

## Review



## Effects of pumpkin on benign prostatic hyperplasia: a systematic review and meta- analysis

Thamali Rangika<sup>1\*</sup>, Madhavi Rathnayake<sup>2</sup>, Moditha Eknaligoda<sup>3</sup>, Mahesh Kumbukage<sup>4</sup>, Buddhika Mahesh<sup>5</sup>, Wasantha Gunathunga<sup>6</sup>, Mahendra Arnold<sup>7</sup>, Ruwan Ferdinando<sup>8</sup>

<sup>1</sup>Medical Officer of Health Office, Millaniya, Sri Lanka; <sup>2</sup>Medical Officer of Health Office, Kurunegala, Sri Lanka; <sup>3</sup>Regional Director of Health Services Office, Kurunegala, Sri Lanka; <sup>4</sup>Family Health Bureau, Ministry of Health, Sri Lanka; <sup>5</sup>Provisional Director of Health Services Office, Colombo, Sri Lanka; <sup>6</sup>Department of Community Medicine, Faculty of Medicine, University of Colombo, Sri Lanka; <sup>7</sup>Ministry of Health, Sri Lanka; <sup>8</sup>National Institute of Health Sciences, Sri Lanka

\*Correspondence: thamali.rangika@gmail.com

<https://orcid.org/0000-0003-2098-7343>

DOI: <https://doi.org/10.4038/jccpsl.v29i2.8566>

Received on 13 Nov 2022

Accepted on 17 May 2023

### Abstract

**Introduction:** Benign prostatic hyperplasia (BPH) is a common condition affecting aging men worldwide. Pumpkin and its extracts are enriched with antioxidant, anti-androgenic and anti-inflammatory properties.

**Objectives:** To systematically review the effect of pumpkin on the reduction of lower urinary tract symptoms (LUTS) due to bladder outflow obstruction in BPH

**Methods:** The review (PROSPERO ID: CRD42020181395) perused PubMed, EMBASE, Cochrane Library, CINAHL and AGRICOLA databases in two rounds independently by two reviewers according to three screening questions: being a pumpkin related human study, having BPH related outcomes and including quantifiable measurements. Risk of bias assessments were done with GRADE and ROBINS-I Criteria. After assessing the clinical, methodological and statistical heterogeneity, meta-analysis was performed for one outcome with mean difference (MD) using Inverse Variance Method with Review Manager 5.4 software.

**Results:** Out of the 242 articles with de-duplication and screening questions, 10 based on interventional studies among adult males with LUTS were selected in third round (8 on pumpkin seeds alone; 2 on pumpkin combined products). International Prostate Symptoms Score (IPSS) was described in nine articles. Other outcomes assessed were quality of life (QOL), prostate volume, Prostate Specific Antigen (PSA), uroflow rate, post-voidal residual volume, frequency of micturition during day and night, nocturia and erectile dysfunction. Meta-analysis of three studies (650 and 631 subjects in experimental and control groups) was performed for IPSS reduction. Pooled MD ( $I^2=0\%$ ) was -1.41 (95% CI: -1.97, -0.85) with random effect assumption. In all relevant studies, the intervention group demonstrated significant IPSS reduction and increased QOL. One study each demonstrated significant reduction in prostate volume and residual volume; three studies in uroflow rate; and none on PSA improvement.

**Conclusions & Recommendations:** Pumpkin seeds may be beneficial in reducing IPSS and to some extent in improving prostate and residual volume, uroflow rate and QOL in BPH. Further studies are needed to strengthen the hypothesis.

**Keywords:** pumpkin, benign prostatic hyperplasia, lower urinary tract symptoms, systematic review, meta-analysis

## Introduction

Benign prostatic hyperplasia (BPH) is one of the commonest benign neoplasms of males (1), specifically affecting the aging men worldwide, with nearly 1 in 4 men suffering from this condition over their lifetime (2). The prevalence of BPH is more than 40% among men aged 50-60 years and 70% among men aged 61-70 years and 90% among men in the ninth decade (3-4).

The BPH is a histological diagnosis based on the proliferation of both smooth muscle and epithelial cells in the prostatic transition zone. It causes bladder outlet obstruction giving rise to associated LUTS comprising voiding symptoms (hesitancy, weak stream, intermittency, terminal dribbling, feeling of incomplete emptying) and storage symptoms (frequency, urgency, nocturia) (5), caused either by thickening of the prostate leading to narrowing of the urethra (static component) or increasing smooth muscle tone (dynamic component) (3, 5-6). Though not a life-threatening condition, BPH may also lead to poor QOL (3). IPSS, developed by the American Urological Association in 1992, is a scoring system that assesses the severity of LUTS and urological QOL. Patients with 0-7 points are categorized as 'mild', 7-19 as 'moderate' and 20-35 as 'severe' symptomatic patients. The treatment for BPH mainly depends on the stage of the disease and range from medical therapy (alpha-adrenergic blockers, 5-alpha-reductase inhibitors, combination therapy) to minimally invasive and surgical therapies (6).

