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Common biological factors implicated in benign prostatic hyperplasia and prostate cancer, conventional and phytotherapeutic approaches employed in management: A review

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Abstract

Introduction: Benign Prostatic Hyperplasia (BPH) and Prostate cancer (PC) are diseases affecting the prostate glands of aging men.

Objective: We reviewed common biological factors in BPH and PC, conventional and phytotherapeutic approaches employed in both conditions.

Method: PubMed, Google Scholar and Web of Science databases were used to search for information using key words, "Common biological factors in BPH and PC", "Conventional approach used in BPH and PC", and "Medicinal plants used in BPH and PC". All 174 articles included in this review were from 1942 to 2023, published in English language as original articles or reviews.

Result: Inflammation, hormones and apoptosis are implicated in both conditions. Conventional interventions include watchful waiting, active surveillance, chemotherapy, immunotherapy, radiotherapy, advanced definitive therapies and surgery. Phytotherapy including *Saw palmetto* believed to inhibit type 1 and 2 isoenzymes of 5α-reductase, *Prunus africana* which possesses anti-inflammatory activity, inhibits synthesis of prostaglandins, aromatase and 5α-reductase activity, suppresses growth factors of the prostate and cholesterol build-up, disrupts congestion of blood vessel, reduce excessive blood, decrease prostate adenoma size, and inhibit cell proliferation in the prostate gland; *Urtica dioica*, *Epilobolium rosmarinifolium*, *Vitex agnus*, amongst others have reportedly demonstrated potentials against BPH and PC.

Conclusion: Researchers give more attention to PC probably because it is more life threatening, even though BPH is more predominant in males than PC. Therefore, it is worthwhile to give more attention to BPH to reduce life-threatening PC.

Keywords: Biological factors; Conventional; Phytotherapeutic; BPH; PC

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1. Introduction

The prostate gland is a walnut-sized organ weighing about 20g in a normal adult, lying below the bladder and surrounds the urethra [1]. In mammals, the secretions from the gland are emptied into the urethra during ejaculation, contributes to seminar fluid and increases the viability of sperm, thereby enhancing occurrence of fertilization between the male's sperm and the female's ovum [2].

The urethra is a tube-like organ which also connects to the urinary bladder where liquid waste in the form of urine are emptied from the kidney after performing its function of blood purification. When the urinary bladder is about 200-300cm^3 filled with urine, it is emptied via autonomic influences through the urethra to the exterior as waste. However, when the prostate gland becomes abnormally enlarged due to effects such as hormonal changes and inflammation, it could lead to a phenomenon known as benign prostatic hyperplasia (BPH), mainly manifesting as histological changes involving presence of stromal glandular hyperplasia within the prostate gland [3].

Benign prostatic hyperplasia (BPH) is basically described as a non-cancerous enlargement of the prostate gland, characterized by rapid proliferation of stromal and epithelial cells of the gland which increases with age [4], [5]. This condition can impair the easy flow of urine through the urethra because of its compressive effects making expulsion of urine difficult, leading to accumulation of urine in the urinary bladder which can therefore lead to disturbing symptoms such as weak urinary stream, nocturnal micturition, frequent urination and urgency with feeling of incomplete bladder emptying, all of which are classified as lower urinary tract symptoms (LUTS) [6]–[8]. The LUTS associated with BPH may also occur as a result of increased tone of the bladder neck smooth muscle and the urethra [9]. Lower urinary tract infections such as bacterial infections which occur as a result of retention of urine in the bladder also characterizes BPH [10]. The disturbing symptoms of BPH may affect patients' quality of life [11], even though it is non-cancerous and can even progress to more life-threatening prostate cancer if not given timely attention [12], [13].

Sources have reported the prevalence of BPH around the world. Histologically diagnosed BPH has a prevalence rate that ranges from 8% in men who are in the age range of 31–40years, 40 to 50 percent in men who are in the range of 51 to 60 years, to over 80% in men who are above 80 years [14], [15]. In 2010, it was reported that BPH affected about 210 million males across the globe which equates to 6% of the population [16]. In 2016 and 2019, an estimated 595.2 million and 305.5 million prevalent cases of BPH among males aged 40 years and above worldwide, were reported respectively, which was forecasted to increase to 373.8 million prevalent cases by 2028 [17]. Men who are older than 50 years of age have a BPH prevalence ranging from 10.6% to 31% as reported in South Korea [18], while in Europe, a prevalence of 10.3% was reported [19]. In 2019, Asia was estimated to have had the largest number of prevalent cases and Oceania was estimated to have had the smallest number of prevalent cases (188.5 million and 2.0 million cases, respectively)[17]. In a study conducted in Nigeria in 2006, it was stated that 25.35% of the study population had BPH-related symptoms [20]. Worthy of note, reports focusing on the prevalence and incidence rate of BPH are insufficient especially in Africa and Sub-Sahara Africa compared to prostate cancer which therefore put the population at risk of prostate cancer since awareness of BPH is reduced due to under-reporting. Therefore, it is of great importance to give serious attention to BPH to avoid or reduce the cases of the more life-threatening PC.

Prostate cancer (PC) represents the most common non-cutaneous cancer that affects the aged male population globally [21]. In the year, 2020, about 1,414,259 new cases of PC were recorded worldwide, while Africa recorded 77,300 new cases of PC in 2020 [22]. Due to this trend, about 2.3 million new cases and 740 000 deaths have been forecasted to occur by 2040, globally [23]. In 2007, it was reported that PC affected 1 out of 6 men [24]. Consequently, in 2006, PC was ranked the third leading cause of cancer-related deaths among men in the USA in 2006 [25] and more recently, in 2021, PC was ranked the second most common form of cancer affecting the elderly male population, and also the fifth most significant cause of cancer-associated mortalities in the world [26].

Several factors have been reported to be associated with the incidence of these two related conditions that affect the prostate gland, as well as different treatment options which have been employed in their management over the years. In this study, we conducted an updated review of the common biological factors associated with their occurrences, as well as the conventional and phytotherapeutic approaches employed in their management.

2. Methods

The databases such as PubMed, Google Scholar and Web of Science were used to search for the required information using the key search words "Common biological factors in benign prostatic hyperplasia and prostate cancer", "Conventional approaches used in management of benign prostatic hyperplasia and prostate cancer", and "Medicinal

plants used in benign prostatic hyperplasia and prostate cancer". All articles included in this review were from 1942 to 2023, published in English language which were accessed in full as either original articles or reviews. Paper titles and abstracts were carefully checked to ensure compliance with required information and articles which did not contain the needed information afterwards, were excluded. A total of 195 full articles were accessed and thereafter, 21 articles which did not meet the set criteria of the required information were excluded, leaving 174 articles which were considered in this review.

3. Results

A total of 174 articles were included in this review. We found that common biological factors implicated in the pathogenesis of BPH and PC include hormones, apoptosis and inflammation. It was also found that the conventional approaches used for the management of BPH and PC include watchful waiting, active surveillance, chemotherapy, immunotherapy, radiation therapy, advanced definitive therapy and surgery, while quite a number of medicinal plants have also demonstrated potentials against these prostatic conditions.

