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The role of phytoandrogens for benign prostatic hyperplasia treatment

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Abstract

Benign prostatic hyperplasia (BPH) is a common urological condition in aging men. High levels of androgens, including testosterone (T) and dihydrotestosterone (DHT), are closely associated with BPH occurrence and development. Currently, the main clinical drugs used for BPH treatment are 5α-reductase inhibitors and α-receptor blockers, both of which aim to decrease abnormal androgenic signaling while having several unignored side effects. Recently, various natural herbs, such as tonifying yang traditional Chinese medicine (TCM), have been found to have androgenic activities, some of which are also effective for BPH treatment. Here, we review the androgenic activities of phytoandrogens, together with their therapeutic effects in BPH, and summarize the mechanisms involved, providing evidence that such herbs serve as selective androgen receptor modulators.

Keywords: Androgen, Benign prostatic hyperplasia, Phytoandrogens, Selective androgen receptor modulators, Traditional Chinese medicine

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Introduction

Benign prostatic hyperplasia (BPH) is a common urinary system disease in older men. With an aging society, the incidence rate of BPH has been increasing rapidly with age increasing. Epidemiological data have shown that the incidence of BPH in men aged 51–60 years is approximately 50%, and it has increased to 75% in men aged between 71 and 80 years[1]. Histologically, BPH is a benign form of prostate enlargement. An increased prostate volume deforms the prostate urethra and compresses the urethra near the bladder neck. It can cause a series of lower urinary tract symptoms (LUTS) such as dysuria, frequent and urgent urination, nocturia, narrow urine flow, urine waiting, and urine dripping. The BPH/LUTS pathogenesis is closely related to androgen and androgen receptors (ARs). At present, 5α-reductase inhibitors are commonly used in the clinic for BPH/LUTS treatment, which decreases the enlarged prostate volume by reducing dihydrotestosterone (DHT) levels. Additionally, α1-adrenergic receptor blockers alleviate LUTS by relaxing stromal tone in the prostate and bladder[2]. Recently, several studies have shown that plant extracts have androgenic-like effects and can be used for treating BPH. We focused on plant-derived components that have been reported to have androgen-like effects and are defined as phytoandrogens. We also summarized the mechanisms of phytoandrogens in the prostate by applying androgenic and anti-androgenic effects on androgen signaling pathway disruption, which may indicate the role of selective AR modulators (SARMs).

Androgen and AR

Androgenic hormones

Male sex hormones are androgens derived from the Greek words andros (man) and gennan (to produce). The androgen function was first reported by Arnold A. Berthold of Gottingen. In 1849, Berthold found a decrease in some male secondary appearances and male-typical behaviors in castrated roosters. Interestingly, these castration-induced changes were reversed by injecting crude testicular extract or prevented by transplantation of the testes. Thus, he concluded that the testes release a substance into the bloodstream that affects behavioral and sexual characteristics. The testicular hormone later known as testosterone was isolated in 1934 by Ernst Laqueur[3]. In the decades to be followed, other androgens were also identified, including dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone

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(DHEA), androstenedione (A), testosterone (T), and DHT[4]. Among these androgens, DHEAS, DHEA, and A are considered pro-androgens that require conversion to testosterone before possessing their androgenic effects[4]. T cells are the primary androgen component in humans. Its structure is mainly a steroid hormone, which is closely related to the growth and development of a person's life[5]. In men, over 95% of T is secreted by the Leydig cells of the testes, which testes produce 5–10 mg/d[6]. The production of T is governed by the negative feedback regulation of luteinizing hormone (LH) and LH-releasing hormone via the gonad-hypothalamus-pituitary axis[7]. In circulation, approximately 55% of T binds to steroid hormone-binding globulin (SHBG). While the remainder is bound to albumin in a low-affinity fashion, and only 1–3% of T normally circulates freely[8]. T enters the target cell through passive diffusion across the plasma membrane. Once inside the target cell, T is irreversibly converted to DHT by 5α reductase isoenzymes (SRD5A; types I and II)[9]. This saturable process follows Michaelis-Menton kinetics and is not affected by age[10]. SRD5As are located in the prostate (type II), skin (type I), liver (types I and II), and hair follicles (primarily type I) and catalyze DHT formation from testosterone[9]. Similar to testosterone, circulating DHT mainly binds to SHBG, but weakly binds to albumin. Generally, protein-bound DHT is inactive, but in some reproductive tissues, when combined with SHBG, megalin (an endocytic receptor) acts as a pathway for cells to take up DHT[11]. T can also be converted to estrogen by aromatase. A considerable part of the estrogen in young people is derived from aromatization of T[12–13].

