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Review

An overview of benign prostatic hyperplasia and its appreciation in Greco-Arab (Unani) system of medicine



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KEYWORDS

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Abstract *Objective:* Conventional treatments for benign prostatic hyperplasia (BPH) like 5 α -reductase inhibitors and invasive surgery are associated with some obvious side effects. Conversely, evidence, though limited, has shown that alternative medicines are safer and have potential to improve the lower urinary tract symptoms (LUTS) and quality of life in addition to improving sexual dysfunction in patients with BPH. The current article aimed to include an overview of BPH, different ways of its management, and particularly its appreciation in Greco-Arab (Unani) system of medicine, one of the alternative medicinal systems.

Methods: PubMed, Scopus, ScienceDirect, Web of Sciences, Google Scholar databases and classical texts of Greco-Arab medicine were searched for data collection.

Results: In Unani system of medicine, BPH, traced under the headings of Waram unuq almathana (bladder neck swelling) and Insidad majra-i-mathana (bladder outlet obstruction), has been managed for centuries with herbal medicines yet demanding a comprehensive scientific validation. Among the herbs, *Cucurbita pepo*, *Tribulus terrestris*, *Urtica dioica*, and *Linum usitatissimum* are worth mentioning.

Conclusion: For achieving the goal of LUTS-free ageing men, and safer and cost-effective future management of BPH, Unani herbal medicine could hopefully prove beneficial.

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1. Introduction

Benign prostatic hyperplasia (BPH), in general, refers to enlargement of the prostate gland, which is the most common disease in elderly men, especially those aged above 50 years. Alternative names given to BPH include benign prostatic hypertrophy, senile enlargement of prostate, adenoma, adenomyoma, and nodular hyperplasia of the prostate gland [1]. Prostatic hyperplasia results in the lower urinary tract symptoms (LUTS). The term LUTS was introduced in 4th international consultation on BPH and was earlier known as "prostatism". LUTS are highly annoying which disturb normal day-to-day activities and affect the quality of life (QoL) [2,3]. The disease involves significant number of men beyond the age of 40 years old and its frequency rises progressively with age so that 90% of men in their 80s get affected [4,5]. Hyperplasia of prostate most commonly involves transitional zone (periu- rethral zone), affecting both the glandular and stromal tissue [5–7]. People who live long enough will undoubtedly develop some histological features of BPH [8]. Even though the relationship between BPH and LUTS is quite important, however, not all men with the evidence of histological BPH develop significant LUTS. Further, it is not necessary that all patients with BPH and LUTS must have prostate enlargement [9,10]. Clinical BPH is defined as having at least two of the following features: (A) Moderate to severe LUTS with International Prostate Symptom Score (IPSS) greater than 8, (B) an enlarged prostate (total prostatic volume >30 mL), and (C) maximum urinary flow rate less than 15 mL/s [11]. In 1989, Hald [12] described a relationship between prostate enlargement, bladder outflow obstruction, and symptoms (prostatism), where the three conditions may develop independently or may coexist. The Fig. 1 depicts ideal relationship between the three.

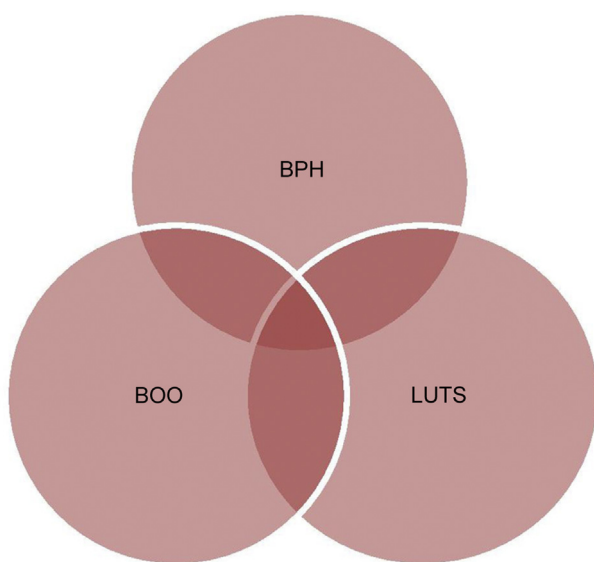


Figure 1 Relationship between benign prostatic hyperplasia (BPH), bladder outlet obstruction (BOO), and lower urinary tract symptoms (LUTS) [12].

