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Khar-e-khasak (*Tribulus terrestris*): An Unani medicine in the management of benign prostatic hyperplasia: A narrative review

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Abstract
Tribulus terrestris referred to as Khar-e-khasak in Unani Medicine and Gokshura, Gokharu in Ayurveda, or puncture vine in English, has long been utilized in Unani, Indian and Chinese medical systems to cure a variety of illnesses. Its many portions include a range of chemical components that are crucial for medicine, including alkaloids, steroidal saponins, flavonoids, and flavonol glycosides. It has a variety of beneficial effects on the body, including diuretic (Mudirr-e-Baul), Aphrodisiac (Muqavi-e-Baah), Antiurolithic (Mufattit & Mukhrij-e-Hasat), Immune modulatory, Antidiabetic, Hypolipidaemic, Cardio tonic (Muqavi-e-Qalb), Anti-inflammatory (Mohallil-e-Waram), Analgesic, Antispasmodic, Antibacterial, and Anthelmintic properties. Extensive study has been conducted in the last few decades to demonstrate its biological activities and the pharmacology of its extracts. The purpose of this review is to provide a database for future research in Unani Medicine on the plant's revealed phytochemical and pharmacological qualities.

Keywords: Khar-e-khasak (*Tribulus terrestris*), Unani medicine, hyperplasia, anti-inflammatory

Introduction
Benign prostatic hyperplasia (BPH), which is a major cause of lower urinary tract symptoms in males, is the non-malignant enlargement or hyperplasia of prostate tissue. It has been demonstrated that prevalence of the disease rises with age. In actuality, the histological occurrence of BPH at autopsy is as high as 50% to 60% for males in their 60s, rising to 80% to 90% for those beyond 70 years of age [1].

The progression of benign prostatic hyperplasia is defined as the proliferation of stromal and epithelial cells in the prostate transition zone (around the urethra). This compression of the urethra and development of bladder outflow obstruction (BOO) can cause clinical presentation of lower urinary tract symptoms (LUTS), retention of urine, or infections as a result of insufficient bladder emptying [2]. Chronic high-pressure retention, a situation that may be life-threatening if left untreated, and long-term bladder detrusor alterations can result from untreated, long-term illness

There are several treatment methods, depending on the disease's severity. There are medications, surgeries, and herbal (Unani & Ayurveda) treatments available. Herbal treatments can be used to treat BPH in mild to moderate cases. Medicines may be administered in cases that are more severe. For this reason, patients have access to many herbal medicines. Phytosterols, β-sitosterol, lectins, and other active substances are most frequently found in them [3].

Khar-e-khasak is also one of the Unani drugs that has been found effective in benign prostatic hyperplasia and here we are presenting a review of the research work has been done on this drug with particular focus on its efficacy in the management of benign prostatic hyperplasia.

Drug Khar-e-khasak consists of dried entire fruits of *Tribulus terrestris* Linn
Family: Zygophyllaceae.
Genus: *Tribulus*
Species: *terrestris* Linn.
Habitat: Throughout India, up to 5400 m [4] and the warmer countries mainly Ceylon and throughout the globe [5]. The fruits are conical and have four spines [4].

Synonyms
Arabic: Akhwas-ul-juz, Khasak.
Persian: Khar-e-khasak.
English: Caltrops fruits Calthrops, Small Caltrops, Puncture Vine.
Sanskrit: Ikshugandha,
Hindi: Gokhru, Gokshri, and Burragokhur.
Urdu: Gokharu [4, 5, 6 7].

Botanical Description
Macroscopic: Fruit stalked, light or greenish yellow, five ribbed or angled, about spherical in shape, covered with short stiff or pubescent hairs, and with noticeable short stiff spines that point downward and measure about 0.5 cm in length (Figure 1). Together, these features form a pentagonal framework around the fruit; ripe fruit that has been divided into five segments. Each cocci is semi-lunar or plano-convex in shape, has one chamber, is equipped with two spines, and contains four or more seeds. Its flavour is mildly astringent.

Microscopic: Transverse section of the fruit reveals the rectangular-shaped small epidermal cells of each coccus, numerous unicellular trochees, 6-10 layers of large parenchymatous cells, and an abundant rosette of calcium oxalate crystals in the mesocarp. The mesocarp is followed by 3-4 compact layers of small cells that contain prismatic calcium oxalate crystals [6].

Parts used: The entire plant, especially the fruit and leaves [5].