Pumpkin (*Cucurbita maxima* L.) belongs to the Cucurbitaceae family and is considered as a popular vegetable all over the world (4). Pumpkin seeds and seed oil are used as common snacks in several cultures. The seed oil has culinary and pharmaceutical applications (7) and is rich in many bioactive components such as fatty acids, essential amino acids, vitamins, phytosterols, tocopherols, squalene and carotenoid pigments (7-10). Pumpkin seed has many properties such as antioxidant, antiandrogenic and anti-inflammatory. In addition, it

has a positive effect on bladder contractility and reduction of prostate gland growth (10). Therefore, the use of pumpkin seeds in the management of patients with LUTS/BPH seems to be effective for improving their symptoms and QOL.

Many of the research findings show that pumpkin seeds are effective in treating patients with BPH. A pilot study on phytotherapy found that an oral combination of pumpkin seed extract, soy germ isoflavonoids and cranberry could be beneficial for BPH patients with mild to moderate LUTS, through a significant decrease in IPSS score and improving QOL (11). Significant improvement of BPH symptoms have also been reported with the use of oil free hydroethanolic pumpkin seed extract (12) and of BPH/LUTS and IPSS related QOL with the use of pumpkin seeds (13). Another study done in Australia with phytotherapy containing pumpkin seed oil reported a significant positive effect on the management of LUTS with significant improvements (14). A randomized clinical trial conducted in Iran using both prazosin and prostafit (contains pumpkin seed oil) also revealed a similar effect of pumpkin, however, the effect was not found to be much effective as prazosin (15). Thus, though many studies have been conducted to justify the use of pumpkin seed to treat BPH, the findings need to be substantiated in a confirmatory study or systematic review (13).

Although a few reviews had been done with regards to pumpkin and BPH, the effect of pumpkin on BPH has not been systematically reviewed comprehensively (10, 16). Such an evaluation would enable establishing more precise interpretations on the effectiveness of pumpkin seed extract as a complementary treatment or preventive mode for BPH. Pumpkin can be easily grown and is consumed as a cheap and freely available vegetable in tropical countries. Therefore, the results of this meta-analysis will be beneficial not only for the patients with BPH but also for the economy of such countries through the reduction of expenses on medication. Thus, we

conducted a systematic review with potential meta-analysis to establish the effectiveness of pumpkin on BPH. The primary outcome of interest was IPSS reduction while the secondary outcomes were changes of post void residual volume, QOL, prostate volume, PSA level and urinary flow.

## Methods

### Protocol and registration

The registration of the review was done in the International Prospective Register of Systemic Reviews (PROSPERO ID: CRD42020181395). Preferred Reporting Items for Systemic reviews and Meta-analysis (PRISMA) guidelines were referred to when preparing the article.

### Eligibility criteria, information sources and study selection

The review question was developed according to PICOS sequence as, “is there an effect of intake of any form of pumpkin on benign prostatic hyperplasia compared to non-intake of it?”. The participants included patients already diagnosed with BPH. The intervention included those with consumption of pumpkin or pumpkin containing product. Comparators were those who did not receive any pumpkin or pumpkin containing product or those who received an alternate product. Reduction of LUTS (hesitancy, intermittency, poor stream, terminal dribbling and incomplete emptying) related to BPH was considered as the main outcome and it was assessed using IPSS reduction. Randomized, quasi-experimental and observational studies (cohort, case control and cross sectional analytical) were utilized for the review.

Electronic bibliographic databases of PubMed, EMBASE, The Cochrane Library, CINAHL and AGRICOLA were used to search for the relevant articles (search strategies used attached as supplementary files). Studies published since the inception of the databases up to the date of completion of searches were selected. The search

was limited to articles in English or with an English translation. The searches were re-run just before the final analysis and further studies were retrieved for inclusion.

The screening of articles for inclusion criteria were independently done by two reviewers and a third reviewer's opinion was sought when there was disagreement between individual judgments. The study selection was completed in two rounds, with the titles and available abstracts being screened in the first round and the full articles in the second round. For this purpose, three screening questions were used; whether the article was on a human study; whether the intervention was related to pumpkin; and whether prostate related quantitative outcomes were there.

### Data extraction process, risk of bias in individual studies

Study design, exposure/intervention, results of outcomes including methodology, results and effect measures were extracted from the articles (Table 1). Data were independently extracted by two reviewers, while a third reviewer was involved in resolving the disagreements between individual judgments. The study investigators were contacted for unreported data or additional details if needed.

The risk of bias of the selected randomized studies was assessed using Grading of Recommendations Assessment Development and Evaluation (GRADE) using the Review Manager software. This assessment was based on seven criteria, namely random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias and any other bias. Non-randomized studies were assessed using Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) Criteria (17-21).

### Summary measures and synthesis of results

After assessing the clinical, methodological and statistical heterogeneity (assessed using  $\chi^2$  test and  $I^2$

test), the meta-analysis was performed for one outcome using Review Manager Software version 5.4. The pooling method used was Inverse Variance Method and mean difference was the effect measure.

