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Benign Prostatic Hyperplasia (BPH): A Comprehensive Analysis of the Malaise and Summarizing Possible Management Options through Phytotherapeutic Agents

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Abstract

Benign prostatic hyperplasia (BPH) is a severe illness affecting middle-aged and geriatric male patients. This disease normally occurs at the age of 40 or above and is also associated with sexual dysfunction. Alpha-blockers and 5α-reductase inhibitors are the preferred drugs practiced to treat BPH. However, invasive surgical therapy remains the gold standard for managing the condition in the case of refractory and intricate BPH conditions. Due to the fear of sexual dysfunction and the detrimental influence on their quality of life, most patients seek to avoid synthetic drugs and surgery. For this reason, several patients turn to phytotherapy and other alternative therapies. The authors looked at the existing perceptions of epidemiology, etiology, and pathophysiology associated with BPH in this review article. In addition, this article contained basic information on the pathological roles of inflammation in BPH and various diagnoses and treatment options. It was well reported that the administration of medicinal herbs played a vital role in managing BPH. In recent years, many researchers worldwide have reported the efficiency and safety of phytochemicals in managing numerous pathological disorders in-vivo and in-vitro conditions and the prevention of illness.

Keywords: benign prostate hyperplasia, etiology, pathogenesis, pathophysiology, phytotherapy

Introduction

Benign prostatic hyperplasia (BPH) is one of the most prevalent illnesses affecting older men. It is the most common cause of lower urinary tract symptoms (LUTS) in men, causing a deterioration in the functioning of the urinary system, heightened risk of urinary tract infections, and an increased risk of severe acute urinary retention. Approximately 50% of men aged 50 years are diagnosed with BPH conditions, and more than 90% of men aged 80 years have BPH, with the most significant prevalence occurring among those aged between 70 and 79 years.[1,2] BPH is a term that refers to a proliferative process of the prostate's cellular parts, an enlarged prostate, or voiding dysfunction caused by prostatic enlargement and bladder outlet blockage. It is a histological term that describes proliferative processes in the stromal and epithelial parts of the prostate gland.[3] BPH conditions usually develop in the periurethral and transition zones of the prostate, and it causes an increase in prostate dimensions and urethral blockage and finally results in LUTS.[2,4] Men suffering from BPH may experience severe urination issues, as well as complications, such as recurring renal failure and severe urinary tract infections.[2] As previously stated, BPH condition has a significant impact on the aging male population; therefore, healthcare practitioners should pay special attention when diagnosing BPH to ensure better identification and the best treatment to manage it effectively.

An important symptom associated with BPH is the formation of hyperplastic nodules in the transition and periurethral regions of the prostate gland. As shown in Figure 1, the formation of hyperplastic nodules results in prostate enlargement and, after that, invades the urethra. This process eventually triggers a set of signs, very commonly known as LUTS. The three major kinds of LUTS associated with BPH conditions are storage (this includes urination urgency, urination frequency, nocturia, and urine incontinence), voiding (which provides for reduced flow of urine and a strong sense of incomplete emptying after urination), and post-void dribbling (Table 1).[5] Validated questionnaires recommended by the International Prostate Symptom Score or the American Urological

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Association (AUA) symptom score are the best means of evaluating the severity of LUTS.[6] In older men, urodynamic abnormalities in the lower urinary tract, including benign prostatic blockage and detrusor overactivity/under activity, are the most common causes of LUTS.[7]

Most male patients with LUTS do not seek any medical assistance or avoid medical treatment to manage this condition, leading to a severe burden that affects their lives. One of the primary reasons for this is their concern about the adverse side effects, particularly those that involve sexual functions and performance.[8] Hence, patients' expectations and goals are becoming increasingly important to manage LUTS and effectively obtain the best possible outcome. All these factors should be considered when choosing an ideal treatment plan. The major therapies recommended for LUTS include watchful waiting, medicinal treatment, and surgical intervention based on pertinent guidelines released by national and international urological societies.[8]

