact on IPSS and Qmax (Giannakopoulos et al., 2002; Hong et al., 2009; Sudeep et al., 2020; Ye et al., 2019).

Extracts from the saw palmetto are commonly derived from the berries of the dwarf palm, and are used to primarily produce lipidosterolic extractions, saw palmetto oil, and carbon dioxide extractions of the herb for treatment (Geavlete et al., 2011). Mechanisms of action attributed to *S. repens* include 5α-reductase inhibitor (antiandrogen) and aromatase inhibitor (antiestrogen) activity, modulation of prolactin signaling, reduction of inflammation (including through lipo- and cyclooxygenase inhibition) and oxidative stress, inhibition of cellular proliferation and upregulation of apoptosis (Buck, 2004; Geavlete et al., 2011; Habib, 2009). LUTS may be improved by *S. repens* through smooth muscle relaxation (Chua et al., 2014) and the modulation of various receptors, including α 1-adrenoceptors, muscarinic cholinoceptors and vanilloid receptors (Suzuki et al., 2009). There were no severe adverse effects reported in any of the articles, confirming that *S. repens* is well-tolerated and safe (Suzuki et al., 2009).

4.2. *Urtica dioica*

U. dioica, commonly known as stinging nettle, is part of the Urticaceae family and is typically native to Asia (Joshi et al., 2014). It has been used to treat BPH due to its biologically active chemical constituents that include polyphenols, flavonoids, fatty acids (palmitic, cis-9,12-linoleic and α-linoleic acid), sterols (β-sitosterol), coumarin (scopoletin), carotenes, ascorbic acid, tocopherols and isolectins (*U. dioica* agglutinine) (Esposito et al., 2019; Ibrahim et al., 2018; Joshi et al., 2014). Although considered a common herb used and investigated in BPH (Azimi et al., 2012; Cicero et al., 2019; Dedhia and McVary, 2008; Kim et al., 2012), the results of this systematic review showed that *U. dioica* was investigated in only 3 articles. This may be due to the specific outcomes used for article inclusion and the Jadad screening used to include only high-quality trials. Furthermore, its efficacy was investigated as a single herb in only one included article where the product Urtidin lead to a significant improvement of IPSS, and an insignificant improvement of PSA (Karami et al., 2020). The remaining 2 articles investigated the efficacy of *U. dioica* in combination with *P. africanum,* where both articles reported insignificant improvement of Qmax (Krzeski et al., 1993;

Melo et al., 2002), IPSS and QoL (Melo et al., 2002). Krzeski et al. reported significant improvement in PRV with a half-dose, while patients receiving a full dose showed insignificant improvement (Krzeski et al., 1993). This agrees with previous articles, where *U. doica* was shown to be more effective when combined with *P. africanum* (Wilt et al., 2000b).

The aqueous extract of the entire plant has been shown to have diuretic, anti-inflammatory, antioxidant, and 5α-reductase inhibitor properties, as well as antiproliferative and anticancer activities (Joshi et al., 2014). Extractions from the root show numerous mechanisms, including inhibition of cell proliferation, modulation of SHBG and aromatase expression, modulation of epidermal growth factors and modulation of prostate steroid membrane receptors. These are all involved in reducing prostatic growth. However, there is less evidence for 5α-reductase and androgen receptor modulation from the plant (Chrubasik et al., 2007). The extractions form the leaves show evidence for immunomodulation in pre-clinical (animal) studies (Chrubasik et al., 2007; Hryb et al., 1995; Nahata and Dixit, 2012). In rats, *U. dioica* inhibits the cellular proliferation and prostatic hyperplasia induced by testosterone, more specifically in the anterior and ventral lobes (Reza Moradi et al., 2015). Furthermore, lipophilic extractions, particularly sterols from the root, inhibit Na^{+}-K^{+}-ATPase activity, which further reduced prostatic hyperplasia (Hirano et al., 1994). β-sitosterol as an important constituent of *U. dioica* and other plant species has shown benefit in the improvement of IPSS, peak urinary flow and mean residual urinary volume, with no effect on prostate size (Berges et al., 1995; Wilt et al., 2000a; Wilt et al., 1999).

