# A Review of Animal and Human Studies for Management of Benign Prostatic Hyperplasia with Natural Products: Perspective of New Pharmacological Agents

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**Abstract:** *objective:* In this paper, we reviewed plants being effective in treatment of BPH for the purpose of finding new sources of pharmaceutical agents.

*Methods:* All pertinent literature databases were searched. The search keywords were plant, herb, herbal therapy, phytotherapy, benign prostatic hyperplasia, BPH, and prostate. All of the human, animal and *in vitro* studies were evaluated.

*Results:* According to the studies, some of the substantial effective constituents of the plants in treatment of BPH are oenothein B, icaritin, xanthohumol, diarylheptanoid, 2,6,4'-trihydroxy-4-methoxybenzophenone, emodin, fatty acids, atraric acid, n-butylbenzene-sulfonamide, curbicin, theaflavin-3,30-digallate, penta-O-galloyl-b-D-glucose, lycopene, sinalbin, β-sitosterol, secoisolariciresinol diglucoside, genistein, apigenin, baicalein, and daidzein. Besides, *Serenoa repens, Pygeum africanum*, *Curcubita pepo*, and *Urtica dioica* as the most prevalent plants used to treat BPH. *S. repens* in human studies showed equivalent effectiveness to tamsulosin and in combination to *U. dioica* revealed equal effects to finastride with less side effects.

*Conclusion:* There are numerous plants that have beneficial influence on BPH although the mechanisms of action in some plants are not well understood yet. Active ingredients of some of these plants are known and can be used as lead components for development of new effective and safe drugs.

**Keywords:** 5α-reductase inhibitor, animal, anti-androgen, anti-inflammatory, antioxidant, anti-proliferative, aromatase inhibitor, benign prostate hyperplasia, human, natural products.

## INTRODUCTION

A proliferating urologic disease in older men, benign prostatic hyperplasia (BPH) is encountered by above 40% of fifty-year-old males. Besides, the frequency of BPH might be about 80% even when the age reaches to 80 years [1]. BPH is characterized by enlargement of prostatic nodules owing to a proliferative process encompassing both the stromal and epithelial element of prostate [2]. Clinical symptoms of BPH divide into obstructive or irritative ones. Obstructive symptoms are pertinent to the narrowing of prostatic urethra, and envelop difficulty embarkation of the urination, weak and frequent urinary stream, and trickling of urine. The irritative symptoms which most of the patients have are relevant to pollakiuria, urgency, nocturia and sensation of incomplete bladder emptying [3]. The etiology of BPH is presumably due to age-related hormonal imbalance. There are two imperative theories involving accumulation of dihydrotestosterone (DHT) which may cause cellular hyperplasia and an increase in prostatic estrogen levels with age. In order to treat BPH, we need to reduce inordinate cell growth by blockage of testosterone conversion into DHT and attachment of estrogen to its receptors in prostate [4]. 5a-reductase inhibitors, $\alpha_1$-adrenoceptor antagonists, and phytotherapeutic agents all have been used in BPH treatment [5]. 5a-reductase inhibitors impede extra production of DHT in prostate tissue that results in reduction of cellular proliferation. Other classes of α-blockers cause muscle relaxation in prostate and bladder neck [1].

Notwithstanding the fact that these drugs have fundamental effects on the patients with BPH, adverse effects like gynecomastia, impairment of muscle growth, and harsh myopathy because of structural resemblance to steroidal hormones progressively enhance interest in drugs of plant origin for the purpose that the herbal drugs might have corresponding effects with less side effects [6]. Furthermore, phytotherapy dates back thousands of years, and it is assessed that currently phytotherapeutic agents constitute almost 50% of all medicines prescribed for BPH in Italy and 90% in Germany and Austria [7].

## METHODS

All electronic databases were comprehensively searched for studies indicating alleviation effects on BPH by

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medicinal plants and their active compounds. The search terms were plant, herb, herbal therapy, phytotherapy, benign prostatic hyperplasia, BPH, and prostate. Moreover, all the reference lists of articles were reviewed for extra pertinent studies.

### Study Selection

All of the *in vitro*, animal and human studies about BPH with consequences of 5α-reductase inhibitory, aromatase inhibitory, anti-androgen, anti-proliferative, anti-inflammatory or antioxidant activities, and alleviation in symptoms of BPH were followed. Data were drawn out according to study design, medicinal plant, family name, part of use, active compound and effects (Tables **1-3**).

## RESULTS

### *In Vitro* Studies

#### *5α-Reductase Inhibitory Activity*

In analysis of the acetone extract fraction of *Alpinia officinarum*, liable constituents for obstruction of the enzyme detected as four diarylheptanoids, 1,7-diphenylhept-4-en-3-one, dihydroyashabushiketol (1,7-diphenyl-5-hydroxy-3-heptanone), 5-hydroxy-7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-3-heptanone, and 5-hydroxy-7-(4"-hydroxyphenyl)-1-phenyl-3-heptanone [8]. The ethyl acetate extract of *Brassica napus* L. revealed vigorous activity in declining secretion of prostate specific antigen (PSA). They isolated five flavonoids from the extract i.e. Naringenin, Luteolin, Kaempferol, Kaempferol 3-(3-E-p-coumaroyl-alpha-L-rhamnopyranoside), and Kaempferol 3-(2,3-di-E-p--alpha-L-rhamnopyranoside) [9]. Ten active phytosterol components of the supercritical CO (2) fluid extract (SFE-CO (2)) of *B. rapa* L. were purified and identified. Linolenic acid and monolinolein had significant 5α-reductase inhibitory action. Besides, 24-methylenecholesterol linolenate, cycloeucalenol-linolenate, 24-methylenecholesterol palmitate, cycloeucal-enol, pollinastanol, 24-methylenecholesterol, and monopal-mitin exhibited forceful aromatase inhibitory property [10]. Penta-O-galloyl-b-D-glucose (5GG) and theaflavin-3,30-digallate, the natural polyphenolic compounds, may have the potency to exert in BPH by two facets involving inhibition of 5α-reductase activity and androgen receptors (AR) functions [11]. The aqueous ethanol extract of Lygodii Spora had testosterone 5α-reductase inhibitory action, which the lipophilic compounds i.e. oleic, linoleic, and palmitic acids were detected as the substantial active principles [12]. The 50% ethanol extracts of Resina Pini unveiled mighty inhibition against testosterone 5α-reductase. The active constituent was identified as abietic acid, a diterpene resin acid. Methyl abietate was inactive, whereas other diterpene resin acids, pimaric and neoabietic acid, had similar effect to abietic acid, demonstrating a non-steroidal anionic diterpene compound could be useful in BPH treatment [13]. The active constituent of Polygoni Multiflori Radix extract was isolated and identified as emodin, an anthraquinone compound. Emodin bore meaningfully less inhibitory activity than riboflavin, whereas it was stronger than alizarin (1,2-dihydroxyanthraquinone), an anthraquinone-type positive control. On the other hand, anthraquinone itself did not show substantially inhibitory effect, representing the hydroxyl group on the structure of emodin have a prime role in inhibitory activity against 5α-eductase [14]. Unsaturated fatty acids i.e. oleic, linoleic, and γ-linolenic acids were observed as primary active principles of 50% ethanol extract of Eijitsu (dried fruits of *Rosa multiflora*) [15]. D-004 (lipid extract of the the Royal palm fruits) inhibited 5α-reductase in a dose-dependent and non-competitive manner [16]. The fatty acids of the saponifiable subfraction of *Serenoa repens* extract encompassing lauric and myristic acids are mostly accountable for the inhibitory effect on 5α-reductase [17].

