Review Article

Phytotherapeutica in common urological conditions in Western integrative medicine: a narrative review

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Background and Objective: Phytotherapy, a scientifically based usage of plant extracts for treatment and prevention of disease, is as old as humanity. In the last century, it has marked a significant advancement in the field of Urology, giving additional treatment options in a variety of unsolved problems in everyday urological practice. Phytotherapeutica has its most prominent place in the therapeutic arsenal of Western Urology regarding benign prostatic hyperplasia (BPH)/lower urinary tract symptoms (LUTS), erectile dysfunction (ED) and sexual disorders, chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS), urinary tract infections (UTIs) and urolithiasis. The aim of this review is to present the most frequently used plant extracts for treatment of those conditions and to discuss on their strengths and weaknesses.

Methods: A literature review was performed on PubMed and Google Scholar for original articles published before May 2021, with a time frame 1995–2021. The used keywords Included: 'Phytotherapy', 'BPH/LUTS', 'Serenoa repens', 'ED', 'CPPS', 'UTI', 'plant extracts', 'herbal medicines'. Only full text articles in English were included.

Key Content and Findings: The review on the literature on usage of plant-based medications on benign urological conditions has confirmed their proven efficacy and safety, but emphasize the scarcity of solid scientific data, its heterogeneity and lack of standardization in conducting research on the subject.

Conclusion: For millenia phytotherapy has its empirically established place in Urology, especially in BPH/LUTS, ED and other sexual disorders, CP/CPPS, UTI and urolithiasis. At the present time significant controversies and incosistencisies exists in conducting clinical trials on the subject in order to achieve the highest possible level of evidence. An evidence-based medicine approach according to all principles of good clinical practice is needed for the phytotherapy to claim its much deserved place in all major international urological guidelines

Keywords: Phytotherapy; prostatic hyperplasia (BPH)/lower urinary tract symptoms (LUTS); erectile dysfunction (ED); chronic pelvic pain syndrome (CPPS); urinary tract infection (UTI)

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Introduction

Phytotherapy, a scientifically based usage of plant extracts for treatment and prevention of disease, is as old as humanity. This knowledge was passed on from person to person in Ancient times, until the development of social structure and writing which helps for much wider distribution of knowledge. First written proof of phytotherapeutica dates 3000 B.C. The Egyptians was the first great civilization which left extensive body of knowledge on the medicinal use of plants (1). This legacy later was carried on and developed by Greek and Roman civilization in ancient Mediterranean. For millennia, the Chinese traditional medicine has the leading and most extensive experience in usage of plant extracts and compounds for urological conditions. The Renaissance marks peak in phytotherapy; modern technology led to unprecedented advancement in the development and use of active ingredients derived from plants in the recent years; at the present moment according to the World Health Organization approximately quarter of modern drugs in US originate from research on phytochemicals (2). Because of this widespread usage of phytotherapeutica urologists must have a solid knowledge on them, their benefits and potential adverse effects, as well as the new insights on the biochemical pathways that are enlightened by the discovery of specific active ingredients in plant extracts.

Phytotherapy has lot to offer in the treatment of benign urological diseases. Organizational factors, like differences in legislation in different countries and low motivation of pharmaceutical companies to perform proper randomized-controlled studies on plant based compounds, have significantly impaired the amount of available research needed for establishing the deserved evidence-based place of phytotherapeutica in Urology (3). This article focuses on those best-confirmed and most widely accepted plant-based medications, aiming to update the knowledge on the subject and outlining the future tendencies in their development.

Urological diseases are extremely common and tend to bear a significant health and social burden, while at the same time a lot of unanswered questions and unmet needs exist in their treatment (significant lack of knowledge on their etiology and pathophysiology, low efficacy of the accepted treatment options, toxicity in short or long-term, low compliance to therapeutic regiment). There are several reasons that urologists should be acquainted to the topic of phytotherapy. Substantial, yet still heterogeneous and controversial, database on efficacy of phytotherapy in conditions in Urology like BPH/LUTS. CP/CPPS, ED and sexual disorders, UTI and urolithiasis (the latter being subject of a separate article in this Special Series on Integrative Medicine in Urology) has been developed, making somewhat near its inclusion in international guidelines (1). Furthermore, the urologists must have knowledge regarding contraindication, toxicity and interactions of plant-based medications.

The objective of this article is to present as a narrative the best scientific evidence and contemporary trends on usage of phytotherapy for treatment of urological conditions in Western medicine. It aims to broaden the urologists' knowledge on those widely accepted, well tolerated and effective therapeutic alternative used for a wide array of urological conditions. We present the following article in accordance with the Narrative Review reporting checklist (available at https://lcm.amegroups.com/article/view/10.21037/lcm-21-38/rc).

