

Pigepil®



è un integratore per la funzionalità della prostata e delle vie urinarie

Lo **zinco** ed il **selenio** contribuiscono alla normale funzione del sistema immunitario e proteggono le cellule dallo stress ossidativo. Lo zinco contribuisce al mantenimento di normali livelli di testosterone nel sangue, alla normale fertilità e alla normale riproduzione, interviene nel processo di divisione delle cellule. Il selenio contribuisce alla normale spermatogenesi, **Serenoa** ed **Epilobio** contribuiscono alla **normale funzionalità della prostata, delle vie urinarie e al drenaggio dei liquidi corporei**. Il **PIGEUM** è risultato utile, secondo numerosi studi scientifici recenti, nel **trattamento dell'Ipertrofia Prostatica Benigna e per la funzionalità della vescica**.

Indicazioni

La sinergia di azione dei suoi componenti è stata studiata per svolgere un'**attività di protezione delle cellule dallo stress ossidativo** e in particolare per **contribuire e favorire una normale funzionalità della prostata e delle vie urinarie** in casi di **prostatite, ingrossamento prostatico e iperplasia prostatica benigna**.

Ingredienti

Agente di carica: Cellulosa microcristallina, Amido di mais; Serenoa (Serenoa repens (W.Bartram) Small) frutti es 5 % Acidi grassi; Pigeum (Prunus africana (Hook. f.) Kalkman) corteccia es; Epilobio (Epilobium angustifolium L.) erba es; Zinco gluconato; L-Seleniomietionina; Antiagglomerante: Mono e digliceridi degli acidi grassi.

Posologia: Si consiglia l'assunzione di 1 compressa al giorno preferibilmente al mattino.

Contenuti medi per 1 compressa e VNR*

	per 1 cpr	VNR%*
Serenoa repens e.s.	160 mg	
Pigeum e.s.	120 mg	
Epilobio e.s.	100 mg	
Zinco	5 mg	50
Selenio	55 mcg	100

(* Valore nutritivo di riferimento)

Avvertenze

Gli integratori non sono intesi come sostituti di una dieta variata ed equilibrata e di un sano stile di vita. Non eccedere la dose consigliata. Tenere lontano dalla portata dei bambini al di sotto dei 3 anni. Conservare il prodotto in luogo fresco e asciutto. Si sconsiglia l'uso in donne in età fertile e in soggetti di entrambi i sessi in età prepubere. Per l'uso del prodotto, chiedere consiglio al medico.

Quali sono i disturbi principali della prostata?

La prostata è una ghiandola presente solo nel genere maschile ed è situata sotto la vescica e circonda l'uretra. La ghiandola insieme alle vescichette seminali adiacenti, produce la maggior parte del liquido seminale. Le dimensioni della prostata, pari a quelle di una noce negli uomini in età giovanile e tendono ad aumentare con l'avanzare dell'età, probabilmente a causa di cambiamenti ormonali. La prostata ingrossata, denominata *Iperplasia Prostatica Benigna*, comprime l'uretra e blocca il flusso di urina creando quindi problemi nella minzione fino a creare una vera e propria ostruzione urinaria. Chi soffre di *IPB*, generalmente presenta difficoltà a svuotare completamente la vescica durante la minzione con la conseguenza che l'urina ristagna nella vescica causando una maggiore predisposizione a infezioni delle vie urinarie e a calcoli vescicali. L'ostruzione prolungata può indebolire la vescica ed infine danneggiare i reni. Stimolo ad urinare frequentemente ed urgentemente, eiaculazioni dolorose potrebbero essere le cause di una prostatite. Una prostatite può essere dovuta a un'infezione batterica che si propaga alla prostata dalle vie urinarie oppure da batteri presenti nel sangue. Le infezioni batteriche possono svilupparsi lentamente, con tendenza a ripresentarsi (prostatite batterica cronica) o possono svilupparsi rapidamente (prostatite batterica acuta).

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Review of the experience and evidence of *Pygeum africanum* in urological practice

[J Salinas-Casado¹](#), [M Esteban-Fuertes²](#), [J Carballido-Rodríguez³](#), [J M Cozar-Olmo⁴](#)

Abstract

Context: *Pygeum africanum* (*P. africanum*) is still being employed in urology practice for the treatment of lower urinary tract symptoms secondary to benign prostate hyperplasia.

Evidence acquisition: A non-exhaustive review has been carried out about *P. africanum*, its mechanisms of action "in vitro" as well as "in vivo", clinical trials and routine clinical practice.

Evidence synthesis: The conclusions of the review and the reflections of the authors on the use of *P. africanum* are described.

Conclusions: Although with an evidence level IV (based on expert opinion) the use of *P. africanum* seems to be an option in the urological therapeutic arsenal.

Keywords: BPH; Hiperplasia benigna de próstata; LUTS; *Pygeum africanum*; Síntomas el tracto urinario inferior; Urodinámica; Urodynamics.

A critical review of the pharmacology of the plant extract of *Pygeum africanum* in the treatment of LUTS

Alan D Edgar¹, Robert Levin², Christos E Constantinou³, Louis Denis⁴

Affiliations expand

Abstract

Despite an unremitting increase in the number of patients presenting symptoms of benign prostate hyperplasia (BPH), the viable treatment options remain relatively limited when compared to other disorders of aging. This has spurred an interest in so-called alternative medicines, many of which continue to be used in spite of the more recent emergence of rationally targeted therapies. Nonetheless, in the case of plant extracts, the vast majority of these have not been subjected to the same rigorous pre-clinical pharmacological testing and large-scale clinical trials now required by health authorities. Furthermore, demonstration of their clinical efficacy in BPH has been hindered by trials of limited duration with a high placebo response. Beginning with a preliminary demonstration of in vitro inhibition of growth factor-mediated fibroblast proliferation with *Pygeum africanum* extract, a detailed series of in vitro and in vivo studies on prostate growth and bladder function were undertaken. These studies, reviewed herein, have permitted the identification of putative molecular targets of *Pygeum africanum* extract affecting both growth factor-mediated prostate growth as well as specific parameters of bladder function. These results, corroborated in part by short-term clinical efficacy, set the stage for a large-scale clinical trial to investigate the efficacy of *Pygeum africanum* extract in the treatment of lower urinary tract symptoms.

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Review of the experience and evidence of *Pygeum africanum* in urological practice

[Article in English, Spanish]

[J Salinas-Casado](#)¹, [M Esteban-Fuertes](#)², [J Carballido-Rodríguez](#)³, [J M Cozar-Olmo](#)⁴

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Review

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Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis

[A Ishani](#)¹, [R MacDonald](#), [D Nelson](#), [I Rutks](#), [T J Wilt](#)

Affiliations expand

Abstract

Purpose: To conduct a systematic review and quantitative meta-analysis of the therapeutic efficacy and tolerability of *Pygeum africanum* in men with symptomatic benign prostatic hyperplasia.

Methods: Studies were identified through the search of Medline (1966 to 2000), Embase, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. Randomized trials were included if participants had symptomatic benign prostatic hyperplasia, the intervention was a preparation of *P. africanum* alone or in combination with other phytotherapeutic agents, a control group received placebo or other pharmacologic therapies for benign prostatic hyperplasia, and treatment duration was at least 30 days. Two investigators independently extracted key data on design features, subject characteristics, and therapy allocation.

Results: A total of 18 randomized controlled trials involving 1,562 men met the inclusion criteria and were analyzed. Many studies did not report results in a method that permitted meta-analysis. Only 1 of the studies reported a method of treatment allocation concealment, although 17 were double-blinded. The mean study duration was 64 days (range 30 to 122). Compared with placebo in 6 studies, *P. africanum* provided a moderately large improvement in the combined outcome of urologic symptoms and flow measures as assessed by an effect size defined by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome (-0.8 SD [95% confidence interval (CI): -1.4 to -0.3]). Summary estimates of individual outcomes were also improved by *P. africanum*. Men were more than twice as likely to report an improvement in overall symptoms (risk ratio = 2.1, 95% CI: 1.40 to 3.1). Nocturia was reduced by 19% and residual urine volume by 24%; peak urine flow was increased by 23%. Adverse effects due to *P. africanum* were mild and similar to placebo. The overall dropout rate was 12% and was similar for *P. africanum* (13%), placebo (11%), and other controls (8%; $P = 0.4$ versus placebo and $P = 0.5$ versus other controls).

Conclusions: The literature on *P. africanum* for the treatment of benign prostatic hyperplasia is limited by the short duration of studies and the variability in study design, the use of phytotherapeutic preparations, and the types of reported outcomes. However, the evidence suggests that *P. africanum* modestly, but significantly, improves urologic symptoms and flow measures. Further research is needed using standardized preparations of *P. africanum* to determine its long-term effectiveness and ability to prevent complications associated with benign prostatic hyperplasia.

Review

Treatment of Benign Prostatic Hyperplasia by Natural Drugs

Eszter Csikós ¹, Adrienn Horváth ², Kamilla Ács ¹, Nóra Papp ¹, Viktória Lilla Balázs ¹, Marija Sollner Dolenc ³ , Maša Kenda ³, Nina Kočevar Glavač ⁴, Milan Nagy ⁵, Michele Protti ⁶ , Laura Mercolini ⁶ , Györgyi Horváth ¹ , Ágnes Farkas ^{1,*}  and on behalf of the OEMONOM [†]

- ¹ Department of Pharmacognosy, Faculty of Pharmacy, University of Pécs, H-7624 Pécs, Hungary; csikos.eszter@gytk.pte.hu (E.C.); kamilla.acs@gmail.com (K.Á.); nora4595@gamma.ttk.pte.hu (N.P.); viktoria.balazs@aok.pte.hu (V.L.B.); horvath.gyorgyi@gytk.pte.hu (G.H.)
 - ² Department of Pharmaceutical Biology, Faculty of Pharmacy, University of Pécs, H-7624 Pécs, Hungary; horvath.adrienn2@pte.hu
 - ³ University of Ljubljana, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, SI-1000 Ljubljana, Slovenia; marija.sollner@ffa.uni-lj.si (M.S.D.); masa.kenda@ffa.uni-lj.si (M.K.)
 - ⁴ University of Ljubljana, Department of Pharmaceutical Biology, Faculty of Pharmacy, SI-1000 Ljubljana, Slovenia; nina.kocevar.glavac@ffa.uni-lj.si
 - ⁵ Department of Pharmacognosy and Botany, Faculty of Pharmacy, Comenius University in Bratislava, SK-832-32 Bratislava, Slovakia; milan.nagy@fpharm.uniba.sk
 - ⁶ Research Group of Pharmacotoxicological Analysis (PTA Lab), Department of Pharmacy and Biotechnology (FaBiT), Alma Mater Studiorum—University of Bologna, 40126 Bologna, Italy; michele.protti2@unibo.it (M.P.); laura.mercolini@unibo.it (L.M.)
- * Correspondence: agnes.farkas@aok.pte.hu
- † Listed at the end of Acknowledgments.



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Abstract: Benign prostatic hyperplasia (BPH) is one of the most common urinary diseases affecting men, generally after the age of 50. The prevalence of this multifactorial disease increases with age. With aging, the plasma level of testosterone decreases, as well as the testosterone/estrogen ratio, resulting in increased estrogen activity, which may facilitate the hyperplasia of the prostate cells. Another theory focuses on dihydrotestosterone (DHT) and the activity of the enzyme 5 α -reductase, which converts testosterone to DHT. In older men, the activity of this enzyme increases, leading to a decreased testosterone/DHT ratio. DHT may promote prostate cell growth, resulting in hyperplasia. Some medicinal plants and their compounds act by modulating this enzyme, and have the above-mentioned targets. This review focuses on herbal drugs that are most widely used in the treatment of BPH, including pumpkin seed, willow herb, tomato, maritime pine bark, Pygeum africanum bark, rye pollen, saw palmetto fruit, and nettle root, highlighting the latest results of preclinical and clinical studies, as well as safety issues. In addition, the pharmaceutical care and other therapeutic options of BPH, including pharmacotherapy and surgical options, are discussed, summarizing and comparing the advantages and disadvantages of each therapy.

Keywords: benign prostatic hyperplasia; medicinal plants; phytotherapy; saw palmetto; preclinical studies; clinical efficacy; safety issues

1. Introduction

Benign prostatic hyperplasia (BPH) is one of the most common urinary diseases in aging men, which can lead to lower urinary tract symptoms (LUTS). One of the most important risk factors in the occurrence of the pathology of BPH is age. The prevalence of the disease increases with age. Other specific risk factors are prostate volume (PV), LUTS, and serum prostate-specific antigen (PSA) [1]. A total of 30% of men over the age of 65 could be affected by LUTS [2]. The most predictive symptoms are nocturia and changes in urinary flow stream. An enlarged prostate and LUTS together form complex symptoms. Firstly, there is a static component, which is the direct bladder outlet obstruction (BOO) from the enlarged tissue. Secondly, there is a dynamic component from the increased

smooth muscle tone of the bladder neck [3]. The obstructive symptoms include, for example, urinary flow intermittency, and a sense of incomplete bladder emptying due to urinary retention, or terminal dribbling. The static component causes irritative symptoms, such as incontinence, nocturia, or hematuria [4]. Moderate and severe urinary symptoms can greatly impair a patient's quality of life. The origin of BPH is not exactly known, but three theories have been proposed: (1) the prostate cells can convert approximately 90% of testosterone to dihydrotestosterone (DHT) by 5 α -reductase. The DHT has a higher affinity to androgen receptors, and seems to stimulate protein synthesis, differentiation, and prostate cell growth [5,6]; (2) The second theory about BPH development is based on the prostate cells, which are androgen-independent and can self-renew in androgen-deficient conditions [7]; (3) The third is based on the interactions between stroma and epithelium. Both of them can convert testosterone into DHT. This process allows the production of various growth factors [7,8].

Depending on the severity of the disease, there are different types of treatment options. Herbal remedies, medicines, and surgery are available. BPH in mild to moderate cases can be treated with herbal remedies. In more severe cases, medicines may be given. Several herbal preparations in this indication are easily available to patients. The most common active ingredients they contain are phytosterols, β -sitosterol, lectins, etc. [9].

2. Medical Therapy of BPH

European and non-European guidelines focusing on therapeutic options of the disease include pharmacotherapy, lifestyle recommendations, surgical options, and phytotherapy, as well [10–13]. In this chapter, we primarily discuss prescription drug therapies and surgical possibilities in more detail.

The diagnosis of BPH involves specialist skills, based on the results of the patient's symptoms, the laboratory, and other tests. Completing the International Prostate Symptom Score (IPSS) could be useful in assessing the severity of the disease and choosing the right therapy. Based on the results of the questionnaire, patients can be classified into mild (IPSS: 0–7), moderate, and severe (IPSS: 20–35) categories [10].

All patients with LUTS should be offered lifestyle advice before (or in combination with) medical treatment. Those whose lifestyles are not impaired by their symptoms can manage with conservative treatment, which is called watchful waiting (WW). WW includes patient education, monitoring, and lifestyle recommendations. In this case, patients should focus on the reduction of fluid intake (especially during the night and while traveling), and avoiding diuretic and irritant agents (e.g., caffeine, alcohol) [14]. The use of relaxation and urination techniques (e.g., double-voiding, perineal pressure, the urethral milking technique, breathing exercises, mental tricks, etc.) help control storage symptoms [10,15]. In the mild or moderate categories, WW can be supplemented by phytotherapeutics (e.g., standardized preparation of saw palmetto, nettle, Pygeum, pumpkin, rye grass pollen, soy isoflavones, and β -sitosterol) [9,16–19]. Moreover, researchers are focusing on new herbal alternatives in regard to BPH treatment, specifically traditional Chinese medicine [20,21].

If the patients suffer from moderate or severe stages of BPH, specialists mostly offer drug therapy or surgical possibilities. The medications based on the pharmacological actions of active compounds include α 1-adrenoceptor antagonists, 5 α -reductase inhibitors, muscarinic receptor antagonists, phosphodiesterase type 5 inhibitors, and vasopressin analogs [10,15].

2.1. α 1-Adrenoceptor Antagonists and 5 α -Reductase Inhibitors

Due to the development and widespread use of medical treatments, surgical options have been pushed into the “second line” of intervention. The most commonly used α 1-adrenoceptor antagonists (α 1-blockers), and 5 α -reductase inhibitors for BPH treatment are summarized in Table 1.

Table 1. Most frequently used active compounds licensed in Europe in the treatment of LUTS [10,11,15].

Active Compound	Pharmacological Effect	Dose (mg)	Administration	Speed of Onset	Interaction May Occur
Alfuzosin	α 1-adrenoceptor antagonist	7.5–10	Immediately following a meal, at the same time each day, depending on the formulation	days	In combination with vasodilators (e.g., PDE5 inhibitors, nitrates), and other antihypertensives. Before cataract surgery, consultation is necessary. In the case of tamsulosin, warfarin and diclofenac co-administration is not recommended.
Doxazosin	α 1-adrenoceptor antagonist	2–8 (TR)	IR: daily once at bedtime ER: daily once with the first meal	days	
Silodosin	α 1-adrenoceptor antagonist	4–8	With a meal, at the same time each day	days	
Tamsulosin	α 1-adrenoceptor antagonist	0.4–0.8	30 min after the first meal	days	
Terazosin	α 1-adrenoceptor antagonist	5–20 (TR)	Daily once at bedtime	days	
Dutasteride	5 α -reductase (type 1 and 2) inhibitor	0.5	Without chewing, at the same time each day	6–12 months	In combination with strong CYP3A4 and CYP2D6 inhibitors.
Finasteride	5 α -reductase (type 2) inhibitor	5	Without chewing, at the same time each day	6–12 months	No drug interactions have been identified.
Alfuzosin+ Finasteride	combination therapy	10/5	Swallow 2 different tablets without chewing, after dinner	days	ama
Tamsulosin+ Dutasteride	combination therapy	0.4/0.5	Swallow 1 tablet without chewing, 30 min after a meal, at the same time each day	days	ama

TR: titration recommended, IR: immediate release, ER: extended-release, ama: as mentioned above.

To improve the clinical symptoms of LUTS and to relax the muscle of the prostate gland, α 1-blockers can be used. They do not reduce prostate gland enlargement, but they inhibit the binding of noradrenaline to the α 1-adrenergic receptors. In this category, alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin are available for BPH treatment

with similar clinical efficacy [10]. Among them, silodosin and tamsulosin are subtype-specific antagonists [22]. During their administration, the most frequent adverse events include asthenia, dizziness, and orthostatic hypotension. Tamsulosin showed the highest risk of intraoperative floppy iris syndrome development in connection with cataract surgery. They may have a small beneficial effect on erectile dysfunction, and they do not adversely affect libido. Because of their rapid onset of action, they belong to the first-line drug treatment [10].

Current treatment includes 5 α -reductase enzyme inhibitors (finasteride, dutasteride), which block androgen signaling via inhibition of DHT production. After a few months, they could reduce the size of the prostate gland. Their relevant side effects include reduced libido, erectile dysfunction, and ejaculation problems. Since relationships between 5 α -reductase enzyme inhibitors and prostate cancer occurrence remained unclear, PSA levels should be monitored during therapy. Due to their slow onset of action, they are only appropriate for long-term medication [10,11].

2.2. Other Medicaments and Combination Therapy in BPH Treatment

Medical treatment of BPH includes both static (reduction of prostate growth with 5 α -reductase inhibitors) and dynamic components (improvement of smooth muscle contractility with α 1-blockers) [22]. Moreover, phosphodiesterase-5 inhibitors (PDE5 inhibitors), muscarinic receptor antagonists, and vasopressin analogs may also have beneficial effects on the BPH-LUTS. Muscarinic receptor antagonists licensed for storage symptoms improvement include darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, and tolterodine. Because the effects of their long-term administration have not been clarified yet, they should be administered with caution and regular IPSS evaluation. PDE5 inhibitors may also have potential in LUTS improvement, via reducing smooth muscle tone of the detrusor, prostate, and urethra. In Europe, among the licensed PDE5 inhibitors (sildenafil, tadalafil, and vardenafil), only tadalafil (5 mg) has been approved for LUTS therapy. Its administration is contraindicated in patients who use nitrates, potassium channel openers, nicorandil, α 1-blockers, or have cardiovascular problems (e.g., unstable angina pectoris, a recent myocardial infarction or stroke, poorly controlled blood pressure, etc.) [10]. In the case of patients with nocturia, desmopressin (vasopressin analog) administration can reduce total urine volume. During its application, regular monitoring of serum sodium levels is essential to prevent hyponatremia [10].

To prevent the disease progression, α 1-blocker + 5 α -reductase inhibitor combinational therapy may also have potential, especially if the patient accepts long-term medication (Table 1). In cases when detrusor overactivity was demonstrated, co-administration of α 1-blockers and muscarinic receptor antagonists showed synergic activity [10,23,24]. In patients with overactive bladder symptoms, β -3 adrenergic agonist (mirabegron) add-on therapy was also investigated as a promising alternative [15]. PDE5 inhibitors in combination with 5 α -reductase inhibitors only showed a slight improvement in patients with a larger prostate [25]. However, before the start of these combinational therapies, cost-effectiveness and clinical relevance should be considered.

2.3. Surgical Therapy

In cases where the symptoms resist the medical therapy or the disease is in an advanced phase, surgical treatment could be a possible solution. Before surgery, the risk/benefit ratio should be considered, as well as the patient's full medical history and condition, focusing on the size and shape of the prostate gland. All patients should be informed about the treatment failure, side effects, and possible retreatment options. Most of the procedures are performed via the urethra where the prostate tissue can be removed, compressed, or destroyed by different energy sources [14].

Various forms of surgical treatment for BPH are available today, including conventional techniques, such as transurethral resection of the prostate (TURP), a modified version of this technique, and minimally invasive options (e.g., urethral microwave therapy (TUMT)

and laser, electrode, transurethral thermal ablation-assisted techniques) [26]. In comparison with TURP, laser-based methods decrease short-term complications. Similarly, thermal ablation therapies may cause fewer adverse events than conventional techniques, but they can be associated with irritative symptoms and urinary catheterization. A prostatic urethral lift also has potential in the preservation of ejaculatory function; however, it was found less effective in improving urological symptom, in both the short- and long-term [27].

Recently, a new method called convective radiofrequency water vapor thermal therapy, creating necrotic tissue in the prostate, became available. In LUTS treatment, this targeted, controlled water vapor energy applying technique could improve the life quality of patients. However, the effectiveness of this method, in comparison with other techniques, remained unclear [28].

3. Medicinal Plants Widely Used in the Treatment of BPH

3.1. *Cucurbita pepo*

Pumpkin (*Cucurbita pepo* L.) belongs to the Cucurbitaceae family, with several varieties grown throughout the world [29]. *C. pepo* is native to South–Central America [30], and has a long tradition of cultivation from Mexico to Argentina and Chile, but it can be successfully grown in Europe, Asia (India and China), and in Western America [31]. Pumpkin is a creeping or climbing annual plant. The oily seeds are ovate-elliptical, flattened, 15–25 × 7–12 mm, and a dark brown to black or creamy white color [32]. Pumpkin seed oil has been used since the end of the 19th century to treat urinary tract problems [33].

Pumpkin contains various biologically active components, such as polysaccharides, para-aminobenzoic acid, sterols, proteins, peptides [34], carotenoids, and γ -aminobutyric acid [35]. Pumpkin seeds have high protein and essential fatty acid content [36], the most important fatty acids being linoleic acid, palmitic acid, stearic acid, oleic acid. Furthermore, it contains non-essential amino acids, e.g., cucurbitin, as well as Δ^5 -, Δ^7 -, and Δ^8 -phytosterols, e.g., sitosterol and stigmasterol [4,30,37]. In addition, pumpkin seeds contain microelements (Na, K, Cr), tocopherol (vitamin E) [38,39], pigments, pyrazine, triterpenoids (e.g., saponins), and phenolic compounds, such as coumarins, and flavonoids [40–43] (Table 2).

3.1.1. Preclinical Studies

Pumpkin seed extract was reported to have antitumor [44], hepatoprotective [45], wound healing, anti-arthritis, hair-growth stimulating [46], anthelmintic [47], and antioxidant effects [48]. Moreover, therapeutic activities of pumpkin seed extract include the relief of symptoms associated with prostate disorders [49–51], urinary bladder complications [52–54], and lower urinary tract diseases [55]. Pumpkin seed extracts can block the increase of prostate weight and protein synthesis induced by testosterone/prazosin [56], inhibiting testosterone-induced hypertrophy [50]; 10 g/day pumpkin extract exerts tonic effects on the bladder and urethra [16,57].

In Europe, pumpkin seed oil has been used in folk medicine for treatment of BPH [58]. Efficiency can be achieved alone or in combination with saw palmetto when used to treat BPH [59]. Pumpkin seed oil has been found to reduce testosterone-induced prostatic hyperplasia in rats. In the experiment, pumpkin seed oil was orally administered to rats at 2 and 4 mg/100 g of body weight for 20 days, and both concentrations decreased the prostate size ratio [50]. The mechanism of action of pumpkin seed oil is supposed to involve 5 α -reductase inhibition [50]. Some studies also found that pumpkin seeds are rich in zinc, and these elements may help shrink an enlarged prostate [16,60] (Table 2).