Literature Review

Prostate Gland: Anatomy and Function

The prostate is a thick fibromuscular gland located in the true pelvis that enables the male reproductive system to function properly. It is a dense structure and has the shape of an inverted cone, with the base above the neck of the urine bladder and the apex below the external urethral sphincter. The major function of the prostate is to release an alkaline solution that protects the sperm from the acidic environment prevalent in the vaginal cavity. The prostate fluid helps to equipoise the vaginal acidity, which extends the sperm's lifespan and allows it to fertilize an egg for the longest possible time. The fluid also comprises several proteins and enzymes that help the sperm grow and thrive. In addition, it adds volume to the semen and sperm to facilitate quicker mechanical propulsion through the urethral canal.[9]

Benign Prostatic Hyperplasia (BPH): Prevalence of BPH and Histologic BPH

Benign prostatic hyperplasia described as the most common benign neoplasm in American men and a chronic condition that is associated with progressive lower urinary tract symptoms and affects almost three of four men during the seventh decade of life.[10] According to the autopsy data, microscopic or anatomic indications of BPH are present in more than 40% and 90% of men aged 50–60 and 80–90 years, respectively.[11] Intercontinental variation is commonly cited as evidence for emphasizing the significance of various environmental factors, especially dietary behavior, in developing BPH conditions. Increased garlic consumption through the diet may cause a lower occurrence of BPH conditions in China.[12] To comprehend the multifactorial alterations that lead to BPH as a pathophysiological modification resulting in complex symptoms within a man's inner and outer environment, it may be helpful to review what is now known about its etiology and pathophysiology.

Role of Etiological Factors

Although the etiology of BPH is unknown, it seems to be a complex process with both mechanical and dynamic components.[13] The static or mechanical component of BPH involves the enlargement of the prostate, whereas the dynamic component is LUTS, which is caused by the heightened tone of the smooth muscle of the prostate. The sympathetic nervous system controls the dynamic components. Androgens and age are the only two well-established variables linked to BPH.[14] In the population-based Olmsted County study, 13% of men aged 40–49 years had moderate to severe urinary signs compared to 28% of those more than 70 years old.[16] The median rate of prostatic volume change per year was 0.6 ml, corresponding to a 2.5% annual growth rate.[16] A substantial tissue-remodeling process occurred within the prostate of aging men, which finally increased the gland volume.[17]

Role of Age and Genetics

Aging is one of the significant risk factors associated with the development of BPH and LUTS. In the prostate

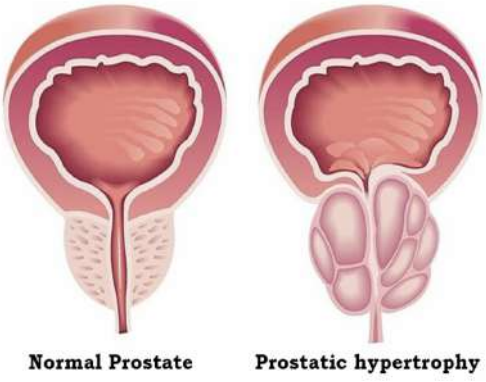

Figure 1. Normal Prostate and Benign Prostatic Hyperplasia

Table 1. Symptoms of Benign Prostatic Hyperplasia

Symptoms	
Associated with Storage	**Associated with Voiding**
Frequency of urination	Difficulty in initiating the urinary stream
Urgency of urination	Hesitancy in urination
Incontinence in urination	Straining to void
Nocturia	Weak urine stream
Dysuria	Decreased urinary flow
	Intermittency
	Dribbling
	Incomplete bladder emptying

gland, the process of aging encompasses cellular mitogenesis and hormonal homeostasis variations, which then lead to chromosomal aberration and death.[18] In addition to this, the aging process is also linked to various inflammatory conditions and microvascular illnesses. All these processes trigger the occurrence of ischemia and oxidative stress, making BPH more likely. Over the last few years, researchers have looked into the linkage of genetic factors associated with the development of clinical BPH in men under the age of 60. Moreover, BPH appears to be an inheritable disease, probably associated with an autosomal overriding pattern. Furthermore, the hereditary components are responsible for more than 70% of the escalated risk that leads to the development of moderate to severe BPH and LUTS in older adults.[19]