Methods

A literature review was performed in 5.2021 searching PubMed and Google Scholar for scientific articles published between January 1995 and May 2021. Inclusion criteria were Original articles in English on phytotherapy in benign urological conditions, excluding Letters to the Editor, Case report, Case series type of publications. The selection process begun with independent review search by all of the three authors, while the final list of included studies was reached by consensus.

The used keywords Included: 'phytotherapy', OR 'BPH/LUTS', OR 'Serenoa repens', OR 'ED', OR 'CPPS', OR 'UTI', OR 'plant extracts', OR 'herbal medicines'. In the following table (*Table 1*) we present the characteristics of our search strategy.

Benign prostatic hyperplasia (BPH)

BPH is one of the most common urological diseases, observed in over 50 % of males over 50 years of age. Contemporary treatment options for BPH and resulting lower urinary tract symptoms (LUTS) include lifestyle modifications, medications and surgery.

The phytotherapeutic agents for BPH, which became increasingly popular since the late 20th century, are highly heterogeneous group of medications, which contain different active ingredient(s) and in different

Table 1 The search strategy summary

Items	Specification
Date of search	May 2021
Databases and other sources searched	PubMed, Google Scholar
Search terms used	'phytotherapy', 'BPH/LUTS', 'Serenoa repens', 'ED', 'CPPS', 'UTI', 'plant extracts', 'herbal medicines'
Time-frame	January 1995–May 2021
Inclusion and exclusion criteria	Original articles in English on phytotherapy in benign urological conditions, excluding Letters to the Editor, Case report, Case series type of publications
Data selection process	Literature search and selection was conducted independently and simultaneously by E. Popov, R. Georgieva and Ch. Slavov. Selected articles approved by consensus

BPH/LUTS, benign prostatic hyperplasia/lower urinary tract symptoms; ED, erectile dysfunction; CPPS, chronic pelvic pain syndrome; UTI, urinary tract infection.

concentrations in their various formulations (3). The use of phytotherapeutica in the treatment of BPH and LUTS has become widely popular and it's prevalence in EU and USA is increasing, reaching up to 50 % in some countries (4), although specific recommendations on phytotherapy are lacking in the EAU and most of other major Guidelines due to product heterogeneity and lack of standardization, limited scientific background, and poor quality with significant potential bias of RCT and systematic reviews and meta-analyses on the subject. All of the aforementioned still prevents phytotherapy to fulfill the criteria of evidence-based medicine and hence be included into Guidelines for BPH/LUTS

The TRIUMPH Study studied the prescription practice in BPH/LUTS medication treatment in six European countries and concluded that despite significant differences in national policies, alpha-blockers were predominant in all countries as monotherapy (79%) followed by phytotherapy (16%) and 5-ARI (5). Another study in primary care (4) shows similar results. About 40% of men on medication therapy for LUTS/BPH in the US use phytotherapy as a monotherapy, or as a part of a combination treatment, with a trend to increase that percentage (6).

Mechanism of action of phytotherapeutica for BPH/LUTS is multi-factorial and still not sufficiently studied. Laboratory studies on cell cultures and animals have elucidated various possible mechanisms of action of the phytotherapeutica—anti-inflammatory, anti-androgenic, and estrogenic effects; decrease SHBG activity; inhibition of aromatase, lipoxygenase, growth factors, alpha-adrenoreceptors, 5-alpha reductase, M-cholinergic receptors, dihydropyridine and vanilloid receptors; and decrease oxidative stress (7-12).

More than three dozens plants and phytotherapeutic compounds are reported and used in the management of BPH/LUTS in the Western Urology, and among them the most popular are *Serenoa repens*, *Pygeum africanum*, *Urtica dioica*, *Cucurbita pepo*, *Hypoxis rooperi*, and *Secale cereale* (13).

Serenoa repens

Saw Palmetto (SP, SeR), [a.k.a. *Serenoa repens*, Dwarf palm plant (*Sabal serrulatum*)], represent the dried ripe fruits of a palm tree, native to North America. SeR has diuretic, uroantiseptic, endocrinological, and anabolic effects. SeR is by far the most widely used phytotherapeutic for BPH/LUTS, alleviating dysuria, urinary frequency, nocturia, and urine retention (14).

It is theorized that the main active substance in SeR are free fatty acids (FFAs), which have inhibitory activity on 5-alpha reductase type 1 and 2 (11,15-18). In an *in vitro* study FFA bind to adrenergic, muscarinic, and dihydropyridine receptors (19).

Inflammatory processes have a pivotal role in BPH/LUTS initiation and progression by activation of growth factors, increasing of oxidative stress, production of several cytokines, secretion of prostaglandins, leukotrienes and nitrates (20). *Saw palmetto* has a proven anti-inflammatory effect on the prostate and BPH-related LUTS, and its synergistic action with selenium (Se), and lycopene (Ly) increase its therapeutic properties.

