

The role of *Cucurbita pepo* in the management of patients affected by lower urinary tract symptoms due to benign prostatic hyperplasia: A narrative review

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Summary *Objective: Phytotherapeutic compounds are largely used in the treatment of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) due to low side-effect profiles and costs, high level of acceptance by patients and a low rate of drop-out. Here, we aimed to analyze all available evidence on the role of Cucurbita pepo in the treatment of LUTS-BPH.*

Material and methods: In May 2016 a systematic search was carried out thorough National Library of Medicine Pubmed, Scopus database and the ISI Web of Knowledge official website in order to identify all published studies on Cucurbita pepo and BPH. The following search strings were used: "Cucurbita pepo" OR "pumpkin seed" AND "prostate"; "Cucurbita pepo" AND "antiandrogen" OR "antiproliferative" OR "anti-inflammatory" OR "antioxidant activities"; "cucurbita pepo" OR "pumpkin seed" AND "LUTS" AND "symptoms improvement" OR "quality of life". We consider for the present analysis only studies related to LUTS-BPH.

Results: Among all 670 screened, 16 were related to LUTS-BPH and finally analyzed. Among all, ten of them were performed in "in vitro setting" showing anti-inflammatory and antiandrogen effect, and a reduction in prostate growth and detrusor activity, while six were clinical studies. In all studies an improvement in International Prostatic Symptoms Score (IPSS) and uroflowmetry parameters has been reported. In 4 studies, an improvement in quality of life has been reported.

Conclusion: On the basis of our narrative review, the use of Cucurbita pepo in the management of patients affected by LUTS-BPH seems to be useful for improving symptoms and quality of life. However, future clinical trials are requested to confirm these promising results.

KEY WORDS: BPH; *Cucurbita pepo*; LUTS; Prostate disease; Pumpkin seed.

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Contributions: RD, TC, CAF, RL data collecting; RD, TC analyzing and manuscript writing; VM, CAF, RL and PF supervision.

INTRODUCTION

Benign prostatic hyperplasia (BPH) affects most men after the age of 50 years and is considered the most common urologic disease among elderly men (1). BPH is a chronic disease with early initiation and slow progression, due to an overgrowth of the epithelial and stromal cells from the transition zone and the periurethral area (2). It is essentially a histological diagnosis, which can be clinically manifested as benign prostatic enlargement (BPE) in almost half of the cases. BPH starts as a simple micro nodular hyperplasia and evolves into a macroscopic nodular enlargement that gradually results in benign prostatic obstruction (BPO). The increase in prostatic size may eventually compress the urethral canal leading to BPO characterized by progressive development of lower urinary tract symptoms (LUTS) as urinary hesitancy and frequency, dysuria, sexual dysfunction, increased risk of urinary infection and at least urinary retention. Aging, dietary factors, presence of androgens, growth factors, oxidative stress and chronic prostatic inflammation are necessary for the development and progression of BPH, but the pathogenesis is still largely unresolved and there is no consensus as to which is the primary one (3). In the management of BPH, is necessary to reduce cell growth by blockage of testosterone conversion in DHT, and reduce the sustaining of the chronic prostatic inflammation. Patient acceptability of treatment is key to decreasing the human and economic burden of this condition. Maintaining sexual function is a crucial topic nowadays. Alpha blockers, 5-alpha reductase inhibitors (i-5AR) and phosphodiesterase 5 inhibitors (i-PDE5), as monotherapy or in combination, have been used in BPH treatment (4). Notwithstanding these drugs have a positive effect on the patient with BPH, side effects (including sexual ones) progressively favor patient withdrawal from therapy and progressively enhance interest in drugs of plant origin with less adverse effects (5). Phytotherapy dates back thousands of years, and currently represent almost 50% of all medicine pre-