#### *Aromatase Inhibitory Activity*

The dichloromethane, ethanol, and methanol extracts of cactus flower blocked aromatase and 5α-reductase activities, whereas the aqueous extract showed a significant antioxidant effect [18]. P9605, an ethanol extract of *Piper cubeba* L. had anti-aromatase, anti-estrogenic and anti-inflammatory properties [19].

#### *Anti-Androgen Activity*

The anti-androgen effect of *Pygeum africanum*, *S. repens*, and *Cucurbita pepo* were rated. A selective dichloromethane extract from the stem barks of *P. africanum* manifested the highest androgen antagonistic activity, and n-butylbenzenesulfonamide (NBBS) was detected as liable. NBBS is identified as a specific AR antagonist. Noticeably, it blocked AR- and progesterone receptor- (PR) mediated transactivation, but not the relevant human glucocorticoid receptor (GR) or the estrogen receptors (ERα or ERβ). NBBS also exhibited inhibitory action on endogenous PSA expression [20, 21]. Atraric acid isolated from extract of *P. africanum* was AR antagonists corresponding to NBBS [22]. The aqueous extract of *Urtica dioica* L. hindered the binding of sex hormone-binding globulin (SHBG) to its receptor [23].

#### *Anti-Proliferative Activity*

A standardized extract of red orange juice (ROE) inhibited proliferation of fibroblast and epithelial prostate cells [24]. An aqueous extract of *Epilobium angustifolium* and its major compound oenothein B (OeB), a dimeric macrocyclic ellagitannin, divulged a frail but statistically notable inhibition effect on cell proliferation [25]. OeB could enact an indispensable role in inhibiting of deoxyribonucleic acid (DNA). *E. angustifolium* was ten times more potent than the other extract of the same species. Inasmuch as, its extract envelops an amount of OeB 40-fold higher [26]. Icaritin, a prenylflavonoid derivative from *Epimedium genus*, induced growth inhibition and apoptosis through signal-regulated kinase signaling way in an ER-independent manner [27]. Genistein, an isoflavonoid, dwindled the growth of BPH in a dose-dependent way, with little extra effect at higher doses [28]. Xanthohumol (XN), the main prenylflavonoid in hops, and its oxidation product (XAL) induced apoptosis and inhibited NF-kappa B (nuclear factor kappa-light-chain-enhancer of activated B cells) activation, indicating it could be useful in BPH [29]. *P. africanum* showed anti-proliferative and apoptotic activity on prostate

**Table 1.** ***In Vitro*** **Studies**

| Plant | Family | Part of Plant | Active Component | Effect | Ref. |
|---|---|---|---|---|---|
| *Alpinia officinarum* | Zingiberaceae | Acetone extract of the rhizome | Diarylheptanoids | 5α-reductase inhibitory activity | [8] |
| *Brassica napus* L. | Brassicaceae | Ethyl acetate extract of pollen | Naringenin, Luteolin, Kaempferol | 5α-reductase inhibitory activity | [9] |
| | | | Apigenin (4-,5,7-trihydroxyflavone) | Anti-proliferative activity | [35] |
| *Brassica rapa* L. | Brassicaceae | Supercritical CO2 fluid extract of Pollen (SFE-CO2) | 24-methylenecholesterol Linolenate, cycloeucalenol linolenate, 24-methylenecholesterol palmitate, cycloeucalenol, pollinastanol, 24-methylenecholesterol, linolenic acid, palmitic acid, monolinolein, and monopalmitin | 5α-reductase and aromatase inhibitory activities | [10] |
| *Camellia sinensis* | Theaceae | Theaflavins of black tea | Theaflavin-3,30-digallate (TF3) | 5α-reductase inhibitory and anti-androgenic activities | [11] |
| *Citrus sinensis* | Rutaceae | Extract | | Anti-proliferative activity | [24] |
| *Epilobium angustifolium* L. | Onagraceae | An aqueous extract of aerial parts | Oenothein B (OeB) | Anti-proliferative activity | [25] |
| *Epilobium parviflorum* | Onagraceae | Water and ethanol extract of leaves | | Anti-inflammatory and antioxidant activities | [36] |
| *Epilobium parviflorum* Schreb | Onagraceae | The aqueous acetone extract of aerial parts | | Anti-inflammatory and antioxidant activities | [37] |
| *Epilobium rosmarinifolium* | Onagraceae | Ethanol extracts of aerial parts | OeB | Anti-proliferative activity | [3] |
| *Epilobium spicatum* | Onagraceae | Ethanol extracts of aerial parts | OeB | Anti-proliferative activity | [3] |
| *Epilobium tetragonum* | Onagraceae | Ethanol extracts of aerial parts | OeB | Anti-proliferative activity | [3] |
| *Epimedium* genus | Berberidaceae | Icaritin | Icaritin | Anti-proliferative activity | [27] |
| *Glycine max* (L.) Merr. | Fabaceae | Genistein | Genistein | Anti-proliferative activity | [28] |
| *Hipoxis hemerocallida* | Hypoxidaceae | Water and ethanol extract | | Anti-inflammatory and antioxidant activities | [36] |
| *Humulus lupulus* L. | Cannabaceae | Xanthohumol (XA) | XA | Anti-proliferative activity | [29] |
| *Lycopersicum esculentum* | Solanaceae | Lycopene | Lycopene | Antioxidant activity | [38] |
| *Lygodium japonicum* (Thunb.) Sw. | Lygodiaceae | The aqueous ethanol extract of spore | Oleic, linoleic, and palmitic acids | 5α-reductase inhibitory activity | [12] |
| *Macaranga tanarins* (L.) | Euphorbiaceae | Leaf | Penta-O-galloyl-b-D-glucose (5GG) | 5α-reductase inhibitory and anti-androgenic activities | [11] |
| *Opuntia ficus-indica* L. | Cactaceae | Cactus flowers extracts | | Aromatase and 5α-reductase inhibitory, and antioxidant activities | [18] |
| *Pinus sp.* | Pinaceae | The 50% ethanol extract from Resina Pini | Abietic acid | 5α-reductase inhibitory activity | [13] |
| Piper cubeba L. | Piperaceae | P9605 (Ethanol extract of seed) | | Aromatase inhibitory and anti-inflammatory activities | [19] |
| Polygonum multiflorum Thunb. | Polygonaceae | 50% ethanol extract of radix | Emodin | 5α-reductase inhibitory activity | [14] |