There is also a great individual-to-individual variation on impact of QoL due to LUTS. Simply, it is the histological condition in prostate, *i.e.*, the presence of stromal-glandular hyperplasia for which the term "BPH" is actually used [13].

2. Historical background

The classical Unani literature reveals that symptoms of the prostate enlargement were managed in the past by different traditional medicines and some surgical procedures like punching, incision, and puncturing. However, a clear pathological picture of the disease was obscure. Jean Riolan, the younger (1577–1657) [14], had first suggested that the enlarged prostate could be the cause for urine retention. Still, least importance was given by the scientists towards the prostate enlargement for a longer time even after the discovery. In the late 18th century, various surgical instruments for the purpose were designed. In early 19th century, it was understood that mere removal of obstruction without paying attention towards the gland could prove fatal for the patient. It was at this juncture when the prostate enlargement gained more attraction of the scientists and with time different modes of treatment, both medical and surgical were introduced. Further, the increase in average human age also became a reason for seeking the best quality treatment in prostate enlargement [15]. The term "prostatism", earlier used for the symptoms of BPH, was marked as obsolete term in 4th international consultation on BPH and was then replaced by the term "LUTS" [9].

3. Epidemiology

It has been examined in several autopsy studies around the world that BPH shows a greater age variation and is approximately 10% for men in their 30s, 20% for men in their 40s, 50%–60% for men in their 60s, 80% for men in their 70s, and 90% for men in their 80s [13]. In India, the data revealed the prevalence of BPH as 25%, 37%, 37%, and 50% for the age group 40–49, 50–59, 60–69, and 70–79 years, respectively [16]. Worldwide, prevalence of BPH generally varies from 20% to 62% in men beyond the age of 50 years [17]. Regarding the economic costs, it was estimated that in the United States alone, direct and indirect costs to the private sector for the treatment of BPH were nearly \$4 billion. The results also revealed the mean individual annual expenditures of \$4193 for men without a medical claim for BPH and \$5729 for men with a claim for BPH. Hence the cost associated with the diagnosis of BPH was estimated at \$1536 annually [17,18]. In the year 2000, about 4.5 million visits were made to physician offices for a primary diagnosis of BPH and nearly 8 million visits with a primary or secondary diagnosis of BPH [19]. A study in Taiwan, China, investigated differences in healthcare service utilization between the patients with and those without BPH. The study concluded that patients with BPH had higher healthcare utilization (two fold greater) in comparison to patients without BPH [20]. Furthermore, BPH is more prevalent among African Americans and Caucasians [17].

3.1. Risk factors

3.1.1. Age

Based on Krimpen and Baltimore longitudinal study of aging, an increase in prostate volume at the rate of 2.0%–2.5% per year was observed in men of older age (>40 years old) [21,22].

3.1.2. Geography

It has been found that prostate volume varies across different regions of the world, being larger in Western regions as compared to South-East Asian regions [23]. Ganpule et al. [24] demonstrated in a large sample size of Indian population that the IPSS is higher at a comparatively lower prostate volume than in Western population.

3.1.3. Heredity

Some findings suggested an autosomal dominant pattern of inheritance for BPH [13]. Men having positive family history tend to have larger prostate volumes at early age, with the early onset of clinical symptoms in them [25–27].

The above-mentioned risk factors (age, geography, and heredity) are called the non-modifiable risk factors which play significant roles in the cause of BPH. On the other hand, factors including metabolic syndrome, obesity, sex hormones, cardiovascular disease, inflammation, and decreased physical activity are said to be modifiable risk factors of BPH. Modifiable risk factors provide newer opportunities for prevention and treatment of BPH [28].

