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Review Article

Treatment Modalities for the Management of Benign Prostatic Hyperplasia: Past, Present and Future Perspectives

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Received: April 11, 2021; **Published:** May 17, 2021

Abstract

Benign prostatic hyperplasia (BPH) is one of the most common conditions affecting men. BPH can lead to a number of symptoms for patients collectively tagged as lower urinary tract symptoms (LUTS). Over the last decade, increased modifiable risk factors, such as metabolic disease and obesity, have resulted in an increased incidence of BPH. We performed a comprehensive search using multiple databases (National Library of Medicine, ResearchGate, PubMed, Cochrane Library, Scopus, Google Scholar, MEDLINE, ScienceDirect) and other sources of grey literature as well as conference proceedings published in English. Current therapies can first be divided into medical or surgical intervention. Pharmacotherapy for BPH includes 5-alpha-reductase inhibitors, alpha-blockers, Phosphodiesterase-5 inhibitors, anticholinergics or a combination of these agents. Surgical interventions include a conventional transurethral resection of the prostate (TURP), as well as newer modalities such as bipolar TURP, holmium laser enucleation of the prostate (HoLEP), GreenLight and thulium laser, and prostatic urethral lift (PUL). Emerging therapies in this field must also be further investigated for safety and efficacy. This narrative review attempts to consolidate past, current, emerging as well as alternative therapy options for BPH and highlights the need for additional investigation on optimizing treatment selection by clinicians.

***Keywords**: Benign Prostatic Hyperplasia; Pharmacotherapy of BPH; Future Therapies; Urologic Surgery; Phytotherapy of BPH*

Abbreviations

AR: Androgen Receptor; 5AR: 5α-Reductase; AUASI: American Urological Association Symptom Index; BOO: Bladder Obstructive Outcomes; BPH: Benign Prostatic Hyperplasia; DHT: Dihydrotestosterone; DRE: Digital Rectal Examination; HoLEP: Holmium Laser Enucleation of the Prostate; I-PSS: International Prostate Symptom Score; LUTS: Lower Urinary Tract Symptoms; OAB: overactive bladder; PSA: Prostate Specific Antigen; PUL: Prostatic Urethral Lift; QOL: Quality Of Life; SRC-1: Steroid Receptor Coactivator 1; TURP: Transurethral Resection of the Prostate; WAW: Watch and Wait; WW: Watchful Waiting

Introduction

The prostate (Figure 1) is an accessory sexual organ that is found only in men. It is a plum-sized gland that weighs about 40g [1]. Anatomically, the prostate is found at the base of the urinary bladder and surrounds the urethra [1,2]. The human prostate consists of 20 to 30 separate glands that open separately into the urethra [1]. The prostatic secretion makes up part of the seminal fluid and is rich in electrolytes such as calcium ion, citrate ion, sodium ion, zinc ion, and phosphate ion as well as clotting enzymes, phospholipids and profibrinolysin [3]. Physiologically, the prostatic secretion successfully aids fertilization. This is so because of its slightly alkaline characteristic

that neutralizes the relatively acidic fluid of the vas deferens as well as the highly acidic vaginal secretions (pH: 3.5 - 4.0). By elevating the pH of the female genital tract to about 6.0 - 6.5, initially non-motile spermatozoa become optimally motile and the chances of fertilization are considerably enhanced.

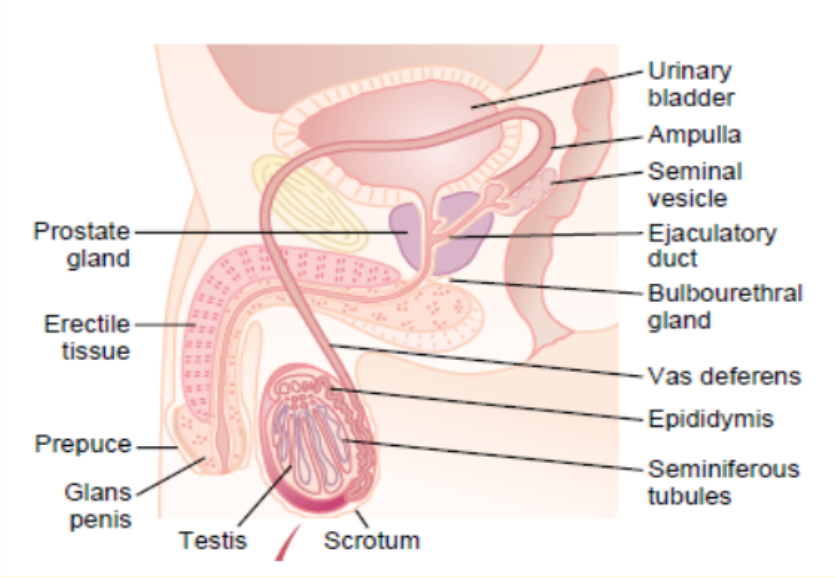

Figure 1: *Male reproductive system [4].*

Prostatic disorders are categorized as benign or non-malignant hyperplasia and malignant hyperplasia. For the purpose of this review, our focus will be on benign prostatic hyperplasia. Benign prostatic hyperplasia (BPH) is clinically defined as the non-malignant enlargement of the prostate gland due to hyperplasia of glandular structures (smooth muscle and epithelial cells) and connective tissues. The enlargement of the prostate compresses the urethra, thus restricting flow of urine from the bladder. From thirty (30) years onward, the prostate gland naturally enlarges due to unknown causes. However, this enlargement could be enhanced by some factors including nutrition, lifestyle choices and environmental factors. Therefore, the purpose of this narrative review is to consolidate the past, current, emerging as well as alternative therapy options for BPH and highlights the need for additional investigation on optimizing treatment selection by clinicians.