**(Table 1) contd…..**

| Plant | Family | Part of Plant | Active Component | Effect | Ref. |
|---|---|---|---|---|---|
| *Pygeum africanum* | Rosaceae | Dichlormethane extract | Atraric acid and N-butylbenzenesulfonamide (NBBS) | Anti-androgenic activity | [22] |
| *Pygeum africanum* | Rosaceae | Extract of bark | | Anti-proliferative activity | [30] |
| *Pygeum africanum* | Rosaceae | NBBS | NBBS | Anti-androgenic activity | [20] |
| *Pygeum africanum* | Rosaceae | Dichloromethane and ethanol extracts of bark | NBBS | Anti-androgenic activity | [21] |
| *Rosa multiflora* Thumb. | Rosaceae | The 50% of ethanol extract of dried fruit | Oleic, linoleic, and γ-linolenic acids | 5α-reductase inhibitory activity | [15] |
| *Roystonea regia* | Arecacea | D-004 (lipid extract of the fruit) | | 5α-reductase inhibitory activity | [16] |
| *Serenoa repens* | Arecacea | Ethanol extract of the fruit | | Anti-proliferative activity | [31] |
| *Serenoa repens* | Arecacea | IDS 89 (Extract of fruit) | Lauric and myristic acids | 5α-reductase inhibitory activity | [17] |
| *Secale cereal* | Poaceae | Cernilton (pollen extract) | Cyclic hydroxamic acid | Anti-proliferative activity | [32] |
| *Trifolium pratense* L. | Fabaceae | Red clover isoflavones | Isoflavones | Anti-proliferative activity | [33] |
| *Urtica dioica* L. | Urticaceae | Extract of root | | Anti-androgenic activity | [23] |
| *Vitex agnus-castus* L. | Lamiaceae | Hydroethanolic extract of fruit | | Anti-proliferative activity | [34] |

fibroblasts and myofibroblasts but not on smooth muscle cells [30]. The ethanol extract of *S. repens* had a dose-dependent anti-proliferative effect [31]. DIBOA (2,4-dihydroxy-2H-1,4-benzoxa- zin-3(4H)-one) which is a cyclic hydroxamic acid and fraction designated V-7 (FV-7) of cernilton caused resembling inhibitory effects on cell growth [32]. Red clover isoflavones suppressed the proliferation of human BPH stromal cells, but it was frailer than finasteride, a 5alpha-reductase inhibitor [33]. Extracts of *Vitex agnus-castus* fruits encompass components which have anti-proliferative properties [34]. Apigenin had a dose-dependent inhibition on cell proliferation. Fruits and vegetables, such as orange, parsley, onions, chamomile, and tea involve apigenin [35].

### *Anti-Inflammatory Activity*

Both the water and ethanol extracts of *Hypoxis hemerocallidea* and *E. parviflorum* scavenged the hydroxyl radical. The ethanol extracts revealed the strongest activity in inhibition of COX-1 (Cyclooxygenase-1) catalysed prostaglandin biosynthesis. Furthermore, the ethanol extract of *E. parviflorum* showed inhibitory effects on not only the COX-1 but also -2 catalysed prostaglandin biosynthesis. In another study, the aqueous acetone extract of *E. parviflorum* exerted anti-inflammatory and lipid peroxidation inhibitory effects in addition to antioxidant activity [36, 37].

### *Antioxidant Activity*

Cells unprotected to lycopene secreted lycopene-enriched exosomes that could enact a vital role in reducing degradation of this antioxidant, and maximized the efficacy [38].

## Animal Studies

### *5α-Reductase Inhibitory Activity*

Both the petroleum ether extract of fruit of *Citrullus colocynthis* and a steroidal compound isolated from that inhibited 5α-reductase [39]. Coconut oil declined the increase in two index of testosterone-induced prostatic hyperplasia (PH) i.e. prostate weight (PW) and PW: body weight (BW) ratio [40]. Tamsulosin, D-004, and Saw palmetto noticeably diminished PH induced with testosterone and the atypical one induced with phenylephrine (PHE) in the rat. D-004 unveiled resembling effectiveness to Saw palmetto, but less than tamsulosin, a selective α(1A)-adrenoceptor antagonist. Tamsulosin (0.05 and 0.1 mg/kg) and D-004 (400-800 mg/kg) in a dose-depend manner also impeded volume voided per micturition (VM) reduction induced with PHE, and their combined therapy demonstrated the superior effects [41].