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scribed for BPH in Italy. Nowadays, due to low side-effect profiles and costs, high level of acceptance by patients and low rate of drop-out, the use of phytotherapy is progressively increasing. Here, we focused our attention on *Cucurbita pepo*. *Cucurbita* is a well-known traditional herbal medicinal product used from centuries worldwide and its medicinal use was described in many manuscripts and textbooks. The *Cucurbita* genus comprises many species widespread in Europe, Asia and America. *Cucurbita pepo* in the form of ethanolic pumpkin seed soft extract has been used for more than thirty years in the European Community, mainly as a remedy for various difficulties associated with an enlarged prostate gland and micturition problems related to overactive bladder (6, 7). The active compounds in *Cucurbita pepo* L. seeds are $\Delta 5$ -, $\Delta 7$ - and $\Delta 8$ -sterols: $\Delta 7$ -sterols, which are largely predominant in *Cucurbita pepo*, are considered to be the key active constituents of pumpkin seed in the treatment of benign prostatic hyperplasia. Much smaller amounts of $\Delta 5$ - and $\Delta 8$ -sterols are also present in *Cucurbita pepo* (7-11). High content of carotenoids, polyunsaturated fatty acids and liposoluble vitamins have also a role in its activity (12). Therefore, in the present narrative review, we summarize all evidence available on the role of *Cucurbita pepo* in the management of patients affected by LUTS due to BPH.

MATERIALS AND METHODS

Search strategy and evidence acquisition

We searched electronic databases including PubMed, the Scopus database and the ISI Web of Knowledge for published studies that analyzed the role of *Cucurbita pepo* in the management of patients affected by LUTS due to BPH up to May 31, 2016. The following Medical Subject Headings terms and free text were used: "*Cucurbita pepo*" OR "*pumpkin seed*" AND "*prostate*"; "*Cucurbita pepo*" AND "*antiandrogen*" OR "*antiproliferative*" OR "*anti-inflammatory*" OR "*antioxidant activities*"; "*cucurbita pepo*" OR "*pumpkin seed*" AND "*LUTS*" AND "*symptoms improvement*" OR "*quality of life*". There was no restriction on population or publication year. Additionally, we conducted a manual search using the bibliographies of all the identified studies, reviews, and editorials to identify references that we may have missed during our primary search. Finally, the search included original articles, review articles and editorials and these were reviewed in order to select relevant articles. When necessary, we contacted the authors to obtain any relevant information we found to be missing from published papers.

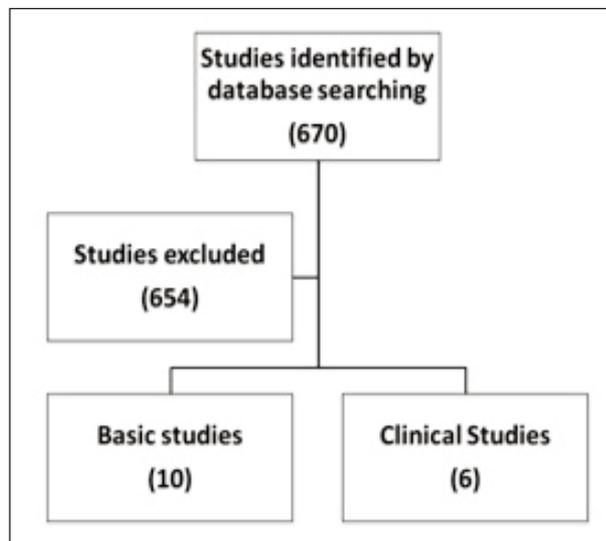
The Figure 1 shows the study selection process diagram.

Selection criteria

Inclusion criteria: (1) all studies related to LUTS-BPH; (2) all pre-clinical and clinical trials.

Exclusion criteria: (1) the language of the studies was not English or German; (2) if multiple publications for the same data from the same study group occurred, only the most informative and recent article was recruited into final analysis; (3) letters to Editor, review articles, commentaries, clinical guidelines, or case reports and case series.