Role of Hormones

The BPH has been definitively related to the generation and maintenance of sex steroid hormones in men. Androgen is the major hormone that has been studied the most. Through dihydrotestosterone (DHT)/androgen receptor signaling, testosterone is transformed into DHT in the prostate, influencing cell proliferation, differentiation, morphogenesis, and functional maintenance.[20] In a clinical environment, 5α-reductase inhibitors are reported to lower DHT levels in the blood and halt the progression of clinical BPH.[19] As said earlier, the prostate is usually considered a target of androgens, but estrogens can play a significant role in prostate growth, differentiation, and development via regulating stromal-epithelial interactions.[21] Additionally, extreme estrogenization during prostate development may contribute to the higher occurrence of BPH in aging men. No clear and reliable relationship has been established between other sex hormones, including dehydroepiandrosterone, androstenedione, and 5α-androstenedione and BPH.

Role of Growth Factors

Multiple growth factors and associated receptors have been well recognized in the stroma and epithelium of the prostate gland. These factors can excite or impede cell division and further differentiation steps that lead to BPH development. Although far from complete, this includes epidermal growth factor, fibroblast growth factor, and transforming growth factor-β. The activation of the abovementioned growth factors, either individually or in combination, can cause stromal cell proliferation, which leads to considerable tissue remodeling and prostate enlargement.[21]

Role of Inflammation

Inflammation has been associated with the development and progression of BPH; however, the precise impact and role(s) of immune cells in these conditions remains unclear. The infiltrates associated with inflammation are the most common histological feature associated with BPH, and the severity of the inflammatory condition is directly proportional to the prostate size and mass.[22] Inflammation has been shown to impact various prostate cell types' growth, morphology, and function. It is hypothesized that inflammation promotes epithelial cell proliferation and differentiation in BPH, leading to abnormal prostatic growth.[23] An increased C-RP level has been recorded in men diagnosed with LUTS, and this may be a probable indication of systemic inflammation.[20]

Role of Metabolic Disorder, Lifestyle Aspects, and Obesity

The latest organized review on the association between metabolic disorder and BPH focused on subsets of metabolic syndrome and their connection with total prostate volume (TPV) and LUTS in men. Contrary to earlier study,[24] no significant variations were observed in the scores of LUTS symptoms between men with and without metabolic syndrome. Furthermore, men with metabolic syndrome had a considerably greater TPV than those without metabolic syndrome (Figure 2). Obese people with low levels of blood high-density lipoprotein cholesterol had considerably more significant TPV disparities. Smoking, inactivity, and a high protein diet can bestow the development of symptomatic BPH and LUTS in men.[25]

Discussion

Association between BPH and Prostate Cancer

The first autopsy of the prostate gland in the 1950s discovered a clear link between BPH, and prostate cancer.[26] Zhang, *et al.*,[27] described significant correlations

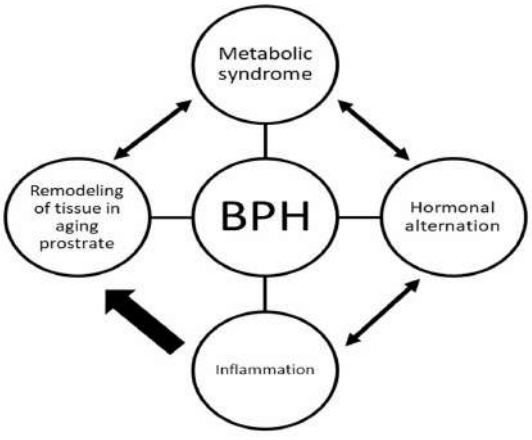

Figure 2. The Association between Aging, Metabolic Disorder, Inflammatory Condition, and Hormonal Changes on the Progress of Benign Prostatic Hyperplasia