A narrative review was done for other outcomes found in studies, which were not included in the meta-analysis due to heterogeneity. The quality of evidence was assessed using the Criteria of GRADE Working Group, with the help of GRADEproGDT application.

## Results

### Selection of studies

Of the 242 articles screened, 91 experimental studies were selected in the first round, out of which 11 studies were excluded in the second round and 67 studies rejected in the third round. Out of the remaining 13 studies, three could not be accessed as full articles, thus only 10 studies (seven randomised and three non-randomised) were selected for the final review (Table 1). Three of them were included in the meta-analysis of the primary outcome of interest (13, 22, 24).

**Table 1: Data items extracted from the studies considered for review**

Population	Intervention	Comparison	Outcome	Study design
Eligibility criteria	Kind of	Number of arms	Primary and	Type of design
Characteristics of the participants	intervention/s done with duration/s	Number participated	secondary outcomes	Year of conduct
		Number completed the allocated exposure	How the outcomes were measured	Study setting
			Number of participants with each outcome	

### Study characteristics

As given in Table 2, majority of the participants included in the 10 selected studies were more than 50 years. In eight studies, pumpkinseeds alone was the intervention and in two, it was a combined product containing pumpkin seeds. IPSS reduction was the primary outcome described in nine articles, while other outcomes included QOL in eight studies (seven assessed urological QOL using the IPSS related QOL question and one using the Life Quality Index); prostate volume, PSA, uroflow rate and post-voidal residual volume in five studies; frequency of micturition during day and night in four studies; nocturia in one study; and erectile dysfunction in one study.

### Risk of bias within studies

All seven randomized studies were with low risk for reporting bias. Blinding of participants was done only in four studies. High risk of bias was due to issues related to selection and attrition bias in one

study each and performance bias in two studies. Information related to the blinding of the outcome assessment was not given in all studies. All three non-randomized studies demonstrated low risk for selection of the reported results. Serious risk was identified only in relation to bias in the classification of intervention. Moderate risk was identified in relation to bias due to confounding and measurement of the outcome in one study each (Figure 2 and Table 3).

### Findings of the meta-analysis

Meta-analysis of the three studies on post intervention IPSS value included 650 in the experimental group (pumpkin seed involved in the experiment) and 631 in the control group (pumpkin seed not involved in the experiment). The studies were not significantly heterogeneous ( $I^2=0\%$ ;  $p=0.96$ ). The pooled mean difference was -1.41 (95% CI: -1.97, -0.85) with random-effect assumption.