Methodology

Multiple online literature searches utilizing the databases of National Library of Medicine, PubMed, Cochrane Library, Scopus, Google Scholar, MEDLINE, ScienceDirect, ResearchGate and other sources of grey literature for original researches, reviews, narratives and trials registries on the most commonly used treatment modalities as well as newer therapies for benign prostatic hyperplasia was performed using keywords like "treatment strategy for benign prostatic hyperplasia", "greenlight therapy", "lower urinary tract symptoms", "transurethral resection of prostate" "food and supplement for managing BPH", "use of plant extracts in the treatment of BPH", "urethral lift", "prostatic surgeries", "thulium laser", "herbal remedies for BPH" and newer therapies for BPH". The study was conducted between December 2020 and March 2021. Although recent articles were prioritized, manuscripts with relevant historical findings were referenced where and when necessary. Evidence was not limited to human data; data on plant remediation of BPH from animal studies were also included in the review. All titles and abstracts of searched articles were screened, full texts were obtained, and inclusion and exclusion criteria were applied to determine the appropriateness and relevance of articles used in this review. To ensure quality assurance, Q1 - Q4 journals

were sought for and prioritized. Also, articles from predatory journals were totally avoided. To overcome bias, full texts of all searched literatures were thoroughly read by all the authors prior to the application for the inclusion and exclusion criteria. Studies were included if they reported past, current, new and emerging modalities for the treatment of BPH as well as the phytotherapy of BPH. All articles on the treatment options for prostate cancer as well as articles not published in English language were excluded.

Results and Discussion

Search results

The initial search discovered a total of 100 studies. Of these, 25 articles were excluded after screening their titles and abstracts, leaving 75 articles for further review. The criteria for exclusion were on suitability and relevance. Thus, 15 articles were not relevant (n = 15), articles not published in English (n = 5) and duplicated articles (n = 5). With the application of the inclusion and exclusion criteria, a further review of the full texts of the 75 articles resulted in the exclusion of 16 additional articles. Thus, 59 studies were used for the present review (Figure 2).

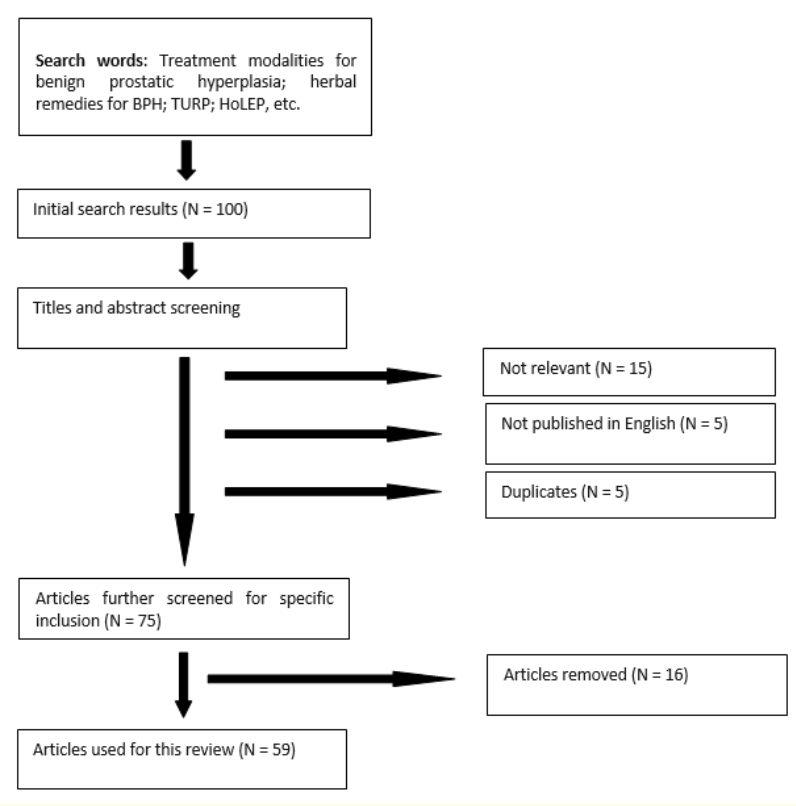

Figure 2: *Flowchart for study selection.*

Disease prevalence

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. Vos., *et al*. [5] reported that the global prevalence of BPH as of 2010 was well over 210 million.

According to Egan [6], more than 50% of men above 50 years as well as about 80% of those aged 80 and older experience lower urinary tract symptoms (LUTS) associated with BPH. Following increase in modifiable metabolic risk factors, especially the lifestyle related disease - obesity, the scorecard for BPH prevalence raises a manifold [7]. Studies have linked male obesity to increased risk of BPH and the severity of LUTS is more pronounced in obese men plagued by BPH [8]. At the age of 85, the prevalence is as high as 95% and 20 - 30% of men aged 80 years may likely require surgical intervention to manage BPH [9]. Wu., *et al.* [10] reported an estimated occurrence of approximately 20% for men aged 40, 60% for men aged 60, and 90% for men aged 70 and above. Histomorphologically, apparently all males aged 50 and older develop glandular changes of the prostate evidence of BPH, however, such may not warrant medical therapy or surgical interventions until it becomes symptomatic.

Pathophysiology of benign prostatic hyperplasia

BPH is highly related to sexual hormone metabolism and aging. In particular, dihydrotestosterone (DHT), to which testosterone is modified by 5α-reductase (5AR), has a significant effect on BPH development. DHT binds to an androgen receptor (AR) and steroid receptor coactivator 1 (SRC-1); then, it induces the proliferation of a prostate cell and expression of prostate specific antigen (PSA). Prostatic enlargement is associated with hyperplasia of the prostatic smooth muscles with a probable bladder outlet obstruction (BOO). Primarily, it is often associated with lower urinary tract symptoms (LUTS), which may further be classified as either obstructive or irritative symptoms [10]. The obstructive symptoms include weak urinary stream, hesitancy, extended voiding time, urinary retention, and urinary incontinence. On the other hand, the irritative symptoms include decreased void volume, urinary frequency, urgency, nocturia, and dysuria. Most times, LUTS include occasional renal failure [11].

Diagnosis of benign prostatic hyperplasia

Since LUTS is not exclusive to BPH, differential diagnosis is the gold standard. Thus, diagnosis of BPH often rules out urinary tract infections (UTI), overactive bladder (OAB), prostatitis, bladder cancer, prostate cancer, bladder stones as well as interstitial cystitis [10]. Although BPH-associated symptoms are often not life-threatening, however, they can exert enfeebling effect on bodily functions and significantly affect the quality of life. Therefore, it is imperative that BPH be properly identified and diagnosed so as to facilitate an effective treatment modality.