3.1.2. Clinical Studies

A multicenter clinical trial in 1998 showed that the symptoms of BPH were relieved after taking capsules with pumpkin seed extract (500 mg) [61]. In a randomized, placebo-controlled, parallel-group trial, which enrolled 1431 men (of average 65 years old) with BPH, the treated group used pumpkin seed extract for 12 months. The treatment showed that the symptoms of BPH were relieved compared to the placebo group [62]. In a study

by Leibbrandt and Coulson, pumpkin seed extract was used for 12 weeks by BPH patients in a randomized, double blind, placebo-controlled clinical trial that included 57 males aged 40–80 years. As a result, the pumpkin seed extract reduced the symptoms of treated group compared to the control group [63]. Leibbrandt et al. reported that the IPSS was reduced by 30% in the group treated with oil-free hydroethanolic pumpkin seed extract [64]. In a study involving 100 BPH patients, the symptoms of BPH were relieved after using pumpkin seed oil for 24 weeks [65]. Hong et al. [66] conducted a clinical trial on 47 men with BPH symptoms. Patients received a mixture of pumpkin seed and saw palmetto oil, which significantly reduced IPSS within 3 months. In a clinical trial, the effects of pumpkin seed oil were evaluated in over 2000 men suffering from BPH. The patients used 500–1000 mg/day of the oil for 12 weeks. As a result, the treatment decreased the IPSS by 41.4% and more than 96% of the patients had no undesired side effects, indicating that pumpkin seed oil significantly improved the urinary dysfunction in patients [67].

Pumpkin seeds are extremely safe, but their use may lead to minor stomach upsets, and can be responsible for indigestion, diarrhea [57], and electrolyte loss (due to its diuretic properties) [68]. For these reasons, pumpkin seed oil is contraindicated in the case of concomitant anticoagulant therapies [30]. The use in children and adolescents under 18 years of age, and in pregnant women, is not recommended, because LUTS—in these populations—require medical supervision [69].

Table 2. Active compounds and biological activities of medicinal plants commonly used in the treatment of BPH, based on preclinical studies. Reference numbers provided in the brackets [].

Plant Species, Drug Part	Active Compounds	Biological Activities/Supposed Mechanism of Action
<i>Cucurbita pepo</i> seed	Polysaccharides, sterols, para-aminobenzoic acid, proteins and peptides, carotenoids, γ -aminobutyric acid [34,35]; seed: fatty acids, phytosterols [36,37]	• Inhibits 5α-reductase [50] • Decrease of DHT level [56] • Inhibits testosterone-induced hypertrophy [50] • Antitumor [44]
<i>Epilobium parviflorum</i> and <i>E. angustifolium</i> aerial parts	Polyphenols, steroids, triterpenoids, fatty acids [70]	• Anti-inflammatory, antioxidative, anti-proliferative, antimicrobial, analgesic, anti-androgenic activities [70–77] • Increase of CYP2D2 [78] • Decrease of CYP3A1 expression [78] • Decrease of CYP2E1 and CYP1A1 expression [79] • Decrease of CYP2B1, CYP2C6, CYP2D2, CYP3A1 protein levels [80]

Table 2. Cont.

Plant Species, Drug Part	Active Compounds	Biological Activities/Supposed Mechanism of Action
<i>Hypoxis hemerocallidea</i> corm	Phytosterols: hypoxoside, rooperol, β -sitosterol, stigmasterol, stigmastanol; hypoxhemerosides A–F, curcapi-cycloside, obtuside A, interjectin, crassifoside F, acuminoside, geraniol glycoside, vanillic acid, β -arbutin, orcinol glycoside [81,82]	• Anti-inflammatory activity [4] • Increase of TGF-β1 expression and protein kinase C-α activity in stromal cells [4]
<i>Solanum lycopersicum</i> fruit	Tetraterpene carotenoids: lycopene, β -carotene, α -carotene; minerals, vitamins [83]	• Antioxidant activity [84] • Decreases the expression of nicotinamide adenine dinucleotide phosphate oxidase [85] • Anticancer and anti-inflammatory activities [86]
<i>Pinus pinaster</i> bark	Procyanidins, taxifolin, cinnamic acid, ferulic acid, caffeic acid, benzoic acid [87,88]	• Anti-inflammatory activity [89,90] • Nitric oxide synthase (eNOS) activity [89,90] • Reduction in malondialdehyde, increased glutathione, catalase and peroxidase levels [91] • Decrease of DHT level [92]
<i>Roystonea regia</i> fruit (oil)	D-004 extract (oleic, lauric, palmitic and myristic acids) [4]	• Inhibition of 5α-reductase [4] • Antioxidant effects [4] • Inhibition of phenylephrine-induced contractions in isolated rat prostate strips [93]
<i>Prunus africana</i> bark	Phytosterols, fatty acids, triterpenes, proanthocyanidins, atraric acid, lauric acid, myristic acid, ferulic acid, atranorin, cholesterol, N-butylbenzene sulfonamide, hydroxybenzoic, linoleic, stearic, arachidonic, behenic, lignoceric acids [94–99]	• Inhibits 5α-reductase [100,101], • Inhibition of DHT and estrogen receptors [4], progesterone and androgen receptors [97]. • Inhibits the basal growth of prostate stromal cells stimulated by EGF, IGF-I, bFGF, TPA, and PDBu [102]

Table 2. Cont.

Plant Species, Drug Part	Active Compounds	Biological Activities/Supposed Mechanism of Action
<i>Secale cereale</i> pollen	Carbohydrates, amino acids, proteins, phenolic compounds, sterols, triglycerides, plant pigments [103–106]	• Inhibition of cyclooxygenase and the 5-lipoxygenase activity [107] • Inhibition of prostaglandin and leukotriene synthesis [107] • Anti-inflammatory activity—decreased TNF-α and IL-6 cytokines levels [108] • Decreased androgen receptor and PSA expression [109]
<i>Serenoa repens</i> fruit	Carbohydrates, sterols, flavonoids, triglycerides, fatty acids [110,111]	• Inhibits 5α-reductase [111] • >Inhibits formation of DHT and some testosterone metabolites [111] • Inhibits the conversion of testosterone into DHT [111] • Inhibition of α-receptor binding [111] • Inhibits the receptor binding of androgens [111] • Anti-proliferative effect [111] • Inhibition of eicosanoid synthesis [111] • Spasmolytic effects [111] • Anti-inflammatory activity [111,112]
<i>Urtica dioica</i> root	Sterols, flavonoids, tannins, acids, minerals, lectins, polysaccharides, ceramides, monoterpenoids, fatty triterpene, and phenylpropane [4,9,113–116]	• Anti-proliferative, anti-inflammatory— inhibition of COX and lipoxygenase [4] • Inhibits TNF activity [4] • Stimulates activity of T-lymphocytes and the complement activation [117] • Inhibits the connecting of sex hormone binding globulin [118] • Inhibits prostate growth [119,120]

3.2. *Epilobium parviflorum* and *E. angustifolium*

Epilobium species, commonly known as willowherbs or fireweeds, are perennial herbaceous, mostly hemicryptophyte plants, members of the evening primrose family (Onagraceae) [121]. The aerial parts of the plant are used as herbal tea or in combination with other herbal substances in herbal medicines. Based on long-standing use, some *Epilobium* species, including *E. angustifolium* L. and *E. parviflorum* Schreb., can be used for the relief of LUTS of BPH, such as difficulty starting urination or a frequent need to urinate [122]. The European and North American traditional uses include treatment of BPH, prostatitis, bladder, and kidney diseases, and other urinary tract associated problems, while based on American traditions, it can also treat diarrhea and other gastrointestinal diseases, cough, various skin and mucosa diseases, bodily injuries, and pain [70].

Plant materials of the *Epilobium* genus are especially rich in polyphenols including flavonoids (kaempferol, quercetin, and myricetin derivatives), phenolic acids (ellagic, chlorogenic, gallic acid), and tannins (ellagitannins and gallotannins in *E. parviflorum*) but some steroids, triterpenoids, and fatty acids were also isolated from them [70] (Table 2).

3.2.1. Preclinical Studies

Epilobium is one of the medicinal plants used against the symptoms of BPH, although its mechanism of action is not completely clarified. Nevertheless, preclinical studies reported anti-inflammatory, antioxidative, anti-proliferative, antimicrobial, analgesic, and antiandrogenic activities of the extract [70,71]. Review articles summarized the biological activities of *E. angustifolium*, including the above-mentioned ones besides cytotoxic, immunomodulatory, photoprotective, anti-ulcer properties, and emphasizing its importance in BPH treatment and prostate cancer prevention [72–74]. A recent assessment was also made about the wound healing properties of *Epilobium* species due to its anti-hyaluronidase, anti-collagenase, and antioxidant activities [75]. In general, polyphenols are thought to be responsible for the effects of *Epilobium* extracts. Ellagitannins are metabolized by the gut microbiota resulting in anti-inflammatory urolithins [72,76]. Oenothien B, a macrocyclic ellagitannin, seems to be at least one of the major bioactive compounds of *Epilobium* species due to its antioxidant, anti-inflammatory, enzyme inhibitory, antitumor, antimicrobial, and immunomodulatory activity described in several preclinical studies [77]. Due to its large molecular size and relatively high polarity, the bioavailability of oenothien B is very poor, similarly to other ellagitannins, but in contrast to them, oenothien B is not metabolized by the human gut microbiota, and its metabolic pathway is still unknown [72,123,124]. In addition, recent studies suggest that catechin and epicatechin (flavonoids) can have a major role in prostatitis related effects of *E. angustifolium* due to their COX-2 inhibition [125], while quercetin, myricetin, and myricitrin, in the case of *E. parviflorum* in cancer therapy [126], based on molecular docking analysis.

Orally administered *E. angustifolium* caused a slight increase of CYP2D2 and a significant decrease of CYP3A1 expression [78]. Intraperitoneal injection of *E. hirsutum* extract decreased the CYP2E1 and CYP1A1 expression in rats [79]. Another article discussed the effect of intraperitoneal *E. hirsutum* extract and ellagic acid injection on drug metabolism in rats, where both test substances inhibited hepatic erythromycin *N*-demethylase, benzphetamine *N*-demethylase and 7-benzoyloxyresorufin-*O*-debenzylase activity, and decreased CYP2B1, CYP2C6, CYP2D2, and CYP3A1 protein levels [80] (Table 2).

3.2.2. Clinical Studies

Despite the promising preclinical results with *Epilobium* species, human clinical trials connected to BPH are limited. Literature search revealed only one randomized, double blind, placebo-controlled clinical trial related to BPH that was performed solely with *Epilobium* extract, and included 128 adult men. The treated group received 500 mg chemically characterized *E. angustifolium* extract (containing $\geq 15\%$ oenothien B) in the form of hard, gastric-resistant capsules daily for 6 months. The *E. angustifolium* treatment significantly improved the IPPS, the post-void residual (PVR), and the number of urinations during the

night, but not the PV or the PSA. Tolerance and safety assessment was also conducted, according to which the *E. angustifolium* food supplement was found to be well tolerated, and did not cause any hepatic or renal toxicity [127]. Other human studies with *E. angustifolium* extract focused on its skin photo-protection and anti-dandruff effect [128,129].

Most clinical studies were performed with combined preparations, containing additional components known for their anti-BPH activity. An herbal preparation containing *Cucurbita pepo*, *E. parviflorum* (equivalent to 500 mg dry herb), lycopene, *Pygeum africanum*, and *Serenoa repens* was examined in a randomized, double blind, placebo-controlled clinical trial, where this herbal medicine significantly improved the symptoms of BPH [63]. Another combined preparation, a food supplement containing water-soluble extracts of *Ononis spinosa*, *Solidago virga-aurea*, *Phyllanthus niruri*, *Peumus boldus*, and *E. angustifolium* (12.5:12.5:18.7:25.0:31.2, respectively, as dried materials) was also studied with 30 patients, and after 1 month of treatment the extract improved the LUTS, such as maximum flow, and the quality of life assessed by the IPPS questionnaire. Related to this study, reduced cell viability and inhibited release of PGE₂ and COX-2 gene expression were also observed in vitro in human prostate PC3 cancer cells [130].

3.3. *Hypoxis hemerocallidea*

The *Hypoxis* genus (family Hypoxidaceae) covers 103 species registered in “The Plant List” [131]. They can be found in most warm temperate and tropical zones of the world (under different synonyms). The most known (and studied) species is *Hypoxis hemerocallidea* Fisch., C.A. Mey. and Avé-Lall. (syn. *Hypoxis rooperi* T. Moore or *Hypoxis rooperi* var. *forbesii* Baker). However, several other *Hypoxis* species and their synonyms were mentioned in published studies in previous years, due to the fact that many *Hypoxis* species are used indiscriminately in traditional medicine and are sold under the common name “African potato” in herbal shops. The plant possesses an underground part, which is neither a tuber, nor a root, nor a rhizoma, but a corm (“bulbous tuber”), a rounded underground storage organ consisting of a thickened base of a stem covered with leaf scales. The dark brown corm (7–10 cm diameter) is covered with bristly hairs, and is bright yellow when freshly cut and turns brown after some time. It has an unpleasant bitter taste.

As described earlier [4], the *Hypoxis* corm is traditionally used to treat a wide variety of diseases/conditions (prostate hypertrophy, burns, cancer, cardiac diseases, dizziness, headaches, impotency, intestinal parasites), and to boost the immune system.

The corm contains (up to 10%, dry weight) a unique secondary metabolite, hypoxoside, its aglycone rooperol, β -sitosterol, stigmasterol, stigmastanol, as well as the newly described hypoxhemerolosides A–F, curcapiacycloside, obtuside A, interjectin, crassifoside F, acuminoside, geraniol glycoside, vanillic acid, β -arbutin, orcinol glycoside [81,82] (Table 2).

3.3.1. Preclinical Studies

In addition to previously summarized data (e.g., β -sitosterol related increase of TGF- β 1 expression and protein kinase C- α activity in the stromal cells of the human prostate, in vitro anti-inflammatory activity of rooperol, or the possibility of an interaction of *Hypoxis* preparations with CYP450 isoforms 1A2, 2A6, 2B6, 2C8, 2C9, 3A4, and 3A5) [4] (Table 2), there are only three new (and not BHP-related) studies with *Hypoxis* or its constituents. Two of these studies, investigating the outcomes of concomitant administration of various *H. hemerocallidea* extracts with indinavir [132] or a lopinavir/ritonavir combination [133], did not find statistically significant changes in the pharmacokinetics of the antiviral agents.

In the case of streptozotocin-induced diabetes mellitus, improved antioxidant enzyme activities were measured in adult male Wistar rats, both under normal and under oxidative stress conditions, following treatment with 800 mg/kg *H. hemerocallidea*. The results obtained in this study showed that effects were dose independent. The sperm motility and morphology showed the greatest improvement in the diabetic group treated with *H. hemerocallidea* [134].

3.3.2. Clinical Studies

Currently, no clinical trials have been published, directed at the application of *Hypoxis* extracts in the treatment of BPH, which of course does not give the opportunity to make a clear position on the therapeutic efficacy of the use of *Hypoxis* extracts (these only at the level of food supplements, not registered drugs), or to assess the benefit–risk ratio.

3.4. *Solanum lycopersicum*

Solanum lycopersicum L. syn. *Lycopersicon esculentum* Mill., or the tomato plant, belongs to the Solanaceae family. It is native to the Andes of South America, from where it has spread to all temperate and tropical regions; it is considered today as one of the world's most important vegetables. It is an annual plant that grows up to 2 m in height and is cultivated today mainly for its edible fruits [135].

S. lycopersicum fruits are typically composed of 94.5% water, 3.89% carbohydrates (1.2% of total dietary fiber and 2.63% of sugars), 0.88% protein and 0.2% total lipid (fat), while other nutrients and phytochemicals include minerals (e.g., 237 mg potassium, 24 mg phosphorus, 11 mg magnesium, 10 mg calcium), vitamins (e.g., 13.7 mg vitamin C, 0.12 mg γ -tocopherol, 0.6 mg niacin), and tetraterpenes (e.g., 449 μ g β -carotene, 101 μ g α -carotene, and 2570 μ g lycopene, collectively known as carotenoids) [83] (Table 2). Lycopene has been widely studied in relation to prostate dysfunctions, including BPH and prostate cancer [136–138].

3.4.1. Preclinical Studies

Lycopene is a non-provitamin A carotenoid with antioxidant activity exerted by quenching of singlet oxygen and scavenging peroxy radicals [84]. Additionally, it was shown to decrease the expression of nicotinamide adenine dinucleotide phosphate oxidase 4, consequently reducing reactive oxygen species generation [85]. Lycopene has also been shown to possess anticancer and anti-inflammatory activities [86] (Table 2). Lycopene can induce cell-to-cell communication and controls cell growth [84]. It antagonized transforming growth factor β -induced metastasis in vitro [85]. In LNCaP human prostate cancer cells, lycopene induced apoptosis, as more cells were in G₂/M cell cycle phase and less were in S-phase upon treatment with 5 μ M lycopene [139]. Another study showed a similar effect of lycopene extract on the induction of apoptosis in primary human prostate cancer cells with an upregulation of p53 and Bax, and downregulation of Bcl-2 [140]. Induction of apoptosis following tomato sauce consumption was seen in dissected tumors of BPH and prostate cancer patients [141]. Tomato and lycopene were also shown to reduce the risk of cardiovascular disease [142]. The underlying mechanism might be the antioxidant activity of lycopene, as it decreased low-density lipoprotein levels and its oxidation [143]. Antithrombotic activity was also observed, as tomato extracts reduced platelet aggregation [144]. The anti-inflammatory activity of tomato and lycopene might also contribute to beneficial effects in cardiovascular health. It was shown to reduce tumor necrosis factor- α concentrations in healthy individuals [145]. Lycopene alleviated chronic prostatitis/chronic pelvic pain syndrome in a rat model, presumably due to its anti-inflammatory properties: cytokines tumor necrosis factor- α , interleukin-1 β , interleukin-2, and interleukin-6 were downregulated; phosphorylation of mitogen-activated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B) decreased, while phosphorylation of nuclear factor erythroid 2-related factor 2 (Nrf2) increased [146]. In normal prostate tissue in rats, lycopene also reduced androgen signaling, insulin-like growth factor 1 (IGF-1) expression and proinflammatory cytokines [147].

3.4.2. Clinical Studies

Lycopene may be beneficial in the prevention of prostate cancer [148]. Patients with BPH are at a higher risk of developing prostate cancer [149], but few clinical studies addressed the use of tomato or derived products in BPH. In a recent phase II clinical study, tomato-based food supplement improved lower urinary tract problems in patients with

BPH [150]. Patients receiving 5 g of the supplement daily for 2 months reported no adverse effects and fewer lower urinary tract problems, leading to a statistically significant improvement of the quality of life. On a molecular level, a reduction in PSA was observed, but was only significant in patients who had higher (above 10 ng/mL) baseline concentrations of PSA. Approximately 11% decrease in PSA concentration upon ingestion of 10 g of tomato paste for 10 weeks was observed in BPH patients in another study [151]. A defined dose of lycopene, i.e., 15 mg daily taken for 6 months was given to patients with histologically determined BPH and absence of prostate cancer in a study by Schwarz et al. [152]. Lycopene-treated patients had a statistically significant reduction in PSA levels as compared with placebo group and experienced an improvement of symptoms. No prostate enlargement occurred in lycopene-treated patients as opposed to the placebo group, where the prostate enlargement was statistically significant at the end of the 6-month study.

Excessive consumption of tomato-based products can have harmful effects, as it can lead to gastroesophageal reflux disease (due to the presence of organic acids), kidney problems (due to high potassium and oxalate concentrations), irritable bowel syndrome (due to high tomato skin and seeds consumption), lycopendermia (orange skin discoloration due to high lycopene blood levels), urinary problems (due to the presence of organic acids), body aches, and arthritis (in case of consumption of unripe green fruit containing higher concentrations of toxic steroidal glycoalkaloids tomatine and solanine) [86]. A combination of lycopene and alcohol induced CYP 2E1 expression and inflammation in rats, but clinical importance of this has not yet been shown [153]. Tomato is a known allergen in some individuals and can lead to anaphylaxis [154,155].

The beneficial effects of tomato and derived products in BPH are mainly attributed to the biologically active carotenoid compound lycopene that has antioxidant, anti-inflammatory, and anticancer activities. The use of tomato-based or lycopene supplements was efficient in alleviating the symptoms of BPH in several clinical studies. However, adverse effects are possible; therefore, more research is needed to determine safe and efficient dosage regimen of tomato and derived products in BPH.

3.5. *Pinus pinaster*

French maritime pine bark extract exhibits antioxidant and anti-inflammatory effects and has been studied in a variety of clinical conditions, including asthma, attention deficit hyperactivity disorder (ADHD), chronic venous insufficiency, cardiovascular disease, diabetes, and erectile dysfunction. However, the publication of many methodologically weak clinical studies makes it difficult to provide clear support for the use of pine bark extract for each condition [156]. The pine bark is harvested, powdered, and typically extracted via a patented methodology to produce Pycnogenol® (Horphag Research, Geneva, Switzerland) [157] and is therefore a patented preparation of *P. pinaster* standardized to $70 \pm 5\%$ procyanidins in compliance with the United States Pharmacopeia [87]. Procyanidins are biopolymers of catechin and epicatechin subunits, important components of human nutrition, with studies increasingly suggesting that this standardized extract has favorable pharmacological properties [158]. Importantly, procyanidins are considered powerful antioxidants found in significant quantities in foods including grapes, berries, and red wine, and are marketed widely through various different health promotional products for various chronic disorders [88]. Additional important constituents include taxifolin, cinnamic, ferulic, caffeic, and benzoic acid (Table 2). Pycnogenol® has been shown to have beneficial effects in a variety of chronic diseases, including obesity, metabolic syndrome, and type 2 diabetes mellitus, alongside associated dyslipidemia and hypertension [87]. Evidence further suggests beneficial effect in UV-induced radiation damage, asthma, and systemic lupus erythematosus, alongside improvements in osteoarthritis, cognitive function, specifically attention deficit disorder (ADD) [157–159]. Pleiotropic effects, including a beneficial effect in BPH, are reported by Rohdewald et al. [160].

Pycnogenol® is considered safe with low toxicity in acute or chronic exposures [158]. The dosages currently recommended through clinical trials range from 100 to 360 mg per

day. Doses of pine bark extract have been studied in clinical trials, most commonly at 150 mg per day in three divided doses [156].

3.5.1. Preclinical Studies

French maritime pine bark protects against oxidative stress by increasing the intracellular synthesis of antioxidant enzymes and by acting as a potent free radical scavenger via the regeneration and protection of vitamins C and E. Anti-inflammatory activity has been demonstrated in vitro and in vivo in animals, including protection against UV radiation-induced erythema. Immunomodulation has been observed in animal models and in patients with lupus. French maritime pine bark counteracts adrenaline and noradrenaline-induced vasoconstriction by increasing endothelial nitric oxide synthase (eNOS) activity and preventing smoking-induced platelet aggregation. It has been shown to relieve some premenstrual symptoms, including abdominal pain. This effect may be related to the spasmolytic action of certain phenolic acids [89,159]. It has many other pharmacological activities, including protection against ovariectomy-induced bone loss in rats [90].

There are generally few studies for Pycnogenol® in male reproduction, especially in preclinical studies. These suggest a beneficial effect on sperm quality. However, there is more substantial evidence for the use of Pycnogenol® in erectile dysfunction. In a rat model, where spermatotoxicity was induced by administration of 30 mg/kg/day α -chlorohydrin for 7 days, co-administration of Pycnogenol® (20 mg/kg/day) showed reduction in malondialdehyde, increased glutathione, catalase and peroxidase levels in the epididymis, improved histopathological changes, reduced apoptosis and resulted in improvement in sperm motility, compared to the control [161].

A study investigating whether Pycnogenol® could prevent BPH induced by testosterone propionate (TP) was conducted in rats. One group was used as normal control rats and the other groups received subcutaneous injections of TP for 4 weeks to induce BPH. In the two treatment groups, Pycnogenol® (20 or 40 mg/kg) was administered daily for 4 weeks by oral gavage, concurrently with the induction of TP. Results indicated that Pycnogenol® inhibits the development of BPH and that this is closely associated with a reduction in DHT levels. [91] (Table 2).

3.5.2. Clinical Studies

A nonrandomized clinical trial studied 19 subfertile men who received 200 mg/day of Pycnogenol® for a period of 3 months. Semen analysis showed an improvement in capacitation (38%) and mannose receptor binding capacity (19%) compared to baseline (before treatment), suggesting that this treatment may improve natural or induced reproductive outcomes in cases of teratozoospermia. Prelox®R is a combination of Pycnogenol®, alongside L-arginine, L-citrulline, and roburin. In a double-blind, randomized, controlled crossover study, subfertile men ($n = 50$) underwent monthly sperm analysis in a pretreatment phase (1 month), followed by a treatment or placebo phase (1 month), then a washout phase (1 month), followed by the crossover phase (1 month). The study showed a significant improvement in sperm volume, concentration, motility, viability, and morphology compared to the placebo treatment, with an increase in intracellular eNOS activity in spermatozoa [92].

