

Drugs and herbs in two divergent lines of benign prostatic hyperplasia therapy

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Abstract : Prostatic adenoma, or benign prostate hypertrophy (BPH), is a natural and common disease in elderly men. Its etiology is multifactorial. BPH is associated with annoying symptoms and morbid complications. The treatment of BPH with drugs, or synthetic chemicals, damages hepatic and renal tissues developing cirrhosis and kidney failure. As an alternative, there has been recourse to the use of medicinal plants or natural health. Pumpkin seeds, nettle leaves and soybeans have been proven to be potent against pain and discomfort in BPH patients. Moreover, plants used at high doses during a long period as treatment, may be toxic and complicate the lifestyle of BPH patients. Both, drugs and plants, used without precaution is a dilemma of prevention and toxicity. The patients simultaneously consume the drug and plants to anticipate healing. Combined drug-plant therapy could have harmful effects on health due to an accumulating antagonistic synergy of chemical and natural.

Keywords: Benign prostate hypertrophy, drugs, medicinal plants, pumpkin, nettle, soybeans, toxicity.

Introduction

Benign prostatic hyperplasia (BPH) is a common dysfunction clinically characterized by enlargement of the prostate and obstructive symptoms seen in men over the age of 50 (AUA, 2003). This urological pathology is mainly due to the excessive growth of prostatic stromal and epithelial cells. It is reported that 90 % of men over 80 years will have BPH (AUA, 2003; Pagano et al., 2014). The etiology and pathogenesis of BPH are still unclear. Other risk factors such as inflammation, androgens and diet are involved in the development of BPH (Isaacs, 1994). The hormone testosterone and its potent derivative dihydrotestosterone (DHT) are significantly involved in the development of male reproductive organs and thus promote

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the rapid growth of BPH in proportion to the progress of the patient's age (Alonso-Alvarez et al., 2007). Testosterone converted to DHT using the enzyme 5-alpha-reductase. DHT binds to its specific receptors in prostate cells ensuring the growth, proliferation of prostate cells and activates the production of growth factors (FGF, EGF, TGF β , etc.) which play an important role in the stimulation of BPH pathogenesis (Ronti et al., 2006). Drugs, as alpha-blockers, contribute to the relaxation of the smooth muscle fibers of the prostate and the bladder neck. Emptying the bladder during urination is better, which reduces the frequent urge to urinate. The benefits are felt quickly after 2 days of the treatment (Perry et al., 2012). These drugs display some side effects. 5-alpha-reductase inhibitors can reduce the production of dihydrotestosterone (or DHT) (Minutoli et al., 2014). Enzyme (5-alpha-reductase) converts testosterone to its active metabolite DHT. Treatment efficacy is observed 3 to 6 months after the beginning of the treatment. Decreased prostate volume suggested in 25 to 30 % of men treated with these drugs. These chemicals are well known for their adverse effects. The best doctor is nature: it cures three-quarters of illnesses and never says anything bad about her colleagues. The eminent scientist-researcher, in medical and biological sciences, Louis Pasteur said that many plant species are known to have a physiological action, and which are used as curative remedies in the form of powder, extracts, infusion or decoction. Folk medicine, with its armada of aromatic plants, is of great contribution to preventing the BPH. Herbs like pumpkin (*Cucurbita pepo*), nettle (*Urtica dioica*) and soy (*Glycine max*) have already shown their benefits against BPH (Dedhia and McVary, 2008). Talking about the drug dilemma is talking about the pros and cons of drug use. The consumption of synthetic chemicals for years certainly reduces the symptoms of diseases and relieves the patient of his pain but it affects the functioning of the metabolic regulating tissues, namely the liver and the kidneys. Synthetic drugs mainly targeted organs regulated homeostasis. Rural population, for various reasons, had returned to health by the natural or traditional medicine. Aromatic plants also have their own dilemma. From certain doses of essential oils and plant part extracts (roots, leaves, stems, flowers and seeds), herbs will become toxic to human health. Plant toxicity may depend on several factors such as the nature of the solvent used for the extraction, methods of extraction, duration of the treatment, the dose of essential oil or extract used for the phyto-therapeutic cure and the synergetic effects of bioactive compounds (polyphenols, flavonoids, alkaloids, terpenes, tanins, saponosides and carboxylic acids). In this investigation for more effective therapies with fewer side effects, many patients have turned

to herbs as alternative treatments for BPH. But neither drugs nor herbs are free from toxicity whether used alone or in combination.

