



Role of Cucurbita Pepo (MAGHZ-E-TUKHME-KADDU-SHIREEN)

In the Management of Benign Prostatic Hyperplasia: A Narrative Review

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Abstract

Objective: Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) are commonly treated with phytotherapeutic substances because of their low cost, fewer side-effect profiles and high degree of patient acceptance. Here, we set out to examine every piece of information we could find regarding the use of Cucurbita pepo in the treatment of LUTS-BPH.

Material and methods: To locate all published studies on Cucurbita pepo and BPH, a thorough search was done. Search terms included "Cucurbita pepo" OR "pumpkin seed" AND "BPH" AND "Cucurbita pepo" OR "pumpkin seed" AND "LUTS" We solely take into account LUTS-BPH-related studies for the current analysis.

Results: Among all published studies, some of them were carried out in "in vitro setting" demonstrating an anti-inflammatory and antiandrogen effect, as well as decrease in size of prostate and detrusor muscle activity. In all "clinical trials" The International Prostatic Symptoms Score (IPSS) and uroflowmetry measures have been reported to have improved.

Conclusion: According to our review the usage of Cucurbita pepo in the treatment of individuals with LUTS-BPH appears to be beneficial for alleviating symptoms and enhancing quality of life. Future clinical trials are needed, to validate these encouraging findings.

Key Words: Benign Prostatic Hyperplasia, Phytotherapy, Pumpkin seeds, IPSS.

Introduction

Benign prostatic hyperplasia (BPH) is a pathological process that is important one but not the only cause of lower urinary tract symptoms (LUTS) in aging men, also described as "male LUTS. BPH is accurately referred to as hyperplasia and not hypertrophy, as is frequently encountered in the older literature, because it is histopathologically characterized by an increased number of epithelial and stromal cells in the periurethral zone of the prostate. This hyperplasia's precise molecular origin is unknown. The increased cell count can be the result of defective programmed cell death that leads to cellular accumulation or epithelial and stromal

growth. Estrogens, androgens, stromal-epithelial interactions, growth factors, and neurotransmitters may play a vital role in the etiology of the hyperplastic process either singly or in combination.

Phytotherapy

Phytotherapy is increasing world widely and with the growth of health food stores and internet companies marketing these medications for the treatment of BPH during the past 20 years, the usage of complementary and alternative medicine has increased to a multi-million dollar industry in the United States. Herbal remedies account for up to 90% of all prescriptions written for the treatment of BPH in Austria, France, and Germany, where they are regarded as first-line treatments for moderate LUTS [5]. In the United States, herbal remedies are used by 40 percent of men who opt for non-surgical BPH treatment, and that percentage is continuing to rise [3].

More than 30 herbal compounds have been described for the treatment of BPH; in this article, we concentrated only on *Cucurbita pepo*. *Cucurbita* (MAGHZ-E-TUKHME-KADDU-SHIREEN) is a well-known traditional Unani herbal remedy. We also employ the different Unani medical terminology and its English translation that were recorded in Unani reference books for pumpkin's temperament, action, and therapeutic purposes. These usages have been documented in numerous Unani publications and Unani manuscripts. Numerous species of the genus *Cucurbita* can be found throughout Europe, Asia, and America. In the European Community, *Cucurbita pepo* has been used for more than 30 years in the form of ethanolic pumpkin seed soft extract, mostly as a treatment for a variety of issues related to an enlarged prostate gland and micturition issues.

In order to highlight the effect of the review drug on various objective parameters related to BPH, such as effect on IPSS, effect on prostate volume and post-void residual volume in USG, and effect on uroflowmetry parameters, we have divided the studies into subtopics during the review process of various clinical trials. This will help us to understand at what level the pumpkin seeds are actually effective in BPH.

The drug Maghz-e-Tukhm-e-Kaddu-Shireen consists of kernels of *Cucurbita moschata* (Duch. ex Lam.) Duch. ex Poir. (F: Cucurbitaceae), an annual, herbaceous, tendril climber, large and spreading, cultivated throughout tropical and sub-tropical regions in India. It is cultivated for its fruit which is used as vegetable.