4. Etiopathology

The cause of BPH is still unclear, but it is of no doubt that androgens play a key role in its development [7,29]. Different researchers have given different opinions for the development of BPH which are discussed below briefly.

4.1. Testosterone

Among elderly people, testosterone is found to be the main culprit for developing BPH, especially the altering ratio between testosterone and dihydrotestosterone (DHT) [30]. In prostate, testosterone, under the influence of an enzyme 5 α -reductase, is converted into DHT, which is considered to be 2–3 times more potent than testosterone [31,32]. DHT along with its metabolite 3 α -androstane-diol acts as a major stimulus for stromal and glandular proliferation. DHT actually binds to the receptors on nucleus and stimulates the synthesis of DNA, RNA, some growth factors, and many more cytoplasmic proteins, which in turn cause hyperplasia to the gland [7,33]. No clear association between the circulating androgens and hyperplasia of the prostate ascertains that it is the intra-prostatic concentration of androgens and androgen receptors which actually contribute to the pathogenesis of BPH. Initially, it was recognized that the concentration of DHT in hyperplastic prostate is about 3–4 times more than

that in normal prostate. This fact was supported by the studies of Meikle et al. [34], Geller et al. [35], Hammond [36], and Krieg et al. [37], respectively. However, conclusive data are lacking because the subsequent studies have not demonstrated any difference of DHT level in normal prostate and BPH tissue [38]. Androgen receptor in adult prostate is primarily expressed in the luminal epithelial cells rather than stromal cells. Castration at any age leads to depletion of testosterone level, loss of secretory luminal epithelial cells, and hence reduction in prostate size [39].

4.2. Estrogen

Commonly thought as an androgen-target tissue, prostate is also an important target for estrogen. Estradiol, which is more potent component of estrogen, is in higher concentration in prostate than in plasma. It was demonstrated that when a combination of 3 α -androstane-diol and 17 β -estradiol was injected in castrated dogs, and a remarkable growth of prostate gland occurred as compared to their individual effects. This showed the synergistic effect of androgen and estrogen for prostatic hyperplasia [30,40]. Although exact mechanism of estrogen in prostate is unclear, yet there is a strong correlation between increasing estradiol: DHT ratio and hypertrophy of stroma. Moreover, dietary estrogens including phytoestrogen, lignans, and flavanoids have been found to be effective in preventing and reducing prostate diseases. This dual effect of estrogen has been seen because of two subtypes of estrogen receptors (ERs), ER α and ER β . ER α is responsible for proliferation and ER β for apoptosis of prostate cells [30,38,40].

4.3. Other gonadal steroids

Luteinizing hormone, follicle stimulating hormone, and progesterone were also said to play some role in BPH and LUTS [36,41].

4.4. Inflammation and local growth factors

A strong link has been observed between histological inflammation of prostate and BPH in surgical specimens. The severity of inflammation corresponds to the magnitude of prostate enlargement and BPH. Conversely, anti-inflammatory agents were found to decrease the risk of BPH and LUTS [28]. Inflammation leads to accumulation of immunocompetent cells, mainly T lymphocytes and macrophages inside the prostate. Accumulation of neutrophils, eosinophils, and mast cells may also be there, depending upon the offending agent. These cells produce cytokines (chemokines, interferons, interleukins, and tumor necrosis factors) and hypoxia-inducible factor-1 α , therefore participate in pathological changes responsible for both BPH and prostate carcinoma [42–44].

Local growth factors found in prostate gland, particularly basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF β) regulate the cell growth in it. bFGF increases fibroblast division (mitosis) and inhibits the division of epithelial cells, while TGF β decreases the growth of both fibroblast and epithelial cells. In day-to-day

wear and tear of urethral epithelium and prostate surrounding urethra, due to micturition, ejaculation, infection, etc, bFGF from stromal tissue, epithelium, and basal membrane leads to stromal growth. Furthermore, experiments have revealed that if there is abundant testosterone in prostate tissue with no growth factor, cell growth would not happen, but when growth factor is added to it, cell growth occurs. In BPH, overexpressed growth factors have been observed in the gland [22,44,45].