### *Anti-Androgen Activity*

Sinalbin and β-sitosterol of *Brassica alba* seed extract showed anti-androgen and anti-inflammatory activities [42]. Lycopene, the red carotenoid of tomato, dwindled local prostatic androgen signaling, insulin-like growth factor 1(IGF-I) expression, and basal inflammatory signals in normal prostate tissue [43]. The aqueous ethanol extract of Lygodii Spora including oleic, linoleic, and palmitic acids had anti-androgenic activity [44]. Both co-treatment and post-treatment with tadenan (made of extract of *P. africanum*) inhibited the effects of DHT on micturition. Furthermore, co-treatment blocked increase in PW [45]. Saw Palmetto extract and Cernilton affected PH through influence on androgen

**Table 2. Animal Studies**

| Plant | Family | Part of Plant | Active Component | Animal | Model | Effect | Ref. |
|---|---|---|---|---|---|---|---|
| *Anemarrhena asphodeloides* Bunge, *Phellodendron amurense* Rupr, *Cinnamomum cassia* Nees | Agavaceae Rutaceae Lauraceae | ZSPE (Zi-Shen Pill extract) | | Rats | Testosterone (T)-induced prostate hyperplasia (PH) after castration | ↓PW, ↓prostatic index, and serum DHT levels | [6] |
| *Brassica alba* | Brassicaceae | Sinalbin and β-sitosterol (a mixture of phytosterols) of seed extract | Sinalbin, β-sitosterol | Mice | T-induced PH | Anti-androgen and anti-inflammation activities | [42] |
| *Chimaphila umbellata, Populus tremula, Pulsatilla pratensis, Equisetum arvense, Triticum aestivum* | Ericaceae Salicaceae Ranunculaceae Equisetaceae Poaceae | Eviprostat (a combination of constituents of these plants) | | Rats | Surgically induced partial bladder-outlet obstruction | Anti-inflammatory activity | [1] |
| *Chimaphila umbellata, Populus tremula, Pulsatilla pratensis, Equisetum arvense, Triticum aestivum* | Ericaceae Salicaceae Ranunculaceae Equisetaceae Poaceae | Eviprostat | | Rabbits | Surgically induced partial bladder-outlet obstruction | Antioxidant activity | [70] |
| *Citrullus colocynthis* Schard | Cucurbitaceae | Petroleum ether extract of fruit | Steroidal compound | Rats | T-induced PH | 5α-reductase inhibitory activity | [39] |
| *Cocos nucifera* L. | Arecaceae | Coconut oil | Lauric and myristic acids | Rats | T-induced PH | Probably 5α-reductase inhibitory activity | [40] |
| *Cucurbita pepo* L. | Cucurbitaceae | Seed | Palmitic, stearic oleic, and linoleic acids, protein, and carbohydrates | Rats | BPH induced with citral | Alleviation of BPH symptoms | [66] |
| *Cucurbita pepo* L. | Cucurbitaceae | Seed | | Rats | Testosterone/ prazosin-induced (T-P) prostate growth | ↓PW:BW and protein synthesis | [67] |
| *Cucurbita pepo* L. | Cucurbitaceae | Seed oil | | Rats | T-induced PH | Inhibition of T-induced hyperplasia | [68] |
| *Curcuma longa+ Zingiber officinale* | Zingiberaceae | Combination of ethanol extracts | | Rats | Normal immature rats | Inhibition of the growth of prostate with little effect on testis growth | [58] |
| | | | 3'-daidzein sulfonate sodium (DSS) | Mice | TP-induced PH | ↓PW, ↓prostate index, ↓serum T, ↓estradiol (E) contents and the T/E2 ratio | [55] |
| | | | Daidzein (Phytoestrogen) | Rats | T-induced PH | Preventive effect on PH | [68] |
| *Echinacea purpurea* (L.) Moench. | Asteraceae | Root | | Rats | BPH induced with estradiol depot and testosterone | Prevent the development of BPH | [56] |
| *Echinacea purpurea* (L.) Moench. | Asteraceae | Root | | Rats | Normal rats | ↓Percentage of testicle and the body mass | [57] |

**(Table 2) contd…..**

| Plant | Family | Part of Plant | Active Component | Animal | Model | Effect | Ref. |
|---|---|---|---|---|---|---|---|
| *Glycine max* (L.) Merr. | Fabaceae | Soybean isoflavone | Isoflavone | Rats | Testosterone propionate (TP)-induced PH | Inhibition of PH, ↑ the expressions of nitric oxide and nitric oxide synthase | [63] |
| *Glycine max* (L.) Merr. | Fabaceae | Soybean isoflavone | Isoflavone | Rats | TP-induced PH | Inhibition of PH, ↑ acid phosphatase and prostate-specific acid phosphatase (PAP) in a dose-dependent manner | [62] |
| *Glycine max* (L.) Merr.+curcumin | Fabaceae+curcumin isolated from ginger family | Soybean isoflavone+curcumin | Isoflavone+curcumin | Mice | Extragenous testosterone administrated by intra-peritoneum | Anti-proliferative activity | [64] |
| *Lepidium latifolium* | Brassicaceae | 50% juice plant+ 50% glycerine (suspension) | | Rats | BPH induced by steroid treatment | ↓Prostate size and volume | [71] |
| *Lepidium meyenii* | Brassicaceae | Aqueous and hydro alcoholic extracts | Benzyl glucosinolate | Rats | Testosterone enanthate (TE) induced BPH | ↓Prostate size | [51] |
| *Lepidium meyenii* | Brassicaceae | Freeze-dried aqueous extract | Benzyl glucosinolate | Rats | Testosterone enanthate (TE) induced BPH | ↓PW in a dose-dependent manner | [52] |
| | | Lycopene | Lycopene | Rats | Normal rats | Anti-androgen and anti-inflammatory activities, ↓IGF-I expression | [43] |
| *Lygodium japonicum* (Thunb.) Sw. | Lygodiaceae | Aqueous ethanol extract of spore | Oleic, linoleic, and palmitic acids | Hamsters, mice | T- or dihydrotestosterone (DHT) - induced PH | Anti-androgenic activity | [12] |
| *Pygeum africanum* | Rosaceae | Extract of bark (Tadenan) | | Rats | DHT-induced prostate growth | Suppressing effects of DHT on prostate | [45] |
| *Roystonea regia, Serenoa repens* | Arecacea | D-004, Saw palmetto lipid extract | | Rats | T-induced PH, Phenylephrine-induced change in prostate tissue, | ↓Volume voided per micturition, ↓PH | [41] |
| *Scutellaria baicalensis* | Lamiaceae | Baicalein | Baicalein | Mice, rats | TP and transplantation of homologous strain fetal mouse urogenital sinus induced PH | Inhibitory effect on PH | [65] |
| *Secale cereal* ±*Serenoa repens* | Poaceae | A water soluble and fat soluble extract (Cernitin)± Saw palmetto Extract of fruit | | Rats | Androgen-induced prostatic enlargement | ↓Prostate size | [46] |
| *Serenoa repens* | Arecacea | Extract of saw palmetto fruit | | Dogs | Dog with BPH | No significantly effect, no adverse effect | [47] |
| *Serenoa repens* | Arecacea | Lipidosterolic extract | | Rats | Hyper prolactinemia (PRL)- induced PH | Anti-androgen effect and ↓the trophic effect of PRL in rat lateral PH | [48] |

