

EFFICACY AND SAFETY OF A UNANI FORMULATION IN THE MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Background: Benign prostate hyperplasia (BPH) is a common urological disease in elderly male population and administration of Phytotherapeutic agents is rapidly growing each day in the management of this urological disorder, with many herbal single and compound drugs being used for the treatment of this condition.

Objectives: The present study investigated the efficacy and safety of a Unani formulation in the management of BPH which has following ingredients: Tribulus terrestris (Khar-e- khasak), Cucurbita pepo (Maghz-e-Tukhm-e-Kaddu Shireen), Matricaria recutita (Babuna),

Linum usitatissimum (Alsi), Pimpinella anisum (Anisoon) and Cucumis sativa (Khyarein). These ingredients are known to have antioxidant, anti-inflammatory, and anti-neoplastic properties. **Materials and Methods:** This was a clinical trial on fifty men with moderate BPH who underwent the evaluation at the baseline and at the end of the treatment. The symptoms were assessed by IPSS (International Prostate Symptom Score), size of the prostate with abdomino- pelvic USG and flow rate of urination with uroflowmetry. **Results:** After 3 months treatment with Unani formulation there was a statistically significant decrease of International Prostate Symptom Score, significant decrease in the size of prostate and significant improvement of maximum flow rate in uroflowmetry without any significant adverse effect. **Conclusion:** based on the results treatment with Unani formulation is safe and effective in the management of mild to moderate BPH.

KEYWORDS: BPH, Unani medicine, Phytotherapy.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common benign tumour in men; it is responsible for urinary symptoms (obstructive and irritative) in majority of men older than 50 years of age. After an initial period in which only α -blockers and 5 α -reductase inhibitors seemed to offer the BPH treatment as only viable medical therapy, but with the development of phytotherapy which is now experiencing a revival of interest in all over the world especially in Europe, North America and Asia, especially as a consequence of patient's dissatisfaction with the adverse effects of the medical therapies there has been an enthusiasm for the research in herbal medicine seen in last 25 years and new pharmacologic both herbal and modern preparations and non-operative approaches for the management of BPH has been developed.

In Unani medicine, any such growth which may be directly or indirectly referred to as Benign Prostatic Hyperplasia (BPH) has not been mentioned as such however, many Unani resource books describe vividly various causes, conditions and pathophysiologies which collectively and indirectly may be correlated to the BPH. Ibn-e-zohar in his book *Kitab-al-Taiseer* described that the cause of retention of urine is —Inflammation at the neck of urinary bladder^[17] Another Unani physician Ibn-ul-Quff has mentioned in his book *Kitab-al- Umdah fi-Al-Jarahat* that —Warm-e-Ghudad is Warm-e-Balghamil^[18]

Phytotherapy

Over the past 20 years the use of complementary and alternative system of medication has widely grown up to a multi-million dollar business in the United States with the expansion of health food stores and internet companies are advertising and selling these medicines for treatment of BPH. In Austria, France and Germany the herbal agents are considered as first line treatment for moderate LUTS and it comprise upto 90% of all prescription written for treatment of BPH (Buck AC, 1996).^[9] In United States 40% of men choose non-surgical treatment for BPH and use herbal preparations alone or in conjunction with other medical treatment and that number continuously growing (Barnes et al, 2007).^[5]

MATERIAL AND METHOD

The aim of the study was to evaluate the efficacy and safety of a Unani Formulation in the management of BPH.

Plant Material

The Unani formulation included the following ingredients: *Tribulus terrestris* (Khar-e-khasak), *Cucurbita pepo* (Maghz-e-Tukhm-e-Kaddu Shireen), *Matricaria recutita* (Babuna), *Linum usitatissimum* (Alsi), *Pimpinella anisum* (Anisoon) and *Cucumis sativa* (Khyarein).



Selection of drugs and preparation of tablets

The ingredients of the test drug have interesting properties including antineoplastic activity, anti-inflammatory effects, antioxidant activity which may be useful in various stages of BPH. The tablets of 750 mg were prepared by Dawakhana Tibbiya College, Aligarh Muslim University, Aligarh. All the drugs were mixed together and pulverized in an electrical grinder. The powder was then filtered with a sieve to get the powder of uniform size. The granules were prepared from the powder, which were used to prepare the tablets of 750 mg.

Dose: - 3 gms /day, two tablets of 750 mg BID.