**Table 2: Table of characteristics of the selected studies for review**

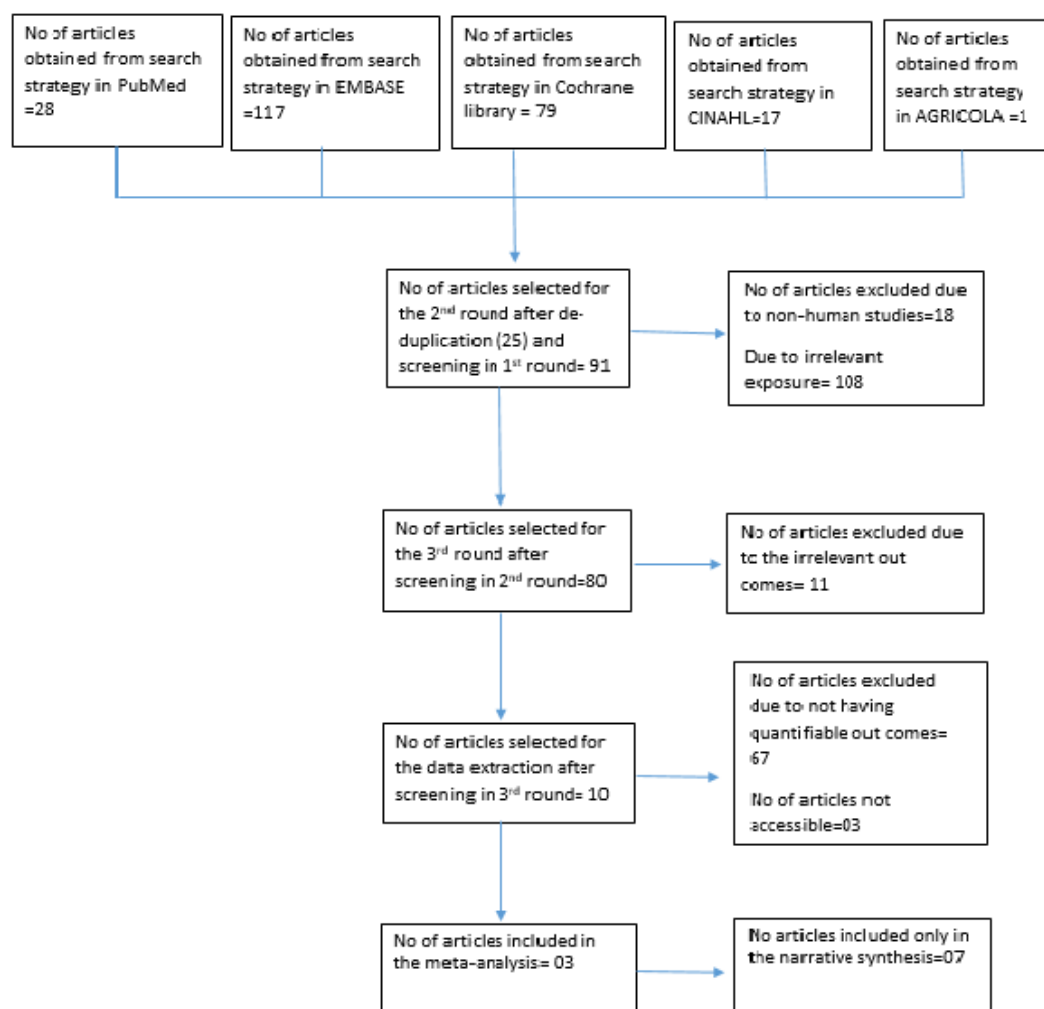
Study	Population	Intervention	Comparison	Type of design and study setting
Nemr et al., 2020 (11)	Men aged $\geq 40$ years with mild to moderate LUTS for at least 6 months	Mixed compound with pumpkin seed, soy germ isflavonoids and cranberry administered orally, 2 tablets daily for 3 months	140	Single-arm prospective open-labelled trial Outpatient settings in several clinics
Leibbrand et al., 2019 (12)	Men aged 50-75 years with symptoms of BPH for at least 6 months	The oil-free hydroethanolic pumpkin seed extract - one tablet daily before going to bed for 12 weeks	60	Single-arm mono-centre pilot study Outpatient setting in one clinic
Vahlensieck et al., 2014 (13)	Men aged 50-80 years with BPH/LUTS for $\geq 6$	Group 1- Pumpkin seed extract Group 2- Pumpkin seed Group 3- Placebo	1431 Group 1- 481 Group 2- 475 Group 3- 475	Randomized partially blinded placebo controlled parallel-group trial Study centres
Coulson et al., 2013 (14)	Males aged 40-80 years with medically diagnosed (histologically) BPH, having a minimum score of 8 on the IPSS questionnaire	The investigation product, ProstateEZE Max and placebo capsules administered as one capsule per day with food for 3 months	60	Phase II randomised double-blind placebo controlled clinical trial Community
Shirvan et al., 2014 (15)	Men $> 50$ years of age with BPH	Randomly divided into equal groups Group 1- Prostafit 2 tablets daily for 6 months Group 2- Prazosin 2 capsules daily for 6 months	100 Group 1=50 Group 2=50	Prospective randomized clinical trial in hospital
Hong et al., 2009 (23)	BPH patients with an IPSS of 8 or more	Group A- Placebo controlled sweet potato starch, 320 mg/day Group B- Pumpkin seed oil, 320 mg/day	47	Randomized double-blind placebo-controlled trial Community

		Group C- Saw palmetto oil, 320 mg/day Group D- Combination of pumpkin seed oil, 320 mg/day and saw palmetto oil, 320 mg/day		
Friederich et al., 2000 (24)	Men with stage 1 and stage 2 BPH (according to Alken) aged 20-90 years	1 ± 2 capsules of Prosta Fink Forte per day for 12 weeks	2245	Multicentre clinical trial
Bach, 2000 (25)	Men with BPH stage I to II according to Alken with an average age of 63 and with an IPSS baseline value of at least 7 points	Pumpkin seed preparation (Prosta Fink forte capsules) Placebo capsules consisting of Macrogol 400, glycerol, gelatine and dyes E 172	542	Randomized placebo-controlled trial  65 study centres (urological practices)
Machado-Leiva et al., 2016 (26)	Patients aged 50-80 years with clinical diagnosis of mild or moderate BPH	Study group- 140 mg of Calprost® daily 8 am and 8 pm Control group- daily 2 mg (one tablet) of terazosin at night given ambulatorily for three months	131	Randomized controlled open labelled exploratory study
Carbin et al., 1990 (36)	Males aged 50-80 years with symptoms of at least 3 months duration	Curbicin contains 160mg of standardised extract PS6 from Cucurbita pepo L. seeds (80 mg) and Sabal serrulate fruits (80 mg). The tablets were swallowed whole in a dose of 2 tablets 3 times a day for 3 months	55	Double-blind placebo-controlled study  In conjunction with 6 general practitioners



**Table 3: Risk of bias in non-randomized studies considered for review**

Study	Bias due to confounding	Bias of selecting the participants in the study	Bias in classification of intervention	Bias due to deviations from intended intervention	Bias due to missing outcome data	Bias in the measurement of the outcome	Bias in the selection of the reported results
Nemr et al., 2020 (11)	Low risk	Low risk	Low risk	No information	No information	No information	Low risk
Leibbrand et al., 2019 (12)	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Friederich et al., 2000 (24)	Moderate risk	No information	Serious risk	Low risk	No information	No information	Low risk