5. Pathophysiology

In BPH, when prostatic urethra or bladder neck gets obstructed, LUTS appear which may be mild, moderate, or severe [46–48]. More explicitly, microscopic BPH in the transitional zone of prostate gland may develop prostate enlargement or smooth muscle hyperplasia followed by bladder outlet obstruction, clinical BPH, and LUTS, or it may directly produce bladder outlet obstruction and hence LUTS [46]. The relation between BPH and development of LUTS has been shown with the help of a flow chart in Fig. 2.

6. Clinical features

The most common manifestations of BPH are LUTS. These symptoms are divided into two categories, namely obstructive and irritative (Table 1) [1,7].

Abrams et al. [49] have divided LUTS into three categories:

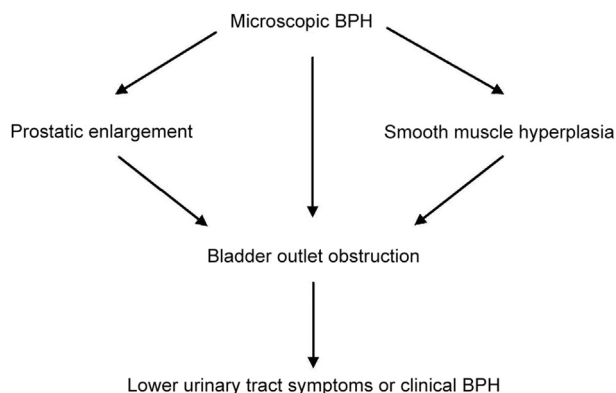


Figure 2 Pathophysiology of benign prostatic hyperplasia (BPH) [46].

Obstructive symptom	Irritative symptom
Hesitancy/straining	-Increased frequency of micturition
Weak flow	-Urgency with urge incontinence
Prolonged voiding	-Nocturia
Overflow incontinence	-Painful urination
Partial or complete urine retention	

- Storage symptoms: Increased frequency, nocturia, urgency, incontinence, and bladder pain.
- Voiding symptoms: Hesitancy, straining, weak stream, intermittency, dysuria, and terminal dribbling.
- Post-void symptoms: Feeling of incomplete emptying and dribbling after micturition.

As already discussed, there are many men with severe LUTS but have a normal sized prostate, whereas many have large prostate but a few or no symptoms of LUTS. The latter condition was called as “silent prostatism” [50]. Bother-some LUTS interfere with the patient’s daily activities, QoL, and sexual functions [3,51].

7. Complications [47,48,52]

- Hydronephrosis and in severe cases, kidney malfunctioning.
- Infection in immunocompromised patients that may lead to death.
- Other complications include bladder stones, nephrolithiasis, acute retention of urine, and gross hematuria.

8. Diagnosis and evaluation

Before 1980, patients having BPH or LUTS were evaluated only with the medical history and physical examination including digital rectal examination and urinalysis. Some blood investigations and radiography were used to rule out any damage to urinary tract or concurrent diagnosis. After 1980, huge innovations in the field of diagnosis and therapy occurred. Ultrasonography, computed tomography, and urodynamic measures were among such innovations. Ultrasonography enabled the accurate measurement of post-void residual urine along with the size of the prostate gland. Measuring serum prostate-specific antigen has also become a routine procedure in male patients with voiding problem. American Urological Association Symptom Index (AUA-SI) or IPSS is the most reliable scale for monitoring BPH patient, severity of the disease, and for planning the management of the disease [53]. American Urologic Association, European Association of Urology, and World Health Organization international consultations on urologic disease have recommended the routine use of AUA-SI or IPSS in the clinical evaluation of suspected BPH patients [3,54]. According to them when the symptoms are mild (IPSS<8), watchful waiting is to be followed, but when the symptoms are moderate to severe (IPSS≥8), treatment plan has to be devised and in case of complications, surgical intervention is obligatory [9,54]. Even though digital rectal examination has many shortcomings, it should be used to assess the shape, symmetry, firmness, and nodular character of enlarged prostate. Invasive techniques like pressure flow studies or formal urodynamic studies are good to determine the obstruction at the neck of urinary bladder, but these are optional tests and are needed in case the symptoms are severe or the surgical intervention is chosen for the management [9,55,56]. Upper urinary tract imaging by intravenous urography or computerized tomography is hardly