**(Table 2) contd…..**

| Plant | Family | Part of Plant | Active Component | Animal | Model | Effect | Ref. |
|---|---|---|---|---|---|---|---|
| *Sophora flavescentis* Ait. | Fabaceae | Extract | | Rats | Rats castrated were administered exogenous testosterone | Anti-proliferative effect | [59] |
| *Theobroma cacao* L. | Sterculiaceae | ACTICOA powder | Polyphenolic compounds | Rats | TP-induced PH | Prevention PH | [53] |
| *Theobroma cacao* L. | Sterculiaceae | ACTICOA powder | Polyphenolic compounds | Rats | TP-induced PH | Effective for reducing established PH | [54] |
| *Trifolium pratense* L. | Fabaceae | Red clover isoflavones | Isoflavones | Mice | Normal mice | Anti-androgenic activity | [49] |
| *Trifolium pratense* L. | Fabaceae | Red clover isoflavones | Isoflavones | Mice | Normal mice | ↓Neoplastic transformation | [50] |
| *Urtica dioica* L. | Urticaceae | Extract of root | | Mice | BPH-model induced by directly implanting an urogenital sinus (UGS) into the ventral prostate gland | Inhibition of induced growth | [60] |
| *Urtica fissa* | Urticaceae | A crude polysaccharide fraction of roots and stems | Polysaccharides | Rats | TP-induced PH | Anti-proliferative effect on prostatic epithelial cells and fibrotic tissues | [61] |

metabolism. In another study observed that finasteride was merely skillful of impeding the outcome of androgens on rat prostate enlargement, whereas saw palmetto barricaded not only the androgenic but also the trophic effect of prolactin in rat lateral PH. Astoundingly in a study, products encompassing extracts of *S. repens* are, in contrast, widely were announced for men with PH, during 91-day treatment of dogs did not noticeably affect the prostate gland of them [46-48]. Red clover (RC)-derived isoflavones via anti-androgenic properties had obvious effect on prostatic growth, and revealed capacity of reducing the enlarged non-malignant prostate. They also are represented as a non-toxic dietary treatment for decrease in the possible for neoplastic transformation [49, 50]. Hydroalcoholic and aqueous extract of Red Maca encompassing benzyl glucosinolate declined prostate size. It seems to have an inhibitory effect on level of post DHT conversion [51, 52]. ACTICOA powder, a cocoa polyphenolic extract, dose dependently could prevent testosterone propionate (TP)-induced increase in prostate size ratio (prostate weight/rat body weight) and serum DHT level. It was also effective for dropping established PH [53, 54]. 3'-Daidzein sulfonate sodium (DSS) exhibited vigorous antagonistic action on BPH induced in mice, which may conclude its adjusting effect on the sex hormone balance [55]. An extract isolated from traditional Chinese medicine Zi-Shen Pill (ZSPE) conspicuously reduced PW, prostatic index, serum DHT levels, and the pathological changes in BPH. Besides, the expressions of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in prostate were blocked during treatment, while the levels of transforming growth factor-beta1 (TGF-beta1) were augmented [6]. Purple cone flower extract evidently diminished the prostate mass in rats with hyperplasia and normal ones. It also reversed degenerative changes in histological structures [56, 57].

### *Anti-Proliferative Activity*

The ethanol extract of Curcuma and Ginger prevented the growth of prostate with little effect on the growth of testis [58]. The extract of *Sophora flavescentis* prevented cell proliferation without evident pertinence to apoptosis [59].

The 20% methanol extract of *U. dioica* root showed the most inhibitory effect on induced cell growth [60]. Crude polysaccharide fraction of *U. fissa* extract remarkably prevented the proliferation of prostatic epithelial cells and fibrotic tissues [61]. Soybean isoflavone dose-dependently inhibited prostate hyperplasia and the increase in acid phosphatase and prostate-specific acid phosphatase (PAP) in rats, whereas it amplified the expressions of nitric oxide (NO) and NO synthase. Besides, Soybean isoflavone+curcu min unveiled anti-proliferative effects [62-64]. Baicalein of the *Scutellaria baicalensis* had an inhibitory consequence on PH in experimental animals [65]. Pumpkin seeds can lessen protein binding prostate (PBP) levels, PW, and improve histology of testis. Pumpkin seed oil alone or in combination with Phytosterol-F conspicuously blocked the increases in PW: BW ratio and protein synthesis [66-68]. The wet weight and the index of the prostate, and secretions in the glandular cavity were obviously declined in rats treated with Daidzein. Nonetheless, expression of estrogen receptor α (ER α) did not have any evident difference between the model group and the other groups, that of ER β was noticeably dwindled in comparison to the normal control [69].