Prelox®R demonstrated also improvement in erectile function in a male cohort ($n = 50$) over a 1-month treatment period in a randomized, placebo-controlled, double-blind crossover study using the International Index of Erectile Function as the primary outcome. Significant improvements in erectile function were reported compared with placebo [162]. This was consistent with previous studies reporting that Prelox®R restored normal erectile dysfunction over 1-month treatment, alongside significant improvements in sexual intercourse frequency (doubled) and increases in serum testosterone and sperm eNOS [163,164]. Taken together, these studies suggest some consistency for the effect of Pycnogenol on erectile dysfunction, however, they are combined with L-arginine; therefore, the effect of Pycnogenol® alone is not clear.

Another study evaluated the efficacy of Pycnogenol® supplementation in terms of safety and tolerability for preclinical or borderline early symptoms of BPH in otherwise healthy subjects over a 60-day period. Seventy-five healthy men with symptoms and signs of incipient BPH were included. Subjects were divided into three groups: (1) control group using standard management (SM) without surgical indications, based on the avoidance of anticholinergic, sympathomimetics, opioids drugs; patients were instructed to void regularly, avoid long seating periods, exercise regularly, hydrate appropriately, preferably avoiding caffeine and spices, follow a low-sugar and low-salt diet; (2) A group using SM plus Pycnogenol® 150 mg/day; (3) A group using standard pharmacological management, including dutasteride (one capsule, 0.5 mg/day) and/or finasteride 5 mg/day.

The results showed BPH symptoms like emptying, frequency, intermittency, urgency, weak flow, straining, nocturia, were all significantly improved with Pycnogenol® ($p < 0.05$) and the difference with both control groups was statistically significant ($p < 0.05$). So Pycnogenol® may be an important option for self-management of BPH in otherwise healthy men [165].

In conclusion, relatively few preclinical or clinical studies have been conducted with *P. pinaster* extracts in andrology [166], and the limited studies suggest a role in protecting against induced spermatotoxicity through improved oxidative stress markers. It is also suggested to be useful in teratozoospermia patients. In combination with L-arginine, L-citrulline, and roburin (Prelox®R), Pycnogenol® may improve fertility outcomes in subfertile males. However, the most significant clinical indication of this combination has been demonstrated in erectile dysfunction. This appears to be independent of the influence of the amino acid L-arginine, and it is mediated by vasodilation. There are few studies, to date, on the use of Pycnogenol® in subfertility, but the evidence is good for the use of Prelox®R in erectile dysfunction. Based on the current evidence, further studies are warranted for the use of Pycnogenol® in andrology, particularly in oxidative stress-induced infertility, erectile dysfunction, and as recent studies show in the treatment of BHP.

3.6. *Roystonea regia*

Roystonea is a genus of the Arecaceae family, which contains ten species, the most famous of which is *Roystonea regia* (Kunth) O.F. Cook, known also as Cuban Royal Palm [167]. It grows from south Florida through Central America and some Caribbean islands to South America. This majestic plant grows from 15 to 21 m tall, with a canopy spread of up to 7.5 m in diameter. The dark purple or black fruits are smooth, ovate, and measure 13 mm in length. The fruit is a rich source of oil [168].

Basic information related to the chemistry of the D-004 extract (a lipid extract of *Roystonea* fruit, containing oleic, lauric, palmitic and myristic acids) was given in an earlier review [4], as well as preclinical studies on this extract (antioxidant effects in prostate tissue, competitively inhibiting the prostatic 5 α -reductase, and the sympathetic-induced contraction of the smooth muscle in rat-isolated deferens tube), as well as in vivo studies on prevention and improving BPH induced by testosterone in rats, and a randomized, double-blind study on healthy volunteers, indicating significant antioxidant effects on plasmatic oxidative markers of D-004 taken for 6 weeks (Table 2). However, some BPH therapy-related articles were omitted in [4]; thus, they will be presented here, together with recent articles.

3.6.1. Preclinical Studies

Arruzazabala et al. investigated the effects of D-004 on phenylephrine-induced contractions in isolated rat prostate strips. D-004 significantly and dose-dependently inhibited the contractions through a noncompetitive mechanism [169] (Table 2).

D-004 extract was evaluated in a subchronic (8 weeks) study in mice. No evidence of treatment-related toxicity was detected. Thus, body weight gain, clinical observations, food consumption, blood biochemical, hematology, organ-weight ratios, and histopathological findings were similar in the control and treated groups. This study supports that D-004

orally administered up to 2000 mg/kg/day did not induce treatment-related toxicity [93]. The same research group investigated the long-term oral toxicity of D-004 in rats. No clinical signs of toxicity were observed throughout the study. Thus, 12 months of oral treatment of rats with D-004 (up to 2000 mg/kg/day) did not show evidence of its toxicity [170]. Finally, Gutiérrez et al. demonstrated that oral administration of D-004 (up to 1500 mg/kg/day) for 24 months was devoid of long-term oral toxicity and/or carcinogenicity in male and female rats, and that the highest dose tested was the NOAEL [171].

Arrebolal et al. (2009) studied a risk of changes in the appearance frequency of micronuclei during oral administration of repeated doses of D-004 in bone marrow male OF-1 mice for 8 weeks. There were no deaths or clinical signs of toxicity or significant differences among controls and treated ones regarding the frequency of micronucleated polychromatophil erythrocytes, and the cytotoxic index. D-004 administered p.o. has neither clastogenic nor cytotoxic activity in vivo [172].

Thus, these mid- and long-term animal experiments indicated with a high degree of certainty that any therapy with D-004-containing products should be non-toxic.

3.6.2. Clinical Studies

The aim of a single recent study was to compare the efficacy and tolerability of D-004 with terazosin on LUTS in 100 men (at least 50 years of age) with BPH in an open, randomized, comparative design. D-004 (320 mg/day) and terazosin (5 mg/day) significantly reduced the IPSS at the end of the 6 months of therapy, by 74.2% and 66.1%, respectively. Although the average size of the prostate was reduced in both groups, this reduction reached statistical significance only for D-004. Both treatments were safe, while D-004 was better tolerated than terazosin [173].

3.7. *Prunus africana*

The African cherry or African plum or African prune tree (*Prunus africana* (Hook. f.) Kalkman) (syn. *Pygeum africanum* Hook. f.) belongs to the Rosaceae family. The tree occurs in the mountain regions above 1500 m above sea level in Southern and Central Africa [174], as on the islands of Grande Comore, Bioko, and São-Tomé [100], and in Madagascar, Comoros Islands, and the Gulf of Guinea [4]. It is an evergreen tree, which grows up to 30–40 m height developing a spreading canopy [94].

The powdered bark has been used by indigenous people for urinary tract disorders and as an aphrodisiac drug in the tropical and subtropical regions of Africa [174,175]. The bark is traditionally applied in the treatment of cough and cold in Kenya [176] and South Africa [177]; asthma [178], malaria and prostate cancer in Kenya [179]; BPH in Ethiopia [180] and Mozambique [181]; as anticancer drug in Uganda [182]; for jaundice in Ethiopia [183]; for tuberculosis, HIV, and stomach problems in South Africa [177]; for mental disorders, diabetes, skin infection, ulcers, gonorrhea, as well as for hypertension; while the root and the fruit for chest pain; the leaf for fever, and e.g., for mental disorders, diabetes, skin infection, ulcers, gonorrhea, and hypertension [184–188].

The effectivity of the peeled bark in the treatment of BPH [189] was detected only in the 1960s [190], which was followed by an intensive bark harvesting in Cameroon in the 1970s [94]. The drug was imported to the European market from French colonies. The bark became a popular and effective drug in Western medicine, followed by even more intensive and inappropriate harvesting methods, which caused an overexploitation of the tree. Numerous international programs were launched to rescue the species, and to supply the medicinal and pharmaceutical demands. The products of the tree are available mostly in French medicine and in the USA [174].

The drug part of African plum is the dark brown bark [100], which can be peeled by various tools from the trunk of the tree [94]. The dried bark can be prepared with organic solvents or supercritical extraction in remedies [174].

The bark contains phytosterols, e.g., β -sitostenone [95], β -sitosterol, and its derivatives [94], including esters and glucosides, e.g., β -sitosterol-3-O-glucoside [96], atraric

acid [96], and ester derivatives of long-chain alcohols, such as n-docosyl-*trans*-ferulate and n-tetracosyl-*trans*-ferulate. In addition, fatty acids (mostly palmitic acid) [100], triterpenes (e.g., oleanolic acid, ursolic acid, 24-O-*trans*-feruloyl-2 α ,3 α -dihydroxy-urs-12-en-28-oic acid) [97], lauric acid, myristic acid, ferulic acid and its esters [191], atranorin, cholesterol, N-butylbenzene sulfonamide [192], proanthocyanidins [113], hydroxybenzoic, linoleic, stearic, arachidonic, behenic, and lignoceric acids [113] were also isolated from the bark extracts, while α -amyrin, phytol, vanillin, benzenedicarboxylic acid, squalene, nicotinic acid, campesterol, stigmasterol, and α -tocopherol were identified in the leaves of the species [96] (Table 2).

3.7.1. Preclinical Studies

The anti-inflammatory effects of the bark [99] contribute to the decrease of the obstructive symptoms of BPH [174]. The effects for prostate hypertrophy were documented in several pharmacological studies, e.g., on mice and rats [57,102,193–196]. The bark inhibits the basal growth of prostate stromal cells in rats, stimulated by EGF, IGF-I, bFGF (direct activators of protein kinase C), TPA (tissue plasminogen activator), and PDBu (phorbol 12,13-dibutyrate) [196].

The inhibitory potential of lipoxygenase was proved in various in vitro studies. The antiproliferative potential of the extracts plays a role to slow or stop the process of hyperplasia and urinary dysfunctions [102,174,196–199]. This effect has been observed in rats, using Tadenan[®], which is an extract of the plant, before and after administration of DHT [200]. This extract prevents the activation of free radicals and metabolizing enzymes, protects the intracellular membrane against the harmful effect of free radicals, and decreases the dysfunction of the urinary bladder [98]. The use with DHT decreased the frequency of micturition as pretreatment in rats, but by itself, it increased the rate of urine production and the volume of micturition. In addition, the weight of the prostate increased in the group treated by the extract and DHT, but it decreased in the animals treated only by the extract. These results also highlight the reducing potential of the extract against the harmful effects of DHT on micturition [201].

In another experiment, primary and organotypic cultures of human prostatic stromal myofibroblast cell line WPMY and prostatic epithelial cell line PNT2 were investigated: the oral intake of the extract resulted in serum levels of active compounds, which inhibited the proliferation of cultured myofibroblasts prostatic cells [202].

The extracts also inhibit the activity of 5 α -reductase [174,203], DHT and estrogen receptors [4], the progesterone and androgen receptors [97]. In addition, its α -adrenergic antagonism potential was also described [4] (Table 2).

In animal models, the extracts decreased the stimulus sensitivity in the urinary bladder, which enhanced the irritative symptoms [174]. In addition, the bark extract regenerates the secretion of the prostate epithelium, and possesses anti-inflammatory activity through the inhibition of 5-lipoxygenase [101].

Cytotoxic activity of the drug was investigated on HLaC79 cells and mucosal keratinocytes, where the extracts increased the apoptotic cell fractions [204].

The mechanisms of the effect of the bark are definitely not clarified yet, and the compounds, which can be responsible for the medicinal effect, were not identified with certainty [174].

3.7.2. Clinical Studies

The activity of the bark extract related to prostate hypertrophy was described in numerous studies [58,175,189,205,206]; however, double blind placebo-controlled trials produced variable results, and inadequate reports are available on the safety and efficacy of the extracts [68,207]. The validation and mechanism of action are poorly defined, possibly including growth factor inhibition, anti-inflammation, and antiandrogenic action of the drug [208], and only a few reviewed studies are available [209].

According to the endorsed monograph in the European Union herbal monograph of the European Medicines Agency (EMA), the plant extracts provided a large improvement in a combined outcome of urologic symptoms with BPH [209]. The clinical benefits of the plant in BPH patients are due to the multiple mechanisms, which include inflammatory, hormonal, and bladder components [210].

An earlier study reported the effect of the bark extract in the case of nocturia and incomplete bladder emptying after 6 weeks therapy, compared to placebo group [211], and the improvement in micturition [212]. In another study, 750 men were involved in a randomized, double blind, placebo-controlled trial, treated twice daily by Tadenan[®] [213,214]. Some randomized clinical trials confirmed its significant efficacy in improving urinary symptoms [4,175], compared to placebo control, such as influencing, e.g., the rate of the urine flow, the urine volume, the urination frequency, and the nocturia in beneficial way [174,208]. The plant extracts were found to be efficient in patients with BPH at doses of 50 mg twice daily and 100 mg once daily, in a 2-month randomized, double-blind study, which was confirmed by further improvement after 12 months [215].

Various remedies of the plant are also available in many countries showing an increased prescription index globally [216]. Tadenan[®] is recently used in France, Germany, and Austria [175]. According to some studies and traded herbal remedies of the drug, the most frequently recommended dose is 100–200 mg/day for 1–2 months [174]. There are no available reports on the overdosage [209].

Further clinical studies are required, e.g., on standardized extracts and for validated methods for more data on the established medicinal and pharmaceutical use of the bark of African plum.

According to recent references, no interactions are known among the remedies of the plant and pharmaceutical products. Only some side effects, such as diarrhea, constipation [174], and mild gastrointestinal problems can be mentioned for its use [19,217]. There are no available tests on reproductive toxicity and carcinogenicity of the extracts [209].

3.8. *Secale cereale*

Secale cereale L., commonly known as rye, is a grass (family Poaceae) originating from Turkey. It grows up to 1.5 m height, with a typical spike inflorescence. It is extensively cultivated today throughout the world, particularly in regions with temperate climate, as a food crop [218]. In terms of treatment of BPH, the medicinal part of the plant is the pollen.

A detailed chemical profile of *S. cereale* pollen is, to the best of our knowledge, not available in scientific literature. Pollen is typically composed of carbohydrates, amino acids, proteins, phenolic compounds, sterols, triglycerides, plant pigments, such as carotenoids and flavonoids, minerals and sporopollenin [103–105,218] (Table 2). A standardized mixture of pollen of *S. cereale* (92%), *Phleum pratense* (timothy; 5%) and *Zea mays* (corn; 3%) branded as Graminex [106] has been studied by Locatelli et al. [219], and carvacrol, a monoterpenoid, was identified as the predominant phenolic compound, followed by polyphenols quercetin, rutin, chlorogenic acid and gallic acid [219]. The microbiologically digested extract of the pollen mixture branded as Cernilton[®] contains a large portion (40%) of *S. cereale* pollen, in addition to timothy (26%), maize (26%), pine (5%), orchard grass (2%), and alder (1%) pollen, as specified by one of the manufacturers [220,221]. Cernilton[®] is a tablet formulation prepared from the cernitin pollen extract, which consists of water-soluble and acetone-soluble fractions, and is known to contain hydroxamic acid and β -sterols [220,222].

3.8.1. Preclinical Studies

Based on early toxicologic and clinical studies, in 1994, Commission E approved the use of *S. cereale*, *P. pratense*, and *Z. mays* pollen extract for treatment of micturition difficulties associated with Alken stage I–II benign prostate enlargement [106,223]. Cernilton[®] has been used to treat BPH for nearly 40 years [220]. The mechanism of action of rye grass pollen is not yet well known. Hydroxamic acid, contained in Cernilton[®], was found to inhibit the

growth of DU-145 prostate cancer cells, but showed little selectivity for prostate cancer cells, as it inhibited the growth of other cancerous cell lines as well [224]. This was not the case with the effect of the water-soluble fraction of Cernilton[®], which selectively inhibited the growth of cells derived from the human prostate [225]. Cernilton[®] was also associated with inhibition of cyclooxygenase and the 5-lipoxygenase activity in rat basophilic leukemia cells, indicating its mechanism of action involves the inhibition of prostaglandin and leukotriene synthesis [226]. In a mouse bladder muscle model, cernitin pollen extract, its water-soluble fraction, and its acetone-soluble fraction induced contractions [107]. In a rat urethral smooth muscle, inhibition of contractions was observed with cernitin pollen extract and both fractions [227]. In an aged and castrated Wistar rat model of sex-hormone induced prostatitis, it had a recovery action [228]. The effect was partially attributed to its anti-inflammatory activity, as cernitin pollen extract reversed increased levels of TNF- α and IL-6 cytokines in this in vivo model. In an in vitro study on human prostatic cell lines and peripheral blood mononuclear cells upregulation of anti-inflammatory, as well as proinflammatory cytokines was observed [229]. Additionally, androgen receptor and PSA expression were decreased in a WPMY-1 human prostate cell line. Cernilton's anti-inflammatory activity was addressed in a study in patients suffering from chronic prostatitis or prostatodynia, where Cernilton[®] was found to decrease leucocyte count in the urine and complement C3/ceruloplasmin levels in the ejaculate [108] (Table 2).

3.8.2. Clinical Studies

Similar to in vitro studies elucidating the mechanism of action of *S. cereale*, the majority of clinical data is available on Cernilton[®] or other pollen mixture extracts, as opposed to pure *S. cereale* extract. Clinical studies in humans confirmed that mixtures containing *S. cereale* pollen extracts were efficient in the treatment of BPH. A study by Yasumoto et al. included 79 patients, who were given 126 mg of cernitin pollen extract for 12 weeks [109]. The results were compared to pre-treatment parameters in these patients. The maximum and average urine flow rates were increased, while residual urine volume was decreased. No changes were observed in PV upon 12 weeks of the treatment, but a decrease in PV was present in subjects who continued the treatment for 1 year. Altogether, the magnitude of the effect of *S. cereale* in BPH was estimated as mildly beneficial. In a double-blind and placebo-controlled study by Buck et al., residual urine volume and anteroposterior prostate diameter upon treatment with Cernilton[®] decreased, while no changes in flow rate were observed [223]. The authors concluded that Cernilton[®] might be beneficial in patients with mild to moderate symptoms of BPH. Similar conclusions were drawn in a systemic review of clinical studies on the use of Cernilton[®] for BPH by MacDonald et al. in 2000 [224]. While the limitations of the available data from clinical studies were pointed out (e.g., short study duration, lack of control groups, limited number of included subjects, insufficient data on the quality of the used extract), Cernilton[®] was found to modestly improve subjective LUTS, such as nocturia in BPH; however, the objectively measured mean urine flow rate was not improved as compared with placebo treatment. In a study published after the systemic review, BPH patients were treated with 375 mg or 750 mg Cernilton[®] daily for 4 years [230]. Both dosage regimens showed an improvement in BPH, but the higher dose was found to be more effective, with no adverse events noted. PSA was monitored in this study and no statistically significant differences were observed in its levels. In a more recent study, Cernilton[®] improved LUTS and sexual function in patients with BPH with moderate to severe prostatitis [231]. Still, more clinical studies are needed on Cernilton[®] for BPH, as exemplified by the withdrawal of the 2011 update of the systemic review by MacDonald et al., which was published in 2000, due to the lack of adequate data [232,233].

The systemic review by MacDonald et al. concluded that Cernilton is well-tolerated [222]. A single case of an adverse effect was reported, and was manifested as mild nausea [222,223]. However, caution should be applied due to a possibility of allergic reactions to ingested pollen [57,234].

In conclusion, *S. cereale* pollen extracts are moderately effective for the treatment of BPH. Patients report mild to moderate improvement of LUTS. However, most data available are on a pollen extract containing a mixture of pollen types, with *S. cereale* constituting just a part of the supplement. More studies with defined dosage of *S. cereale* pollen extract in a long-term treatment and with appropriate controls are needed to fully elucidate the effectiveness of *S. cereale* in BPH.

3.9. *Serenoa repens*

The genus *Serenoa* contains a single species *Serenoa repens* (W. Bartram) Small, known as saw palmetto, with ten botanical synonyms, the most popular being *Sabal serrulata* (Michx.) Schult. f. [235]. It grows in southern coastal regions of USA, and tropical Middle and South-America. The plant is a small (up to 2 m) perennial bush with 1 m wide leaves having 15 to 30 sharp-ending segments. The fruit is an ovoid or subspherical, dark brown or blackish drupe, one-seeded, up to 2.5 cm long and 1.5 cm in diameter [236]. The European Pharmacopoeia requires minimum 11.0% of total fatty acids in the dried ripe fruit of *S. repens* [237].

Based on a large amount of verified scientific data, the drug *Sabal serrulatae* fructus was classified as a starting material for herbal medicines in the category of well-established use for the symptomatic treatment of BPH, ATC code: G04CX0, and as a traditional medicinal product for the relief of LUTS related to BPH, after serious conditions have been excluded by a doctor [110]. Therefore, this article only presents relevant and more recent data that are not part of the related assessment report [238] (Table 2).

Clinical Studies

In a randomized, double blind trial, the effect of a hexanic extract from *S. repens* (320 mg per day for 6 months) on prostatic inflammation was investigated in patients, using specific histological and immunohistochemical criteria. The results showed that treatment with this extract resulted in significant decrease in all scores (histologic grading, aggressiveness grading, and total score) at the second biopsy. The difference in inflammation improvement was significant for the extract group when compared with the control group [111].

In a recent randomized, double-blind, placebo-controlled study, 44 Japanese men aged 40–69 years who were experiencing urination issues, such as urinary urgency, increased urinary frequency, urinary incontinence, and awoken ≥ 2 times at night to urinate were enrolled. The intervention period was 12 weeks. Capsules tested contained either 320 mg of *S. repens* fruit supercritical fluid extract or placebo. The extract group showed a significant decrease in subjective symptoms related to urination issues. No adverse effects were observed [112].

The systematic review and meta-analysis to compare *S. repens* with tamsulosin in the treatment of BPH after at least 6-month treatment cycle was done by Cai et al. Four studies involving 1080 patients (543 in the *S. repens* group and 537 in the tamsulosin group) were included in the meta-analysis. The results were as follows: compared with tamsulosin, *S. repens* had the same effect in treating BPH in terms of IPSS. The incidence of adverse reactions was similar for *S. repens* and tamsulosin, such as rhinitis, fatigue, dizziness, postural hypotension, dry mouth, and headache. For side effects, *S. repens* was well tolerated compared with tamsulosin, especially in ejaculation disorders [239].

Different conclusions were made in the very recent network meta-analysis of 2115 articles. Authors demonstrated that in a short-term follow up, no clinically meaningful improvement in IPSS of (non)hexanic lipidosterolic extract of *S. repens* has been demonstrated over placebo or α -blockers. On the contrary, they could demonstrate a long-term (12 months) benefit of these extracts in the treatment of men with LUTS secondary to benign prostatic enlargement. Hexanic extracts showed a greater improvement than non-hexanic ones. Overall, both hexanic and non-hexanic extracts showed a lower value of

rank compared with all α -blockers. However, for patients who want to avoid side effects of α -blockers and do not need rapid efficacy, *S. repens* extracts could have a rationale [240].

Interpretation of recent clinical studies or a meta-analysis of all published trials does not provide unambiguous conclusions regarding the efficiency of *Serenoa repens* medicines. The magnitude of effects of hexanic extracts and non-hexanic ones, in terms of clinically meaningful improvement, was similar to the placebo for IPSS. One may speculate that the mechanism of action of extracts needs much more time (more than one year), and extract action is related to the quality of the plant source as well as to the method of preparation (extraction). Finally, side effects of *Serenoa* extracts treatment are variable because of the above-mentioned extract quality.

3.10. *Urtica dioica*

Urtica dioica L. (Urticaceae family), is known under the common names stinging nettle, common nettle, and Ortiga. It is a perennial herbaceous plant native to Eurasia, which grows on damp soils, meadows, and abandoned fields in dappled-shaded spots [241]. The root extract has been used traditionally for the treatment of symptomatic BPH [68]. The fresh and dried flower parts are traditionally used for joint pain and urinary tract infections, as well. Moreover, it can be used externally as a remedy for hair loss, against seborrhea and dandruff of the scalp [30]. Moreover, it is used to treat diarrhea, acne, and diabetes, and to improve circulation and low blood pressure [4,114].

The most important active compounds of the leaves are sterols (β -sitosterol, hydroxy-sitosterol) and flavonoids (rutin, kaempferol, quercetin). Moreover, the leaves contain minerals (calcium, potassium), tannins, acids (salicylic, malic acids, caffeic acid), and amines (histamine) [4,98]. The roots of stinging nettle contain a mixture of water-soluble compounds, including lectins (mixture of isolectins from 0.2 to 0.6%), phenolics (p-hydroxy benzaldehyde, lignans), and sterols [9]. The root contains polysaccharides (glucans, glucogalacturonans, arabinogalactan acid) in large quantities, 6-methoxy-7-hydroxycoumarin (scopoletin), ceramides, monoterpenoids, and their glycosides, fatty triterpene, and phenylpropane (homovanillyl alcohol, and its 4-O-glycoside) [115,241,242] (Table 2).