Figure 1.
Selection process of studies.



RESULTS

Six-hundred and seventy studies were selected up to May 31, 2016. After the first-step analysis, 16 studies were included in this narrative review. Ten studies were considered in the pre-clinical setting and 6 in the clinical setting.

Pre-clinical setting

Antioxidant activity. Four commercially available pumpkin seeds (*Cucurbita pepo*, *Cucurbita moschata*, *Cucurbita maxima* and *Cucurbita mixta*) extracts were screened for their antioxidant activity and their inhibitory activity against lipid peroxidation (13). The results showed that radical scavenging activity depends on their total phenolic content. In particular, pumpkin seed water extracts inhibited lipid peroxidation at 1.5 mg/ml, while the acetone extracts inhibit 50% of lipoxygenase activity at the range from 0.16 to 0.80 mg/ml.

Antiandrogen activity. In an *in vitro* study in human prostate fibroblasts, the isolated pumpkin $\Delta 7$ -sterols showed antiandrogenic activity dose-dependently blocking 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. The binding rate in the control 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 (14).

Furthermore, Schmidlin and Kreuter (15) described influence of the *Cucurbita pepo* extract on activity of aromatase and 5- α -reductase Type II in the homogenates of human and rat placenta. By using 10 mg/ml-concentration extract, about 50% reduction of aromatase activity and 90% of 5- α -reductase Type II inhibition were achieved. Subsequently, in the "*in vivo*" prostate hypertrophy model the pumpkin extract (100mg/kg) reduced prostate weight of 31% vs 76% of the subcutaneous Finasteride injection (1 mg/kg).

Anti-inflammatory activity. Three different extracts of pumpkin seeds showed immunological activity suppressing dose dependently mitogen-induced neopterin production and tryptophan degradation induced by cytokine interferon- γ (IFN- γ) (16). In particular, pumpkin seeds of *Cucurbita pepo* (citrullinina GREB, var. *styriaca* GREB) from biological culture were finely grounded (10 g of the powder was added to 100 ml of medium *Roswell Park Memorial Institute* (RPMI 1640). Then the peripheral blood mononuclear cells (PMBC) were isolated from the whole blood from healthy human donors and stimulated with phytohaemagglutinin and concanavalin-A. Tryptophan and neopterin concentrations, two biochemical pathways stimulated by cytokine interferon- γ , were measured in the supernatants in order to assess the anti-inflammatory activity of the pumpkin seeds extracts. Finally, a dose dependant suppression of mitogen-induced neopterin production and tryptophan degradation was recorded compared to control PMBCs. Likewise, *Fahim et al.* (17) used an experimental murine model of arthritis to test anti-inflammatory activity of pumpkin seed oil administered in intramuscular injection. For comparison, other two groups of rats respectively received indomethacin – a classic anti-inflammatory agent – and no further treatment. Blood samples were collected to measure: blood glutation (GSH), plasma total proteins, albumin serum sulfhydryl group (SH-gps), ceruloplasmin (CP) and lysosomal marker – N-acetyl- β -D-glucosaminidase (NAG). After completing the experiment, liver samples were used for determination of glucose-6-phosphate dehydrogenase (G6P DH) activity and protein content of liver homogenates was established. Adjuvant inoculation resulted in decrease of serum SH-gps, with an increase of serum CP reduction of blood glutathione and total proteins and albumins levels. Liver G6P DH activity was markedly increased. The treatment with pumpkin seed oil resulted in normalization of altered parameters, notably in chronic phase, except serum NAG influence. Pumpkin oil administration inhibited paw oedema during the chronic phase in about 44% as compared to the control untreated group. It reduced also liver G6P DH activity to almost 50% of the arthritic groups' level. No increase in the anti-inflammatory effects of indomethacin combined with pumpkin seed oil was observed.