Androgen receptor

The AR is a ligand-dependent transcription factor and a member of the nuclear receptor (NR) superfamily, also classified as NR3C4 (NR subfamily 3, group C, gene 4)[14]. Members of this superfamily are ligand-responsive and share structural and functional similarities[15]. The NR superfamily includes over 100 members, and among this large family of proteins, the AR is classified in the same group as other steroid receptors: estrogen receptor (ER), glucocorticoid receptor, mineralocorticoid receptor, and progesterone receptor[16]. The human AR gene is located on the X chromosome at the locus Xq11-Xq12 and is oriented with the 5′ end toward the centromere. It comprises eight exons and produces cDNA of approximately 2,760 nucleotides in length. The first exon codes for the N-terminal domain (NTD), exons 2 and 3 encode the DNA-binding domain (DBD), and exons 4–8 encode the ligand-binding domain (LBD)[17–18]. The AR gene encodes a 98 kDa protein (110–112 kDa on SDS-PAGE) comprising 919 amino acids[19]. The amino acid length of AR varies because of polymorphic genetic sequences and/or alternative splicing. The most commonly reported full-length AR protein product translated from the 10.6 kb transcript comprises 919 amino acids with a predicted molecular mass of 98.8 kDa, when the AR protein is detected using AR-specific antibody on western blots, it appears as a closely spaced doublet at 110–112 kDa because of post-translational modifications such as phosphorylation[20–21]. Similar to other NRs, the AR is organized into four distinctive functional domains, including NTD, DBD, hinge region (HR), and LBD, all of which are important for receptor function[22].

N-terminal domain

The NTD accounts for more than half of the size of AR, corresponds to the first 558 residues, and contains the activation function (AF1) functional region (amino acid 142-485)[22].

AR NTD plays an important role in several protein–protein interactions and retains at least 65% of the transcriptional activity of full-length NTD. It serves as a binding site for co-repressors, co-activators, and many transcription machinery components, including transcription factor IIF (TFIIF) and transcription factor IIH (TFIIH) proteins[23–24].

DNA-binding domain

The DBD (amino acids 556–623) is a cysteine-rich region that is the most conserved domain among steroid hormone receptors[25]. It recognizes specific DNA sequences called androgen response elements (AREs), which are usually found in the promoter and/or enhancer regions of the AR target genes[17].

Hinge region

HR contains a nuclear localization signal (NLS) sequence (amino acid 617–634) that is formed by two clusters of basic residues belonging to the C-terminus of the DBD and the N-terminus of the HR[26]. The NLS is a bipartite sequence that can interact with nuclear import factors, such as importin-α, to facilitate AR nuclear translocation through the nuclear pore complex[27]. Besides nuclear localization, HR, particularly its 629-RKLKKL-634 motif, was also found to play a complex role in DNA binding, co-activator recruitment, and N/C interaction and is a target site for acetylation, ubiquitylation, and methylation[19].

Ligand-binding domain

The LBD surface also contains a hydrophobic cleft, known as the Activation Function 2 region (AF2)[22], which is involved in protein–protein interactions between the LBD and coregulatory proteins such as a family of p160 co-activators[28–29]. Additionally, the AF2 domain preferentially binds to the FXXLF motif in the NTD to form an N/C interaction, which is essential for AR transcriptional activity[30].

AR signaling pathway

In the absence of ligands, AR primarily resides in the cytoplasm and is associated with chaperone molecules, such as heat shock proteins 70 and 90, co-chaperones, and cytoskeletal proteins[15,31]. The molecular chaperone complex is essential for the maintenance of the tertiary structure of the AR LBD in a particular conformation to allow ligand binding[32], which causes a chain of molecular events, including conformational change,

intramolecular N/C interaction, and AR protein folding, forcing dissociation from the chaperone complex, and interaction with co-regulators such as ARA70 (binds to AR-DBD and AR-LBD). AR is then translocated into the nucleus and binds directly to the specific ARE in the promoter region of its target genes[22]. Once bound to its response element, AR leads to the recruitment of co-activators (CBP/p300, P/CAF, and SRC/p160 co-activator family members), resulting in chromatin remodeling. This allows the binding of TATA-binding protein followed by general transcription factors and RNApolII to begin transcription[33–36]. Overall, genomic AR binding and the expression of AR-responsive genes are tightly regulated by various mechanisms. Three key steps must be accomplished: (1) recruitment of protein complexes by the DNA-bound AR, (2) remodeling of chromatin structure to open up regulatory regions and the promoter, and (3) recruitment of the general transcription machinery to the promoter to enhance transcription initiation and/or elongation.