The main obstacle in obtaining solid scientific evidence on SeR effectiveness in BPH/LUTS is the absence of standardization. There are numerous brands of SeR

preparations, with significant variations in quality and quantity of active ingredients owing to the different origin of source plant and different extraction techniques (21,22).

In a recent updated Cochrane review (23) SeR extracts failed to show statistically significant improvement over placebo in LUTS scores or Qmax associated with BPH (23,24). However, in this review the heterogeneity between the studies regarding inclusion criteria is a source of significant bias. A significant variability exists in IPPS score of the patients, ranging from 6 (healthy) up to 32—patients with severe LUTS where medications are almost inevitably destined to fail.

In recent years, a lot of scientific interest has attracted the combination phytotherapy including SeR and other plant extracts for urinary symptoms (*C. pepo*, *Epilobium parviflorum*, lycopene, *P. africanum*) as well as the combination of selenium, lycopene and Serenoa, and significantly increased activity on alleviating LUTS/BPH is observed (25,26). In a systematic review of adverse events of SeR, the vast majority of them are mild, rare, and reversible, similar to those observed in placebo arms (27).

Some of the other commonly used phytotherapeutica for BPH/LUTS are:

Pygenum africanum

Native of Africa; plant source is the bark of African plum tree; main active ingredients are phytosterols and other sterols and steroid precursors and metabolites (28-30); several RCT and a meta-analysis confirm its efficacy (31-33).

Urtica dioica

Common or stinging nettle; native to Europe, Asia, parts of Africa and North America. This medicinal plant usage is known since medieval times as a diuretic and remedy for joint problems. Among its various medicinal usage are as a treatment for diabetes, hypotension, anemia. At the present moment it is also used in LUTS/BPH treatment, although rarely as monotherapy (34-36).

Cucurbita pepo

Also known as pumpkin; native of South-central America, universally spread and cultivated. Pumpkin seeds have therapeutic effect in a number of urological conditions like LUTS/BPH and urinary tract infections (UTIs). Although being widely used since ancient times, the active ingredients of pumpkins are scarcely studied. The Δ7-sterols, a specific active ingredient of pumpkin seeds, resemble the structure of DHT, presumably acting as a competitive inhibitor on DHT receptors (37). In other studies *C. pepo* extract has been found to have an effect on aromatase and 5-α-reductase Type II (38), as well as antioxidant and anti-inflammatory activity, immunological, antiviral, and antifungal properties (39).

Hypoxis rooperi

South African star grass (a.k.a. African potato, *Hypoxis hemerocallidea*, yellow star).

Native of South-East Africa. The main active ingredients of *Hypoxis* are thought to be the sterols, exerting antiandrogenic and anti-inflammatory effect (3).

Erectile dysfunction (ED) and fertility

ED is a prevalent condition with an increasing incidence rate—up to 31% of the male population is estimated to be affected (40) Standard ED treatments include prescription medications, vacuum pumps, implants and surgery, with inconsistent and sometimes unsatisfactory results. Even though the past 20 years saw major developments in the field of evidence-based sexual medicine, including the development of effective treatment options for ED, many patients still feel dissatisfied. A substantial percentage of the affected men resort to herbal-based therapy as an alternative to Western-based therapies. Many contemporary studies show phytotherapy as a viable treatment method in these cases.

Korean red ginseng

Korean ginseng has traditionally been used as an aphrodisiac since centuries. It has become one of the most popular herbal supplements taken for reproductive disorders, including sexual performance and ED (41).

Ginsenosides, which represents steroid-like saponins, are the unique active substances specific to ginseng species, along with polysaccharides, alkaloids, and phenolic molecules (42). The effect of ginseng necessitates saponin and non-saponin compounds to work synergistic (43). They result in endothelium NO synthesis, leading to vasodilation of the corpora cavernosa and hence improved erection (44). Ginseng has been shown to increase testosterone plasma levels in animal models.

Pygnogenol

Pinus pinaster (Maritime pine) is a tree species native to Southern France (45). Pygnogenol is extracted from the powdered *Pinus pinaster* bark. Procyanidins have significant antioxidant properties that have numerous health benefits (46).

Pygnogenol has significant antioxidant and anti-inflammatory properties. They have been shown to increase vascular NO synthesis and vasodilation which can improve symptoms of ED (47).

One double-blind RCT compared combination of L-arginine aspartate and Pygnogenol with placebo PRO (patients-reported outcomes), combined with monitoring of plasma testosterone concentration endothelial NO synthase activity (48). A one month intake of Pycnogenol normalises erectile function, with almost doubling the frequency of intercourse, as well as significant increase of e-NOS in spermatozoa and testosterone plasma levels. Another beneficial effect was the observed decrease of Cholesterol and normalization of blood pressure.

