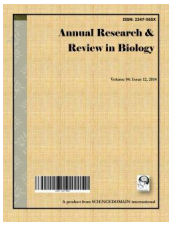

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Therapeutic Management of Benign Prostatic Hyperplasia: From Synthetics to Naturals

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MK and KV designed the study, prepared the framework and monitored the manuscript preparation. Author AKJ managed the literature searches and drafted the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a common urological disorder of men with multi-factorial etiology, particularly affecting the lifestyle of elderly patients. Sex steroid hormones essential for the development and growth of normal prostate are recognized as major risk factors, though many others such as aging, genetic, diet, hypertension, obesity, smoking, alcohol and physical activity have been identified as playing a significant role. Depending on the stage of BPH, and complications involved, the treatment includes different classes of synthetic drugs and/or surgery while some phytotherapeutic agents also represent the first line of treatment. Numerous plant extracts, fruits, and beverages are used alone or in combinations for the management of BPH with few having emerged as the choicest treatment. The public interest in natural agents is largely because of the side effects related to synthetics and a general fear of morbidity arising out of surgery. The phytotherapeutic agents represent the most promising and safe alternative as antiBPH agents signifying a strong area for further exploration by medicinal chemists. This review provides a complete insight on the epidemiology, pathophysiology, various risk factors involved, and different therapeutic approaches available. A brief outline of the surgical and synthetic treatment with detailed note on phytotherapeutics as the treatment options for the prevention and management of benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS) is

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provided.

Keywords: Enlarged prostate; BPH/LUTS; epidemiology; pathophysiology; risk factors; management, synthetics; surgery; phytotherapeutics.

1. INTRODUCTION

Benign prostatic hyperplasia (BPH), characterized by the augmented cell proliferation in prostate is a disease of long-duration in the older men and affects patient's quality of life [1]. The major aspects involved in prostatic hyperplasia are increase in the smooth muscle tone and non-malignant enlargement of the gland. The lower urinary tract symptoms (LUTS) are a result of increased smooth muscle tone in the prostate, its capsule, bladder neck, and prostatic urethra. The complications associated with the BPH include recurrent urinary retention (UR), urinary tract infections (UTI), and rare post-renal failure. Clinical BPH is prevalent in most of the patients and about 60% of the men show clinical symptoms at the age of 60 years, whereas histological BPH can show up at an age of as early as 30 years [2]. The etiology of prostatic hyperplasia is multi-factorial involving the hormonal [3], genetic [4] and nutritional factors [5] although none of these is completely understood. The sex steroid hormones, testosterone, and dihydrotestosterone are essential for the development and growth of normal prostate, but their imbalance is also known to cause BPH [3].

The management of BPH is particularly symptomatic and it affects the lifestyle of a patient. Males with initial symptoms which are not troublesome can be monitored by watchful waiting (WW) without any medical or surgical intervention. The disease progression, however, is generally controlled with α-blockers, 5α-reductase (5αR) inhibitors or both in combination as the first line treatment while complications further need surgical management. Currently, most developed countries worldwide are focusing on natural substances which include plant extracts, phytochemicals, fruits, beverages, and many clinical trials have been reported in the last few decades. Though a number of reports are available on the possible risk factors for the disease progression [6-13] and to the best of our knowledge, none of these reports cover all the possible risk factors along with its management. Further, none of these reviews describe at full length the role of medicinal plants, extracts, and phytochemicals in the management of BPH. Thus, this review summarizes the different risk factors and the treatment strategies available covering additionally all data existing on natural substances for the prevention and cure of BPH.

2. METHODS

2.1 Search Strategy

The intensive literature search for articles published till date were carried out in various databases, including Google Scholar, SciFinder, Web of Science and Scopus. The search terms included "epidemiology of benign prostatic hyperplasia", "pathophysiology of benign prostatic hyperplasia", "risk factors of benign prostatic hyperplasia", "surgical treatments for benign prostatic hyperplasia", "synthetic agents for benign prostatic hyperplasia", "phytotherapeutic agents for benign prostatic hyperplasia". References from reviews about phytotherapy and BPH were examined for additional research articles and case reports. However, up to now, no systematical review has been carried out on this particular disease focussing particularly on different risk factors and detailed phytotherapeutic management of BPH at one place.

2.2 Inclusion and Exclusion Criteria

The selection criteria included articles which used different parameters for benign prostatic hyperplasia/lower urinary tract symptoms and different therapeutic approaches available for the treatment of BPH/LUTS by means of animal studies and clinical trials, and compared phytotherapeutic treatment *vs.* control treatments (placebo or active therapy). The detailed molecular basis of disease progression of BPH, other forms of BPH treatment than phytotherapeutic agents were excluded from the study. Also publications in languages other than English were excluded.

2.3 Epidemiology

BPH affects approximately 30 million males worldwide and the proportion of symptoms exactly doubles with each decade of life [14]. In the last two decades, many clinical studies based on epidemiology have been conducted but

the prevalence of clinical BPH remains undetermined. The incidence of BPH increases by 10% every 10 years and reaches up to 80% at the age of 80 years [15]. The frequency of symptoms in men has been reported to increase from 14% in their 40s to 43% in their 60s in Scotland and Netherlands [16]. The cohort study reported 23% males have moderate-to-severe symptoms in Canada [17]. The European epidemiological studies suggested approximately 30% German males showed symptoms at the age of 50 to 80 years [18]. The symptoms of BPH in white and African-American males are similar, but are more severe and progressive in the latter [14]. The incidence of symptomatic BPH is less in far Eastern countries probably due to the rich presence of phytoestrogens in their diet [19]. In the USA, the Olmsted County Study found the prevalence of moderate to severe LUTS for Caucasian men in the fifth, sixth, seventh, and eighth decades of life to be 26, 33, 41, and 46%, respectively. In Europe, the similar findings reported that the average prostatic volume is 25 cm^3 at the age of 30 years which increases to 45 cm^3 in their 70's [20]. In Iran, the frequency of BPH due to prostate obstruction increased with age, from 1.2% during 40-49 years to 36% above 70 years [21]. Another US study reported that the incidence of development of BPH in African-Americans and Latinos may be higher in comparison to majority of white population, with autonomic hyperactivity and metabolic abnormalities as the possible reasons [22]. In a meta-analysis study performed in China, the occurrence rate of BPH in the age groups 40-49, 50-59, 60-69, 70-79, and above 80 years was found to be 2.9, 29.0, 44.7, 58.1, and 69.2%, respectively [23].

2.4 Pathophysiology

The transition zone of the prostate is the first place where BPH develops. The two foremost factors responsible for the development of BPH are aging and circulating androgens. The prostate enlargement also involves increase in the periuretheral glands, smooth muscle, and connective tissue [24]. The decrease in the smooth muscle myosin heavy chain and significant increase in the non-muscle myosin heavy chain signifies either proliferation or loss of normal modulation pathways. Some authors have reported that detrusor blood flow decreases with increasing age and in the presence of bladder outlet obstruction. This results in hypoxia, neuronal, and muscular tissue damage, leading to collagen deposition, and impaired contractibility, thus behaving like skeletal muscle [25]. The adrenergic neurotransmitters have been involved both in the smooth muscle regulation and contraction, and hence α-adrenergic blockers significantly decrease smooth muscle myosin heavy chain protein expression. The intracellular 5αR enzyme converts circulating testosterone to dihydrotestosterone (DHT), which plays a major role in the stromal-epithelial interactions. In addition to the androgens, other factors like epidermal growth factor (EGF), insulin growth factor (IGF), basic fibroblast growth factor (bFGF), and nerve growth factor (NGF) have a marked mitogenic effect on the proliferation of prostatic stromal and epithelial cells [26]. Further, estrogen plays a role by inducing the nuclear androgen receptors. As a result, the development of BPH is probably an imbalance of androgens and various growth factors as explained in Fig. 1.

2.5 Signs, Symptoms and Complications

The symptoms of BPH involve problems in either emptying the bladder (hesitancy, straining, dribbling, weak flow, and dysuria) or complications with bladder storage (nocturia, frequent urination, and urge to urinate). Acute urinary retention is the first symptom which may be aggravated by excessive fluid intake, diuretics, infection, and drugs (anticholinergics or antidepressants) [26]. The lower urinary tract symptoms, enlargement of prostate, and bladder outlet obstruction are common with the age and impact socio-economic life of patients. An enlarged prostate can press the urethral tube which causes pain to begin urination, prevent easy flowing, and take longer duration to empty bladder subsequently leading to the urinary retention with an increased risk of UTI, haematuria, bladder stones, urinary incontinence, and kidney damage. The prevalence of bladder stones is reported to be eight times higher in men with a histological diagnosis of BPH, than in control with no incidence of the kidney stones [27]. Incontinence is one of the most feared complications from surgical intervention for BPH that affect up to half or more of all the patients. The vascular lesions can be the cause of haematuria with clots and is very common among the patients [28]. Urgency is a general problem associated with BPH/LUTS. In this, the nerves inside bladder are not able to signal the brain properly leading to a sudden, dramatic need to urinate with an uncomfortable feeling in the bladder. The untreated BPH can

lead to serious complications and in extreme cases even death may result. The common symptoms and complications associated with BPH are summarized in Fig. 2.