Historical use

The association of humans with herbs found its origin since the beginning of life on earth. According to the literature, aromatic and medicinal plants have been used as drugs by Egyptian, Chinese and Indians since 5000 years and by Greek 2500 years ago (Ang-Lee et al., 2001). There has been reports mentioned the benefits of using the essential oils and extracts of the leaves or other parts of the plant to cure different pathologies and metabolic disorders, i.e. diabetes, prostatic hyperplasia, inflammation, rheumatoid and hypertension (Farzami et al., 2003). Since a long time, people believed to remedy their illness using natural health. The World Health Organization (WHO) allowed that medicinal plants could be used for their weak toxicity to treat diseases (Tilburt and Kaptchuk, 2008). They have been more used than chemicals because they induce less complication and fewer side effects. Hippocrates, the founder of Greek medicine, used aromatic plants for the treatment of diseases (Lindberg-Madsen and Bertelsen, 1995). Greeks wrote an encyclopedia, entitled *De Materia Medica*, describing 600 useful medicinal plants (Lindberg-Madsen and Bertelsen, 1995). In the 13th and 18th centuries, Persian as Avicenna, Razi, and Ibn al-Baitar, described the properties of almost 1400 plants (Gurib-Fakim, 2006). Folk medicine, or phytotherapy, is worldwide used to prevent pains and ailments due to the modern diseases.

Dosage forms

Herbal dosage forms are the physical form (liquid, solid, semi-solid) of herbal products produced from herbs, with or without excipients, in a particular formulation (such as decoctions, tablets and ointments). They are produced either from herbal materials (such as dried roots or fresh juices) or herbal preparations (such as extracts) (WHO, 2003). Medicinal plants can be used in different ways and forms, including whole all plant, essential oils, aqueous and alcoholic extracts, capsules that contain a powdered form of its dried extract. Plants extracts or yield of essential oils vary in the solvent used for extraction, temperature, and extraction time, a type of the extraction method (decoction, maceration and infusion), the plant parts (roots, leaves, seeds, stems and flowers) (Benzie and Wachtel-Galor, 2011). Decoctions are processed by boiling the herb in water to extract the secondary metabolites or therapeutic bioactive compounds (Green, 2002). Decoctions are used for solid plant materials such as stems and roots. Decoctions are considered as immediate method used, within a 24 to 72 hours as maximum limit (Ghiware et al., 2010). Herbal oils are suspension of herbal

materials dissolved in oil. Infused oils are often called macerated oils (Bruton-Seal and Seal, 2009).

Mechanism of action

Among herbs that prevent the development of benign prostate hypertrophy (BPH), it had been suggested ones most widely used such as *Cucurbita pepo*, *Hypoxis rooperi*, *Pygeum africanum*, *Secale cereale*, *Urtica dioica*, and *Serenoa repens* (Keehn and Lowe, 2015). Experiments have revealed possible mechanisms of action for the preventive phyto-therapeutic compounds. There have been several bioactive molecules described for the management of BPH (figure 01). Studies *in vitro* have showed that different plant part extracts could have antiandrogenic and estrogenic effects, decrease sexual hormone binding globulin, inhibit aromatase, growth factor-stimulated proliferation of prostatic cells, α -adrenoceptors, 5- α -reductase and neutralize reactive oxygen species or free radicals (Colado-Vela'zquez et al., 2015). The detailed mechanisms of action of plant extracts remain unclear.

