

Review Article

The Pharmacological Effects of Natural Products and Herbs in Benign Prostatic Hyperplasia

Kao CL¹, Hsieh CJ¹, Chen CY² and Liu CM^{1*}¹Department of Nursing, Tzu Hui Institute of Technology, Taiwan²School of Medical and Health Sciences, Fooyin University, Taiwan***Corresponding author:** Liu CM, Department of Nursing, Tzu Hui Institute of Technology, Pingtung County 92641, Taiwan, Tel: +886-8-8647367, ext. 248; Fax: +886-8-8647123; Email: beagleliu@gmail.com**Received:** July 04, 2014; **Accepted:** November 26, 2014; **Published:** November 29, 2014**Abstract**

Benign Prostatic Hyperplasia (BPH) is a common disease in older men. The symptoms of BPH is urination frequency, frequent night urination and a sense of urgency. Herbal medicine is commonly used as a treatment for BPH. Herbs and natural products are acceptable for improving quality of life or adjuvant use in Western countries. In this review article, we will introduce the pharmacological action of herbs and natural products in controlling the lower urinary tract symptoms associated with BPH.

Method: This review gathers the information from electronic and scientific literature database such as Pubmed, Medline, ScienceDirect and so on. In this review, we focus on the pharmacological effects of *Serenoa repenes*, lycopene (extraction from tomato), *Urtica dioica* (root), *Pygeum africanum* (bark).

Conclusions: Phytotherapy is well acceptable for the alleviating the symptoms of BPH. There are a lot of plants with multi-pharmacological effects in the controlling BPH. The active ingredients could be developed as a new drug in the future.

Keyword: Benign prostatic hyperplasia; *Serenoa repens*; *Urtica dioica*; Lycopene; *Pygeum africanum*; Apoptosis

Introduction

The development of BPH (benign prostatic hyperplasia) and LUTS (Lower urinary tract symptoms) correlates with age [1]. The symptoms of BPH include increased urination frequency, frequent night urination and a sense of urgency. The phenomenon is mainly due to enlarged prostate bladder neck oppressed. It is well known that the treatment options include α_1 -adrenoreceptor antagonists, 5 α -reductase inhibitors, transurethral resection of the prostate, transurethral microwave thermotherapy and herbal treatments. α_1 -adrenoreceptor antagonists are currently the preferred first-line therapy for all men with moderate or severe LUTS/BPH [2]. α_1 -adrenoreceptor antagonists relax prostatic and bladder neck smooth muscle and partially relieve LUTS by improving bladder outlet obstruction.

5 α -reductases are a family of enzymes and transform steroid precursors into active hormones and neurosteroids. The 5 α -reductases catalyzed reaction is the rate limiting step in the conversion of testosterone to dihydrotestosterone (DHT) [3]. Testosterone and DHT induces stromal and epithelial cells growth. 5 α -reductase inhibitor such as finasteride inhibits 5 α -reductase blocking the conversion of testosterone to DHT. 5 α -reductase inhibitors, α_1 -adrenoceptor antagonists and plant extracts are available to relieve symptoms of BPH. In the USA, phototherapies are available for BPH as dietary supplements. In this review article, we will focus on plant extracts and reveal the pharmacological mechanisms of actions.

Serenoa repens

Serenoa repens is known as saw palmetto and classified as in the genus *Serena*. The fruits Saw Palmetto Extraction (SPE) is used for the

symptomatic treatment of BPH. SPE contain fatty acids, glycerides, sterols and sitosterol derivates. *Serenoa repens* (Permixon) is a mixture of various compounds from an n-hexane lipido/sterolic extract of American dwarf palm tree (saw palmetto, *Serenoa repens*) [4].