Habitat: It is native to N. Mexico and Eastern U.S.A, Now commonly cultivated in Northern India [16, 17].

Synonyms: Urdu: Kaddu. Arabic: Q'ra. Persian: Khayar-e-Kaddu. English: Pumpkin, Marrow [26, 16, 17].

Chemical Constituents: Avenasterol, codisterol, clerosterol, isofucosterol, compesterol, sitosterol, spinasterol, palmitic, palmitoleic, stearic, oleic, linoleic acid, rhamnase, fructose, glucose, galactose, sucrose and raffinose have been reported in the plant [26]. The roasted and fresh seeds yield 32.2 and 38.0% of fatty oil, respectively. The oil filled capsules were administered to patients suffering from hypertrophy of the prostate. Results showed that the frequent urge to urinate decreased and the urine residues were minimized. The oil consists of the glycerides of linoleic (45%), oleic (25%), palmitic and stearic acids (30%). Sterols have been isolated. Pumpkin (*Cucurbita maxima* and *C. pepo*) seeds contain B vitamins, Vitamin A; minerals, calcium, iron, phosphorus, zinc; cucurbitacins; linolenic acid [16].

Temperament: Cold² & Moist¹ [21, 23], Cold³ & Moist³ [14], Cold² & Moist² [15].

Action: Daf-e-Kirm-e-Ama (Anthelmintic), Mudirr-e-Baul (Diuretic), Musakkin-e-Baul, Mulaiyin-e-Shikam (Laxative), Tonic, Demulcent. [26, 16, 17, 21, 14, 15]

Therapeutic uses: Qurooh (Ulcer), Mufatteh Sudad (Deobstruent), Yarqan (Jaundice), Zarb-wa-Khilfah (Sprue/Malabsorption Syndrome). Seeds are used as diuretic and given in gonorrhoea, urinary diseases [22], irritated bladder condition [21, 23], micturition problems of benign prostatic hyperplasia stages 1 and 2 (*German Commission E, The British Herbal Pharmacopoeia.*) and in childhood enuresis nocturna, (*Expanded Commission E.*). An infusion of seeds (2–3 teaspoons) is taken as a diuretic and in hypertrophy of prostate [16]. It has long been a popular remedy for worm in Europe [17].

Dose: 4-8 g

Pumpkin seeds and its products in BPH

In Vitro studies

Anti-inflammatory Activity

the inflammatory cell infiltrates seen in many men with BPH. A large number of cytokines and their receptors are seen in BPH tissue [18]. Specifically, significant levels of interleukins IL-2, IL-4, IL-7, and IL-17, interferon- γ (IFN- γ), and their relevant receptors are found in BPH tissue [19]. IL-2, IL-7, and IFN- γ stimulate the proliferation of prostatic stromal cells in vitro. Prostatic epithelial cell senescence results in increased expression of IL-8, which can promote proliferation of non-senescent epithelial and stromal cells. *Fahim et al* [10] investigated the effect of pumpkin-seed oil (PSO) on the level of free radical scavengers which is induced during adjuvant-arthritis in rats. It was seen that administration of PSO is helpful in modulating most of the abnormal parameters affected due to arthritis. Liver G6P DH activity is also reduced to 50% in the arthritic groups and it produced a remarkable reduction of paw oedema. This study demonstrates the efficacy of pumpkin seed as potential anti-inflammatory property. *Christiana et al* [7] pumpkin seeds anti-inflammatory property was observed. In a dose-dependent way extracts of pumpkin seeds inhibited the production of mitogen-induced neopterin and degradation of tryptophan. These findings clearly show potential of immunoregulatory compounds in pumpkin seeds.