Study procedure

At the initial visit, a detailed medical history, with special emphasis on history of urinary obstructive and irritative symptoms (hesitancy, straining, intermittency, frequency, nocturia,

poor flow and sensation of incomplete voiding) were obtained from all the patients. A thorough systemic examination and digital rectal examination (DRE) of all the patients along with routine blood and urinalysis were done. In addition, abdomen-o-pelvic Ultrasonography was done at beginning and after completing the study to estimate the approximate prostate weight and size and to measure the full bladder volume and post void residual volume (PVRV). Uroflowmetry was also done at the initial visit and after completing the study to measure the flow rate. The severity of the urinary parameters was evaluated using I-PSS symptom score.

Inclusion criteria: Subjects were considered eligible for inclusion in this trial only if all of the following criteria were applicable:

Male patients with confirmed BPH diagnosis through medical history physical examination including a digital rectal examination (DRE); Aged more than 40 years have a maximum urinary flow > 5 mL/sec; Voided volume should be >125 mL; Post void residual urine (PVRV) less than 250 mL; Patients who give their written informed consent;

Exclusion Criteria: Patients with third grade BPH, prostatic carcinoma, carcinoma bladder, neurogenic bladder, stricture urethra, vesical calculus, has been excluded from the study.

RESULTS AND OBSERVATION

The study was conducted on 50 diagnosed patients of Benign Prostatic Hyperplasia. Patients received two tablets of the compound Unani formulation twice daily for three months.

In the study it was found that the maximum patients were in the age group of 55-65 (mean age 61.42 ± 11.38) i.e. 35%.

IPSS

Table 1: Mean IPSS Symptom Score.

IPSS	N=50	
	Pre-treatment	Post-treatment
Mean IPSS Symptom Score	14 ± 3.17	6.42 ± 3.10

Table 1 shows mean Score of IPSS of pre-treatment patients were 14 ± 3.17 and after treatment it became 6.42 ± 3.10 .

The mean and SD difference was 7.58 ± 1.96 . There is highly significant difference ($p < 0.0001$) between pre-treatment and post-treatment mean score of IPSS.

Table 2: Mean Weight of The Prostate (gm).

USG	N= 50	
Mean weight of the prostate	Pre-treatment	Post-treatment
	33.25±9.48	27.69±8.90

Table 2 and graph 2 shows mean weight of the prostate (gm) ultrasonographically of pre-treatment patients were 33.25±9.48 gm and after treatment it became 27.69±8.90 gm.

The mean and SD difference was 5.56±6.44 gm. There is highly significant difference ($p<0.0001$) between pre-treatment and post-treatment mean weight of the prostate (gm).

Table 3: Mean Maximum Flow Rate (ml/sec).

Uroflowmetry	N=50	
	Pre-treatment	Post-treatment
Mean maximum flow rate (ml/sec)	11.14±4.45	14.14±5.24

Table 3 shows mean maximum flow rate (ml/sec) (Uroflowmetry) of pre-treatment patients were 11.14±4.45 (ml/sec) respectively and after treatment it became 14.14±5.24 (ml/sec).

The mean and SD difference was 3.00±2.32 (ml/sec). There is highly significant difference ($p<0.0001$) between pre-treatment and post-treatment mean maximum flow rate (ml/sec).

DISCUSSION

The enthusiasm for research in phytotherapy has been seen in last two decades due to limitations and high cost of modern medical therapies; and some single and polyherbal compounds have been shown effective in the management of BPH and LUTS such as *Serenoa repens* (Sabal serrulata, Saw palmetto berry, American dwarf palm)^[8,9,29], *Hypoxis rooperi*, (South African star grass) *Pygeum africanum* (African plum tree)^[43], *Urtica dioica* (Stinging nettle)^[23], *Cucurbita pepo* (Pumpkin seed)^[14,15], *Tribulus terrestris* (Khar-e-khasak)^[19,37], *Linum usitatissimum* (Alsi)^[12,46], β -Sitosterol^[7], black soybean (*Glycine max* (L.))^[44], Cranberry powder^[42], *Ganoderma lucidum*^[28], *Bixa orellana*^[45], *Iresine celosia* (Odyliresin)^[30], *Peganum harmala*^[39] and *Physalis Alkekengi*^[6] etc. The findings of different studies on plant drugs as mentioned above indicate that plant drugs used in different traditional medicines have ample potential to manage the cases of BPH. The present study on a Unani formulation is important because it is being used by Unani physicians since long and has an age-old history of successfully treating the patients of LUTS. The scientific validation of the test drug may pave the way for the development of an effective and safe drug useful in

the management of BPH.