recommended because such patients do not have any increased incidence of lesions.

9. Management

As a matter of fact, when the symptoms in BPH are mild or moderate but not bothering, watchful waiting is followed and when the symptoms are moderate to severe, causing distress to the patient, treatment plan is to be followed [9,48]. Treatment plans for BPH may be of two types, medical and surgical. Treatment strategy is selected on the basis of need and by the mutual understanding of doctor and patient. Before 1990, surgical intervention (prostatectomy) was considered as the only accepted treatment for BPH. Transurethral incision of prostate and later, transurethral resection of prostate (TURP) were very much popular treatment of BPH. Nowadays medical intervention has become more popular, creating a major breakthrough in the management of BPH. Medical therapy involves the use of alpha-adrenergic antagonists, 5alpha-reductase inhibitors, antimuscarinics, beta adrenergic agonists, phosphodiesterase type 5 inhibitors, vasopressin analogs, and phytotherapeutics [9,54,57]. The most commonly used medicines for LUTS associated with BPH include alpha-adrenergic antagonists followed by 5alpha-reductase inhibitors, and the most common surgical intervention for the same is TURP. Although much effective in improving bothersome LUTS and QoL, these treatment modalities also have some associated side effects. Among the side effects, erectile dysfunction, loss of libido, and ejaculatory disorder are highly troublesome for the patients. Various minimally invasive techniques developed for the management of BPH such as transurethral microwave thermotherapy, transurethral needle ablation, transurethral vaporization of prostate, interstitial laser coagulation, prostatic urethral lift, laser enucleation, Aquablation, water vapor thermal therapy-Rezum (NxThera, Maple Grove, MN, USA), and prostate artery embolization are noteworthy [9,54,58]. Yet, most of these techniques either have limited evidences of their efficacy or have higher retreatment rates than that of TURP. This is why TURP is still considered as the gold standard for surgical management of BPH. Some novel interventions yet not recommended as standard therapies include absolute ethanol injection, temporary implantable nitinol device, intraprostatic botulinum toxin injection, and histotripsy [58,59].

9.1. Alternative medicines for the management of BPH

Alternative medicines such as traditional Chinese medicine, homeopathic, Ayurveda, Unani, and other forms of traditional medicines also take a promising position to tackle BPH. Due to multiple side effects associated with the conventional treatment, herbal medicines and alternative therapies are becoming more and more popular even in Western countries. In the present era, experts advise to focus on the prevention of the disease in order to be safe