Table 2. Collation of General Features of Benign Prostatic Hyperplasia and Prostate Cancer

Benign Prostatic Hyperplasia	Prostate Cancer
Normally the non-malignant type of cells which are localized with enlarged size.	Usually malignant cell type. Tumor cells will show clear multiplication and significant spreading ability.
The maximum affected area is the central zone.	The sides of the prostate are affected maximum.
Higher levels of prostate specific antigen (PSA)	Higher levels of both PSA and alkaline phosphatase
Symptomatic treatments with several other options are available.	Treatment is decided based on the patients' health and stage of cancer.
As per the biopsies, inflammation is observed in major cases.	Same as that of benign prostatic hyperplasia
Partly associated with metabolic disorder.	Here also, it is partly associated with metabolic disorder.
No blood will be observed in the semen.	No blood will be observed in the semen.

between prostatitis, BPH, and prostate cancer. Persons with history of prostatitis are more vulnerable to BPH.[27] Still, no consensus has been reached to prove the association. The BPH is a non-malignant prostate gland enlargement caused by cellular hyperplasia within the transitional zone.[28] Prostate cancer is purely an adenocarcinoma that primarily develops in the peripheral location of the prostate gland.[29] Surprisingly, BPH and prostate cancer share a few common features (Table 2). Chronic inflammation, metabolic distraction, and genetic variation play essential roles in developing BPH and prostate cancer.[30] A collation of general features of BPH and prostate cancer is briefed in Table 2.

Diagnosis Method Available for BPH

The standard investigation of BPH may include bedside urine dipstick, post-void residual, International Prostate Symptom Score (IPSS), and urine flow studies to establish if there is evidence of obstructive voiding. Further tests include prostate-specific antigen (PSA), Ultrasound, Flow Studies, Urethrocystoscopy, and Transrectal ultrasound scanning.

Therapeutics and Management of BPH

The major drugs available for managing BPH conditions include alpha-blockers, Phosphodiesterase inhibitors, Anticholinergics, and Beta-3 agonists. It is often difficult to achieve satisfactory efficacy with a single drug in LUTS-BPH patients, and patients often discontinue treatment due to the side effects. As a result, there is an urgent need to develop novel combination therapies with acceptable efficacy and disease progression inhibition that improve patient adherence to treatment. However, the combination of different drugs may result in additional side effects. Thus, it is imperative to find alternative drugs for managing BPH, especially those derived from medicinal plants.

Role of Phytotherapy in the Managing BPH

Phytotherapy uses plant extracts as medicine to treat various urinary system problems. Due to their benefits of minimal side effects, high positive effects, excellent curative effects, and reduction of signs and symptoms, these alternative therapies are gaining popularity in treating BPH.[31] In many parts of the world, herbal supplements formulated from medicinal plants are also widely employed as an alternative or complementary therapy technique for male patients who have been diagnosed with BPH and prostate cancer.[31]

Effect of Prunus Africana *in Managing BPH*

P. africana bark extracts are used to treat BPH. The bark of this plant is used to treat various conditions like inflammation, urogenital problems, kidney disease, malaria, allergies, fever, and stomach aches. In 1966, a patent was administered with the *P. africana* bark extracts to treat BPH.[32] In the study by Nyamai, *et al.*, the bark extracts significantly affected chronic BPH symptoms such as inability to urinate, frequent urination, nocturnal urination, voiding volume, residual urine, prostate volume, and peak flow.[32] The scientific study on the therapeutic effects of the bark extract clearly demonstrates that the synergistic activity of several bioactive compounds counteracts the functional and biochemical changes that characterize the formation of BPH.[32]

Serenoa repens *(Saw palmetto)*

S. repens is a 20 to 25-foot-tall evergreen shrub with horizontal rhizomes.[33,34] *S. repens* extracts are one of the predominantly used phototherapeutic agents in treating BPH conditions. Saw palmetto-based herbal preparations are widely used to manage BPH symptoms in several parts of the world.[35] This preparation has a significant advantage over conventional therapy as it does not affect PSA levels and has fewer side effects.[36,37] Unfortunately, conventionally used drugs like Proscar significantly lower the PSA level, which in turn masks prostate cancer because PSA levels in serum are generally used as screening tests to measure prostate cancer.

