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PHYTOTHERAPEUTIC APPROACH TO BENIGN PROSTATIC HYPERPLASIA TREATMENT BY PUMPKIN SEED (*CUCURBITA PEPO L.,* CUCURBITACEAE)

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Benign prostatic hyperplasia (BPH) is a noncancerous enlargement of the prostate gland caused by proliferation of both stromal and epithelial cells. BPH develops after the age of 40 and has high morbidity and low mortality rate. Male lower urinary tract symptoms (LUTS) are mostly associated with BPH and they are very common in the ageing population. Herbal medicines have been used for the treatment of numerous chronic and severe diseases. The main aim of phytotherapy in benign prostatic hyperplasia is to relieve symptoms and to improve patient's quality of life (QoL). Pumpkin (*Cucurbita pepo L.*), a member of Cucurbitaceae family, is a herbaceous, monoecious, annual plant. Pumpkin extracts, from different parts of the plant, have shown various therapeutic effects due to their biologically active components. Pumpkin seeds are valued for high proportions of proteins, essential amino acids, fatty acids and microelements. In the therapy of small urinary disorders, prostate gland and the urinary bladder diseases, pumpkin seeds have shown positive results. Synthetic drug therapy and surgical procedures show many side effects and complications, so herbal medicines are promising in mild to moderate BPH. *Acta Medica Medianae 2016;55(3):76-84.*

Key words: benign prostatic hyperplasia, male lower urinary tract symptoms, pumpkin seed, phytotherapy

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Introduction

Benign prostatic hyperplasia (BPH) is considered a public health problem. BPH develops after the age of 40 and has high morbidity and low mortality rate. It ranges in prevalence from over 50% at 60 years of age to as high as 90% by 85 years of age (1).

BPH is a noncancerous enlargement of the prostate gland caused by proliferation of both stromal and epithelial cells. The main underlying mechanism is the change in prostatic androgen metabolism. The conversion rate of testosterone to dihydrotestosterone (DHT) by 5α-reductase increases within the prostate, which results in prostatic accumulation of DHT that causes cell proliferation (2). The voiding dysfunction that appears from prostate gland enlargement and bladder outlet obstruction (BOO) has been generically termed as the lower urinary tract symptoms (LUTS). The problems associated with BPH are usually progressive and considerably affect the quality of life (QoL) (3).

Many herbal medicines have been used for the treatment of numerous chronic and severe diseases. Traditional drugs are relatively safe, easily available and affordable, less toxic with limited side effects compared to synthetic drugs. For such reasons, traditional and complementary medicines have seen an upsurge in their popularity for the treatment of different diseases. Although phytotherapy is widely used in most countries, only few plants received scientific or medical trust (4).

Traditional medicine is a promising area of research in BPH/LUTS therapy. The main aim of the therapy is to relieve symptoms and to improve patient's QoL. These products are usually derived from roots, seeds, berries or fruits of the plants, and are commercialized as extracts that contain a wide range of chemical compounds (phytosterols, fatty acids, flavonoids) (5, 6). Many researchers have investigated the efficacy of these herbs in

preventing the clinical progression of mild to moderate BPH (stages I and II). Phytotherapy for BPH primarily consists of *Serenoa repens* (7-9), *Pygeum africanum* (10-12), *Urtica dioica* (13), *Epilobium spp*. (14), *Hypoxis rooperi* (15), *Secale cereal* (16), and *Cucurbita pepo* (17).

In the present article we summarize the chemical and biological characteristics, and therapeutic potential of pumpkin seed (*C. pepo* L., semen). This article also discusses major advantages and disadvantages of using pumpkin seed for the treatment of BPH/LUTS.

BPH and LUTS

The male lower urinary tract symptoms (LUTS) are mostly associated with BPH and they are very common with the ageing population. Male LUTS etiology except BPH involves age-related bladder dysfunction, malignant prostatic diseases, and urethral diseases. Clinical manifestations of LUTS include urinary frequency, urgency (storage sym-ptoms), poor flow, hesitancy, straining (voiding symptoms), and incomplete bladder emptying (post-voiding symptoms) (18).