The lipido/sterolic extract of *Serenoa repens* has anti-inflammatory activity, anti-androgen properties and anti-edema effects in the prostate [4-9]. Oleic and lauric acids of SPE have both 5 α -reductase (1 and 2) inhibition activities and play an important role in the treatment of BPH [10]. Oleic and lauric acids of SPE also has α_1 -adrenergic, muscarinic and 1,4-dihydropyridine receptors binding activity in rat tissues [11]. Fatty acid of SPE causes inhibition of prostatic smooth muscle contractions [12]. A clinical study has reported a significant decrease testosterone in BPH patients receiving Permixon (320 mg/day) for 3 months [13]. It is suggested that Permixon has 5 α -reductase (1 and 2) inhibition in human prostate.

Proliferation and apoptosis are physiological mechanisms involved in the maintenance of prostate function. The imbalance of apoptosis and proliferation can cause BPH. SPE has anti-proliferative activity and apoptotic activity in primary prostate cells and BPH patients [14-16]. Moreover, SPE increases bax/bcl-2 ratio and caspase-3 activity in prostatic specimens from BPH patients [14].

Recent studies have shown chronic prostatic inflammation play a major role in the development of BPH [17,18]. Permixon potently antagonizes the cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) metabolites production or suppress the expression of inflammatory mediators such as MCP-1 and VCAM-1 [19,20]. The metabolites form 5-lipoxygenase was inhibited at a concentration of 5 μ g/mL.

The interaction between herb and drug has been concerned because herbs have a lot of constituents. Until now, no drug interaction with SPE has been published. Studies have shown that SPE had no significant effect on cytochrome P-450 (CYP) such as CYP1A2, CYP2D6, CYP2E1, or CYP3A4 [21,22].

Serenoa repens in combination with selenium and lycopene is more effective than saw palmetto alone in controlling BPH [18,23-25]. Study has shown that *serenoa repens* /selenium/lycopene decrease prostatic growth and the effect might contribute from induction of programmed cell death. *Serenoa repens* /selenium/lycopene has potent anti-inflammatory. *Serenoa repens* /selenium/lycopene caused a greater inhibitory effect on the expression of COX-2, 5-LOX and iNOS than palmetto alone *in vitro* study [18].

Lycopene

Lycopene is present in the red vegetables and fruits, which is the red carotenoid pigment. Tomatoes and its products are one of the main sources for lycopene. Oxidative stress damages to biomolecules such as DNA, lipids and proteins, leading to several chronic diseases, including inflammatory disease, cardiovascular disease and cancer [26,27]. Chronic and acute inflammation can promote the proliferation of prostate epithelial cells through oxidative stress [28]. By assessing malondialdehyde (MDA), the marker of lipid peroxidation, results showed the evidence of association of oxidative stress in BPH patients [29,30].

The consumption of tomatoes and tomato products significantly reduced plasma prostate specific antigen (PSA) levels in patients with benign prostate hyperplasia [31]. A controlled clinical study reported that lycopene supplementation at a dose of 15 mg/d for 6 month may increase plasma lycopene concentration and inhibit the serum levels of PSA in BPH patients [32].

Lycopene has the ability to reduce oxidative DNA damage [33]. Lycopene is able to against the reactive oxygen species, including hydrogen peroxide, nitrogen dioxide, thyl (RS) and sulphonyl (RSO₂) radicals [34-37]. Evidence suggests that lycopene increased the levels of non-enzymatic antioxidant such as vitamin C, vitamin E and reduced glutathione, and enhancing the activity of the phase II detoxifying enzymes Glutathione Peroxidase (GPx), glutathione-S-transferase (GST) and Glutathione Reductase (GR) [38-40]. Insulin-like growth factor 1 (IGF-I) overexpression causes prostatic epithelial neoplasia [41] and facilitate the emergence of hyperplastic lesions in transgenic mice [38,42].

Lycopene supplementation reduced expression of IGF-I and inflammatory markers such as IL-1 β , L-selectin and MIP-2 (macrophage inflammatory proteins) in normal rats prostate tissue [43]. Experimental studies have shown that lycopene interfere with

Table 1: The pharmacological effects of plant extracts in the treatment of BPH.