Androgen signaling in BPH

The prostate

The prostate is the largest substantive organ in the accessory sex glands of the male genitalia and is located around the bladder neck. Prostate development comprises three stages. The first is the fetal period, the second is adolescence, and the third is middle age and lasts throughout old age. Prostate gland differentiation and growth begin in the 12th week of pregnancy[37] and are completed at birth when it weighs approximately 2 g[38]. During puberty, the prostate weighs approximately 20 g[38]. After adulthood, the prostate gland remained stable.

Benign prostatic hyperplasia

The prostate begins to develop slowly again from middle age for various reasons and continues throughout old age. The prostate tissue is composed of epithelial and mesenchymal cells. BPH is an expansion of the transition zone, which is characterized by the proliferation of prostatic mesenchyme and epithelial cells, forming large discrete nodules. The histological subtypes of BPH nodules include glandular hyperplasia, dilation, and interstitial fibromuscular hyperplasia[39]. BPH is pathologically due to an enlarged prostate compressing the bladder neck, causing various urinary discomfort symptoms, and its incidence increases with age. The incidence rate over 80 years old reaches 80–90%[40]. In traditional Chinese medicine (TCM), BPH is identified with the features of "retention of urine" and "prostatic hypertrophy"[41], and its basic pathogenesis is considered to be the disturbance of *qi* transformation in the bladder, deficiency of kidney and the poor blood circulation that together lead to the dysfunction of the TCM "kidney" in elderly men. Therefore, TCMs for BPH treatment have mainly focused on benefiting *qi*, tonifying the kidney, invigorating blood, and drying damp[41-42]. A series of TCMs have been successfully applied for BPH therapies in the form of drug combinations, including prescriptions and decoctions.

Androgen induces BPH

With increasing age, BPH incidence increases as serum T levels decrease with a decline in testicular function[43]. The prostate is an androgen-dependent organ and androgens induce BPH. It is well accepted that DHT binds to ARs present in the prostate, triggering gland enlargement. There are different opinions regarding the onset of BPH, and its relationship with T is inseparable[44–45]. However, clinically, there is no correlation between serum testosterone levels and prostate size[46–48]. Some studies suggest that prostate growth is very sensitive to changes in the concentration of androgen at very low concentrations, but it is not sensitive to high androgen concentrations. This saturation mode indicates that androgen mainly exerts its prostate function by binding to AR, and when the serum testosterone concentration is far below the physiological range, androgen AR binding reaches its maximum[49]. Studies have shown that the use of wild-type epithelial cells and AR-deficient mesenchymal recombinant tissues for culturing fails to develop normally[50]. In contrast, when the recombinant tissue is composed of AR-deficient epithelium and wild-type mesenchyme, the prostate normally develops, producing acinar cells and secreting products, indicating that AR mediates androgen regulation of epithelial–stromal cell interaction, which is necessary for prostate differentiation[50].

Phytoandrogens are beneficial for BPH development

The pharmacological management of BPH involves various types of medications, such as α-adrenoceptor antagonists, hormonal control of 5α-reductase inhibitors, stimulation of the nitric oxide/cyclic GMP pathway by tadalafil, and phosphodiesterase type 5 inhibitors[51]. Several achievements have been made in drug development for the improvement of benign prostatic syndrome. Recent data have shown that several candidates have been in clinical or preclinical investigative states and do have some effects on prostate tissue, which may provide hope to exert their future beneficial outcomes in BPH treatment[52]. These candidates include (1) nitric oxide donor drugs[53–54], agonists/antagonists of endogenous peptides[55–56], botulinum toxin[57–59], and NX-1207[60–61], which mainly focus on interfering with peripheral neuromuscular/neuronal mechanisms; (2) cetrorelix[62–64] and lonidamine[65], which target the steroidal axis or metabolic turnover; and (3) combination therapy with drugs already established for treating BPH-LUTS[51]. However, side effects have also been observed with anti-BPH drugs and candidates. Among α-blockers, asthenia, dizziness, orthostatic intolerance (dizziness, hypotension, or syncope), intraoperative floppy iris syndrome, and ejaculatory dysfunction are common symptoms[51]. 5α-reductase inhibitors have been found to cause reduced libido, erectile dysfunction, gynecomastia, and ejaculatory dysfunction during long-term use[51]. Headache, hyponatremia, insomnia, hypertension, abdominal pain (up to 4%), and nausea were found when patients received a vasopressin analog[51]. Taken together, these results indicate that more effort is needed to develop new and suitable therapeutic modalities for managing BPH and BPH-related LUTS.