**Table 3. Human Studies**

| Plant | Family | Part of Plant | Active Component | Study Design | No. of Patient | Comparator | Duration of Treatment | Effect | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| *Allium sativum* L. | Alliaceae | Aqueous garlic extract | | Clinical trial | 27 | Pre - treatment parameters | 1 m | ↓Mass of prostate, ↓urinary frequency, ↑urine flow rate | [93] |
| *Bixa Orellana* L. | Bixaceae | | | Double-blind randomized placebo-controlled study | 136 | Placebo | 12 m | No effect | [7] |
| *Chimaphila umbellata* (L.) Barton, *Populus tremula*, *Pulsatilla pratensis* (L.) Mill., *Equisetum arvense* L., *Triticum aestivum* L. | Ericaceae Salicaceae Ranunculaceae Equisetaceae Poaceae | Eviprostat | | Clinical trial | 9 | Pre - treatment parameters | 4 w | ↓IPSS and QoL score, ↑lower urinary 8-OHdG levels (the urinary oxidative stress marker) | [70] |
| *Chimaphila umbellata* (L.) Barton, *Populus tremula*, *Pulsatilla pratensis* (L.) Mill., *Equisetum arvense* L., *Triticum aestivum* L. | Ericaceae Salicaceae Ranunculaceae Equisetaceae Poaceae | Eviprostat | | Open, multi-central clinical trial | 100 | Pre - treatment parameters | 3 m | ↓IPSS, QOL score, Qmax, Qave, Ru, and PSA level | [91] |
| *Cucurbita pepo* L. | Cucurbitaceae | Pumpkin seed oil | | Randomized, double-blind, placebo-controlled trial | 47 | Placebo | 12 m | ↓IPSS and improved QoL score | [81] |
| *Cucurbita pepo* L. | Cucurbitaceae | Pumpkin seed extract (Prosta Fink Forte capsule) | | Multi centric surveillance study | 2245 | Pre-treatment parameters | 12 m | ↓IPSS and improved QoL score | [85] |
| *Cucurbita pepo* L. | Cucurbitaceae | Pumpkin seed oil capsules (Peponen) | | | 60 | Pre-treatment parameters | 10 m | ↑Uroflow, relief of dysuria and painful discharge, ↓the frequency of nocturnal urination | [86] |
| *Cucurbita pepo* L., *Serenoa repens* (Bartram) Small. | Cucurbitaceae Arecacea | Curbicin | Curbicin | Randomized, double-blind study | 53 | Placebo | 3 m | Improvement in urinary flow, micturition time, Ru, and frequency of micturition | [87] |
| | | | β-sitosterol | Randomized, double-blind, placebo-controlled multi-center study | 200 | Placebo | 6 m | ↓IPSS, ↓mean residual urinary volume, and ↑peak flow | [90] |
| *Linum usitatissimum* L. | Linaceae | A flaxseed lignan extract | Secoisolariciresinol diglucoside (SDG) | Randomized, double-blind, placebo-controlled clinical trial | 78 | Placebo | 4 m | ↓IPSS and QOL score, ↑Maximum urinary flows, ↓post voiding urine volume | [94] |
| *Pygeum africanum* | Rosaseae | Extract | | Randomized controlled clinical trials | 1562 | Placebo and standard BPH medications | 64 d | Improvement in urologic symptoms and Flow measures | [72] |

**(Table 3) contd…..**

| Plant | Family | Part of Plant | Active Component | Study Design | No. of Patient | Comparator | Duration of Treatment | Effect | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| *Pygeum africanum* | Rosaseae | Extract | | Placebo-controlled double-blind multicenter study | 263 | Placebo | 60 d | Clinical improvement of BPH | [73] |
| *Pygeum africanum* | Rosaseae | Extract | | Randomized, double-blind study, with long-term open label extension | 209 | Comparison of once and twice daily dosage forms and Pre-treatment parameters | 12 m | ↓IPSS and QOL score, ↑Qmax | [74] |
| *Pygeum africanum+Urtica dioica* L. | Rosaseae Urticaceae | Combination of extracts | | Double-blind, randomized, placebo controlled trial | 49 | Placebo | 6 m | Similar to placebo | [75] |
| *Pygeum africanum+Urtica dioica* L. | Rosaseae Urticaceae | Combination of extracts | | Double-blind comparison of two doses | 134 | Comparison of half and full standard dose and Pre-treatment parameters | 8 w | ↓Urine flow, Ru, and nycturia | [76] |
| *Roystonea regia* | Arecaceae | D-004 | | Randomized, double-blind and placebo-controlled study | 34 | Placebo | 6 w | Antioxidant effects on plasma oxidative markers in healthy men | [92] |
| *Secale cereal* L. | Poaceae | Cernilton (Pollen extract) | | Randomized controlled trial | 240 | Control group and pre treatment parameters | 4 y | Improving symptomatic BPH and preventing the clinical progression of BPH | [96] |
| *Serenoa repens* Bartam. | Arecacea | Permixon (fruit extract) | | Randomized study | 144 | Control group | 2 m | ↓Intra- and post-operative complications | [77] |
| *Serenoa repens* Bartam. | Arecacea | Permixon | | Double-blind randomized controlled trial | 704 | Tamsulosin | 12 m | ↓IPSS and QOL score | [78] |
| *Serenoa repens* Bartam. | Arecacea | Extract of the berry of fruit | | Double-blind randomized placebo controlled trial | 44 | Placebo | 6 | Slightly better than placebo | [79] |
| *Serenoa repens* Bartam. | Arecacea | Permixon | | Randomized placebo clinical trials and open-label trials | 4280 | Placebo | 21-720 D | ↑Peak flow rate, ↓IPSS, ↓ nocturia | [80] |
| *Serenoarepens* (Bartram) Small. | Arecacea | Oil | | Randomized, double-blind, placebo-controlled trial | 47 | Placebo | 12 m | ↓IPSS, ↑Qmax, improved QoL | [81] |
| *Serenoarepens* (Bartram) Small.+*Urtica dioica* L. | Arecacea Urticaceae | Combination of ethanolic extracts of sabal fruit and urtica root (PRO 160/120) | | Placebo-controlled double-blind multicenter study | 257 | Placebo | 48 w | ↓IPSS, improved obstructive and irritative symptoms | [82] |
| *Serenoa repens* (Bartram) Small.+*Urtica dioica* L. | Arecacea Urticaceae | PRO 160/120 | | Open-label extension of a randomized, double-blind clinical trial | 257 | Placebo, pre-treatment parameters | 96 w | ↓IPSS, ↑peak and average urinary flow increased, and ↓Ru volume | [83] |