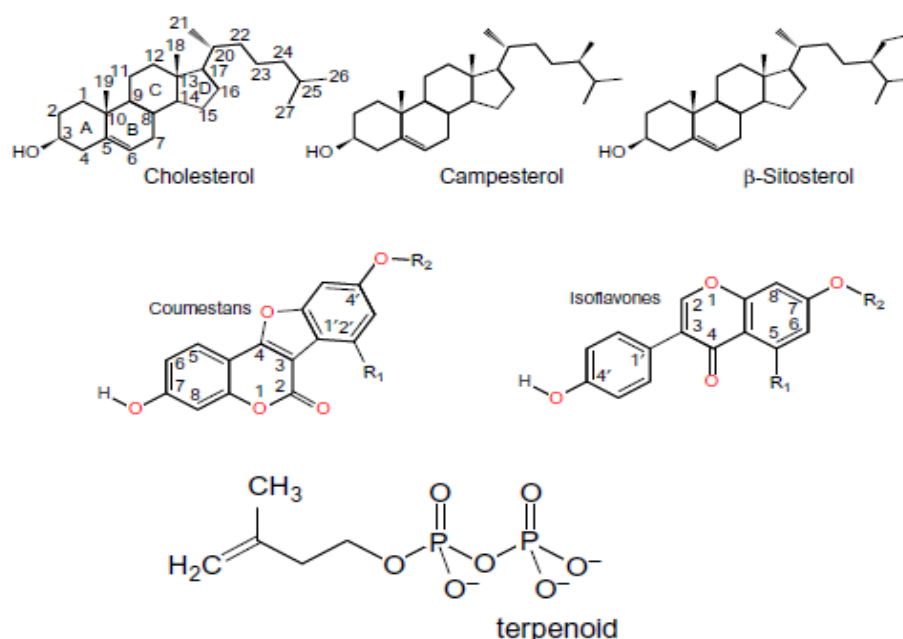


Figure 01: Phyto-therapeutic compounds extracted from plants (Keehn and Lowe, 2015).

In vivo and *in vitro* studies showed that pumpkin seeds have antiandrogen effects and reduce prostate growth (Damiano et al., 2016). Some studies, conducted on rats, showed that *Cucurbita pepo* (or pumpkin) seeds extract resulted in the stopping of the elevation of prostate weight and protein synthesis induced by testosterone and inhibiting testosterone-induced BPH

(Tsai et al., 2006). The phytosterol extracted from pumpkin seeds prevented testosterone-induced BPH by inhibiting the conversion of testosterone to DHT (Gossell-Williams et al., 2008). The Δ^7 -sterols, found in pumpkin seeds, are structurally similar to DHT and could inhibit the binding of DHT to its receptors (Gossell-Williams et al., 2008) (figure 02).

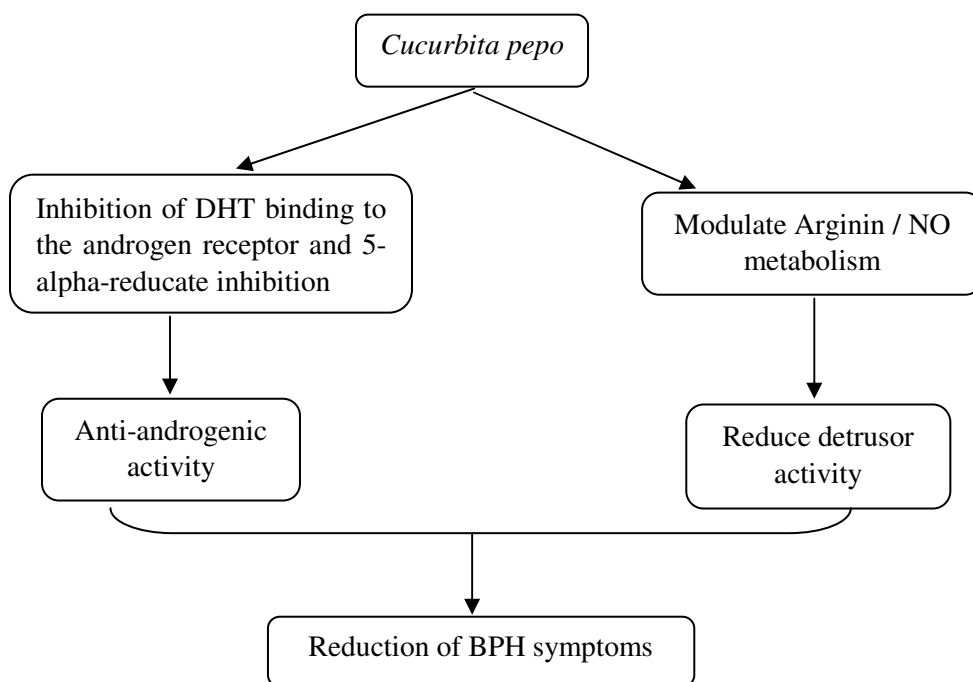


Figure 02: Mechanism of action of *Cucurbita pepo* seeds in the treatment of BPH.