Double-blind research studies found that medicinal herbs effectively alleviate urinary symptoms. The preparations made from this species are thought to work by in-

hibiting the type 1 and 2 isoenzymes of 5α-reductase, the crucial enzyme which converts testosterone to dihydrotestosterone.[38] Anti-inflammatory and anti-estrogenic activities of saw palmetto liposterolic extracts had been demonstrated in BPH patients. Moreover, this extract can inhibit the production of growth factors and prolactin-induced cell proliferation.[39] This extract also lowers levels of testosterone binding globulin.[40] This will significantly ameliorate the symptoms associated with the urinary tract and urine flow in men diagnosed with BPH. The effect is almost comparable to finasteride in terms of effectiveness, but it is less expensive and has fewer side effects.

Crataeva nurvala

C. nurvala comprising herbal formula named PR-2000 at a dose of 2 tablets three times daily for continuous six months improved urine peak flow rate (PFR) and decreased sonographic prostate size in study subjects diagnosed with BPH.[41] *C. nurvala* is one of the major constituents in Himalaya Himplasiatablets (Himalaya Company) that promotes optimum prostate health, urogenital function, bladder function. This medicine has been shown to have 5α-reductase inhibitory and adrenoreceptor antagonist properties.[42] Inhibiting 5α-reductase prevents testosterone from converting to dihydrotestosterone, the primary hormone responsible for developing BPH.[42] Furthermore, an aqueous extract of *C. nurvala* was found to be protective against ethylene glycol-induced nephrotoxicity.[43]

Tribulus terrestris

T. terrestris has significant diuretic properties because of the large amounts of nitrates and essential oils present in the whole fruit. *T. terrestris* water extract can induce a positive diuresis. In addition to the *T. terrestris* extract, it can significantly increase the tonicity of the smooth muscles and its diuresis property, aiding in the effective propulsion of kidney stones.[44] This plant was also reported to prevent the formation of kidney stones in several models of urolithiasis studied using ethylene glycol and sodium glycolate.[45] *T. terrestris* inhibits glycolate oxidase, which accounts for its antiurolithic properties. *T. terrestris* ethanolic extract can significantly reduce the expression of inflammatory mediators and cytokines, which provides significant relief from various inflammatory diseases.[46] Additionally, *T. terrestris* alcoholic extract was very effective against both gram-positive and negative bacteria. However, its petroleum ether and chloroform extracts recorded only moderate antibacterial activity.[47]

Boerhaavia diffusa

Many experimental studies have shown that *B. diffusa* treatment significantly reduces prostate weight and prostatic index in rats. The prostate weight to body weight ratio is used to calculate the prostate index, one of the most important disease markers. An in-vitro research study suggests that herbal extracts have a beneficial outcome on the smooth muscle prostate, which will result in the alleviation of various symptoms associated with the urinary system. *B. diffusa* extract has been shown to have anti-inflammatory and anti-proliferative properties.[48]

Quercetin

Quercetin is a rich flavonoid molecule in fruits, vegetables, andgreeneries.[49] This molecule is widely used to manage various inflammatory conditions as well as prostate cancer as it can deplete oxidative stress,[50] lower the DHT level, and possess significant anticancer properties.[51] An earlier study by Shoskes and co-workers showed that it could significantly improve the symptoms associated with prostatitis (both acute and chronic).[52] All of the effects quercetin has on the prostate signifies its possible role in managing the BPH condition. Ghorbanibirgani, *et al.*, conducted a clinical trial on 200 BPH-confirmed patients to confirm the effectiveness of quercetin in managing the condition.[53] The BPH-confirmed male patients were split into two groups, namely the quercetin and placebo. The quercetin group received 40 drops of quercetin daily three times, whereas the placebo group received 40 drops daily three times for three months.[53] In the quercetin group, the mean AUA symptom score was 4.6 less, and the mean maximal urine flow rate was 3.2 ml/s more than in the placebo group.[53] From those reports, it can be concluded that quercetin has improved effects on lowering BPH indications and further increases the flow rate of urine compared to placebo.