The current study was performed on 50 patients of BPH, and we investigated that how the BPH patients respond to the prepared compound of Unani Formulation and interestingly a very significant beneficial response was observed by decreasing in IPSS symptom score of both obstructive and irritative types. More than 80% of IPSS symptoms decreased from moderate to mild symptoms, mean value decreased from 14 ± 3.17 to 6.42 ± 3.10 ($p < 0.0001$). It also reduced the weight of the prostate significantly as more than 80% of the patients showed significant reduction in their prostate size from 33.25 ± 9.48 gm and after treatment it became 27.69 ± 8.90 gm, there is also satisfactory improvement in Qmax which was found to be significant statistically, from 11.14 ± 4.45 (ml/sec) to 14.14 ± 5.24 (ml/sec).

The effectiveness of the Unani formulation was attributed to its anti-inflammatory^[10,13,21,27] and anti-tumour^[1,40] and 5α reductase inhibitor^[34,35,36] properties of its ingredients and at the end the diuretic effects^[2,27] of the administered Unani formulation can further improve the urinary flow rate without any effect on urgency.

There are about 50 phytotherapeutic agents have been identified and studied as a single or compound form in the management of BPH and the number is growing each day, most of the studies on these herbal agents have shown decrease in score of total IPSS symptom score along with significant improvement in maximum flow rate and only few of them significantly decrease the size of the prostate. 90% of patients felt a very good or good improvement of their urinary symptoms and Qmax increases from 15.4 to 18 ml/sec after treatment with Cucurbita pepo reported by (Hamvas et al, 1991).^[15] There was a decrease in IPSS -7.4 points and increasing peak flow rate 15.2 ml/s from 9.9 ml/s with the beta-sitosterol-treated patients after 6 months treatment reported by (Berges et al, 1995).^[7] Permixon (Serenova repen extract) decreased the IPSS by -37% and Peak urinary flow rate increases by +25% (Carraro et al 1996).^[11] IPSS scores improved by 8.2 units and increase in Qmax by 4.5ml/s treated with compound preparation of extracts (Azuprostal) after 6 months treatment (Klippel et al 1997).^[22] IPSS reduced by 60%, Prostatic volume decreased by 12% and Qmax increased by 22% after 1 year treatment with extract of Serenova repens (Braeckman, et al 1998).^[8] The mean reduction in IPSS of 6.7 points (from 17.6 to 10.9) and no significant changes were evident in prostate volume after one year treatment with pumpkin seeds (Bach et al 2000).^[4] IPSS values decreased from 18.9 to 12.7 after three month with the treatment of a combination of natural products (cernitin, saw palmetto, B-sitosterol, vitamin E) and