2.6 Diagnosis

There are eight sets of clinical practice guidelines (CPGs) developed by different organizations *viz* American Urological Association (AUA), European Association of Urology (EAU), International Consensus Committee (WHO) and five countries Australia, Germany, Malaysia, Singapore, and United Kingdom which are available for the diagnosis of BPH/LUTS. The patient history, urine analysis, and physical examination are the compulsory diagnostic options for all the guidelines, and symptoms are assessed using a validated parameter of 'International Prostate Symptom Score' (IPSS) [29]. There is a 7-question assessment, which measures the extent to which patients tolerate their symptoms rather than evaluating their quality of life and has a point score from 0 to 35. The severity of symptoms is described as: minimally symptomatic (0-7), moderately symptomatic (8-19), and severely symptomatic (20-35). The evaluation of the symptom severity with a score is an important part of the initial assessment of a patient. Minimally, moderate and severely symptomatic patients are appropriately managed by watchful waiting, pharmacotherapy, and prostatectomy, respectively. Depending upon the clinical symptoms, the different diagnostic parameters

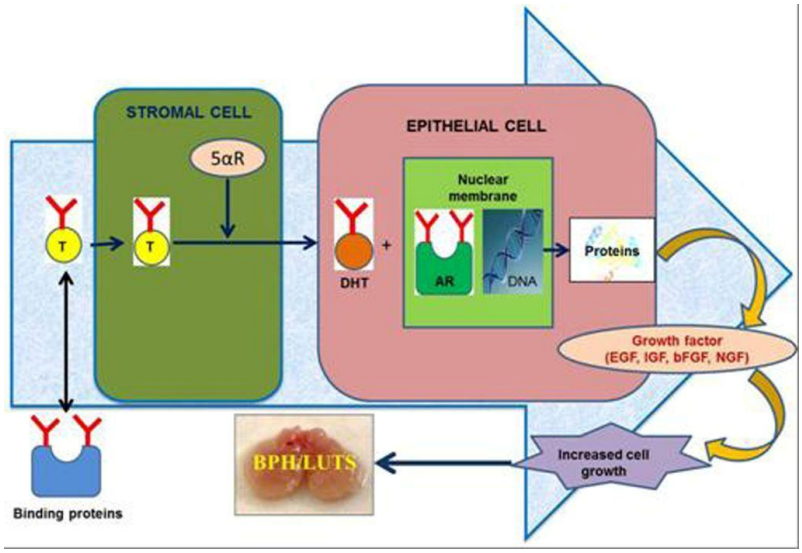


Fig. 1. Pathophysiology of BPH

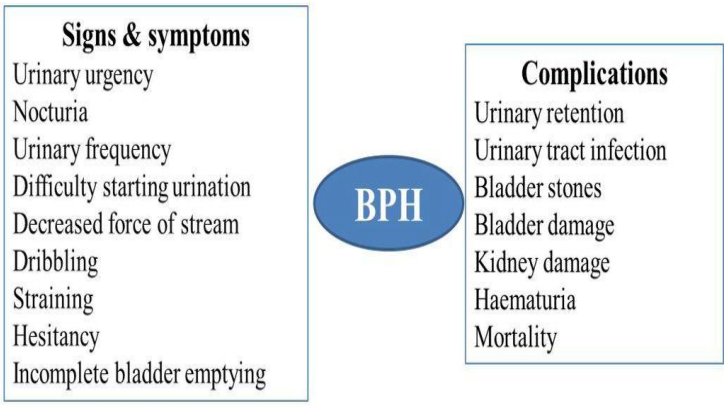


Fig. 2. Signs, symptoms and complications associated with BPH

recommended for the diagnosis of BPH are: measurement of prostate-specific antigen, creatinine, urine flow, voiding, and imaging of the urinary tract, endoscopy, and digital rectal examinations (Table 1).

2.7 Risk Factors

The only factual factors related to the development and growths of the diseases are age [31] and sex hormones [32]. Probably, the genetic disposition also plays a key role, but the involvement of genes is still not well known [22]. At present, there is no strong evidence that diet [33], smoking [34], alcohol intake [35] and lack of physical activity [36] are the potential risk factors for BPH, but the chronic conditions like diabetes and hypertension [37] are suggestive of clinical BPH. The consequences of different epidemiological studies are provocative, probably because of the variances in analysis method and sampling size. The different risk factors associated with BPH/LUTS are shown in Fig. 3.

Table 1. Different type of diagnostic tests and recommended investigations for BPH [30]

Type of diagnostic tests	Recommended investigations
IPSS	Clinical history, symptom assessment, physical examination and validated symptom score
Prostate-specific antigen (PSA) measurement	Diagnosis of prostatic carcinoma and enlarged prostate
Creatinine measurement	Evaluate renal insufficiency and highly recommended
Urinalysis	Recommended in the primary evaluation
Digital rectal examination	Evaluation of size of the prostate gland and early diagnosis of prostatic carcinoma
Voiding charts (diaries)	Non-invasive, inexpensive method and provides important insights into LUTS
Uroflowmetry	Simple, non-invasive test and is an obligatory test prior to surgical intervention
Urodynamic studies	Optional test in open cases presenting for the first time with LUTS and provide information regarding the outcome of surgical therapies of BPH
Endoscopy	Considered an optional test and recommended at the time of surgical treatment
Imaging of the urinary tract	Recommended for patients with LUTS to diagnose UTI, urolithiasis, haematuria and UR

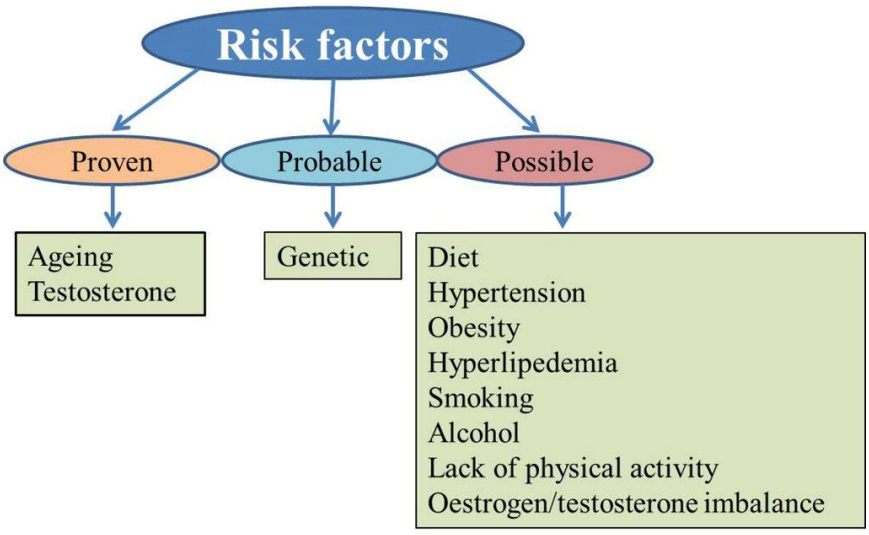


Fig. 3. Risk factors responsible for the progression of BPH

2.7.1 Aging

It is the most significant risk factor involved in the progress of BPH/LUTS and is usually uncommon in men below the age of 40 years [38]. As the age advances, significant tissue remodelling occurs in the transition zone of the prostate. The most important modification takes place in the basal cells, which become enlarged and hypertrophic by changing intracellular metabolism. It is supported by the occurrence of corpora amylacea and prostatic calculi which contain phosphate salts of the calcium, magnesium, potassium, calcium carbonate, or calcium oxalate. An abnormal regulation of the apoptosis may be associated with BPH with the involvement of two key proteins transforming growth factor (TGF)–β1 and apoptosis suppressor (Bcl-2) [39]. More than 60% of men aged over 50 years have histological evidence of BPH and above the age of 70, the proportion increases to 80% [1]. It has been assessed that 75% of male population above the age of 50 years develop the symptoms and 20-30% require surgical intervention at the age of 80 years for suitable management [6].

2.7.2 Androgens

The androgens are required for the normal growth and development of the prostate and have been implicated in the pathogenesis of BPH [3]. Free testosterone can enter prostatic cells and get converted to DHT by the 5αR enzyme present in the fibroblasts of stroma and in the basal epithelial cells [7]. The elevated level of the DHT elucidates its important role in the progression of the disease. In BPH, the expression of different androgen-responsive genes *i.e.* ELL-associated factor 2, elongation factor, RNA polymerase II and phosphoserine aminotransferase-1 increase as compared to the normal glandular tissue. The increasing estrogenic stimulation of the prostate leads to the reactivation of prostatic growth by stimulating the stromal cell proliferation and the up-regulation of bFGF-2 [40].