BPH is a histological diagnosis and is characterized by an increased number of stromal and epithelial cells within the transition zone of the prostate (represents only 5% of prostatic volume), with further development of BPH within the more proximal periurethral area of the prostate (nodular hyperplasia) (19). The symptoms occur when the enlarged prostate gland compresses the urethra which increases urine flow resistance, and sometimes it is associated with the inflammation (prostatitis). This clinical picture is called "prostatism" (20).

Etiology and pathogenesis of BPH

The epithelial and stromal components are involved in the pathogenesis and evolution of BPH. Proliferation of the stromal and, to a lesser extent, epithelial compartment of the prostate is mediated through several proposed mechanisms (21).

One of them is an increase in 5α-reductase activity which leads to a change in prostatic androgen metabolism and an abnormal accumulation of DHT (22). In the prostate, DHT is produced from testosterone by the enzyme 5α-reductase and it is a far more potent androgen. DHT binds to androgen receptors with higher affinity than TE, and stimulates protein synthesis, differentiation, and prostate cell growth (23, 24).

An increase in estrogen/androgen ratio and increased synthesis of sex hormone binding globulin (SHBG) are also involved in BPH genesis (25). Estrogens act in synergy with androgens. They enhance the expression of the enzyme that catalyzes the peripheral conversion of androgens into estrogens (aromatase) and the expression of estrogen receptors at the transition zone of prostate tissue (26).

BPH strongly implicates many growth factors and inflammatory cytokines in its pathogenesis. A number of growth-regulatory proteins includes fibroblasts, insulin-like, and transforming growth factor families. These proteins and their downstream effector molecules, in addition to the interleukins, increase stromal and epithelial growth and mesenchymal cell differentiation (27). Local inflammation of prostate gland is also linked with BPH. Prostatitis stimulates the overexpression of the inflammatory cascade associated with nuclear factor kappa-B (NF-B), inducible nitric oxide synthase (iNOS), and 5-lipoxigenase (5-LOX) activation, cyclooxygenase-2 (COX-2), and cytokine and leukotriene production (28). The inflammatory infiltrates in BPH are composed primarily of activated T-lymphocytes that release cytokines. These factors, released from inflammatory cells create an environment that supports the fibromuscular growth (29).

An imbalance between cell proliferation and cell death (reduced apoptosis) (22), and the interactions between stroma and epithelium may cause BPH. This interaction of stroma and epithelium induces conversion of TE into DHT, allowing the production of growth factors (30).

Enhanced prostatic alpha1-adrenoceptors are considered in the pathophysiology of the lower urinary tract symptoms (LUTS) in patients with benign prostate obstruction (BPO). Alpha1-adrenergic mediated smooth muscle contraction can contribute to bladder outlet obstruction. The alpha1-blockers improve symptoms and consequently patient's QoL, and still represent a gold standard in the treatment of LUTS (31).

The role of multipotent stem cells has been investigated in stromal hyperplasia. The examination of hyperproliferative stem cells that are capable of differentiation into muscle cells, osteoblasts and adipocytes has shown that the presence of adult stem cells in prostate stromal tissue is associated with hyperplastic expansion of prostate gland (32).

Metabolic syndrome (MetS), a cluster of cardiovascular (CV) risk factors including obesity, hypertension, dyslipidemia, and hyperglycemia, has been recently recognized as a contributor to the development of BPH. BPH and its related LUTS represent clinical conditions frequently observed in subjects with MetS. MetS and its components such as hypogonadism and systemic inflammation play a significant role in inducing BPH (33).

Treatment options for BPH/LUTS

Therapeutic approaches currently available for the treatment of BPH consist of watchful waiting, surgery, pharmacological therapy and the use of medicinal plants. The choice of treatment should be individualized, according to patient's personal preference, and to the disease severity (34).

Periodic revaluations of clinical conditions (watchful waiting) and some changes in lifestyle are recommended for patients with mild symptoms (35). In case of severe symptoms and, as the post-void residual volume increases, pharmacological therapies are proposed. The two main classes of drugs are alpha1-antagonists, 5α-reductase inhibitors, or their combination (36).