Antiandrogen Activity

Schilcher et al, stated that the isolated pumpkin Δ^7 -sterols in an vitro study in human prostate fibroblasts exhibited the antiandrogenic activity and dose-dependently inhibiting the binding of dihydrotestosterone (DHT). The cultures were incubated with 120 ng labeled DHT for 24 hours and the binding rate was calculated as a difference from the concentration remaining in the supernatant. In the control group binding rate was 63%. In the cultures pre-treated with 120 ng or 240 ng pumpkin sterols (each in a double set-up) the binding rate was 51.7% and 43.3% or 37.5% and 38.3%, respectively [24]. *Schmidlin et al* described the effect of the extract of Cucurbitae pepo on activity of aromatase and 5- α -reductase Type II in the homogenates of human and rat placenta. They revealed that there is about 50% inhibition of aromatase activity and 90% reduction of 5- α -reductase Type II. Subsequently, "in vivo" study the pumpkin seed extract in a prostate hypertrophy model, exhibits the reduction of prostate weight by 31% vs 76% of the Finasteride injection subcutaneously [25].

Bladder Function

Hata et al tested the activity of water soluble extract of pumpkin seeds and soybean germ extract on in-bladder pressure (cystometrogram) and frequency of urination in male rats. Pumpkin seed and soybean germ extracts increased bladder volume significantly, frequency of urination decreased and urination delay index increased. They also observed the bladder relaxation and decrease of in-bladder pressure. This study clearly indicates that the pumpkin seeds will be helpful to overcome the symptoms of prostatism [12].

Prostate Gland Growth

Abdel-Rahman et al performed a comparative study to see the efficacy of pumpkin seeds diet implementation on growth of prostate. BPH was created in ventral prostate by giving citral (C₁₀H₁₆O) orally to male rats, and pumpkin seeds also administered orally. It was noticed that pumpkin seeds inhibited dose-dependently the hyperplasia of the prostate induced by citral. Results of the study imply that pumpkin seeds can decrease the symptoms of BPH, it can reduce the weight and size of ventral prostate, and can improve the histology of testis which is effective in the management of early stage of BPH [1]. Efficacy of pumpkin seed oil (PSO) alone or mixed with Phytosterol-F examined on growth of prostate in rats induced by testosterone/prazosin (T-P). Pumpkin seed oil (PSO) (2.5 ml/kg/day) was given together with T-P and compared with T-P alone group. The T-P group treated with PSO had significant lower prostate weight ratio for ventral prostate ($p = 0.01$) and reduced protein levels within ventral lobe and dorso-lateral lobe ($p = 0.03$ and $p = 0.003$, respectively) both study clearly indicate that pumpkin seeds and its derivatives can significantly reduce the prostate growth and therefore it can be a potential drug for BPH [27].

Clinical studies

Effect on International Prostate Symptom Score (IPSS)

International Prostate Symptom Score (IPSS) is recommended as the symptom scoring instrument it is used for the assessment of symptom severity in men with LUTS, When it is used, symptoms are classified as mild (0 to 7), moderate (8 to 19), or severe (20 to 35) [4].