Bladder contractility. The effects of non-specified water soluble extract of pumpkin seeds and soybean germ extract on in-bladder pressure (cystometrogram) and urination frequency of male rats were tested (18). Pumpkin seed water-soluble extract (250 mg/kg) compared to control solvent (1% dimethyl sulfoxide diluted in sterile physiological saline) and soybean germ extract significantly increased bladder volume, decreased urination frequency and increased urination delay index. According to the authors, the observed effects of the relaxation of the bladder and decrease of in-bladder pressure are related to the increased productions of NO via the arginine/NO pathway. Arginine is present in the pumpkin seed extract in two fold the concentrations of other amino acids. It was suggested that arginine/NO metabolism, independently of adrenaline and acetylcholine, is involved in relaxation of urination muscle at a stage of full bladder (19).

Prostate gland growth. *Abdel-Rahman et al.* (20) performed a comparative study to examine the effect of pumpkin seeds diet implementation on prostate growth. The authors used an experimental model where benign prostatic hyperplasia (BPH) in ventral prostate was induced by orally administering citral (C10H16O) into stomach of male rats. Citral was administered to all rats except negative control group. The rats were subsequently grouped according to their diet – normal or different level of pumpkin seeds – and sacrificed. Briefly, citral significantly increased prostate weight ($P < 0.05$), while pumpkin seeds given orally dose-dependently inhibited citral induced hyperplasia of the prostate, especially at high concentration seed dose (10%, $p < 0.02$). In a testosterone-induced BPH murine model *Gossell-Williams et al.* found that administration of testosterone significantly increased prostate size ratio (weight of prostate/b.w. of the rat) ($p < 0.05$) although this increase was significantly inhibited by treatment with pumpkin seed oil at 4.0 mg/100 g b.w. *Gossell-Williams* (21). Likewise, *Tsai et al.* (22) tested pumpkin seed oil efficacy for 14 days, in experiments performed in rats on the model of prostatic growth induced by subcutaneous daily injection of testosterone (1.25 mg/kg/day) together with prazosin (30 μ g/kg/day) (T-P). Pumpkin seed oil (PSO) (2.5 ml/kg/day) extracted from pumpkin seeds was administered concomitantly together with T-P. As compared with T-P alone group, the T-P group treated with PSO had significant lower weight ratio for ventral prostate ($p = 0.01$) and lower protein levels within ventral lobe and dorsolateral lobe ($p = 0.03$ and $p = 0.003$, respectively).

Table 1 summarizes all evidence available in the pre-clinical setting.

Clinical setting

Hamvas et al. (23) reported an overall improvement of urinary symptoms after 10 months of medication with *Cucurbita pepo*. The daily dosage was 3 x 2 capsules in the first month and 3 x 1 capsule for the rest of the time. Changes despite pre-treatment conditions in uroflow test and patients symptoms perception were the used outcomes. Control visits were scheduled after 4-7-10 months of medication. At the end of follow up, an improvement in uroflowmetry parameters was recorded (respectively: Q_{max} 15.4 vs 18 ml/sec, Q_{ave} 9.5 vs 12.5 ml/sec, post voiding residual 90 vs 50 ml). Furthermore, a reduction of nocturia, urinary frequency and relief of urinary pain were reported. Finally, about 90% of patients felt a “very good” or “good” improvement of their urinary symptoms after therapy. In a multicentre setting, *Bach et al.* (24) performed a randomized double-blind, placebo-controlled study enrolling 476 men (mean age 63 yrs) suffering from mild or moderate BPH symptoms and at early stages (I or II) of clinical BPH as defined by *Alken* (25). The study was carried out in accordance with recommendations of the International Consultation on Benign Prostatic Hyperplasia (26). The duration of treatment was 12 months and the main efficacy criterion was the International Prostate Symptom Score (IPSS). After a 1 - month run-in-period under placebo, patients were randomized to daily treatment for 12 months with either 2 x 500 mg of the soft extract (15-25:1, ethanol 92%,

Table 1.
Summary of experimental studies supporting a role of pumpkin seeds in the treatment of BPH-LUTS.