The alpha1-adrenergic antagonists are considered the mainstay of therapy (37). The alpha1-blockers improve symptoms and consequently patient's QoL. The most common side effects are dizziness, tachycardia, postural hypotension (38), retrograde ejaculation (reversible after discontinuation of therapy) (36, 39). The 5α-reductase inhibitors cause androgen reduction. They are more effective in patients with a significant enlargement of the prostate gland (40). The antimuscarinic drugs (39), prostate antigen-specific antibodies (known as afala) (41), β3-agonists, lonidamine, and botulinum neurotoxin (42–44) are some of the further approaches in the treatment.

In the worst cases of symptomatic BPH, invasive surgery (open prostatectomy-OP) or minimally invasive procedures (transurethral resection, transurethral microwave thermotherapy, laser ablation endoscopic, etc.) are necessary. The most common side effects are retrograde ejaculation (81%), urinary tract infections (3%), incontinence, impotence, and hemorrhages (45).

Because of many side effects of drug therapy and surgical procedures, prevention of BPH is very important. The herbal medicines show some of the same effects as synthetic drugs (5-alpha reductase inhibitors and alpha1-receptor antagonists). Many of the herbal drugs currently used for BPH can be found in health food stores and are often available without medical prescription (46).

Pumpkin (Cucurbita pepo L., Cucurbitaceae)

Botanical description

Pumpkin (C. pepo L.), a member of Cucurbitaceae family is a herbaceous, monoecious, annual plant. Most Cucurbita species are creeping or climbing vines that are compact or semi-shrub with five rigid, slightly angular stems. The plant stem produces tendrils to help it climb adjacent plants and structures or extend along the ground. In some species, tendrils are branched or they are simple and little developed (47).

The leaves have 5 to 25 cm strong petioles that are ovate–cordate to suborbicular–cordate, have three to five rounded or obtuse, apiculate lobules, the central one bigger than lateral ones, often with white spots on the surface near the veins.

It has pollen producing male and female flowers on a single plant appearing from the leaf axils. Male flowers are long and have a campanulate calyx that is 5 to 10 mm long, 5–15 x 1–2 mm linear sepals, and yellow to pale orange corolla that is broader towards the base, 6 to 12 cm long. Male flowers in Cucurbitaceae generally have five stamens, but in *Cucurbita* there are only three. Female flowers are 3 to 5 cm long and have small calyx, an ovoid to elliptical, multilocular ovary with three lobate stigmas, sepals that are sometimes foliaceous, and a corolla that is larger than that of the male flowers.

Fruit size and shape varies considerably. It is globose to ovoid–elliptical, with three color patterns: (1) light or dark green, (2) minutely spotted white and green; (3) orange, white, cream or flesh white. The middle fleshy mesocarp is cream to yellowish or pale orange, varies from being soft and sweet to fibrous and bitter (48). Seeds are elliptical and flattened, 15–25 x 7–12 mm, and a dark green in a yellow-white husk (hulled or husked seeds), although some seeds may have only very thin dark-green skin without husk (47).

Nutritional value

Pumpkin is native to South-Central America. The oldest evidence of pumpkin seeds were found in Mexico. Pumpkins were dispersed to other continents by transoceanic voyagers and have become a familiar and important vegetable crop in many countries. Nowadays, it is widely planted for its edible seeds, fruits, and greens. The most cultivated species are *C. pepo* L., *C. maxima*, and *C. moschata* (49).

In some countries, pumpkins are grown for the production of oil from the seeds. Pumpkin seed is low-fat and protein-rich and it is a valuable functional food. The seeds can be minced into a powder and mixed with cereals for making bread, or roasted and consumed as a snack (50).

Pumpkin fruit also has a nutritional significance. The immature fruit is cooked as a vegetable, while the mature fruit is sweet and used to make confectionaries and beverages. The fruit contains sterols, beta-carotene, carbohydrates, vitamins, and minerals, so it is healthy and nourishing for consumption (51).