Lepidium meyenii

Lepidium meyenii (Maca or Peruvian bark), is native to the Central Andes Mountains of Peru (50). It has been used for >2,000 years for its medicinal purposes—extracts from the maca root have been known to improve erectile function even in healthy humans (49). In recent years it has become one of the most popular supplements for the improvement of sexual desire (51).

Research on animals shows that maca has beneficial effects on spermatogenesis and fertility, presumably owing to phytosterols or phytoestrogens. Recent clinical trials have also suggested its potential for improvement of sperm count and mobility and enhancing sexual function in humans (52). Macaridine, macamides, macaene, glucosinolates, maca alkaloid, and maca nutrients are some of the proposed active substances.

Contemporary literature lacks sufficient data to formulate a systematic review on the topic—additional research is needed before recommendations on efficacy and safety could be done.

Although reported as well tolerated *Lepidium meyenii* may have some psychological adverse effects, namely anxiety, mood changes, hallucinations, and potential for addiction (53).

CPPS

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is defined as pelvic or perineal pain, in the absence of UTI, lasting longer than 3 months. The pain can range from mild to debilitating, causing voiding difficulties. This condition vastly deteriorates the patient`s quality of life. There is no “gold standard” of treatment for this pathology. Because of the lack of specialized treatment (antibiotics, NSAIDs, and alpha-adrenolitics), phytotherapy has emerged as a safe efficient alternative for these patients providing numerous benefits with limited side effects.

Pollen extract (cernilton)

Cernilton (a standardized pollen extract mixture) is included in the therapeutic strategy for the treatment of CP/CPPS for almost 20 years (54). Its exact mechanism of action is largely unknown. Some authors suggest that the anti-inflammatory effect results from inhibition of cyclo-oxygenase and lipoxygenase.

One placebo-controlled study found that male patients with CP/CPPS receiving pollen extract for 12 weeks had significantly higher improvement in symptoms compared to placebo (55). The most substantial improvement was observed in pain relief, which is verified by the observed significant improvement in PRO such as total NIH-CPSI score and the QoL.

Quercetin

Quercetin is universally found in many fruits, vegetables, leaves, and grains. It has significant anti-neoplastic activity, as well as anti-inflammatory and oxidative stress reducing properties (56).

Quercetin has antioxidant properties, as free radical scavengers as well as inhibitor of xanthine oxidase, and anti-inflammatory properties. They modulate the activation of tyrosine kinase enzymes, which leads to inhibition of the division and growth of T cells and prostate cancer cells. Quercetin additionally has antimicrobial and antifungal properties.

In one study combination of quercetin with bromelain and papain led to improvement in the NIH symptom score from an average of 25.1 to 14.6, mean improvement of 44%. 82% of those patients reported at least a 25% improvement (57).

Piper methysticum (kava) root and Pedicularis spp. (lousewort)

Piper methysticum (kava) root and *Pedicularis* spp. (lousewort) are effective pelvic analgesics. Kava has traditionally been used as a medicinal herb in southern and western Pacific regions. It has been studied as an analgesic and systemic anxiolytic. It is indicated when pelvic pain is accompanied by concomitant anxiety, which is a substantial percentage of the affected patients. Lousewort has not been the subject of any clinical trials but historically it has been reported to have similar, if not superior, results than Kava. Both herbs are effective skeletal muscle relaxants.

UTI

UTI is an extremely common urological condition with significant morbidity and mortality, in addition to the negative effect on the QoL of the affected patients. Antibiotic therapy is the method of choice in symptomatic UTI. Bacterial resistance, antibiotics side effects, tendency of recurrence and other accompanying problems necessitates alternative approaches in controlling and preventing UTIs.

Western herbal medicines for lower UTI can be divided in two categories: those for symptomatic and antibacterial treatment during the acute episode and those used for prevention of recurrences.

The urinary bacterial pathogens use fimbria to attach to the glycolipids and glycoproteins found on the urothelium. That way they can evade being expelled by the urinary flow and successfully colonize the urinary tract. The bacteria also excrete hemolysin, and other biologically active substances, that injure the urothelium, allowing bacterial invasion, and increasing the risk of infection Uropathogens also can internalize into host epithelial cells and divide internally, providing a reservoir for recurrent infection. The focus of the phytotherapeutica used in UTI is to counteract on these mechanisms of evasion of the natural protective mechanisms of the urinary tract.

Arctostaphylos uva-ursi

Arctostaphylos uva-ursi (bearberry) is a plant species of the genus Arctostaphylos. Its leaves have been traditionally used as diuretics. It is approved in Germany as a therapeutic alternative for cystitis, especially in cases where E. *coli is involved* (58).