4.3. Curcubita pepo

C. pepo, commonly known as field pumpkin, is part of the Cucurbitaceae family and is native to North America (Damiano et al., 2016). Here, extractions from the seeds are commonly used for LUTS and BPH management (Damiano et al., 2016). Nutritional and medicinal benefits are due to the content of proteins (25 – 50%) and oils (40 – 60%) (Abdel-Rahman, 2006). *C. pepo* oil is rich in oleic, linolenic, palmitic and stearic fatty acids, alongside squalene, tocopherols, phytosterols and carotenoids (lutein and zeaxanthin) (Ramak and Mahboubi, 2019; Ratnam et al., 2017). Important phytosteroids includes β-sitosterol, spinasterol, campesterol, stigmasterol, with Δ5-, Δ7-, and Δ8- sterols being prominent (Damiano et al., 2016; Ramak and Mahboubi, 2019). Although considered a common herb used and investigated in BPH (Azimi et al., 2012; Cicero et al., 2019; Dedhia and McVary, 2008; Hong et al., 2009), *C. pepo* was investigated in only four articles included in this systematic review (Carbin et al., 1990; Coulson et al., 2013; Giannakopoulos et al., 2002; Vahlensieck et al., 2015). This may be explained by the rigid inclusion criteria based on the quality of the articles. Two articles investigated the efficacy of *C.pepo* individually, however they used three entirely distinct administrations of the plant: *C. pepo* seed extract (Granu Fink), whole *C. pepo* seeds, and *C. pepo* oil (Hong et al., 2009; Vahlensieck et al., 2015). A significant improvement of IPSS/AUASI was reported in the groups treated with whole *C.pepo* seeds and *C. pepo* oil, however there was an insignificant improvement in the group treated with *C. pepo* seed extract oil (Hong et al., 2009; Vahlensieck et al., 2015). A significant improvement was also reported in Qmax, and QoL in the group treated with *C.pepo* oil (Hong et al., 2009). *C. pepo* was investigated as part of a polyherbal blend in 3 articles (Carbin et al., 1990; Coulson et al., 2013; Hong et al., 2009). In combination with just *S. repens,* a significant improvement in IPSS, Qmax, PSA, QoL, and PRV were reported (Carbin et al., 1990; Hong et al., 2009). Treatment with ProstateEZEMAX, composed of *C. pepo* seed oil, *E. parviflorum*, lycopene, *P. africana*, and *S. repens* demonstrated a significant improvement of IPSS (Coulson et al., 2013), supporting the previous evidence showing that *C. pepo* may be more effective when combined with Serona or Pygeum (Wilt et al., 2000b).

Proposed mechanisms include reduced lipoperoxidation, anti-inflammatory activity (cyclooxygenase and pipo-oxygenase inhibition), inhibition of aromatase and 5α-reductase activity, reduced bladder contractibility, inhibition of cellular proliferation and testosterone-induced prostatic hyperplasia (Damiano et al., 2016; Fornara et al., 2020; Ramak and Mahboubi, 2019). Isolated Δ7- sterols inhibit the binding of DHT to androgen receptor in human prostate fibroblasts, however, the activity of these sterols is relatively weak compared to finasteride or antiandrogens, and thereby may need to be administered at a high dose for 12 months or more (Fornara et al., 2020).

4.4. Lycopene

Lycopene is a natural carotenoid that is responsible for the color of red foods, and is predominantly found and consumed in tomatoes (Story et al., 2010). In the body, lycopene is found in high concentrations in the liver, adrenals, prostate and testes, and it is present in seminal fluid. Furthermore, lycopene administration in animals increases prostate concentrations (Cicero et al., 2019; Wertz et al., 2004). Although lycopene is a common plant constituent associated with BPH (Eleazu et al., 2017), this systematic review found only one article (3.6%) that investigated the efficacy of lycopene in the treatment of BPH (Schwarz et al., 2008). A significant improvement in IPSS and PSA were reported while any improvement of QoL was insignificant (Schwarz et al., 2008). In a systematic review and meta-analysis, lycopene was not found to reduce the incidence of BPH (Ilic and Misso, 2012). In three articles, lycopene was used in combination with other herbs and/or components (Coulson et al., 2013; Morgia et al., 2017, 2014). Of these articles, a significant improvement of IPSS/AUASI was reported in all of the articles where it was reported as an outcome (Coulson et al., 2013; Morgia et al., 2017). A significant improvement of PSA was found (Morgia et al., 2014), with no statistically significant improvement of Qmax (Morgia et al., 2017). Schwarz et al. used synthetic lycopene (77% all-trans and 23% total cis-lycopene) as part of their treatment formulation (Schwarz et al., 2008). Profluss, which includes a combination of *S.repens*, selenium, and lycopene, was used in two out of the four articles investigating lycopene (Morgia et al., 2017, 2014). ProstateEZE MAX, containing *C. pepo* seed oil, *E. parviflorum*, lycopene, *P.africana*, and *S. repens* was used as a combination treatment in one article (Coulson et al., 2013).

Lycopene has the potential to inhibit inflammatory mediators (cyclooxygenase, lipo-oxygenase and proinflammatory cytokines), affect the synthesis of eicosanoids, inhibit NF-kβ pathway, reduce the generation of reactive oxygen species, and induce apoptosis, all of which may explain why symptoms improve in BPH patients (Ilic and Misso, 2012; Palozza et al., 2010; Schwarz et al., 2008). Its capability to inhibit cell growth, IGF-1 signal transduction, IL-6 expression, androgen activation and signaling, and induce apoptosis has indicated that lycopene has the potential to prevent and treat BPH (Wertz et al., 2004).

4.5. Pygeum africanum

Pygeum africanum, commonly known as the African prune tree, is part of the Rosaceae family (Bodeker et al., 2014; Komakech et al., 2017). As its name suggests, *P. africanum* is typically found in the tropical and mountainous regions of central and southern Africa (Bodeker et al., 2014; Komakech et al., 2017). Lipophilic extracts from its bark have been used for the treatment of prostatitis, BPH and prostate cancer (Papaioannou et al., 2010). Constituents include pentacyclic triterpenoid saponins (urosolic acid and oleanolic acid), triterpenes (β-amyrin), phenols (ferulic acid, atraric acid and N-butylbenzene--sulfonamide (NBBS), sterols (β-sitosterol) and fatty acids (lauric acid) (Komakech et al., 2017; Papaioannou et al., 2010; Schleich et al., 2006a).

