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Herbal Management of Benign Prostatic Hyperplasia

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Abstract

Benign prostatic hyperplasia (BPH) is an age dependent condition that affects old men. The condition is associated with symptoms like frequency in urination, hesistancy, nocturia, weak urine stream and sexual dysfunction. There is thus, need for update of the medications of the disease. Most BPH patients use conventional methods that include drugs targeting 5-alpha reductase enzyme and invasive surgery. These conventional methods lead to severe side effects including erectile dysfunction and gynecomastia. People prefer to go for phytotherapy for the management of the condition to avoid these adverse effects. Finasteride, for example has been found to cause erectile disfunction unlike *Serenoa repens* whose side effects are infrequent and mild. This review provides information on conventional methods of alleviating the condition as well as phytotherapy options. Alternative medicine alleviate the symptoms of BPH but have less severe or no side effects.

Keywords: Benign prostate hyperplasia; Nocturia; 5-alpha reductase; Hesitancy; Phytotherapy

Introduction

Benign prostatic hyperplasia (BPH) is a progressive noncancerous enlargement of the epithelial cells and smooth muscle of the prostate gland accompanied by lower urinary tract symptoms [1]. The enlargement of the prostate compresses the urethra, thus restricting flow of from the bladder. The prevalence of BPH is age dependent with approximately 50% of men developing BPH-related symptoms at 50 years of age but the condition is not common before age 40. At the age of 85, the prevalence is as high as 95% and 20-30% of men at the age of 80 years require surgical intervention to manage BPH [1,2]. The prevalence of bothersome symptoms, just like the histologic evidence increases with age. Moderate to severe lower urinary tract symptoms have been reported on half of the men who have histologic diagnosis of BPH. Risks of developing morbidities and complications is currently unclear as data on population based studies has only been availed recently. Currently, there is no specific time frame at which a certain symptom complex develops to complete urine retention [3]. Serious BPH-related complications are uncommon and BPH-related mortality is rare.

BPH symptoms are known as lower urinary tract symptoms and can be subdivided into storage symptoms and voiding symptoms [4]. Storage symptoms include nocturia, frequency and urgency in passing urine. Voiding symptoms include intermittency, hesitancy, dribbling, straining and decreased urine stream. The severity of BPH can be measured by using the international prostate symptom score (IPSS) questionnaire that has questions about the urinary symptoms and Quality of Life (QoL) questions about how much the patient is bothered by the symptoms [3]. Most symptoms that lead to constriction of urinary flow are directly attributed to prostatic hyperplasia but some men have concurrent overactive bladder or bladder detrusor over-activity. In addition to the treatment of BPH, these men will therefore require therapy for OAB [3].

Several mechanisms seem to be involved in the development of and progression of BPH and thus the etiology still remains uncertain in some aspects. BPH is caused by increased growth of the prostate gland and increased smooth muscle tone of the prostate [5]. Dihydrotestosterone (DHT), a metabolite of testosterone is the main mediator of prostate growth. Dihydrotestosterone is formed by breakdown of testosterone by 5-alpha reductase enzyme in the prostate cell [6].This enzyme is the target for drug therapy aimed at reducing the size of the prostate. The method to be used for management of BPH patients depends on the progression of the condition and whether the symptoms affect the quality of life of patients. BPH patients with symptoms that do not bother them to need surgical or drug intervention are advised to undergo watchful waiting [6]. Watchful waiting involves education and lifestyles modification, periodic monitoring to establish the severity of LUTS, weight loss and increase physical activity to decrease risk factors and reduce symptoms associated with BPH [6].

The two main classes of conventional therapeutic agents used to manage BPH are the 5-alpha reductase inhibitors (5-ARIs) and the alpha blockers [7]. 5-alpha reductase inhibitors act by inhibiting conversion of testosterone to dihydrotestosterone, the main sex hormone in prostate cells and mediator of BPH progression [6]. They slow prostate growth and initiate decrease in prostate size. Alpha blockers, on the other hand work to relax the smooth muscle at the prostate and bladder neck and mediate cellular hypertrophy by blocking alpha-1a receptors. By relaxing the prostate at the prostate neck, the urinary channel is opened, allowing a less constricted urinary flow. Alpha blockers are classified into two: second generation drugs-doxazosin (cardura) and terazosin (hytrin) and third generation drugs which include alfuzosin, tamsulosin and silodosin [8]. Minimally invasive surgical therapies are also used as an option if medical therapy does not alleviate urinary symptoms. Transurethral resection of the prostate (TURP) is the most common surgical procedure [9]. The procedure involves removal of the prostatic urethra creating a channel for the patient to void through.