Urtica. dioica, named nettle or stinging nettle, also used to treat BPH (Pagano et al., 2014). The leaves contain sterols (sitosterol), glycoproteins, acids (salicylic, malic, carbonic and formic), flavonoids (rutin, kaempferol and quercetin) and tannins. The roots contain polysaccharides, lectins, sterols and their glucosides (3-beta-sitosterol, sitosterol-3-D-glucoside, etc.), Lignans, fatty acids and scopoletin (Capasso et al., 2003). The lignans inhibits the binding of the SHBG to its receptor in the membrane of human prostatic cells. The lectins can block the binding between the epidermal growth factor, secreted by the prostate tissue, and its receptors, with suppression of prostate cellular metabolism and its growth (Pagano et al., 2014). Stigmasterol and campesterol, contained in roots, contribute to prevent BPH through inhibiting the prostatic sodium/potassium pump (Hirano et al., 1994). Nettle has insignificant effects on 5- α -reductase and does not strongly exert the binding of DHT to the receptor (Konrad et al., 2000) (figure 03).

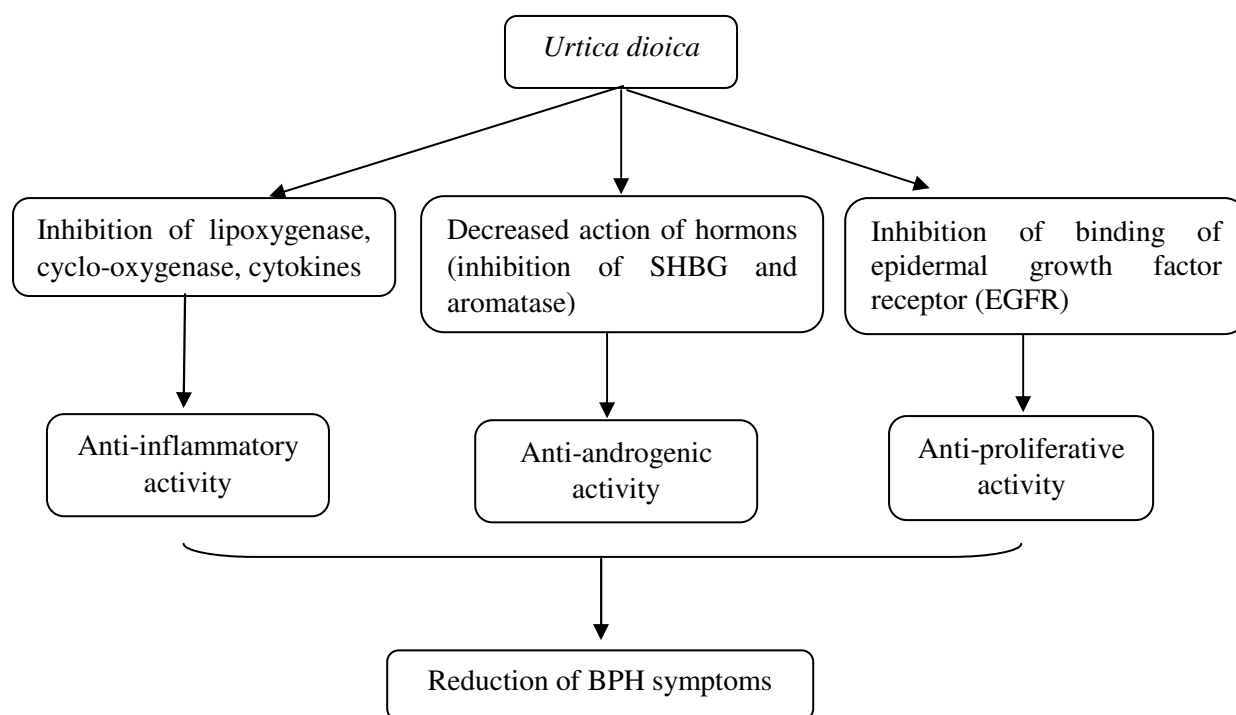


Figure 03: Mechanism of action for *Urtica dioica* nettle in the treatment of BHP.