Name	Main mechanisms of action
Saw Palmetto extraction	5 α -reductase inhibition; blockage androgen receptors; anti-proliferation; anti-inflammatory activity; prostate smooth muscle relaxation;
Lycopene	5 α -reductase inhibition; anti-proliferation; anti-inflammatory; anti-oxidant activity
Urtica dioica extract	Decreased action of sex hormones; weak 5 α -reductase inhibition
Pygeum africanum extract	5 α -reductase inhibition; anti-inflammatory activity

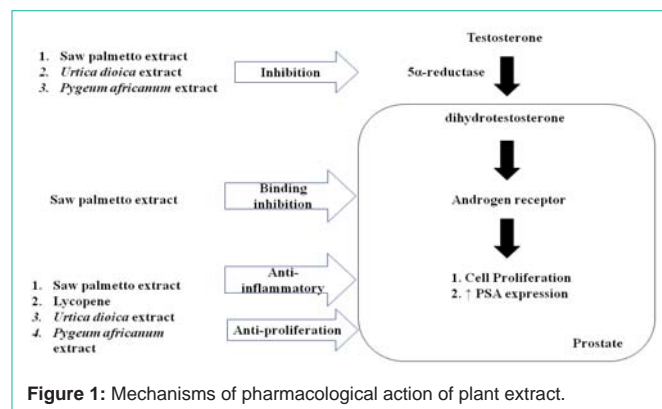
the cell growth in human prostate, mammary and lung cancer cells [44,45]. Lycopene inhibits cell growth cells via regulation cell cycle-related genes, such as cyclins D1 and E, Cyclin-Dependent Kinases (CDK) 2 and CDK4 and p27 [46-48]. Similar results were obtained in inhibition of the growth of normal prostate epithelial cells via down-regulation of cyclin D1 protein expression and consequent cell cycle arrest at the G₀/G₁ phase [49]. Enhanced expression of anti-apoptotic proteins like bcl-2, surviving, leading to a growth imbalance in cell proliferation might promote prostatic hyperplasia [50,51]. Tomato consumption increased the apoptotic index in hyperplastic and neoplastic cells of prostate cancer patients [52], but it has not been found in benign prostate hyperplasia cells [53].

Urtica dioica

Urtica dioica is also called common nettle or stinging nettle native to Europe, Asia, northern Africa, and North America. The plant is used for folk medicine against various diseases. The roots of *Urtica dioica* (Urticaceae) extraction is currently for the treatment of BPH [54-57]. The roots of *Urtica dioica* extraction contain sterols, glycosides, glycoproteins, polysaccharides, fatty acids, and so on. Studies have shown that extractions have anti-proliferation activity associated with sex hormone binding globulin, epidermal growth factor, prostate steroid membrane receptors binding activity and weak 5 α -reductase inhibition [58,59]. An *in vitro* study has shown that the extraction decreased serum testosterone and PSA levels against prostatic hyperplasia induced by testosterone [60]. There is no drug interaction with the extraction to date. The benefit of extraction in the treatment of BPH should be conducted more clinical studies in the future.

Pygeum africanum

Pygeum africanum is extracted from the bark of the African plum tree. It has been used in Europe since 1969 as a treatment of symptomatic BPH [61]. Preliminary clinical studies investigated that *Pygeum africanum* may moderate urologic symptoms and flow measures [62]. In animal models, *Pygeum africanum* extract may significantly improve disorders of micturition, effectively inhibit enlargement of the prostate and reduce prostatic weight [63,64]. A study showed that *Pygeum africanum* extract has 5 α -reductase inhibition activity [65]. In addition, *Pygeum africanum* extract antagonizes 5-lipoxygenase metabolite production in BPH [66]. Moreover, some evidence pointed that *Pygeum africanum* extract has anti-proliferation [67-69] and apoptotic activity in prostatic myofibroblasts and fibroblasts [69].



Conclusion

The pharmacological effects of plant extractions are summarized in Table 1 and Figure 1. There are more and more plant extracts and natural products in the treatment of BPH. Herbs and natural products are usually combined with prescription drugs. Therefore, the active ingredients of natural products should be analyzed and the drug interaction should be concerned. Fortunately, phytotherapy is well tolerated and no serve drug interaction reported by users so far. More clinical studies should be conducted in the future.

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