It was observed that there is improvement in IPSS by 41% (from 18.6 to 10.9) and quality of life index also improved by 46% (from 3.4 to 1.8). The average micturition frequency declined from 6.7 to 5.1 during the daytime and while during the night it decreases from 2.3 to 1. Improvement in other urinary symptoms like pain during urination, burning micturition, sense of pressure and tension was recorded from 52 % of the patients. After 4 weeks of treatment diary recorded frequency of micturition during day and night was decreased to mean values of 5.8 (day) and 2.1 (night), and after 8 weeks of treatment improvement was 5.2 and 1.5, and finally after receiving 12 weeks of treatment it was 4.8 during the daytime and 1.1 during the night. Nocturia was most importantly improved. Nocturia was decreased by 60% (from 2.35 to 0.94) [11]. In a placebo-controlled trial 476 patients were included in the study and two tablets of 500mg pumpkin seed extract was prescribed daily and followed for 12 months. In the pumpkin seed group at the end of study IPSS was reduced of 6.7 points (from 17.6 to 10.9) and this reduction was significantly higher than the mean reduction of 5.5 points (from 17.7 to 12.2) after placebo treatment ($p = 0.014$). This one point difference between two groups was statistically significant [2]. In a retrospective survey 185 patients (aged between 44 and 85 years) received pumpkin seed soft extract and were evaluated. Most patients (63%) received 1 capsule per day, 27% took 2 capsules/day and 9% of the patients were given more than 2 capsules/day. 81% of patients reported improvement in urgency and micturition frequency within the first 3 months of treatment. At the start of treatment 90% patients reported more than one episode of micturition at night but at the end of treatment it was reduced to 30% [6]. A 12 months randomized, double-blind, placebo-controlled trial on 47 BPH patients was carried out with average age of 53.3 years, and IPSS score over 8. Sweet potato starch was given to Group A (placebo, 320 mg/day), while Group B received pumpkin seed oil (PSO) (320 mg/day), Group C received saw palmetto oil (320 mg/day) and group D received pumpkin seed oil plus saw palmetto oil (each 320 mg/day). It was observed that in groups B, C and D, IPSS score were decreased after 3 months, in group B IPSS was reduced from 20.7 to 8.7 by 12.0 points (58.0% change), after 12-month treatment. In group C IPSS was also reduced from 18.2 to 9.1 by 9.2 points (50.3% change), In group D IPSS declined constantly from the beginning (19.0) to the end of the 12-month treatment (4.7) by 14.3 points, and it indicates that there is 75.3% improvement in symptoms, in group D reduction of IPSS was highest. There was also improvement in Quality of life score [13]. In a parallel-group trial that was randomised, placebo-controlled, and partially blinded, 1431 patients (aged 50 to 80) were assigned at random to receive either placebo, extract of pumpkin seed capsules (500 mg twice a day), or 5 g of pumpkin seed twice a day. The mean IPSS score in all groups continues to decline after a three-month therapy period. The relief of urgency, incomplete emptying, and weak stream by 1.0, 0.9, and 0.9 points, respectively, accounted for the majority of the overall IPSS improvement from baseline in the pumpkin seed group after a year. All individual symptoms had improved in all groups. In all study groups, the mean values for IPSS-related QoL and diary-recorded nocturia reduced over time. At the conclusion of the study, the mean reduction in nocturia from baseline was 1, 0.9, and 0.8, respectively, with pumpkin seed, pumpkin seed extract, and placebo. The average improvement in quality of life was 36, 33, and 29.2%, respectively, with pumpkin seed, pumpkin seed extract, and placebo [28]. *Coulson et al* performed a clinical investigation to assess the effectiveness and safety of Prostate EZE Max, combining Cucurbita pepo, Epilobium parviflorum, lycopene, Pygeum africanum, and Serenoa repens. The trial involved 57 BPH patients between the ages of 40 and 80. The herbal formula ($n = 32$) or a matched placebo capsule ($n = 25$) were to be taken orally by the patients for a total of three months (1 capsule per day). The IPSS was dramatically decreased throughout the course of the three-month treatment period, with the active group's overall median score being reduced by 36% as opposed to the placebo group's being 8% ($p < 0.05$). In the active group, the frequency of daytime urination also significantly decreased

throughout the course of the 3-month intervention (7.0-5.9 times per day, a decrease of 15.6 percent compared to 6.2-6.3 times per day for the placebo group; $p < 0.03$). Additionally, there was a substantial decrease in nocturia in the active group (2.9-1.8, 39.3% vs. 2.8-2.6 times, 7%; $P < 0.004$). [8]. Tamsulosin and pumpkin seed oil (*Cucurbita pepo*) were compared for the treatment of BPH symptoms, both groups saw a significant improvement in QoL and a significant decline in IPSS. None of the patients in the pumpkin group experienced drug side effects, whereas in the tamsulosin group dizziness, headache, retrograde ejaculation, and erythema with pruritus were reported. This is despite the fact that the IPSS decrease from baseline to 1 month and 3 months was significantly higher in the tamsulosin group compared to the pumpkin group ($P < 0.048$ and $P < 0.020$, respectively) [29]. *Leibbrand et al* conducted a single-arm, single-centre pilot trial to look at how a patented oil free hydroethanolic pumpkin seed extract affected the BPH symptoms. Assessment of IPSS change during the therapy period was done. The frequency of nocturia was noted, and ultrasound was used to measure the volume of post void leftover urine. After 12 weeks of treatment, there has been a considerable decrease in IPSS symptoms, with an average drop of 30.1 percent from baseline (95% CI: 23.1–37.1). After 8 and 12 weeks of the intervention, there was a significant improvement in quality of life ($P < 0.001$). Over time, nocturia significantly lowered ($P < 0.001$) [20].