BPH-LUTS etiology role	Author, year	Part of plant	Model	Main study finding
Inflammatory	Xanthopoulos 2009	Seed extract	Biochemical for Lipid peroxidation	Inhibited lipid peroxidation
	Winkler 2005	Seed extract	Biochemical: blood stimulated mononuclear cells from healthy men	Inflammatory induced pathways (IFN- γ mediated) were reduced
	Fahim et al. 1995	Seed oil	Arthritis rats model	Oxidative parameters commonly altered during arthritis were modulate; furthermore a reduction of rats' paw oedema was achieved
Androgen	Schilcher 1990	Pumpkin $\Delta 7$ -sterols	Biochemical: human prostate fibroblasts culture	Dihydrotestosterone binding
	Schmidlin and Kreuter 2003	Seed extract	Biochemical: homogenates of human and rat placenta	Aromatase and 5- α -reductase Type II activity reduction; reduction of prostate weight
Bladder contractility	Hata 2005	Seed extract	Urodynamic test in rats	Increase bladder volume Decrease frequency
Prostate growth	Abdel-Rahman 2006	Seed	BPH induced with citral in rats	High concentration seed dose inhibites prostate growth
	Gossell-Williams 2006	Seed oil	BPH induced with testosterone in rats	Inhibition of testosterone induced prostatic hyperplasia
	Tsai 2006	Seed	Testosterone plus Prazosin induced prostate growth in rats	Prostate weight was decreased

m/m) from pumpkin seeds ($n = 233$) or placebo ($n = 243$). Five post-randomization visits were scheduled after 1, 3, 6, 9 and 12 months. An improvement of at least 5 points in the IPSS at study end was defined as a therapy response. Even though the 'placebo effect' was considerable, this therapy response was reported by significantly more patients in the Cucurbita group than in the placebo group (65% vs. 54%, $p = 0.021$). Also, an improvement of at least 3 points in the IPSS was reported by more patients in the Cucurbita group (82.5%) than in the placebo group (67.9%, ITT population). The mean reduction in IPSS of 6.7 points (from 17.6 to 10.9) in the pumpkin seed group was significantly greater than the mean reduction of 5.5 points (from 17.7 to 12.2) after placebo treatment ($p = 0.014$). No significant changes were evident in either group in uroflowmetry parameters, residual urine, quality of life, prostate volume or serum prostate specific antigen levels. Likewise, Friederich (27) performed an observational study including 2245 patients with mild or moderate BPH symptoms and administering 500 mg or 1.000 mg of pumpkin seed soft extract daily for 12 weeks. During therapy IPSS scores improved by 41% (7.7 points, from 18.6 to 10.9) and quality of life index scores by 46% (from 3.4 to 1.8). The average frequency of micturition decreased from 6.7 to 5.1 during the day and from 2.3 to 1 during the night. Improvement of dysuric disorders, such as painful urination, micturition burning, feeling of pressure and tension was reported by 52 % of the patients. Diary recorded micturition frequency during the day and during the night was reduced within just 4 weeks to mean values of

5.8 (day) and 2.1 (night), with further improvement after 8 weeks to 5.2 and 1.5, reaching 4.8 during the day and 1.1 during the night after 12 weeks of treatment. At subgroup analyses, the most pronounced improvement was observed for the micturition frequency during the night, whereas patients with acute disorders benefited most. In these patients nocturia was reduced by 60% (from 2.35 to 0.94), and in patients with chronic complaints by 48% (from 2.75 to 1.43). In a retrospective survey involving urologists in private practice the treatment progression of 185 patients (aged between 44 and 85 years) receiving pumpkin seed soft extract was recorded and evaluated (28). Among those, 173 patients received pumpkin seed soft extract as therapy to treat LUTS due to BPH. Most patients (63%) took 1 capsule per day, 27% took 2 capsules, and 9% of the patients were treated with more than 2 capsules. The recorded observation periods for individual patients ranged between one week and several years. However, for the majority (81%) data on the course of treatment were recorded within the first 3 months. Urge symptoms and micturition frequency were reduced in most patients. The proportion of patients having reported more than one micturition during the night at start of treatment was reduced from 90% to 30%. Residual urine was found to be reduced in 80% of the patients. Hong et al. (29) carried out a randomized, double-blind, placebo-controlled trial over 12 months, enrolling 47 patients with BPH with mean age of 53.3 years and international prostate symptom score over 8. The study design contemplated four comparative study arms: sweet potato starch (group