**(Table 3) contd…..**

| Plant | Family | Part of Plant | Active Component | Study Design | No. of Patient | Comparator | Duration of Treatment | Effect | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| *Serenoa repens* (Bartram) Small.+*Urtica dioica* L. | Arecacea Urticaceae | PRO 160/120 | | Randomized, multicenter, double-blind clinical trial | 543 | Finasteride | 24 w | ↓IPSS, ↑urinary flow | [84] |
| *Tribulus terrestris* L, *Caesalpinia bonducella* (L.) Fleming, *Asparagus racemosus* Willd., *Areca catechu* L., *Crataeva nurvala* Buch-Ham. | Zygophyllaceae, Fabaceae, Asparagaceae, Arecaceae, Capparaceae | PR-2000 (multiple plants extracts) | | Open, non-comparative clinical trial | 68 | Pre - treatment parameters | 6 m | ↓AUA score, ↑peak flow rate ↓prostate size | [2] |
| *Tribulus terrestris* L, *Caesalpinia bonducella* (L.) Fleming, *Asparagus racemosus* Willd., *Areca catechu* L., *Crataeva nurvala* Buch-Ham. | Zygophyllaceae, Fabaceae, Asparagaceae, Arecaceae, Capparaceae | PR-2000 | | Randomized-double-blind, placebo-control study | 30 | Pre - treatment parameters | 5 m | ↓Prostatic volume, ↓AUA score, ↓ urine residual volume | [95] |
| *Trifolium pretense* L. | Fabaceae | Extract | Isoflavone | Clinical trial | 20 | Pre-treatment parameters | 1y | ↓PSA level, prostate volume, and IPSS | [97] |
| *Urtica dioica* L. | Urticaceae | Extract | | Double-blind, placebo-controlled, randomized, partial crossover, comparative trial | 558 | Placebo | 18 m | Improvement in IPSS, Qmax and Peak flow rates, a mild decrease in prostate size | [88] |
| *Urtia dioica* L. | Urticaceae | Bazoton uno (dry extract of root) | | Rrandomized, double-blind, placebo controlled multicenter study | 246 | Placebo | 1y | ↓IPSS and residual volume,↑Qmax | [89] |
| *Vaccinium macrocarpon* Aiton. | Ericaceae | | | Randomized controlled trial | 42 | Placebo | 6 m | Improvement in LUTS and urination parameters | [98] |
| *Pteris multifidae* | | Fengweicao granule (FWCG), | | Clinical trial | 155 | Finasteride | 3 m | Improvement in IPSS and Ru | [99] |

**Abbreviation:** d; day, w; week, m; month, y; year, PW; prostate weight, IPSS; the total International Prostate Symptom Score, QoL score; quality of life, 8-OHdG; 8-hydroxy-2'-deoxyguanosine, Qmax; maximum urinary flow rate, Qave; average urinary flow rate, Ru; residual urine, AUA; the American Urological Association, SHBG; sex hormone binding globulin.

### *Anti-Inflammatory Activity*

Eviprostat, a combination of constituents from multiple natural sources, suppressed expression of NF-kappa B, and pro-inflammatory cytokines at the transcriptional level. It also had antioxidant effect [1, 70].

### *Lepidium Latifolium Being Useful in the Alleviation of BPH with Unclear Mechanism*

An integral suspension of the plant meaningfully reduced prostate volume and size in rats with unclear function that may be due to the presence of flavonoids [71].

## Human Studies

### *Anti-Androgen Activity*

The extract of *P. africanum* significantly alleviate urologic symptoms and flow measures in comparison with the placebo group. No evident side effects were observed in subjects. Furthermore, the combination of 25 mg *P. africanum* and 300 mg stinging nettle extracts had effects corresponding to placebo. Five patients reported adverse effects during treatment [72-76]. *S. repens* was not more effective than finasteride or tamsulosin. It caused a significant improvement in peak flow rate and increase in

nocturia better than placebo. Pre-treatment with *S. repens* before surgery for BPH is effective in lessening intra- and postoperative complications. In contrast, in a trial revealed that Permixon (fruit extract) and tamsulosin are equal in the medical treatment of LUTS in patients with BPH, during and up to 12 months of therapy. PRO 160/120 (combination of ethanolic extracts of sabal fruit and urtica root) was significantly better than placebo in alleviation of LUTS. It enhanced obstructive and irritative signs, and was beneficial for patients with moderate and severe symptoms. The subjects showed good tolerance to the plant extract. In addition, the effectiveness of both PRO 160/120 was similar to finasteride and independent to prostate volume with better tolerability in patients [77-84].

### *Anti-Proliferative Activity*

Administrations of pumpkin seed oil and saw palmetto oil was clinically safe and effective. Hence, they are suggested as complementary and alternative treatments for BPH. Prosta Fink Forte capsule (pumpkin seed extract) showed more beneficial effects on BPH symptoms in early stages [81, 85-87].

### *Anti-Inflammatory Activity*

*U. dioica* had notable effects in the treatment of symptomatic BPH. Treatment with Bazoton uno (dry extract of root) could decrease irritative symptoms and benign prostatic syndrome (BPS)-associated complications because of the postulated anti-phlogistic and anti-proliferative properties of the stinging nettle extract. It was tolerated by patients well and no side effects were reported [88, 89]. β-sitosterol caused conspicuous improvement in symptoms and urinary flow parameters, indicating effectiveness of β-sitosterol in BPH treatment that like β-sitosterol of *B. alba* seed extract might be due to androgen and anti-inflammatory activities [90].