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These conventional methods of BPH management have adverse side effects. Most alpha blockers require dose titration because of their anti-hypertensive properties [8]. Alpha blockers quickly improve urine flow but do not reduce the size of the prostate and thus they do not decrease the risk of future urinary retention and most patients will ultimately undergo BPH-related surgery [10]. Some alpha blockers also cause dizziness, headache, weakness, asthenia, retrograde ejaculation and nasal congestion. However, a long term combination therapy with finasteride and doxazosin help reduce the symptoms associated with BPH compared to using each drug alone [6]. 5-alpha reductase inhibitors lead to ejaculatory dysfunction, erectile dysfunction and gynecomastia thus these side effects should be monitored when using these drugs [11]. 5-alpha reductase inhibitors also lower PSA by 50% after 6 months on therapy and thus they affect prostate cancer diagnosis [11]. Risks from the minimally invasive surgery include urinary tract information, permanent sexual side effects and rarely, urinary incontinence. Minimally Invasive Therapies (MITs) and TURPs are expensive and health care systems do not advice BPH patients to undergo these procedures. These side effects have resulted to BPH patients turning to phytotherapy for the management of BPH. *Prunus africana* and *Serenoa repens* are the two main plants extracts that have been used in the management of BPH but there are also other herbal preparations in use [12]. This review paper provides information on the bioactive compounds in these plants and how they contribute to BPH management.

Prunus africana as a herbal remedy for BPH

Prunus africana is an evergreen tree with shining foliage, greenish or white flowers a height of more than 40 meters and a stem diameter of up to 1 meter [13]. The species is geographically widespread in African mountains at altitudes above 1500 meters. *Prunus africana* bark extracts are used to make capsules for benign prostatic hyperplasia a condition common in aging men. Traditionally, the bark is powdered and drunk as a tea for inflammation, genito-urinary complaints, kidney disease, malaria, allergies, fever and stomachache. A patent for use of the bark extracts for the treatment of benign prostate hyperplasia was issued in 1966 [14]. Use of the bark extracts is shown to be effective to alleviate BPH symptoms like failure to urinate, frequent urination, nocturnal urination, voiding volume, residual urine, prostate volume and peak flow. Clinical trials using the extracts have shown significant reduction of prostate size and symptoms, and clearance of bladder neck urethra obstruction. The bark contains three groups of active constituents: pentacyclic triterpenoids (including friedelin, oleanolic and ursolic acids), phytosterols (including beta-sitosterol), and ferulic esters of long-chain fatty alcohols (including ferulic esters of docosanol and tetracosanol) [15].

Initially, the therapeutic effects of *Prunus africana* were attributed to β-sitosterol, and its glycoside and to n-docosanol [16]. This finding is unlikely to be true given the low amounts of n-docosanol in *Prunus africana* extracts and high levels of triterpenes and sterols [17]. The therapeutic effects of *Prunus africana* bark extracts are now believed to be as a result of a pharmacological combination whereby several compounds act synergistically thus counteracting the functional and biochemical changes that characterize BPH [14]. The pharmacologically active compounds in the bark extract include pentacyclic triterpenes, phytosterols and ferulic acid esters of long chain unsaturated fatty acids. Two new compounds have been identified: 4-O-ß-D-glucopyranosyl-(7,8)-dimethoxyisolariciresinol [18] and 24-O-trans-ferulyl-2", 3"-dihydroxy-urs-12-en-28-oic acid [19]. The phytosterols, mainly β-sitosterol, have anti-inflammatory effect and inhibits the stimulation and synthesis of prostaglandins, aromatase activity and 5-alpha-reductase activity [20-22]. β-sitosterol helps reduce the elevated levels of prostaglandins in BPH patients [20] and suppresses prostatic growth factors and cholesterol accumulation. These phytosterols also eliminate vasal congestion and excess blood hence reduces the size of prostate adenomas. The pentacyclic triterpenoids block enzymatic activity thus inhibits inflammation in the prostate [23]. They also have anti-edema effects and help increase the integrity of capillaries and small veins. Ferulic esters in the bark extracts act by inhibiting the absorption and metabolism of cholesterol [17,18]. BPH and other cases of enlarged prostates are characterized by containing abnormally high levels of cholesterol. Pentacyclic triterpenoids also counteract inflammation in the prostate [22]. Cyanidin-o-galactoside, cyanidin-3-o-rutinoside, procyanidin B5 and robinetinidol-(4-α-8) catechin-(6,4-α) robinetinol are members of the flavonoid group and their derivatives in *Prunus africana* bark extracts are believed to inhibit cell proliferation in the prostate gland [15,24].