Table 2.
Clinical studies on pumpkin seeds in men affected of BPH-LUTS.

Author, year	Study design	Patients number	Comparator	Treatment length	Outcomes measured
Hamvas 1991		60	Pre-treatment	10 mo	- Uroflow features improvement: Qmax 15.4 vs 18 ml/s; Qave 9.5 vs 12.5 ml/s; - Decrease in nocturia time, relief of dysuria and painful discharge - About 90% referred a mild or very good improvement in symptoms gravity
Bach 2000	Randomized controlled trial	476	Placebo	12 mo	- Significant Increase in response rate (ITT population): 67.5% vs 56.2% - Decrease in IPSS 17.6 ± 3.7 vs 10.9 ± 4.5 - Mean IPSS after treatment/change to baseline (ITT): 10.9 ± 4.5 change: -6.7 (-38%) vs 12.2 ± 5.1 change: -5.5 (-31%)
Friederich 2000	Multicentric	2245	Pre-treatment	12 weeks	- IPSS decreased from 18.6 to 10.9 (by 1.4%) and QoL score improved from 3.4 to 1.8 (by 46.1%) - 96% reported no undesired side effects
Burbach 2002	Retrospective	185	Pre-treatment	3 mo	- Decrease in storage symptoms, nocturia (and PVR)
Hong 2009	Randomized placebo-controlled trial	47	Placebo (four arms)	12 mo	Overall: - Decrease IPSS: 20.7 ± 2.3 vs 8.7 ± 1.5 - Improvement of QoL score: 3.4 ± 0.4 vs 2.5 ± 0.4
Vahlensieck 2015	Randomized controlled trial	1431	Placebo (three arms: pumpkin seed, pumpkin seed extract and placebo)	12 mo	- Decrease in IPSS (ITT): -5.4 ± 5.1, -4.2 ± 5.4 vs -4.0 ± 5.6 - IPSS response rate increased by 6% - Improve in QoL 36% and 33,4% vs 29,2%

A, placebo, 320 mg/day), pumpkin seed oil (group B, 320 mg/day), saw palmetto oil (group C, 320 mg/day) or pumpkin seed oil plus saw palmetto oil (group D, each 320 mg/day). International prostate symptom score, quality of life, serum prostate specific antigen, prostate volume and maximal urinary flow rate were measured. So far, in groups B, C and D, the international prostate symptom score were reduced after 3 months (respectively from 20.7 ± 2.3, 18.3 ± 2.0, 19.0 ± 2.6 to 8.7 ± 1.5, 9.1 ± 1.4, 4.7 ± 17). Quality of life score was improved after 6 months in group D (pumpkin seed oil plus saw palmetto oil) from 3.8 ± 0.4 to 2.5 ± 0.4 and was maintained stable afterwards while those of groups B (pumpkin seed oil) and C were improved after 3 months, compared to the baseline value respectively from 4.2 ± 0.4 to 3.0 ± 0.4 and from 3.6 ± 0.3 to 3.0 ± 0.4). Finally, no difference was found in prostate volume in all treatment groups. Maximal urinary flow rate were gradually improved in groups B (pumpkin seed oil) and C, with statistical significance after 6 months in group B and after 12 months in group C. More recently, Vahlensieck *et al.* (30) investigated the efficacy of pumpkin seed in men with LUTS suggestive of BPH performing a placebo controlled three-armed randomized trial. Overall 1431 patients (aged 50-80 years) were randomly assigned to either pumpkin seed (5 g b.i.d.), capsules with pumpkin seed extract (500 mg b.i.d.) or placebo. The primary outcome was a decrease in IPSS of > 5 points from baseline after 12 months. Secondary outcome measure included IPSS – related quality of life, IPSS single items and diary recorded nocturia. After 12 months, the