from its noxious outcomes and the adverse effects of the drugs used for treatment of the disease [60]. Herbal medicines are much safer than synthetic medicines and also effective in prevention and treatment of mild to moderate conditions of BPH. Crenilton, one such medicine prepared from rye grass pollen extract is a registered pharmaceutical product in Western Europe, Japan, Korea, and Argentina. According to data available, Crenilton is well-tolerated and improves overall urological symptoms [61]. Similarly, Saxifrage tablet prepared from the extract of *Saxifraga stolonifera*, potently improves urine flow rate, QoL, and prostate volume. The extract of *Ganoderma lucidum* has shown the strongest 5alpha-reductase inhibitor activity [61]. Saw palmetto is commonly used phytoedicine for enlarged prostate in USA. *Pygeum africanum* and *Urtica dioica* were revealed to have a great potential in improving symptoms of BPH [62]. Homeopathic constitutional medicines including Thuja, Hydrangea, Conium, Sulphur, Lycopodium, Iodeum, Pulsatilla, Mercurius solubilis, Baryta carbonica, Natrum muriaticum, Lyssin, Tuberculinum, Calcarea carbonica, Lachesis, Gelsemium, Carcinosis, Staphysagria, and organopathic medicines such as *Sabal serrulata*, Hydrangea, Chimaphilla, Solidago, Senecio, Triticum, Ferrum picricum, and Picricum acidum were found to improve BPH and its symptoms significantly [63]. In Ayurveda, Gokshura (*Tribulus terrestris* Linn), Varuna (*Crataeva religiosa*), and Kshaaras (alkaline salts obtained from the ash of some medicinal plants) have been prescribed in BPH and LUTS for a long time. Likewise, white Chandan (*Santalum album*), Shatavari (*Asparagus racemosus*), Gorakhmundi (*Sphaeranthus hirtus*), Varunadi vati (*Crataeva nurvala*) and Kachnar guggul are also used for the same purpose [61]. In Unani, Banadiql bazoor and other polyherbal formulation containing Kharkhask (*T. terrestris*), Maghz tukhm-i-kaddu shireen (*Cucurbita pepo*), Babuna (*Matricaria recutita*), Alsi (*Linum usitatissimum*), Anisoon (*Pimpinella anisum*), and Khayareen (*Cucumis sativus*) have been found to reduce symptoms and improve QoL in BPH patients [64]. Flaxseed and pumpkin seed have also been observed to be effective when used individually [65,66]. Acupuncture is also contributing for better prostate health, improving BPH symptoms and QoL [67]. Growing popularity of alternative medicines for BPH may also be because of their sexual function enhancing capability. Most of these herbs and therapies increase libido, sexual desire, and improve erectile dysfunction.

Despite the promising benefits of alternative medicine in improving BPH, its associated symptoms, and QoL, a complete scientific validation is still lacking.

10. Appreciation of BPH in Greco-Arab (Unani) system of medicine

Greco-Arab (Unani) medicine practiced in Indian subcontinent and Central Asia is based on the teachings of Hippocrates, the Greek physician, and the father of medicine. This system of medicine is based on classical humoral theory stating that everybody contains a definite ratio of four humors, viz. blood (Dam), yellow bile (Safra), phlegm

(Balgham), and black bile (Sawda). A unique blend of these humors determines the temperament (Mizāj) of that body, and any disturbance in their equilibrium will lead to distemperament (Sū'-i-mizāj) and hence disease. Predominance of blood makes sanguine temperament; yellow bile makes bilious; phlegm makes phlegmatic; and black bile makes melancholic temperament. Sanguine and bilious temperaments are hot, whereas phlegmatic and melancholic temperaments are cold in nature. Basic principle of treatment in Unani medicine for any disease includes elimination of cause (Azala sabab), correction of humoral equilibrium (Tadeele akhlat), and normalization of organ/tissue (Tadeele aza). Here we describe BPH in Unani medicine.

Literal translation of BPH is Sal'a ghudda-i-madhi, a non-malignant growth of prostate gland which is an adversary to prostate cancer, a malignant growth. It has also been called as Azm ghudda-i-madhī (prostatomegaly) or Waram ghudda-i-madhī (swelling of the prostate gland) by a majority of Unani experts. Swelling of this type is, however, different from inflammation (Iltihāb). All types of swellings have been called as inflammation (Iltihāb) in the Unani system of medicine except tumor (Sal'a), which is a swelling but not inflammation.

10.1. Etiopathology (Asbab-wa-mahiyate marad)

The term Sal'a ghudda-i-madhī or Waram ghudda-i-madhī (BPH) is nowhere mentioned in Unani classical texts, but it can be traced under the headings of Waram unuq al-mathāna (bladder neck swelling) and Insidād majrā-i-mathāna (bladder outlet obstruction) [68].