Several recommendations for the diagnosis of BPH have been made and adopted by numerous reputable health authorities [12]. The recommendations enshrines that patients presenting with LUTS as well as experiencing negative changes in their QOL must be evaluated as summarized in Figure 3.

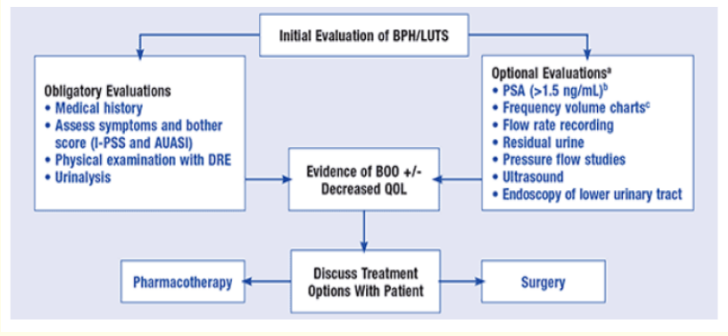

Figure 3: *Diagnosis of benign prostatic hyperplasia. AUASI: American Urological Association Symptom Index; I-PSS: International Prostate Symptom Score; DRE: Digital Rectal Examination; BOO: Bladder Obstructive Outcomes; QOL: Quality of Life; PSA: Prostate Specific Antigen; LUTS: Lower Urinary Tract Symptoms [12].*

Past management options

Over the past two decades, the medical therapy for benign prostatic hyperplasia has experienced colossal evaluations and re-evaluations. Drug therapy for the condition was first registered in the late 1960s and early 1970s especially few small uncontrolled, non-randomized studies postulated alpha blockers and hormonal modulation as therapies for BPH. However, it was in the late 1980s that multicentre, randomized, double-blind, placebo-controlled studies reported the safety as well as the efficaciousness of α_1-adrenergic antagonists and 5α-reductase inhibitors as choicest drugs in the treatment of benign prostatic hyperplasia. These controlled studies demonstrated beyond reasonable doubts that these therapeutic agents were well tolerated by the research participants. However, the α_1-adrenergic antagonists recorded more effective outcomes. During the 20th century, BPH received huge attention with nonsurgical management as the most preferred treatment option.

Current trends in the management of benign prostatic hyperplasia

In the 21st century treatment strategy for BPH has been re-evaluated to include watchful waiting or watch and wait (WW and WAW respectively) for mild BPH-associated symptoms, behavioural and/or lifestyle modification, medical therapy, and surgery. Therefore, the above-mentioned options are exploited by management of BPH, however, medical and surgical interventions are the mainstay and are dependent on the time of presentation as well as the stage of disease progression i.e. mild, moderate or severe.

Watchful waiting: WAW is a time-honoured approach used in the management of patients with early and BPH-associated symptoms. Successful management with this approach is dependent chiefly on better understanding of the natural history of the disease condition. Historically, there exist gaps in the understanding of BPH, making it a bit challenging for clinicians to determine who would be a good candidate for the watch and wait approach.

Medical therapy: The pharmacotherapy for the condition entails the prescription of α_1-adrenergic antagonists (terazosin, doxazosin, alfuzosin, tamsulosin, silodosin and naftopidil), 5α-reductase inhibitors (finasteride and dutasteride), muscarinic receptor antagonists (tolterodine, trospium, solifenacin, fesoterodine, propiverine, oxybutynin and imidafenacin) and phosphodiesterase type-5 (Tadalafil, sildenafil, and vardenafil) inhibitors either as monotherapy or combinatorial therapy. In the current medical therapy for BPH, tamsulosin is frequently/widely prescribed of all the α_1-adrenergic blockers. As with all medicines as well as surgical procedures, there is always a very narrow margin for the exception of undesirable outcomes - what we here refer to as side effects. Therefore, the most frequent side effects of alpha-blockers experienced by patients are asthenia, dizziness, and postural hypotension. Patients with cardiovascular comorbidity or vasoactive co-medication may be susceptible to alpha-blocker-induced vasodilation. As reported by Yeo., *et al*. [13], α_1-blockers have no adverse effect on libido; however, they exert a small beneficial effect on erectile function but occasional degree of abnormal ejaculation. Intriguingly, tamsulosin has greater risk for abnormal ejaculation in men diagnosed of BPH. The propensity for drug-related side effects during medical therapy of BPH is heightened in the elderly with multiple comorbidities such as renal disorders, cardiovascular disease, diabetes mellitus, or hypertension and the need for anaesthesia. Although monotherapy, with alpha blockers and 5α reductase inhibitors, is beneficial, the combination of these drugs is highly effective. McConnell., *et al*. [14] reported a 34%, 39% and 66% clinical risk reduction on finasteride, doxazosin and combination therapy respectively. Similarly, a staggering treatment outcome with combination therapy as against monotherapy for BPH and associated symptoms has been reported.

Surgical interventions

This is generally offered to patients with tenacious or chronic BPH-related symptoms recalcitrant to pharmacotherapy. In comparison with drug therapy, surgical interventions is regarded by most patients and their families as very expensive and problematic, however, the cost of continuous drug therapy for 5 years sure exceed the costs of early surgery [15]. Due to the proportional increase in BPH cases managed solely by pharmacotherapy, some school of thoughts opines that BPH is more of a chronic condition with a colossal economic

burden, especially on a long term. Interventional management of BPH includes traditional open surgery, transurethral resection of the prostate (TURP) and most recent modalities like as bipolar TURP, laser ablation therapies such as holmium laser enucleation of the prostate (HoLEP), greenlight and thulium laser as well as prostatic urethral lift (PUL).