Although considered a common herb used and investigated in BPH (Azimi et al., 2012; Cicero et al., 2019; Dedhia and McVary, 2008; Hong et al., 2009), the present systematic review included only 4 articles utilizing *P. africanum* as an intervention (Chatelain et al., 1999; Coulson

et al., 2013; Krzeski et al., 1993; Melo et al., 2002). Chatelain et al. reported a significant improvement of IPSS after treatment with *P. africanum* extract (Chatelain et al., 1999). In combination with *U. dioica,* PRV significantly improved, while an insignificant improvement of IPSS, Qmax, and QoL was also reported (Krzeski et al., 1993; Melo et al., 2002). In the polyherbal ProstateEZEMAX formulation, IPSS was significantly improved (Coulson et al., 2013). This is in agreement with a previous systematic reviews that concluded *P. africanum* to improve combined outcomes of urologic symptoms and flow measures (*i.e.* nocturia - 19%, residual volume - 24%, and peak urinary flow - 23%) compared to placebo (Ishani et al., 2000; Wilt and Ishani, 1998). This was further supported by *in vitro* and clinical articles where *P. africanum* was found to have efficacy in the treatment of BPH (Andro and Riffaud, 1995; Salinas-Casado et al., 2020).

In vivo and *in vitro* articles have suggested that the inhibition of growth factors responsible for prostate inflammation and growth could be the mechanism of action through which *P. africana* is beneficial in the treatment of prostate disorders (Salinas-Casado et al., 2020). Anti-proliferative and anti-inflammatory activity have also been reported. This is attributed to the inhibition of leukotrienes chemotactic activity, inhibition of LOX metabolites, reduced EGF, IGF-1 and bFGF, and increased apoptosis (Andro and Riffaud, 1995; Boulbès et al., 2006; Salinas-Casado et al., 2020). Antiandrogenic (particularly DHT) activity of *P. africana* has also been demonstrated, and specifically for atraric acid and N-butylbenzene-sulfonamide, particularly via inhibiting the nuclear translocation of the androgen receptor (Papaioannou et al., 2010; Salinas-Casado et al., 2020; Schleich et al., 2006b, 2006a). *P. africanum* also modulates hypercontractility of the bladder, and improves prostate histology and secretions in BPH models (Andro and Riffaud, 1995; Salinas-Casado et al., 2020).

4.6. Linum usitatissmum

L. *usitatissmum*, commonly known as flaxseed (human consumption) or linseed (industrial uses), belongs to the Lineaceae family. This nutritional plant is found in over 50 countries, with Canada, India, China, the United States, and Ethiopia being the leading producers of the plant (Kajla et al., 2015; Singh et al., 2011). Oils obtained from the seeds are used for nutritional and medicinal purposes in humans, containing ~55% alpha-linolenic acid (ALA), 30% protein (particularly the amino acids arginine, aspartic acid, and glutamic acid) and 35% fibers (cellulose, hemicellulose and lignin and insoluble fibers, and water-soluble polysaccharides as soluble fiber). L. *usitatissmum* is rich is phenols (particularly phenolic acids, flavonoids and lignans), alongside high cysteine and methionine, that account for antioxidant properties. Ligans provide a source of phytoestrogens, where secoisolariciresinol diglycoside (SDG) is the most prominent along with matairesinol, pinoresinol, lariciresinol and isolariciresinol (Kajla et al., 2015; Parikh et al., 2019; Singh et al., 2011). In this systematic review, L. *usitatissmum* extract, specifically SDG, was used in the treatment of BPH as either LinumLifeEXTRA or Beneflax (Simons et al., 2015; Zhang et al., 2008). A significant improvement of IPSS and PV was reported in both articles. Zhang et al. reported a significant improvement of Qmax and QoL (Zhang et al., 2008). PRV was reported to have significantly improved in one article, while insignificantly improving in the other article using L. *usitatissmum* as the intervention (Simons et al., 2015; Zhang et al., 2008).

Lignans have been shown to have protective effects against the emergence and progression of hormone-related disorders, including BPH and prostate cancer (Bisson et al., 2014; Thompson et al., 1996). Furthermore, *in vivo* articles have shown L. *usitatissmum* to inhibit testosterone-propionate induced prostate growth comparable to finasteride, likely mediated through the downregulation of prostatic VEGF and epithelial cellular proliferation and increased testosterone:estrogen ratio (Bisson et al., 2014; Said et al., 2015). Lignans further show antioxidant activity, protecting against DNA damage and lipid peroxidation (Kajla et al., 2015; Parikh et al., 2019; Singh et al., 2011).

4.7. Limitations

This review included any herbal medicine intervention for BPH, based on different herbs and/or herbal combinations. The majority of articles suggests herbal medicine to be effective as a treatment for BPH. However, the included articles were widely heterogeneous in terms of study design, type of interventions and controls used, the extraction method for the herbal medicine, and the outcomes measured or reported. This makes the analysis of the results particularly challenging. There are limited clinical articles of high quality investigating herbal interventions on BPH, where each individual herb has not been sufficiently investigated using a consistent extraction method. In addition, these studies lack long term follow up data. Furthermore, any proposed mechanisms of action are in animal and *in vitro* studies, which may not translate into human pathophysiology. These factors limit the interpretation of results provided in this systematic review. However, the use of specific keywords relevant to BPH and herbal interventions, alongside a specific eligibility criterion based on PRISMA guidelines provided an appropriate search for relevant clinical trials. The use of specific outcomes further provided some standardized interpretation, particularly for the IPSS as a clinical outcome. Moreover, Jadad scoring ensured that all of the articles included in the review can be considered high quality trials based on appropriate reporting that includes blinded, randomization, and accounting for all of the patients through to the end of the study.