response rate differed significantly between pumpkin seed and placebo (58% vs 47%). Overall, 12 months of treatment with pumpkin seed led to a clinically relevant reduction in IPSS from (15.9 ± 1.8 and 15.8 ± 1.9, to 11.4 ± 5.5 and 10.2 ± 5.1) compared with placebo (from 16.1 ± 1.9 to 11.7 ± 5.4).

Adverse effects

To note, no adverse effects were registered from above open clinical studies of pumpkin seeds. Only mild gastrointestinal complaints (diarrhoea, nausea, vomiting) in

Figure 2.
International Prostatic Symptoms Score analyzed in clinical studies.

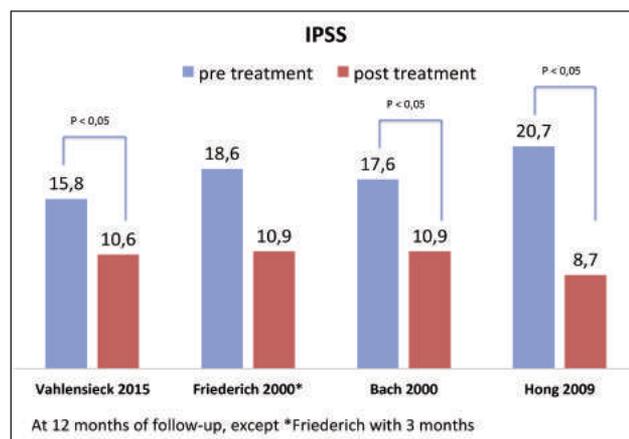


Figure 3.
Quality of Life assessment.

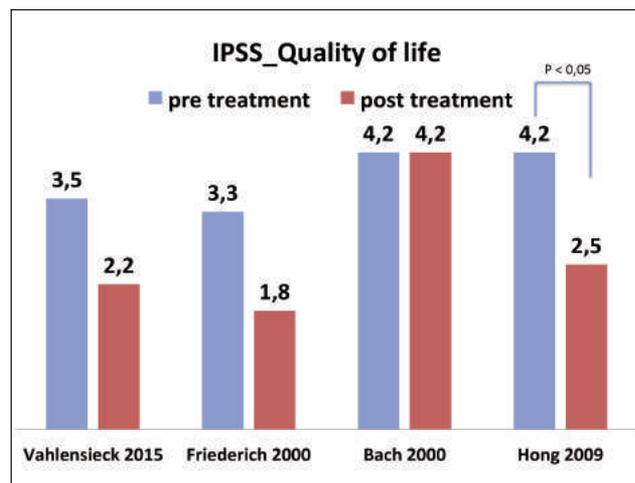
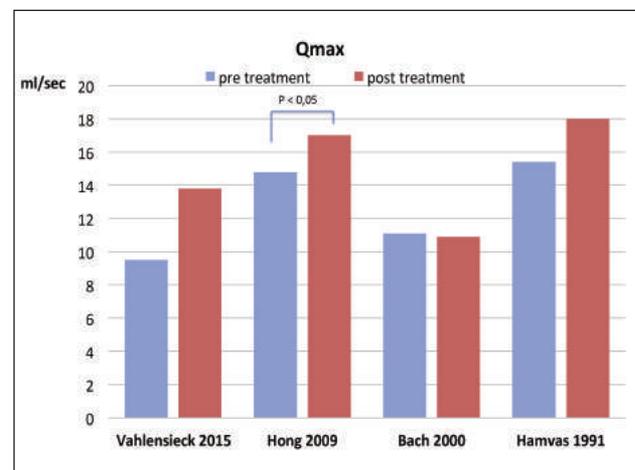