Its active ingredient is glycoside arbutoside, which is metabolised to hydroquinone glucuronide. In alkaline urine (such as in UTI), the hydroquinone glucuronide decomposes and hydroquinone (acting as a direct antimicrobial agent) is released. In addition the plant contains tannins, which could enhance the antibacterial effect of β-lactam antibiotics against methicillin-resistant S. aureus (MRSA).

There is data that long term use of synthetic hydroquinone could be carcinogenic. Hence the recommendation that this phytotherapeutica should not be used for more than 2 weeks.

Juniperus communis

Juniperus communis (juniper) belongs to the *Cupressaceae* family. The terpenoids contained in the leaves and berries are responsible for its antibacterial and diuretic effects. The main antibacterial activity of this plant results from terpinen-4-ol. This plant contains several other important active ingredients including oxygenated sesquiterpene, β-pinene, sabinene, monoterpene hydrocarbons, limonene, and myrcene (59).

Vaccinium macrocarpon (cranberry)

Vaccinium macrocarpon belongs to the *Ericaceae* family. It has been a subject to numerous studies, because of its effectiveness against E. coli (60). It exerts its effect through inhibition of the adhesion of type I and P-fimbria of the uropathogens to the uroepithelium, thus reducing the bacteria's ability to attach to the bladder wall. Cranberry juice consumption limits the ability for formation of biofilm in both Gram-negative and Gram-positive bacteria.

Cranberry is reach in proanthocyanidins, which contribute to the anti-adhesion ability. Studies show additional effect against S. aureus, P. aeruginosa, K. pneumoniae, and P. mirabilis.

Other biologically active compounds include anthocyanidin, catechin, flavanols, myricetin, quercetin, and phenolics (61).

Cinnamon

Cinnamon belongs to the *Lauraceae* family and exerts significant antioxidant and antibacterial abilities. It contains bioactive molecules such as trans-cinnamaldehyde, eugenol,

trans-cinnamyl acetate, and proanthocyanidins, which have beneficial effect in UTI treatment (62).

Amalaradjou *et al.* (63) reports that trans-cinnamaldehyde in the form of essential oil has inhibitory activity on biofilm formation of E. coli on urinary catheters, which is achieved by down regulating main genes of bacterial virulence. Additional mechanisms contribute to the antibacterial abilities of essential oils: (I) they are hydrophobic, hence their molecules target the lipid-containing bacterial cell membrane and mitochondria, altering their permeability and disrupting their function; (II) inhibitory activity on energy production and glucose uptake; and (III) inhibition of vital enzymes such as amino acid decarboxylases (64).

Echinacea angustifolia

Echinacea angustifolia (purple coneflower) root is a widely used immune stimulant. It is mainly utilized in treating and preventing infections in patients who are immunocompromised or when therapeutic failure is present with other agents (65). Purple coneflower should be avoided in patients with significant autoimmune diseases or those taking immunosuppressive drugs.

A short description of main characteristics of some of most popular phytotherapeutica in Western medicine, discussed in this article are presented in *Table 2*.

Conclusions

The therapeutic approaches for LUTS/BPH, ED, CP/CPPS and UTI at the present time are highly sophisticated and innovative, and more and more centered on the patients` expectations and concerns. Phytotherapy is one of the most widely used forms of treatment. Several concerns

Table 2 Characteristics of main phytotherapeutica in western medicine

Indication	Plants and plants-based ingredients	Therapeutic effects	Main active substances	Dosage	Side effects	Existing studies	Limitations
BPH	Serenoa repens	Diuretic, uroantiseptic, endocrinological, and anabolic	FFA	Variable	None	11–27	Different concentrations from brand to brand
BPH	Pygeum africanum	Endocrinological, and anabolic	Phytosterols	25 to 200 mg/day	GI	28–33	Different concentrations from brand to brand
BPH	Urtica dioica	Diuretic, uroantiseptic	Flavonoids, phenolic acids	Variable	Hives or rash	34–36	A lot of compounds with overlapping activities
BPH	Cucurbita pepo	Uroantiseptic, endocrinological, and anabolic	Δ7-sterols	Variable	None	37–39	Limited study on active ingredients
BPH	Hypoxis rooperi	Uroantiseptic, endocrinological, and anabolic	Phytosterols	Variable	GI	3	Variability in extracts
ED	Korean red ginseng	Vasodilatation, improvement of erection	Ginsenosides	Variable	Insomnia	41–44	Mostly in vitro and animal studies
ED	Pygnogenol	Vasodilatation, improvement of erection	Pygnogenol	100 mg/d	None	45–48	–

Table 2 (*continued*)

Table 2 (*continued*)