3.1. Androgens and Roles in BPH and PC

Our search revealed that part of the predominant biological factors implicated in both BPH and PC are androgens, predominantly testosterone. Dihydrotestosterone (DHT), the active form of testosterone, provokes prostatic glandular epithelial growth and it has been implicated as a leading cause of prostate enlargement. The enzyme, 5α- reductase has been implicated in the pathogenesis of the disease. 5α-reductase converts testosterone to dihydrotestosterone (DHT) which is the active form of the hormone believed to contribute to stimulation of the prostate gland resulting to its abnormal enlargement [27]. Studies demonstrated that men lacking 5α-reductase had hypoplastic prostates [28]. The inhibition of 5α-reductase type II by finasteride, an effect which halts synthesis of DHT, leading to a decrease in growth of the prostate, also validates the involvement of DHT in BPH. High levels of DHT may lead to an increase in prostatic growth [29], and this is corroborated by the report that PC do not affect eunuchs but its incidence was higher in men who used androgens as anabolic agents or therapeutics [30].

3.2. Estrogen and Roles in BPH and PC

Our search showed that the pathogenesis of BPH and PC implicates estrogen. The enzyme, aromatase has been implicated in these conditions. Aromatase converts androstenedione to estrone and estradiol which are forms of estrogen. Estrogen is believed to play a role in the abnormal enlargement of the prostate gland by increasing the expression of androgen receptors thereby increasing the effect of dihydrotestosterone on the prostate [27].

In a previous study, human prostates were found to contain receptors for estrogen and enzymes involved in estrogen biotransformation [31]. The growth and differentiation of the prostate gland could be modified by estrogen due to report that an environment with abundance of estrogen may result to high synthesis of androgen receptors thus enhancing the enlargement of the prostate by causing prostatic sensitization to androgens [27]. It is hypothesized that the prostate synthesizes estrogens locally for epithelial and stromal cells modulation. This is supported by studies which demonstrated that selective estrogen receptor modulators combined with 5-α reductase inhibitors showed significant efficacy in reducing stromal cell proliferation in human BPH [32].

The enzyme, aromatase, catalysis the conversion of androstenedione to estrone. Further evidence from studies support claims that estrogens are implicated in the initiation and progression of PC. These studies reported that DNA synthesis and metaplastic epithelial morphology were stimulated by estrogens in both human [33] and rat prostate [34]. In another study, carcinogenesis was reportedly stimulated in adult male rats due to exposure to high doses of testosterone in combination with estradiol [35]. It was also reported that PC did not occur in estrogen deficient mice whose aromatase genes were deleted [36]. Epidemiological studies have also shown that high serum levels of estrogens is associated with higher risk of developing PC in men [37].

3.3. Apoptosis and Roles in BPH and PC

Our results also revealed that apoptosis is involved in both BPH and PC. Apoptosis is a physiological regulatory mechanism which involves a series of molecular events culminating in cell death. Increased expression of growth factors or other proteins, which are key players in apoptosis may result to an overall enhancement of cellular growth [39].

One of the most significant defenses against cancer is apoptosis as it eliminates abnormal cells. Therefore, the pathogenesis of cancer is very much associated with under-activity of apoptotic mechanism. The over expression of Bcl-2, an anti-apoptotic protein, has been linked with resistance to androgen ablation and poor remission in some PC

patients who went through radiotherapy [40]. Furthermore, it was reported that the deficiency of p53 and Rb tumour suppressors which are pro-apoptotic proteins in the epithelium of the prostate led to metastatic cancer in mice [41].

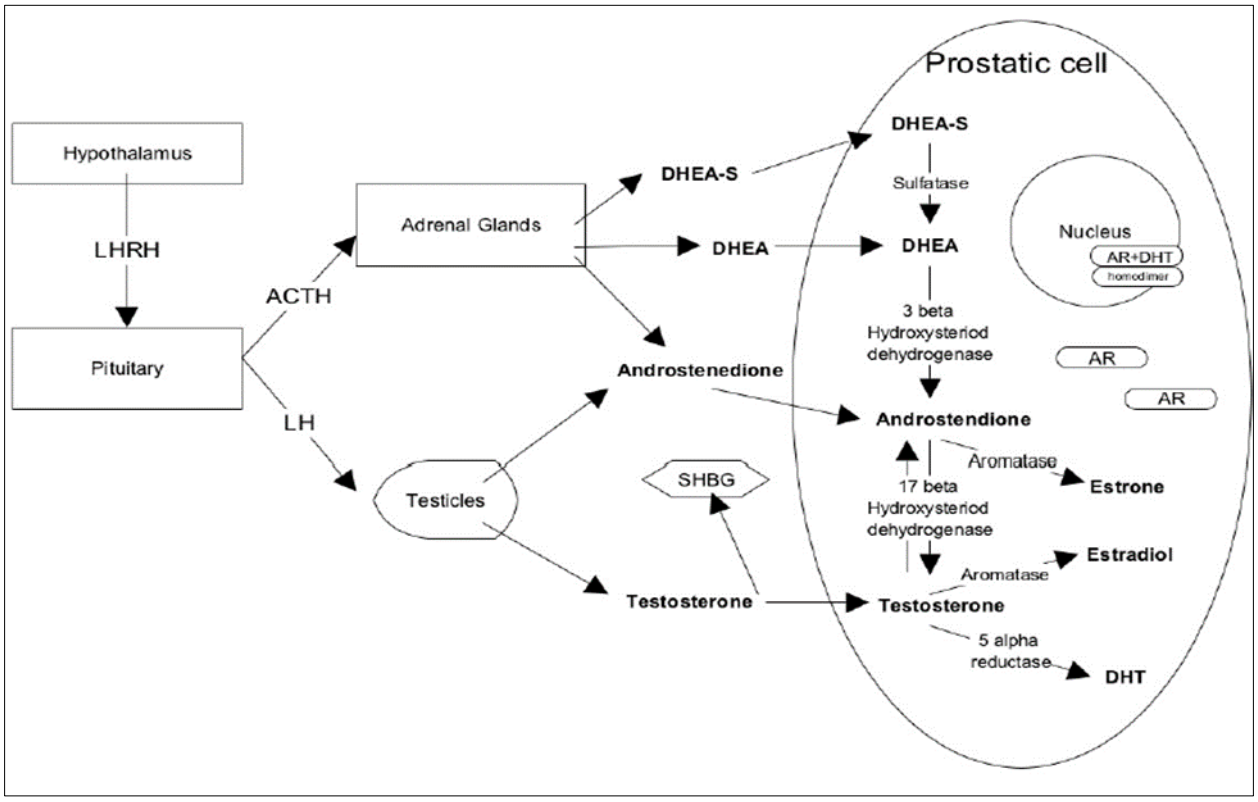

Figure 1 Biosynthesis of androgens and estrogens [38]

3.4. Inflammation and Roles in BPH and PC

Inflammation is also implicated and common in both BPH and PC causing abnormal cell proliferation of the prostate gland as inflammatory mediators such as interleukin 6, prostaglandin E2 and Leukotriene B4 have been seen expressed in the tissues of people with these conditions.

Histological studies found inflammatory cells of various densities in BPH tissues in 30% to 50% of cases [42]. Macrophages and lymphocytes are known to release growth factors such as bFGF, and cytokines including IL-1 and IL-6. Initiation and progression of chronic immune response and induced fibromuscular growth may be provoked by IL-6, IL-8, and IL-17 via induction of cyclo-oxygenase 2 (COX-2) expression [43]. The conversion of arachidonic acid to prostaglandins is usually catalyzed by COX-2, and prostaglandins play pivotal roles in mediating and moderating inflammation which promotes BPH progression [43].