Effect on Prostate Volume and Post Void Residual Urine

Trans abdominal ultrasonography is a reliable method for assessing prostate volume and the post void residual urine volume in patients with benign prostatic hyperplasia. *Vahlensieck et al* observed that there was no clinically significant improvement in mean prostate volume and no relevant reduction in Post Void Residual Urine volume or PSA levels were seen [28]. Under placebo and the plant extract, the prostate volume and post-void residual urine volume remained unchanged in both group [2]. Post Void Residual Urine had considerably decreased (baseline: 83.67 mL [95% CI: 58.02-109.3]; after 12-week result: 63.11 mL [95% CI: 45.37-80.85]; $P < 0.0394$) [20].

Effect on Uroflowmetry parameters

Uroflowmetry is a significant worldwide investigation tool that offers urologists a reliable, uncomplicated, low-cost, and non-invasive approach of measuring and recording the urine flow rate throughout micturition. It was invented and published by American surgeon Willard M. Drake Jr [9]. The maximum flow rate with pumpkin seed oil improved by 14.9%, rising from 14.8 ml/second at the start of the research to 17.0 ml/second at the end of study. After a 12-month course of treatment, the maximum flow rate with saw palmetto increased from 14.0 to 21.2 ml/second, a 51.4 percent improvement. While there was little change in the maximum flow rate score with combined formulation of pumpkin seed and saw palmetto during the treatment period [13]. The maximum flow rate increased by 4.3, 3.6 and 3.6 ml/s with pumpkin seed, pumpkin seed extract and placebo, respectively [28]. With Prosta Fink forte, no noticeable improvements in uroflowmetry parameters were recorded [2]. There was significant differences in the result of various studies on the same drug it require further large clinical trial to establish the effect of pumpkin seeds on the objective parameters of Uroflowmetry

Conclusion

BPH is a problem for public health with a high rate of morbidity and a low rate of mortality. It may have a significant impact on quality of life (QoL). Male lower urinary tract symptoms (LUTS) are highly prevalent among the elderly and are typically linked to BPH. Watchful waiting, surgery, pharmaceutical therapy, and the use of medicinal herbs are the current therapeutic modalities for BPH/LUTS. Herbal therapies hold promise in the treatment of mild to moderate BPH because synthetic medication therapy and surgical methods have numerous side effects and dangers. The primary goals of phytotherapy are to reduce symptoms and enhance patients' quality of life. The pumpkin, (*Cucurbita pepo* L.) is a native of South and Central America and a member of the Cucurbitaceae family. It is a plant that we can eat and which will benefit our general health. Pumpkin seeds and seed extracts are a rich blend of nutrients that support and protect health.

Phytochemicals, carotenoids, proteins, vital amino acids, fatty acids, microelements, and vitamins are the key beneficial components of pumpkin. Pumpkin seed allergies are quite rare. Some Symptoms like oral allergy syndrome (local reaction), gastrointestinal symptoms (nausea, diarrhea), or pruritus are sometimes typically manifest. Various studies have been done either *in vitro* or in animal models to analyse the effects of pumpkin seed in BPH/LUTS. In human studies, various clinical trials were carried out but most of the clinical trials were done only on IPSS and the pumpkin effects on prostate size, post void residual volume and uroflowmetry parameters were not recorded. Therefore more controlled clinical trials are strongly needed to confirm these health-beneficial effects in human subjects.

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