Figure 4.
 Q_{max} assessment in clinical studies.



no more than 4% of the patients was reported in Friederich study whereby it seems that upon administration within the therapeutic dose range, there is no risk of serious side effects on all three RCTs. No sexual side effects were reported during the use of *Cucurbita pepo* compounds.

Table 2 shows all clinical studies performed in the management of LUTS-BPH. Moreover, Figure 2, Figure 3 and Figure 4 show impact of the *Cucurbita pepo* on IPSS, uroflowmetry parameters and patients QoL, respectively.

DISCUSSION

Main findings

Several studies performed in the pre-clinical and clinical setting showed that the use of *Cucurbita pepo* in the management of patients affected by LUTS-BPH seems to be useful for improving symptoms and quality of life. Several aspects should be taken into account; in particu-

lar, some limitations of the evidence available need to be considered.

Analysis of the evidences in the context of the current knowledge

More recent knowledge about the physiological regulation of bladder function makes it plausible that ubiquitous substances may also contribute to the overall effect of pumpkin seeds, in particular for maintaining normal bladder function and preventing functional disorders. Fatty oil of pumpkin seeds is characterized by a high content of linoleic acid, accounting for 35-68% of the total fatty acids (31, 32) Administration of this essential precursor of prostaglandin metabolism (formation of PGE2 and PG2 α) might cause an increase in prostaglandin synthesis. Prostaglandins are formed by the detrusor muscle and increase its tone (33) resulting in an improved bladder function.

The average tocopherol content of soft-shelled pumpkin seeds is 0.5 mg/g, whereas – in contrast to most other plant oils – γ -tocopherol is present in five- to ten-fold higher concentrations than the α -isomer (34, 35).

According to more recent studies, γ -tocopherol is thought to be significantly involved in the preventive role of vitamin E and also to have a beneficial effect in chronic inflammation (36-40). Medicinal pumpkin seeds are rich in amino acids such as the NO precursors arginine, glutamine and aspartic acid as well as γ -aminobutyric acids. These are involved in the regulation of bladder function as direct or indirect central neurotransmitters (41-43).

Observational studies (27), retrospective surveys (28) and randomized controlled trials (24, 29, 30) provide further evidence on beneficial effects of *Cucurbita pepo* for patients with LUTS related to benign prostatic hyperplasia, as reduction of urge and micturition frequency was observed. The published literature shows that the benefits of pumpkin seeds treatment depend on the tonic influence on the bladder, sphincter relaxation and alleviation of micturition symptoms. It was therefore suggested that pumpkin seeds could be used in patients without significant obstruction of the prostate and low risk for disease progression (44). Provided that the patient undergoes regular urological control visits, medical treatment with seeds of *Cucurbita pepo* can be recommended for patients with micturition symptoms related to BPH in early disease stages, including those with symptoms of overactive bladder.

Limits

The few available studies were often outdated and enrolled a small number of patients, and only three RCTs were of good quality. Other limits are difficulties in data extraction on changes in patients classification (Alken versus IPSS). Nevertheless all studies analyzed showed improvement in micturition parameters related to LUTS/BPH.

CONCLUSION

In the context of the present narrative review, *Cucurbita pepo* seems to show significant efficacy in improving urinary symptoms with mild adverse effects however few clinical studies support the use of that drug. Moreover,

all clinical studies are based on the evidence raising from experimental studies in pre-clinical setting that showed an interesting action of pumpkin seed elements on some BPH etiological mechanism. Large randomized study are needed to confirm these interesting result and recommend the use of pumpkin seed in the management of patients affected by LUTS due to BPH.

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