3.10.1. Preclinical Studies

Nettle root is recommended for relief of BPH and other prostate problems. It is also used for its cardiovascular effects and as a natural remedy to treat or prevent baldness [116,243–246]. It is proved that the polysaccharides and lectins prevent the prostate cellular metabolism and its growth [98]. Nettle extract inhibits TNF activity, while the lectins, malic acid, and caffeic acid show prostatic anti-proliferative and anti-inflammatory activities [30], due to the inhibition of COX and lipoxygenase [4]. However, it is important to emphasize that the polysaccharides stimulate the activity of T-lymphocytes and the complement activation [247]. Dreikorn [117] proved that the root extract can inhibit the connecting of a binding globulin (sex hormone binding globulin—SHBG) and its receptor in the membrane of the human prostatic cells. SHBG is a plasma protein that binds to sex hormones (estrogens and androgens), and regulates their plasma free fraction. The lignans contained in stinging nettle seem to have a high affinity for receptor of SHBG [30], and the extract inhibits prostate cell proliferation [116] (Table 2). The leaf extract has inhibitory effect against the activity of adenosine deaminase, which is the most important enzyme of the nucleotide metabolism. The inhibition is dose-dependent and it might be one of the mechanisms that leads to improvement of a patient's symptoms [118]. Animal studies indicate that *U. dioica* markedly inhibits platelet aggregation and improves the lipid profile, due to the flavonoid content [248,249]. It was also found that the methanol extract of stinging nettle significantly inhibited the prostate growth induced experimentally [119,250]. The effects of stinging nettle on testosterone-induced BPH were investigated in rats. Simultaneous administration of petroleum ether and ethanolic extracts (10, 20 and 50 mg/kg^{−1} per os) and isolated β -sitosterol (10 and 20 mg/kg^{−1} per os) was undertaken. Measurement of prostate/body weight ratio, weekly urine output and serum testosterone levels, PSA levels (on day 28), and histological examinations carried out on prostates

from each group allowed the conclusion that *U. dioica* can be used as an effective drug for the management of BPH [120].

3.10.2. Clinical Studies

Clinical trials suggest a benefit of nettle extract for men with milder forms of BPH [251,252]. First, the effectiveness of a root extract (600 mg, 2 times/days/20 weeks) was demonstrated in the multicenter study of 4051 patients in various stages of BPH [253]. Friesen [254] reported the results in a multicenter long-term study for a total of 4480 patients who received nettle extract for 224 days on average, at doses of 600 mg twice/day for 3 months and then 600 mg daily during the remaining time. The extract improved urinary symptoms associated with BPH in 78% of patients after 3 months and in 91% of patients after 6 months. The diurnal and nocturnal urinary frequency was significantly improved, as well as the mean urine output [255]. Another randomized and double blind clinical study compared the effect of the aqueous root extract to placebo group. The dose was 120 mg; the patients used the root extract 3 times per day, for 6 months. Thanks to the treatment, the symptoms were relieved compared to the placebo group. The prevention effect of the treatment was identified after 18 months as well [256]. In an open-label extension of a randomized, double-blind clinical trial, the long-term efficacy and tolerability of a fixed combination of 160 mg Sabal fruit extract and 120 mg Urtica root extract per capsule (PRO 160/120) were investigated in elderly men with moderate or severe LUTS caused by BPH. Two hundred and fifty-seven patients were randomly treated with 2 × 1 capsule/day PRO 160/120 or placebo for 24 weeks, followed by a 24-week control period and a 48-week follow-up period in which all patients received PRO 160/120. It was concluded that the treatment with Sabal fruit and Urtica root provides a clinically relevant benefit over a period of 96 weeks [257]. Based on the previous clinical studies, it can be established that an increase in mean and maximum urinary flow rates and a reduction in PV and residual urine level were observed after treatment with nettle extract. Nettle root should be used for 6–12 months, as its use is possible for a long time without any serious adverse effects [255,258].

Adverse reactions could include mild gastrointestinal disturbances [57]. *U. dioica* contains tannins, which could interact with a concomitant intake of iron, causing a reduction of the effects in patients who need iron supplements. It is therefore, recommended to separate the times of administration of these components for at least 2 h. Edema and urticaria related to allergic reactions induced by the plant have been rarely reported [30].

4. Pharmaceutical Care

Men over the age of 45 are eligible for pharmaceutical management of BPH. There are three main target groups:

1. Men over 45 years of age who consult a pharmacist about lower urinary tract complaints;
2. Men over 45 years of age who purchase medication for the treatment of BPH;
3. Men over 45 years of age who have inadequate patient co-morbidity for BPH, in terms of medication management [11].

In all cases, there is a multi-step process involving pharmacist care for BPH.

The main points include the following:

1. Interviewing (in regard to the symptoms);
2. Questions related to the diagnosis;
3. Filling out the IPSS questionnaire;
4. Lifestyle advice;
5. Advice on OTC medicines;
6. Adherence (patient cooperation) questions;
7. Information on prescription medicines;
8. Referral to a doctor.

Patients in the first group have lower urinary tract complaints, and within this group, they can be further divided into subgroups.

1. Men with BPH-like symptoms. Patients should be interviewed about their symptoms, in this case, it is important to know if the urine stream is thinner, if it is intermittent or how often the patients have to get up to urinate at night. In addition, patients should be asked if they have ever seen a urologist or general practitioner about these symptoms. It is advisable at this time for patients to complete the IPSS questionnaire. This specific questionnaire based on the frequency and severity of symptoms can be used to assess the probability of mild, moderate, and severe BPH. Three categories of symptoms were described using the IPSS: mild 0–7, moderate 8–19, and severe 20–35. It is important to stress that an accurate diagnosis can only be made by a specialist after other tests have been carried out [10,11];
2. For patients diagnosed by a doctor with BPH, the pharmacist should inform the patient about safe medication use in the context of prescribed therapy. It is important to identify problems with safe medication use if they arise, and emphasis should be placed on increasing patient adherence;
3. There may be cases where patients present with other, non-BPH-like symptoms. Such cases are usually associated with alarm symptoms and should be referred to a doctor immediately. Alarm symptoms include painful urination, fever, bloody or cloudy urine in the last 3 months and urinary incontinence. These symptoms may indicate a urinary tract infection or chronic obstruction of the bladder. Thus, they definitely require medical attention.

Group 2 includes patients who buy BPH medication. When buying over-the-counter medicines, the pharmacist is obliged to inform patients about, for example, the indications, expected effects, and risks of herbal preparations. For prescription medicines, patients must also be informed and safety concerns identified, and information on lifestyle and over-the-counter products must be provided. With regard to lifestyle advice, it is recommended to reduce fluid intake to reduce the urge to urinate. Especially when the urge to urinate is most disturbing, e.g., at night or occasionally in public. Avoiding or reducing caffeine and alcohol consumption is also advisable. Regular exercise of the bladder is also suggested. This will increase the capacity of the bladder and may help to hold back urine when there is an urgent need to urinate.

Group 3 includes the non-adherent patients, who either do not take BPH medication or take them poorly.

In this case, the pharmacist should try to gain the patient's trust and, thus, increase the patient's adherence to the therapy.

Another important task for pharmacists is to detect drug interactions. Of the possible interactions, the effect on anticoagulant therapy is particularly important, as some drugs or herbal preparations may enhance the anticoagulant effects [11–13].

The issues outlined above illustrate the importance of pharmacists for the effectiveness of therapy.

5. Conclusions

The treatment of BPH is a complex process due to its multifactorial origins. Protocols of this disease include classic medical treatment, lifestyle and behavioral modifications, and phytotherapy. Moreover, regarding BPH research, researchers are focusing on new alternatives in the field of surgical treatment (e.g., water vapor thermal therapy), combination therapies (e.g., combination of PDE5 inhibitors with 5 α -reductase inhibitors, a β -3 adrenergic agonist with α 1-adrenoceptor antagonists), and herbal supplements (particularly among the herbs of TCM, e.g., *Coptis chinensis*). In mild or moderate cases, most patients ask for advice from a healthcare professional about non-prescription phytotherapeutics, or they choose a product on their own. In these cases, patients can be involved in the decision-making process, such as the choice of the pharmaceutical form. Herbal medicines are available in tablets, capsules, and oils, while synthetic medicines are only offered in tablet or capsule form. However, it is always important to advise the patient about the "category" of the product. This is crucial because traditional herbal medicines

are regulated by the authorities, whereas dietary supplements are not. Another advantage of these natural products is that they can be easily combined with each other (e.g., saw palmetto fruit with pumpkin seed oil), to act on several targets at the same time. More serious conditions require medical prescriptions by a doctor. Because of the rapid onsets of action, first-line drug treatments include α 1-blockers, 5 α -reductase inhibitors, and their combinations, while herbal supplements require more time to achieve their effectiveness. It should be noted that well-tolerated phytotherapeutics showed fewer side effects and interactions by most patients in contrast to the above-mentioned medications. On the other hand, we should note that more information is needed about herb–drug and herb–herb interactions, to improve the safe use of these herbal supplements.

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REVIEW

Nutraceutical treatment and prevention of benign prostatic hyperplasia and prostate cancer

Arrigo F.G. Cicero ¹, Olta Allkanjari ², Gian Maria Busetto ³, Tommaso Cai ⁴, Gaetano Larganà ⁵, Vittorio Magri ⁶, Gianpaolo Perletti ⁷, Francesco Saverio Robustelli Della Cuna ⁸, Giorgio Ivan Russo ⁵, Kostantinos Stamatiou ⁹, Alberto Trinchieri ¹⁰, Annabella Vitalone ²

¹ Dip. di Scienze Mediche e Chirurgiche, Alma Mater Studiorum Università di Bologna, Bologna, Italy;

² Dipartimento di Farmacologia e Fisiologia "V. Erspamer", Sapienza, Università di Roma, Roma, Italy;

³ Department of Urology, Sapienza Università di Roma, Policlinico Umberto I, Roma, Italy;

⁴ Department of Urology, Santa Chiara Regional Hospital, Trento, Italy;

⁵ Urology Department, University of Catania, Catania, Italy;

⁶ Ambulatorio Territoriale di Urologia ed Ecografia Urologica, ASST Nord Milano, Milano, Italy;

⁷ Dipartimento di Biotecnologie e Scienze della Vita, Sezione di Scienze Mediche e Chirurgiche, Università degli Studi dell'Insubria, Varese, Italy, and Faculty of Medicine and Medical Sciences, Ghent University, Ghent Belgium;

⁸ Department of Drugs Sciences, University of Pavia, Pavia, Italy;

⁹ Urology Department, Tzaneion Hospital, Piraeus, Greece;

¹⁰ CDC Ambrosiana Milano, Italy.

Summary

During the last years, pharmaceutical innovations in primary care are dramatically less frequent and will be even more rare in the next future. In this context, preclinical and clinical research oriented their interest toward natural compounds efficacy and safety, supporting the development of a new "nutraceutical" science. Medicinal plants, in the form of plant parts or extracts of them, are commonly used for the treatment of prostate diseases such as benign hypertrophy, prostatitis and chronic pelvic pain syndrome.

The pharmacological properties searched for the treatment of prostatic diseases are anti-androgenic, anti-estrogenic, anti-proliferative, antioxidant and anti-inflammatory. The most studied and used medicinal plants are *Serenoa repens*, *Pygeum africanum* and *Urtica dioica*. Other promising plants are *Cucurbita pepo*, *Epilobium* spp, *Lycopersum esculentum*, *Secale cereale*, *Roystonea regia*, *Vaccinium macrocarpon*. In parallel, epidemiological studies demonstrated that diet may play an important role on incidence and development of prostatic diseases. The Mediterranean diet is rich of elements with anti-oxidant properties that act as a protective factor for prostatic cancer. Similarly, low intake of animal protein, high intake of fruits and vegetable, lycopene and zinc are a protective factor for benign prostatic hyperplasia (BPH).

Serenoa repens in the treatment of symptoms of BPH has been tested either alone or, more frequently, in combination with other medicinal plants, alpha-blockers and inhibitors of 5-alpha reductase (5-ARI). Recent meta-analyses found the effectiveness of *Serenoa repens* similar or inferior of that of finasteride and tamsulosin but clearly higher than that of placebo in the treatment of mild and moderate low urinary tract symptoms (LUTS), nocturia and discomfort. Clinical trials showed potential synergistic effect of *Serenoa repens* with other medicinal plants and drugs. In addition to *Serenoa repens*, there are many other medicinal plants for which clinical evidence is still controversial. *Urtica dioica*, *Pygeum africanum* and *Cucurbita pepo* can be considered as an adjunct to the common therapies and their use is supported by studies showing improvement of symptoms and flowmetric indices. Lycopene and selenium are

natural products with antioxidant and anti-inflammatory action. The combination of lycopene and selenium with *Serenoa repens* was able to reduce inflammation in histological prostate sections and to further improve symptom scores and urinary flow in patients with BPH on tamsulosin treatment. Similar effects could be obtained with the use of other carotenoids, such as astaxanthin, and/or zinc. Efficacy on symptoms of patients with BPH of some polyphenols such as quercetin, equol and curcumin have been demonstrated by clinical studies. Pollen extract is a mixture of natural components able to inhibit several cytokines and prostaglandin and leukotriene synthesis resulting in a potent anti-inflammatory effect. Pollen extracts significantly improve symptoms, pain, and quality of life in patients affected by chronic pelvic pain syndrome and chronic prostatitis. Beta-sitosterol is a sterol able to improve urinary symptoms and flow measures, but not to reduce the size of the prostate gland.

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide-signaling molecule with anti-inflammatory and neuro-protective effects that can have an interesting role in the management of chronic pelvic pain syndrome and chronic urological pain.

Finally, several plant-based products have been subjected to preclinical, in vitro and in vivo, investigations for their potential pharmacological activity against prostate cancer. Some epidemiological studies or clinical trials evaluated the effects of beverages, extracts or food preparations on the risk of prostate cancer. Some plant species deserved more intense investigation, such as *Camelia sinensis* (green or black tea), *Solanum lycopersicum* (common tomato), *Punica granatum* (pomegranate), *Glycine max* (common soy) and *Linum usitatissimum* (linen).

KEY WORDS: Medicinal plant; Prostate; Benign prostatic hyperplasia; Prostate cancer; Antiproliferative effect; 5 α -reductase; *Serenoa repens*; *Pygeum africanum*; *Urtica dioica*; *Cucurbita pepo*; Lycopene; Selenium; Polyphenols; Pollen extract; Beta-sitosterol; Palmitoylethanolamide.

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INTRODUCTION TO NUTRACEUTICAL PRESCRIPTION

(Arrigo F.G. Cicero)

During the last years, the pharmaceutical innovation in primary care are dramatically less frequent and will be even more rare in the next future. In this context, pre-clinical and clinical research oriented their interest toward natural compounds efficacy and safety, supporting the development of a new nutraceutical science. The term “*nutraceutical*” has been created by Stephen De Felice in 1989 from the union of the words “*nutrition*” and “*pharmaceutical*”, to include dietary components or (more generically) botanical bioactive compounds with positive effects on well-being and health preservation, but also for the cure of some common health disorders (1).

The most part of nutraceuticals has been identified in vegetables (2) such as β -glucans, tocotrienols, plant sterols/stanols, polifenols (anthocyanins, proanthocyanidins, flavonols, stilbens, catechins, epicatechins, cumarins, ellagic acid, isoflavons, lignans, etc.) whose biological activities are numerous and often well-documented. Much less numerous are the nutraceuticals of animal origin, even if some of them, as the omega 3 polyunsaturated fatty acids are among the most used nutraceuticals around the world (4).

There are a large number of medical areas where nutraceuticals are currently used, among them urology and andrology. To warrant the consumer safety and to help the citizens to correctly choose the most adequate nutraceuticals, current laws state that the marketed products should be safe and adequately labelled.

Then, the *European Commission* promoted specific rules on the nutritional and healthy properties of dietary supplements that can be disclaimed on nutraceutical boxes (*Health Claims*) (December 20th, 2006) (5, 6).

The *European Commission* approved health claims are based on the opinions of an external agency, the *European Food Safety Authority* (EFSA), that periodically should organize meeting of expert panels selected to evaluate and re-evaluate health claims based on the available preclinical and clinical scientific data (7, 8).

Currently, the use of dietary supplements and functional foods for the health maintenance and disease prevention is in continuous increase and the number of available products in the market is growing even more intensively. So, how to navigate (as prescribers, sellers or consumers) among 20-30 products containing similar bioactives, in different combinations, that suggest similar effects but with costs often really different? For some of them we have (almost) complete preclinical and clinical pharmacotoxicological dossiers, till the availability of meta-analysis of randomized clinical trials. However, in the most part of cases, what is known about single bioactives is transferred to the combined marketed products without any kind of test on the final formulation. The main reasons of this are resumed in Table 1.

In fact, the companies need to market new (at least apparently) “*unique*” products in a context where the registration and copyright are easily copied and scarcely protected. The cost of the high quality bioactives and the need to create original products often push the industries to add more and more low-dosed components in a single

Table 1.

Factors limiting the application of available scientific data to the combinations of nutraceutical products available in the market.

- | |
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| <ul style="list-style-type: none"> • No legal need to prove efficacy • No legal possibility to declare efficacy (lack of approved health claim) • Incomplete pharmacotoxicological dossiers • Cost of high quality bioactives and/or of pharmaceutical technologies used to make them bioavailable (for instance Coenzyme Q10, Resveratrol, Lycopene) • Industry need to differentiate their product from the other ones • Need to produce absolutely safe products (often limiting the dosage under the efficacy level) |
|--|

pill/tablet to make the product more complex (“*original*”) trying to make up eventual synergies, almost never demonstrated. Of course, the use of low-dosed bioactives is a warranty of product safety and tolerability and to avoid the comparison to pharmacological drugs of natural origin, however it reduces the probability to observe a clinical effect. Thus, how to recognize a serious product? As regards monocomponent products, it is relatively easy. The proposed nutraceuticals should have an adequate bibliography support that should include (at least):

- The description of the mechanism of action, eventually associated with notes on pharmacokinetic (for instance, resveratrol has an oral bioavailability near to zero, being the supplementation of the raw form of the molecule very doubtful);
- A therapeutic indication supported by randomized, double-blind, placebo-controlled clinical trials carried out on subjects similar to the ones we need to treat in regard to age, ethnicity, and disease profile;
- Quality (bioactive titration) and dosage similar to the one shown to be efficacious and safe in clinical trial.

As regards nutraceuticals in combination, the requirement are similar if the single components are all supported by scientific evidence of efficacy and safety, and if they are included in the same pill/tablet at the tested doses. If a kind of synergy of components is suggested, this has to be clearly demonstrated with specific trials or, alternatively, it should be never mentioned. Of course, the risk of interaction between the components of a combined nutraceutical should also be considered (9).

When the informative brochure of the product is complete and correct, this will help the prescriber to adequately select the more adequate product in the market, being also more protected from a legal point of view (10).

We have to remember that the final responsibility of the prescriber remains in the knowledge to of the effective dosages of the bioactives (based on the results of adequately designed clinical trials or their meta-analysis), of possible pharmacological interaction and adverse events, and of the adequate length of treatment (in particular, avoiding short cyclic treatment for chronic diseases).

PRECLINICAL STUDIES ON MEDICINAL PLANTS, USED IN THE TREATMENT OF PROSTATIC DISEASES

(Annabella Vitalone, Olta Allkanjari)

Phytotherapy could be useful in the treatment and pre-

vention of mild to moderate prostatic diseases. The etiology of prostatitis, *benign prostatic hyperplasia* and hypertrophy (BPH) can be complex and the intervention is often multi-targeted.

The pharmacological properties useful for the treatment of the urinary tract diseases are anti-androgenic, anti-estrogenic, anti-proliferative, antioxidant and anti-inflammatory.

The most studied and used medicinal plants are: *Serenoa repens*, *Pygeum africanum* and *Urtica dioica*. Phytosterols and fatty acids are the pharmacologically active phytochemicals usually found in these plants; however, they are more used as a phytocomplex (total extract of the plant) than as isolated compounds. In preclinical research, *Serenoa* is responsible of numerous mechanisms of action, including: inhibition of the *dihydrotestosterone binding* (DHT) to its receptors present in the cytosol of prostatic cells, of 5 α -reductase (both isoforms), of *cyclooxygenase* (COX) and of *5-lipoxygenase* (LOX); it induces apoptosis of prostatic epithelial cells and it presents antiestrogenic activity, spasmolytic effect due to blockage of calcium channels and β -adrenergic antagonism (11). Similar mechanisms have been found for *Pygeum* and nettle, probably due to the presence of β -sitosterol and consisting in the inhibition of 5 α -reductase, of prostatic cell proliferation, blockage of the cell cycle in the G2 phase and induction of apoptosis in prostate cancer cells (12, 13). Furthermore, atranorin and atraric acid, present in *Pygeum*, inhibit the androgen receptor nuclear translocation, endogenous PSA expression, and fibroblast proliferation in human prostate cells. Lignans, lectins and polysaccharides contained in nettle extract, seem to exert anti-proliferative and anti-inflammatory activity, and to inhibit the binding of sex hormones to the sex hormone binding globulin.

Other promising plants are *Cucurbita pepo*, *Epilobium spp* (14), *Lycopersum esculentum*, *Secale cereale*, *Roystonea regia*, *Vaccinium macrocarpon*. They have anti-inflammatory and anti-androgenic properties. In particular, the tomato fruit extract (containing lycopene, polyphenols, etc.) down-regulates 5 α -reductase and inhibits COX.

The inhibitory properties against 5 α -reductase appear also for *Roystonea regia*, probably exerted by the fatty acids. Furthermore, in vitro, antiproliferative, antimicrobial, antioxidant and radical scavenger properties seem encouraging for epilobio, tomato, pollen extracts of *Secale cereale* and *Roystonea regia* (15). *Vaccinium macrocarpon* inhibits aromatase and is helpful in the urinary tract infection, because it acidifies the urine and inhibits bacterial adherence to uroepithelial cells (16). The mechanism of action of the plants listed above has to be confirmed in in vivo models. Other specific plants and/or substances have still limited scientific evidence.

NUTRITIONAL EPIDEMIOLOGICAL STUDIES AND PROSTATE DISEASES

(Giorgio Ivan Russo, Gaetano Larganà)

Prostatic diseases, like *prostatic cancer* (PCa) and *benign prostatic hyperplasia* (BPH), are influenced by different factors, like age, hormone profile and genetics. Several epidemiologic studies demonstrated how diet may play

an important role in prostatic diseases incidence and development.

Knowledge of the different kind of effects of foods on prostate could help us to understand how better prevent and treat these diseases, exploiting synergic effects of specific drugs.

PCa represented the most common incident cancer in men in developed countries in 2013 (17).

Western diet, characterized by high intake of energy, red and processed meats and fat but low intake of fibres has been associated to an increased risk to develop an advanced PCa (18, 19). Instead, *Mediterranean diet* (MeDi), that is characterized by use of olive oil and high intake of fibres, fish, fruits, vegetables, legumes and cereals in association with moderate to low intake of dairy products and moderate intake of wine, is a diet rich of components with anti-oxidant proprieties that could protect from PCa (20). In fact, countries following MeDi, particularly Southern European countries, have a lower incidence and mortality from PCa, compared to other European countries (21, 22).

A 2015 review included several papers evaluating the effect of single components of MeDi on incidence and development of PCa: olive oil, an unsaturated fat, was not associated with the risk of advanced PCa, that was increased for saturated fat (23-26); in a 2010 metanalysis (27) there was an association between fish consumption and a significant reduction of PCa-specific mortality; higher intake of legumes and cereals has been associated with a decreased risk of several cancer (28), included PCa (29, 30); there was a positive association between dairy product consumption and PCa (31); a 2010 review showed how a moderate daily intake of alcohol, 3 drinks per day, does not appear to influence PCa risk (32); lastly Russo *et al.* showed how consumption of food rich of phenolic acids, like fruits, vegetable, coffee, tea and cacao were associated to a reduced risk of PCa development (33).

BPH is one of the most common medical conditions in older men (34). A study evaluating more than 3500 patients showed that total protein intake (particularly animal protein) is positively associated with the risk of BPH, while in men who consumed at least 4 servings per day of fruits and vegetable, there was a lower risk of BPH (35-38). Lycopene, contained in tomatoes, seems to help to reduce *lower urinary tract symptoms* (LUTS) and to inhibits BPH progression, as well as epigallocatechin-3-gallate, contained in green tea (39, 40). The human prostate gland contains higher level of zinc than other tissues and Kristal *et al.* (38) showed that zinc could have a protective role for BPH, although excessive consumption may significantly increase the risk of advanced PCa (41-43). Like for PCa, high alcohol intake may be associated with BPH (44).

In conclusion, epidemiologic studies demonstrated that diet habits could help to prevent PCa and BPH incidence and their development and could be used in a multimodal therapy to prevent and treat these diseases. Particularly, MeDi, a diet rich of elements with anti-oxidant properties related to use of olive oil, high intake of fibres, fish, fruits, vegetables, legumes and cereals, moderate to low intake of dairy products and moderate intake of wine, is a protective factor for PCa. Similarly,

low intake of animal protein, high intake of fruits and vegetable, lycopene and zinc are a protective factor for BPH. Instead, high intake of saturated fats and animal meat, and excessive alcohol consumption could be a risk for both PCa and BPH development.

CLINICAL USE OF *SERENOA REPENS* IN BPH TREATMENT

(Kostantinos Stamatiou)

A variety of phytotherapeutic agents are used in traditional and alternative medicine to treat lower urinary tract symptoms. The most commonly used preparations originate from the species *Saw palmetto*. Their extract *Serenoa repens* (SR) exhibits marked anti-inflammatory, anti-androgenic and anti-proliferative effects. For this reason, it has been the subject of clinical and experimental research on the treatment of symptoms of benign prostatic hyperplasia.