Furthermore, CYP19, an aromatase gene is regulated by a promoter (PII), which responds to stimulation by inflammatory cytokines [44]. In addition, further evidence suggests correlation between chronic inflammation and risk of PC. Besides being inflammatory mediators, tumour promotion, progression and metastasis are believed to be driven by the eicosanoids which are generated by the cyclo-oxygenases (COXs) and lipoxygenases (LOXs) pathways. A marked increase in 5 and 12-LOX expressions were dominant in prostatic intraepithelial neoplasia (PIN) and PC tissues compared to low amounts found in BPH and normal prostate tissues [45]. Furthermore, LOX inhibitors reduced the growth of PC cell lines via apoptosis, in a dose dependent manner [45]. Moreso, the use of NSAIDs was reportedly associated with a reduced risk of PC [46].

3.5. Conventional Approach Employed in BPH and PC

There are basically three treatment approaches of BPH involving stages such as watchful waiting, medications, and surgical intervention [47] (Table 1). Studies have shown that watchful waiting, an active monitoring of patients with BPH symptoms is an appropriate management option for patients who surgery is not indicated [48], [49]. Whereas watchful waiting which involves the implementation of dietary changes, exercise, education, and regular review is

recommended by the American Urological Association (AUA) for patients yet to be affected by mild LUTS [50], it is ineffective and not advisable for patients who experience severe LUTS, as it may delay timely treatment, hence, such group of patients require timely use of appropriate medications [11]. The goal of therapy is targeted at providing fast and sustained relief of the symptoms as well as control disease progression when symptoms affect quality of life of patients [51].

Conventional pharmacological options include α1-blockers, 5α-reductase inhibitors, or combination of drugs from both classes [50] are the drugs of choice used for BPH [11], [47] which are also used in PC as well [52], [53] (Table 1). It is important to note that the risk of urinary retention or need for surgery cannot be influenced by the use of α-blockers but can be influenced by the 5α--reductase inhibitors which reportedly reduce the risk of these two complications in patients [54], [55]. It was reported in a clinical trial conducted in men with enlarged prostates $\geq$ 30ml, that dutasteride, a 5α--reductase inhibitor, demonstrated significant improvement in symptoms when compared with tamsulosin, an α-1a—blocker [56]. Moreso, the combined use of dutasteride and tamsulosin gave better improvement in symptoms compared with each used as a single therapy [56]. This was corroborated with the outcome of a similar study that used finasteride and doxazosin in combination [57].

Physiologically, when the α1-adrenergic receptors, sub-divided into α-1a, α-1b, and α-1c, which are anatomically located in the bladder neck, urethra and prostate gland are stimulated, there is contraction leading to increase in urethral resistance [58]. Therefore, the α1-blockers on binding to these receptors especially on the urethral smooth muscle cells, cause relaxation in smooth muscle tone, which in turn results to decrease in resistance of the urethra, to facilitate urine expulsion, hence abrogates LUTS [59]. This effect is normally achieved within few days, making α-blockers have relatively quicker effect compared to 5α-reductase inhibitors that may elicit their symptoms-relieving effects in 6 to 12 months, which they do by shrinking the hyperplastic tissue in the prostate via blockade of active dihydrotestosterone (DHT) synthesis, from testosterone [9], [60]. According to reports, the prognosis of low-risk prostate cancer patients may be improved by the 5α-reductase inhibitors such as dutasteride [52], [53] and finasteride [61]. However, finasteride may increase the risk of high-grade Gleason prostate tumours [61].

Several sources have reported associated side effects with the use of these drugs. Patients with prostate conditions whether BPH or PC, who use alpha blockers may experience side effects ranging from postural hypotension which may occur with the less selective drugs such as doxazosin and terazosin, rare dizziness that has been reported with more selective α-1a-blockers such as alfuzosin or tamsulosin, to asthenia, abnormal ejaculation, and intraoperative floppy iris syndrome (IFIS), which could probably be attributed to the anatomical distribution of the various subtypes of the α-1-adrenoceptors [58], [59]. The side effect of postural hypotension associated with the less selective α-blockers can be controlled by slowly increasing doses during treatment and administration at bedtime. Also, α-blockers may occasionally cause retrograde ejaculation [62].

Amongst the US FDA approved α-blockers are alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin [11]. These drugs however differ in their efficacies. For instance, urinary voiding symptoms is better improved with silodosin probably due to its stronger affinity for α1-a-adrenergic receptors [63] compared to tamsulosin, but the associated risk of retrograde ejaculatory side effects was found to be higher with silodosin [64], [65].

Researchers have shed light on the probable mechanism that may be responsible for the ejaculatory dysfunction caused by the α1-adrenergic receptor blockers in BPH patients which include insufficient rhythmic contraction of the muscles of the pelvic floor, and the loss of seminal emission as well as insufficient contraction of the seminal vesicles [66], [67] as a result of the blockade of α1-adrenoceptors located in spermatic ducts and seminal vesicles [68]. On a positive side with the risk of ejaculatory side effect associated with the α1-adrenoceptor blockers, it was reported in another study that alfuzosin could improve ejaculatory function [69]. In the same vein, an α1d-blocker known as naftopidil has been reported to have low risk of ejaculatory problems when used, and in terms of efficacy on LUTS, both silodosin and naftopidil are said to be similar, however, silodosin, an α1a-blocker, has an advantage in terms of alleviating voiding symptoms, but with respect to preserving sexual function regarding ejaculation, naftopidil takes the lead compared to silodosin [70].

Whereas 5 α-reductase inhibitors may interfere with sexual drive, cause gynecomastia, and erectile dysfunction (ED) for some men, they are relatively well tolerated [11], [62]. With respect to the efficacy and safety of both drugs in the 5 α-reductase inhibitors class (dutasteride and finasteride) in treatment of BPH, no obvious differences between them but less sexual side effects and gynecomastia risk is associated with finasteride compared to dutasteride in BPH management [71]. However, worthy of note is that while dutasteride can inhibit both 5α-reductase types I and II, finasteride can only inhibit type I [60].

Other groups of drugs which are also indicated but not commonly used include muscarinic anticholinergic drugs, phosphodiesterase inhibitors, β3-adrenoceptor agonists and plant extracts [47]. The actions of the muscarinic anticholinergic drugs acting as antagonists at the muscarinic cholinergic receptors subtypes M2 and M3, which are distributed in the bladder, urothelium and afferent nerves, leads to relief or reduction of storage symptoms when used in BPH patients. [72]. The US FDA has approved a number of these class of drugs including oxybutynin, tolterodine, darifenacin, solifenacin, fesoterodine, and trospium, which are primarily used to alleviate storage symptoms including frequent micturition, urinary urgency, and urgent urinary incontinence (UUI) that may occur due to LUTS and hyperactive bladder [73]. Reported side effects include pruritus, dry mouth, constipation, dizziness, problem with micturition and nasopharyngitis, with the most common being dry mouth [74]. The occurrence of dry mouth is more common with oxybutynin compared to tolterodine [75]. Besides these mentioned side effects, acute urinary retention (AUR) has been reported as the most serious side effects of the anticholinergic agents [76].