Phytoandrogens

Phytoandrogens are a class of plant-derived natural products that can bind to AR[66–67]. They either activate or suppress downstream AR-mediated signaling events, which act as agonists, antagonists, or have mixed agonist/antagonist effects on AR. Phytoandrogens, which have agonist properties, work with androgenic hormones, thereby supporting, restoring, enhancing, or substituting one or more of its functions[67]. An example of an herbal medicine that can act as an agonist of AR is the bark of *Eucommia ulmoides* Oliv. Luciferase reporter gene and radioligand displacement assays showed that the ethanolic extract of *E. ulmoides* Oliv. exerted androgenic activity by competitively displacing T from the LBD of the AR and weakly activating AR transcriptional activity in a dose-dependent manner. However, the combination of *E. ulmoides* Oliv. extract and testosterone lead to increased AR transcriptional activity[68]. Conversely, phytoandrogens, which act as AR antagonists, work against androgenic hormones by diminishing, quenching, or blocking one or more of the effects of androgenic hormones[67]. Several natural compounds have been reported to exhibit anti-androgenic activities, such as triptolide from *Tripterygium wilford*ii Hook F.[69], icarisid II from *Epimedium* sp.[70], baicalein from *Scutellaria baicalensis* Georgi[71], tanshinone IIA, and cryptotanshinone from *Salvia miltiorrhiza* Bunge[72–73].

Moreover, some phytoandrogens interfere with androgen-metabolizing enzymes, thus having a complex effect on the AR signaling pathway. For example, epigallocatechin from green tea and *Ganoderma lucidum* extract inhibit the conversion of testosterone from 5-α-reductase to DHT[74–75], and a compound extracted from white peony was found to inhibit testosterone production and increase aromatase activity, thereby promoting its conversion to estrogen[76].

Selective AR Modulators

Selective hormone receptor modulators (SARMs) have different stimulatory or inhibitory effects on receptors in different tissues[77], which has attracted widespread attention as hormone replacement therapy. Studies have shown that selective ER modulators (SERMs) significantly increase ERβ transcription and protein levels in BPH stromal cells while significantly reducing the ERα protein level[78]. Similarly, SARMs cause anabolic cell activity while avoiding the side effects of the currently available anabolic steroids. The possibility of obtaining compounds with tissue-selective activities that are different from those of the endogenous benchmark T might be derived from typical AR activation, which is initiated by binding a molecule with affinity to the LBD of AR. RNA synthesis is then activated or suppressed RNA synthesis from AR-modulated genes, and finally receptor degradation[79]. Because each receptor-ligand complex topology is unique to that ligand structure, the interaction between any specific ligand-receptor complex and the regulatory protein is likely to be unique to the ligand. Additionally, in each type of androgen-targeted cell, the expression level of AR, the conformation and expression level of core regulatory proteins, and the pattern of post-transcriptional regulatory events are different, and the topology of AR regulatory sites in the genome is uniform for each gene.

We can search for SARMs with a desirable tissue-selective pharmacological pattern, such as high anabolic but limited androgenic activity. Miller et al. reported that RAD-140, which is an effective anabolic SARM, has an antagonistic effect on the prostate and seminal vesicles but does not affect the levator ani bulbocavernosus muscle[80]. Nejishima et al. compared flutamide with S-40542, a novel SARM, in a rat model of BPH[81]. Both agents dose-dependently decreased prostate weight to a similar extent; however, S-40542 had a weaker effect on the levator ani muscle than flutamide[81]. Meanwhile, S-40542 showed no effect on T or LH levels, both of which were increased by flutamide[81]. Additionally, another study by Gao et al. compared S-1 and S-4, two SARMs, with finasteride (5α-reductase inhibitor) and hydroxyflutamide (anti-androgen) for the treatment of BPH in a rat model[82]. Both finasteride and S-1 selectively decreased prostate weight to a similar extent, without changing the levator ani muscle and increasing the plasma levels of T, follicle-stimulating hormone (FSH), and LH, and hydroxyflutamide decreased both the prostate and levator ani muscle weights without selectivity and increased plasma hormone levels[82]. Interestingly, S-1 and S-4 weakly decreased 5α-reductase levels, indicating that they reduced prostate size via a mechanism different from that of finasteride[82]. These results raise the possibility of using SARMs as adjuncts or monotherapy for BPH due to minimal side effects.