Cucurbita pepo *seed (Pumpkin)*

The *Cucurbitaceae* family includes pumpkins, often known as dubba and the scientific name is *C. pepo*. It is a well-known traditional herbal medication, especially in Europe, for treating various diseases, including diabetic conditions, hypertension, BPH, and several types of microbiological infections.[54] Pumpkin seed oils have anti-inflammatory and antiandrogenic properties and the ability to reduce prostate enlargement, and have antioxidant properties. The properties showed the excellence of pumpkin seeds in treating BPH conditions.[55] Pumpkin seeds have also been shown to inhibit testosterone conversion to DHT, preventing testosterone-induced BPH in a rat model and treating BPH.[56]

Lycopene

Lycopene is found in tomatoes. A well-designed clinical study,[57] suggested that lycopene can effectively prevent BPH development and alleviate the symptoms asso-

ciated with the BPH condition. In addition to this, supplements comprising lycopene are safe for humans.

β-sitosterol

β-sitosterol is an important constituent of phytosterols, a class of compounds under phytosterols. It has a similar structure to that of cholesterol. Even though β-sitosterol has a similar structure to cholesterol, it cannot be converted to testosterone. This compound can also inhibit aromatase and 5α-reductase. A placebo-controlled double-blind clinical study using a 20 mg β-sitosterol found that the treatment group had increased urinary flow and decreased residual volume in the bladder.[58]

Conclusion

Benign prostatic hyperplasia prevalence is expected to rise as the world's population ages. The primary health care professionals must understand the definition, pathophysiology, related risk issues, examination, diagnosis, therapy, prevention, and consequences of BPH condition. In addition, the medications used for managing BPH conditions have a diverse set of clinical applications, pharmacological actions, and adverse effects. It is also known that the treatment efficacy and side effects may vary within the same patient group. Moreover, different BPH patient populations' susceptibility to the same BPH medicine may vary. For these reasons, there is no one-size-fits-all treatment for BPH-LUTS patients. Hence, personalized treatment strategies are essential to ensure the best medical resources for patients. Advice on exercise and diet, in addition to drugs, is a key method for enabling the patient to self-manage the disease condition. This could help avoid the need for surgery, which is known to have several possible side effects and high jeopardy of long-term recurrence in the patients.

Benign prostatic hyperplasia is also not the initial step in developing prostate cancer, and it is time to conduct a large-scale study to clarify the relationship between the two. Various clinical studies have found that medicinal plants have a significant effect in managing the BPH condition, comparable to synthetic medications. Plant extracts are thus much more helpful for patients with minimal risk of advancement since they are well brooked and have no contraindications or interactions with other medicines. Hence, advanced research is required to study the effects of herbal extracts and phytochemicals in managing BPH conditions with special emphasis on the therapeutic goals, including the normalization of nutrient levels in the prostate, further restoration of steroid hormones to normal levels, impediment of surplus production of DHT, reduction of inflammatory markers and curbing of promoters required for the hyperplastic process.

Abbreviations

BPH: Benign Prostatic Hyperplasia; LUTS: Lower Urinary Tract Symptoms; AUA: American Urological Association; DHT: dihydrotestosterone; TPV: Total Prostate Volume; PSA: Prostate Specific Antigen; PFR: Peak Flow Rate.

Ethics Approval and Consent to Participate

Not Applicable

Competing Interest

The author declares that there are no significant competing financial, professional, or personal interests that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

The analyzed dataset is available in published documents and on the internet.

Authors' Contribution

SS is the primary contributor to the article who meticulously conducted the literature review and wrote the manuscript drafts. KPS, SP, AB, SKD, and HNJ initiated the project, supervised the work, and edited the final manuscript.

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