Therapeutic possibilities

Even early medicine recognized the benefits of pumpkin. Galen, Hippocrates, Plinius and Dioscorides used compressed pumpkin seeds against swelling. Later, pumpkin was used for many diseases such as nephritis, tuberculosis, internal worms and parasites (52).

Pumpkin extracts from different parts of the plant have shown various therapeutic effects due to their biologically active components (53). The fruits are a rich source of carotenoids and gama-aminobutyric acid (54, 55). The leaves of pumpkin contain phytochemicals such as phenolic glycosides, 13-hydroxy-9Z, 11E, 15E-octadecatrienoic acid (56, 57). Pumpkin seeds are valued for high proportions of proteins, essential amino acids, fat-

ty acids and microelements. Many studies have confirmed beneficial activities of these polysaccharides from leaves and proteins from pumpkin seeds such as: 1) antibacterial (58); 2) hypocholesterolaemic and antioxidant (59); 3) immunomodulatory (60); 4) antimutagenic (61); 5) anthelmintic (62); 6) anticarcinogenic (63); and 7) antidiabetic (64).

In the therapy of small urinary disorders, prostate gland and the urinary bladder diseases, pumpkin seeds have shown positive results (50). In traditional medicine, the oil of pumpkin seeds is used for its antioxidant and anti-inflammatory activities in the treatment of BPH and LUTS (65).

Recent studies found that phytosterols from pumpkin seed in free form are not efficiently absorbed in the human gastrointestinal tract. These results suggest that free Δ7-phytosterols are not effective agents for the treatment for BHP, but pumpkin seeds also contain esterified Δ7-phytosterols to various sugar molecules, which could improve their bioavailability (66).

Allergies and toxicity

Symptoms of pumpkin seed allergy usually present an oral allergy syndrome (local reaction), gastrointestinal symptoms (nausea, diarrhea), or pruritus. Hypersensitivity reactions to pumpkin allergens are mediated by IgE-antibodies (67).

Allergic reactions to ingestion of seeds and fruits of the Cucurbitaceae family have rarely been reported. Ingestive food allergy to pumpkin seed has been reported in individuals who were sensitized through an inhalative pathway by using pumpkin seed flour. Few investigations about reactions between members of the Cucurbitaceae family (cucumber and watermelon) and cross-reactivity have been made (68).

Reindl et al. (69) reported 4 cases of allergy to ingestion of *C. pepo* L., including double-blind, placebo-controlled food challenges (DBPCFCs); detection of specific IgE-antibodies to pumpkin; and characterization of allergens and their cross-reactivity to pollen and food allergens. They suggested that allergy to pumpkin can occur as a consequence of primary sensitization to pumpkin, cross-reactions to the panallergen profilin and cross reacting carbohydrate determinants.

Figueredo et al. (70) described the first case report with the patient who experienced systemic reaction after eating cooked pumpkin. The diagnosis was based on a positive case history, positive skin test response and detection of specific IgE-antibodies, and confirmed by an open oral challenge test to pumpkin.

In 30 clinical studies that include more than 15,000 patients who were treated with pumpkin seed preparations, only 0.5% of patients had mild gastrointestinal disturbances (71). Two groups of children in Thailand suffering from crystalluria also received pumpkin seed. Daily dose was about 6 g/kg, and it was well tolerated by all included children (72).

Although some allergy reactions have been described, mainly gastrointestinal disorders, or potential electrolyte loss secondary to its diuretic properties, pumpkin seed is considered as safe herbal medicine for all ages and during pregnancy and lactation.

Pumpkin seed and its products in BPH/ LUTS

In vitro and *in vivo* experiments

Gossell-Williams et al. (73) examined pumpkin seed oil on testosterone-induced hyperplasia of the prostate of Sprague-Dawley rats. Hyperplasia was induced by subcutaneous administration of testosterone (0.3 mg/100 g of body weight) for 20 days. Oral administration of either pumpkin seed oil (2.0 and 4.0 mg/100 g of body weight) or corn oil (vehicle) was given for 20 days. On day 21, they measured prostate weight/rat body weight (prostate size ratio). Researchers observed that testosterone significantly increased prostate size ratio that was reduced in rats fed with pumpkin seed oil at 2.0 mg/100 g of body weight.