5. Conclusion

BPH is a common and increasing clinical concern in aging males, where there has been an increase in the demand and prescriptions for holistic, herbal-based medicines. Although literature on herbal medicines in BPH is vast and heterogeneous, we applied a JADAD score > 4 with objective outcomes as inclusion criteria in order to select more standardised high-quality clinical studies. However, there are only a few high-quality clinical trials ($n = 28$) investigating herbal medicine on BPH that have been identified in this systematic review. Furthermore, most high-quality studies are of registered products (46%), where industry may be important in the development and clinical evaluation of standardized herbal products for BPH. *S. repens* is the most frequently research herb, showing significant potential in isolation or in combination with other herbs for BPH treatment. However, although popular and recommended for BPH, *C. pepo, U. dioica, P. africanum,* and lycopene are relatively under-represented in high quality clinical trials compared to *S. repens*. L. *usitatissimum* shows potential for BPH treatment, although only 2 trials on registered products are identified, and further investigation of this herb is warranted. While the articles included in this review showed improvement in patient's symptoms, there was great variability in the study design and herbal combinations used which made it a challenge to analyze the results. Supported by *in vivo* and *in vitro* studies on potential mechanisms of action of these herbs, further clinical research is recommended to confirm indications for treatment, comparison of efficacy of mono-herbal and poly-herbal approaches, standardized extract based on identification of active constituents, as well as dosage and long-term safety.

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Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

References

Abdel-Rahman, M.K., 2006. Effect of Pumpkin Seed (Cucurbita pepo L.) Diets on Benign Prostatic Hyperplasia (BPH): chemical and Morphometric Evaluation in Rats. World J. Chem. 1, 33–40.

Andro, M.C., Riffaud, J.P., 1995. Pygeum africanum extract for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience. Curr. Ther. Res. 56, 796–817.

Azimi, H., Khakshur, A.-A.A., Aghdasi, I., Fallah-Tafti, M., Abdollahi, M., 2012. A review of animal and human studies for management of benign prostatic hyperplasia with natural products: perspective of new pharmacological agents. Inflamm. Allergy Drug Targets 11, 207–221.

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., Kaplan, S.A., McCullough, A., Andriole, G.L., Naslund, M.J., Williams, O.D., Kusek, J.W., Meyers, C.M., Betz, J.M., Cantor, A., McVary, K.T., 2011. Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: a randomized trial. JAMA - J. Am. Med. Assoc. 306, 1344–1351. https://doi.org/10.1001/jama.2011.1364.

Bent, S., Kane, C., Shinohara, K., Neuhaus, J., Hudes, E., Goldberg, H., Avins, A., 2006. Saw palmetto for benign prostatic hyperplasia. N Engl J Med 354, 557–566. https://doi.org/10.1056/nejmoa053085.

Berger, V., Alperson, S., 2009. A General Framework for the Evaluation of Clinical Trial Quality. Rev. Recent Clin. Trials 4, 79–88. https://doi.org/10.2174/157488709788186021.

Berges, R.R., Windeler, J., Trampisch, H.J., Senge, T., 1995. Randomised, placebo-controlled, double-blind clinical trial of beta-sitosterol in patients with benign prostatic hyperplasia. Beta-sitosterol Study Group. Lancet 345, 1529–1532.

Bisson, J.F., Hidalgo, S., Simons, R., Verbruggen, M., 2014. Preventive effects of lignan extract from flax hulls on experimentally induced benign prostate hyperplasia. J. Med. Food 17, 650–656.

Bodeker, G., Van'T Klooster, C., Weisbord, E., 2014. Prunus africana (Hook.f.) Kalkman: the overexploitation of a medicinal plant species and its legal context. J. Altern. Complement. Med. 20, 810–822.

Boulbès, D., Soustelle, L., Costa, P., Haddoum, M., Bali, J.P., Hollande, F., Magous, R., 2006. Pygeum africanum extract inhibits proliferation of human cultured prostatic fibroblasts and myofibroblasts. BJU Int 98, 1106–1113.

Boyle, P., Robertson, C., Lowe, F., Roehrborn, C., 2004. Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. BJU Int 93, 751–756.

Braeckman, J., Bruhwyler, J., Vandekerckhove, K., Géczy, J., 1997. Efficacy and safety of the extract of Serenoa repens in the treatment of benign prostatic hyperplasia: therapeutic equivalence between twice and once daily dosage forms. Phyther. Res. 11, 558–563. https://doi.org/10.1002/(SICI)1099-1573(199712)11:8<558::AID-PTR158>3.0.CO;2-U.

Buck, A.C., 2004. Is there a scientific basis for the therapeutic effects of Serenoa repens in benign prostatic hyperplasia? Mechanisms of action. J. Urol. 172, 1792–1799.

Carbin, B., Larsson, B., Lindahl, O., 1990. Treatment of benign prostatic hyperplasia with phytosterols. Br. J. Urol. 66, 639–641. https://doi.org/10.1111/j.1464-410X.1990.tb07199.x.

Chatelain, C., Autet, W., Brackman, F., 1999. Comparison of once and twice daily dosage forms of Pygeum africanum extract in patients with benign prostatic hyperplasia: a randomized, double- blind study, with long-term open label extension. Urology 54, 473–478. https://doi.org/10.1016/S0090-4295(99)00147-8.