maximum and average urinary flow rates showed no statistically significant differences, from 11.2 ± 0.8 to 11.8 ± 0.7 ml/sec (Preuss et al, 2001).^[31] A compound formulation Himplasia containing Tribulus terrestris and other ingredients reduced the IPSS up to 64% and mean value reduced significantly from 23.73 to 8.52, and there was a reduction in the mean prostate weight from 37.72gm to 34.02gm and Qmax increases from 10.85 ± 7.08 ml/sec to 16.46 ± 6.88 ml/sec ($p < 0.001$) the duration of treatment was three month (Sahu et al, 2003).^[33] The total IPSS score was reduced by 53% ($P < 0.001$) and peak and average urinary flow increased by 19% ($P < 0.001$) and residual urine volume decreased by 44% ($P = 0.03$) with the combination of Sabal serrulata and Urtica dioica (Lopatkin et al, 2007).^[23] IPSS of 18 of 46 patients (39.1%) showed an improvement, decrease of 3 or greater after intervention with Saw palmetto soft gel capsule and maximum urinary flow rate was significantly improved ($p < 0.001$) but There was no significant difference in mean prostate volume (Shi et al 2008).^[38] With the treatment of Flax seed extract in different doses IPSS decreased -3.67 ± 1.56 , -7.33 ± 1.18 , and -6.88 ± 1.43 and Qmax increased by 0.43 ± 1.57 , 1.86 ± 1.08 , and 2.7 ± 1.93 ml/second with placebo, 300mg and 600mg doses of flax seed extracts respectively (Zhang et al, 2008).^[46] IPSS declined from 19.0 to 4.7 by 14.3 points, indicating 75.3% improvement in symptoms and the Qmax increased from 14.8 ml/second to 17.0 ml/second at the end there is an improvement of 14.9%, and the Qmax increased from 14.0 to 21.2 ml/second with pumpkin seed, but no difference was observed in prostate volume (Hong et al 2009).^[16] IPSS declined from 17.0 (12.0-19.0) to 9.0 (5.0-13.0) and Prostate volume reduced from 33.5 ml to 31.6 ml ($P = 0.04$) with Murraya koenigii- and Tribulus terrestris-based oral formulation (Sengupta et al, 2011).^[37] The mean AUA symptom score changed from 14.60 ± 3.20 to 9.2 ± 2.60 and Prostate weight (gms) pre- treatment was 34.60 ± 8.70 and at the end of treatment it was 32.60 ± 9.40 with compound formulation containing Tribulus terrestris and other herbal ingredients (Jeyaraman and Patki 2012).^[19] IPSS improvement was 54.10%, which was found to be significant ($p < 0.001$) (Arun et al 2013).^[32] After the 1 year treatment period, the mean differences compared with baseline were -5.4 ± 5.1 , -4.2 ± 5.4 and -4.0 ± 5.5 with pumpkin seed, pumpkin seed extract and placebo, respectively The Qmax increased by 4.3, 3.6 and 3.6 ml/s but there was no clinically significant change in mean prostate volume in any of the groups (Vahlensieck et al, 2014).^[41] IPSS decreased by -3.1 and -4.1 in the 250 mg and 500 mg doses of cranberry powder, ($p = 0.05$) and ($p < 0.001$) respectively (Vidlar et al 2016).^[42] A significant reduction in the overall IPSS scale was reported, before treatment it was 11 ± 12 and finally it was 4 ± 5 ($p < 0.0001$) and Prostatic volumes initially was 38 ± 27 ml decreased to 36 ± 26 significantly ($p=0.002$) with the treatment of extract of pumpkin seed oil

(Machado-Leiva et al 2016)^[24].^[28] The mean IPSS score before and after treatment was 14.30 ± 3.92 and 12.04 ± 1.19 respectively and significant ($p=0.063$) increase in urinary flow rate on uroflowmetry with the treatment of a compound Unani formulation Banadiqul-bozoor (Khesal et al 2017).^[20] IPSS reduced by -4.8 , ($p=0.000$), Prostatic adenoma decreased by $-$ ($p=0.000$) and significant improvement of mean values of Qmax ($+1.2$, $p=0.050$), average flow rate ($+0.47$, $p>0.002$) (Porru et al 2017).^[30] IPSS values changed from 13.0 ± 4.5 (Mean \pm SD) to 7.6 ± 4.1 (Mean \pm SD) and Total prostate volume, (ml) at base line in study group was 37.7 ± 19.9 (Mean \pm SD) and after 4 week it was 35.0 ± 16.4 (Mean \pm SD) and the Qmax (ml/s) improved from 11.7 ± 2.9 ml/sec (Mean \pm SD) to 14.2 ± 5.4 ml/sec (Mean \pm SD) with fermented whey product (Ausmees et al 2018).^[3] Prostocare an Ayurvedic compound Unani formulation is statistically highly significant ($p<0.001$) for all seven parameters of IPSS (Moiz et al, 2018).^[26]

It was observed that compound formulations have shown significant therapeutic results in short time period three to six months, and in case of single drug treatment duration must be 10-12 months or more for therapeutic outcome especially for reducing the size of the prostate, and while it is also a well-known fact that BPH has a multifactorial etiology therefore the compound drug may be more beneficial in alleviating the LUTS due to BPH, in decreasing the size of prostatic adenoma and for improving the maximum flow rate.

CONCLUSION

The present study has demonstrated the clinical efficacy and safety of Unani formulation in the management of benign prostatic hyperplasia; it provides statistically significant decrease in IPSS and size of the prostate and statistically significant improvement in maximum flow rate. Therefore the study drug (Unani formulation) can be used as a safe and effective agent in the management of BPH. Further, since it is cost effective and relatively safe drug therefore it should ideally be used on preferential basis.

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