Clinical studies

There are more three clinical studies that assessed the efficiency of *Cucurbita pepo* seed extracts in BPH patients. The most important study, performed in this field, was that of Friederich et al. led on 2245 men with moderate BPH symptoms. BPH patients were treated daily for 3 months with 1 g of *C. pepo* seed extract. Results showed that 46.1 % with a quality of life improved during therapy. The frequency of nocturnal urination has decreased. A recent German study has investigated the efficiency of *C. pepo* seeds in men with BPH (Vahlensieck et al., 2015). About 1431 elderly men, with BPH symptoms, were daily treated with pumpkin seed (5 g) and placebo (500 mg). After one year of treatment, results revealed a significant response between pumpkin seed and placebo (pumpkin seed extract) illustrated by rates of 58 % and 47 % respectively. Several randomized and double-blind clinical trials have explored the effect of *U. dioica* root extracts on symptoms of BPH. In the widest study, Safarinejad et al. evaluated daily 120 mg of *U. dioica* root in 558 BPH patients (aged 55-72) during 6 months. The rate of 81 %, after treatment, displayed improved quality

of life with a significant reduction of urinary complications. Other clinical studies were carried out to assess the efficacy of different medicinal plants related to the prevention of the BPH development (Table 01).

Table 01: Outcomes of clinical studies (Kane et al., 2011).

Main Author	Year of publication	Journal	Study design	Outcomes / Conclusion
Anceschi	2010	Minerva Urol Nefro	RCT	Treatment with Saw Palmetto in BPH patients is effective in reducing urinary complication
Lee	2009	Urology	RCT	Pluvio extract has been evaluated in BPH patients and IPSS, PSA prostate volume were measured. Pluvio is highly efficient to treat BPH.
Boyle	2004	BJUI	Meta-analysis	Significant improvement in LUTS and flow rate in BPH patients treated with Saw palmetto
Melo	2002	Int Braz J Urol	RCT	Combination of Pygeum and Urtica dioica nettle roots produced urodynamic effects similar to placebo

RTC: randomized clinical trial

Toxicities of synthetic drugs and medicinal plants

Thousands of people wide-world, each year, died from side effects of synthetic drugs. In USA, more people were killed by the toxicities of pharmaceutical drugs (Haq, 2001). Hence, people turn to the traditional medicine because they believe herbs are free from undesirable adverse effects. Although medicinal plants are widely used and considered to be efficient, however, they can potentially be toxic. The poisoning from herbs could be due to the form in which they were sold, or incorrectly prepared and administration route followed by badly trained people. Physicians used herbal medicines as an alternative and non-scientific health-care practice for those without access to “real” medical care (Tolouian and Hernandez, 2013). According to the World Health Organization (WHO), 90 % of the world’s populations rely on traditional medicine for their primary health care including the use of plant extracts or their active components (Robinson and Zhang, 2011). The medical and scientific communities have accepted the use of the medicinal plants because of their potential advantages (Isolated compounds from herbal extracts and natural synergism). However, pharmaceutical industry

has not accepted the phyto-therapy because of lacks safety and efficacy validation and regulations, as well as quality control, mistakes in nomenclature, difficulties in identifying active ingredients and determining their complex modes of action that says the use of herbal medicines showed limitations (Raskin and Ripoll, 2004). From a widely used food and outside the therapeutic role, pumpkin seeds have no toxicity. Prolonged or excessive use may result in a decrease of potassium levels (Reindl et al, 2000). The acute toxicity of nettle is very low (LD50 of aerial plant parts aqueous extracts is 3.625 g / kg body weight, mice, PI) (Lasheras et al., 1986). Drugs, as alpha-blockers (tamsulosin, terazosin, doxazosin and alfuzosin), display adverse effects such as dizziness, fatigue, or low pressure (Perry et al., 2012). The 5-alpha-reductase inhibitors (finasteride and dutasteride) could induce erectile dysfunction in 4 % of men under treatment (Di Silverio et al., 2005).