**Figure 1: Study selection flow diagram**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bach 2000	?	?	+	?	+	+	+
CarbinBe,Larsson and Lindahl 1990	+	?	+	?	+	+	+
Coulson S et al 2013	+	?	+	?	?	+	+
Hong,Kim and Maeng 2009	-	?	+	?	-	+	+
Machado-Leiva et al 2016	+	?	-	?	?	+	+
Shirvan et al 2014	+	?	?	?	+	+	?
Vahlensieck W et al 2015	+	+	-	?	+	+	+

Figure 2: Risk of bias in randomized studies

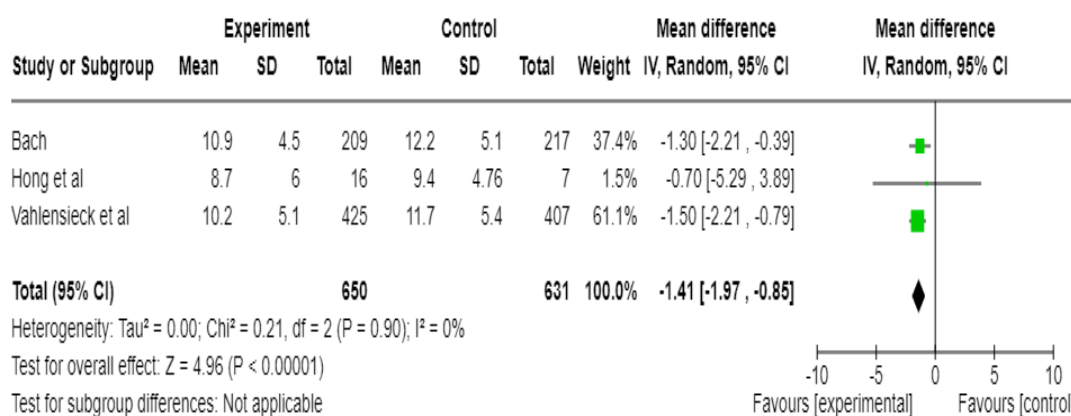


Figure 3: Forest plot

### Findings of the narrative synthesis

IPSS - Nine studies (11-15, 22-25) described a significant reduction of IPSS in the intervention group. The IPSS median score was observed to be reduced from 15 to 9 within a period of three months

( $p < 0.001$ ) in a one-arm trial (11); by 36% in the active group ( $p < 0.05$ ) in a randomized double-blinded clinical trial (14); from 15.7 to 10.8 within a period of 12 weeks ( $p < 0.0001$ ) IPSS median score by 36% in the active group ( $p < 0.05$ ) (12). In addition, in



another randomized clinical trial, the mean IPSS score was 14.5, 11.9 and 9.24 at the baseline, 3 months and 6 months respectively following treatment (15). Further, another placebo controlled study showed a statistically significant difference in five-point reduction of IPSS score between the placebo group (54.2%) and treatment group (64.8%) after 12 months (24).

**QOL** - Eight studies demonstrated QOL as an outcome. A randomized placebo-controlled study demonstrated an improvement of QOL by 36% in the treatment group compared to 29.2% in the placebo group (13). In another study, the life quality score was reduced by 46.1% (23). Urological QOL was significantly decreased from a median of 4 at baseline to 3 at one month and 2 at 3 months ( $p<0.001$ ) (11). An improvement in QOL was observed in 69% of the treatment group compared to 31% of the control group (25).

**Prostate volume** - Although five studies (13, 15, 24-25) demonstrated prostate volume as an outcome, one study showed a significant reduction. Median prostate volume was significantly reduced in the treatment group ( $p=0.002$ ) compared to no significant reduction in the control group ( $p=0.438$ ) (24).

**Uroflow rate** - Out of the five studies (13, 15, 22, 24, 35), uroflow rate was significantly increased in three studies (15, 22, 35). A randomized clinical trial stated an improvement in the mean uroflow rate from 14.5 ml/s to 19.0 ml/s in the treatment group (15). Another study showed a significant improvement by 14.9% following a period of 12 months (22). Furthermore, another study stated a statistically significant improvement in uroflow rate ( $p<0.001$ ) (35).

**Post-voidal residual volume** - Out of the five studies with the outcome of post-voidal residual volume (12-13, 24-25, 35), three studies showed a significant reduction. One study showed a significant reduction from 83.67 ml at baseline to 63.11 ml at the end of

intervention. ( $p=0.0394$ ) (12). In addition, another study demonstrated a significant improvement in residual volume ( $p=0.01$ ) (35).

**Erectile dysfunction** - One study (11) revealed a positive effect on the International Index of Erectile Dysfunction Score. The median score was improved from 15 at baseline to 17 after 3 months ( $p<0.001$ ) (12). Out of the five studies with the outcome of PSA (12-13, 15, 22, 24), none showed a significant difference.