The bladder is dominated by β3-adrenoceptors compared to the other subtypes of β-receptors but the β-receptors are all present in the bladder, urethra and prostate [77]. The β3-adrenoceptor agonists have the primary mechanism of causing decrease in tone of the detrusor muscle and promoting urine storage since β3-adrenoceptor stimulation causes relaxation of the smooth muscle and detrusor, both in the urethra and bladder [78]. The only selective drug for the β3-adrenoceptor approved by the FDA is Mirabegron [11], which is said to be a well-tolerated alternative to the muscarinic anti-cholinergic drugs [79], but its use may be associated with nasopharyngitis, hypertension, headache and urinary tract infections [80].

The type 5 isoform of the phosphodiesterase enzyme (PDE5) is found throughout the urinary tract, prostate tissue, ureter, vascular smooth muscle, as well as the bladder detrusor, The agents which inhibit this enzyme referred to as phosphodiesterase type 5 inhibitors (PDE5Is) cause relaxation of the smooth muscles of the urinary tract and bladder detrusor, hence ameliorate LUTS, with a mechanism involving increase in the intracellular cyclic guanosine monophosphate (cGMP) concentration [81]. The overall pharmacological effect on the smooth muscle of the urinary tract is mediated by the nitric oxide (NO) pathway [82]. Amongst the PDE5Is such as vardenafil, tadalafil, and sildenafil which have reportedly demonstrated activity against LUTS-BPH patients, the only approved drug by the FDA for treatment of patients with BPH is tadalafil [83]. Side effects that may be associated with the PDE5Is include gastroesophageal reflux, nasal congestion, flushing, indigestion, headache and back pain [65].

In recent years, in addition to the earlier known drugs for management of BPH, there has been advances to discover drugs with potentials against the condition. These include an α-adrenoceptor antagonist known as RS17503 which has affinity for α1-adrenoceptor, hence has promising potentials for BPH management, an endogenous organic nitrate referred to as RONO2 which was reported in various *in vitro* studies to increase Q-max and mean voided urine volume with a concomitant reduction in postvoid residual volume (PVR), and International Prostate Symptom Score (IPSS), an antagonist of the vasopressin receptor subtype V1a, known as SR49050 which could also be a good drug for BPH owing to vasopressin's physiological role in smooth muscle contraction in both the prostate and urethra [84], as well as a vitamin D3 agonist known as BXL-628, the only one of them which was tested in clinical trials but didn't pass and was therefore terminated [85]. Worthwhile however to note, that the drug candidates above are yet to be approved by the FDA for BPH treatment especially since they have not all gone through the stage of clinical trials.

The American Urological Association (AUA) guidelines stipulates that surgical approach could be considered for patients with BPH with severe LUTS or other complications such as renal insufficiency, recurrent bladder stones, recurrent urinary tract infections, acute urinary retention (AUR), gross hematuria due to BPH or patients who are hesitant to drug therapy [86]. Apart from Transurethral Resection of the Prostate (TURP) which has been the standard surgical approach, there are other less invasive surgical therapies for patients with severe LUTS, with reduced risk of long term side effects and appreciable improvement in urinary symptoms in ideal patients, which include transurethral laser prostatectomy, transurethral microwave therapy of the prostate, transurethral incision of the prostate, and prostatic urethral lift [9], [86].

Even though for quite a number of years, TURP has been the standard treatment [87], [88], the incidence of post-surgery complications such as bleeding and TUR syndrome (hypervolemic hyponatremia related to absorption of large volumes of irritant) have stimulated interest in search for alternative methods of prostate ablation [9]. To this end, a number of laser procedures have emerged as energy delivery means to the prostate, such as Holmium laser enucleation of the prostate (HoLEP) which recapitulates BPH adenoma excision, mainly conducted by open simple prostatectomy, with equivalent treatment outcome as TURP, though could be a tedious procedure that may not easily be learnt by majority which could therefore hinder massive adoption of the procedure [89].

There are several PC treatments including active surveillance, watchful waiting, prostatectomy, radiation therapy, chemotherapy, immunotherapy and androgen deprivation therapy (ADT) [9] (Table 2). Active surveillance and watchful waiting are two similar but different phenomena. While the former involves almost consistent prostate biopsies and close PSA monitoring and follow up as well as patients need to identify the risk of needing definitive therapy as well as the potential for progression to more life-threatening incurable PC, the latter involves monitoring of men with limited life expectancy or severe comorbid disease for the occurrence of challenging and complicated local extension or metastatic disease before palliative therapy is initiated [9], [90]. Active surveillance was recommended as a first-line option for patients with low-risk of PC [90].

Either prostatectomy or radiotherapy can be used to treat localized PC, and remarkable outcomes have been reported with radical retropubic prostatectomy (RRP) done by experts in surgical anatomy with urinary incontinence occurring in less than 10% of patients [91]. Another surgical method is the robot-assisted laparoscopic radical prostatectomy (RALRP) which has been highly employed [92]. Owing to the advancement in the medical technology, whereby techniques for increasing the radiation delivered to the prostate while excluding the bladder and bowel from being affected have emerged, radiation therapy for prostate cancer has become more effective with less risk of side effects, though bladder or rectal toxicity which present as either haematuria,, haematochezia, or irritative LUTS as well as second malignancy may occur [93]. However, treatment outcomes may be improved by combination of both androgen deprivation therapy (ADT) and radiotherapy [94], [95].

The fast growing advances in the medical field has given rise to the emergence of definitive therapies such as high intensity focused ultrasound (HIFU) and cryotherapy for prostate cancer[96], [97]. The HIFU technique mostly used in the European countries, is a minimally invasive procedure that entails imagery of the prostate with transrectal ultrasound while delivering ultrasound energy to produce tissue heating and cavitation, hence there has been high interest in this technique [98], [99].

Primary and salvage management of PC can be done with the aid of cryotherapy performed through the transperineal route under the guidance of Transrectal ultrasound (TRUS), and associated incidence including local complications such as urethral fistulas can be overcome by improvement in available equipment [100]. This technique recorded a 94% disease specific survival at 5 years [100], [101], however, occurrence of erectile dysfunction (ED) after cryotherapy is high compared to prostatectomy or brachytherapy [102], [103].

Chemotherapy is also employed in the management of PC. Specifically, the taxanes such as docetaxel and cabazitaxel which are sometimes used with a glucocorticoid such as prednisone are used in management of prostate cancer [104], [105]. The mechanism of action of the taxanes in PC involves binding to microtubules and preventing androgen receptor nuclear translocation and causing apoptosis through B-cell lymphoma (Bcl-2) phosphorylation [105]. Reported side effects of the taxanes include neutropenia, febrile neutropenia, and abnormal liver function [104].

Furthermore, a novel immunotherapeutic drug known as enzalutamide has also found its place in the treatment of PC. The drug act by disrupting testosterone's interaction with prostate cancer cells. Specifically, it binds competitively with androgen receptors (AR), hence prevents androgens such as testosterone from binding to AR, thereby preventing translocation of the AR from the cytoplasm to the nucleus. In addition, it inhibits AR binding to chromosomal DNA which stops further transcription of the cancerous genes [106], [107]. Seizure which is usually dose dependent has been reported as a side effect of this drug[107]. Androgen deprivation therapy via orchiectomy, anti-androgens such as bicalutamide and / or leuprolide, an analogue of luteinizing hormone releasing hormone (LHRH), is the mainstay of therapy for metastatic PC [108], [109] (Table 2).