Open surgery: When used for BPH treatment, this procedure is known as simple prostatectomy. It is used in patients with very large prostates, especially when pharmacotherapy and minimal invasive treatment options for BPH are unsuccessful. It is different from the radical prostatectomy (used in localized prostate cancer) in that it favours the enucleation of the hyperplastic prostatic adenoma whereas radical prostatectomy suggests the en bloc removal of the prostate gland, seminal vesicles and vas deferens [16]. Usually, open prostatectomy may be performed either via the suprapubic, retropubic and perineal regions. Simple suprapubic prostatectomy enucleates the hyperplastic prostatic tissue via an extraperitoneal incision of the lower anterior bladder wall whereas retropubic prostatectomy is done via a direct incision of the anterior prostatic capsule [16]. The frequently observed disadvantages of this procedure are postoperative urinary incontinence, intraoperative bleeding, longer hospital stay and increased morbidity. It is worthy of note that simple prostatectomy is contraindicated in patients experiencing LUTS where prostate cancer is not ruled out, hence the need for proper and prompt diagnosis. In current practice, due to the advent of robot-assisted techniques, simple prostatectomy is often not performed as a traditional open surgery rather it is a minimally invasive procedure.

Transurethral resection of the prostate (TURP): Historically, this procedure is considered 'gold standard for the surgical treatment of BPH' [17]. TURP at one point was the second most commonly performed operation in the United States. The procedure is carried out using a resectoscope, which is inserted at the tip of the penis, passed through the urethra until it reaches the prostate and used to trim section of the enlarged gland causing LUTS. The major complication of TURP is the transurethral resection syndrome (TURS), which is caused by resorption of excessive electrolyte-free irrigation fluids used during TURP into the patient's body. The full clinical manifestation of TURS consists of neurological disturbance, arterial hypertension, cardiogenic shock, renal failure, cerebral as well as pulmonary oedema amongst others [18]. Due to the potentially life-threatening outcome of TURS, the late 1990s witnessed an improved surgical technique called bipolar TURP [8]. Bipolar TURP employs isotonic irrigation solutions and reduces the risk of electrolyte imbalances including TUR syndrome [18]. Retrograde ejaculation is the commonest side effect experienced by most patients that undergoes both monopolar and bipolar TURP procedures. In the late 20th century, more than 70% of all surgical treatment for BPH was TURP. However, the 21st century witnessed the introduction of new/improved surgical techniques for the treatment of BPH.

Holmium laser enucleation of the prostate (HoLEP): This surgical technique involves the telescopic removal of obstructing prostate tissue using a laser and temporary insertion of a catheter for bladder irrigation. The holmium laser is a pulsed laser, utilizing a solid medium that combines both carbon dioxide and neodymium: yttrium-aluminium-garnet (Nd: YAG). The laser is used to separate the obstructing prostate tissue from its surrounding capsule and to push it in large chunks into the bladder. An instrument is then used through the telescope to remove the prostate tissue from the bladder. A catheter is normally left to drain the bladder at the end of the procedure. This surgical technique was first reported in 1996 as a viable treatment intervention for BPH. Many studies have compared the treatment outcomes of HoLEP with TURP. Barboza., *et al*. [19] reported that HoLEP was as effective as TURP in terms of patient outcomes and operative time especially as patients whose BPH-associated symptoms were managed with HoLEP had shorter catheterization times, hospital stays with better treatment outcomes than patients treated with TURP. Due to its viability and effectiveness, HoLEP has been described as 'emerging gold standard' as regards surgical interventions for BPH of the 21st century. Despite these reports, HoLEP is not devoid of some undesired outcomes. For example, it is associated with "higher rates of early postoperative urgency urinary incontinence compared to TURP". As with both monopolar and bipolar TURP, retrograde ejaculation is experienced in BPH patients treated with HoLEP procedure.

GreenLight laser therapy: GreenLight laser therapy is used to evaporate the hyperplastic prostatic adenoma blocking the outlet of the urinary bladder. It uses a high-powered potassium-titanyl-phosphate (KTP) 532-nm wavelength photo-selective vaporization system [8]. Usually, a telescope is inserted through the urethra up to the prostate. The surgeon uses this to guide the laser fibre while the hyperplas-

tic prostatic tissue is expeditiously but gently vaporized. By vaporizing the obstructing prostatic tissue, natural urinary flow is restored providing symptomatic relief from LUTS and other worrisome BPH-related symptoms. The full transmission of this laser energy through aqueous irrigating agent and absorption by high oxy-haemoglobin rich tissue (e.g. prostate gland) tissue makes GreenLight highly photoselective. Based on this, the procedure is otherwise termed 'Photoselective Vaporization of the Prostate' (PVP). Currently, this outpatient procedure has witnessed significant improvement especially with the advent of GreenLight HPS system that employs a higher powered (120 or 180 Watts) over the original GreenLight laser (80 Watts) [20]. The GreenLight HPS has comparative advantage over the original version because of its expeditious nature. Thus, the benefits of this therapy include shorter hospital stay, minimal bleeding, minimal catheterization time as well as rapid recovery time over traditional surgical procedures. Common adverse effects associated with PVP are irritation of the urethra, retrograde ejaculation, haematuria, polyuria, urinary incontinence, irritation of the bladder, etc. Studies have equally reported the comparable efficacies and outcomes of GreenLight and HoLEP procedures.

Thulium laser therapy (ThuLEP): As technology advances, new surgical techniques evolve. Thus, thulium laser enucleation of the prostate (ThuLEP) emerged as a novel treatment modality for BOO. It employs a rare elemental metal, thulium, to provide a continuous (though pulsatile) wave laser that offers advanced/improved prostatic tissue vaporization. The technique is highly recommended for very large prostates (> 80 mL). Studies have documented 2005 as the entrant year of ThuLEP into clinical practice. The initial ThuLEP laser energy was between 50 - 120 Watts. Similar to the edge of the GreenLight HPS system over the original system, current thulium devices are powered between 150 - 200 Watts [21]. In contrast to the pulsed holmium laser, thulium laser ensures smooth tissue incisions and rapid vaporization providing the surgeon the enabling environment to remove the hyperplastic prostatic adenoma at the level of the prostatic capsule. Thulium laser therapy has also been compared to other laser therapies. Palmero-Martí., *et al*. [22] reported that the comparison GreenLight HPS (120 W) to ThuLEP had equivalent treatment outcomes (complications, patient reoperations and postoperative PSA levels). Both thulium vapoenucleation of the prostate (ThuVEP) and HoLEP were reported as equivalent and satisfactory in alleviating bothersome urinary symptoms associated with BPH. Also, these authors reported that the comparison of the two laser-based modalities recorded low perioperative morbidities. It has been reported that a one year follow-up on a pilot study using a high-power thulium laser to perform ThuLEP in patients from the general or unselected public showed that both ThuLEP and TURP provided symptomatic relieve of LUTS with a low rate of complications. These findings and others lends credence to each laser therapy as being at par or even superior to TURP as a gold standard surgery for the treatment of BPH. The major setback of laser ablation techniques is that their proper utilization and desired outcomes are dependent on the expertise of the surgeon.