Chrubasik, J.E., Roufogalis, B.D., Wagner, H., Chrubasik, S., 2007. A comprehensive review on the stinging nettle effect and efficacy profiles. Part II: urticae radix. Phytomedicine 14, 568–579.

Chua, T., Eise, N.T., Simpson, J.S., Ventura, S., 2014. Pharmacological characterization and chemical fractionation of a liposterolic extract of saw palmetto (Serenoa repens): effects on rat prostate contractility. J. Ethnopharmacol. 152, 283–291.

Chughtai, B., Forde, J.C., Thomas, D.D.M., Laor, L., Hossack, T., Woo, H.H., Te, A.E., Kaplan, S.A., 2016. Benign prostatic hyperplasia. Nat. Rev. Dis. Prim. 2, 16031. https://doi.org/10.1038/nrdp.2016.31.

Cicero, A.F.G., Allkanjari, O., Vitalone, A., Busetto, G.M., Cai, T., Larganà, G., Russo, G.I., Magri, V., Perletti, G., della Cuna, F.S.R., Stamatiou, K., Trinchieri, A., 2019. Nutraceutical treatment and prevention of benign prostatic hyperplasia and prostate cancer. Arch. Ital. di Urol. e Androl. 91, 139–152.

Coulson, S., Rao, A., Beck, S.L., Steels, E., Gramotnev, H., Vitetta, L., 2013. A phase II randomised double-blind placebo-controlled clinical trial investigating the efficacy and safety of ProstateEZE Max: a herbal medicine preparation for the management of symptoms of benign prostatic hypertrophy. Complement. Ther. Med. 21, 172–179. https://doi.org/10.1016/j.ctim.2013.01.007.

Damiano, R., Cai, T., Fornara, P., Franzese, C.A., Leonardi, R., Mirone, V., 2016. The role of Cucurbita pepo in the management of patients affected by lower urinary tract symptoms due to benign prostatic hyperplasia: a narrative review. Arch. Ital. di Urol. e Androl. 88, 136–143.

De Nunzio, C., Presicce, F., Tubaro, A., 2016. Inflammatory mediators in the development and progression of benign prostatic hyperplasia. Nat. Rev. Urol. 13, 613–626. https://doi.org/10.1038/nrurol.2016.168.

Dedhia, R.C., McVary, K.T., 2008. Phytotherapy for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. J. Urol. 179, 2119–2125.

Dhami, N., 2013. Trends in Pharmacognosy: a modern science of natural medicines. J. Herb. Med. https://doi.org/10.1016/j.hermed.2013.06.001.

Egan, K.B., 2016. The epidemiology of benign prostatic hyperplasia associated with lower urinary tract symptoms: prevalence and incident rates. Urol. Clin. North Am. 43, 289–297. https://doi.org/10.1016/j.ucl.2016.04.001.

Eleazu, C., Eleazu, K., Kalu, W., 2017. Management of benign prostatic hyperplasia: could dietary polyphenols be an alternative to existing therapies? Front. Pharmacol. 8, 234. https://doi.org/10.3389/fphar.2017.00234.

Esposito, S., Bianco, A., Russo, R., Maro, A.Di, Isernia, C., Pedone, P.V., 2019. Therapeutic Perspectives of Molecules from Urtica dioica Extracts for Cancer Treatment. Molecules 24, 2753. https://doi.org/10.3390/molecules24152753.

Foo, K.T., 2019. What is a disease? What is the disease clinical benign prostatic hyperplasia (BPH)? World J. Urol. 37, 1293–1296. https://doi.org/10.1007/s00345-019-02691-0.

Fornara, P., Madersbacher, S., Vahlensieck, W., Bracher, F., Romics, I., Kil, P., 2020. Phytotherapy Adds to the Therapeutic Armamentarium for the Treatment of Mild-To-Moderate Lower Urinary Tract Symptoms in Men. Urol. Int. 104, 333–342.

Geavlete, P., Multescu, R., Geavlete, B., 2011. Serenoa repens extract in the treatment of benign prostatic hyperplasia. Ther. Adv. Urol. 3, 193–198.

Giannakopoulos, X., Baltogiannis, D., Giannakis, D., Tasos, A., Sofikitis, N., Charalabopoulos, K., Evangelou, A., Ħubner, W.D., 2002. The lipidosterolic extract of Serenoa repens in the treatment of benign prostatic hyperplasia: a comparison of two dosage regimens. Adv. Ther. 19, 285–296. https://doi.org/10.1007/BF02853174.

Habib, F.K., 2009. Serenoa repens: the Scientific Basis for the Treatment of Benign Prostatic Hyperplasia. Eur. Urol. Suppl. 8, 887–893.

Heinrich, M., Anagnostou, S., 2017. From Pharmacognosia to DNA-Based Medicinal Plant Authentication - Pharmacognosy through the Centuries. Planta Med 83, 1110–1116. https://doi.org/10.1055/s-0043-108999.

Hirano, T., Homma, M., Oka, K., 1994. Effects of stinging nettle root extracts and their steroidal components on the Na+,K(+)-ATPase of the benign prostatic hyperplasia. Planta Med 60, 30–33.

Hong, H., Kim, C.-S., Maeng, S., 2009. Effects of pumpkin seed oil and saw palmetto oil in Korean men with symptomatic benign prostatic hyperplasia. Nutr. Res. Pract. 3, 323. https://doi.org/10.4162/nrp.2009.3.4.323.