Medicinal herbs effects in phytomedicine of BPH

Oils extracted from soybean and pumpkin seeds, and nettle alcohol extracts relieve BPH patients' symptoms and complications (Badr et al., 2010; Tsai et al., 2006; Chrubasik et al., 2007; Konrad et al., 2000; Bercovich and Saccomanni, 2010). Pumpkin seed oils contain mainly saturated fatty acids (palmitic and stearic acids) and unsaturated fatty acids (oleic and linoleic acids) (Rabrenovi et al., 2013). Other components, in significant proportions, are proteins and sugar (Rabrenovi et al., 2013; Gossell-Williams et al., 2008). Phytosterols, less than 1 %, have significant pharmacological activities. There are Δ^7 -sterols with their glycosides, Δ^5 -sterols (stigmasterol and campesterol) and tocopherols (vitamin E) well known for their anti-helminthic activity (Rabrenovi et al., 2013; Breinhölder et al., 2002; Mandl et al., 1999). Pharmacological studies have shown that sterols of pumpkin seeds inhibited the binding of dihydrotestosterone (DHT) on cell cultures of prostate (Gossell-Williams et al., 2006; Al-Masry, 2015). In laboratory animals, pumpkin seed oils have shown urodynamic action on the bladder, anti-inflammatory effects, and lower cholesterol (Al-Zuhair et al., 1997). Nettle roots contain scopoletol, phenylpropanic derivatives, monoterpenes, tannins, lignans and their glucosides, lectin and N-acetylglucosamine (Zunino et al., 2017). A study in dogs with BPH has shown that nettle roots could reduce the initial volume of the prostate by 70 % (Bauer, 1992). Bioactive compounds of root extracts inhibit the growth of human prostate cells, but the mechanism of action remains unknown (Upton and Dayu, 2013). Studies suggested the possibility of an interaction between substances in nettle and androgen-binding serum proteins. Interaction induces a change in the concentration of free testosterone and DHT. Bioactive compounds like lignan and octadecenoic acids interfered with the

hormone SHBG (sex hormone-binding globulin) which would reduce its binding capacity (Pagano et al., 2014). It has also been suggested that steroids of nettle root extracts inhibit the activity of the Na^+ , K^+ ATPase membrane of the prostate, which stopped a growth (Hirano et al., 1994). Soybean oil contains carbohydrates (fibers), proteins, phospholipids, isoflavonoids (genistein, daidzein and glycitein), terpenes, saponosides, fatty acids (stearic, palmitic, α -linolenic, oleic and linoleic acids), phytosterols (β -sitosterol, campesterol and stigmasterol), tocopherols (vitamin E) and carotenoids (Antonny, 2000; Nagata et al., 2001). The high oxalate content in soybeans may promote the formation of kidney stones (Massey et al., 2001). Table 02 summarized effects of some herbs compared to those of drugs commonly used by population and sold at pharmacies.

Table 02: Comparison of drugs and herbs in two divergent lines of BPH therapy (Kane et al., 2011).

Main Author	Journal (Year of publication)	Drugs (Outcomes)	Medicinal herbs (Outcomes)
Hutchisson	Eur Urol (2006)	Tamsulosin and finasteride (BPH patients) were most effective and improved urinary symptoms (68 %).	<i>Saw palmetto</i> and <i>Pygeum</i> improved urinary symptoms (43 %).
Debruyne	Eur Urol (2004)	Tamsulosin (0.4 mg daily) improved slightly urinary symptoms.	<i>Saw palmetto</i> (320 mg daily) improved urinary symptoms better.
Sokeland root	J Urol (2000)	Finasteride improved slightly urinary symptoms	Combined Sabal and nettle extract (160/120) had better tolerability than drug.

Conclusion

Any remedy, whatever its nature and composition, has its own advantages and disadvantages. The unavailability of synthetic drugs, their high cost, their side effects and their chemical toxicities prompt the poor and the middle class to use local plants which are cheaper and available. Herbs and drugs are toxic from a certain dose. The question is to know under what conditions and from when we could use one or the other. The use of herbs does not generally involve “drug” actions or adverse effects. Although medicinal plants are widely used and assumed to be efficient, they can potentially be toxic. The toxicity of medicinal plants could

be due to misidentification of the plants, the way they are sold, or ignorance of the preparation and incorrectly administration by inadequately trained people.

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