Indication	Plants and plants-based ingredients	Therapeutic effects	Main active substances	Dosage	Side effects	Existing studies	Limitations
ED	Lepidium meyenii	Enhancement of sexual desire	Phytosterols or phytoestrogens	1,500–3,000 mg/d	Psychological	49–53	Insufficient data for systematic analysis
CPPS	Cernilton	Anti-inflammatory	Unknown	126 mg 2–3/d	GI	54–55	Insufficient data on mechanism of action
CPPS	Quercetin	Anti-inflammatory, oxidative stress reducing	Quercetin	12.5 to 25 mg per kg body weight	None	56–57	–
CPPS	Piper methysticum	Anxiolytic, analgesic	Kavalactones	100–400 mg/d	Indigestion, mouth numbness, rash, headache, drowsiness, and visual disturbances, hepatotoxicity	57	Poorly studied
UTI	Arctostaphylos uva-ursi	Antimicrobial	Glycoside arbutoside	420–600 mg/d	Carcinogenic if used in long term	58	Lack of human studies
UTI	Juniperus communis	Antimicrobial, diuretic	Terpenoids	Variable	Nephrotoxicity, seizures	59	–
UTI	Vaccinium macrocarpon	Inhibition of bacterial adhesion	Proanthocyanidins	120–1,600 mg/d	None	60–61	–
UTI	Cinnamon	Antioxidant and antibacterial	Trans-cinnamaldehyde	1 to 3 g/day	None	62–64	Only episodic data
UTI	Echinacea angustifolia	Immunostimulation	Unknown	Dry powdered extract: 300–500 mg 3×/D	GI	65	Variability in extracts

BPH, benign prostatic hyperplasia; ED, erectile dysfunction; CPPS, chronic pelvic pain syndrome; UTI, urinary tract infection; FFA, free fatty acid; GI, gastrointestinal.

related to phytotherapeutica are that this type of treatment should not be used as an OTC without appropriate diagnostic work-up, and should be reserved for patients with mild or moderate symptoms.

Several conceptual problems generalized to phytotherapy and preventing it to take its deserved place in evidence-based medicine are the need to standardize the different source plants and extraction process, to better understand the mechanism of action of the different and frequently multiple active substances, to perform clinical trials with sophisticated design and protocol to evaluate the efficacy and safety of the various phytotherapica, and finally to obtain the highest level of evidence by running systematic reviews and meta-analyses, aiming to include phytotherapy in the most important international guidelines.

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References

1. Petrovska BB. Historical review of medicinal plants' usage. Pharmacogn Rev 2012;6:1-5.
2. Judith S. The natural history of medicinal plants. Portland: Timber Press, 2000.
3. Lowe FC, Ku JC. Phytotherapy in treatment of benign prostatic hyperplasia: a critical review. Urology 1996;48:12-20.
4. Fourcade RO, Théret N, Taïeb C, et al. Profile and management of patients treated for the first time for lower urinary tract symptoms/benign prostatic hyperplasia in four European countries. BJU Int 2008;101:1111-8.
5. Hutchison A, Farmer R, Verhamme K, et al. The efficacy of drugs for the treatment of LUTS/BPH, a study in 6 European countries. Eur Urol 2007;51:207-15; discussion 215-6.
6. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. Natl Health Stat Report 2008;(12):1-23.
7. Wein A, Kavoussi L, Partin A, et al. Campbell-Walsh urology. 11th ed. Elsevier, 2015.
8. Colado-Velázquez J III, Mailloux-Salinas P, Medina-Contreras J, et al. Effect of Serenoa Repens on Oxidative Stress, Inflammatory and Growth Factors in Obese Wistar Rats with Benign Prostatic Hyperplasia. Phytother Res 2015;29:1525-31.
9. Minutoli L, Altavilla D, Marini H, et al. Inhibitors of apoptosis proteins in experimental benign prostatic hyperplasia: effects of serenoa repens, selenium and lycopene. J Biomed Sci 2014;21:19.
10. Madersbacher S, Berger I, Ponholzer A, et al. Plant extracts: sense or nonsense? Curr Opin Urol 2008;18:16-20.
11. Buck AC. Is there a scientific basis for the therapeutic effects of serenoa repens in benign prostatic hyperplasia? Mechanisms of action. J Urol 2004;172:1792-9.
12. Levin RM, Das AK. A scientific basis for the therapeutic effects of Pygeum africanum and Serenoa repens. Urol Res 2000;28:201-9.
13. Keehn A, Lowe FC. Complementary and alternative medications for benign prostatic hyperplasia. Can J Urol 2015;22 Suppl 1:18-23.
14. Bayne CW, Ross M, Donnelly F, et al. The selectivity and specificity of the actions of the lipido-sterolic extract of Serenoa repens (Permixon) on the prostate. J Urol 2000;164:876-81.
15. Keehn A, Taylor J, Lowe FC. Phytotherapy for Benign Prostatic Hyperplasia. Curr Urol Rep 2016;17:53.
16. Cheetham PJ. Role of complimentary therapy for male LUTS. Curr Urol Rep 2013;14:606-13.
17. Iehlé C, Délos S, Guirou O, et al. Human prostatic steroid 5 alpha-reductase isoforms--a comparative study of selective inhibitors. J Steroid Biochem Mol Biol 1995;54:273-9.
18. Comhaire F, Mahmoud A. Preventing diseases of the prostate in the elderly using hormones and nutriceuticals. Aging Male 2004;7:155-69.
19. Abe M, Ito Y, Oyunzul L, et al. Pharmacologically relevant receptor binding characteristics and 5alpha-reductase inhibitory activity of free Fatty acids contained in saw palmetto extract. Biol Pharm Bull 2009;32:646-50.
20. Sciarra A, Di Silverio F, Salciccia S, et al. Inflammation and chronic prostatic diseases: evidence for a link? Eur Urol 2007;52:964-72.
21. Habib FK, Wyllie MG. Not all brands are created equal:

a comparison of selected components of different brands of Serenoa repens extract. Prostate Cancer Prostatic Dis 2004;7:195-200.
22. De Monte C, Carradori S, Granese A, et al. Modern extraction techniques and their impact on the pharmacological profile of Serenoa repens extracts for the treatment of lower urinary tract symptoms. BMC Urol 2014;14:63.
23. Tacklind J, Macdonald R, Rutks I, et al. Serenoa repens for benign prostatic hyperplasia. Cochrane Database Syst Rev 2012;12:CD001423.
24. MacDonald R, Tacklind JW, Rutks I, et al. Serenoa repens monotherapy for benign prostatic hyperplasia (BPH): an updated Cochrane systematic review. BJU Int 2012;109:1756-61.
25. Minutoli L, Bitto A, Squadrito F, et al. Serenoa Repens, lycopene and selenium: a triple therapeutic approach to manage benign prostatic hyperplasia. Curr Med Chem 2013;20:1306-12.
26. Russo A, Capogrosso P, La Croce G, et al. Serenoa repens, selenium and lycopene to manage lower urinary tract symptoms suggestive for benign prostatic hyperplasia. Expert Opin Drug Saf 2016;15:1661-70.
27. Agbabiaka TB, Pittler MH, Wider B, et al. Serenoa repens (saw palmetto): a systematic review of adverse events. Drug Saf 2009;32:637-47.
28. European Medicines Agency. Assessment report on Prunus afrricana. Committee on Herbal Medicinal Products, 2015.
29. Bombardelli E, Morazzoni P. Prunus africana (Hook f.) Kalkm. Fitoterapia 1997;68:205-18.
30. Bruneton J. Prunus africana. Pharmacognosie, phytochimie, plantes medicinales. Paris: Lavoisier, 1999:161-2.
31. Ishani A, MacDonald R, Nelson D, et al. Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. Am J Med 2000;109:654-64.
32. Andro MC, Riffaud JP. Pygeum africanum extract for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience. Curr Ther Res1995;56:796-817.
33. Pygeum africanum (Prunus africanus) (African plum tree). Monograph. Altern Med Rev 2002;7:71-4.
34. Pagano E, Laudato M, Griffo M, et al. Phytotherapy of benign prostatic hyperplasia. A minireview. Phytother Res 2014;28:949-55.
35. Calvo MI, Akerreta S, Cavero RY. Pharmaceutical ethnobotany in the Riverside of Navarra (Iberian Peninsula). J Ethnopharmacol 2011;135:22-33.
36. Chrubasik JE, Roufogalis BD, Wagner H, et al. A comprehensive review on the stinging nettle effect and efficacy profiles. Part II: urticae radix. Phytomedicine 2007;14:568-79.
37. Schilcher H, Schneider HJ. Beurteilung von K€urbissamen in fixer Kombination mit weiteren pflanzlichen Wirkstoffen zur Behandlung des Symptomenkomplexes bei BPH. Urologe B 1990;30:62-6.
38. Schmidlin CB, Kreuter MH. Cucurbita pepo. M€oglicher Einfluss auf hormonelle Ungleichgewichtebei Inkontinenz. Z Phytotherapie 2003;3:16-8.
39. European Medicines Agency. Assessment report on Cucurbita pepo L., semen. Committee on Herbal Medicinal Products, 2011.
40. Karadeniz T, Topsakal M, Aydogmus A, et al. Erectile dysfunction under age 40: etiology and role of contributing factors. ScientificWorldJournal 2004;4 Suppl 1:171-4.
41. Patel DP, Pastuszak AW, Hotaling JM. Emerging Treatments for Erectile Dysfunction: a Review of Novel, Non-surgical Options. Curr Urol Rep 2019;20:44.
42. Choi MK, Song IS. Interactions of ginseng with therapeutic drugs. Arch Pharm Res 2019;42:862-78.
43. Hyun SH, Kim SW, Seo HW, et al. Physiological and pharmacological features of the non-saponin components in Korean Red Ginseng. J Ginseng Res 2020;44:527-37.
44. Leung KW, Wong AS. Ginseng and male reproductive function. Spermatogenesis 2013;3:e26391.
45. Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. Int J Clin Pharmacol Ther 2002;40:158-68.
46. Schoonees A, Visser J, Musekiwa A, et al. Pycnogenol® (extract of French maritime pine bark) for the treatment of chronic disorders. Cochrane Database Syst Rev 2012;(4):CD008294.
47. Comhaire FH, Mahmoud A. The role of food supplements in the treatment of the infertile man. Reprod Biomed Online 2003;7:385-91.
48. Aoki H, Nagao J, Ueda T, et al. Clinical assessment of a supplement of Pycnogenol® and L-arginine in Japanese patients with mild to moderate erectile dysfunction. Phytother Res 2012;26:204-7.
49. Gonzales GF. Ethnobiology and Ethnopharmacology of Lepidium meyenii (Maca), a Plant from the Peruvian Highlands. Evid Based Complement Alternat Med 2012;2012:193496.
50. Beharry S, Heinrich M. Is the hype around the