Temperament: Hot[1] & Dry[1] [8, 9, 10], Cold[1] & Dry[1] [11] Morakkab-ul-quwa [12, 13].

Chemical Constituents
The fruit contains an alkaloid in traces, a fixed oil 35% mainly of unsaturated acid, an essential oil in small quantities, resins and fair amount of Potassium nitrate sterols, sapogenin with Pyroketone ring (diosgenin), gitogenin and hecogenins, [6, 7]. The plant contains saponins, which on hydrolysis yield sapogenins-diosgenin, gitogenin, chlorogenin, ruscogenin, 25D-spirosta-3, 5-diene, among others. Flavonoids-rutin, quercetin, kaempferol, kaempferol-3-glucoside and-rutinoside, and tribuloside have been isolated from the leaves and fruits. The seeds contain carboline alkaloids- harmane and harmine. Harmol is also reported from the herb [4].

Action: Munzij, Mulaiyin, Jali, Mudirr-e-Baul (diuretic), Mudirr-e-Haiz, Mufattit-e-Hasat [6, 8, 9, 10, 13].

Therapeutic uses
It is beneficial in retention of urine (habs-e-baul), burning micturition and post micturition dribbling [12], and anti-inflammatory, anabolic, spasmolytic, muscle relaxant, hypotensive, hypoglycaemic and aphrodisiac. It is used in genitourinary diseases like chronic cystitis, strangury, calculus affections, urolithiasis, crystalluria, urinary discharges, spermatorrhoea, and phosphaturia, incontinence of urine and as a tonic in sexual inadequacy [7]. In Southern India, the fruit is highly valued as a diuretic. In many cases where this has been tried, the result was quite perceptible in the increase of the urinary secretion [13]. Diuretic (more than furosemide), proerectile, hypoglycaemic (40– 67% in diabetic mice) activities have been confirmed in several experimental studies [4].

Fig 1: Fruit of *Tribulus terrestris*

Action and uses Mentioned in Unani Medicine
Fruits: Munzij, Mulaiyin, Jali, Mudirr-e-Baul (Diuretic), Mudirr-e-Haiz, Mufattit-e-Hasat, [6, 8, 9, 10, 13]. It is beneficial in retention of urine (Habs-e-Baul), burning micturition and post micturition dribbling [12], (Mohallil-e-Waram) anti-inflammatory, anabolic, spasmolytic, Muscle relaxant, Hypotensive, Hypoglycaemic and Aphrodisiac. It is used in genitourinary diseases like chronic cystitis, Strangury, calculus affections, Urolithiasis, Crystalluria, urinary discharges, Spermatorrhoea, and Phosphaturia, incontinence of urine and as a tonic in sexual inadequacy [7]. In Southern India, the fruit is highly valued as a diuretic. In many cases where this has been tried, the result was quite perceptible in the increase of the urinary secretion [13]. Diuretic (more than furosemide), Proerectile, hypoglycaemic (40– 67% in diabetic mice) activities have been confirmed in several experimental studies [4].

Dose: 5 to 7 g [6].

Important formulations: Sharbat-e-Buzoori Motadil

The principal pharmacological actions
***In Vitro* studies**
Diuretic activity
The diuretic effect of *T. Terrestris* is due to large quantity of nitrates and essential oil present in its fruits and seeds. The diuretic activity can also be attributed to the presence of potassium salts in high concentration. Ali *et al*. In a rat model examined the T. Terrestris aqueous extract made from its fruit and leaves. Strips of isolated Guinea pig ileum were utilized for the contractility test. A positive diuresis was produced by the oral dose of 5 g/kg, which was marginally greater than that of furosemide. The amounts of sodium and chloride in the urine have increased. Additionally, T. Terrestris extract improved the smooth muscles' tonicity. It assisted in the propulsion of stones down the urinary canal in addition to its diuretic effects [14]. Saurabh *et al*., undertook a comparative analysis of the diuretic effects of various Tribulus terrestris fruit extracts, including aqueous, methanolic, Kwatha-high strength, Kwatha-low strength, and powder extracts. Kwatha-high strength demonstrated a diuretic effect comparable to that of the reference standard furosemide as well as an extra benefit of potassium-sparing effect. T. Terrestris functions as an

effective anti-hypertensive due to its diuretic properties [15].