Prostatic urethral lift (PUL): It is a minimally invasive surgical procedure used in the treatment of LUTS secondary to BPH. In 2013 The United States Food and Drug Administration (FDA) approved PUL as a BPH treatment option and since then it has been used by clinicians to a manifold. PUL involves the endoscopic insertion of mechanical implants through the urethra. These implants then retract the obstructing hyperplastic prostatic lobes, keeping them away from the prostatic urethra. It is done using an instrument called Urolift device. The sole aim of PUL is to "create an anterolateral channel from the bladder neck to the verumontanum". The latter is a structure found on the floor of the posterior urethra, distal to the entrance of the ejaculatory ducts and marks the boundary between the membranous and the prostatic segment. PUL is ideal for very large prostates (> 100 mL) of which the observed bladder obstruction outcome (BOO) is due to the enlargement of the lateral lobe. Additionally, it is a viable option for patients with medical history of prior pelvic surgeries or urinary retention. Studies have reported the clinical outcome of PUL to be efficacious, rapid and durable with no incidence of serious adverse effects as seen with other treatment options for BPH and related cases. Findings revealed that the Urolift procedure significantly improved symptom scores, quality of life and preservation of sexual function (i.e. no erectile dysfunction, low libido as well as retrograde ejaculation) [23]. The preservation of sexual function attributed to the PUL procedure is chiefly because it causes no thermal tissue damage to the prostate and surrounding structures or does it threatens the integrity of the bladder neck. Thus, with the integrity of the bladder neck preserved, retrograde ejaculation is significantly ruled out. The tissue-sparing property extensively reduces the risk of erectile dysfunction in men with BPH/LUTS. The procedure is described as safe with mild to moderate, transient and rapidly resolved side effects.

Commonly reported adverse effects are transient post-PUL dysuria, haematuria, urinary incontinence, pelvic pain, urinary urgency etc., which are usually resolved within 1 - 2 week following the Urolift procedure. The major setback of the prostate urethral lift procedure is its retreatment rate (1.4 - 16%) either as repeat PUL, TURP or laser therapy. Nonetheless, with the documented safety and beneficial profile of PUL, it should be considered as effective minimally invasive alternate therapy especially for sexually active men with bothersome LUTS secondary to BPH who are repugnant to pharmacotherapy, TURP and laser surgeries due to associated adverse events.

Other therapies: Several other techniques that utilize the delivery of thermal energy of different levels to induce thermoablation of the prostatic tissue are available. The application of heat on the prostate induces tissue necrosis and the necrotic prostatic tissues are sloughed. This causes significant reduction of the prostate volume and thus relieves BPH-mediated BOO and LUTS. These techniques include microwaves, radiofrequency, ultrasound and water-induced thermotherapy. Their route of administration can be any of the following: intraurethral, interstitial, transrectal, and recently transperineal and is dependent on the expertise of the physician.

Future and/or novel options

This review demonstrates that within the past decade, there has been an active-continuous progress in the field of BPH therapy. As with other disease conditions, medicine is an ever-changing field of endeavour, thus as our understanding of the anatomy and pathophysiology of the prostate, urinary bladder and surrounding structures especially at the molecular level deepens, newer approaches (drugs and devices) for the treatment of BPH ensues. With respect to medical therapy for BPH, numerous researches done in this field aims at investigating the role of inflammation, the vitamin D receptor (VDR) signalling pathway and β_3-receptors agonist in BPH patients experiencing LUTS.

Anti-inflammatory mediators: The pathogenesis and progression of BPH is associated with inflammation. These authors demonstrated that the active involvement of proinflammatory cytokines and other inflammatory mediators increases the risk of BPH. Since the cyclooxygenase (COX) pathways are activated during inflammation, the pharmacological usefulness of non-steroidal anti-inflammatory drugs has been postulated [24]. Significant improvement in symptom scores has been reported with the combination of finasteride and rofecoxib (COX-2 inhibitor) compared to monotherapy. Nonetheless, clinical evidence on the use of COX inhibitors in the management of BPH is still lacking and thus their exploitation in the treatment of BPH should be experimental.

Nanotherapy: The effect of gold nanoparticles on testosterone-induced BPH was studied in a rat model. The findings of the study demonstrated first-hand that gold nanoparticles (AuNPs) can inhibit the testosterone-induced BPH progression in a size-dependent manner [25]. The authors reported that while treatment with 20 nm AuNPs ameliorated BPH chiefly by significantly reducing the elevated inflammatory mediators (TGF-β1, IL-6, and VEGF-A) in the prostatic tissue, thus inhibiting prostatic cell proliferation, inflammation and angiogenesis, the 50 nm AuNPs rather caused significant elevations of these endogenous biomarkers of inflammation. Also, only treatment with 20 nm AuNPs restored the histomorphological alterations observed in the rats' prostate. The authors therefore concluded that by enhancing the inflammatory process, larger sized AuNPs could rather aggravate the development of BPH instead of ameliorating it.

Vitamin D receptor (VDR) signalling pathway agonists: Studies have postulated the association of VDR signalling pathway BPH-mediated LUTS [26]. The pathophysiology of BPH suggests prostatic cell proliferation due to the activity of testosterone and other androgens. Based on this probable mechanism, the apoptotic and anti-proliferative potential of elocalcitol, a synthetic VDR agonist has been studied, with positive outcome. Elocalcitol has been described with the potentials to likely inhibit cellular proliferation of the prostate gland mediated both by androgens and other factors. Also, elocalcitol reportedly blocked the NF-kB pathway, causing significant decrease in the secretion of IL-8 by inflammatory cells localized in the prostate gland [26]. Findings from a phase II randomized clinical trial of 57 men with prostate volumes ≥ 40 mL treated with elocalcitol for 3 months presented a significant reduction of prostate growth compared to placebo. Despite its safety profile in humans, elocalcitol demonstrates limited efficacy on BPH-mediated LUTS. There is an on-going clinical evaluation on its potentials and candidacy as a therapeutic agent in the pharmacotherapy of BPH and overactive bladder (OAB).