2.7.2 Genetic factors

Inheritance is associated with the larger prostate volume, though the genes involved remain unidentified. A population based study concluded that male relatives of the men with early onset of BPH had a 66% cumulative lifetime risk of prostatectomy for BPH, compared to 17% among control relatives. A 4-fold increase in the age-specific risk of prostatectomy for BPH was possible among relatives of the men who had undergone prostatectomy, while brothers of these affected cases had a 6-fold increase in risk as compared to control [4]. These findings recognize family history of BPH as a risk factor for the clinical BPH and suggest the presence of a predisposing gene for its early onset [4]. There is 3 times more risk of BPH in monozygotic twins with an affected sibling indicating that the family history may be a risk factor, although it remains ambiguous [7]. Most of the studies suggested that there is a significant association of the gene polymorphism and BPH, especially the cytokine genes have a promising role in the disease progression [8].

2.7.3 Diet

The men taking high energy and protein intake are found to be associated with an increased risk of BPH compared to those taking a low energy and protein diet [41]. A report states that the daily meat consumption triples the risk of prostate enlargement, daily milk consumption doubles the risk and failing to consume vegetables nearly quadruples the same [9]. The high energy intake is said to be associated with the LUTS [41], while high protein intake has been positively associated with the prostate growth due to the increased plasma levels of IGF-1 [42]. In a recent case-control analysis, an increased risk of the BPH was found only in relation to the poultry and egg consumption, but the fish intake was not associated with BPH [5].

2.7.4 Hypertension

There is not much indication of positive and null association of hypertension with the BPH/LUTS from the literature, although one health study concluded that higher diastolic blood pressure was modestly associated with an increased risk of prostatectomy [43]. The Flint Cohort Study and National Health and Nutrition Examination Survey (NHANES III) reports that hypertension was concomitant with a 76% increased risk of the BPH [43]. However, Massachusetts Male Aging Study indicated that there is no significant correlation of hypertension with the clinical BPH [10].

2.7.5 Obesity

The obesity is substantially related to an increased risk of BPH. Health professional's follow-up study, prostate cancer prevention trial

and a case control study involving the male population of Italy showed a positive association between obesity and BPH [44,45]. In a recent multicenter cross-sectional prospective study, it was reported that the central obesity rather than overall obesity is a better predictor of LUTS [46], and the waist circumference is said to be more consistently associated with the BPH [11]. It is believed to be associated with an increased estrogen-to-androgen ratio and the sympathetic activity, and both the factors are individually hypothesized to promote the development of prostatic hyperplasia [42]. Obesity at one time was related to the prostate size and prostate growth, but body mass index (BMI) and BPH are not inter-related [11].

2.7.6 Hyperlipidemia

It is one of the important risk factors in the pathogenesis of the BPH and experimental studies also indicated enlargement of the prostate gland in the hyperlipidemic rats [12]. The presence of BPH with hyperlipidemia is a frequently noted condition under the clinical set-ups. The decreased levels of the high density lipoprotein-cholesterol as well as the increased levels of the serum low density lipoprotein are reported to be associated with the enlargement of prostate gland with a greater risk of BPH [47].

2.7.7 Smoking

Smoking is associated with higher levels of testosterone, which is a leading factor in the development of BPH and LUTS [11]. Smokers are reported to develop LUTS more likely than the non-smokers, as nicotine increases the sympathetic nervous system activity which contributes to the progression of LUTS by increasing the tone of prostate and bladder smooth muscle [48]. It also causes DHT accumulation in the prostate which further leads to BPH [49].

2.7.8 Alcohol

Light to medium alcohol consumption is considered to be protective towards the BPH, but high consumption on the other hand deteriorates the condition [48]. An increased risk of the LUTS was observed in men with a very high daily alcohol intake of 72 g/day (approximately 5 drinks/day), however, light-to-moderate alcohol consumption improves sensitivity towards the insulin and decreases the testosterone concentration concomitantly [50].

2.7.9 Physical activity

The physical activity is reported to be inversely associated with the BPH/LUTS. The men engaged in a regular-to-moderate activity such as walking shows significantly reduced risk of BPH and this may be related to the improved sensitivity towards insulin [11].

2.7.10 Estrogen/testosterone imbalance

The circulating estradiol increases with the increasing adiposity in men, whereas the circulating testosterone and the sex hormone-binding globulin concentrations are inversely proportional to adiposity. The elevated ratio of the estrogen to testosterone has been postulated to increase the risk of BPH by induction of the androgen receptor and DHT formation [13].

2.8 Current Treatment

The choice of treatment depends on the level of patient's incommodious condition. Generally, the patients with an IPSS score of < 8 do not require any treatment; but a score of 8-19 may need management with the medical therapy, if patient's lifestyle is affected by the symptoms. However, patients with a score of 20-35, although can be treated with the medical therapy, but more invasive intervention like surgery may be required. In addition, there are several situations like renal failure, persistent haematuria, recurrent urinary retention and bladder calculi that require multiple therapies even if the patients are not concerned about their health [20]. The treatment approach towards BPH has changed over the last three decades from surgical to more of medical therapy. A US medicare data indicated that the number of prostatectomy cases decreased significantly from 250,000 in the late 1980s to 88,000 in 2000 [51]. This two-third fall in number of surgery cases is most likely due to well-tolerated and effective medical therapies available in the modern era, that emphasize more towards the prevention of disease progression and the related complications [52].

2.9 Different Therapeutic Approaches

There are a number of therapeutic approaches available to counteract the multifactorial consequences of the BPH. The treatment of BPH with the available drugs (both synthetic and phytotherapeutic) is not an alternative to surgery, but definitely leads to the prevention of the early

stage of the disease progression. The different treatment regimens include:

A. Watchful waiting
B. Medical therapies
    i. Synthetic compounds
    ii. Surgical treatments
    iii. Natural substances

2.9.1 Watchful waiting or active surveillance

This is a management approach wherein, the patient is supervised by his physician and usually re-examined yearly [53]. It is the most preferred way of management for the patients with mild symptoms, and also for those patients having moderate symptoms, but without the LUTS and bladder outlet obstruction. Various components like educating the patient, periodic monitoring, and reassurance can be used to optimize WW. A simple lifestyle modification by decreasing the caffeine and alcohol consumption, less fluid intake at the bedtime and avoiding antihistamines may further help to reduce the symptoms distress.

2.9.2 Medical therapies

2.9.2.1 Role of synthetic compounds

In the past, the treatment of LUTS was largely based on the surgical interventions, such as transurethral resection of the prostate or open enucleation of the enlarged adenoma. During the last decade, however, non-surgical treatments have been immensely explored and developed. Medical therapies now represent the first line treatment used by both the primary care physicians and urologists over surgery and also to curb healthcare expenditures. The different classes of medical treatments available are briefly summarized below:

2.9.2.1.1 α-Adrenergic receptor blockers

These are categorized as the most prescribed medication treatment that act *via* sympathetic nervous system inhibiting the smooth muscle contraction, thereby decreasing the urethral pressure and resistance together with reduced bladder outlet obstruction [54]. α-Adrenergic receptor blockers are of two types (i) selective, and (ii) non-selective.

2.9.2.1.2 Selective α_1-adrenoceptor antagonists

These are used as a first-line treatment for BPH patients [7]. Multiple subtypes of α_1-adrenoceptor antagonists have been discovered and classified as α_{1a}, α_{1b}, and α_{1d}. The α_1-adrenoceptor antagonistic drugs are believed to have approximately equal affinity towards each subtype with orthostatic hypotension as the major side effect, which is considered to be largely due to the lack of selectivity [55]. Among all subtypes, α_{1a} plays a major role in the control of smooth muscle contraction of prostate without causing cardiovascular (CV) side effects in animals [56] and is predominant in prostate, bladder neck, and urethra. The subtype α_{1d} is also involved in the intervention of LUTS and α_{1b} is more associated with CV-related side effects [57]. Hence, the drugs having a balance of subtype $\alpha_{1a}/_{1d}$ selectivity profile like tamsulosin are said to be efficacious for treating both BPH and LUTS [55]. Most widely used selective α_1-adrenoceptor antagonists are doxazosin, prazosin, alfuzosin, terazosin, nicergoline, indoramin, and tamsulosin.

2.9.2.1.3 Phosphodiesterase type 5 (PDE5) inhibitors

Recent reports suggest that phosphodiesterase type 5 (PDE5) inhibitors play a key role in the treatment of LUTS/BPH. The most widely known PDE5 inhibitors are sildenafil, vardenafil, tadalafil, and avanafil. These agents have been known to be the first-line treatment for erectile dysfunction (ED) and are preferred by health care practitioners and patients because of their ease of use, quick onset of action, and tolerability [58]. PDE5 inhibitors are known to exert their effects by increasing levels of nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) [59]. The common side effects associated with these drugs include headache, flushing, nasal congestion, nasopharyngitis, dyspepsia and some serious effects are priapism, visual abnormalities, sudden hearing loss, back pain and myalgia [58]. The combination therapy with alpha-blockers and 5αRs provides greater satisfaction to the patients with a pre-specified analysis [60].