A non-systematic search was performed in electronic libraries for clinical trials, experimental studies and systematic reviews on the topic. Main outcomes of the abovementioned studies are displayed in Table 2.

SR in the treatment of symptoms of BPH has been tested either alone or, more frequently, in combination or in comparison with other phytotherapeutics, alpha-blockers and inhibitors of 5- α reductase (5-ARI).

With regard to studies using SR extract as monotherapy for men with BPH an confirmed lower urinary tract symptoms (LUTS), Lopatkin *et al.* and Giulianelli *et al.* showed significant improvement in symptom scores (IPSS and IIEF-5) and uroflowmetry at 6-month follow up (45, 46). Accordingly, Sinescu *et al.* (47) demonstrated a significant improvement of mild or moderate LUTS, quality of life (QoL), urinary flow, residual urinary volume and erectile function and Gerber *et al.* demonstrated improvement in urinary symptoms compared with placebo (but no measurable effect on urinary flow) (48). On the contrary, the large trial of CAMUS Study Group found no differences between improvements of urinary symptoms between SR extract and placebo group at 72-week follow-up (49) in accordance to other placebo-controlled trials (50, 51). Recently, Ye *et al.* (52) in a double blind, placebo-controlled study found significant improvements in the urinary flow, IPSS, male sexual function (MSF-4 and IIEF scores) in the SR extract group. In none of these studies significant side effects of SR were observed. Higher doses of SR cannot influence neither the impact on LUTS nor the quality of sexual performance (53, 54).

Efficacy of SR was compared to other treatments. Alcaraz *et al.* (55) found equivalent efficacy with respect to alpha-blockers and 5-ARI in LUTS improvement; Pytel *et al.* (56, 57) confirmed similar results as measured by IPSS, QoL, index of sexual function (MSF-4), size of the prostate, urodynamic parameters (but no change of plasma sexual hormones). A prospective multicentre double-blind randomized study comparing tamsulosin (0.4 mg/24h) with SR (320 mg/24h) found no differences in IPSS, urinary flow and PSA at 12-month follow up (58). SR was used in combination with other treatment. The addition of dietary supplements or other phytotherapeutic agents improved the effect of SR (59, 60). The combination of SR with alpha-blockers agents (tamsulosin,

silodosin) was more effective than monotherapy according to some Authors (61, 62) although others were not able to demonstrate no extra benefits by combination therapy (63-68).

Recent meta-analyses found the effectiveness of SR similar or inferior of that of finasteride and tamsulosin but clearly higher than that of placebo in the treatment of mild and moderate LUTS, nocturia and discomfort (69-71).

The ability of SR to reduce prostatic size is controversial, although the association with other natural compounds (such as lycopene, other carotenoids and selenium) could enhance the activity of SR alone by augmenting pro-apoptotic effects and suppressing growth factors expression in hyperplastic prostates (72). The evaluation of the results of BPH treatment with SR is made difficult by the variability of the composition of products of different brands in relation to the concentration of free fatty acids and the method of extract preparation.

Table 2.

Design of studies of *Serenoa repens* for BPH treatment.

	Placebo	SR	5ARI	Alpha-blockers	Pinus + Crocus +SR	SR+LY+SE	Alpha-blocker SR+LY+SE	Alpha-blocker SR
Dedhia (50)	+	+						
Bent (51)	+	+						
Ye (52)	+	++						
Barry (53)	+	+						
Alcaraz (55)		+	+	+				
Debruyne (58)		+		+				
Cai (59)		+			++			
Morgia (60)		+				++		
Morgia (61)				+		+	++	
Ryu (63)				+				++
Boeri (62)		+		+				++
Argirovic (64)		+		+				+
Bertaccini (67)		+						+
Gerber (48)	+	++						
Helfand (49)	+	+						
Glemain (65)		+		+				+
Hizli & Uygur (66)		+		+				+

CLINICAL USE OF OTHER MEDICINAL PLANTS FOR BPH TREATMENT: *URTICA DIOICA*, *PYGEUM AFRICANUM* E *CUCURBITA PEPO*

(Gian Maria Busetto)

Alongside the traditional 5 α -reductase and β -blockers, medical therapy for LUTS secondary to BPH, is based on nutraceuticals and compounds. In addition to *Serenoa repens*, which has been extensively studied, there are many other substances for which scientific evidence is often controversial.

Urtica dioica has the capability to decrease testosterone conversion to *dydrotestosterone* (DHT), interact with *sex hormone-binding globulin* (SHBG) and block the conversion of androgens to estrogens. Other studies report even an antiproliferative action on prostate cancer cells.

Pygeum africanum is rich in phytosterols and antioxidants. An inhibitory effect on prostate growth factors, on androgenic hormones and an effect on the contractility of

Table 3.Symptoms, IPSS and flowmetric indices after treatment with *Urtica dioica*, *Pygeum africanum* and *Cucurbita pepo*.

Author, year	Study design	Patients & Controls n° and response rate	Comparator	Outcomes measured
Safarinejad 2005 (73)	Urtica dioica Double-blind placebo-controlled randomized Patients with LUTS secondary to BPH	305 (287 evaluable) Urtica dioica 315 (271 evaluable) placebo	Placebo	Urtica dioica vs placebo - Improved LUTS 81% vs 16% ($p < 0.001$) - IPSS 19.8 to 11.8 vs 19.7 to 17.7 ($p = 0.007$) - Peak flow rates +8.2 mL/s vs +3.4 mL/s ($p < 0.05$) - PVR 73 to 36 ml vs no change ($p < 0.05$) - PSA and testosterone unchanged in both groups - Prostate volume by TRUS 40.1 to 36.3 cc vs no change ($p < 0.001$) - No side effects
Pavone 2010 (74)	Serenoa repens 320 mg + Urtica dioica 120 mg + Pinus pinaster 5 mg for 30-365 days in LUTS associated to BPH (46%) or CP/CPPS (43%) or other conditions (11%)	320 patients (80 evaluable)	-	Symptom score significant benefit in 85% No change of prostate volume and Q_{max}
Lopatkin 2005 (75)	160 mg sabal fruit extract (Serenoa) + 120 mg urtica root extract 2 capsule/day RCT 24 weeks	129 (127 evaluable) 128 (126 evaluable)	Placebo	Treated vs placebo IPSS -6 points vs -4 points ($p = 0.003$) - excellent tolerability
Lopatkin 2007 (76)	160 mg sabal fruit extract (Serenoa) + 120 mg urtica root extract 2 x 1 capsule/day open-label extension of RCT for 96 weeks	219 subjects	-	I-PSS -53% ($p < 0.001$) Peak and average urinary flow +19% ($p < 0.001$) PVR -44% ($p = 0.03$) adverse events 1/1,181
Changping 2016 (77)	Metanalysis of 5 papers LUTS associated with BPH	1128 patients	Placebo	Standardized mean difference (SMD) IPSS 10.47 (95% CI 18.12 to -2.82, $p = 0.007$) Peak urinary flow rate (Q_{max}) 4.37 (95%CI = 1.55 to 7.19, $p = 0.002$) Prostate volume 3.63 (95%CI = -4.67 to -2.57, $p < 0.00001$) PSA 0.08 (95%CI = -0.23 to 0.07, $p = 0.31$)
Barlet 1990 (78)	Pygeum africanum extract (50 mg) or placebo (1 capsule BID) double-blind 60 days 8 centres (Germany, France, Austria)	263 patients	Placebo	micturition improvement 66% vs 31% $p < 0.001$ gastrointestinal side effects in 5 patients
Barth 1981 (79)	Pygeum africanum	215 patients	-	Improvement Nocturia, Q_{max} , PVR
Wilt & Ishani 1998 (80)	Pygeum africanum Metanalysis of 18 RCTs Treatment of BPH	1562 patients mean study duration was 64 days (range, 30 to 122 days)	Placebo	Effect size of combined outcome of urologic symptoms and flow measures: (-0.8 SD [95% CI -1.4 to -0.3]) ($n = 6$ studies) improvement symptoms (RR = 2.1, 95% CI = 1.4 to 3.1) nocturia - 19%, residual urine volume - 24%, peak urine flow + 23% mild adverse effects
Hong 2009 (81)	Pumpkin seed oil 320 mg day randomized, double-blind, placebo-controlled trial 12 months BPH patients	47 patients	Placebo Saw palmetto oil Pumpkin+Saw Palmetto	IPSS & QoL reduced after Pumpkin, Saw Palmetto, Pumpkin+Saw palmetto PSA reduced after Pumpkin+Saw palmetto Q_{max} increased after Pumpkin and Saw Palmetto Prostate volume no change
Friedrich 2000 (82)	Pumpkin seed extract multicentric clinical trial BPH (stage I to II according to Alken) 12 weeks	2245	-	IPSS decreased by 41.4% life quality improved by 46.1% no side effects in 96%
Vahlensieck 2015 (83)	Pumpkin seed 5 gr BID or Pumpkin seed extract 500 mg BID Randomized partially blinded placebo-controlled parallel-group trial 12 months patients with LUTS suggestive of BPH	1431	Placebo	Responders (IPSS decrease ≥ 5 points) pumpkin seed vs placebo 58.5% vs 47.3% no difference between pumpkin seed extract and placebo
Damiano 2016 (84)	Narrative review	6 clinical studies	-	IPSS and uroflowmetry improvement in 6 studies QoL improvement in 4 studies

the detrusor musculature of the bladder have been hypothesized. Some authors have also reported an improvement in the parameters of the semen, in particular on sperm motility.

Cucurbita pepo mainly contain fatty acids, specific sterols, tocopherol, carotenoids, vitamins and micronutrients. It is mainly the high Δ -7-sterol content that has the therapeutic effect and that has been shown to reduce prostate volume in the main animal models.

These treatments can be considered as an adjunct to the common therapies and their effect is supported by improving symptoms, IPSS and flowmetric indices (Table 3) (73-84). Their action on the volume of the prostate gland and on inflammation is more controversial. The literature is lacking data and double-blind placebo-controlled studies able to improve levels of evidence. It is therefore necessary to continue studying these substances, commissioning adequate trials with

high statistical power, strict inclusion and exclusion criteria and with adequate case studies.

CAROTENOIDS AND MINERAL SUPPLEMENTS

(Vittorio Magri)

Lycopene and selenium are two natural products with antioxidant and anti-inflammatory action. Lycopenes are carotenoids, natural pigments widely distributed in the environment that are synthesized both by plants and bacteria, but not by the animals that must take them with the diet. Lycopene accumulates in the prostate and is secreted in the seminal fluid. Dietary supplementation of rats resulted in accumulation of lycopene in all prostatic lobes, but preferentially in the lateral lobes. Lycopene concentrations are gradually increased and interfered with local prostate androgenic signaling, IGF-1 expression, and inflammatory mediators (85, 86). Selenium has an essential role in some enzymatic activities such as glutathione-peroxidases (87, 88) that can reduce hydrogen peroxide, and lipid and phospholipid hydroperoxides, counteracting free radical damage and oxygen-reactive species (ROS). Furthermore, selenium is important for maintaining an efficient immune response (89, 90). Studies *in vitro* and on animal models, have shown that *Serenoa repens*-Selenium-Lycopene (SeR-Se-Ly) administered in combination, are synergistic and amplify their action both on the inflammatory and proliferative component (91-93). Some clinical studies have confirmed the efficacy of the SR-Se-Ly association in patients with BPH. In the FLOG study the administration of SR-Se-Ly in patients who had to undergo prostatic re-biopsy due to suspected prostate cancer showed a significant reduction in inflammation and the number of lymphocytes and macrophages in histological sections (94).

In the PROCOMB study (61), patients treated with SR-Se-Ly + tamsulosin had a greater reduction in the IPSS score, an increase in Q_{max} and a reduction in the post-voiding urinary volume, compared to those treated with tamsulosin alone. A randomized double-blind study of patients with BPH treated with an herbal mixture that also contains lycopene showed a significant reduction in the total IPSS score, pollakiuria and nocturia in treated patients (95).

Similar effects to those obtained with lycopene and selenium could be obtained with the use of other carotenoids and/or zinc. Astaxanthin, at low concentration, was able to inhibit *in vitro* 5 α -reductase by 98% and to decrease growth of cultured prostate cancer cell lines (96). The accumulation of zinc in prostate tissue depends, more than on dietary intake, on the activity of specific transporters (ZnT4 and ZIP4) that can be modulated by natural products as diadzein and genistein (97, 98). In patients with symptomatic BPH a combination of zinc, daidzein and Isolase (a mixture of enzymes that increases the bioavailability of plant polyphenols) improved at 6-month follow up IPSS score, peak urinary flow rate and quality of life (99).

The close correlation between prostatic inflammation and LUTS associated to BPH, as demonstrated by MTOPS and REDUCE clinical studies (100, 101), suggests a new systematic approach to the medical therapy of symptomatic BPH based on the association of a drug with anti-inflammatory activity to alpha-blockers and/or 5ARI drugs. Considering the side effects of non-steroidal anti-inflamma-

tory drugs (NSAID), the use of natural substances with a low risk of complications is attractive. Further studies are needed to evaluate the short and long-term efficacy of this approach to validate its use in the daily clinical practice for treatment of benign prostate diseases.

POLYPHENOLS

(Alberto Trinchieri)

Polyphenols are a large class of organic chemicals (> 8000) characterized by the presence of large multiples of phenols structural units. They can be differentiated according to the chemical structure of the polyphenol skeleton. Flavonoids, lignins, phenolic acids, stilbenes and other polyphenols belong to this class (Table 4). Polyphenols can act on prostatic hyperplasia with different mechanisms: inhibition of 5 α -reductase; decreased expression of growth factors (IGF-I and IGF-II); anti-inflammatory action (reduction of interleukin levels IL 1- β , IL 6, IL-16 and tumor necrosis factor TNF- α , inhibition of COX-2 and 5-lipoxygenase, increased synthesis of nitric oxide and expression of nitric oxide synthase); induction of apoptotic activity (increased expression of pro-apoptotic caspase-3 protein, up-regulation of peroxisomal proliferation receptors PPAR α and γ , increased expression of G protein estrogen receptor 1 coupled GPER); increased antioxidant activity (superoxide dismutase, glutathione peroxidase). Experimental evidences based on *in vitro* studies on homogenates of hyperplastic prostate cells or prostatic cell lines demonstrated prevalent inhibitory effect of 5 α -reductase type 2 of isoflavones (phytoestrogens), while flavonols and flavones show inhibitory effect of 5 α -reductase type 1 but also anti-inflammatory and antioxidant effects and induction of apoptosis (102, 103). Phenolic acids and lignins also have a combined action on 5 α -reductase and induction of apoptosis (104). In experimental models of BPH in rats, the efficacy of cocoa extract, soy-derived isoflavones, quercetin, a mixture of baicalin and catechin (flavocoxid), equol, anthocyanins derived from black soy, flavonoids extracted from *Garcinia kola* (kolaviron), epigallocatechin-3-gallate, secoisolariciresinol and curcumin was demonstrated (105-115). Clinical studies in patients with BPH have demonstrated the efficacy of quercetin, a flavonol contained in various foods such as onions, citrus fruits, cranberry, spices, tea and red wine (116), of equol (a metabolite of daidzein which is a soy isoflavone) (117), a flaxseed extract containing the lignin *secoisolariciresinol diglucoside* (SDG) (118) and of curcumin, a derivative of the spice *Curcuma longa* (119). Conversely, resveratrol has not been shown to be effective in reducing prostate volume and levels of testosterone, dihydrotestosterone (DHT) and PSA (120). Different types of polyphenols are contained in medicinal plants that have been used in the treatment of IPB, such as eplobium (121) and extract from the bark of French maritime pine (122).

POLLEN EXTRACT, BETA-SITOSTEROL AND PALMITOYLETHANOLAMIDE (PEA)

(Tommaso Cai)

Pollen extract is a mixture of natural components, such as amino acids, carbohydrates, lipids, vitamins, phytos-

Table 4.

Classification, sources, biological and clinical activity of polyphenols used for BPH treatment.

Classification	Name	Source	In vitro 5-AR	In vitro other effects	Animal models	Clinical studies
FLAVONOIDS C6-C3-C6 general structural backbone with two C6 units of phenolic nature						
Flavonols	Quercetin	onions citrus cranberry spices tea red wine	5-AR type 1 inhibition (?) Decreased DHT by androgen-independent effect SHBG	Antiinflammatory (decrease cytokines, suppressed TNF- α and MCP-1 expression by NF-kappa B inhibition) Antioxidant Proapoptotic (IGF increase)	Decreased prostate volume	IPSS decreased Q _{max} increased
	Mirecetin	red wine	5-AR type 1 inhibition	-	No	
	Fisetin	strawberry apples grapes	5-AR type 1 inhibition	-	No	
Flavanons	GB1 e GB2 kolaflavonone binaringonina (Kolaviron)	Garcinia kola	-	Antioxidant	Decreased prostate volume	
Flavan-3-ols	Epigallocatechin-gallate	Green tea		Antiinflammatory (decreased IL-1 β , IL-16, and TNF- α) Antioxidant Decreased IGF-I e IGF-II Proapoptotic PPAR- α e PPAR- γ up-regulation	Decreased prostate volume	
Flavones	Baicalin	Scutellaria baicalensis and Scutellaria lateriflora	5-AR type 1 inhibition	Antiinflammatory (inhibition cyclooxygenase 2 and 5-lipoxygenase) Decrease growth factors	Decreased prostate volume by a mixture of baicalin and catechin (flavocoxid),	
	Kaempferol	Apples broccoli, onions, tomatoes	5-AR type 1 inhibition		No	
Anthocyanidins	Anthocianin	Black soy		Proapoptotic	Decreased prostate volume	
Isoflavones (phytoestrogens)	Daidzein	Soy	5-AR type 2 inhibition		Decreased prostate volume	
	Genistein	Soy Fava beans	5-AR type 2 inhibition		by soy-derived isoflavones	
	Biochanin A	Soy Peanuts	5-AR type 2 inhibition			IPSS decrease DHT
	Equol	Soy	5-AR type 2 inhibition		Decreased prostate volume	Decrease
STILBENS	Hydroxylated derivatives of stilbene with C6-C2-C6 structure					
	Resveratrol	Grapes Red wine				No decrease prostate volume No effect on testosterone and DHT
LIGNANS	Two units of a phenylpropane derivative					
	Secoisolarici-resinol diglucoside	Flaxseed		Proapoptotic Increased GPER expression	Decreased prostate volume	
	Enterolactone	Sesame Flaxseed	5-AR type 2 inhibition		No	
FENOLIC ACIDS	Phenolic ring and an organic carboxylic acid function (C6-C1 skeleton)				No	
	Caffeic Acid Phenethyl Ester (CAPE)	Propoli	5-AR type 2 inhibition			
OTHER POLYPHENOLS	Curcumin	Curcuma longa (spice)		Decreased growth factors (VEGF, TGF- β 1, and IGF1).	Decreased prostate volume	IPSS decrease

terols and minerals (123). The compound of the pollen extract is able to inhibit several cytokines, such as prostaglandin and leukotriene synthesis and this effect is comparable to that of diclofenac and indomethacin and approximately 10 times higher than that of aspirin (124). The pharmacological effects are due to the inhibiting activity of carvacrol, a pollen extract component, on the NF-KB (Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells). The inhibition of NF-KB reduce the

levels of prostaglandin E2 and increase the production of beta-endorphins with inflammation decrease and pain relief (125). Moreover, several authors demonstrated that pollen extract has a possible pro-apoptotic effect on the prostate via the androgen metabolism. In particular, it protects acinar prostate epithelial cells and inhibits stromal proliferation in association with enhanced apoptosis. Finally, several in vitro studies demonstrated that pollen extract is able to inhibit the prostate cancer cell growth

Table 5.
Pre-clinical and clinical trials about the use of pollen-extract.

Author, year	Study design	Patients & controls n° and response rate	Comparator	Outcomes measured
Buck AC, 1989 (132)	Prospective trial (phase II)	15 (86.6)		Pollen extract effective in the treatment of chronic prostatitis and prostatodynia
Cai T, 2013 (133)	Prospective trial (phase II)	20 (90.0)		Pollen extract significantly improved total symptoms, pain, and QoL in patients with non-inflammatory CP/CPPS without severe side effects
Cai T, 2014 (134)	Randomized controlled trial	41 (75.6) 46 (41.3)	Ibuprofen	Pollen extract significantly improved quality of life of patients when compared with those treated with ibuprofen (treatment difference in the NIH-CPSI pain domain, -2.14 ± 0.51 , $p < 0.001$; QoL scores, $p = 0.002$)
Elist J, 2006 (135)	Randomized controlled trial	30 (73.3) 28 (64.2)	Placebo	Pollen extract is superior to placebo in providing symptomatic relief in men with chronic nonbacterial prostatitis/chronic pelvic pain syndrome
Iwamura H, 2015 (136)	Randomized placebo-controlled trial	50 (78.1) 50 (88.2)	Eviprost (phyto-therapeutic agent)	Pollen extract significantly reduced the symptoms of category III CP/CPPS without any adverse events, in terms of NIH-CPSI, IPSS, and QoL
Jodai A, 1988 (137)	Prospective trial (phase II)	32 (75.0)		Pollen extract significantly reduced the symptoms in 75.0% of all treated patients
Monden K, 2002 (138)	Prospective trial (phase II)	24 (91.6)		Pollen extract significantly reduced the symptoms of chronic prostatitis group
Rugendorff EW, 1993 (139)	Prospective trial (phase II)	90 (62.2)		Pollen extract significantly reduced the symptoms of category III CP/CPPS without any adverse events, in terms of urinary symptoms and QoL
Suzuki T, 1992 (140)	Prospective trial (phase II)	25 (96.0)		Pollen extract significantly reduced the symptoms of prostatitis patients without any adverse events
Wagenlehner FM, 2009 (141)	Randomized controlled trial	70 (70.6) 69 (49.3)	Placebo	Pollen extract significantly improved total symptoms, pain, and QoL in patients with inflammatory CP/CPPS without severe side-effects

and this effect is even more pronounced in the hormone-independent models, suggesting that there might be a place for the pollen extract in the control of abnormal growth in hormone-insensitive cells (126-130).

On the clinical point of view, pollen extracts significantly improve symptoms, pain, and quality of life in patients affected by chronic pelvic pain syndrome and chronic prostatitis. These evidences have been done by a recent systematic review and meta-analysis (131) of 4 RCTs, that demonstrated that the use of flower pollen extracts in the management of CP/CPPS patients is associated with a high rate of clinical response without any significant adverse events. The Table 5 of all pre-clinical and clinical trials about the use of pollen-extract. No side effects are reported in all clinical trials (132-141).

Beta-sitosterol is a sterol commonly present in the almost all plants, such as rice bran, wheat germ, peanuts, corn oils, soybeans, saw palmetto, rye grass pollen and pygeum. Its activity is due to the fact that cannot be converted to testosterone and inhibits aromatase and 5 α -reductase (142). Due to these pharmacological properties, beta-sitosterol is able to improve urinary symptoms and flow measures, as demonstrated by a Cochrane Review (143). On the other hand, beta-sitosterol is not able to reduce the size of the prostate gland. In general, no adverse effects are reported during therapy, even if

gastrointestinal side effects are the most common. However, we need consider that this compound can enhance the cholesterol-lowering effects of antihyperlipidemic medications.

Palmitoylethanolamide (PEA), an endogenous fatty acid amide-signaling molecule has well-known anti-inflammatory and neuroprotective effects. The clinical anti-inflammatory effect is due to the downregulation of mediator release from mast cells, monocytes and macrophages. In particular, in recent experience, PEA seems to have interesting activities in regulation of neurogenic and neuropathic pain. It has been demonstrated that PEA is able to act on TRPV1 channels, by indirect activity and desensitization. Several authors showed an interesting role in the management of chronic pelvic pain syndrome and chronic urological pain (144-146).

MEDICINAL PLANTS FOR PREVENTION AND TREATMENT OF PROSTATIC CARCINOMA (Gianpaolo Perletti)

Medicinal plants and herbal products, in the form of plant parts or extracts of them, are commonly used for the treatment of prostate diseases such as benign hypertrophy, prostatitis and chronic pelvic pain syndrome. Over the past 20 years, dozens of plant-based products

have been subjected to preclinical in vitro and in vivo investigations for their potential pharmacological activity against prostate cancer (PCa). Less numerous but worthy of special attention are epidemiological studies or clinical trials in which plant species, administered in the form of beverages, extracts or food preparations, have been studied for their effect on prostate cancer. Here follows an example of plant species which have been subjected to deeper investigation.

Camelia sinensis (CS), in the form of unfermented (green) or fermented (black) tea, is rich in polyphenols, the most representative and investigated being epigallocatechin-3-gallate (EGCG; green tea contains about 10-fold EGCG compared to black tea). A number of epidemiological and clinical studies have attempted to investigate the preventive effect of CS intake on prostate cancer. Such studies have been pooled in at least 6 meta-analyses, among which the work of *Fei et al.* (147), including 29 data series, appears to be the most comprehensive.