3.6. Plant-Based Approach Employed in BPH and PC

Besides conventional medicine and surgery, there are some popular alternative plant-based therapies. Table 3 shows popular alternative phytotherapeutic medications employed in the management of BPH patients. Extracts from *Saw palmetto*, *Prunus africana, Urtica dioica* L, *Cucurbita pepo* L. and *Secale cereale* L. have been reportedly used in the management of BPH [110]. *Saw palmetto* (*Serenoa repens or Serenoa serrulata)* has a wide patronage in the United States and Europe and has been reported to possess actions similar to finasteride with better safety profile [111].

Observation shows that preparations from *Saw palmetto* especially from the ripe berries helped to improve symptoms of BPH [111]. Studies have also shown that herbal supplements from the species are used to support therapies for men with PC [112]. The herbal preparations of *Saw palmetto* are reportedly more advantageous compared to orthodox medicine because they do not alter prostate specific antigen (PSA) levels unlike drugs like finasteride (Proscar) and are more tolerated [113]. Urinary symptoms have also been reportedly improved by *Serenoa repens.* Inhibition of 5α-

reductase types 1 and type 2, is believed to be the mechanism of action of the herbal preparations of *Saw palmetto* [114]. Liposterolic extracts of *Serenoa repens* have been reported to have anti-inflammatory and anti-estrogenic effects and to inhibit growth factor and prolactin-induced cell proliferation in BPH patients [115].

Moreso, *Serenoa repens* extract also referred to as Permixon at a concentration of 10 µg/mL inhibited over 70% of the activities of 5α-reductase I & II [116], and inhibited aromatase enzyme with IC_{50} of 100 µg/mL [117]. Another study also reported that the plant extract inhibited the incorporation of thymidine in LNCaP and PC-3 cell lines by more than 50% at 100 µg/mL of the extract [118]. The efficacy of Permixon (hexanic extract of *S. palmetto*) was said to be similar to α -blockers and 5α-reductase inhibitors in improving symptoms of BPH patients [119].

Phytochemical screening has shown that the main chemical components in the berries of *Saw palmetto* are fatty acids, monoacylglycerides, polyphenols and phytosterols. The phytosterols and fatty acids are believed to be the biologically active compounds of *Saw palmetto*. The inhibition of 5α-reductase enzyme has been attributed to the fatty acid components of *Saw Palmetto* [120]. Findings have also shown that phytosterols in *Saw palmetto* also inhibits 5α-reductase and BPH symptoms [121]. Generally, the beneficial effects of *Saw palmetto* have been speculated to be due to synergistic effect from both fatty acids and phytosterols.

Prunus africana also known as Pygeum africanum is another novel herbal product that has been proven to be effective in the management of BPH and PC. It is a novel green tree having white or green flowers, growing up to a height of more than 40 meters, from which medicinal preparations are made [122]. The species is said to be geographically located in African mountains at altitudes above 1500 meters, and the bark extracts of *Prunus africana* are used to make capsules for treatment of BPH, while also reportedly powdered and drunk as a tea for inflammation, genito-urinary complaints, kidney disease, malaria, allergies, fever and stomach ache [123], [124]. The use of the bark extract of *P. africana* for treatment of benign prostatic hyperplasia dated as far back as 1966 when a patent was issued for this purpose [125]. The use of the bark extracts has been shown to be effective in reducing LUTS in BPH patients [123], [124]. It was also reported that due to the apoptotic and antiproliferative effect of the bark extracts of the plant, it improved urologic symptoms in prostate cancer patients [126].

Furthermore, extract of *Prunus africana* at a concentration of 600 µg/mL inhibited androgen's action by 40-60 fold [127], and also inhibited the incorporation of thymidine in LNCaP and PC-3 cell lines with an IC_{50} of 2.5 µg/mL [128]. Phytochemical screening has revealed that the bark contains three groups of active constituents which include 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) [123].

The therapeutic effects of *Prunus africana* bark extracts have been attributed to different compounds which act synergistically to counteract the functional and biochemical changes that are involved in BPH [125]. Pentacyclic triterpenes, phytosterols and ferulic acid esters have been identified as the pharmacologic active compounds of the bark extracts of *Prunus africana*. In addition, two new compounds have been identified: 4-O-ß-D-glucopyranosyl- (7,8) dimethoxyisolariciresinol [129] and 24-O-trans-ferulyl-2", 3"-dihydroxy-urs-12-en-28-oic acid [130]. It has been shown that the phytosterols, mainly β-sitosterol, possess anti-inflammatory activity and inhibit the stimulation and synthesis of prostaglandins, aromatase activity and 5α- reductase activity [131]. β-sitosterol reportedly helps in the reduction of high levels of prostaglandins in BPH patients [132] and suppresses prostatic growth factors and cholesterol accumulation. Phytosterols have also been reported to eliminate blood vessel congestion and excess blood and consequently, reduce the size of prostate adenomas. Ferulic esters which are also bioactive components of the bark extracts of *P. africana* have been reported to exert their effects by inhibiting the absorption and metabolism of cholesterol [129]. Abnormally high levels of cholesterol have been implicated in BPH and other cases of enlarged prostate. Inflammation in the prostate which is also involved in the pathogenesis of BPH has also been reported to be inhibited by pentacyclic triterpenoids [133].

Furthermore, flavonoids from the bark extract of *Prunus africana* and the bioactive compounds, Cyanidin-o-galactoside, cyanidin-3-o-rutinoside, procyanidin B5 and robinetinidol-(4-α-8) catechin-(6,4-α) robinetinol which are also members of the flavonoid group are believed to inhibit cell proliferation in the prostate gland [123]. Regarding the safety profile of the plant, *Prunus africana* extract is a well-tolerated and efficacious herbal product for the treatment of BPH-associated symptoms [134]. Remarkable results have been achieved in most clinical trials testing the use of *Prunus africana* in treatment of BPH [135]. Outcome of most of the trials revealed a reduction in urine frequency and increase in urine flow. In trials involving higher doses, it was reported that prostate size and irritative symptoms decreased [136]. Patients who took 200 mg of the extract daily for two months were reported to have shown a decrease in sexual disorders associated with chronic BPH [137]. The extract is reported to be effective in genital infections that is associated with BPH without administration of antibiotics [138]. The bark of *Prunus africana* has also been reported to

possess gamma-tocopherol [123]. Vitamin E (Tocopherol) is known to prevent oxidation and peroxidation of membrane phospholipids and triggers apoptosis of prostate cancer cells [139]. Interestingly, it has also been reported that *Prunus africana* bark also contains selenium and zinc which are believed to help alleviate urinary tract symptoms.

Prostate cancer cells are deficient in selenium and glutathione peroxidase, which are antioxidants that protect cells against hydroxyl radical-induced membrane damage. The protective benefits of selenium are better achieved when its therapy is initiated as early as possible. Selenium can also protect against doxorubicin-induced heart damage and radiation-induced bladder cancer [140]. Furthermore, research has it that zinc deficiency is rampant among aged people [141]. Zinc is known to play an important role in prevention of prostatitis and prostate epithelial cells are reported to secrete zinc which kills bacteria on contact [142].