reproductive health claims of maca (Lepidium meyenii Walp.) justified? J Ethnopharmacol 2018;211:126-70.
51. Shin BC, Lee MS, Yang EJ, et al. Maca (L. meyenii) for improving sexual function: a systematic review. BMC Complement Altern Med 2010;10:44.
52. Zhang Y, Zhou F, Ge F. Effects of combined extracts of Lepidium meyenii and Allium tuberosum Rottl. on erectile dysfunction. BMC Complement Altern Med 2019;19:135.
53. Corazza O, Martinotti G, Santacroce R, et al. Sexual enhancement products for sale online: raising awareness of the psychoactive effects of yohimbine, maca, horny goat weed, and Ginkgo biloba. Biomed Res Int 2014;2014:841798.
54. Monden K, Tsugawa M, Ninomiya Y, et al. A Japanese version of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI, Okayama version) and the clinical evaluation of cernitin pollen extract for chronic non-bacterial prostatitis. Nihon Hinyokika Gakkai Zasshi 2002;93:539-47.
55. Guan Q, Zheng Y, Wei X, et al. The Effect of Flavonoids on Chronic Prostatitis: A Meta-analysis of Published Randomized Controlled Trials. J Natl Med Assoc 2019;111:555-62.
56. Cheng LY, Zheng XL, Shi H. Experimental study on therapeutic effects of quercetin on abacterial prostatitis. Chinese Journal of Clinical Pharmacology and Therapeutics 2008;13:648-53.
57. Hu M, Wazir J, Ullah R, et al. Phytotherapy and physical therapy in the management of chronic prostatitis-chronic pelvic pain syndrome. Int Urol Nephrol 2019;51:1081-8.
58. Yarnell E. Botanical medicines for the urinary tract. World J Urol 2002;20:285-93.
59. Lagha R, Ben Abdallah F, Al-Sarhan BO, et al. Antibacterial and Biofilm Inhibitory Activity of Medicinal Plant Essential Oils Against Escherichia coli Isolated from UTI Patients. Molecules 2019.
60. Fu Z, Liska D, Talan D, et al. Cranberry Reduces the Risk of Urinary Tract Infection Recurrence in Otherwise Healthy Women: A Systematic Review and Meta-Analysis. J Nutr 2017;147:2282-8.
61. Koradia P, Kapadia S, Trivedi Y, et al. Probiotic and cranberry supplementation for preventing recurrent uncomplicated urinary tract infections in premenopausal women: a controlled pilot study. Expert Rev Anti Infect Ther 2019;17:733-40.
62. Al-Qurashi FM, Kadhum ZI. Antibacterial Effect of some Herbal plants against Pathogenic Bacteria Isolated from Patients with Urinary Tract Infections (UTI). AL-yarmouk Journall 2019;11:36-47.
63. Amalaradjou MA, Venkitanarayanan K. Effect of trans-cinnamaldehyde on inhibition and inactivation of Cronobacter sakazakii biofilm on abiotic surfaces. J Food Prot 2011;74:200-8.
64. Noreen S, Aslam B, Alina Z, et al. Antibacterial Activity of Medicinal Plants (Clove, Cinnamon, Garlic) Extracts and their Combined Effect with Antibiotics in Urinary Tract Infection Caused by Escherichia coli. International Journal of Pharmaceutics & Pharmacology 2018;2:1-4.
65. Samuel DS, Priyadarshoni SP. Echinacea purpurea - A potent medicinal herb. Drug Invention Today 2019;11:448-52.

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