We deemed interesting to integrate such meta-analysis with the more recent studies of *Lassed et al.* (280 patients, risk ratio = 0.51; 95% CI: 0.14-1.82) and *Sen et al.*, (142, 196 men, of which 7036 PCa cases; risk ratio: 1.06; 95% CI: 0.98-1.14) (148, 149). Our meta-analysis (Figure 1) (150) shows that, in contrast to the significant

data of *Fei* and coworkers (147), (risk ratio = 0.84; 95% CI: 0.71-0.98), the addition of the *Lassed* and *Sen* (148, 149) trials results in a non-significant pooled risk ratio (0.89; 95% CI: 0.77-1.02). The publication bias for this pooled analysis is not significant (Egger's test: $p = 0.542$; Begg&Mazumdar's test: $p = 0.311$), but the analysis shows substantial heterogeneity ($I^2 = 0.69$).

More focused analyses, investigating the effect of high doses of green tea catechins, tested in the frame of randomized-controlled studies, resulted in a significant protective effect against PCa.

Thus, whereas studies about consumption of CS infusions in the general population have given contradictory results – probably also due to uncertain dosage, length of therapy, herb quality, patient compliance, etc. –, rigorous, controlled clinical trials seem to provide encouraging evidence about the antitumor activity of CS catechins.

Solanum lycopersicum, the common tomato, contains high quantities of lycopene, a carotenoid antioxidant hydrocarbon (C₄₀H₅₆) devoid of vitamin-A activity. Lycopene, investigated in the frame of meta-analyses of epidemiological studies, doesn't seem to show a significant PCa preventive activity (151, 152). However, single studies suggest that lycopene shows indeed protective activity (153), and can as well lower PSA levels in prostate cancer

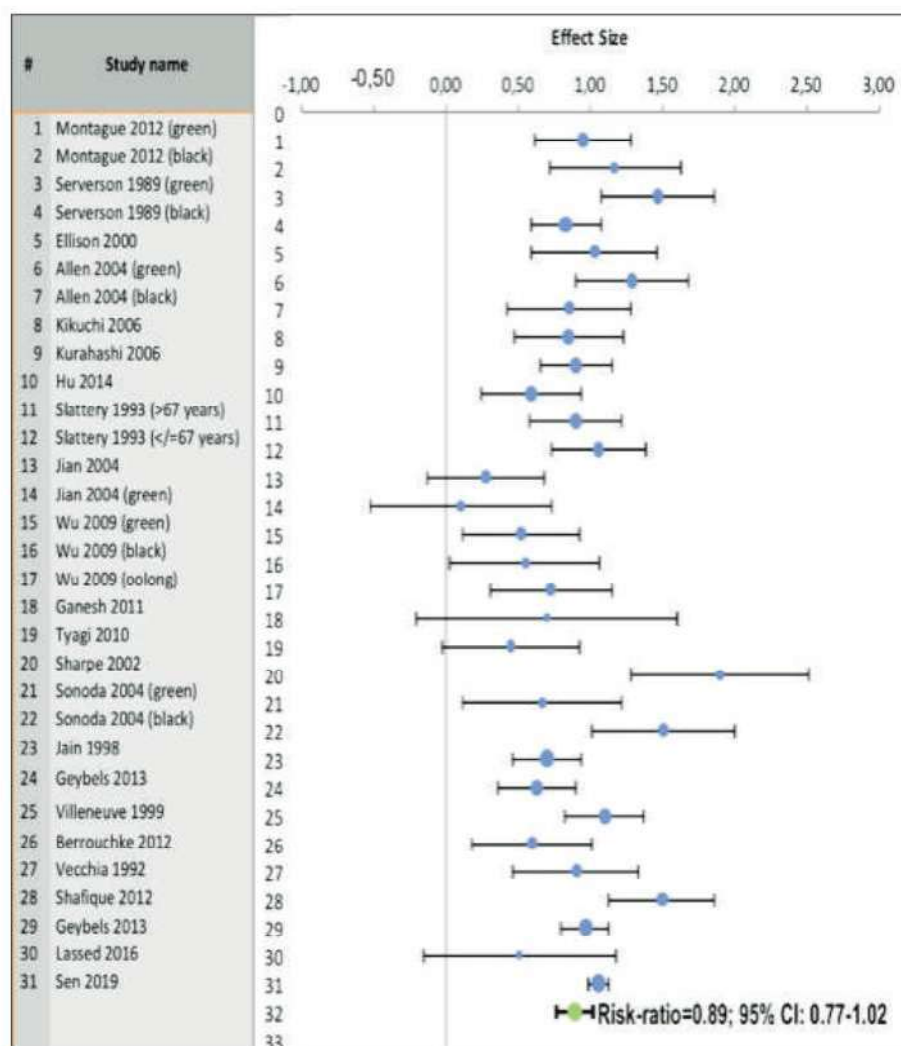


Figure 1.

Forest plot.

Risk-ratio for the association between the consumption of various preparations of tea (beverage, concentrates, etc.) and prostate cancer, assessed by pooling 23 epidemiological studies (31 data series).

The values at the right of the no-effect unit ($n = 1$) show an increased relative risk for prostate cancer, whereas data plotted on the left show a protective effect of tea intake against prostate cancer.

Arch Ital Urol Androl, this issue.

Random effect model, Mantel-Haenszel statistics, Meta-Essentials software.

patients (154). *Punica granatum*, pomegranate (PG), contains a number of active polyphenol compounds (e.g., elagitannins) and fatty acids (punicic acid). Promising pre-clinical results have not been translated so far into sound clinical evidence. Whereas in earlier clinical studies PG seemed to significantly prolong the PSA doubling time in patients with localized PCa (155), recent placebo-controlled trials failed to show increased PSA doubling times by PG preparations, compared to placebo (156, 157).

Glycine max, the common soy, and *Linum usitatissimum*, known as flax or linseed, contain isoflavones (e.g., genistein) and lignans which are known to act as phytoestrogens. These compounds, which have been hypothesized to be active against PCa growth, have been tested in the frame of clinical trials in PCa patients. It is not clear whether soy extracts show any effect on PCa and PSA, as clinical data produced so far didn't show univocal therapeutic effects (158, 159). Similarly, single clinical trials and meta-analyses suggest that flax lignans do not seem to have a significant therapeutic activity (160). However, a metaanalysis of observational studies by He and coworkers has evidenced a significant association between high serum levels of the lignan metabolite enterolactone and a reduced odds of prostate cancer (OR = 0.76, 95% CI: 0.60-0.97) (He et al.).

In conclusion, *Camelia Sinensis* catechins, *Solanum lycopersicum* lycopene and the flax lignan metabolite enterolactone have shown some chemopreventive or therapeutic activity against PCa. The major limitation of the clinical studies and meta-analyses produced so far is the great variability of key elements such as (i) compound quality (poor standardization), (ii) patient compliance (virtually unknown in observational studies), (iii) active drug dosages (extremely diverse according to dietary customs worldwide), and (iv) preparation modalities. Randomized controlled trials versus placebo or versus compounds of established efficacy are still scant. To draw any final conclusion concerning the efficacy of medicinal plants and fruits for preventing or treating PCa, additional well-designed, adequately powered clinical trials are urgently needed.

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Correspondence

Arrigo F.G. Cicero, MD

arrigo.cicero@unibo.it

Dip. di Scienze Mediche e Chirurgiche, Alma Mater Studiorum,

Università di Bologna

Presidente Società Italiana di Nutraceutica

Olta Allkanjari, MD

olta.allkanjari@uniroma1.it

Annabella Vitalone, PhD

annabella.vitalone@uniroma1.it

Dept. of Physiology and Pharmacology "V. Erspamer", Sapienza, University of Rome, (Rome, Italy)

Gian Maria Busetto, MD

gianmaria.busetto@uniroma1.it

Sapienza Università di Roma, Policlinico Umberto I, Roma (Italy)

Tommaso Cai, MD

ktommy@libero.it

Department of Urology, Santa Chiara Regional Hospital, Trento (Italy)

Gaetano Larganà, MD

Giorgio Ivan Russo, MD

giorgioivan1987@gmail.com

Urology Section, University of Catania, Catania (Italy)

Vittorio Magri, MD

vittorio.magri@virgilio.it

Ambulatorio Territoriale di Urologia ed Ecografia Urologica

ASST Nord Milano, Milano (Italy)

Gianpaolo Perletti, PhD

gianpaolo.perletti@uninsubria.it

Dipartimento di Biotecnologie e Scienze della Vita, Sezione di Scienze Mediche e Chirurgiche, Università degli Studi dell'Insubria, Busto Arsizio (VA), (Italy)

Francesco Saverio Robustelli Della Cuna, PhD

fsaveriorobustelli@unipv.it

Department of Drugs Sciences, University of Pavia, Pavia (Italy)

Kostantinos Stamatiou

stamatiouk@gmail.com

Urology Dpt, Tzaneion Hospital, Piraeus (Greece)

Alberto Trinchieri, MD (Corresponding Author)

alberto.trinchieri@gmail.com

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[Intervention Review]

Pygeum africanum for benign prostatic hyperplasia

Timothy J Wilt¹, Areef Ishani²

¹General Internal Medicine (111-0), VAMC, Minneapolis, Minnesota, USA. ²Department of Medicine (111), VA Medical Center, Minneapolis, Minnesota, USA

Contact address: Timothy J Wilt, General Internal Medicine (111-0), VAMC, One Veterans Drive, Minneapolis, Minnesota, 55417, USA.
Tim.Wilt@med.va.gov.

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ABSTRACT

Background

Benign prostatic hyperplasia (BPH), nonmalignant enlargement of the prostate, can lead to obstructive and irritative lower urinary tract symptoms (LUTS). The pharmacologic use of plants and herbs (phytotherapy) for the treatment of LUTS associated with BPH has been growing steadily. The extract of the African prune tree, *Pygeum africanum*, is one of the several phytotherapeutic agents available for the treatment of BPH.

Objectives

To investigate the evidence whether extracts of *Pygeum africanum* (1) are more effective than placebo in the treatment of Benign Prostatic Hyperplasia (BPH), (2) are as effective as standard pharmacologic BPH treatments, and (3) have less side effects compared to standard BPH drugs.

Search methods

Trials were searched in computerized general and specialized databases (MEDLINE (1966 to 2000), EMBASE, Cochrane Library, Phytodok), by checking bibliographies, and by contacting relevant manufacturers and researchers.

Selection criteria

Trials were eligible if they (1) were randomized (2) included men with BPH (3) compared preparations of *Pygeum africanum* (alone or in combination) with placebo or other BPH medications (4) included clinical outcomes such as urologic symptom scales, symptoms, or urodynamic measurements. Eligibility was assessed by at least two independent observers.

Data collection and analysis

Information on patients, interventions, and outcomes were extracted by at least two independent reviewers using a standard form. The main outcome measure for comparing the effectiveness of *Pygeum africanum* with placebo and standard BPH medications was the change in urologic symptoms scale scores. Secondary outcomes included change in urologic symptoms including nocturia and urodynamic measures (peak and mean urine flow, prostate size). The main outcome measure for adverse effects was the number of men reporting adverse effects.

Main results

A total of 18 randomized controlled trials involving 1562 men met inclusion criteria and were analyzed. Only one of the studies reported a method of treatment allocation concealment, though 17 were double blinded. There were no studies comparing *Pygeum africanum* to standard pharmacologic interventions such as alpha-adrenergic blockers or 5-alpha reductase inhibitors. The mean study duration was 64 days (range, 30 to 122 days). Many studies did not report results in a method that permitted meta-analysis. Compared to men receiving

placebo, *Pygeum africanum* provided a moderately large improvement in the combined outcome of urologic symptoms and flow measures as assessed by an effect size defined by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome (-0.8 SD [95% confidence interval (CI), -1.4 to -0.3 ($n = 6$ studies)]). Men using *Pygeum africanum* were more than twice as likely to report an improvement in overall symptoms (RR=2.1, 95% CI = 1.4 to 3.1). Nocturia was reduced by 19%, residual urine volume by 24% and peak urine flow was increased by 23%. Adverse effects due to *Pygeum Africanum* were mild and comparable to placebo. The overall dropout rate was 12% and was similar between *Pygeum Africanum* (13%), placebo (11%) and other controls (8%).

Authors' conclusions

A standardized preparation of *Pygeum africanum* may be a useful treatment option for men with lower urinary symptoms consistent with benign prostatic hyperplasia. However, the reviewed studies were small in size, were of short duration, used varied doses and preparations and rarely reported outcomes using standardized validated measures of efficacy. Additional placebo-controlled trials are needed as well as studies that compare *Pygeum africanum* to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. These trials should be of sufficient size and duration to detect important differences in clinically relevant endpoints and use standardized urologic symptom scale scores.

PLAIN LANGUAGE SUMMARY

Extracts from the African prune tree (*Pygeum africanum*) may be able to help relieve urinary symptoms caused by enlarged prostate (benign prostatic hyperplasia)

Benign prostatic hyperplasia (BPH), enlargement of the prostate gland, is common in older men. An enlarged prostate can interfere with urination, increasing the frequency and urge, or causing problems emptying the bladder. Both surgery and drugs are used to try to treat BPH. However, using herbal medicines to try to relieve the symptoms of BPH is becoming common. *Pygeum africanum* is one of several popular herbal remedies for BPH. The review found that *pygeum africanum* is well tolerated, cheaper than many prescription medicines used for BPH, and provides moderate relief from the urinary problems caused by an enlarged prostate.

BACKGROUND

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate. Symptoms related to BPH are one of the most common problems in older men. Histological evidence of BPH is found in more than 40% of men in their fifties and nearly 90% of men in their eighties (Berry 1984). The majority of men over the age of 60 are considered to have urinary symptoms attributable to BPH. In the United States treatment of BPH accounts for approximately 1.7 million physician office visits (Guess 1992) and results in more than 300,000 prostatectomies annually (McConnell 1994). The proliferative disorder resulting in BPH affects both the stromal and the epithelial portions of the prostate. The enlarging prostate results in the progressive occlusion of the proximal urethra and can result in both obstructive and irritative urinary tract symptoms. The obstructive symptoms of BPH include weak urinary stream, hesitancy, intermittency, incomplete bladder emptying, terminal urine dribbling and abdominal straining (Christensen 1990; Caine 1987). The irritative symptoms include urinary frequency, urgency and nocturia. The treatment goal in the vast majority of patients with BPH is to relieve these bothersome symptoms.

The use of plants and herbs for medicinal purposes (phytotherapy) including treatment of BPH symptoms has been growing steadily in most countries. Usage of plant extracts is common in Europe and is increasing in the United States. Phytotherapeutic agents represent nearly half of the medications dispensed for BPH in Italy, compared with 5% for alpha blockers and 5% for 5-alpha reductase inhibitors (Di Silverio 1993). In Germany and Austria, phytotherapy is the first-line treatment for mild to moderate urinary obstructive symptoms and represents > 90% of all drugs prescribed for the treatment of BPH (Buck 1996). In the United States their use has also markedly increased, they are readily available as nonprescription dietary supplements and are often recommended in "natural health food stores or books" for self treatment of BPH symptoms.

Pygeum africanum, an extract from the bark of the African prune tree, has been utilized in Europe since 1969 for the treatment of mild to moderate symptomatic benign prostatic hyperplasia. The mechanism of action of *Pygeum africanum* remains unclear. In animal models, *Pygeum africanum* has been shown to have pharmacologic properties that may be beneficial in the treatment of benign prostatic hyperplasia. These include modulation of bladder contractility, anti-inflammatory activity, decreased production of leukotrienes and other 5-lipoxygenase metabolites (Sidoti 1993; Paubert-Braquet 1994), inhibition of fibroblast production (Yablonsky 1997; Paubert-Braquet 1993) effects on adrenal androgens (Thieblot 1977), and restoration of secretory activity of prostate epithelium.

Despite the wide-spread use of *Pygeum africanum* uncertainty remains regarding treatment effectiveness and tolerability. A previous qualitative summary did not meet criteria for a systematic review (Andro 1995). This review included results from open-labelled uncontrolled studies, did not assess study quality nor conduct a quantitative meta-analysis to estimate the magnitude or statistical significance of treatment efficacy and was sponsored by a manufacturer of *Pygeum africanum* extract. We conducted a systematic review including a quantitative meta-analysis, where possible, of the evidence from randomized controlled trials to determine the therapeutic efficacy and tolerability of *Pygeum*

africanum, alone or in combination with other herbal agents, for men with symptomatic benign prostatic hyperplasia.

OBJECTIVES

The aim of our review was to provide a comprehensive overview including a quantitative meta-analysis of the existing evidence to determine the therapeutic efficacy and the adverse effects of the plant extract *Pygeum africanum*. Specifically, was *Pygeum africanum* more effective than placebo in improving the symptoms and/or urodynamics of BPH and as effective as current medical therapies.

Main comparison

Determine if *Pygeum africanum* was more efficacious than placebo in improving validated and standardized urologic symptom scores in men with symptomatic BPH.

Secondary comparisons

1. Determine if *Pygeum africanum* is more efficacious than placebo in improving urodynamic measurements and urinary symptoms including peak urine flow, mean urine flow, residual urine, prostate size, nocturia, dysuria, and urinary frequency.
2. Determine if *Pygeum africanum* is as efficacious as active controls in improving urologic symptom scores and urodynamic measures.
3. Determine the adverse effects of *Pygeum africanum*.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials.

Types of participants

Men with symptomatic benign prostatic hyperplasia

Types of interventions

Comparison of preparations of *Pygeum africanum* with placebo or medical therapies for BPH with a treatment duration of at least 30 days.

Types of outcome measures

Urologic symptom scores (Boyarsky, American Urologic Association Score, International Prostate Symptom Score:IPSS); Urodynamic measures (defined as change in peak urine flow (PUF), mean urine flow (MUF), residual urine volume; changes in prostate size (measured in cc); urinary frequency, nocturia (times/per evening); quality of life score (QOL); and overall physician/patient health assessment.

Search methods for identification of studies

We searched MEDLINE for 1966 to 2000 using a combination of the March 1996 update of the optimally sensitive search strategy for trials from the Cochrane Collaboration with the MeSH headings "prostatic hyperplasia," "phytotherapy," "plant extracts," "Pygeum africanum," "Tadenan," "Docosonal", and "Pigenil" including all subheadings (Dickersin 1994). A search of EMBASE, years 1974 to 1999 was done by using a similar approach to that for Medline. We also searched the private database Phytodok, Munich Germany,

and the Cochrane Library, including the database of the Cochrane Prostate Diseases and Urologic Malignancies Review Group and the Cochrane Field for Complementary Medicine. Reference lists of all identified trials and previous reviews were searched for additional trials. The manufacturer and authors were contacted for missing data or additional trials. There were no language restrictions.

Data collection and analysis

Eligibility:

Two investigators (AI and RM) independently determined if identified studies met inclusion criteria.

Extraction:

The following data were extracted from each included study: study characteristics, demographics of patients, enrollment criteria, outcomes, adverse effects, and number and reasons for dropout. Missing or additional information was sought from authors/sponsors. Included and excluded studies as well as extracted data were reviewed and discrepancies resolved by discussion and consensus.

Assessment of methodological quality:

Study quality was assessed using the method outlined by Schulz and colleagues (Schulz 1995) assigning 1 to poorest quality and 3 to best quality: 1 = trials in which concealment was inadequate (e.g. alteration or reference to case record numbers or to dates of birth); 2 = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories; and 3 = trials deemed to have adequate measures to conceal allocations (e.g. central randomization; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes etc. that contained elements convincing of concealment).

Summarizing results of primary studies:

Outcomes:

The mean urologic symptom score (points), peak and mean urine flow (mL/sec), residual urine volume (mL), prostate size (cc), frequency (% men reporting), urgency (% men reporting), dysuria (% men reporting) and nocturia (# times). The number and percent of men reporting specific side effects and/or withdrawing from the study.

Meta-analysis:

Because no common outcome measure was available from all eighteen studies we utilized two methods for combining data. One method, reported by Saint 1995, assesses treatment effect size for continuous variables by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome when trials report different outcome measures of effectiveness (e.g. symptom scale scores, nocturia, peak urine flow rate). The second method calculates a summary measure for individual outcomes using studies that provide similar outcome measures and utilizes standard meta-analytic techniques described below.

For determining effect size we utilized the outcome that was determined a priori to be most clinically significant (order of clinical importance: symptom scale score > nocturia > peak urine flow > residual urine volume). One outcome from each study was then transformed into units of standard deviations (SD), giving a

comparable effect size for each study. The study-specific overall effect size was the difference in mean outcome for the *Pygeum africanum* and placebo groups, divided by the pooled SD of the outcome measure. The summary effect size across studies was calculated as the weighted average of the study-specific effect size, with weights equal to the inverse of the estimated variance of each using standard meta-analytic methodology as developed by DerSimonian and Laird (DerSimonian 1986; Laird 1990). We used the same definition of standardized effect sizes to look at individual and comparable continuous outcomes when available (nocturia and peak urine flow). The statistical significance of the summary effect size was assessed by comparing it with the standard normal distribution. A scale for effect size suggested by Cohen 1988 was used with 0.8 reflecting a large effect, 0.5 a moderate effect, and 0.2 a small effect.

Additional meta-analyses considered the difference between *Pygeum africanum* treatment and the control treatment in the mean change from baseline to end of follow-up for each separate continuous outcome. For those studies not reporting mean change scores and the corresponding standard errors, the standard errors for the mean change scores were approximated using the standard errors of the outcomes at baseline and followup. The approximation used the methodology reported by Laird 1990 and Lau 1996 based on the correlation between outcomes. Analyses were conducted for three different assumed values for this correlation (0.25, 0.50, 0.75). This approach was taken to examine the sensitivity of the results to the value of this unknown parameter. Weighted mean differences were calculated using the methodology outlined above. There were no qualitative differences between the meta-analysis results for the three assumed correlation values; we present here the results for the assumed correlation of 0.50. For categorical outcome measures weighted relative risks and 95% CI were calculated using standard meta-analytic techniques.

Chi squared tests were used for analysis of bivariate comparisons (adverse events and dropouts) using simple pooling of data. To assess the percentage of patients having improvement in urologic symptoms, a modified intention-to-treat analysis was performed (i.e., men who dropped out or were lost to follow-up were considered to have had worsening symptoms) (Lavori 1992). The denominator for the modified intention-to-treat analysis included the number randomized to treatment at baseline, and the numerator included the number completing the trial and showing improvement. A test for heterogeneity was calculated according to standard formulas (DerSimonian 1986; Saint 1995) and a random effects model utilized for all summary estimates.

RESULTS

Description of studies

The combined search strategies identified 31 trials; 18 met inclusion criteria. None were conducted in the United States and 12 were reported in a non-English language [German (1), Italian (10), French (2)]. Fourteen trials were excluded because they did not include a control group (Anonymous 1973; Breza 1998; Diz 1973; Grasset 1974; Greiner 1970; Grévy 1970; Guillard-Vallée 1970; Guillemin 1970; Huet 1970; Lange 1970; Lhez 1970; Martínez-Piñero '73; Robineau 1976; Rometti 1970). The majority of studies examined *Pygeum africanum* alone versus placebo alone (n = 11) (Barlet 1990; Bassi 1987; Blitz 1985; Bongli 1972; Donkervoort 1977; Dufour 1984; Frassetto 1986; Maver 1972; Ranno

1986; Rizzo 1985). Two trials comparing *Pygeum africanum* against an anti-inflammatory drug (Gagliardi 1983; Rigatti 1983). One study comparing *Pygeum Africanum* to placebo included an additional treatment arm of *Pygeum africanum* in combination with a steroid (Giacobini 1986). Two studies compared *Pygeum africanum* alone to one or more herbal agents and versus placebo (Barth 1981; Mandressi 1983), one trial compared *Pygeum africanum* to another herbal agent (Dutkiewicz 1996), one trial compared different daily dosage forms of *Pygeum africanum* (Chatelain 1999), and one trial compared two different doses of *Pygeum africanum* in combination with another herbal extract (Krzeski 1993). None of the "active comparison" arms have been conclusively demonstrated to be effective in treating symptomatic benign prostatic hyperplasia.

A total of 1562 participants were randomized in the 18 trials. The mean treatment duration was 64 ± 21.1 days and ranged from 30 to 122 days. The majority of the studies ($n = 14$; participants = 1103) utilized a standardized extract of *Pygeum africanum*. The doses of *Pygeum africanum* ranged between 75 to 200 mg per day. Of the placebo controlled trials 1 utilized a dose of *Pygeum africanum* equal to 75 mg per day, 7 utilized a dose of 100 mg per day, 4 utilized a dose of 200 mg/day and one did not report the dosage (Dutkiewicz 1996). For studies that provided baseline data, results did not vary between treatment arms and were consistent with men typically presenting with moderate benign prostatic hyperplasia. The mean age was 66 ± 6.9 years (9 studies, $n = 845$, range 42 to 89); nocturia = 3 ± 0.7 times per evening (4 studies, $n = 413$); peak urine flow = 12 ± 3.6 mL/sec (5 studies, $n = 416$); residual urine volume = 40 ± 25.6 mL (2 studies, $n = 284$). Not all studies could be pooled because of differences in reporting methods. Of the 13 trials of *Pygeum africanum* versus placebo identified, 12 reported a beneficial effect of *Pygeum africanum* on at least one measure of effectiveness: overall symptoms, nocturia, peak urine flow or residual volume. Only one trial demonstrated no difference between *Pygeum africanum* and placebo (Rizzo 1985). This trial assessed the effect of *Pygeum africanum* on nocturia, peak urine flow and overall symptom change in 20 men over 12 weeks. None of the trials showed an effect of *Pygeum africanum* worse than placebo or "active control."