Furthermore, the extracts from *Cucurbita pepo* L. are also reportedly employed in the treatment of BPH patients [143]. Some other interesting phytotherapeutic agents against BPH include extracts from the fruits of *Brahea aramata* [144] and Cuban royal palm [145], which also belongs to the same Arecaceae family as *Saw Palmetto*. Others are Lycopene, the primary carotenoid in tomatoes [146], Silymarin, polyphenolic flavonoid from *Silybum marianum* [147], Indole-3-carbinol, a naturally occurring compound found in vegetables of the Brassica genus [148] and Isoflavones from Soya extracts [149].

Urtica dioica is another plant whose ethanol extracts reportedly inhibited aromatase activity with IC_{50} of >100 µg/mL [117]. Also, the anti-inflammatory, anti-androgenic and anti-proliferative effects of *Epilobolium rosmarinifolium* also known as *Epilobolium* willow herb has also been reported. At 75-100 µg/mL, the extract of *E. rosmarinifolium* inhibited incorporation of thymidine in PZ-HPV-7 cell line [116]. Also, the enzyme, 5α-reductase, was inhibited by *Epilobolium parviflorum* extract with IC_{50} of 160 µg/mL [150]. The extract of *Vitex agnus-castus* fruit at 10-30 µg/mL also demonstrated anti-proliferative activity against prostate cancer cell lines, an inhibition of 50% [151].

Whereas there have been some controversies with respect to recognition and approval of the use of phytotherapy in the management of BPH and PC by the European Association of Urology (EAU) and American Urological Association (AUA) probably due to the issues surrounding methods and heterogeneity during the so far conducted clinical trials [11], in the United States and various European countries such as Poland, France, Hungary and Germany, phytotherapy have been prescribed in clinical practice for patients with BPH who are uncomfortable with the use of standard medical treatments [152]. Quite a number of medicinal plants of Indian origin have also been reported to possess interesting properties against prostatic diseases such as BPH [1], [153] (Table 3).

Table 1 Approaches including Watchful Waiting, Surgical Interventions and Conventional Medications Targeted at Interference with Sympathetic effect and Change of Hormonal Status in BPH Treatment

Approach	**Mechanisms**	***Primary effects***	**Examples**	**Side effects**
Watchful waiting	Active monitoring of patients with BPH symptoms through implementation of dietary changes, exercise, education, and regular review [48]–[50]	Since LUTS can signify a number of other disease states, the patient evaluation, which includes a digital rectal examination, will allow time for careful diagnosis [154]	NA	May delay timely treatment for patients who experience severe LUTS [11]
Surgery	Surgical removal of excess prostate tissue Laser enucleation of the prostate	Improved LUTS	Transurethral resection of the prostate (TURP) [88], [155] Holmium laser enucleation of the prostate (HoLEP) [89]	Bleeding and TUR syndrome (hypervolemic hyponatremia related to absorption of large volumes of irritant)[9].

α1-adrenergic receptor blockers (non-selective) [11], [47], [50]	Blocks α-adrenoceptors, which cause the contraction of smooth muscles in the prostate and bladder.	Leads to relaxation of the bladder and prostate muscles, leading to symptoms relief of BPH (difficulty in urination).	Terazosin, Doxazosin,	Postural hypotension, Dizziness, asthenia, abnormal ejaculation, and intraoperative floppy iris syndrome (IFIS), which could probably be attributed to the anatomical distribution of the various subtypes of the α-1-adrenoceptors [58], [59]
Selective α1-adrenergic receptor blockers [11], [47], [50]	More selective α1-adrenoceptor blockers which are the dominant α-adrenoceptors in the prostate.	Specifically for symptomatic treatment of BPH.	Tamsulosin Silodosin Alfuzosin	Headache, dizziness, abnormal ejaculation, Retrograde ejaculation, dizziness, diarrhoea Dizziness, upper respiratory tract infection, headache [11]
5α-reductase type II inhibitor [11], [47], [50]	Inhibition of the conversion of testosterone into DHT by 5α reductase Type II.	Halts the growth of the prostate.	Finasteride	Erectile dysfunction, decreased sex drive, gynaecomastia. [11], [62]
5α-reductase types I & II inhibitor [11], [47], [50]	Inhibits the conversion of testosterone into DHT by targeting both isoforms of 5α-reductase.	Reduce DHT production. hence, halts the growth of the prostate.	Dutasteride	Similar to finasteride
Muscarinic receptors antagonist [72]	Inhibits M2 and M3 receptors which have roles in the control of urinary bladder function.	Relieves LUTS	Tolterodine oxybutynin, darifenacin, solifenacin, fesoterodine, and trospium	Dry mouth, constipation, dry eyes, dizziness, blurred vision, upset stomach, headache, acute urinary retention [74], [76]
B_3-adrenoceptor agonist [11]	Decrease in tone of the detrusor muscle and promoting urine storage since β3-adrenoceptor stimulation causes relaxation of the smooth muscle and detrusor, both in the urethra and bladder [78].	Improves LUTS	Mirabegron	Nasopharyngitis, hypertension, headache and urinary tract infections [80].

Phosphodiesterase type 5 enzyme inhibitors (PDE5Is) [81]	Increase in the intracellular cyclic guanosine monophosphate (cGMP) concentration [81].	Cause relaxation of the smooth muscles of the urinary tract and bladder detrusor, hence, ameliorate LUTS	Tadalafil	Gastroesophageal reflux, nasal congestion, flushing, indigestion, headache and back pain [65].

NA = Not applicable

Table 2 Conventional approaches employed in PC Treatment

Approach	**Mechanism**	**Primary effects**	**Examples**	**Side effects**
Watchful waiting	Consistent prostate biopsies and close PSA monitoring and follow up as well as patients need to identify the risk of needing definitive therapy as well as the potential for progression to more life-threatening incurable PC [9], [90].	Men with compromised health can avoid the side effects associated with repeated tests and biopsies [9]	NA	NA
Active surveillance	Monitoring of men with limited life expectancy or severe comorbid disease for the occurrence of challenging and complicated local extension or metastatic disease before palliative therapy is initiated. [9], [90].	Men with compromised health can avoid the side effects associated with repeated tests and biopsies [9]	NA	NA
Surgery	Surgical ablation of the cancerous prostate tissues, halts androgen production and actions. Reduces testosterone surge and flare [9]	Excellent outcome [9]. At early stage, removing the prostate gland may provide cure if it has not spread beyond the prostate gland.	Prostatectomy, (radical retropubic prostatectomy (RRP)) [91]. Robot-assisted laparoscopic radical prostatectomy (RALRP) [92].	Urinary incontinence occurring in less than 10% of patients [91].