B_3-receptors agonists: Molecular studies of the bladder reveal that β_3-receptor subtype is the most predominant β-adrenoceptor. When the β_3-adrenoceptors are activated, the bladder increases it capacity; however, this occurs without any change in micturition pressure, residual volume, or voiding contraction. In a randomized, double-blind, phase II study involving 200 men experiencing BOO, Nitti., *et al.* [27] reported that that treatment with mirabegron, a β_3-receptor agonist (50, 100 mg or placebo) effectively reduced urinary urgency and frequency especially at 50 mg/kg body weight of mirabegron. These significant findings support the utilization of mirabegron as a second line therapy for BPH and OAB following failure of muscarinic receptor antagonists. In a randomized phase 4 study (PLUS), Kaplan., *et al.* [28] investigated the efficacy and safety of mirabegron add-on therapy in men with overactive bladder symptoms treated with tamsulosin for any underlying LUTS secondary to BPH and reported superiorly enhanced effects of tamsulosin plus mirabegron in reducing frequency of micturition, mean volume voided per micturition, urinary urgency amongst other scores compared to tamsulosin plus placebo. The findings suggest the utilization mirabegron add-on therapy in the management of OAB attributable to BPH.

Intraprostatic injections: Furthermore, intraprostatic injections such as botulinum neurotoxin A (BoNT-A), NX-1207 and PRX302 are also being investigated for the management of BHP-mediated BOO and other LUTS [29]. BoNT-A down-regulates the alpha 1a receptors with a resultant significant reduction in bladder contractility [8]. PRX302 is a bacterial protoxin activated by the activities of the prostate specific antigen (PSA). It binds to cellular membranes, creating transmembrane pores that induce lysis and prostatic involution. PRX302 have been reported to cause extensive, organ-confined prostatic shrinkage in animal models. In a human phase II trial, a relatively small sample (n = 18) who received intraprostatic injection of PRX302 is associated with interesting preliminary outcomes. Interestingly, none of the patients studied presented distorted sexual function post-intraprostatic injection [30]. Despite the intriguing outcome, PRX302 is still considered an experimental agent especially as the small study population limits its full utilization. NX-1207 causes atrophy of the prostate by inducing prostatic apoptosis. In animal models, Shore [31] reported that the protein molecule promotes focal apoptosis, significantly reducing prostate volumes. Also, some human phase II studies associated intraprostatic injection of NX-1207 with significant reduction of American Urological Association (AUA) Symptom Score with no bothersome adverse effects [31]. Currently, we are still expecting results from 2 phase III clinical trials so as to determine the candidacy of NX-1207 for the pharmacotherapy of BPH and associated symptoms.

Prostate artery embolization (PAE): This is a minimally invasive interventional radiology technique that is promising as a viable treatment option for BHP. From inception, PAE was developed to manage prostatic bleeding secondary to other prostatic disorders. However, it was later utilized in the treatment of BPH due to reported significant alleviation of LUTS alongside satisfactory bleeding outcomes [32]. Several clinical trials have reported PAE to be associated with improved symptom scores and QoL etc. [32,33]. As of now, the use of PAE for treatment of BPH-associated LUTS is still experimental. Due to concerns about its safety profile including radiation exposure, vascular access and post-embolization syndrome, PAE is not recommended by the AUA for treatment of LUTS secondary to BPH outside the context of clinical trials [32].

Transurethral water vapour therapy (Rezum system): The Rezum system (NxThera, Maple Grove, MN, USA) is a novel, minimally invasive ablative transurethral therapy. It utilizes stored thermal energy (from sterile water vapour) delivered directly to the transition zone of the prostate gland to treat BPH. When in contact with the hyperplastic prostatic tissue, the water vapour rapidly condenses into its liquid state, releasing the stored thermal energy which then induces instant denaturing of the cell membranes and cell death occurs. Currently, the Rezum system is considered an investigational device. There is an on-going prospective, randomized, controlled, single-blind clinical trial in the United States of America (ClinicalTrials.gov identifier NCT01912339) evaluating its efficacy and safety as a potential surgical intervention for LUTS secondary to BPH.

Fractionation of prostatic tissue: This novel concept is based on the development of new technologies able to deliver high intensity energy enough to cause tissue emulsification without thermal effects. Two cutting edge technologies are under development, and are considered as experimental treatments under investigation, i.e. histotripsy and aquablation. The former is a technique initially conceived and

developed at the University of Michigan. It uses acoustic energy to breakdown or fractionates the prostatic tissue. The physical mechanism is similar to shockwave lithotripsy. The acoustic energy comes as short pulses but with very high intensities that induces mechanical homogenization of the prostatic tissue. Aquablation is a novel minimally invasive transurethral surgical intervention for BPH [34]. The procedure employs a robot-assisted, high-velocity waterjet with transrectal ultrasound guidance (AquaBeam, PROCEPT BioRobotics Inc., Redwood Shores, CA, USA). The resection of the prostatic tissue is done without any thermal energy but with a high-pressure saline stream to remove parenchymal tissue through the mechanism of hydrodissection. It represents one of the latest robotic technologies in the field of urology.

Alternative treatment options

Complementary and alternative therapies (CAM): Acupuncture and moxibustion are the most commonly used CAM in the treatment of BPH. In a systematic review on the effect of acupuncture on BPH, Zhang., *et al.* [35] reported that acupuncture caused significant changes in the short-term follow-up endpoints in patients with moderate to severe BPH. A meta-analysis of clinical trials examining the use of moxibustion, (a form of Chinese traditional medicine in which dried plant materials called moxa are burned on or very near the surface of the skin) suggested that it is also effective in treating BPH patients [36].