Risk of bias in included studies

Only one of the studies reported a method for concealment of treatment allocation (score = 2) but 17 of the 18 studies were double-blinded. Most studies did not provide baseline patient information nor provide clinically relevant baseline or outcomes data in a standardized fashion. No placebo-controlled studies utilized standardized, validated symptom scales (the outcome measure of greatest clinical significance). There was no information on patient race, comorbid conditions, prostate size or standardized/validated urologic symptom scale scores. All studies were of short treatment duration with none having a follow up greater than four months.

Effects of interventions

Summary Effect Sizes:

Six studies involving 474 participants (54% of all participants enrolled in placebo controlled trials) could be pooled to provide a weighted estimate of effectiveness (Barlet 1990; Bonggi 1972; Giacobini 1986; Mandressi 1983; Maver 1972; Rizzo 1985). All involved *Pygeum africanum* alone versus placebo, and five utilized a standardized preparation of *Pygeum africanum*. The overall

summary effect size was -0.8 SD (95% CI -1.4 to -0.3) indicating a statistically significant large improvement with *Pygeum africanum*. The summary effect size from three studies that provided data on nocturia was -0.8 SD (95% CI -1.4 to -0.1) (Barlet 1990; Bonggi 1972; Mandressi 1983). This indicates that *Pygeum africanum* resulted in a statistically significant moderate to large improvement in nocturia. Summary results from the four studies providing data on peak urine flow demonstrated a mean effect size of 0.7 SD (95% CI 1.3 to 0.0) indicating a moderate effect on peak urine flow (Barlet 1990; Giacobini 1986; Maver 1972; Rizzo 1985).

Urinary symptoms and flow measures:

Consistent with the results seen in the summary effect sizes, *Pygeum africanum* improved specific urinary symptoms and flow measures. In 5 double-blind trials involving 430 participants, men receiving *Pygeum africanum* were more than twice as likely to be rated by their physician as having overall improvement in symptoms compared to men taking placebo (65% vs. 30%; RR = 2.1; 95% CI = 1.4 to 3.1) (Barlet 1990; Blitz 1985; Bonggi 1972; Donkervoort 1977; Mandressi 1983). *Pygeum africanum* reduced nocturia compared to placebo by 19% (weighted mean difference (WMD) = -0.9 times per evening; 95% CI = -2.0 to 0.1) though this did not reach statistical significance (Barlet 1990; Bonggi 1972; Mandressi 1983). *Pygeum africanum* also increased peak urine flow compared to placebo by 23%, WMD = 2.5 mL/sec (95% CI = 0.3 to 4.7) (Barlet 1990; Giacobini 1986; Maver 1972; Rizzo 1985). *Pygeum africanum* reduced residual urine volume by 24% (WMD = -13 mL; 95% CI = -23.3 to -3.0) (Barlet 1990; Giacobini 1986).

To assess for publication bias we constructed funnel plots from published trials providing data for calculation of summary effect size, overall symptom improvement, nocturia and peak urine flow. The few studies available for funnel plot analysis make assessment difficult and do not provide clear evidence for or against publication bias.

Adverse Events:

All studies provided information on the percentage of men who dropped-out or were lost to follow up, potentially the most reliable indicator of tolerability. The mean percentage of participants who dropped out was 12% ($n = 179$), ranged from 0% to 45% and did not differ between *Pygeum africanum* (13%), placebo (11%) and other controls (8%) ($P = 0.4$ vs placebo and $P = 0.5$ vs other control). Three studies (two placebo controlled) had drop out rates > 20%. The reason for the high drop out rate was not reported but two of the trials (Barth 1981; Chatelain 1999) indicated that adverse effects were "infrequent and mild" in participants completing the trial. None of these three trials reported outcome data in a method suitable for incorporation into the effect size analyses. Thirteen of the eighteen studies provided information on specific adverse events. Adverse events due to *Pygeum africanum* were generally mild in nature and comparable in frequency to placebo. The most frequently reported adverse events were gastrointestinal and occurred among seven men in five trials.

DISCUSSION

This systematic review summarizes the available evidence from randomized controlled trials regarding the efficacy and tolerability of *Pygeum africanum* for the treatment of lower urinary tract symptoms attributable to benign prostatic hyperplasia. Our results suggest that *Pygeum africanum* improves urinary symptoms and flow measures and that the point estimate for the effect size

is moderate in magnitude. Because of the diversity of outcome measures, a summary estimate of the effect of *Pygeum africanum* was based on units of SD available from 6 studies involving 474 participants. This method is useful for determining if an overall benefit exists but only indicates whether the overall effect is of small, moderate or large magnitude. Our analyses of individual effect sizes for nocturia and peak urinary flow indicate that improvement of comparable magnitude occurred in both urinary symptoms and flow measures.

Summary risk ratios and weighted mean differences comparing *Pygeum africanum* to placebo for overall symptoms, peak urine flow, and residual urine volume demonstrated a statistically significant improvement as well as a trend towards improvement for nocturia. These findings are considered clinically significant, comparable to other widely used treatment options and consistent with the results obtained utilizing effect sizes. The results from individual trials demonstrated that all but one study noted an improvement with *Pygeum africanum* for symptoms attributable to benign prostatic hyperplasia. Additionally, *Pygeum africanum* was well tolerated with the drop out rate for men receiving *Pygeum africanum* not different than for men receiving placebo.

While studies utilized different quantities, dosing intervals and preparations of *Pygeum africanum* the majority of studies utilized a standardized extract of *Pygeum africanum* at a dose of 100 to 200 mg per day. Five of the six studies providing data for summary estimates of effect size utilized the standardized extract of *Pygeum africanum*. All summary efficacy data were derived from placebo-controlled, double blind studies utilizing a "noncombination" source of *Pygeum africanum*. This suggests that a standardized preparation of *Pygeum africanum* is associated with the observed improvement in symptoms and flow measures.

No study was conducted in the United States and many studies did not report means and standard deviations making completion of a quantitative review difficult. There was no information provided to determine if *Pygeum africanum* prevented long-term complications of benign prostatic hyperplasia such as acute urinary retention, renal insufficiency or the need for surgical intervention. No studies compared *Pygeum africanum* with medical interventions of demonstrated effectiveness including alpha adrenergic blockers and 5-alpha reductase inhibitors. The "active controls" used in the studies have not been convincingly demonstrated to have beneficial effects.

A possible source of bias is that outcomes included in the effect size calculation could have been selected to favor *Pygeum africanum*. However, we ranked outcome measures for inclusion in the effect size calculation prior to data abstraction and analysis. Furthermore, effectiveness was consistently observed in all but one of the studies and regardless of whether the results were reported as physician rating of patient's global symptom improvement (n = 6 trials; 430 patients); nocturia (n = 3 trials; 325 participants); peak urine flow (n = 4 trials; 363 participants); or residual volume (n = 4 trials; 264 participants). An additional source of bias could result from failure to publish small negative studies (publication bias) or outcomes that were not favorably affected. This would enhance the summary effect size estimates and could contribute to our finding that only one out of seventeen reported studies was negative. Funnel plots were constructed to assess for publication bias, however few studies could be included in the plot construction.

AUTHORS' CONCLUSIONS

Implications for practice

The overall standardized effect size and the summary improvement in global symptoms, nocturia, peak urine flow and residual urine volume suggests that *Pygeum africanum* is effective in men with symptomatic benign prostatic hyperplasia. This benefit is of modest size and appears to be clinically significant. *Pygeum africanum* is well tolerated and costs less than most prescription medications. A standardized preparation of *Pygeum africanum*, may be a useful treatment option, at least in the short term, for men with lower urinary symptoms consistent with benign prostatic hyperplasia.

Implications for research

Additional placebo-controlled trials are needed as well as studies that compare *Pygeum africanum* to active controls that have been convincingly demonstrated to have beneficial effects on lower urinary tract symptoms related to BPH. Future trials should be of sufficient size and duration (e.g. > 6 months) to detect important differences in clinically relevant endpoints and use standardized urologic symptom scale scores.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Barlet 1990

Methods	Multicentre study. Double blinded: yes.
Participants	N=263 European men with symptomatic BPH, age > 50. Age range 50-85, mean 67. Lost to follow-up: 8 (3%).
Interventions	Control: placebo (n=132). Treatment: P. africanum extract (Tadenan) 100 mg twice daily (n=131). Treatment duration: 60 days.
Outcomes	Overall improvement in symptoms (MD/subject - rating); Nocturia; peak urine flow; residual volume. Adverse events.
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement

Pygeum africanum for benign prostatic hyperplasia (Review)

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Barlet 1990 (Continued)

Allocation concealment (selection bias)	Unclear risk	B - Unclear
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Barth 1981

Methods	Double blinded: yes.
Participants	N=215 European men with symptomatic BPH, age > 50. Lost to follow-up: 67 (31%).
Interventions	Control 1: placebo (n=46). Treatment 2: P. africanum extract (Docosanol) 100 mg daily (n=50). Control 2: Sitosterin 30 mg (n=34). Treatment 2: P. africanum extract (Docosanol) 100 mg daily (n=37). Control 3: ERU* 300 mg (n=24). Treatment 3: P. africanum extract (Docosanol) 100 mg daily (n=24). Treatment duration: 8 weeks.
Outcomes	Nocturia; peak urine flow; residual volume. Adverse events.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bassi 1987

Methods	Double blinded: yes.
Participants	N=40 Italian men with symptomatic BPH. Mean age: 67 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=20). Treatment: P. africanum extract (Pigenil) 100 mg daily (n=20). Treatment duration: 60 days.
Outcomes	Nocturia; peak urine flow. Adverse events.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Pygeum africanum for benign prostatic hyperplasia (Review)

Blitz 1985

Methods	Double blinded: yes.
Participants	N=57 French men with symptomatic BPH. Lost to follow-up: 0.
Interventions	Control: placebo Treatment: P. africanum extract (Tadenan) 100 mg daily Treatment duration: 60 days.
Outcomes	Overall improvement in symptoms.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Bongi 1972

Methods	Double blinded: yes.
Participants	N=50 Italian men with symptomatic BPH, residual volume < 200 ml. Age range: 49-84. Lost to follow-up: 0.
Interventions	Control: placebo Treatment: P. africanum extract (Tadenan) 75 mg daily Treatment duration: 60 days
Outcomes	Nocturia; residual volume.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Chatelain 1999

Methods	Double blinded: yes.
Participants	N=209 French men with symptomatic BPH, age > 50, IPSS 10 or >, PUF < 15 ml/s, residual volume < 150 ml. Mean age: 66 years.

Pygeum africanum for benign prostatic hyperplasia (Review)

Chatelain 1999 (Continued)

Lost to follow-up: 26 (11.1%).

Interventions	Treatment 1: P. africanum extract (Tadenan) 50 mg x 2 daily (n=101). Treatment 2: P. africanum extract (Tadenan) 100 mg daily (n=108). Treatment duration: 60 days.
Outcomes	Symptom score (IPSS); peak urine flow. Adverse events.
Notes	235 men were randomized, 223 completed the comparative phase, but only 209 men were valid for per-protocol analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Donkervoort 1977

Methods	Double blinded: yes.
Participants	N=20 Dutch men with symptomatic BPH. Lost to follow-up: 4 (20%).
Interventions	Control: placebo Treatment: P. africanum extract (Tadenan) 75 mg daily Treatment duration: 12 weeks.
Outcomes	Overall improvement in symptoms; Nocturia; peak urine flow.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dufour 1984

Methods	Double blinded: yes.
Participants	N=120 French men with symptomatic BPH not in need of surgery. Lost to follow-up: 56 (47%).
Interventions	Control: placebo (n=60). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=60). Treatment duration: 6 weeks.

Pygeum africanum for benign prostatic hyperplasia (Review)

Dufour 1984 (Continued)

Outcomes Nocturia.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Dutkiewicz 1996

Methods Single-site study.
Double blinded:
no.
Randomization: unclear
Patients not blinded: Providers not blinded:
Lost to follow-up: none

Participants N=89 Polish men with symptomatic BPH. Age range: 50-68.
Lost to follow-up: 0.

Interventions Control: Cernilton 2 tablets three times daily x 2 weeks followed by 1 tablet three times daily up to 4 months (n=51).
Treatment: Tadenan 2 tablets twice daily (38).
Treatment duration: 24 weeks.

Outcomes Obstructive symptom score
Irritative symptom score;
peak urine flow;
residual volume;
prostate volume.
Adverse events.

Notes Exclusions: No details provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Frassetto 1986

Methods Double blinded:
yes.

Participants N=20 Italian men with symptomatic BPH. Age range: 50-84, mean 67 years.
Lost to follow-up: 0.

Interventions Control: placebo (n=10).

Pygeum africanum for benign prostatic hyperplasia (Review)

Frassetto 1986 (Continued)

Treatment: P. africanum extract (Tadenan) 75 mg daily (n=10).
Treatment duration: 60 days

Outcomes	"Dysuric symptoms" (nocturia, pollachiuria, reduced strenght of flux). Adverse events.
Notes	Prostate size evaluated by ultrasonography.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gagliardi 1983

Methods	Double blinded: yes.
Participants	N=40 Italian men with symptomatic BPH. Age range: 50-84, mean 67 years. Lost to follow-up: 1 (2.5%).
Interventions	Control: Anti-inflammatory (not identified) (n=20) Treatment: P. africanum extract (Tadenan) 100 mg daily (n=20). Treatment duration: 30 days.
Outcomes	Nocturia; residual volume. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Giacobini 1986

Methods	Double blinded: yes.
Participants	N=21 Italian men with symptomatic BPH. Age range: 48-70. Lost to follow-up: 0.
Interventions	Control: placebo (n=7). Treatment 1: P. africanum extract (Tadenan) 200 mg daily (n=7). Treatment 1: P. africanum extract (Tadenan) 200 mg daily + medroxyprogesterone acetate (Farlutal) (n=7). Treatment duration: 90 days.
Outcomes	Peak flow rate; residual volume. Adverse events.

Pygeum africanum for benign prostatic hyperplasia (Review)

Giacobini 1986 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Krzeski 1993

Methods	Double blinded: yes.
Participants	N=134 Polish men with symptomatic BPH (> 1 symptom). Age range: 53-84, mean 64 years. Lost to follow-up: 14.2%.
Interventions	Treatment 1: P. africanum 25 mg + Urtica dioica 300 mg (n=67). Treatment 2: half dose of above (n=67). Treatment duration: 8 weeks.
Outcomes	Overall improvement in symptoms; nocturia; peak flow rate; residual volume. Adverse events.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Mandressi 1983

Methods	Double blinded: yes. Randomization: Identical packaging
Participants	N=60 Italian men with symptomatic BPH. Age range: 50-80.
Interventions	Control 1: placebo (n=20). Control 2: Permixon 320mg daily (n=20). Treatment: Pygeum africanum extract Average (n=20). Treatment duration: 30 days. Lost to follow-up: unclear
Outcomes	Patient self-rating of "Dysuric symptoms" (pain on voiding) Nocturia. Adverse events. Dropouts due to side effects: none

Notes

Pygeum africanum for benign prostatic hyperplasia (Review)

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Mandressi 1983 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Maver 1972

Methods	Double blinded: yes.
Participants	N=60 Italian men with symptomatic BPH. Age range: 55-85, mean 66 years.
Interventions	Control: placebo (n=30). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=30). Treatment duration: 60 days.
Outcomes	Nocturia; residual volume. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ranno 1986

Methods	Double blinded: yes.
Participants	N=39 Italian men with symptomatic BPH. Mean age: 70 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=19). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=20). Treatment duration: 2 months.
Outcomes	Nocturia; peak urine flow. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rigatti 1983

Methods	Double blinded: yes.
Participants	N=49 Italian men with symptomatic BPH. Lost to follow-up: 0.
Interventions	Control: NSAID (n=25). Treatment: P. africanum extract (Tadenan) 100 mg daily (n=24). Treatment duration: 60 days.
Outcomes	Residual volume. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rizzo 1985

Methods	Double blinded: yes.
Participants	N=40 Italian men with symptomatic BPH. Age range: 42-74, mean 62 years. Lost to follow-up: 0.
Interventions	Control: placebo (n=20). Treatment: P. africanum extract (Tadenan) 100 mg twice daily (n=20). Treatment duration: 60 days.
Outcomes	Nocturia; peak urine flow; residual volume. Adverse events.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

* Extract of Rad. urticae

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Anonymous 1973	No control group.

Pygeum africanum for benign prostatic hyperplasia (Review)

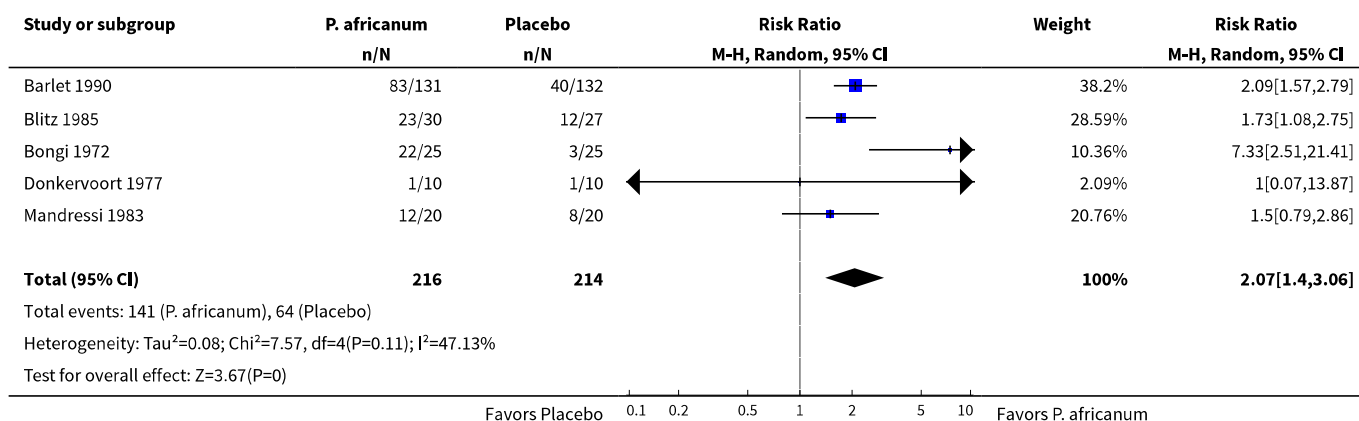
Study	Reason for exclusion
Breza 1998	No control group.
Diz 1973	No control group.
Grasset 1974	No control group.
Greiner 1970	No control group.
Grévy 1970	No control group.
Guilland-Vallée 1970	No control group.
Guillemin 1970	No control group.
Huet 1970	No control group.
Lange 1970	No control group.
Lhez 1970	No control group.
Martínez-Piñeiro '73	No control group.
Robineau 1976	No control group.
Rometti 1970	No control group.

DATA AND ANALYSES

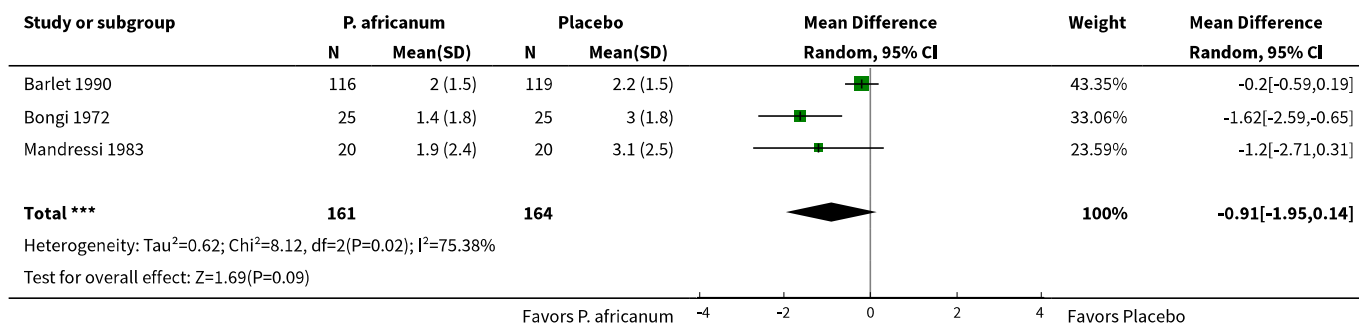
Comparison 1. Pygeum africanum vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptoms improvement: Overall improvement/Global assessment/MD rating	5	430	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.40, 3.06]
2 Nocturia (times per evening)	3	325	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.95, 0.14]
3 Peak urine flow (mL/sec)	4	363	Mean Difference (IV, Random, 95% CI)	2.50 [0.29, 4.71]
4 Residual volume (mL)	2	264	Mean Difference (IV, Random, 95% CI)	-13.17 [-23.34, -2.99]

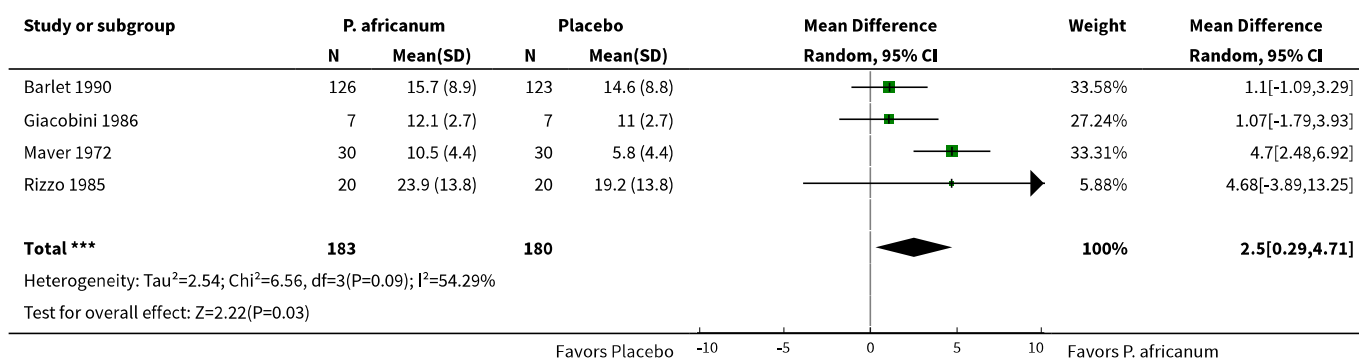
Analysis 1.1. Comparison 1 Pygeum africanum vs. placebo, Outcome 1 Symptoms improvement: Overall improvement/Global assessment/MD rating.



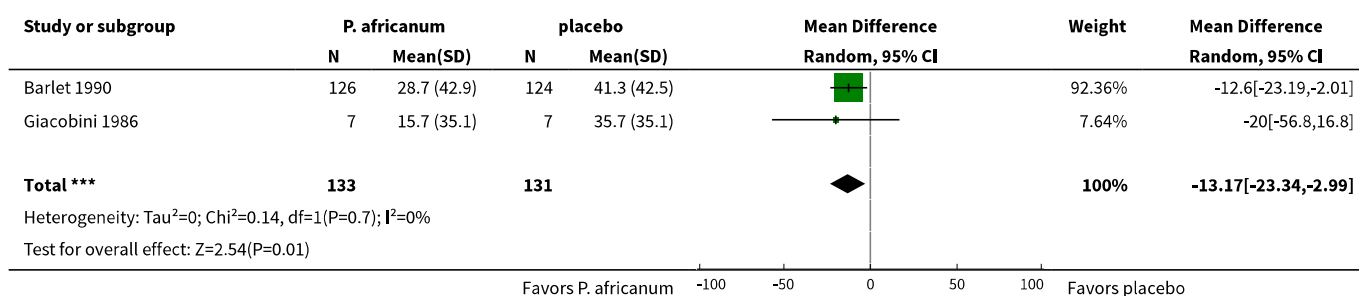
Analysis 1.2. Comparison 1 Pygeum africanum vs. placebo, Outcome 2 Nocturia (times per evening).



Analysis 1.3. Comparison 1 Pygeum africanum vs. placebo, Outcome 3 Peak urine flow (mL/sec).



Analysis 1.4. Comparison 1 Pygeum africanum vs. placebo, Outcome 4 Residual volume (mL).



WHAT'S NEW

Date	Event	Description
28 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 2, 2002

Date	Event	Description
26 November 1997	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Veterans Affairs Health Services Research and Development (HSRD) Office, USA.
- Minneapolis/VISN-13 Center for Chronic Diseases Outcomes Research (CCDOR), USA.

External sources

- No sources of support supplied

NOTES

This review is out of date and has been withdrawn.