Chemotherapy Immunotherapy	Bind to microtubules and prevent androgen receptor nuclear translocation and causing apoptosis through B-cell lymphoma (Bcl-2) phosphorylation [105] Disrupts testosterone's interaction with cancer cells [106], [107]	Improvement in disease-related symptoms, including pain, fatigue, and loss of energy	Taxanes (Docetaxel, Cabazitaxel) given with prednisone [104], [105] Enzalutamide	Neutropenia, febrile neutropenia, abnormal liver function [104] Dose - dependent risk of seizure[107]
Radiation therapy [91]	kills prostate cancer cells by using high energy rays or particles [91].	Improved LUTS. Outcomes improved by combination of both androgen deprivation therapy (ADT) and radiotherapy [94], [95].	External Beam Radiation Therapy (EBRT), Intensity-Modulated Radiation Therapy (IMRT), Proton Beam Therapy, Stereotactic Body Radiation Therapy (SBRT) or Stereotactic Ablative Radiation Therapy (SABR), Image-guided Radiation Therapy (IGRT), Brachytherapy, Radium-223 Therapy.[9]	Bladder or rectal toxicity which present as either haematuria, haematochezia, or irritative LUTS as well as second malignancy may occur [93]

Advanced medical definitive therapies [96], [97]	**HIFU** destroys prostate cancer through the delivery of precise and focused sound waves to a targeted spot of diseased prostate tissue. **Cryotherapy** involves the use of transrectal ultrasound (TRUS) to guide several thin needles into the prostate. Very cold gases are then passed through the needles to create an ice ball that freezes and destroys the prostate tissue. [96], [97]	Destroy tumour cells, while improving localization of the disease and preserving healthy surrounding tissues. Freezes tumour cells, causing their death.	High intensity focused ultrasound (HIFU) Cryotherapy [96], [97].	Incontinence, fistula, urethra stenosis, acute urinary retention, urinary tract infection, post-operative pain [156] Local complications such as urethral fistulas [100]. Erectile dysfunction (ED) [102], [103]
Androgen deprivation/Ablation therapy (ADT) [9], [108]	Drastic reductions in the rates of testicular androgen synthesis and levels of circulating androgens, thereby minimizing AR ligand availability and subsequent AR-mediated proliferative effects on the prostate [108]	Suppresses androgen signalling	Orchiectomy Anti-androgens (bicalutamide) Luteinizing hormone releasing hormone (LHRH) analogue (leuprolide) [108], [109]	Cardiometabolic syndrome, loss of bone mineralization [157]

. NA, Not applicable; AR, Androgen receptor

Table 3 Some Plants with Phytotherapeutic Potentials against BPH and PC

Plant Extracts	**Mechanisms**	**Reported Potentials**
Saw palmetto Active compounds: Sterols (b-sitosterol, campesterol, stigmasterol) and flavonoids	Anti-inflammatory Apoptotic effects Inhibits aromatase Inhibits 5α-reductase I&II Anti-proliferative effects Anti-androgenic Anti-estrogenic	At 10 µg/mL, it inhibited >70% of the activities of 5α reductase I &II [116] At 100 µg/mL, it inhibited aromatase enzyme Inhibited thymidine incorporation in LNCaP, and PC-3 cell lines by more than 50% at 100 µg/mL [117]
Prunus africana Active compounds: Sterols, acidic phenols, Triterpenoids	Prevents proliferation induced by PKC, bFGF, EGF, IGF of rat prostatic fibroblasts. Mild anti-inflammatory effects, Antiandrogenic activity	Inhibited androgen's action by 40-60 fold at 600 µg/mL [127].

		At 2.5 µg/mL, it inhibited thymidine incorporation in LNCaP and PC-3 cell lines [128].
Urtica dioica Active compounds: Sterols, triterpenic acids, lignans, phenols	Inhibits aromatase Inhibits leukocytes Immuno-modulatory Anti-proliferative effects	Inhibited aromatase activity with IC_{50} >100 µg/mL [117].
Epilobolium rosmarinifolium Active compounds: Sterols, triterpenes, flavonoid glycosides.	Anti-inflammatory Anti-androgenic Anti-proliferative effects	At 160 µg/mL, inhibited 5α-reductase [150]. Inhibited thymidine incorporation in PZ-HPV-7 cell line at 75-100 µg/mL [116].
Vitex agnus Active compounds: Flavonoids, iridoid glycosides, and terpenoids	Antiproliferative effects Apoptotic effects Reduces prolactin levels	Inhibited proliferation of prostate cancer cell lines by 50% at 10-30 µg/mL [151]

PKC, Protein Kinase C; bFGF, Basic Fibroblast Growth Factor; FGF, Fibroblast Growth Factor; EGF, Epidermal Growth Factor; IGF, Insulin-like Growth Factor; LNCaP, Human Prostate Adenocarcinoma Cells; PC-3, Human Prostate Cancer Cells; PZ-HPV-7, Human Prostatic Epithelial Cells from the peripheral zone of the prostate

4. Discussion

Prostate cancer (PC) and benign prostatic hyperplasia (BPH) both being age related diseases will increase in prevalence as the number of aging men increases. The advances in technology eased acceptance of surgical intervention of these diseases for men who are unsuccessful with medical management or who prefer surgical intervention [9]. It is known that men aged 50 years and above are at risk of BPH [14], [15], which if not diagnosed and controlled early enough, may progress to PC [12], [13]. We conducted a review on the common biological factors implicated in both benign prostatic hyperplasia (BPH) and prostate cancer (PC), as well as the conventional and phytotherapeutic approaches employed in their management. Our search results revealed that watchful waiting, active surveillance, surgery, radiotherapy, chemotherapy and immunotherapy are the conventional approaches employed in the management of these prostatic conditions [1], [9], [11], [47].

The American Urological Association (AUA) recommends watchful waiting for patients who are yet to experience severe lower urinary tract infections (LUTS) that affect quality of life (QOL) [50], but patients with problematic LUTS may not benefit from it as this may even delay timely interventions with appropriate medications [11]. The United Kingdom's National Health Service has recommended active surveillance as a first-choice approach for low-risk PC patients, and it entails repeated biopsies of the prostate and a routine follow up of PSA coupled with awareness creation to patients in order for them to know the risk of seeking definitive therapy *vis-à-vis* the potentials of disease development to an incurable state [90].

Studies have shown that some men with prostatic conditions do not show positive outcomes to medical management of their disease symptoms, some experience disturbing side effects while others are uncomfortable with the use of chronic medications, which therefore leaves these category of patients with surgical intervention options for their conditions [9]. Ablative surgical intervention has been the predominant approach for the management of BPH for more than 60 years [1]. Hence, urologists have reevaluated the protocols for conventional diagnosis and treatment of these conditions owing to the acquired knowledge on the epidemiology and pathophysiology of these conditions [158], which has also given rise to the search and introduction of novel methods in medical interventions especially in the domain of surgical approach to management of these conditions, to allow optimal outcomes [9].

Therefore, the introduction and emergence of medical advances in technology with respect to minimally invasive surgical options such as thermotherapy which involves transurethral microwave therapy (TUMT) or transurethral needle ablation (TUNA) with the benefit of reduced risk of long-term side effect and appreciable improvement in urinary symptoms has brought relief to BPH patients who prefer this approach [9].

Similarly, modern advanced better tolerated surgical interventions in prostate cancer management have since emerged which include radical retropubic prostatectomy (RRP) and robot-assisted laparoscopic radical prostatectomy (RALRP) with relatively excellent outcomes [92].

In the same vein, the availability of less problematic and better tolerated techniques for the delivery of radiotherapy has made the approach more effective for prostate cancer treatment, even though occasional side effects such as bladder or rectal toxicity and risk of second malignancy have been reported [93]. However, it has been reported that treatment outcomes with radiation therapy could improve when used in combination with androgen deprivation therapy [94].