Phytotherapy: Plant extracts and their derivatives have been exploited either as adjuvant or as mainstay in the phytotherapeutic management of mild-to-moderate LUTS secondary to BPH. Clinical trials have shown efficacy in the treatment of BPH-mediated LUTS; however, many products are not standardized and there is paucity of data on the long-term safety of these products. *Prunus africana* and *Serenoa repens* (saw palmetto) are the major plants extracts that have been extensively studied as therapy options for BPH management. Others include *Cucurbita pepo, Urtica dioica, Pygeum africanum,* etc. Despite the on-going clinical trials of these products, none of the alternatives (CAM and Plant-based therapies) to the conventional therapies (medical and surgical) are recommended by AUA for the treatment of LUTS secondary to BPH. It is imperative to weigh the risks against the possible benefits of all available alternative treatment options so as to make sound informed decisions.

***Prunus africana*:** *P. africana* bark extracts have been exploited as herbal or dietary supplements for the treatment of BPH. It received its patent for use in the treatment of BPH in 1966. Nyamai., *et al.* [37] demonstrated its ethnopharmacological usefulness in relieving LUTS secondary to BPH. Clinical trials have associated administration of *P. africana* extracts with significant reduction of prostate volumes, improved symptom scores, and clearance of BOO. The tree bark contains pentacyclic triterpenoids, phytosterols and ferulic esters of long-chain fatty alcohols as groups of bioactive phytochemical constituents. It has been reported that the efficacy of *S. repens* and *P. africana* is equivalent to that of α-blockers and finasteride.

***Serenoa repens*:** Herbal preparations from saw palmetto are used to improve symptoms of benign prostatic hyperplasia. 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. 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. This extract also reduces testosterone binding globulin levels. Administration of saw palmetto berry extracts reduces the action of dihydrotestosterone androgen by blocking alpha-adrenergic receptors. 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. Sudeep., *et al.* [38] compared the efficacy of β-sitosterol enriched saw palmetto oil (VISPO) and conventional saw palmetto oil (SPO) extracted using supercritical fluid extraction, in alleviating the BPH complications using testosterone-induced BPH model rats and reported that VISPO exhibited superior efficacy compared to SPO made possible by the significant reduction in prostate weight, serum testosterone level as well as enhanced growth inhibition of prostate tissue compared to BPH group (untreated). Also, VISPO showed better attenuation

of the prostatic hyperplastic patterns as evident from the histological examination of prostate tissue compared to SPO. Furthermore, the authors stated that VISPO significantly regulated the expression of inflammatory and apoptotic marker proteins in BPH rats, and concluded that their findings gives credence to the exploitation of β-sitosterol enriched saw palmetto oil compared to the conventional saw palmetto oil preparations in the treatment of BPH-associated complications.

Combined *Sabal* and *Urtica* extracts (WS® 1541): This is a plant-based formulation made up of *Sabal serrulata* fruits extract (WS® 1473) and *Urtica dioica* root extract (WS® 1031). Pigat., *et al.* [39] reported the efficaciousness of WS® 1541 to attenuate the histopathological hallmarks of BPH in a validated preclinical model, including tissue growth and stromal inflammation. The molecular profiling of prostate glands eviscerated from mice administered WS® 1541 revealed that the herbal formula exerted an inhibitory effect on the expression of several pro-inflammatory mediators (e.g. cytokines, chemokines etc.), down-regulating their receptors. Also, WS® 1541 had inhibitory effect on enzymes and growth factors involved in the pathogenesis and progression of BPH. Their findings validate the ethnobotanical usefulness of WS® 1541 in the treatment of BPH and associated symptoms.

Moringa oleifera: In 2017, Ishola and colleagues evaluated the effect of the subacute administration of ethanol leaf extract of *M. oleifera* on testosterone-induced BPH in a rat model. From their findings, *M. oleifera* leaf extract reversed the pathological indices such as distorted levels of prostate tissue antioxidant enzymes (GSH, CAT, SOD, etc.), elevated prostate weight, increased prostate index (PI), increased serum levels of testosterone and PSA as well as the histomorphological alterations caused by subcutaneous administration of testosterone to the experimental animals. The authors attributed the observed pharmacological effect to the intrinsic potent antioxidant properties of the plant extract and suggested that plant extract may be exploited as an adjuvant in the therapy of BPH [40].

Paecilomyces tenuipes: *P. tenuipes* is a mushroom that has been popularized by the artificial cultivation of fruiting bodies based on silkworms by researchers from the Republic of Korea. Choi., *et al.* [41] studied the effect of *P. tenuipes* on testosterone-induced BPH in a rat model and their findings lends credence that the plant extract improves symptoms associated with testosterone propionate-induced BPH in rats. The authors partly attributed their findings to decreased levels of dihydrotestosterone in the prostate as well as the inhibition of androgen receptors (AR), 5α-reductase type 2 (5AR2), and PSA protein expression in prostate tissue. As a result, these changes caused significant shrinkage of the rats' prostate. Furthermore, the authors suggested that *P. tenuipes* may possess pharmacological potentials that can be exploited in the therapy for BPH and thus concluded it could be used as a functional food for BPH.

***Rhodobacter sphaeroides* extract lycogen™:** This is a commercial carotenoid product derived from the extracts of the photobacterium *R. sphaeroides* WL-APD911. It is a potent antioxidant and anti-inflammatory agent. Wang., *et al.* [42] studied the attenuating effects of Lycogen™ on testosterone-induced BPH in a rat-model. The extract was reported to significantly cause a dose-dependent decrease in prostate index (PI) as well as reversed the prostatic histopathological outcomes of exposure to testosterone in the experimental rats. The authors concluded that Lycogen™ may be utilized in the prophylaxis and management of BPH.

Lespedeza cuneata: The 6 weeks administration of *L. cuneata* (25, 50 and 100 mg/kg) to testosterone-induced BPH rats decreased the expression of prostatic inflammatory mediators, proliferating cell nuclear antigen (PCNA) and fibroblast growth factor-2 (FGF-2) as well as respectively inhibited serum dihydrotestosterone levels (54.5, 51.2 and 54.1%) and mRNA expression of 5a-reductase (54.3, 61.3 and 73.6%). Furthermore, the authors reported the plant extract to be inhibitory to the transcription of AR and PSA in a human BPH cell line type (BPH-1), and thereby concluded that the plant extract is a novel pharmacological candidate for the treatment of BPH [43].