Antibacterial activity

The Yemeni Tribulus terrestris had no detectable antibacterial activity against Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, while only the fruits and leaves of Indian Tribulus terrestris were specifically active against Enterococcus faecalis. All parts (fruits, stems, leaves, and roots) of Turkish and Iranian Tribulus terrestris demonstrated antibacterial activity against Enterococcus faecalis, Staphylococcus aureus, and Escherichia coli. These varied outcomes in terms of Tribulus terrestris' antibacterial activity could be the consequence of employing various strains, assay techniques, and geographic sources of the plant. Most effective against both gram-positive and gram-negative bacteria was found to be the methanolic extract of Tribulus terrestris fruits, whereas its petroleum ether and chloroform extracts showed only moderate activity [16, 17].

Anti-inflammatory Activity

In lipopolysaccharide-stimulated RAW264.7 cells, the ethanolic extract of TT reduced the production of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Additionally, it reduced the expression of pro-inflammatory cytokines in the macrophage cell25 line, including tumor necrosis factor-alpha (TNF-alpha) and interleukin (IL)-4. As a result, the ethanolic extract of TT reduces the expression of inflammatory cytokines and mediators, which is effective for treating a variety of inflammatory disorders [18]. In rats with carrageenan-induced inflammation, the methanolic extract of TT demonstrated a dose-dependent reduction of rat paw volume.

Antispasmodic Activity

In a dose-dependent manner, the plant's lyophilized saponin combination significantly reduced the peristaltic motions of a rabbit jejunum preparation. These findings suggested that the saponin mixture might be helpful for colic discomfort or smooth muscle spasms [19]. Tribulus Terrestris has become a highly specific medicine in the management of BPH because inflammation is one of the etiologies of BPH and because the prostate gland contains a significant amount of smooth muscle, the antispasmodic activity of the drug is useful to decrease the tone of the prostate.

Clinical studies

Effect on International Prostate Symptom Score (IPSS)

The intensity of lower urinary tract symptoms can be determined using the International Prostate Symptom Score (IPSS). It is a verified, repeatable scoring system for evaluating the severity of the disease and the therapeutic response. The seven questions that make up the IPSS are all about voiding and storage symptoms. Mild symptoms are represented by a score of 0 to 7, moderate symptoms by a score of 8 to 19, and severe symptoms by a score of 20 to 35 [20]. *Sahu et al*, conducted a study on 25 elderly male patients with BPH between the ages of 45 and 90 were the subjects of an open clinical trial at the Shalya Shalakya Department of Sir Sundarlal Hospital, Institute of Medical Sciences, BHU, Varanasi. Himplasia was administered twice daily for three months at a dose of two pills. Gokshura (Tribulus terrestris) 140 mg, Putikaranja (Caesalpinia bonducella) 120 mg, Puga (Areca catechu) 100 mg, Shatavari (Asparagus racemosus) 80 mg, Akik pisthi 80 mg, and Vanga bhasma 80 mg are all present in each tablet of Himplasia. Every patient was monitored for three months at intervals of four weeks. They were assessed based on their uroflowdynamics and IPSS scores. IPSS decreased by up to 64%, and the mean score dropped from 23.73 to 8.52 considerably. Significantly, serum PSA dropped from 4.57 to 2.89. Himplasia significantly reduced the signs and symptoms of BPH [21].