The deployment of chemotherapeutic approach has been the first management option in BPH patients who are already experiencing LUTS [9]. While drug classes such as muscarinic cholinergic antagonists including, tolterodine, oxybutynin, darifenacin, solifenacin, fesoterodine, and trospium; β3-adrenoceptor agonist including mirabegron; and phosphodiesterase type 5 inhibitors such as tadalafil, are available, the main drugs mostly used for the management of BPH and in some cases, for PC as well, are the selective α1-adrenoceptor antagonists such as silodosin, tamsulosin, alfuzosin etc and the 5-α-reductase inhibitors such as finasteride and dutasteride, or a combination of drugs from both classes [9], [11], [47], [50]. However, these drugs have their set-backs in terms of their safety profiles. For instance, the α1-antagonists could cause a range of side effects such as ejaculatory dysfunction, intraoperative floppy iris syndrome (IFIS), postural hypotension, dizziness, and asthenia [59], which may be attributed to the wide range of distribution of the various subtypes of the α-1 receptors such as α-1a, α-1b and α-1d [58]. Furthermore, though the 5α-reductase inhibitors may interfere with sexual drive, cause gynecomastia, and erectile dysfunction (ED) for some men, they are relatively well tolerated compared to α-1 blockers [11], [62]. However, despite their shortcomings, the α-1 blockers are reportedly the ideal drugs for BPH patients with lower prostate specific antigen (PSA) levels, while 5α-reductase inhibitors or in combination with α-1 blockers may be more appropriate for patients with higher PSA levels [11], and this is further corroborated by the outcome of a probing clinical trial [56]. Our search result also identified the use of enzalutamide, a novel immunotherapeutic drug which act by disrupting testosterone's interaction with prostate cancer cells [106], [107], with seizure being a possible side effect that may be associated with its use [107].

In a further development, urologists have also witnessed the emergence of novel definitive prostate cancer therapies with better tolerance profiles such as high intensity focused ultrasound (HIFU) and cryotherapy [96], [97]. These minimally invasive procedures have gained massive interests since their emergence [9]. Giving the pivotal roles androgens play in the prostatic diseases such as BPH and PC, androgen deprivation therapy (ADT) also referred to as androgen ablation therapy still takes the center stage as the mainstay of therapy especially in metastatic prostate cancer [108], [109].

However, one important concern that has been raised with the use of the ADT is the occurrence of adverse effects such as loss of bone mineralization and cardiometabolic syndrome which may jeopardize quality of life of patients and may even cause mortalities in some more vulnerable patients [159], especially the elderly that are known to experience complications of bone fractures leading to severe mortalities and deaths [160]. A risk to benefit ratio analysis supports the use of ADT especially in men who are in the advanced stages of prostate cancer [157]. Considering the burden of these prostatic diseases especially prostate cancer, there has been a recent call for more action to be taken to improve management of these conditions. Some of these include further scientific exploration to develop more drugs with better safety profiles [157], searching for predictors of prostate cancer lethality and treatment effect in order to maximize benefits, of which one promising approach to this, could be the detection of prostate specific membrane antigen expression with positron-emission tomography [161].

Furthermore, other suggested measures that could be considered, range from incorporation of physical fitness programmes in forms of exercises, high surveillance and management of cardiovascular disease risk factors, to close monitoring of bone mineral density during androgen deprivation targeted therapies as well as in clinical trials [157].

For quite a number of years, medicinal plants have remain significant in the treatment of various ailments and for enhancement of overall human health [162]. In recent years, there has been a growing acceptance of plant-based therapies as alternatives to orthodox medicines probably due to their perceived better safety profile, better therapeutic activities and cost-effectiveness [163].

Thus, giving the challenges still facing treatment outcomes despite the advances in technologies targeted at these prostatic diseases, there is need for a global re-awakening of ethno-pharmacological interests in medicinal plants which may probably proffer the needed solutions to the burden of BPH and PC. So far, in this review, we have uncovered some medicinal plants with potentials against these prostatic conditions, supported by scientific research evidences,

including *Saw palmetto* [116], [117], *Prunus africana* [127], [128], *Urtica dioica* [117], *Epilobolium rosmarinifolium* [116], [150], *Vitex agnus* [151] amongst others.

Furthermore, we also gathered that despite the proven benefits of *Saw palmetto*'s activities against these prostatic conditions, few studies have reported contrary outcomes [164], [165]. These discrepancies, however, could be attributed to either the method of preparation, extraction method, location and period of collection of the plant materials [166].

Several biological factors have been reported to be associated with the risk of these prostatic conditions, including inflammation, apoptosis, and hormonal imbalance. Studies have demonstrated a strong correlation between inflammation and BPH as inflammatory cytokines are said to be over-expressed in BPH tissues [167]–[170]. Apoptosis has been shown to have a close relationship with BPH and PC and a reduced rate of apoptosis may lead to their progression [39], [40]. Hormones such as androgens and estrogens are key players in BPH and PC. The enzyme, 5α reductase has been implicated in the pathogenesis of the disease. 5α-reductase converts testosterone to dihydrotestosterone (DHT) which is the active form of the hormone believed to contribute to stimulation of the prostate gland resulting to its abnormal enlargement [27]. Also, aromatase converts androstenedione to estrone and estradiol which are forms of estrogen. Estrogen is believed to play a role in the abnormal enlargement of the prostate gland by increasing the expression of androgen receptors thereby increasing the effect of dihydrotestosterone on the prostate [27].

Also, since the risk of these prostatic conditions could also be downplayed by awareness of some basic life-style changes, it is important to mention some known life-style modifications that could keep the prostate healthy as men age, so as to reduce the risk of exposure to BPH and PC. Nutrition is a significant determinant of the health of an individual as it has been reported that about one third of the 500,000 cancer mortalities that occur in the United States in a year is related to dietary factors [171].

It has been observed that daily intake of red meat triples the chances of prostate disease just as daily milk intake doubles the risk of the disease. Fruits and vegetables are generally good for healthy living and failure to cultivate the habit of taking these (Fruits and vegetables) increases the risk of BPH and PC. Tomatoes are known to be very good as they contain good quantities of lycopene which is a very good antioxidant. Also, Zinc-rich food are known to be very essential for male sexuality and fertility. Alcohol consumption should either be minimized or stopped as soon as one observes urinary symptoms associated with prostate enlargement. This is because, the more fluid that goes into the system means more fluid to be passed out [171]–[174].

Furthermore, since BPH has been identified as the most common age-related urologic diseases that affect the elderly men [11], which could progress to prostate cancer if not identified and managed early enough [12], [13], it is worthwhile therefore to give more attention to diagnosis and treatment of BPH as a way forward to reducing and preventing the more life-threatening prostate cancer. Additionally, more research should be carried out to identify the current incidence and prevalence rate of BPH especially in Africa to alert the public on the need to modify lifestyles that could lead to BPH thus, prevent it and subsequently prevent prostate cancer.

5. Conclusion

In this review, we pulled information from different sources concerning common biological factors, prevalence, pathogenesis, and management of BPH and PC, and suggested possible approaches that can be undertaken to mitigate the occurrence of BPH and PC in the society. Possible scientific approaches for treatment of BPH and PC which have been identified by different researchers have also been captured in this comprehensive review. Finally, it should be borne in mind that updated knowledge on any disease condition will undoubtedly help in its amelioration of which benign prostatic hyperplasia and prostate cancer are not exempted.

Compliance with ethical standards

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Authorship Contribution Statement

All authors collaborated in the conduct of this research. GCP, JHO, PGM, and BG, conceptualized the study. GCP sourced for data from the literature and wrote the first draft of the manuscript. GCP, JHO, PGM and BG finalized the second draft of the manuscript. All authors read and adopted the final manuscript.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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