## Discussion

This was the first comprehensive systematic review which included a meta-analysis component on the effectiveness of pumpkin on BPH. The results revealed that pumpkin seeds contribute to the reduction of symptoms of BPH.

Several steps were taken to ensure the quality of this systematic review and meta-analysis. Firstly, the data search was done without restricting to a time period. It is mentioned that searching all available data is a better strategy in systematic reviews (27). Risk of bias estimates were not done by averaging the several components of the bias estimates but by utilizing recommended guidelines (17, 28-29). Blinding was not done in one study and there was a high risk for performance bias in two studies. Strict categorizing criteria were adhered to in the estimation of bias. It is recommended to consider the statistical, clinical and methodological heterogeneity in interpreting the quality of meta-analysis (30-32). The statistical heterogeneity of the studies was seemingly acceptable. Measures to minimize methodological bias were adhered to when selecting the studies and expressing the risk of bias of each study. Furthermore, the control groups of the studies had been recruited from similar settings.

The primary outcome of this study was IPSS reduction with a pooled mean difference of -1.41 for post intervention IPSS value between intervention

group and control group. Out of nine studies where the IPSS reduction was described, all showed a significant reduction in IPSS in the intervention group. This is comparable with the study done by Leibbrand et al. (2019) where a reduction of IPSS of 30.1% was seen between the baseline and end of intervention and in the placebo group, the effect observed was a reduction from IPSS 17.7 to 12.2 (12). The findings are in line with other investigations with pumpkin seed extract. In the patient group treated with pumpkin seed extract, there was a continuous improvement in IPSS score over the entire treatment period, while there were no significant changes in the placebo group after the 6th month of treatment. All laboratory and vital signs showed no negative changes over the entire study period. In addition, no significant adverse events restricting the tolerance were found (24). Vahlensieck et al. (2015) have revealed that treatment with pumpkin seed results in a substantial improvement in LUTS related to BPH (13).

Overproduction of 5- $\alpha$ -reductase followed by a hormonal imbalance between androgens and oestrogens leads to symptoms related to IPSS such as frequent micturition and urinary incontinence (17). In vitro as well as in vivo studies have shown that pumpkin seed has an inhibitory effect on inhibition of 5- $\alpha$  reductase and aromatase enzymes leading to inhibition of prostate tissue growth (12, 33). Of the LUTS symptoms, irritative symptoms have the most profound effects on the patient's QOL. Of these, the reduction in nocturia would have the most positive effect (34). None of the studies revealed a positive effect on PSA level. Uroflow rate was increased in three studies postulated by reduction in size of the prostate gland. Post-voidal and prostate volume were improved in one study each. Even though the alpha blockers and 5- $\alpha$  reductase inhibitors were given as treatment for BPH, side effects such as erectile dysfunction and orthostatic hypotension were observed. However, pumpkin seeds did not show

significant side effects according to most of the studies, while one study revealed a positive effect on the International Index of Erectile Function score (11, 13).

Though pumpkin is a commonly found cheaper vegetable in Sri Lanka, pumpkin seeds are not utilized or commercially available. By promoting production and consumption of pumpkin seeds will not only have the health benefits described above but also indirectly aid on country's economy. This systematic review and the meta-analysis act as a foundation for the development of health policies. Utilization of pumpkin seed extracts can be promoted hand in hand with the clinical treatments. As a result, it may contribute to achieve a significant improvement in the quality of life in BPH patients through reduction of symptoms. Furthermore, commercially prepared pumpkin seeds can be promoted to use in the regular diet. In addition, new health interventions with pumpkin seed extracts can be encouraged with this review.

This systematic review has several limitations. The studies included showed substantial heterogeneity with respect to the analysed population size, follow-up length and baseline age. Due to the low number of studies available and the heterogeneity, meta-analysis was performed only for post intervention IPSS value and three studies were used for the meta-analysis. In line with this, it is also not possible to assess publication bias and small study effects.

## Conclusions & Recommendations

The review suggests that pumpkin may be beneficial for the reduction of IPSS, and to some extent for the improvement of QOL, the reduction of prostate volume, residual volume and uroflow rate in relation to the control of BPH. Further studies are recommended to strengthen the hypothesis.

### Public Health Implications

- Subfertility is a significant medical and social problem in its high prevalence and impact on psychological wellbeing. Attention for this issue is low in both the preventive and curative sectors. The study revealed that the provision of field-level facilities by the MOH units is not satisfactory and has less integration with the secondary and tertiary government hospitals.
- Almost all ART facilities were available in the private sector. Therefore, attention should be focused on providing patient-centred care at field level with providing ART facilities to some extent in the government sector. Rational public health policies need to be developed regarding the provision of field-level and advanced care.

### Author Declarations

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** Self-funded

**Acknowledgements:** We are grateful to authors who conducted the original research which we included in this systematic review and meta-analysis.