Notably, both phytoandrogens and SARMs can activate or interfere with androgenic signaling pathways that may contribute to BPH therapies; however, only certain phytoandrogens exhibit SARMs activity since they may induce androgenic-like responses in some organs, as well as in all organs, indicating a relatively larger scale of phytoandrogens than SARMs. For example, permixon is an effective inhibitor of both 5α-reductase type I and II isoenzymes in prostate cells, but no similar 5α-reductase activity inhibition is observed in fibroblasts and epithelial cells from the epididymis, testes, kidney, skin, and breast. However, baicalin could inhibit the overgrowth of LNCaP prostate cancer cells stimulated by DHT and inhibit nuclear translocation of the AR stimulated by DHT in human dermal papilla cells[83]. Their relationship is the same as that of the complex relationship of both phytoestrogens and SERMs, in which different types of phytoestrogens have different potencies[84–86].

Phytoandrogens in the treatment of BPH

The clinical use of T replacement therapy for BPH is increasing. When people experience adverse reactions, they try to grasp the advantages of androgen deprivation therapy without its side effects. Therefore, researchers have begun to look for compounds from plants that can play an important role, such as testosterone, which are called phytoandrogens. Some researchers have shown that many herbal medicines containing phytoandrogens inhibit BPH occurrence and development, but the mechanisms are different. Moreover, these herbal medicines have been used in folk medicine for treating BPH, such as *Cynomorii herba*, *Psoraleae fructus*, *Ginseng radix et*

rhizome, *Salviae miltiorrhizae radix et rhizoma*, which have medicinal efficacy similar to benefiting Qi, tonifying the kidney, and invigorating blood, *Scutellariae radix*, which has medicinal efficacy in the TCM theory for BPH treatment. These herbal medicines are briefly discussed below.

C. herba is frequently used in TCM, traditional Mongolian medicine, and traditional Uighur medicine. It has medicinal efficacy that tonifies kidney yang, benefits essence and blood, moistens intestines, and relieves constipation[87]. In TCM, it is seen as an important herbal medicine for androgen-deficient diseases including erectile dysfunction, premature ejaculation, menstrual problems, kidney *yang* deficiency, and infertility[88–89]. Recently, it was reported that some chemical compounds isolated from *C. herba*, including luteolin, rutin, and epicatechin gallate, exhibit androgenic-like activities by enhancing AR nuclear translocation in LNCaP cells[90]. In another study, Abdel-Magied et al. reported an androgenic-like effect of *C. herba*[91]. After being fed an aqueous extract (47 mg/100 g body weight) of *C. herba* for 6 days, immature 20-day-old male Wistar rats exhibited an increase in testicular weight compared to the control group. Interestingly, serum levels of testosterone and FSH were lower in animals fed the aqueous extract of *C. herba* than in control animals[91]. In the estrogen/androgen-induced prostate of BPH rats, Wang et al. found that treatment with *C. herba* extract can significantly downregulate the expression of AR and ERα and increase the expression of ERβ to inhibit BPH[90]. At the cellular level, Tao also found that the main active components of *C. herba* can significantly inhibit the E_2 or DHT-induced proliferation in BPH-1 cells[92].

P. fructus is a natural medicinal plant with thousands of years of clinical applications and has attracted much attention in the research field because of its excellent potential as a drug[93]. It has medicinal efficacy that warms the kidney, assists *yang*, improves *Qi* reception, and relieves asthma[87]. The major constituent of *P. fructus* is bakuchiol, which effectively blocks testosterone-induced AR transcription in the LNCaP cell model[94]. Miao et al. reported that bakuchiol suppresses estrogen/testosterone-induced BPH by upregulating epithelial ERβ and downregulating matrix aromatase[95].