Abdel-Rahman (74) investigated the chemical composition of pumpkin seeds and its effect on citral-induced hyperplasia of the prostate in Wistar rats. Fifty adult Wistar male rats were divided into five groups: negative control group that have no BPH and fed on basal diet, positive group rats have BPH and fed on basal diet only, the remaining groups had BPH and were fed on different level of pumpkin seeds. Four weeks later, all rats were sacrificed and results indicated that pumpkin seed can relieve the signs of BPH. Researchers concluded that pumpkin seed in dose-dependent manner can inhibit citral-induced hyperplasia of the ventral prostate lobe as observed in reducing protein-binding prostate levels, weight of ventral prostate lobe and improve histology of testis.

Tsai et al. (75) reported the effects of pumpkin seed oil alone or combined with Phytosterol-F on testosterone/prazosin-induced (T-P) prostate growth in forty adult Wistar rats. The rats were divided into five groups: a control group (treated with vehicle only), a group treated with T-P, and two groups of T-P-treated rats, one of them received orally pumpkin seed oil alone and other group received orally pumpkin seed oil combined with Phytosterol-F. They concluded that pumpkin seed oil alone or combined with Phytosterol-F can block the T-P-induced increases in prostate size ratio.

Schleich et al. (76) tested three different plant species *Serenoa repens*, C. *pepo L.*, and *Pygeum africanum* and their antiadrogenic activity in cell culture. A twelve-month, randomized, placebo-controlled, double-blind trial showed a reduction in IPSS, but all other parameters did not change (prostate size, PSA level) in *C. pepo* L. group

compared to the placebo group.

Clinical studies

Vahlensieck et al. (17) performed a randomized, partially blinded, placebo-controlled, parallel-group trial that investigated the efficacy of pumpkin seeds in 1.431 men with BPH/LUTS. Subjects randomly received the seeds (5 g b.i.d.), capsules with the seeds ethanol extract (500 mg b.i.d.), or matching placebo. The primary response criterion was a decrease in IPSS of ≥5 points from baseline after 12 months. Secondary outcome measures included QoL, IPSS and nocturia. After 12 months, the response rate did not differ between pumpkin seed extract and placebo. Twelve-month pumpkin seed treatment led to a clinically relevant reduction of IPSS compared to placebo.

Shirvan et al. (77) performed the clinical trial study in 2011-2012. They included 100 patients with BPH who were randomly divided into two equal groups receiving pumpkin seed oil (prostafit) and prazosin (alpha1-blocker). QoL and IPSS questionnaire were filled. PSA level, uroflowmetry and prostate volume were measured at baseline, 3 and 6 months after the medication. IPSS had significant differences at baseline and 6 months after the treatment in both groups. QoL was also better in both groups. PSA level did not change after the treatment. They concluded that prostafit was an effective and safe treatment in BPH but not as much effective as prozasin.

Coulson et al. (7) evaluated the efficacy and safety of Prostate EZE Max (herbal preparation containing *C. pepo* L., *Epilobium parviflorum*, *Lycopene*, *Pygeum africanum* and *Serenoa repens*) in medically diagnosed BPH in a short-term phase II randomized double-blind placebo controlled clinical trial. The trial included 57 males aged 40-80 years. They received three-month treatment with either herbal preparation (n=32), or a matched placebo capsule (n=25). The outcome was shown as IPSS. There was a significant reduction in IPSS in the active group compared to 8% for the placebo group, during the three-month intervention.