Initial *in vivo* studies to be done with *Prunus africana* extracts showed that the extract prevented hyperplasia in rats that had been injected with human prostate tissue and induced prostate secretions in normal tissue. Men without BPH showed similar results though they had insufficient prostate secretion [25]. Administration of *Prunus africana* extract orally in rats stimulates secretory processes in cells of bulbourethral gland and in the prostate [26]. The extract also stimulates seminal vesicle secretion in castrated rats acting as testosterone antagonist in these organs. In castrated rats that have been adrenalectomised, the extract increases contents of gonadotropins in the pituitary and testosterone activity. *Prunus africana* extract is thus believed to be involved with the pituitary gland and adrenal cortex [27]. The extracts exhibit reduced vascular permeability due to histamine and anti-oedema and anti-inflammatory activity in rats [23]. The extracts also reduce bladder hyperactivity in guinea pigs and have modulating activity on age-related contraction of bladders of rats [27].

Prunus africana extract is a well-tolerated effective drug for the treatment of symptoms associated with BPH [28,24]. Use of the extracts in treatment of BPH has been demonstrated in open and double-blind placebo controlled clinical trials with most trials showing excellent results. The trials were carried out for treatment periods from 6 weeks to three months and with doses ranging from 75-200 mg daily. Once and twice daily dosages of *Prunus africana* extracts when compared were found to be equally safe and effective [28]. In most of the trials, urine frequency decreased and urine flow increased. In trials with higher doses, prostate size and irritative symptoms decreased [29]. Patients taking 200 mg of the extract daily for two months showed a decrease in sexual disorders associated with chronic prostatis or BPH [30]. Treatment of genital infection that is associated with BPH with the extract is believed to be effective even without administering antibiotics [31]. The extract also increases protein secretion and the activity of prostatic acid phosphatase in patients whose activity is low [32]. Gamma-tocopherol has been reported in the bark of *Prunus africana* [15]. Vitamin E prevents oxidation and peroxidation of membrane phospholipids and triggers apoptosis of prostate cancer cells [33].

Prunus africana bark also contains selenium and zinc which are believed to alleviate urinary tract symptoms. Prostate cancer cells are deficient in selenium and glutathione peroxidase, two antioxidants that protect cells against hydroxyl radical-induced membrane damage. The earlier in life selenium is started, the greater are the protective benefits [34]. Selenium can also protect against doxorubicin-induced heart damage and radiation-induced bladder cancer [34]. Studies

show that marginal zinc deficiency is common, especially among the elderly [35]. Zinc also plays an important role in preventing prostatitis. Secreted by prostate epithelial cells, zinc kills bacteria on contact [36]. Men with chronic bacterial prostatitis have extremely low prostate zinc concentrations despite normal serum zinc levels. Although taking supplemental zinc won't normalize prostate zinc levels [36], it can improve prostatitis-induced infertility [37]. Zinc can also inhibit prostate cancer cell growth and enhance apoptosis [38].

Pygeum efficacy is determined by measuring the effects of the herb on numerous parameters, including dysuria, nycturia, frequent urination, abdominal heaviness, residual urine, voiding volume, prostate volume, and peak flow. Consumption of pygeum has been shown to result in significant amelioration of symptoms, reduction in prostate size, and clearance of bladder neck urethral obstruction [39]. Transient side effects involving gastrointestinal irritation (inducing nausea and abdominal pain) have been reported in clinical trials.

Serenoa repens (Saw palmetto) as a herbal remedy for BPH

Serenoa repens is an evergreen shrub with horizontal rhizomes and grows to heights up to 20 to 25 feet [40,41]. The extracts of *Serenoa repens* are the most common phytotherapeutic herbal agent used in the management of BPH. The products used for medicinal purpose are derived from the ripe berries of the species. The species is native to the sandy soils of Louisiana, Texas, Georgia and the islands in Cuba and Bahamas. The berries turn color from green to bluish-black when ripe. Herbal preparations from saw palmetto are used to improve symptoms of benign prostatic hyperplasia [42]. Herbal supplements from the species are also used as alternative or complementary medicine modalities for men with prostate cancer [43]. Saw palmetto herbal preparations have advantages over conventional therapy in that they do not change prostate specific antigen (PSA) levels and have minimal side effects [44,45]. Drugs like proscar lower PSA levels and may mask prostate cancer as tests for screening prostate cancer involve measuring PSA levels. Double-blind studies have proved the herb to be effective in improving urinary symptoms.