2.9.2.1.4 Non-selective α-adrenoceptor antagonists

These agents cause relaxation of smooth muscle both in arterioles and bladder neck and are reported to play a role in the management of BPH. The drugs like phenoxybenzamine and phentolamine are amongst the earliest known therapies for BPH which antagonize both α_1 and α_2 adrenergic receptors, and having higher

incidence of side effects. However, they are less well tolerated than selective α-adrenoceptor antagonists [61], although phenoxybenzamine happens to be the first α-blocker reported to be effective in the treatment of BPH [62].

Some of the well marketed drugs from both selective and non-selective antagonists are given in Table 2:

2.9.2.1.5 Endocrine therapies

The androgen suppression therapies like antiandrogens, 5αR inhibitors, and gonadotropin-releasing hormone (GnRH) antagonists have been extensively investigated for the treatment of BPH. Cyproterone acetate is the most frequently used steroidal antiandrogen, which increases the testosterone secretion by crossing the blood brain barrier resulting in an increased luteinizing hormone (LH) secretion [77]. The nonsteroidal antiandrogens like, flutamide and bicalutamide inhibit the activity of the androgens by competitively blocking the interaction of the testosterone and DHT with the androgen receptor without exerting agonistic or any other hormonal activity [78]. The 5αR is a membrane-bound, NADPH-dependent enzyme that is responsible for the conversion of testosterone, the major circulating androgen in adult males, to DHT. These inhibitors, especially finasteride and dutasteride address the static component of BPH by reducing the prostate volume and prevent the progression of the disease. GnRH antagonists like leuprolide bind directly to the GnRH receptor in the pituitary and competitively block the release of LH and follicular stimulating hormone resulting in reduction of the serum testosterone levels [79].

2.9.2.1.6 Combination therapies

Considering the beneficial effects of each class of drugs, the use of α_1ARA/5αRI therapy has become the most preferable treatment of choice over the monotherapy for patients with moderate to severe symptomatic BPH. Different studies have been carried out to evaluate the combination therapy, which is briefly discussed below:

The MTOPS study: BPH may or may not be a progressive complaint and this was indicated by the results of 4-year Proscar Long-term Efficacy and Safety Study (PLESS) of finasteride [80]. The Medical Therapy of Prostatic Symptoms (MTOPS) study was undertaken to determine whether monotherapy with the α_1ARA doxazosin (4 to 8 mg/day) or the 5αRI finasteride (5 mg/day), or combined therapy could delay or prevent the progression of symptomatic BPH [80]. The risk of long-term clinical progression (≥ 4 point rise in AUA-SI score, acute urinary retention (AUR), renal insufficiency, recurrent urinary tract infection, urosepsis or incontinence) was reduced by 66% with combination therapy and to a greater extent either by finasteride (34%) or doxazosin (39%) monotherapy, respectively [80].

The CombAT study: Another large-scale combination study (dutasteride & tamsulosin) has been completed both as monotherapy and in combination towards the symptoms and progression of BPH. In the Combination of Avodart and Tamsulosin (CombAT), trials were used to select patients who were at higher risk of disease progression [81] This therapy had a significant impact on developing AUR and thus posed a need for BPH-related surgery as compared to tamsulosin (65.8% risk reduction) and dutasteride (19.6% risk reduction) [6].

The SMART study: The withdrawal of α_1ARA (tamsulosin) from combination therapy (α_1ARA/5αRI) was thought to affect LUTS and this was investigated by Symptom Management after Reducing Therapy (SMART) study [51]. It has been proposed that using combination of α_1ARA/5αRI therapy initially, then withdrawing the agent and continuing with 5αRI monotherapy might result in symptomatic benefit (as 5ARIs require several months to achieve clinical efficacy or to reduce prostate volume and progression whereas α_1ARA have a relatively rapid onset of action, improves urinary flow and is less effective in reducing prostate volume [82]. The 36 week study concluded that patients in both treatment groups had similar improvements in IPSS. However, 43% experienced deterioration in symptoms after withdrawal of tamsulosin. Use of sustained combination therapy may be more appropriate in patients with severe symptoms [82].

The PREDICT study: The 1 year duration Prospective European Doxazosin and Combination Therapy (PREDICT) trial evaluating the α_1ARA doxazosin (1-8 mg/day), the 5αRI finasteride (5 mg/day), and their combination was performed. There were significant improvements (IPSS and peak urinary flow) in patients receiving doxazosin monotherapy and doxazosin/finasteride combination therapy compared with finasteride monotherapy [83].

2.9.2.2 Role of surgical treatment

The surgical treatment remains the most effective management for the complicated and severe symptomatic BPH, particularly when the symptoms are bothersome. However, the side effects and invasive nature have led to the search for other alternatives too. The choice of surgery depends on the level of discomfort, medical test results and urologist's suggestions. The widely accepted surgical procedure includes Transurethral Resection of the Prostate (TURP), Transurethral Incision of the Prostate (TUIP), Minimally Invasive Treatment (MIT) like laser therapies, thermal based therapies and ablative therapies.

Transurethral resection of the prostate (TURP)

Clinically the indication of prostate surgery includes bladder outlet obstruction, urinary retention, bladder stones and haematuria. Transurethral resection of the prostate (TURP) is considered to be the standard treatment for the patient with an enlarged prostate and obstructive symptoms over the last 50 years [84]. It is safe and an efficient procedure to boot out the sympotoms associated with LUTS. It decreases 70% mean IPSS, 50% patient feels there is half decrease of IPSS, mean increase in uroflowmetry (Q_{max}) is increased by 125% and 90% patients have a Q_{max} greater than 15 mL/s [85]. However 20% of patients have persistent urinary retention and dissatisfied with the results of surgery. Mortality has decreased from 2.5 to 0.2% over the past 30 years but morbidity is still about 20% which includes hypertension, mental confusion, nausea, clot retention, bleeding necessitating transfusion, bladder neck contracture, sexual dysfunction with impotence, retrograde ejaculation and infection [86]. Open prostatectomy is the choice for patients, when the prostate volume is larger than 80-100 mL, large bladder stones, or if resection of large bladder diverticula is indicated [87].

Transurethral incision of the prostate (TUIP)

Transurethral incision of the prostate (TUIP) is a simpler, cost effective, less invasive, less operative time, shorter hospital stay and a shorter catheterization period than TURP [87,88]. This procedure is recommended for patients to preserve erectile function and antegrade ejaculation. Despite the encouraging results of TUIP, patient is concerned with duration of its efficacy, prostate size and the re-operation rate [88]. In this procedure instead of removing prostatic tissue, an electrical knife is used to make incision(s) which is deep enough to penetrate the prostate tissue from inside the bladder neck down to the verumontanum. The incisions may be single (at 6 o'clock position) or bilateral (at 5 and 7 o'clock positions) [87].

Minimally invasive treatment (MIT)

Currently available minimally invasive treatment options include (i) laser therapies, (ii) thermal-based therapies, (iii) ablative therapies and (iv) others.

Laser therapies: Laser is an alternative to TURP for symptomatic treatment of medical resistant BPH. Laser energy can be used to produce coagulation necrosis, vaporisation of tissue or resection of tissue without bleeding. The different laser techniques are Visual Laser Ablation of the Prostate (VLAP), Interstitial Laser Coagulation (ILC), Holmium-Laser Resection (HoLR) [89].

Thermal-based therapies: These therapies use microwave, radio frequency waves, High Intensity Focused Ultrasound (HIFU) and hot water as a source of temperature to induce a coagulation necrosis within the prostate. Based on the temperature range this could be low-energy thermotherapy (45-60 °C) and high-energy thermotherapy (> 60 °C) [89].

Abaltive therapies: The ablative therapy mainly includes Transurethral Vaporisation of the Prostate (TUVP) in which a special, grooved, roller electrode (cylinder shaped) is being inserted through a resectoscope that delivers a strong electric current [90]. Whenever the roller electrode is rolled over the tissue, it vapourises 1-3 mm of tissue. The major disadvantage of TUVP is that the clinical efficacy of the electrode rapidly decreases as tissue desiccates and with each pass of the roller, the layer below the vaporised tissue becomes more solid or coagulated, which is harder to vapourise [89,90]. The 5-year long-term data showed a significant improvement of IPSS, Qmax and post-void residual volume in both arms [91].

Botulinum toxin A injection (BoNT-A): Botulinum Toxin A Injection in the bladder neck has recently been emerged as an attractive minimally invasive, tolerated, and cost-effective therapeutic alternative for the management of

lower urinary tract symptoms (LUTS) often associated with BPH in patients who can't be treated medically or surgically [92,93]. The transurethral injection significantly improves the maximum urinary flow rate, quality-of-life index, and reduces the IPSS, prostate-specific antigen (PSA) level, post void residual volume and prostate volume [92]. The toxin acts by reducing the level of obstruction by the high bladder neck and relaxes the smooth muscle [94].

Urolift: This is a minimally invasive approach that lifts the enlarged prostate and relieves the obstruction. This is performed under local anaesthesia avoiding the complications and disadvantages of existing drug and surgical therapies [93,95]. It is an option for the patients who wish to avoid long-term drug therapy, their side effects or traditional surgical treatments. It does not harm ejaculatory function or affect the orgasmic sensation. The major advantages of this technique include shorter procedure time, improvement of IPSS and quality of life [96,97].