Hong et al. (78) investigated the role of complementary and alternative medicine in the prevention and treatment of BPH. For this purpose, a randomized, double-blind, placebo-controlled trial was performed over 12 months on 47 BPH patients. Subjects received eithersweet potato (*Ipomoea batatas*) starch (group A, placebo), pumpkin seed oil (group B), saw palmetto (*Serenoa repens*) oil (group C), or pumpkin seed oil plus saw palmetto oil (group D). IPSS improved in groups B, C and D (after 3 months) and quality of life score was reduced in groups B, C (after 3 months), and D (after 6 months). PSA was reduced in group D. There was no difference in prostate volume in the all groups. Therapeutic efficiency was not improved by a combination of pumpkin seed oil and saw palmetto oil. They suggested that administrations of the seed oil and saw palmetto oil are safe and may be effective as complementary medicine treatments for BPH.

Friederich et al. (79) reported a clinical trial in 2.245 patients suffering from BPH who were taking pumpkin seed extract for 12 weeks (1-2 capsules Prosta Fink Forte per day). Urinary symptoms were recorded by IPSS, and the influence on QoL has been recorded by a QoL questionnaire (LQ Index). The patients' IPSS decreased by 41.4 %, and QoL improved by 46. 1 % during therapy.

Conclusion

Benign prostatic hyperplasia (BPH) is a public health problem with high morbidity and a low mortality rate. It can considerably affect quality of life (QoL). Male lower urinary tract symptoms (LUTS) are mostly associated with BPH and are very common with the ageing population.

Current therapeutic approaches for BPH/ LUTS are watchful waiting, surgery, pharmacological therapy, and the use of medicinal plants. Synthetic drug therapy and surgical procedures show many side effects and complications, so herbal medicines are promising in mild to moderate BPH. The main aim of the phytotherapy is to relieve symptoms and to improve patient's QoL.

Pumpkin (*Cucurbita pepo* L.) is a member of Cucurbitaceae family, native to South and Central America. It is an edible plant that can improve our overall health. Pumpkin seeds and seed extracts represent a complex mixture of substances which maintain and safeguard the health. The main beneficial ingredients from pumpkin are phytochemicals, carotenoids, proteins, essential amino acids, fatty acids, micro-elements, and vitamins.

Allergic reactions to pumpkin seeds are very rare. They usually present as an oral allergy syndrome (local reaction), gastrointestinal symptoms (nausea, diarrhea), or pruritus.

Various studies have been done either *in vitro* or in animal models to analyze the effects of pumpkin seed in BPH/LUTS. In human studies, controlled clinical trials are strongly needed to confirm these health-beneficial effects in human subjects.

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Fitoterapijski pristup tretmanu benigne hiperplazije prostate semenom bundeve (*Cucurbita pepo* L., Cucurbitaceae)

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Benigna hiperplazija prostate (BPH) je nekancerozno uvećanje prostate izazvano proliferacijom stromalnih i epitelnih ćelija. Razvija se nakon četrdesete godine života i ima visoku stopu morbiditeta i nisku stopu mortaliteta. Simptomi donjeg urinarnog trakta kod muškaraca (LUTS) su uglavnom povezani sa BPH i veoma su česti u starijoj populaciji. Biljni lekovi se koriste za lečenje brojnih hroničnih i teških bolesti. Glavni cilj fitoterapije u benignoj hiperplaziji prostate je da ublaži simptome i poboljša kvalitet života bolesnika (QoL). Bundeva (*Cucurbita pepo L.*), član porodice Cucurbitaceae, je zeljasta, jednodomna, jednogodišnja biljka. Ekstrakti iz različitih delova bundeve su pokazali različite terapijske efekte zbog svojih biološki aktivnih komponenti. Seme bundeve je korisno zbog visoke koncentracije proteina, esencijalnih aminokiselina, masnih kiselina i mikro elemenata. Seme bundeve je pokazalo pozitivne rezultate u terapiji blagih urinarnih poremećaja, bolesti prostate i mokraćne bešike. Terapija sintetičkim lekovima i hirurške procedure daju mnoge neželjene efekte i komplikacije, tako da su biljni lekovi obe-ćavajući u blagim i umerenim formama BPH. *Acta Medica Medianae 2016;55(3):76-84.*

Ključne reči: *benigna hiperplazija prostate, simptomi donjeg urinarnog trakta muškaraca, seme bundeve, fitoterapija*