G. radix et rhizoma, also known as Chinese ginseng or Korean Ginseng, has been used worldwide as an herbal medicine to treat many diseases. It has medicinal efficacy that supplements original *Qi* powerfully, restores pulse to rescue from desertion, supplements the spleen and boosts the lung, promotes fluid production and nourishes blood, calms the mind, and benefits intelligence[87]. Raw ginseng is subdivided into white ginseng and red ginseng based on the processing conditions, such as steaming and drying[96]. Ginsenosides are the principal active constituent of ginseng. It can be classified into two major categories: 20(*S*)-protopanaxadiol (aPPD) (eg, Ral, Ra2, Rc, Rd, Rg3, and Rh2) and 20(*S*)-protopanaxatriol (aPPT) (eg, Re, Rf, Rgl, and Rh1)[97]. In recent decades, ginseng extract and its chemical constituents, especially ginsenosides RG3 and 20(S)-protopanaxadiol, have been reported to be AR antagonists. Cao et al. showed the ability of 20(S)-protopanaxadiol-aglycone (PPD) to suppress AR transcriptional activity by inhibiting AR protein expression and induction of proteasome-mediated AR degradation[98]. In another study, aPPD displayed inhibitory activity against AR NTD[99]. In addition, Ginsenoside RG3 has been shown to block T-induced LNCaP cell proliferation and inhibit AR mRNA and protein expression[100]. The beneficial effects of ginseng in the prevention and inhibition of BPH have been addressed in animal models. Bae et al. found that the aqueous extract of Korean red ginseng antagonized T-induced BPH in rats, indicating the ability of ginseng extract to suppress the AR signaling pathway[100]. Lee et al. also showed that red ginseng oil suppressed T-propionate-induced BPH via inhibition of AR and 5α-reductase expression, as well as by reducing DHT levels[101].

S. radix, also known as Chinese Skullcap, is a well-known Chinese herbal medicine. It clears heat and dries dampness, reduces fire to remove toxins, stops bleeding, and calms the fetus[87]. Moreover, its dried root has been applied in the treatment of diarrhea, dysentery, hypertension, hemorrhaging, insomnia, inflammation, and respiratory infections[102]. Flavonoids are major chemical constituents, among which the most abundant include baicalin, baicalein, and wogonin[102]. According to Kim *et al., S. radix* extract inhibits the nuclear translocation of AR, suppresses AR expression, and antagonizes the effects of DHT on the proliferation of LNCaP cells[83]. Apart from *S. radix* extract, baicalein (5,6,7-trihydroxyflavone) has been reported to suppress the AR signaling pathway by inhibiting AR protein expression, AR N/C interactions, and AR-co-activator interactions[71,103]. Additionally, Chen et al. reported that wogonin exhibited anti-androgenic activity by downregulating AR and prostate-specific antigen protein expression in LNCaP cells[104]. Moreover, Jin et al. demonstrated that baicalin effectively improved the rat BPH model induced by T propionate and inhibited the proliferation of DHT-induced RWPE-1 and WPMY-1 cells through activation of the intrinsic apoptosis pathway and inhibition of the activity of type II 5α-reductase and DHT production[105].

S. miltiorrhizae radix et rhizoma is one of the most well-known Chinese herbs. It has medicinal efficacy that promotes blood circulation to remove blood stasis, relieve pain by stimulating menstruation, clear the heart to eliminate fidgety, and cool blood to eliminate carbuncle[87], which has been clinically used to treat cardiovascular- and cerebrovascular-related disorders[106]. The chemical constituents of *S. miltiorrhizae radix et rhizoma* are classified into two groups: diterpenoid quinones, including tanshinone I, tanshinone IIA, and cryptotanshinone, and hydrophilic phenolic acids, such as salvianolic acid A and danshensu[106]. Among these chemical compounds, cryptotanshinone and tanshinone IIA have been reported to affect the AR signaling pathway. However, the crude extract of *S. miltiorrhizae radix et rhizoma* has no documented phytoandrogenic activity. According to Xu et al., cryptotanshinone effectively antagonizes DHT-induced AR transactivation and AR target gene expression[72]. The mechanism by which cryptotanshinone exerts its anti-androgenic activity is mainly through its ability to interfere with AR N–C dimerization and AR-co-regulator complex formation[72]. Although cryptotanshinone is a promising therapeutic agent for BPH, no

studies have investigated its effects in rats with BPH. Several studies have reported the anti-androgenic effects of tanshinone IIA. In mutant and wild-type AR-positive prostate cancer cell lines, tanshinone IIA efficiently inhibits AR transactivation by inhibiting AR nuclear translocation and promoting AR protein degradation via the 26S proteasomal pathway[73,107–109]. Interestingly, it has been reported to have the therapeutic potential of tanshinone IIA in BPH prevention and treatment. In a rat model of BPH induced by estradiol/testosterone at a ratio of 1:100, tanshinone IIA inhibited the increase in the thickness of the periglandular smooth muscle layer and downregulated the AR, ERα, cyclin B1, and cyclin D1 expression[9].