Hryb, D.J., Khan, M.S., Romas, N.A., Rosner, W., 1995. The effect of extracts of the roots of the stinging nettle (Urtica dioica) on the interaction of SHBG with its receptor on human prostatic membranes. Planta Med 61, 31–32.

Ibrahim, M., Rehman, K., Razzaq, A., Hussain, I., Farooq, T., Hussain, A., Akash, M.S.H., 2018. Investigations of Phytochemical Constituents and Their Pharmacological Properties Isolated from the Genus Urtica: critical Review and Analysis. Crit. Rev. Eukaryot. Gene Expr. 28, 25–66.

Ilic, D., Misso, M., 2012. Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: a systematic review. Maturitas.

Ishani, A., MacDonald, R., Nelson, D., Rutks, I., Wilt, T.J., 2000. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. Am. J. Med. 109, 654–664.

Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J.M., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control. Clin. Trials 17, 1–12.

Joshi, B.C., Mukhija, M., Kalia, A.N., 2014. Pharmacognostical review of Urtica dioica L. Int. J. Green Pharm. 8, 201–209.

Kajla, P., Sharma, A., Sood, D.R., 2015. Flaxseed—A potential functional food source. J. Food Sci. Technol. 52, 1857–1871.

Karami, A.A., Sheikhsoleimani, M., Memarzadeh, M.R., Haddadi, E., Bakhshpour, M., Mohammadi, N., Mirhashemi, S.M., 2020. Urtica dioica root extract on clinical and biochemical parameters in patients with benign prostatic hyperplasia, randomized controlled trial. Pakistan J. Biol. Sci. 23, 1338–1344. https://doi.org/10.3923/pjbs.2020.1338.1344.

Keehn, A., Taylor, J., Lowe, F.C., 2016. Phytotherapy for benign prostatic hyperplasia. Curr. Urol. Rep. 17, 53. https://doi.org/10.1007/s11934-016-0609-z.

Kennedy, D.O., Wightman, E.L., 2011. Herbal Extracts and Phytochemicals: plant Secondary Metabolites and the Enhancement of Human Brain function. Adv. Nutr. 2, 32–50. https://doi.org/10.3945/an.110.000117.

Kim, E.H., Larson, J.A., Andriole, G.L., 2016. Management of benign prostatic hyperplasia. Annu. Rev. Med. 67, 137–151. https://doi.org/10.1146/annurev-med-063014-123902.

Kim, T.H., Lim, H.J., Kim, M.S., Lee, M.S., 2012. Dietary supplements for benign prostatic hyperplasia: an overview of systematic reviews. Maturitas 73, 180–185.

Komakech, R., Kang, Y., Lee, J.-H., Omujal, F., 2017. A Review of the Potential of Phytochemicals from Prunus africana (Hook f.) Kalkman Stem Bark for