A double-blind, double-dummy, randomized controlled experiment was conducted to compare the effectiveness of Murraya koenigii and Tribulus terrestris-based oral formulation to tamsulosin in the treatment of BPH in males aged >50 years. For 12 weeks, patients either received tamsulosin 400 mg once day or the plant medication in a dose of 2 capsules BID. After 12 weeks of treatment, IPSS decreased with the plant medication from 17.0 (12.0-19.0) to 9.0 (5.0-13.0) and with tamsulosin from 14.0 (11.0-18.0) to 8.0 (6.0-13.0) [22]. An herbal formulation's effectiveness and safety in treating BPH was tested. A single blind, randomized, and placebo-controlled research was conducted. The ingredients of the polyherbal formulation were as follows: 32 mg of Mushali (*Curculigo orchioides*), 8 mg of Vanya Kahu (Lactuca scariola), 16 mg of Kokilaksha (Asteracantha longifolia), 20 mg of Kapikachchu (Mucuna pruriens), 32 mg of Shaileyam (Parmelia perlata), 64 mg of Vriddhadaru (Argyreia speciosa), 64 mg Gokshura (Tribulus terrestris), and 64mg Jeevanti (*Leptadenia reticulata*). The study comprised 60 participants with a BPH diagnosis in total. Randomization was used to assign each patient to one of two groups: polyherbal (n = 30) or placebo (n = 30). For two months, each patient took either a polyherbal formulation or a placebo in a dose of two capsules twice a day with meals. The mean AUA symptom score significantly improved; at the beginning of treatment, the AUA scores for the Polyherbal formulation and placebo groups were 14.60±3.20 and 13.80±4.60, respectively, and at the end of therapy, they were 9.2±2.60 and 12.90±3.80, respectively (p value 0.0001) [23]. 32 patients from Mootraghata who met the criteria for BPH were randomly assigned to one of three treatment groups, and a study on the use of Gokshuradi Vati and Dhanyaka Gokshura Ghrita Matra Basti in the management of BPH was done. Gokshuradi compound (GC) Vati (GV) 500 mg was given three times daily with lukewarm water after meals in group A. Dhanyaka Gokshura Ghrita (DGG) as Matra Basti (MB) 60 ml was given once daily right after lunch in group B. Group C received combined therapy of both formulations. Out of 32 patients, 30 patients (ten in each group) finished the 21-day therapy cycle. In terms of outcomes, group C showed a 54.09% improvement, compared to group A's 45.67% and group B's 47.99% in symptoms [24]. These clinical trials, in which tribulus terristeris was a key constituent in the formulation, demonstrated a promising efficacy in the treatment of symptoms of prostatism.

Effect on Prostate Volume and Post Void Residual Urine

Patients with benign prostatic hyperplasia can reliably measure their prostate volume and post-void residual urine volume using trans- abdominal ultrasonography. The post-void residual urine significantly decreased from 80.01 to 39.91, and the mean prostate weight decreased from 37.72

to 34.02 on average. Himplasia significantly decreased prostate weight and post-void residual urine [21]. Prostate volume decreased from 33.5 (26.2-45.9) ml to 31.6 (26.1-37.5) ml (P = 0.040) as a result of the plant medication. Tamsulosin caused a similar drop in volume from 41.3 (29.4-51.3) ml to 39.9 (32.6-52.3), although it was not statistically significant [22]. Prostate weight (Gms) in the placebo group and Polyherbal formulation was 34.60±8.70 and 32.60±8.30 at the beginning of treatment which becomes 32.60±9.40 and 34.50±6.60, respectively, at the end of treatment. Post-void residual (PVR) volume (ml) in the Polyherbal formulation and placebo group at the beginning of treatment was 85.30±20.20 and 86.20±18.20 and at the end of therapy it was 52.10±23.10 and 89.70±28.30, respectively (p-value 0.0001) [23]. Prostate gland's size had significantly decreased [24].

Effect on Uroflowmetry parameters

Urologists can measure and record the flow rate of urine during micturition using the dependable, simple, inexpensive, and non-invasive method provided by Uroflowmetry, a key research tool used around the world. Willard M. Drake Jr., an American surgeon, created and published it [25]. Himplasia also significantly increased the peak flow rate, which increased by more than 50% from 10.85±7.08 ml/sec to 16.46±6.88 ml/sec on average after treatment. Pre-treatment average flow rate was 4.51±2.30 ml/sec, and post-treatment average flow rate was 8.84±2.48 ml/sec Himplasia significantly improved the urinary flow rate [21]. Peak urine flow rate didn't significantly alter [24].

Conclusion

Tribulus Terrestris, a widely accessible drug, has great utility in the conventional medical systems, i.e. Unani Medicine, Ayurveda, Chinese medicine and Siddha. Tribulus Terrestris is also a well-known herb used in the traditional medicine of many nations to treat a variety of ailments. For its phytochemical and pharmacological properties, including its diuretic, aphrodisiac, antiurolithic, immune-modulatory, antihypertensive, anthelmintic, antibacterial, analgesic, and anti-inflammatory effects. The entire plant of Tribulus Terrestris has been thoroughly investigated. The plant may offer potential as an effective herbal therapy for benign Prostatic Hyperplasia, as BPH is an ageing disease it also has extra benefit in controlling Blood Pressure given its diuretic activity (potassium sparing), anti-hyperlipidaemic activity, and cardio-protective activity, according to the literature that is currently accessible on Tribulus Terrestris. More investigations at the molecular level are required to better understand the mechanism by which Tribulus Terrestris affects the disease condition, even though it has been used widely for millennia and there is currently scientific evidence regarding its pharmacological effects being produced.

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Conflict of Interest

Not available

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Not available

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