Cucurbita pepo semen belongs to the Cucurbitaceae family, with several varieties grown worldwide[110]. In Europe, *C. pepo semen* oil has been used in folk medicine to treat BPH[111]. Gossell et al[112]. and Tsai et al[113]. reported that *C. pepo semen* oil inhibited testosterone-induced BPH in rats by inhibiting 5α-reductase and reducing DHT levels. Furthermore, Kang et al. found that phytosterols in *C. pepo semen* oil inhibited AR transcription[114].

Epilobium angustifolium herba is used as a herbal tea or in combination with other herbs to relieve BPH, prostatitis, bladder and kidney diseases, and other urinary tract-associated problems in European and North American traditional therapies[115]. Some researchers have reported that these extracts have anti-androgenic and androgenic activities[116–117].

Roystonea regia fructus is native to South Florida, Mexico, and parts of Central America. Some studies have shown that its extract D-004 inhibited testosterone-induced rat BPH through competitive inhibition of 5α-reductase activity and sympathetic-induced smooth muscle contraction in isolated rat deferens tubes[110,118].

Prunus africana cortex has been used by indigenous people for urinary tract disorders and as an aphrodisiac

Table 1

Brief description of herbal medicines with phytoandrogens and their mechanisms in BPH

Herbal medicines	Plant name	Compounds	Mechanisms
Cynomorii herba	*Cynomorium songaricum* Rupr.	Luteolin, Rutin, Epicatechin gallate	• Enhancing the nuclear translocation of AR[90] • Decreasing the expression of AR and ERα and raising the expression of ERβ[90] • Inhibiting cells proliferation induced by the E_2 or DHT[92] • Inhibiting the conversion of testosterone from 5α-reductase to DHT[74–75]
Psoraleae fructus	*Psoralea corylifolia* L.	Bakuchiol	• Blocking AR transcription induced by testosterone[94] • Upregulating epithelial ERβ and downregulating matrix aromatase[95]
Ginseng radix et rhizoma	*Panax ginseng C. A.* Mey.	Ginsenoside RG3, 20(S)-protopanaxadiol, 20(S)-protopanaxadiol-aglycone	• Suppressing AR transcriptional activity by inhibiting AR protein expression and induction of proteasome-mediated AR degradation[98] • Inhibitory activity against the AR NTD[99] • Inhibiting cells proliferation induced by T[100] • Inhibiting expression of 5α-reductase[101]. • Reducing DHT levels[101]
Scutellariae radix	*Scutellaria baicalensis* Georgi	Baicalin, Baicalein, Wogonin	• Inhibiting the nuclear translocation and protein expression of AR[83] • Inhibiting cells proliferation induced by DHT[83] • Suppressing AR N/C interaction, and AR-co-activator interaction[72,103] • Downregulating protein expression of PSA[104] • Inhibiting the activity of 5α-reductase[105] • Reducing DHT levels[105]
Salviae miltiorrhizae radix et rhizoma	*Salvia miltiorrhiza* Bge.	Cryptotanshinone, Tanshinone IIA	• Antagonizing the DHT-induced AR transactivation and AR target genes expressions by interfering with the AR N–C dimerization and the AR-coregulator complex formation[72] • Inhibiting AR transactivation by inhibition of AR nuclear translocation and promotion of AR protein degradation via 26S proteasomal pathway[73,107–109]
Cucurbita pepo semen	*Cucurbita pepo* L.	Phytosterols	• Inhibiting 5α-reductase[112] • Reducing DHT level[113] • Inhibiting AR transcription[114]
Epilobium angustifolium herba	*Epilobium angustifolium L.*	Polyphenols, Steroids, Triterpenoids	• Anti-androgenic and androgenic activity[116–117]
Roystonea regia fructus	*Roystonea regia* (Kunth) O. F. Cook	D-004 extract (oleic, lauric, palmitic, and myristic acids)	• Inhibition of 5α-reductase[118]
Prunus africana cortex	*Prunus africana* (Hook.f.) Kalkman (*syn. Pygeum africanum* Hook.f.)	N-butylbenzenesulfonamide, Atraric acid	• Anti-androgenic activity[119] • Inhibiting the transactivation mediated by the ligand-activated human AR[120]
Serenoa repens fructus	*Sabal serrulate* (Michx.) Schult. f.	Permixon	• Inhibits 5α-reductase[123] • Anti-androgenic activity[119,122]

AR: Androgen receptor; BPH: Benign prostatic hyperplasia; DHT: Dihydrotestosterone; ERα: Estrogen receptor α; ERβ: Estrogen receptor β; NTD: N-Terminal Domain; PSA: Prostate-specific antigen; T: Testosterone.