The mechanism of action of the preparations from this species is believed to be inhibition of type 1 and type 2 isoenzymes of 5-alpha reductase, the enzyme that converts testosterone to dihydrotestosterone [46]. Saw palmetto liposterolic extracts have been reported to have anti-inflammatory and anti-estrogenic effects and to inhibit growth factor and prolactin-induced cell proliferation in BPH patients [47]. This extract also reduces testosterone binding globulin levels [48].

Administration of saw palmetto berry extracts reduces the action of dihydrotestosterone androgen by blocking alpha-adrenergic receptors [47,48]. The main chemical compounds in the berries of *Serenoa repens* are fatty acids, monoacylglycerides, polyphenols and phytosterols. The biologically active components of saw palmetto are believed to be phytosterols and fatty acids. The extracts mainly consist of fatty acids with high quantities of saturated and medium chain myristate (14.0) and laurate (12.0) fatty acids [49]. The fatty acids in saw palmetto extracts are believed to be responsible for the inhibition of 5α-treductase enzyme [50]. Some studies show that phytosterols in saw palmetto also inhibits 5α-reductase and BPH symptoms [51] however the phytosterols (campesterol, β-sitosterol and stigmasterol) are not unique to the saw palmetto extracts. The beneficial effects of saw palmetto herbal preparations may be due to synergistic effect from both fatty acids and phytosterols. Based on the results of a systematic review of 18 randomized controlled studies involving 2,939 men, Wilt et al. concluded that saw palmetto improves urinary tract symptoms and flow measures in men with BPH, and compares favorably with the effectiveness of finasteride, but costs less and causes fewer side effects.

Other plants with therapeutic effects on BPH

Cernilton herbal preparation from rye-grass pollen has also been used in BPH management. It has been used worldwide and has been registered as a pharmaceutical product in Korea Western Europe, Japan and Argentina [52]. This product has been found to improve all urologic symptoms associated by inhibiting 5-α reductase activity with BPH and has been reported to be well tolerated by patients. Cernilton blocks arachidonic acid metabolism and alpha-adrenergic receptors, relaxes the external sphincter musculature, lowers urethral pressure and decreases swelling of the prostate and inflammation [52]. *Saxifraga stolonifera herb has been reported to contain protocatechic acid, bergenin, gallic acid, quercetin, mesocomic acid and succinic acid [53]. The herb has been used in the manufacture of herbal Saxifrage tablets. Gallic acid, mesoconic acid, protocatechic acid and succinic acid are phenolic acids and have been reported to have anti-oxidant activity and are thus important components in the treatment of cancer, diabetes and cardiovascular diseases* [54,55]. Quercitin and bergenin belong to flavonoids group and are known to have free radical scavenging activity and also inhibit cell proliferation [55,56]. These flavonoids also have the ability to inhibit protein kinases and topoisomerases in addition to their ability to modulate cell differentiation and apoptosis and their antioxidant activity [57,58]. Although *Serenoa repens* lowers residual volume after voiding and prostate size, the changes are not significantly different compared to placebo groups as reported in CAMUS trial [59]. The study reported that treatment of the experimental group with 160 mg of saw palmetto twice daily did not improve BPH related symptoms [59].

American Urological Association Guidelines (AUA) guidelines do not recommend use of dietary supplements and phytotherapeutic agents for the management of BPH although they have been in use in Europe [60]. It has been reported that the efficacy of *Serenoa repens* and *Prunus africana* is equivalent to that of α-blockers and finasteride. The guidelines states that these agents are not purified and their content has not been declared and no health authority to control them. The exact mechanism of action of these phytotherapeutic compounds need to be established for them to be included in the AUA guidelines for the treatment of BPH [60].

Conclusion

Traditional medicine has remained a pillar component in healthcare systems of resource poor economies. Their upsurge in use is dependent in long term clinical experience. A growing body of scientific evidence also supports that complementary and alternative health care practices that improves the health and well-being of patients. *Prunus africana, Serenoa repens* (Saw palmetto) and *Saxifraga stolonifera* have been used traditionally and in modern medicines in the management of BPH. Therefore, provision of information on the bioactive compounds in these plants and how they contribute to benign prostatic hyperplasia is key as treatment/management intervention approaches. Phytotherapy has, however, some limitations in that as compared conventional medical therapy, it has short duration, short follow-up, and the improvement measurements is not uniform and some is not adequate.

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