2.9.2.3 Role of natural substances

Natural therapies for the treatment of BPH and related disorders are more prevalent all over the globe especially in Europe for many years and have recently gained popularity in the USA. The patients suffering from BPH prefer the use of traditional medicines over the synthetic ones especially fearing the risk of mortality and long term morbidity associated with the surgical procedures. The composition of plant extracts is very complex and no strong evidence is available as to which component of the plant is responsible for the activity. Most of the literature suggests phytosterols, terpenoids, and phytoestrogens to be therapeutically active but their mechanism of action is uncertain. Many *in vitro* studies have established the mechanism of action and numerous mechanisms have been proposed till date [98]. Various plant extracts that have been used either singly or in combinations for the treatment of LUTS, secondary to BPH are shown in Table 3. The different fruits and beverages effective in the management of BPH are listed in Table 4.

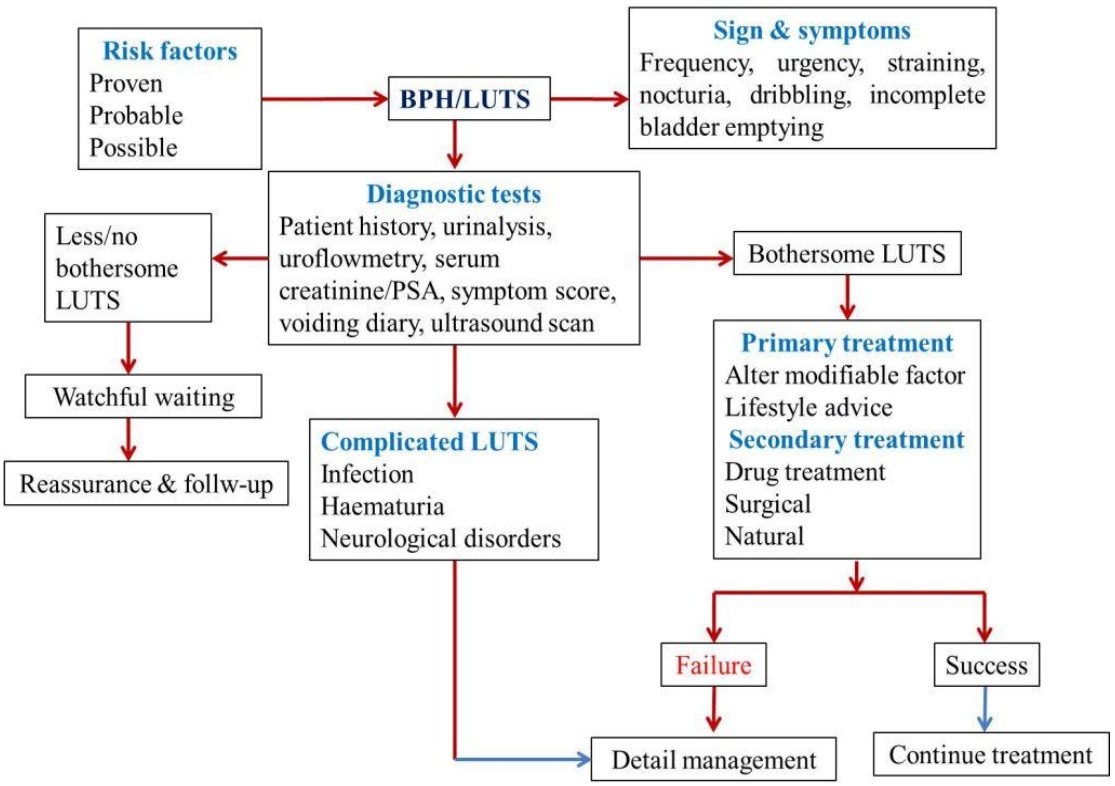


Fig. 4. Schematic diagram of risk factors, symptoms and management of BPH

Table 2. Different α-adrenergic receptor blockers used for the treatment of BPH

Class of drug	Name of drug	Dosage	Improvements/advantages	Side effects	References
Selective α_1-adrenoceptor antagonists	Alfuzosin	2.5 mg/t.i.d, 5.0 mg/ b.d and 10 or 15 mg/o.d	Improves urinary flow rate by decreasing detrusor pressure during voiding	Dizziness, malaise, postural hypotension, and painful ejaculation	[63]
	Prazosin	2-4 mg/day	Reduces residual urine, peak urethral pressure, and increases the urine flow rate	Requires dose titration to avert the cardiovascular side effects like dizziness and syncope (due to both arterial and venous vasodilatation action)	[64,65]
	Terazosin	1, 10 and 20 mg/day	Single dose/day significantly increases the mean urinary flow rate and useful for the patients having BPH along with hypertension	Dizziness, asthenia, and light-headedness	[65,66,67]
	Doxazosin	1 mg/day, may increase up to 8 mg once daily	Improve symptom scores and peak flow rate. Choice for patients having BPH along with hypertension, lower the cholesterol level, and having longer duration of action	Orthostatic hypotension and dizziness	[65,66,68]
	Nicergoline	8 mg/day	Peak and mean flow rate increases, and nocturnal micturition decreases	No side effects reported	[69,70]
Subtype-selective α_1-adrenoceptor antagonists	Indoramin	20 mg/bid	Affinity ratio between the α_{1a} and α_{1b} adrenoceptors ranges from 10 fold and 3-4 fold; does not require dose titration to prevent 'first-dose' effects	Lassitude and sedation	[65,71]
	Tamsulosin	0.4-0.8 mg/day	Significantly increases the peak and mean urinary flow rate and shows 13-15 fold selectivity towards α_{1a} than α_{1b} receptor but has equal affinities for the α_{1a} and α_{1d} adrenoceptors; does not require dose titration	No cardiovascular side effects	[65,72,73,74]
Non-selective α-adrenoceptor antagonists	Phenoxybe-nzamine	5, 10 and 20 mg/day	Increases both mean and peak urine flow rate and reduces urinary frequency both during day and night by blocking the norepinephrine-induced contraction	Dizziness, nasal stuffiness, impotence, and ejaculatory dysfunction	[65]
	Phentolamine	10 mg/day	Reduces the acute urinary retention and urethral pressure without abolishing tone in the external sphincter. Used for the treatment of dermal necrosis, pheochromocytoma-related hypertension, erectile dysfunction, and nasal decongestion	Induces cardiac stimulation	[65,75,76]

Table 3. Different plants/extracts used in the treatment of BPH

Region	Plant name	Plant part/extract(s)	Constituent(s)	Mechanism of action	Side effects/toxicity	Reference(s)
African phytomedicines	*Agathosma betulina* (P.J.Bergius) (Rutaceae) (Honey buchu)	Leaf preparations	Volatile oils and flavonoids	NR	NR	[99,100]
	Bidens pilosa L. (Compositae) (Black-jack)	Unspecified parts	NA	Inhibits prostaglandin synthesis	NR	[101]
	Hypoxis hemerocallidea Fisch. & C.A. Mey., syn. *H. rooperi* T. Moore (Hypoxidaceae) (African potato)	Hot aqueous extracts of dried or fresh corns	*β*-Sitosterol and rooperol	Inhibits 5αR	NR	[102,103]
	Prunus africana (Hook. f.) Kalkman. syn. *Pygeum africanum* Hook. f.) (Rosaceae) **(**African cherry)	Lipophilic extract	*β*-Sitosterol and *n*-docosanol	Inhibits the formation of prostaglandin, inhibition of 5αR	NR	[104,105]
Western phytomedicines	*Serenoa serrulata* (Michx.) G. Nicholson, syn. *S. repens* (W. Bartram) (Arecaceae) (Saw palmetto)	Berries	Flavonoids, *β*- sitosterol, campesterol, and stigmasterol	Inhibits 5αR, androgen and estrogen receptors	Rarely decreased libido	[106,107]
	Urtica dioica (L.) (Urticaceae) (Stinging nettle)	Root extract	*β*-Sitosterol and lignans	Inhibits cyclooxygenase enzyme	Mild gastro-intestinal upset	[108,109]
	Cucurbita pepo L. (Cucurbitaceae) (Pumpkin)	Seed oil	NA	Improves functioning of the bladder and urethra	Minor stomach upset	[105,110]
	Secale cereale L. (Poaceae) (Rye grass)	Pollen	Hydroxamic acid and 2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one	Inhibits biosynthesis of prostaglandin, leukotriene, and growth of the prostate	Allergy	[111,112]
Chinese phytomedicines	*Isatis indigotica* Fortune ex Lindl. (Brassicaceae); *Glycyrrhiza glabra* L. (Leguminosae); *Scutellaria baicalensis* Georgi, (Lamiaceae); *Ganoderma lucidum* W.Curt: Fr., *Serenoa serrulata* (Michx.) G. Nicholson (Arecaceae); *Panax ginseng* C.A. Mey, (Araliaceae); *Denodrantherma morifolium* (Ramat.) Tzvelev (Asteraceae) and *Rabdosia rubescens* (Hemsl.) H.Hara (Lamiaceae)	Eight-herb Chinese formulation	NA	Significant anti-androgenic effects and decrease PSA	Gynecomastia, nipple tendernes, loss of libido, and impotency	[113,114]
	Zea mays L (Poaceae) (Corn silk)	NA	NR	Soothes and relaxes the lining of urinary tubules and bladder relieving irritation, thereby improving urine excretion	NR	[115]