Table 2

Classification and pharmacological actions of phytoandrogens in BPH

Classification	Compounds	Mechanisms	Reference(s)
Flavonoid	Luteolin, rutin, baicalin, baicalein, wogonin, icarisid II	• Regulating the nuclear translocation and protein expression of AR • Decreasing the expression of ERα, and raising the expression of ERβ • Inhibiting cells proliferation induced by the E_2 or DHT • Suppressing AR N/C interaction and AR-co-activator interaction • Inhibiting the activity of 5α-reductase. • Reducing DHT levels	[72,90,92,105]
Terpenoid	Triptolide, ginsenoside RG3, 20(S)-protopanaxadiol, 20(S)-protopanaxadiol-aglycone, cryptotanshinone, tanshinone IIA	• Suppressing AR transcriptional activity by inhibiting AR protein expression and induction of proteasome-mediated AR degradation • Inhibitory activity against the AR NTD • Inhibiting cells proliferation induced by T • Antagonizing the DHT-induced AR transactivation and AR target genes expressions by interfering with the AR N–C dimerization and the AR-coregulator complex formation • Inhibiting AR transactivation by inhibition of AR nuclear translocation and promotion of AR protein degradation via 26S proteasomal pathway • Anti-androgenic and androgenic activity • Reducing DHT levels	[72,73,98–100, 107–109,116–117,124]
Gallate ester	Epicatechin gallate	• Inhibiting the conversion of testosterone from 5-α-reductase to DHT	[74–75]
Phenols	Bakuchiol Atraric acid	• Blocking AR transcription induced by testosterone • Upregulating epithelial ERβ and downregulating matrix aromatase • Inhibiting the transactivation mediated by the ligand-activated human AR	[94–95,120]
Phytosterols	Not described in detail	• Inhibiting 5α-reductase • Reducing DHT level • Inhibiting AR transcription • Anti-androgenic and androgenic activity	[112–114,116–117]
Sulfonamides	N-butylbenzenesulfonamide	• Anti-androgenic activity	[119]

AR: Androgen receptor; BPH: Benign prostatic hyperplasia; DHT: Dihydrotestosterone; ERα: Estrogen receptor α; ERβ: Estrogen receptor β; NTD: N-Terminal Domain; PSA: Prostate-specific antigen; T: Testosterone.

drug in the tropical and subtropical regions of Africa[110]. Schleich et al[119]. and Papaioannou et al[120]. found that the extracts of *P. africana cortex*, its active compound N-butylbenzenesulfonamide, and atraric acid have anti-androgenic activity through the inactivation of AR.

Serenoa repens fructus, a traditional medicinal product, has been established for the relief of LUTS related to BPH by the European Medicines Agency (ATC code: G04CX0)[121]. Some researchers have reported that Permixon extracts of *S. repens fructus* have anti-androgenic activity[119,122] and inhibit 5α-reductase[123].

At present, phytoandrogen treatment for BPH research is in full swing (Tables 1 and 2). Although phytoandrogens have many advantages and potential in the treatment of BPH, the specific mechanism classification still needs to be further studied, which is an urgent goal to solve the problem of BPH.

Conclusion

Considerable evidence has shown that testosterone plays an important role in BPH development. Evidence also indicates that androgen action mediated by AR may regulate the etiology and progression of multiple prostate disease states. These findings provide new avenues and alternative approaches for treating prostate diseases including BPH. Since different phytoandrogens may act through different targets in prostate diseases, the multi-target and multi-dimensional effects of phytoandrogens may provide the most beneficial treatment strategy in future clinical trials.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Yaoxin Wu and Nuttapong Wichai wrote the manuscript. Xiaohua Yang and Yaxuan Ma searched for and collected the published data. Tongchuan Suo, and Lin Miao revised the manuscript. All authors have read and approved the final manuscript.

Ethical approval of studies and informed consent

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