### *Antioxidant Activity*

The patients who received Eviprostat showed improvement in symptoms of BPH. It seems the antioxidant activity of Eviprostat is liable for its beneficial effects [70, 91]. Treatment with D-004 caused reductions of plasma malondialdehyde (MDA), total hydroxyl peroxides (TOH), sulphydryl (SH) groups and total antioxidant status (TAS), presenting antioxidant effects on plasma oxidative markers in healthy men [92].

## The Plants Being Useful in the Alleviation of BPH with Unclear Mechanism

### *Allium sativum* L.

Garlic extract caused obvious improvement in disease parameters of BPH [93].

### *Linum usitatissimum* L.

Flaxseed lignan extract significantly caused alleviation in lower urinary tract symptoms (LUTS) in BPH patients being comparable to α1A-adrenoceptor blockers and 5α-reductase inhibitors commonly used [94].

### *Tribulus terrestris L+Caesalpinia bonducella* (L.) Fleming+*Asparagus racemosus* Willd.+*Areca catechu* L.+*Crataeva nurvala* Buch-Ham.

The results of trial showed improvement in the American Urological Association (AUA) symptom score with PR-2000, a herbal formulation. Pelvic ultrasonography unveiled a decline in the average size of prostate, while no change in biochemical markers and no unpleasant side effects were observed during the study [2, 95].

### *Secale cereal* L.

Cernilton in comparison with control group, improved the total International Prostate Symptom Score (IPSS), maximum urinary flow rate (Qmax), and post-void residual urine, but there were no obvious changes in PSA between the pre-and post-treatment of the experimental or control group. No adverse effects were reported in subjects [96].

### *Trifolium pretense* L.

An isoflavone extract remarkably augmented liver transaminases and caused a decrease in total PSA levels. The patients indicated no side effects [97].

### *Vaccinium macrocarpon* Aiton.

The patients who received cranberry discernibly showed an improvement in IPSS, QoL, urination parameters encompassing voiding parameters (rate of urine flow, average flow, total volume and post-void Ru volume), and lower total PSA level. On the other hand, no influence on blood testosterone or serum C-reactive protein (CRP) levels were observed. Besides, no statistically notable improvement in the control group were detected [98].

### *Pteris multifidae*

IPSS, maximum flowing rate of urine (MFR) and Ru conspicuously alleviated in both groups of finasteride and Fengweicao granule (FWCG), a Chinese herbal preparation made of herba Pteris multifidae, but with no remarkable change in the volume of prostate. Furthermore, FWCG revealed less adverse reaction in comparison to finasteride [99].

## DISCUSSION

In this review, we collected and discussed the plants which can be effective in the relief of BPH, without date limitation. They are considered beneficial due to different mechanisms encompassing anti-androgenic, anti-spasmolytic, antioxidant, anti-inflammatory, 5α-reductas inhibitory, anti-proliferative, and apoptotic effects, and alleviation of BPH symptoms. Atraric acid, n-butylbenzene-sulfonamide, curbicin, and penta-O-galloyl-b-D-glucose showed anti-androgenic effect [11, 20, 22, 87]. The plants with flavonoids encompassing naringenin, luteolin, kaempferol, kaempferol 3-(3-E-p-coumaroyl-alpha-L-rhamnopyranoside), kaempferol 3-(2,3-di-E-p--alpha-L-rhamnopyranoside), icaritin, xanthohumol, baicalein, and soybean isoflavone had anti-BPH effects, such as 5α-reductase enzyme inhibitory or anti-proliferative consequences [9, 24, 27-

29, 65]. Fatty acids such as oleic, linoleic, γ-linolenic, lauric myristic, and palmitic acids could inhibit 5α-reductase enzyme [15, 17]. The plants including phenolic and steroidal components revealed vigorous effect on BPH. For illustration, OeB showed anti-proliferative action, β-sitosterol exhibited anti-inflammatory and anti-androgenic effects in mice, and theaflavin-3,30-digallate unveiled anti-androgenic influence [11, 24, 26, 42]. Lycopene, a carotene compound, shed anti-oxidant, anti-androgenic, and anti-inflammatory effects [38, 43]. Emodin, an anthraquinone derivative, inhibited 5α-reductase enzyme [14]. The plants with glucosinolate derivative i.e. sinalbin caused anti-BPH effects [42, 51]. Lginans such as secoisolariciresinol diglucoside alleviated symptoms of patients [94]. The plants with diarylheptanoids as *A. officinarum* showed 5α-reductase inhibitory activity [8]. Polysaccharides in some plants like *U. fissa* may be liable for anti-BPH effect [61]. *S. repens*, *P. africanum*, *C. pepo*, and *U. dioica* are the most prevalent plants used to treat BPH [100]. On the other hand, their liable compounds are not exactly recognized. Effects of these plants may be due to existence of constituents such as fatty acids, phytosterols, β-carotenes, lutein, γ- and β-tocopherols, lignans, and polysaccharides [30, 31, 67, 100, 101]. The effects of *U. dioica* in diabetes was recently reviewed and antioxidant effects were found the major mechanism of beneficial effects [102] that can be extended to BPH too [103]. Also in support of the present findings, phytoestrogens were found effective in prevention of bone resorption in postmenopausal women as evidenced by a major meta-analysis [104]. Interestingly, combination of β-carotenes and *U. dioica* is found more beneficial by increasing antioxidant potential and effectiveness in a broad range of diseases related to oxidative stress [105]. In this regard, with the same mechanism of action the *Satureja* species were found effective in many oxidative stress related disorders including male reproductive system [106] that needs to be studied for BPH.

Therefore, although some mechanisms are clear but further studies are still needed to identify complete efficacy of these natural products in both animal models and human trials.

## CONCLUSION

There are few effective chemical drugs in treatment of BPH, which have several adverse effects [7]. In contrast, there are numerous plants having valuable effects in treatment of BPH with long history of use, which amplifies interest in carrying out of immense studies for finding new drugs being more effective in BPH which has high prevalence between old men [1].

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## CONFLICT OF INTEREST

Declared none.

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