**Author contributions:** Equal contributions by all.

### References

1. Langan RC. Benign prostatic hyperplasia. *Prim Care* 2019; 46(2): 223-232. <https://doi.org/10.1016/j.pop.2019.02.003>.
2. Lee SWH, Chan EMC, Lai YK. The global burden of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: A systematic review and meta-analysis. *Sci Rep* 2017; 7(1): 7984. <https://doi.org/10.1038/s41598-017-06628-8>.
3. McVary KT. BPH: epidemiology and comorbidities. *Am J Manag Care* 2006; 12(Suppl 5): S122-128. PMID: 16613526.
4. Amin MZ, Islam T, Mostofa F, Uddin MJ, Rahman MM, Satter MA. Comparative assessment of the physicochemical and biochemical properties of native and hybrid varieties of pumpkin seed and seed oil (*Cucurbita maxima* Linn.). *Heliyon* 2019; 5(12): e02994. <https://doi.org/10.1016/j.heliyon.2019.e02994>.
5. Auffenberg GB, Helfand BT, McVary KT. Established medical therapy for benign prostatic hyperplasia. *Urol Clin North Am* 2009; 36(4): 443-459. <https://doi.org/10.1016/j.ucl.2009.07.004>.
6. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011; 185(5): 1793-1803. <https://doi.org/10.1016/j.juro.2011.01.074>.
7. Rico X, Gullón B, Alonso JL, Yáñez R. Recovery of high value-added compounds from pineapple, melon, watermelon and pumpkin processing by-products: An overview. *Food Res Int* 2020; 132: 109086. <https://doi.org/10.1016/j.foodres.2020.109086>.
8. Cuco RP, Cardozo-Filho L, Silva C. Simultaneous extraction of seed oil and active compounds from peel of pumpkin (*Cucurbita maxima*) using pressurized carbon dioxide as solvent. *J Supercrit Fluids* 2019; 143: 8-15. <https://doi.org/10.1016/j.supflu.2018.08.002>.
9. Nyam KL, Tan CP, Lai OM, Long K, Che Man YB. Physicochemical properties and bioactive compounds of selected seed oils. *LWT - Food Sci Technol* 2009; 42(8): 1396-1403. <https://doi.org/10.1016/j.lwt.2009.03.006>.
10. Damiano R, Cai T, Fornara P, Franzese CA, Leonardi R, Mirone V. The role of *Cucurbita pepo* in the management of patients affected by lower urinary tract symptoms due to benign prostatic hyperplasia: A narrative review. *Arch Ital di Urol e Androl* 2016; 88(2): 136-143. <https://doi.org/10.4081/aiua.2016.2.136>.
11. Nemr E, El Helou E, Mjaess G, Semaan A, Chebel JA. Prospective multicenter open-label one-arm

- trial investigating a pumpkin seed, isoflavonoids, and cranberry mix in lower urinary tract symptoms/benign prostatic hyperplasia: A pilot study. *Adv Urol* 2020; 2020: 6325490. <https://doi.org/10.1155/2020/6325490>.
12. Leibbrand M, Siefer S, Schön C, Perrinjaquet-Moccetti T, Kompek A, Csernich A, et al. Effects of an oil-free hydroethanolic pumpkin seed extract on symptom frequency and severity in men with benign prostatic hyperplasia: a pilot study in humans. *J Med Food* 2019; 22(6): 551-559. <https://doi.org/10.1089/jmf.2018.0106>.
  13. Vahlensieck W, Theurer C, Pfitzer E, Patz B, Banik N, Engelmann U. Effects of pumpkin seed in men with lower urinary tract symptoms due to benign prostatic hyperplasia in the one-year, randomized, placebo-controlled GRANU study. *Urol Int* 2015; 94(3): 286-295. <https://doi.org/10.1159/000362903>.
  14. Coulson S, Rao A, Beck SL, Steels E, Gramotnev H, Vitetta L. A phase II randomised double-blind placebo-controlled clinical trial investigating the efficacy and safety of ProstateEZE Max: A herbal medicine preparation for the management of symptoms of benign prostatic hypertrophy. *Complement Ther Med* 2013; 21(3): 172-179. <https://doi.org/10.1016/j.ctim.2013.01.007>.
  15. Shirvan MK, Mahboob MRD, Masuminia M, Mohammadi S. Pumpkin seed oil (Prostafit) or prazosin? which one is better in the treatment of symptomatic benign prostatic hyperplasia. *J Pak Med Assoc* 2014; 64(6): 683-685. PMID: 25252490.
  16. Dreikorn K. The role of phytotherapy in treating lower urinary tract symptoms and benign prostatic hyperplasia. *World J Urol* 2002; 19: 426-435. <https://doi.org/10.1007/s00345-002-0247-6>.
  17. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence - study limitations (risk of bias). *J Clin Epidemiol* 2011; 64(4): 407-415. <https://doi.org/10.1016/j.jclinepi.2010.07.017>.
  18. Morche J, Freitag S, Hoffmann F, Rissling O, Langer G, Nußbaumer-Streit B, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *Z Evid Fortbild Qual Gesundheitsw* 2020; 150-152: 124-133. <https://doi.org/10.1016/j.zefq.2019.11.003>.
  19. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355: i4919. <https://doi.org/10.1136/bmj.i4919>.
  20. BMJ. *The seven domains of bias addressed in the ROBINS-I Assessment Tool*. Available from: [https://www.bmj.com/content/bmj/suppl/2016/10/12/bmj.i4919.DC1/stej032658.w1\\_default.pdf](https://www.bmj.com/content/bmj/suppl/2016/10/12/bmj.i4919.DC1/stej032658.w1_default.pdf).
  21. Julian PT Higgins, Jelena Savović, Matthew J Page, Roy G Elbers, Jonathan AC Sterne. Chapter 8: *Assessing risk of bias in a randomized trial*. Cochrane Training. Available from <https://training.cochrane.org/handbook/current/chapter-08>
  22. Hong H, Kim C-S, Maeng S. Effects of pumpkin seed oil and saw palmetto oil in Korean men with symptomatic benign prostatic hyperplasia. *Nutr Res Pract* 2009; 3(4): 323-327. <https://doi.org/10.4162/nrp.2009.3.4.323>.
  23. Friederich M, Theurer C, Schiebel-Schlosser G. Prosta fink forteð-kapseln in der behandlung der benignen prostatahyperplasie: Eine multizentrische Anwendungsbeobachtung a 2245 Patienten. *Forsch Komplementäre rmed Klass Naturheilkd* 2000; 7: 200-204. <https://doi.org/10.1159/000021344>. PMID: 11025395.
  24. Bach D. A study with pumpkin seed extract for BPH-related micturition complaints. *Der Urologe B* 2000; 437-443. <https://doi.org/10.1007/s001310050432>.
  25. Machado-Leiva M, Jiménez-Rodríguez D, Festary-Casanovas T, Silveira-Pacheco DC, Barroso-de La Cruz ES, Suárez-Reyes M, et al. Clinical evaluation of patients with benign prostatic hyperplasia, treated with the natural product Calprost®: a randomized, controlled study. *J Pharm Pharmacogn Res* 2016; 4(5): 187-198. <http://jppres.com/jppres>.