INDEX TERMS

Medical Subject Headings (MeSH)

*Phytotherapy; Plant Bark [chemistry]; Plant Extracts [therapeutic use]; Prostatic Hyperplasia [*drug therapy]; Randomized Controlled Trials as Topic; Urination Disorders [drug therapy]

MeSH check words

Humans; Male



Use of saw palmetto (*Serenoa repens*) extract for benign prostatic hyperplasia

Youngjoo Kwon¹

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Abstract Benign prostatic hyperplasia (BPH) is a non-cancerous growth of the prostate. BPH commonly occurs in elderly men. Lower urinary tract symptoms (LUTS) secondary to BPH (LUTS/BPH) have significant impacts on their health. Saw palmetto (*Serenoa repens*) extract (SPE) has been evaluated for its effectiveness in improvement of LUTS/BPH at preclinical and clinical levels. Potential mechanisms of actions include anti-androgenic, pro-apoptotic, and anti-inflammatory effects. However, SPE efficacy was inconsistent, at least partly due to a lack of a standardized SPE formula. A hexane extract (free fatty acids, > 80%) provided more consistent results. Free fatty acids (lauric acid) were effective in inhibition of 5 α -reductase, and phytosterol (β -sitosterol) reduced prostatic inflammation. Multiple actions derived from different constituents may contribute to SPE efficacy. Evaluation of the clinical relevance of these bioactive components is required for standardization of SPE, thereby enabling consistent efficacy and recommendations for the use in the prevention and treatment of BPH.

Keywords Benign prostatic hyperplasia · Fatty acids · Phytosterol · Saw palmetto extract · Standardized formula

Introduction

Benign prostatic hyperplasia (BPH) refers to nonmalignant growth of the prostate. Histologically, BPH is described as a proliferative process of both the stromal and epithelial elements of the prostate gland. BPH commonly occurs in elderly men. Nearly all men develop histologic evidence of BPH by 80 years of age (Lepor, 2005).

BPH arises in the periurethral and transition zones of the prostate. Human prostate grows with age. This continued growth (hyperplasia) can enlarge the prostate to the extent that it compresses the urethra and limits the flow of urine, causing urinary symptoms (Lepor, 2005). However, prostatic enlargement varies in degree in different individuals (Lepor, 2005). Therefore, not all men with histologic BPH will develop significant symptoms (Roehrborn, 2005). The most common manifestation of BPH is lower urinary tract symptoms (LUTS), a group of clinical symptoms comprising obstructive symptoms including hesitancy, poor stream, incomplete voiding, urinary retention, and overflow incontinence as well as irritative symptoms including frequent urination, urgent urination, nocturia, and urge incontinence (Roehrborn, 2005).

A recent systemic review estimated that the prevalence of symptomatic BPH increases from 14.8% in males aged 40 to 36.8% in males aged 80 and above, although marked differences in estimated prevalence among different studies were observed largely due to the heterogeneity in BPH definition and the variation in case definitions used (reviewed in Lee et al., 2017). As the numbers of the elderly increase rapidly worldwide, the incidence and prevalence of BPH will increase and LUTS secondary to BPH will have a significant impact on the health of older men and on associated health-care costs.

✉ Youngjoo Kwon
Youngjoo.Kwon@ewha.ac.kr

¹ Department of Food Science and Engineering, Ewha Womans University, 52 Ewhayeodae-gil, Seodaemun-gu, Seoul 03760, Korea

The reasons causing the prostate to enlarge are still poorly understood. In general, dihydrotestosterone (DHT), a metabolite of testosterone, is thought to be a critical mediator of prostatic growth (Rhodes et al., 1993). DHT is derived from testosterone in specific tissues including the prostate gland via the action of 5 α -reductase. DHT binds to nuclear androgen receptors and activates the transcription of androgen-regulated genes that are mitogenic to both epithelial and stromal cells (Saad et al., 2011).

Treatment options are medication and surgery. Medication for the treatment of mild to moderate BPH has become a standard of care since well-designed clinical studies showed that finasteride, a 5 α -reductase inhibitor (5-ARI), and terazosin, an α -blocker, significantly improved LUTS and increased peak urinary flow rates in men with BPH (Lepor, 1989). Subsequently, many clinical trials have validated the effectiveness of two 5-ARIs (finasteride and dutasteride) and five α -blockers (terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin), which were subsequently approved by the US Food and Drug Administration for the treatment of BPH (Lepor, 2011).

Alpha-blockers, also known as α -adrenergic receptor antagonists, relax smooth muscles in the prostate and the bladder neck, thus decreasing the blockage of urine flow and allowing urine to flow more easily. Alpha-blockers begin to work quickly with no effect on prostate size and are usually recommended as a first-line treatment for men with mild to moderate symptoms (Lepor, 2016). 5-ARIs, also known as DHT blockers, inhibit the 5 α -reductase enzyme, and thus can prevent the prostate from growing further. In addition, phytotherapy including extract of the fruit from saw palmetto (*Serenoa repens*), the American dwarf palm tree has been used. Although many physicians remain skeptical regarding its therapeutic use, there is continued growing interest in the use of saw palmetto extract (SPE) in patients with BPH due to drug-related adverse effects associated with α -blockers (e.g., postural hypotension and retrograde ejaculation) and with 5-ARIs (e.g., impairment of erection) (Debruyne et al., 2004).

The present study reviewed the effects and potential mechanisms of action of SPE and putative bioactive components in SPE. The objective of the review was to manifest the importance of standardization of formula in preparation of dietary supplements such as SPE in order to recommend their preventive and therapeutic use based on their consistent efficacy.

Effect of saw palmetto extract on lower urinary track symptoms

Historically, Native Americans were known to use the fruit of saw palmetto to treat urinary and reproductive system problems (Suzuki et al., 2009). SPE is commonly used to

treat BPH in Europe (Suzuki et al., 2009). SPE use in the treatment of BPH-related LUTS has been extensively evaluated. However, many of the reported studies (Cham-pault et al., 1984; Reece Smith et al., 1986) were short-term studies conducted for 3 months or less and were performed before the development of validated symptom scores such as the international prostatic symptoms scale (IPSS) and the international index of erectile function (IESS) (MacDonald et al., 2012). This review included SPE clinical trials that used standardized screening tools such as IPSS to monitor the severity of the symptom of LUTS secondary to BPH.

Some non-comparative observational studies suggested that daily intake of 320 mg SPE for 24 months was effective in improving IPSS and IESS scores as well as quality of life (Sinescu et al., 2011) and that treatment for 15 years prevented progression of BPH (Vinarov et al., 2018). In contrast, a randomized and controlled study found that taking 320 mg SPE extract daily did not improve symptoms or urinary flow compared to placebo (Bent et al., 2006). Moreover, longer follow-up (72 weeks) and use of higher doses (640 or 960 mg) did not improve LUTS compared to placebo (Barry et al., 2011; Tacklind et al., 2012). Therefore, recommendations for the use of SPE in BPH cannot be proposed currently.

However, of note, disparity in composition of SPE may contribute to heterogeneity in efficacy (Habib and Wyllie, 2004). Different products derived from the same plant can have different activity due to differences in the composition of bioactive components in the plant extracts (Novara et al., 2016). Permixon is a hexane extract of saw palmetto and is the most studied. Many SPE products were found to have significantly different relative contents of putative active components, fatty acids and phytosterols (Habib and Wyllie, 2004; Penugonda and Lindshield, 2013). Permixon contained the highest content (> 80%) of free fatty acids among 14 products available in Europe (Habib and Wyllie, 2004). Permixon also showed the highest efficacy in inhibition of 5 α -reductase (Scaglione et al., 2012). Consistently, clinical studies with Permixon have produced reproducible results of improvement of urinary symptoms (MacDonald et al., 2012; Pytel et al., 2002). A meta-analysis that includes all available randomized control trials and observational studies showed that Permixon reduced nocturia and improved maximum urinary flow compared with placebo (Vela-Navarrete et al., 2018). Moreover, Permixon had a similar efficacy to tamsulosin (a commonly prescribed α -blocker) (Debruyne et al., 2004) and 5-ARIs (Vela-Navarrete et al., 2018) in relieving LUTS. These data suggested that the hexane extract of saw palmetto (Permixon) is an efficacious therapeutic option for the long-term treatment of LUTS secondary to BPH. Different brands of SPE may show marked variation in

content. Therefore, standardization of SPE formula, and control of the content of active components in SPE may be critical to achieving consistent efficacy of SPE and recommendations for its use in prevention and treatment of BPH (Fagelman and Lowe, 2001).

In general, saw palmetto extracts are well tolerated in men with BPH. There is agreement that adverse effects of saw palmetto extracts are few and mild, and that their incidences are not significantly different compared to placebo (MacDonald et al., 2012; Tacklind et al., 2012; Wilt et al., 2002).

Mechanisms of action of saw palmetto extract

The exact mechanisms of action of SPE are unknown in relieving LUTS associated with BPH. Suggested mechanisms include anti-androgenic, pro-apoptotic, and anti-inflammatory effects (Fig. 1) as described below.

Anti-androgenic effect

Inhibition of receptor binding of androgens has also been studied (Sultan et al., 1984) but is less evident. The most studied area is the inhibitory activity of SPE on 5α -reductase. SPE non-selectively inhibited both type I and type II isoenzymes of 5α -reductase in comparison to finasteride, which selectively inhibits the type 2 isoform (Lehle et al., 1995). Inhibitory effects of SPE on 5α -reductase were also reported in human foreskin fibroblasts (Sultan et al., 1984) and a human prostate cancer cell line (Anderson, 2005).

In agreement with in vitro studies, a 3-month randomized study reported that Permixon (320 mg/day) effectively decreased DHT and increased testosterone in the periurethral region of the prostate in patients with BPH (Di Silverio et al., 1998), suggesting the inhibition of 5α -reductase by SPE in vivo. However, Permixon did not inhibit serum levels of either testosterone or DHT in healthy men consuming 80 mg SPE twice a day for up to a week, in

contrast to the effective reduction of serum DHT level by a single dose of 5 mg finasteride (Strauch et al., 1994). SPE may require longer treatment or higher dose to achieve effective inhibition of 5α -reductase. It is also possible that SPE may alter testosterone or DHT metabolism differently in men with or without LUTS, although mechanisms are unknown. Therefore, studies suggest that SPE may inhibit 5α -reductase in men with symptomatic BPH. However, of note, many studies (Opoku-Acheampong et al., 2016; Talpur et al., 2003) indicate that SPE may modulate androgen metabolism and/or block the effects of androgens because of mitigation of androgen-induced increase in prostatic mass in castrated or non-castrated rodent models. However, more recently, prostate hyperplasia has been suggested to be induced by prostatic inflammation mediated by androgens as well as other factors including proinflammatory cytokines (Chughtai et al., 2011). Hence, inhibition of androgen-induced growth of the prostate by SPE may also be attributed to anti-inflammatory effect.

Pro-apoptotic effect

Studies also suggested that SPE treatment can inhibit the growth of prostate by increase of apoptosis as described below. Treatment with SPE inhibited cell growth via inhibition of insulin growth factor-1-induced proliferation and increased apoptotic index [cleavage of poly (ADP-ribose) polymerase] in the P69 prostate epithelial cell line (Wadsworth et al., 2004). SPE induced apoptotic cell death in PC3 and LNCaP human prostate cancer cells through the intrinsic apoptotic pathway (Baron et al., 2009). SPE-induced apoptosis was also observed in other types of cancer cell lines including MCF-7 breast cancer cells and HCT116 colon cancer cells (Hostanska et al., 2007).

In addition, apoptotic index (Bax-to-Bcl2 ratio) was significantly increased in transurethral prostate tissues obtained from men with symptomatic BPH by surgery after treatment with 320 mg Permixon daily for 3 months compared to those obtained from untreated controls (Vela-

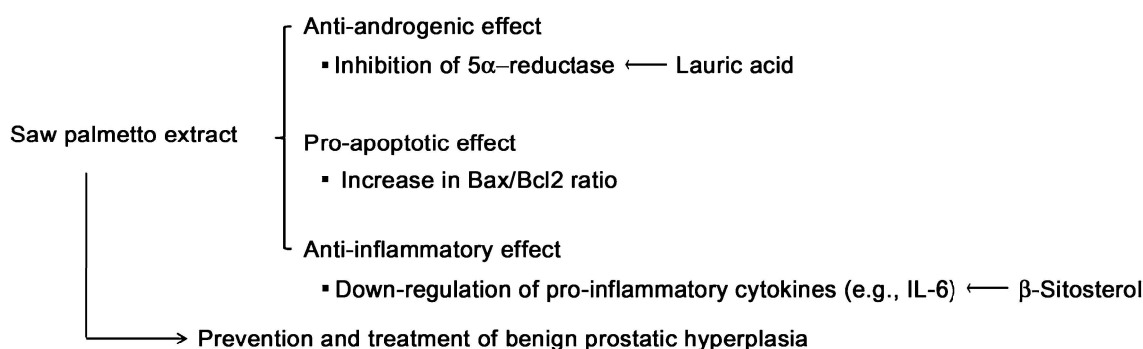


Fig. 1 Putative mechanisms of action of saw palmetto extract (SPE) and its constituents in relief of lower urinary track symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH)

Navarrete et al., 2005). Therefore, consumption of SPE may reduce prostate size by increasing apoptosis. However, most studies have conducted in cancer cell lines and more studies are required to prove its effect in vivo.

Anti-inflammatory effect

More recent studies have highlighted the observation that intraprostatic inflammation mediates the development and/or progression of BPH (Gandaglia et al., 2013; Mishra et al., 2007). The risk of urinary retention due to BPH was significantly greater in men with prostatic inflammation than in those without prostatic inflammation (Mishra et al., 2007). Chronic prostatic inflammation was related to larger prostate volumes, more severe LUTS, and poorer response to BPH medical treatment (Gandaglia et al., 2013). These findings suggested that anti-inflammatory effect of SPE can be beneficial in treatment of BPH symptoms.

Treatment with Permixon significantly reduced the expression of inflammation-regulated genes including *IL-6*, *CCL-5*, *CCL-2*, *COX-2*, and *iNOS* in the human prostate cancer cell lines LNCaP and PC3, as well as in primary human prostate cancer cells (Silvestri et al., 2013). A oral dose (100 mg/kg body weight/day) of Permixon for 28 days significantly decreased tissue weight and proliferation index (Ki-76 immunostaining) in mouse model of prostate hyperplasia involving prostate-specific over-expression of a prolactin (*Prl*) transgene, namely probasin (Pb)-Prl model (Bernichtein et al., 2015). In this Pb-Prl model, administration of Permixon reduced prostatic inflammation both histologically and molecularly (e.g., down-regulation of pro-inflammatory cytokine profiles with significant reduction of *CCR7*, *CXCL6*, *IL-6*, and *IL-17* expression) (Bernichtein et al., 2015).

At a clinical level, patients receiving a daily oral dose of Permixon (320 mg) for 3 months showed reduced levels of inflammatory marker at mRNA levels in the lumen of the prostate gland and this effect was more effective compared to that of tamsulosin (0.4 mg) (Latil et al., 2015). In addition, in the same study, the number of patients who expressed urinary CCL2 and CXCL10 proteins was decreased and expression of urinary macrophage migration inhibitory factor was significantly reduced in the Permixon-treated group than in the tamsulosin-treated group (Latil et al., 2015). Therefore, preclinical and clinical studies indicated that SPE, particularly, Permixon may effectively relieve BPH symptoms through anti-inflammatory mechanisms. However, different studies used different inflammatory markers and the relevance of these markers in BPH needs to be validated. Moreover, it should be further evaluated whether inflammation causes development of LUTS/BPH and vice versa.

In summary, anti-androgenic effect of SPE has been primarily studied in relation to its efficacy in BPH-related LUTS. As described above, studies also suggested that pro-apoptotic and anti-inflammatory effects are involved in beneficial effect of SPE (Fig. 1). Unfortunately, reported studies were largely conducted in vitro and the relevance of the mechanisms described above in prevention and treatment of BPH-related LUTS should be further validated at a clinical level (Fagelman and Lowe, 2001). It was also suggested that SPE efficacy may related to relaxation of lower urinary tract smooth muscles. SPE inhibited ligand binding to human α 1-adrenergic (Goepel et al., 1999; Suzuki et al., 2007) and muscarinic (Suzuki et al., 2007) receptors. However, there are only few studies that evaluate the effects of SPE on relaxation of smooth muscle.

Bioactive components in saw palmetto extract

The bioactive components of SPE are considered to be fatty acids and phytosterols (Table 1). The fruit of saw palmetto typically contains 70–90% free fatty acids of caprylic, capric, lauric, myristic, palmitic, stearic, oleic, linoleic, and linolenic acids (Booker et al., 2014). The composition of the various brands of saw palmetto varies depending on extraction methods, source of the plant, and additional ingredients (Penugonda and Lindshield, 2013). The content of total free fatty acids was found to range from 40.7 to 80.7% (Table 1) in 14 SPE extracts commercially available for the treatment of LUTS (Habib and Wyllie, 2004). When 57 different products containing saw palmetto as mono-preparations or as a part of multicomponent supplements from nine countries were analyzed using gas chromatography, total fatty acid was found to be in the range of 8.43–1473 mg in a manufacturer-claimed therapeutic dose (Booker et al., 2014). In addition, the contents of free fatty acids and phytosterols were also found to vary depending on supplement types such as liquid, powder, dried berry, or tincture (Penugonda and Lindshield, 2013).

In spite of various concentrations of total fatty acid depending on SPE products, the composition of saw palmetto prepared by a similar extraction method was found to be comparable (Booker et al., 2014). The percentage of the nine different single fatty acids (capric acid, caprylic acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid) was similar in products prepared by a similar extraction method (Booker et al., 2014). Saw palmetto fruits contained high amounts of oleic acid as well as lauric acid (Table 1) and each fatty acid was comprised approximately 30–40% of the total fatty acids (Booker et al., 2014). Oleic acid and lauric acid were also the predominant fatty acids irrespective of

Table 1 Composition of fatty acids and phytosterols in saw palmetto extract (SPE)

Content in SPE	Proportion for each category (Penugonda and Lindshield, 2013)	
Fatty acids (Habib and Wyllie, 2004) (40–80%)	Oleic acid	> 30%
	Lauric acid	30%
	Myristic acid	10%
	Linolenic acid	10%
	Palmitic acid	10%
	Stearic acid	< 5%
	β -Sitosterol	80%
Phytosterols (Penugonda and Lindshield, 2013; Weisser et al., 1996) (< 1%)	Campesterol	< 15%
	Stigmasterol	< 10%

supplement types of liquid, powder, dried berry, or tincture (Penugonda and Lindshield, 2013). β -Sitosterol was the most abundant phytosterol, although phytosterol content varied in different supplement types (Penugonda and Lindshield, 2013).

SPE is a mixture of various compounds. One of the main difficulties in assessing the efficacy of SPE is the absence of standardization in composition (Fagelman and Lowe, 2001), which may result in varying efficacy of SPE in BPH treatment. Therefore, a standard formulation is essential to ensure a consistent biological effect of SPE. Permixon, the *n*-hexane lipidosterolic extract of saw palmetto, is the most studied form of SPE and studies with Permixon have produced relatively consistent beneficial effects on LUTS at preclinical and clinical levels. Therefore, it is important to identify major biologically active components of SPE in treatment of BPH and create a standardized formula for consistent beneficial effects on health. So far, only the European Pharmacopoeia has a specified requirement for saw palmetto preparations, requiring lauric acid to be at least 20% of total fatty acids (Booker et al., 2014).

Fatty acids

Fatty acids are the major constituents of SPE. The main fatty acids in SPE showed α_1 -adrenergic receptor-binding activity as well as inhibitory effects on 5α -reductase (Abe et al., 2009a; 2009b), suggesting that fatty acids in SPE contribute to relieving BPH symptoms via relaxation of muscle tone and inhibition of testosterone metabolism. Sub-fractionation of SPE further demonstrated that free fatty acids are largely responsible for inhibitory effects of SPE on 5α -reductase. When SPE was sub-fractionated into saponifiable, nonsaponifiable, and hydrophilic fractions, the saponifiable subfraction that consists mainly of lauric acid, oleic acid, myristic acid, and palmitic acid showed

non-competitive and dose-dependent inhibition of 5α -reductase in the prostatic epithelium and stroma homogenates (Weisser et al., 1996). In contrast, the nonsaponifiable and hydrophilic subfractions showed only a slight and no inhibition of 5α -reductase, respectively (Weisser et al., 1996). 5α -Reductase derived from rat liver was also inhibited by the fatty acids (Liu et al., 2009). Inhibition of type 1 and type 2 5α -reductase activity was only observed with fatty acids whereas esterified fatty acids, alcohols, and sterols were inactive in inhibition of either type 1 or type 2 isoforms (Raynaud et al., 2002). Consistently, compared with fatty acids active in inhibition of 5α -reductase, methyl ester and alcohol analogs of these inhibitory fatty acids were either inactive or only slightly active in rat liver, suggesting that the free $-\text{COOH}$ group is important for the inhibition of 5α -reductase (Liu et al., 2009).

Inhibitory activity of individual fatty acids has been found to vary in different studies as described below, probably due to the use of different assay systems. Lauric acid and myristic acid were the most effective in inhibition of 5α -reductase present in the prostatic epithelium and stroma homogenates whereas oleic acid and palmitic acids had almost no inhibitory effect (Weisser et al., 1996). When two isoforms of 5α -reductase were tested separately, lauric acid was active against both isoforms whereas palmitic acid and stearic acid were inactive against both isoforms (Raynaud et al., 2002). Oleic acid and linolenic acid were selectively effective against type 1 isoform (Raynaud et al., 2002). Myristic acid had a strong inhibitory effect against type 2 with its effect against type 1 being unevaluated (Raynaud et al., 2002). Similar results were observed in 5α -reductase derived from rat liver; among the saturated fatty acids, the inhibitory effects of shorter fatty acids such as lauric and myristic acids were greater (Liu et al., 2009). Inhibitory activity against 5α -reductase in the liver was similar for lauric acid, oleic acid, myristic acid, linoleic

acid, but no inhibitory effect of palmitic acid was found among the tested fatty acids (Abe et al., 2009a). Therefore, the main free fatty acid constituents in SPE, lauric acid, oleic acid, and myristic acid, appear to be effective in inhibition of 5 α -reductase.

In addition, lauric acid, myristic acid, and oleic acid significantly inhibited the contraction induced by phenylephrine in isolated rat vas deferens (a thick-walled tube in the male reproductive system) with lauric acid showing the highest at the same relative concentration present in SPE (Arruzazabala et al., 2011). Alpha-1 adrenergic receptors mediate smooth muscle contraction. Fatty acids such as lauric acid and oleic acid significantly inhibited the specific binding of radiolabeled ligands to α 1-adrenergic, muscarinic, and 1,4-dihydropyridine calcium channel (Abe et al., 2009a). Thus, as described above, studies have suggested that activity of 5 α -reductase and α 1-adrenergic receptor-binding can be effectively inhibited by free fatty acids, particularly lauric acid, the main constituent of total fatty acids in SPE. However, inhibitory effect on 5 α -reductase were mostly performed in vitro and their relevance in vivo needs to be validated. In addition, the bioavailable concentration of these fatty acids and SPE in the prostate tissue needs to be evaluated.

Phytosterols

Phytosterols are relatively minor constituents (Table 1) of SPE (Penugonda and Lindshield, 2013; Weisser et al., 1996). Studies have suggested that phytosterols may be beneficial in BPH treatment due to their anti-inflammatory and cholesterol-lowering effects (Freeman and Solomon, 2011; Scholtyssek et al., 2009). β -Sitosterol inhibited proliferation of human prostate cancer cells (von Holtz et al., 1998) and growth of tumors derived from PC-3 human prostate cancer cells (Awad et al., 2001).

In a randomized, double-blind, and placebo-controlled clinical trial, treatment with 130 mg free β -sitosterol daily for 6 months significantly improved IPSS and quality of life index with an increase in peak urinary flow rates and decrease in post-void residual urinary volume over placebo (Klippel et al., 1997). Similar results were observed with another randomized, double-blind, and placebo-controlled multicentric study that a mixture of phytosterols (60 mg β -sitosterol per day) was treated for 6 months in patients with symptomatic BPH (Berges et al., 1995). Moreover, results for the 18-month follow-up of the trial suggested that the beneficial effects of β -sitosterol were maintained in patients who continued β -sitosterol treatment for 18 months after the initial 6-month trial (Berges et al., 2000). In addition, taking phytosterol prepared from pumpkin seeds and saw palmetto for 3 months significantly

improved BPH symptoms with no side effects in a randomized, double-blind study (Carbin et al., 1990). Therefore, well-designed clinical trials supported beneficial effects of phytosterols in treating BPH symptoms. However, clinical studies mentioned above were mostly observational studies and were conducted in 1990's. SPE contains only small amount of phytosterols (< 1%) and the quantity may not be sufficient to exert the beneficial effect of phytosterol treatment. Moreover, the phytosterol-rich extracts were often prepared from various plants that also contain other components in small quantities, leaving open the possibility that components other than phytosterols may have been involved in the observed beneficial effects.

In conclusion, saw palmetto extract has therapeutic potential. However, efficacy of SPE has been found to be inconsistent, at least partly due to a lack of standardization of the SPE formula. Free fatty acids such as lauric acid, the main constituents of SPE, have been shown to be effective in inhibition of 5 α -reductase and phytosterol (β -sitosterol), minor constituents of SPE, was found to effectively reduce prostatic inflammation. Multiple rather than single mechanisms may be involved in the beneficial effects of SPE in BPH treatment. Therefore, it is important to standardize SPE products for consistent efficacy and to enable recommendations for SPE use in prevention and treatment of BPH.

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