Other plants	*Epilobium parviflorum* Schreb. (Onagraceae) (Hoary Willowherb)	NA	Oenothein B	Inhibits 5αR	NR	[116,117]
	Althaea officinalis L. (Malvaceae) (Marshmallow)	NA	Flavonoids and phenolic acids	Soothes the mucous membrane	NR	[115]
	Equisetum arvense L. (Equisetaceae) (Horsetail)	NA	Silicic acid and silicates	Astringent effect on genito-urinary system	NR	[115]
	Lepidium latifolium L. (Brassicaceae) (Pepper grass)	Integral suspension	Flavonoids	Inhibition of 5αR and dehydrogenase-17*β*-hydroxy steroid	NR	[118]
	Orbignya speciosa (Mart. ex Spreng.) (Arecaceae) (Babassu)	Ethanolic extract of kernel	NR	Disorganization of actin microfilaments and damaging cell membrane integrity by increasing LDH release	NR	[119]
	Urtica fissa E. Pritz (Urticaceae)	Aqueous extract of roots and stems	Polysaccharides	Inhibits prostatic cell proliferation	NR	[120]
	Cimicifuga racemosa L. Nutt. (Ranunculaceae) (Black cohosh)	Aqueous/ethanolic extract	NR	Inhibits 5αR activity	NR	[121]
	Trifolium pratense L. (Fabaceae) (Red clover)	Ethyl acetate and methanol extract	Daidzein, calycosin, genistein, pratensin, formononetin, prunetin, and biochanin A	Acts by α_1 adrenoceptor antagonists	NR	[122]
	Radix urticae (Urticaceae) (Nettle root)	Whole plant extract	Steroid-glycoside composition	Inhibits plasma and intracellular sex hormone binding globulin	NR	[123]
	Abacopteris penangiana (Hook.) Ching (Thelypteridaceae)	Rhizomes	Flavan-4-ol glycosides and 7-hydroxy-4'-methoxy-6,8-dimethylanthocyanidin	Inhibits 5αR, decreases prostatic EGF, bFGF levels, and attenuate apoptosis disruption	NR	[124]
	Olea europaea L. (Oleaceae)	Olive oil from fruit	Oleuropein	Reduces cell viability and induces thiol group modifications, g-glutamylcysteine synthetase, reactive oxygen species, and heme oxygenase-1.	NR	[125]
Fungi	*Ganoderma lucidum* (Fr. Krast) (Reishi)	Ethanolic extract	Ganoderol B	Inhibits 5αR and androgen-induced LNCaP cell growth	NR	[126,127]

NA = not available; NR = not reported

Table 4. Miscellaneous agents in the management of BPH

Category	Example	Constituent(s)	Mechanism of action	Reference(s)
Fruits, vegetables and seeds	Tomato and tomato products	Lycopene, phytoene, phytofluene, *ζ*-carotene, *γ*-carotene, *β*-carotene, neurosporene, and lutein	Reduces proliferation of normal prostatic epithelial cells, DNA damage, and improves oxidative stress by inhibiting prostatic insulin like growth factor-1 signalling, interleukin-6 expression, and androgen signalling	[128,129]
	Grapes	Resveratrol	Significant protection against the hypoxic effects of ischemia and ischemia/reperfusion and up-regulation of superoxide dismutase, and catalase	[130,131]
	Pomegranate	Polyphenol rich extract	Increase in NO levels appears to be a key factor in lowering the tension of smooth muscle of the lower urinary tract via the NO/cGMP pathway, and subsequently improves LUTS symptoms	[132]
	Flax seed	Omega-3 fatty acids, enterediol, and enterolactone	Block the overproduction of estrone within the fat cells	[24,133]
	Onion and garlic	*S*-Allylmercaptocysteine	Inhibits key enzymes involved in cholesterol and fatty acid synthesis	[134]
Lipids	Butter and margarine	Palmitic acid	Inverses risk of BPH and an enlarged prostate	[135]
Beverages	Green tea	Flavonols or catechins (epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate)	Inhibit 5αR isoenzymes, modulate the production and biologic actions of androgens, and other hormones	[136]
	Beer and wine	NR	Increases serum estrogen and decreases testosterone and sex hormone binding globulin levels, and depletes testicular gonadotrophin receptors	[137,138]
Vitamin	Vitamin D	BXL628 (vitamin D3 analogue)	Inhibits growth factor stimulated human BPH cell proliferation by disrupting the signal transduction and inducing apoptosis	[139]

Table 5. Summary of different plants/constituents in placebo-controlled clinical trials on BPH patients

Name of plant	No. of patients	Dosage (mg/day)	Period of treatment (months)	Improvements	References
Urtica dioica L. (Stinging nettle)	287	459 mg/day	6 & 12	Significant reduction in serum PSA, IPSS, and prostate size	[109,162]
Soy isofavones	176	40 mg/day	12	Improvement in IPSS, Qmax and post residual urine volume from baseline	[161]
Secale cereale L. (Rye pollen)	163	63 mg, 2 caps twice/day	3-6	Well tolerated and modestly improved overall urological symptoms	[163]
Serenoa repens W. Bartram (Saw palmetto)	17 225 582	320 mg, 2 caps/day 160 mg, twice/day 160 mg, twice/day	1-6 12 18	Improvement in peak flow rate and reduction in nocturia	[106,164,165]
Prunus africana (Hook. f.) Kalkman. (Pygeum)	41 18	100-200 mg/day 200 mg/day	2	Improvement in post residual urine volume, nocturia, and reduces prostate size	[166,167]
Cucurbita pepo L. (Pumpkin seed)	476 47	500 mg, twice/day 2 tablets daily	12 6	Reduction in IPSS score, prostate volume, and PSA level	[168,169,170]
Hypoxis rooperi T. Moore (South African star grass)	200	65 mg, twice/day	6	Reduction in IPSS score and improvement in Qmax	[171]
Lycopersicum esculentum Mill. (Solanaceae) (Tomato)	40	15 mg/day	6	Improvement in overall symptoms and inhibits progression of BPH	[172]
Roystonea regia (Kunth) O.F.Cook (Arecaceae) (Royal palm)	34	320 mg/day	1.5	Improvement in antioxidant effects on plasma oxidative markers	[173]
β-Sitosterol	519 177	10-20 mg, thrice/day 65 mg, twice/day	6 6	Reduced IPSS and improved urological symptoms, and flow measures	[174,175]

Phytotherapeutic agents represent nearly half of the medications dispensed in Italy for the management of BPH, as compared to 5% drugs constituting α-adrenergic antagonists and 5αR inhibitors [140]. In Austria and Germany, phytotherapy represents about 90% of all the prescribed drugs for BPH and is considered as the first-line treatment. In the USA, phytotherapeutic agents for BPH are available as dietary supplements [141] and about 40% men opt for herbal supplements alone or in combination with other medical preparations. *Pygeum,* saw palmetto, *Secale cereale,* pumpkins, soy beans, and nettle are few of the most important plants along with other nutraceuticals used for the treatment of BPH [140] which are summarized below.

2.9.2.4 Internationally recognized plants

2.9.2.4.1 *Prunus africana* (Hook.f.) Kalkman

The bark of *Pygeum* (*Prunus africana* (Hook.f.) Kalkman, Rosaceae), official in the United States Pharmacopoeia, British Pharmacopoeia, and European Pharmacopoeia is native to Africa and has been widely used by Africans in the form of a tea to treat urinary disorders particularly the BPH. It is recommended as the first line treatment for BPH and related disorders especially in Europe, the United States of America, and Africa [140,142]. The active constituents responsible for BPH are N-N-butylbenzenesulfonamide, atraric acid [143], *β*-sitosterol and n-docosanol [104,105]. It is reported to act by inhibiting the formation of prostaglandin, 5αR, cellular growth factors (fibroblast and epidermal growth factors) and 5-lipoxygenase enzyme [104,105]. Headache and mild gastrointestinal problems are drug induced adverse effects [142]. Recently the other species of *Prunus* like *P. amygdalus, P. armeniaca, P. cerasoides, P. domestica* and *P. persica* have been reported to be active against BPH in rat model which act by inhibiting 5αR enzyme [144].