Chemoprevention and Chemotherapy of Prostate Cancer. Evid. Based. Complement. Alternat. Med. 2017, 3014019.
Krzeski, T., Kazón, M., Borkowski, A., Witeska, A., Kuczera, J., 1993. Combined extracts of Urtica dioica and Pygeum africanum in the treatment of benign prostatic hyperplasia: double-blind comparison of two doses. Clin Ther 15, 1011–1020.
Lepor, H., 1998. The pathophysiology of lower urinary tract symptoms in the ageing male population. Br. J. Urol. 81, 29–33. https://doi.org/10.1046/j.1464-410x.1998.0810s1029.x.
Liao, C.H., Li, H.Y., Chung, S.D., Chiang, H.S., Yu, H.J., 2012. Significant association between serum dihydrotestosterone level and prostate volume among Taiwanese men aged 40-79 years. Aging Male 15, 28–33. https://doi.org/10.3109/13685538.2010.550660.
MacDonald, R., Tacklind, J.W., Rutks, I., Wilt, T.J., 2012. Serenoa repens monotherapy for benign prostatic hyperplasia (BPH): an updated Cochrane systematic review. BJU Int 109, 1756–1761.
Madersbacher, S., Sampson, N., Culig, Z., 2019. Pathophysiology of benign prostatic hyperplasia and benign prostatic enlargement: a mini-review. Gerontology 65, 458–464. https://doi.org/10.1159/000496289.
Marks, L.S., Partin, A.W., Epstein, J.I., Tyler, V.E., Simon, I., Macairan, M.L., Chan, T.L., Dorey, F.J., Garris, J.B., Veltri, R.W., Santos, P.B.C., Stonebrook, K.A., DeKernion, J. B., 2000. Effects of a saw palmetto herbal blend in men with symptomatic benign prostatic hyperplasia. J. Urol. 163, 1451–1456. https://doi.org/10.1016/S0022-5347(05)67641-0.
Melo, É.A., Bertero, E.B., Rios, L.A.S., Mattos, D., 2002. Evaluating the efficiency of a combination of Pygeum africanum and stinging nettle (Urtica dioica) extracts in treating benign prostatic hyperplasia (BPH): double-blind, randomized, placebo controlled trial. Int. Braz J Urol 28, 418–425.
Morgia, G., Micali, A., Rinaldi, M., Irrera, N., Marini, H., Puzzolo, D., Pisani, A., Privitera, S., Russo, G.I., Cimino, S., Ieni, A., Trichilo, V., Altavilla, D., Squadrito, F., Minutoli, L., 2017. Survivin and NAIP in human benign prostatic hyperplasia: protective role of the association of Serenoa repens, lycopene and selenium from the randomized clinical study. Int. J. Mol. Sci. 18, 680. https://doi.org/10.3390/ijms18030680.
Morgia, G., Russo, G.I., Voce, S., Palmieri, F., Gentile, M., Giannantoni, A., Blefari, F., Carini, M., Minervini, A., Ginepri, A., Salvia, G., Vespasiani, G., Santelli, G., Cimino, S., Allegro, R., Collura, Z., Fragalà, E., Arnone, S., Pareo, R.M., 2014. Serenoa repens, lycopene and selenium *versus* tamsulosin for the treatment of LUTS/BPH. An Italian multicenter double-blinded randomized study between single or combination therapy (PROCOMB Trial). Prostate 74, 1471–1480. https://doi.org/10.1002/pros.22866.
Nahata, A., Dixit, V.K., 2012. Ameliorative effects of stinging nettle (Urtica dioica) on testosterone-induced prostatic hyperplasia in rats. Andrologia 44, 396–409.
Nakai, Y., Nonomura, N., 2013. Inflammation and prostate carcinogenesis. Int. J. Urol. 20, 150–160. https://doi.org/10.1111/j.1442-2042.2012.03101.x.
Nicholson, T.M., Ricke, W.A., 2011. Androgens and estrogens in benign prostatic hyperplasia: past, present and future. Differentiation 82, 184–199. https://doi.org/10.1016/j.diff.2011.04.006.
Nickel, J.C., Aaron, L., Barkin, J., Elterman, D., Nachabé, M., Zorn, K.C., 2018. Canadian Urological Association guideline on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH): 2018 update. Can. Urol. Assoc. J. 12, 303–312. https://doi.org/10.5489/cuaj.5616.
Nilsen, E.S., Sæterdal, I., Underland, V., 2012. Serenoa repens for benign prostatic hyperplasia. Altern. Ther. Health Med. 17, 8–10.
Olivo, S.A., Macedo, L.G., Gadotti, I.C., Fuentes, J., Stanton, T., Magee, D.J., 2008. Scales to assess the quality of randomized controlled trials: a systematic review. Phys. Ther. 88, 156–175. https://doi.org/10.2522/ptj.20070147.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372.
Palozza, P., Parrone, N., Catalano, A., Simone, R., 2010. Tomato Lycopene and Inflammatory Cascade: basic Interactions and Clinical Implications. Curr. Med. Chem. 17, 2547–2563.
Papaioannou, M., Schleich, S., Roell, D., Schubert, U., Tanner, T., Claessens, F., Matusch, R., Baniahmad, A., 2010. NBBS isolated from Pygeum africanum bark exhibits androgen antagonistic activity, inhibits AR nuclear translocation and prostate cancer cell growth. Invest. New Drugs 28, 729–743.
Parikh, M., Maddaford, T.G., Austria, J.A., Aliani, M., Netticadan, T., Pierce, G.N., 2019. Dietary flaxseed as a strategy for improving human health. Nutrients 11.
Preuss, H.G., Marcusen, C., Regan, J., Klimberg, I.W., Welebir, T.A., Jones, W.A., 2001. Randomized trial of a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) on symptoms of benign prostatic hyperplasia (BPH). Int. Urol. Nephrol. 33, 217–225. https://doi.org/10.1023/A:1015227604041.
Ramak, P., Mahboubi, M., 2019. The beneficial effects of Pumpkin (Cucurbita pepo L.) seed oil for health condition of men. Food Rev. Int. 35, 166–176.
Ratnam, N.V., Najibullah, M., Ibrahim, M., 2017. A Review on Cucurbita pepo. Int. J. Pharmacogn. Phytochem. Res. 9, 1190–1194.
Reza Moradi, H., Erfani Majd, N., Esmaeilzadeh, S., Reza Fatemi Tabatabaei, S., 2015. The histological and histometrical effects of Urtica dioica extract on rat's prostate hyperplasia. Vet. Res. Forum 6, 23–29.