26. Dib PT, Trigo-Rocha F, Gomes CM, Srougi M. Urodynamic evaluation in diabetic patients with prostate enlargement and lower urinary tract symptoms. *Urol Int* 2008; 80(4): 378-382. <https://doi.org/10.1159/000132695>.
27. Rockers PC, Tugwell P, Grimshaw J, Oliver S, Atun R, Røttingen JA, et al. Quasi-experimental study designs series—paper 12: strengthening global capacity for evidence synthesis of quasi-experimental health systems research. *J Clin Epidemiol* 2017; 89: 98-105. <https://doi.org/10.1016/j.jclinepi.2016.03.034>.
28. Conway A, Clarke MJ, Treweek S, Schünemann H, Santesso N, Morgan RL, et al. Summary of findings tables for communicating key findings of systematic reviews. *Cochrane Database Syst Rev* 2017; 2: Art No. MR000044. <https://doi.org/10.1002/14651858.MR000044>.
29. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from: [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).
30. Bown MJ & Sutton AJ. Quality control in systematic reviews and meta-analyses. *Eur J Vasc Endovasc Surg* 2010; 40(5): 669-677. <https://doi.org/10.1016/j.ejvs.2010.07.011>.
31. Gagnier JJ, Moher D, Boon H, Beyene J, Bombardier C. Investigating clinical heterogeneity in systematic reviews: a methodologic review of guidance in the literature. *BMC Med Res Methodol* 2012; 12: 111. <https://doi.org/10.1186/1471-2288-12-111>.
32. West SL, Gartlehner G, Mansfield AJ, Poole C, Tant E, Lenfestey N, et al. *Comparative effectiveness review methods: clinical heterogeneity. comparative effectiveness review methods: clinical heterogeneity [Internet]*. Rockville (MD): Agency for Healthcare Research and Quality (US), 2010. Report No. 10-EHC070-EF. PMID: 21433337.
33. Weisser H & Krieg M. Benign prostatic hyperplasia--the outcome of age-induced alteration of androgen-estrogen balance? *Urologe A* 1997; 36(1): 3-9. <https://doi.org/10.1007/s001200050060>.
34. Konstantinidis C, Samarinas M, Andreadakis S, Xanthis S, Skriapas K. Lower urinary tract symptoms associated with benign prostatic hyperplasia: combined treatment with fesoterodine fumarate extended-release and tamsulosin--a prospective study. *Urol Int* 2013; 90(2): 156-160. <https://doi.org/10.1159/000345050>.
35. Carbin BE, Larsson B, Lindahl O. Treatment of benign prostatic hyperplasia with phytosterols. *Br J Urol* 1990; 66(6): 639-641. <https://doi.org/10.1111/j.1464-410x.1990.tb07199.x>.