2.9.2.4.2 *Serenoa repens* W. Bartram

The fruits of saw palmetto (*Serenoa repens* W. Bartram, Arecaceae), native to south-eastern USA and West Indies have been widely used for relieving the symptoms related to BPH [106,142]. The popularity makes it one of the top 10 selling supplements in the USA [145]. It has been suggested that the clinical benefit was due to free fatty acid, glycerides, methyl and ethyl esters content of the plant. Saw palmetto acts through multiple mechanisms, including anti-androgen effects [146], anti-inflammatory activity via inhibition of synthesis of cyclooxygenase and expression of pro-inflammatory genes [147], induction of apoptosis of epithelial cells by inhibiting signal transduction pathway [148] and altering cholesterol metabolism [149]. Some reported side effects include headache, gastrointestinal problems, decreased libido [106], coagulopathy [150], hepatitis [151] and pancreatitis [152].

2.9.2.4.3 *Secale cereale* L.

The drug is obtained from a microbial digestion of pollens of *Secale cereale* and is widespread in temperate zones especially in Sweden and Switzerland [142]. The exact constituents responsible for the activity are still unknown but the presence of proteins, carbohydrates, vitamins, minerals and *β*-sitosterol has been reported [153]. Several mechanisms of action have been proposed for this dietary supplement including: inhibition of 5αR, inhibition of leukotriene and prostaglandin biosynthesis, increase of serum and prostatic zinc concentration, increase in prostate gland epithelial cells apoptosis and bladder muscle contraction [142]. Common side effects have been reported as allergic respiratory reactions, skin hypersensitivities and gastrointestinal symptoms [105].

2.9.2.4.4 *Urtica dioica* L.

The nettle (*Urtica dioica* L. Urticaceae) is a thorny herbaceous plant that commonly grows all over the world, especially wild around the rural houses [154]. The root extract is used in BPH and the components particularly important are lectines, polysaccharides (glucans, glucogalacturonans, arabinogalactan acid) hydroxycoumarins (scopoletin), sterols (*β*-sitosterol, stigmasterol, campesterol) and acids (salicylic and malic acid). A number of mechanisms of the root have been proposed for the treatment of BPH. It inhibit 5αR activity, probably due to the presence of scopoletin and *β*-sitosterol [155], the lectines may contribute the antiproliferative and anti-inflammatory activities [154]. It is also proposed that the lignans present in extract inhibit the action of sex hormones, block the binding of the epidermal growth factor to its receptor with suppression of prostate cell metabolism [156]. It has shown promising antiBPH effect when taken in combination with saw palmetto and *Pygeum* [157,158]. The drug is

well tolerated with exception of rare allergic reactions, mild gastrointestinal effects, diarrhoea and respiratory system diseases [157].

2.9.2.4.5 *Cucurbita pepo* L.

The pumpkin (*Cucurbita pepo* L. Cucurbitaceae), is an annual herbaceous plant native to South-Central America used traditionally in the treatment of BPH and related urinary disorders [154]. The Δ^7-sterols (avenasterol and spinasterol) are considered to be active components responsible for the activity by decreasing elevated levels of DHT. The seeds are rich in zinc content and it may help shrink an enlarged prostate [159]. Pumpkin also produces a tonic effect on the bladder and causes relaxation of sphincter at the bladder neck in BPH patients [154,160]. No major side effects have been reported except mild stomach upset [110].

2.9.2.4.6 Hypoxis rooperi T. Moore

The African potato or yellow star (*Hypoxis rooperi* T. Moore, Hypoxidaceae) is a perennial herbaceous plant native to South-East African regions, particularly of KwaZulu Natal and Transkei [142]. The pharmacological effects of tubers of *Hypoxis* could be attributed to sterols (*β*-sitosterol and *β*-sitosterol glycoside) and lignans (rooperol). The improvement of BPH related symptoms owes to increase of TGF-β1 expression and protein kinase C-alpha activity by *β*-sitosterol [142]. Rooperol have anti-inflammatory activity by inhibiting COX-1, COX-2 and interfere with the synthesis of inflammatory mediators such as prostaglandins [105].

2.9.2.4.7 Glycine max L.

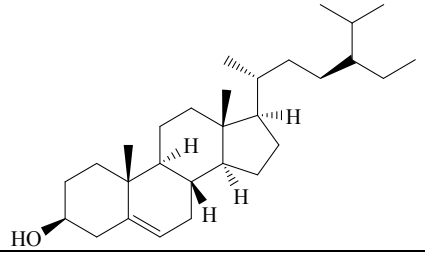
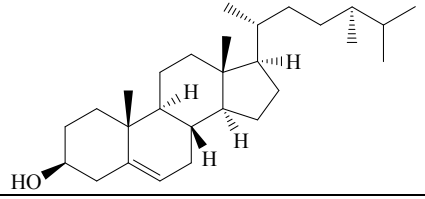
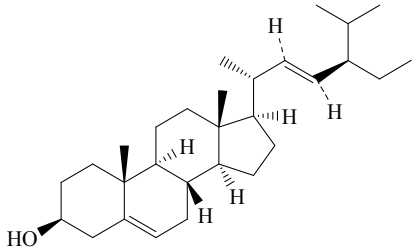
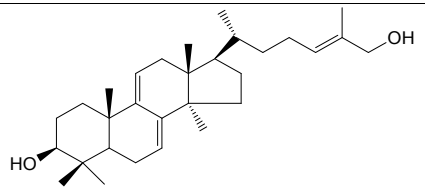
The isoflavones of soy beans (*Glycine max* L. Merr. Leguminosae), a herb native to East Asia is commonly used as a dietary supplement among the BPH patients [140]. The isoflavones commonly responsible in dietary supplements contain genistein and daidzein [161]. Several studies have shown that isoflavones act by inhibiting 5αR, aromatase and activating uroidine 5-diphospho-glucuronsyltransferase. The clinical investigations have shown that soy has been well tolerated [161].

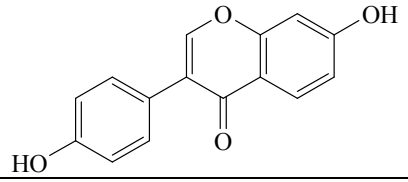
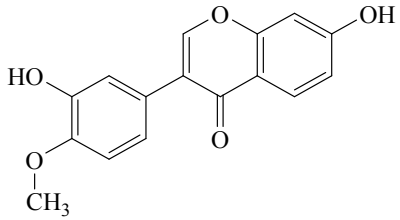
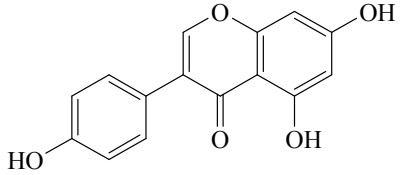
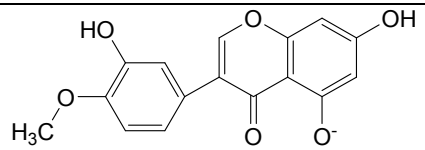
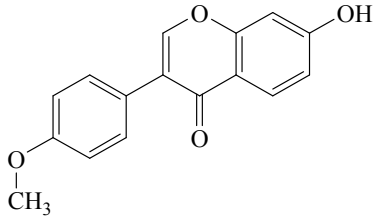
A good number of clinical trials have been conducted on several plants/extracts/ phytochemicals. Table 5 lists the clinical trials of some of the important plants and their extracts/phytochemicals. The chemical structures of phytoconstituents, considered responsible for the activity, are also highlighted in Table 6. The proposed mechanism of action together with the side effects/toxicity is also mentioned wherever reported.

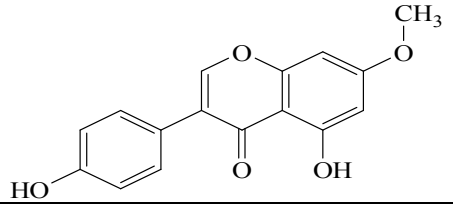
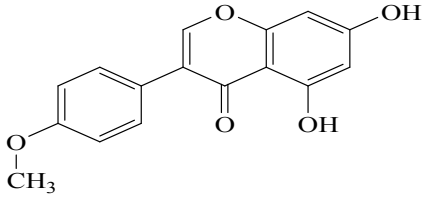
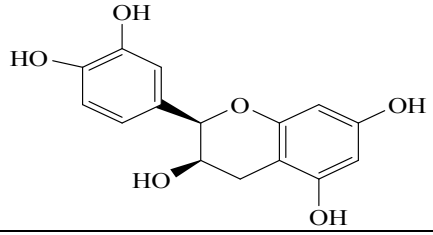
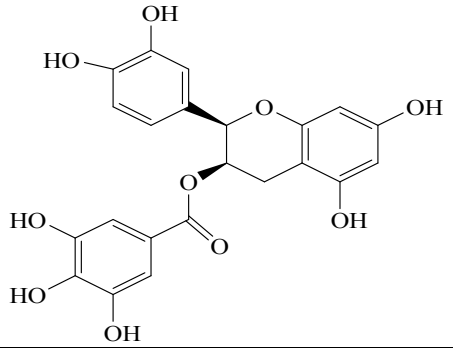
3. IMMINENT PERSPECTIVE