Roy Upton, R.H., 2015. Traditional Herbal Medicine, Pharmacognosy, and Pharmacopoeial Standards: a Discussion at the Crossroads, in: Mukherjee, P. (Ed.), Evidence-Based Validation of Herbal Medicine. Elsevier Inc., pp. 46–85. doi:10.1016/B978-0-12-800874-4.00003-9.
Said, M.M., Hassan, N.S., Schlicht, M.J., Bosland, M.C., 2015. Flaxseed Suppressed Prostatic Epithelial Proliferation in a Rat Model of Benign Prostatic Hyperplasia. J. Toxicol. Environ. Heal. - Part A Curr. Issues 78, 453–465.
Salinas-Casado, J., Esteban-Fuertes, M., Carballido-Rodríguez, J., Cozar-Olmo, J.M., 2020. Review of the experience and evidence of Pygeum africanum in urological practice. Actas Urol. Esp. 44, 9–13.
Santos Dias, J., 2012. Benign Prostatic Hyperplasia: clinical Manifestations and Evaluation. Tech. Vasc. Interv. Radiol. 15, 265–269.
Schleich, S., Papaioannou, M., Baniahmad, A., Matusch, R., 2006a. Activity-guided isolation of an antiandrogenic compound of Pygeum africanum. Planta Med 72, 547–551. https://doi.org/10.1055/s-2006-941472.
Schleich, S., Papaioannou, M., Baniahmad, A., Matusch, R., 2006b. Extracts from Pygeum africanum and other ethnobotanical species with antiandrogenic activity. Planta Med 72, 807–813.
Schwarz, S., Obermüller-Jevic, U.C., Hellmis, E., Koch, W., Jacobi, G., Biesalski, H.K., 2008. Lycopene inhibits disease progression in patients with benign prostate hyperplasia. J. Nutr. 138, 49–53.
Shi, R., Xie, Q., Gang, X., Lun, J., Cheng, L., Pantuck, A., Rao, J., 2008. Effect of saw palmetto soft gel capsule on lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized trial in Shanghai. China. J. Urol. 179, 610–615. https://doi.org/10.1016/j.juro.2007.09.032.
Simons, R., Sonawane, N., Verbruggen, M., Chaudhary, J., 2015. Efficacy and safety of a flaxseed hull extract in the symptomatic management of benign prostatic hyperplasia: a parallel, randomized, double-blind, placebo-controlled, pilot study. J. Med. Food 18, 233–240. https://doi.org/10.1089/jmf.2013.3129.
Singh, K.K., Mridula, D., Rehal, J., Barnwal, P., 2011. Flaxseed: a potential source of food, feed and fiber. Crit. Rev. Food Sci. Nutr. 51, 210–222.
Story, E.N., Kopec, R.E., Schwartz, S.J., Keith Harris, G., 2010. An update on the health effects of tomato lycopene. Annu. Rev. Food Sci. Technol. 1, 189–210.
Sudeep, H.V., Thomas, J.V., Shyamprasad, K., 2020. A double blind, placebo-controlled randomized comparative study on the efficacy of phytosterol-enriched and conventional saw palmetto oil in mitigating benign prostate hyperplasia and androgen deficiency. BMC Urol 20, 86. https://doi.org/10.1186/s12894-020-00648-9.
Suzuki, M., Ito, Y., Fujino, T., Abe, M., Umegaki, K., Onoue, S., Noguchi, H., Yamada, S., 2009. Pharmacological effects of saw palmetto extract in the lower urinary tract. Acta Pharmacol. Sin. 30, 271–281.
Tacklind, J., MacDonald, R., Rutks, I., Wilt, T.J., 2009. Serenoa repens for benign prostatic hyperplasia. Cochrane Database Syst. Rev. 15, CD001423.
Thompson, L.U., Rickard, S.E., Orcheson, L.J., Seidl, M.M., 1996. Flaxseed and its lignan and oil components reduce mammary tumor growth at a late stage of carcinogenesis. Carcinogenesis 17, 1373–1376.
Vahlensieck, W., Theurer, C., Pfitzer, E., Patz, B., Banik, N., Engelmann, U., 2015. Effects of pumpkin seed in men with lower urinary tract symptoms due to benign prostatic hyperplasia in the one-year, randomized, placebo-controlled GRANU study. Urol. Int. 94, 286–295. https://doi.org/10.1159/000362903.
Vuichoud, C., Loughlin, K.R., 2015. Benign prostatic hyperplasia: epidemiology, economics and evaluation. Can. J. Urol. 22, 1–6.
Wertz, K., Siler, U., Goralczyk, R., 2004. Lycopene: modes of action to promote prostate health. Arch. Biochem. Biophys. 430, 127–134.
Willetts, K.E., Clements, M.S., Champion, S., Ehsman, S., Eden, J.A., 2003. Serenoa repens extract for benign prostate hyperplasia: a randomized controlled trial. BJU Int 92, 267–270. https://doi.org/10.1046/j.1464-410X.2003.04316.x.
Wilt, T., Ishani, A., Mac Donald, R., 2002. Serenoa repens for benign prostatic hyperplasia. Cochrane database Syst. Rev., CD001423
Wilt, T., Ishani, A., MacDonald, R., Stark, G., Mulrow, C., Lau, J., 2000a. Beta-sitosterols for benign prostatic hyperplasia. Cochrane database Syst. Rev., CD001043
Wilt, T.J., Ishani, A., 1998. Pygeum africanum for benign prostatic hyperplasia. Cochrane Database Syst. Rev. 1998, CD001044.
Wilt, T.J., Ishani, A., Rutks, I., MacDonald, R., 2000b. Phytotherapy for benign prostatic hyperplasia. Public Health Nutr 3, 459–472.
Wilt, T.J., MacDonald, R., Ishani, A., 1999. beta-sitosterol for the treatment of benign prostatic hyperplasia: a systematic review. BJU Int 83, 976–983.
Ye, Z., Huang, J., Zhou, L., Chen, S., Wang, Zengjun, Ma, L., Wang, D., Wang, G., Wang, S., Liang, C., Qiu, S., Gu, X., Liu, J., Weng, Z., Wu, C., Wei, Q., Xie, L., Wu, W., Cheng, Y., Hu, J., Wang, Zhixian, Zeng, X., 2019. Efficacy and safety of Serenoa repens extract among patients with benign prostatic hyperplasia in China: a multicenter, randomized, double-blind, placebo-controlled trial. Urology 129, 172–179. https://doi.org/10.1016/j.urology.2019.02.030.
Zhang, W., Wang, X., Liu, Y., Tian, H., Flickinger, B., Empie, M.W., Sun, S.Z., 2008. Effects of dietary flaxseed lignan extract on symptoms of benign prostatic hyperplasia. J. Med. Food 11, 207–214. https://doi.org/10.1089/jmf.2007.602.