Standardized *Cornus officinalis* and *Psoralea corylifolia* L. extracts (HBX-6): HBX-6 is a laboratory reconstituted herbal formula from two medicinal plants; *C. officinalis* and *P. corylifolia.* Jin., *et al.* [44] reported the inhibitory effect of the formula on cellular proliferation of the prostate superior to that of finasteride in a testosterone-induced BPH mouse model. The authors demonstrated that HBX-6 attenuated the observed pathological abnormalities of the prostate induced by testosterone administration. The molecular mechanism for this pharmacological action was attributed to inhibition of the E2F1-Rb pathway and decreased expression of cyclin D1. Based on these results, the authors strongly suggested the exploitation of HBX-6 as a therapeutic agent for the medical therapy of BPH.

Cynanchum wilfordii: Lee., *et al.* [45] investigated the protective effect of an aqueous extract of *C. wilfordii* (CWW) against BPH development in a testosterone-induced BPH rat model and reported significant prostate growth inhibition rates across all the treatment groups of experimental rats. These authors also reported a mechanistic downregulation of mRNA expression levels of the androgen receptor, 5α-reductase, and B-cell lymphoma-2 (Bcl-2) in the BPH/CWW200 group compared with those in the testosterone-induced groups and concluded that CWW effectively slows the progression of testosterone-induced BPH in rats.

Botanical formulation HX109: HX109 is a polyherbal botanical formulation that comprises of *Taraxacum officinale, Cuscuta australis* and *Nelumbo nucifera* extracts. These medicinal plants have been exploited traditionally in the treatment of urinary diseases. According to Lim., *et al.* [46], the oral administration of HX109 ameliorated prostate enlargement and histological changes induced by testosterone propionate in a testosterone propionate (TP)-induced prostate hyperplasia rat model. The authors also reported the repressing potentials of HX109 on AR-mediated cell proliferation as well as the induction of androgen receptor (AR) target genes at the transcriptional level without affecting the translocation or expression of AR in a human prostate epithelial cell line (LNCaP cells) and strongly suggested that HX109 might be a potential candidate for the development of therapeutic agents for the treatment of BPH.

Cinnamomi cortex (dried bark of *Cinnamomum verum*): This medicinal plant is regarded as a very important drug in Traditional Korean Medicine, especially as it is used to enhance blood circulation. Choi., *et al.* [47] assayed the effect of Cinnamomi cortex aqueous extract on BPH in a testosterone propionate-induced BPH rat model and reported the plant extract to cause significant reduction of the prostate weight and prostatic index. The authors further stated that the histological changes induced by testosterone administration were reversed by treatment with Cinnamomi cortex extract. The plant extract also significantly suppressed or downregulated the expressions of prostate specific antigen, estrogen receptor α (ERα), androgen receptor (AR), 5α-reductase (5AR) and steroid receptor coactivator 1 in the testosterone-induced BPH rat model. According to the authors, these findings strongly suggest Cinnamomi cortex as a potential drug candidate that should be exploited in the treatment of BPH.

Ponciri fructus: *P. fructus* are widely used in traditional oriental medicine for the therapy of various diseases. Jeon., *et al.* [48] investigated the protective effects of a *P. fructus* extract (PFE) on the development of BPH in a testosterone propionate-induced BPH rat model. From their findings, PFE caused significant reductions in relative prostate weight, the serum and prostatic tissue testosterone and DHT levels, prostatic hyperplasia, and expression of PCNA. Also, the plant extract significantly increased the antioxidant enzymes and inhibited the development of BPH. However, PFE showed a weak inhibitory activity on 5α-reductase. The authors attributed the antiproliferative and antioxidant properties to the phytochemical constituents of the plant material and concluded that their findings suggest that PFE could be exploited as a therapeutic agent for the treatment of benign prostatic hyperplasia.

***Croton membranaceus*:** Asare., *et al.* [49] validated the use of freeze-dried *Croton membranaceus* ethanolic root extract (CMRE) in the treatment of benign prostatic hyperplasia and reported that 33 patients were observed pre-and- post (90 days) oral administration of 20 mg CMRE t.i.d. Of this population, 30 patients completed the study. The IPSS results showed 37% had severe, 40% moderate, and 23% mild symptoms pre-treatment with CMRE; while 57% and 43% had moderate and mild symptoms, respectively, post-treatment with CMRE. The IIED results showed patients with severe (30%), moderate (40%), mild-moderate (24%), mild (3%), and 3% no erectile dysfunction prior to treatment and 20% severe, 43% moderate, and 37% mild-moderate dysfunction, post-treatment. Treatment with CMRE caused significant but non-pathological increases in total and indirect bilirubin as well as apolipoprotein A. Also, a significant reduction in tPSA, fPSA and prostate volume were recorded. The authors concluded that *C. membranaceus* shrinks the prostate and improves QoL.

Conclusion

In recent decades, there has been a proportionate growth in treatment options for BPH. It is therefore imperative that physicians determine optimal and suitable management modalities (medical/pharmacotherapy or surgical interventions) for individual patients. Such determination takes into consideration the patients' and physician's preference as well as the surgical candidacy. As with any other dis-

ease, it is important that clinicians discuss the risks, benefits, side effects, and alternatives before deciding on a treatment plan for patients with BPH. The changing nature of modifiable risk factors for BPH necessitates further research into optimizing treatment rationale for the disease. The two common uncontrollable risk factors of BPH are age and family history, however, it is worth noting that lifestyle modification (regular exercise, proper diets, rest, moderate alcohol consumption, normal weight level amongst others) which on its own cannot prevent BPH, significantly reduces the risk of BPH development. This review attempts to consolidate past, current, emerging as well as alternative therapy options for BPH and highlights the need for additional investigation on optimizing treatment selection by clinicians.

Conflict of Interest

Authors have declared that no competing interests exist.

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