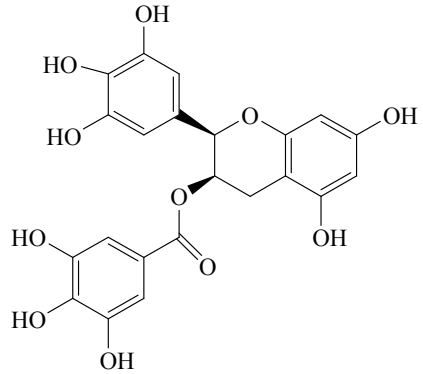
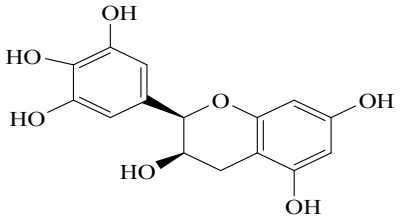
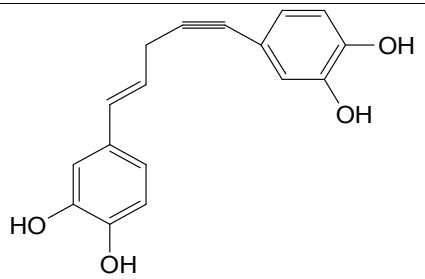
BPH is not a life-threatening situation, but the impact of BPH on the quality of life is noteworthy and should not be undervalued. In the present review, different risk factors responsible for the development of BPH together with various approaches and practices used for the prevention and cure of BPH have been discussed (Fig. 4). Depending on the severity of disease different treatment regimens available are: watchful waiting, drug therapy, surgery and phytotherapeutics. Synthetic compounds like α-adrenergic receptor blockers, 5αR inhibitors and surgery represent well established medical therapy for the management of BPH. The patients with mild to moderate BPH can be effectively managed with phytotherapeutic agents, but patients with severe symptoms having renal dysfunction, bladder stone disease and recurrent infections, need conventional medical/surgical therapy as a preferred line of action. The effectiveness of phytotherapeutic agents in the treatment of symptomatic BPH has gained extensive popularity in the developed countries like USA, Europe (Italy, Germany and Austria) over the last decades. *Prunus africana, Serenoa repens, Urtica dioica, Secale cereale, Hypoxis rooperi* and *Cucurbita pepo* are some of the most predominant plant based medicine used for the management of BPH and of all the *Pygeum* (*Prunus africana*) has been exploited commercially to an extent leading to endangering of the species. Numerous clinical trials have proved the efficacy of the phytotherapeutic agents against BPH. At present the existing data suggest that phytotherapeutic agents are well tolerated by most of the patients and are not associated with serious adverse effects as in conventional medicine. One striking aspect of phytotherapeutics is their good tolerability that renders this approach particularly of interest to those patients who want to avoid sexual side effects of α1-blockers and 5αRIs.

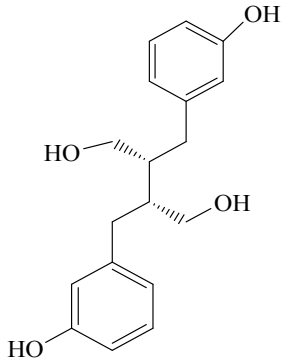
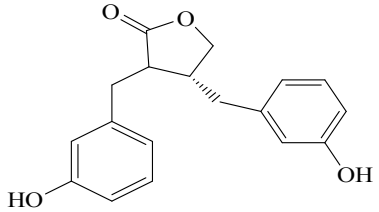
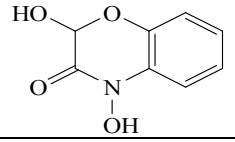
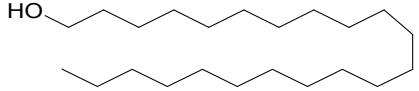
Table 6. Chemical structure (Source: Pubchem) of different phytoconstituent(s) responsible for the BPH protection

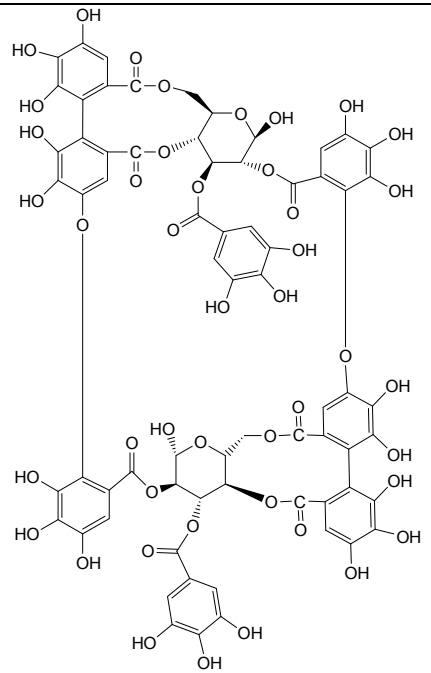
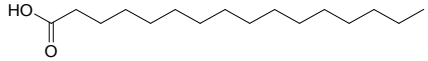
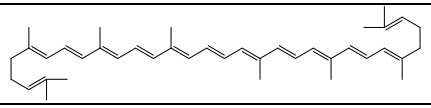
Class of phytoconstituent(s)	Name of phytoconstituent(s)	Structure	Reference(s)
Phytosterols	*B*-Sitosterol		[105]
	Campesterol		
	Stigmasterol		
	Ganoderol B		[126,127]

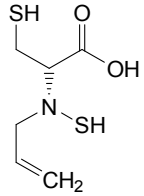
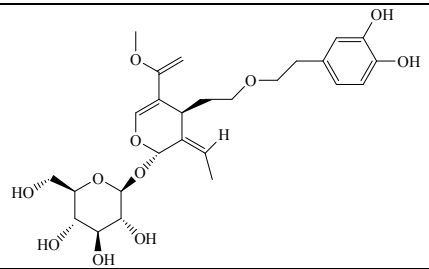
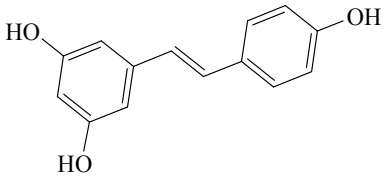
Class of phytoconstituent(s)	Name of phytoconstituent(s)	Structure	Reference(s)
Flavonoids	Daidzein		[122]
	Calycosin		
	Genistein		
	Pratensin		
	Formononetin		

Class of phytoconstituent(s)	Name of phytoconstituent(s)	Structure	Reference(s)
	Prunetin		
	Biochanin A		
	Epicatechin		[135,136]
	Epicatechin gallate		

Class of phytoconstituent(s)	Name of phytoconstituent(s)	Structure	Reference(s)
	Epigallocatechin-3-gallate		
	Epigallocatechin		
Lignans	Rooperol		[176]

Class of phytoconstituent(s)	Name of phytoconstituent(s)	Structure	Reference(s)
	Enterodiol		[177]
	Enterolactone		
Acids and alcohols	2,4-Dihydroxy-2H-1,4-benzoxazin-3(4H)-one		[112]
	n-Docosanol		[105]

Class of phytoconstituent(s)	Name of phytoconstituent(s)	Structure	Reference(s)
Tannins	Oenothein B		[116]
	Palmitic acid		[135]
Carotenoids	Lycopene		[128]

Class of phytoconstituent(s)	Name of phytoconstituent(s)	Structure	Reference(s)
Amino acid derivative	*S*-Allylmercaptocysteine		[178]
Iridoids	Oleuropein		[125]
Stilbenoids	Resveratrol		[130]

However, numerous products available in the market are not standardized and data relating to their safety, clinical efficacy is not always accessible, hence the inferences are inconsistent as a result of less number of patients, short follow-ups and methodological quality of the trials. Moreover, individual proprietary products need proper standardization and analysis to establish their therapeutic value, as the usefulness of one extract cannot be extrapolated to another one due to many factors including variation in different origins, extraction techniques and compositions.

3. CONCLUSIONS

Aging is a natural process and decreasing the health burden with age will be a major arena for future research. BPH is one of the most common urological disorders of elderly men that visibly influence the life style of a patient. Therefore, developing a wide vision to increase the average life expectancy by providing better health care and education is a need of the hour. Advances in molecular biology, pharmacology, and the relationship of different risk factors will ultimately lead to the advancement of preventive medical therapy for the pathogenesis and management of BPH. A recent study reported that the growth hormone releasing hormone (GHRH) antagonists lower prostate weight by decreasing the protein levels of IL-1β, NF-κβ/p65, and cyclooxygenase-2 (COX-2) [179] suggesting a need for further investigations of their role in BPH therapy. Recently, a nanoparticle extract of *Orbignya speciosa* Mart.ex Spreng Arecaceae has been developed and is reported to be safe for the management of BPH [119]. Before we can realize these future aspects of BPH, significant exploration and research is required to be made on natural sources besides understanding in more depth the pathogenesis of this disorder. Further, good clinical practice based upon the clinical evidence, measurement of the disease severity and outcomes, concepts for drug therapy, and the lifestyle interventions will strengthen the management of the disease, thereby improving the quality life of patients. It is expected that natural products will emerge as a dominating therapy for the treatment of BPH and related disorders.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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