Waram Unuq al-Mathāna (bladder neck swelling) results in obstruction to the flow of urine [68]. According to Avicenna (Persian physician and philosopher [980–1037 CE]), this swelling may be hot (Waram hārr) or hard (Waram sulb). Hot swelling (Waram hārr), which means inflammation (Iltihāb), produces symptoms of hot distemperament (Sū'-i-mizāj hārr) like burning micturition, increased thirst, and fever, in addition to the obstructive urinary symptoms. On the other hand, hard swelling (Waram sulb), which often develops after inflammation or due to wear and tear, produces hindrance to both urine and stool outlets, leading to dysuria, anuria, dribbling, and constipation [69]. Avicenna has mentioned that this swelling can intrude into the bladder and obstruct its outlet, so that urine is retained and bladder gets expanded with time. Because of expansion and flaccidity of muscles of urinary bladder, there is a weak and narrow stream of urine with interrupted flow [69]. Allama Jurjani (Persian physician [1041–1136 CE]) has categorized the swelling at the bladder neck into hot swelling (Waram hārr) and cold swelling (Waram bārid). According to him, hot swelling is due to humors of hot temperaments, which are blood or yellow bile, and cold swelling is due to humors of cold temperaments, which are phlegm or black bile. He also says that in cold swelling (Waram bārid) urinary symptoms are associated with constipation [70]. This description vindicates the resemblance of such types of swellings, *i.e.*, hot and cold, with modern day's prostatitis and prostatic hyperplasia respectively.

Insidād Majrā-i-Mathāna (bladder outlet obstruction) may be due to stone or swelling (Waram) [68,69,71]. It is mentioned in the reputed Unani texts like "The Canon of Medicine" and "Treasure of Khwarzamsah" that a type of constrictive swelling (Waram-i-dāghit) presses upon the urethra or neck of the bladder leading to its obstruction which in turn develops the urinary symptoms like dysuria ('Usr al-bawl), dribbling (Taqtīr al-bawl), and anuria (Ihtibas al-bawl) [69,70].

It is therefore certain that the above discussed Unani pathologies are responsible for developing LUTS. The symptoms developed by an obstruction due to cold swelling (Waram bārid) resemble the symptoms of BPH. As discussed in the beginning of this section, Unani pathology is based on the humoral theory, which states that any disturbance in the ratio of four humors is responsible for a disease. Furthermore, hormones are categorized in white humor or phlegm [72]. This strongly supports our viewpoint that hormonal disequilibrium is actually a humoral disequilibrium, because the most accepted cause of BPH in the modern world is the disturbed testosterone and DHT ratio or simply a hormonal cause [48], and the basic cause of prostatic hyperplasia as per Unani perspective is deranged ratio of humors especially the preponderance of phlegm. Thus, the Greco-Arab perception coincides with the modern study regarding the cause of BPH. Moreover, classical texts of Unani medicine have given detailed list of symptoms produced in phlegmatic diseases, the most important being abnormally white colored urine (Bawl-i-abyad), increased frequency of micturition or polyurea, and urgency incontinence [73]. A vast classical literature also reveals the discussion and management of symptoms of lower urinary tract, known as LUTS in the current era, including dysuria ('Usr al-bawl), anuria (Ihtibas al-bawl), dribbling (Taqtīr al-bawl), incontinence (Salas al-bawl), and increased frequency of micturition and urgency. All these symptoms mainly appear due to hypertrophy or swelling at the bladder neck (Waram unuq al-mathāna) and bladder outlet obstruction (Insidād majrā-i-mathāna) as mentioned above. Here we briefly explain them.

10.2. Clinical features and management (Alāmāt wa llāj)

10.2.1. Dysuria ('Usr al-bawl)

Difficulty in micturition is called dysuria ('Usral-bawl), which happens due to incomplete obstruction in the urinary outlet [69,71,74]. One of the important causes of this incomplete obstruction is hypertrophy of the muscle surrounding the neck of the urinary bladder [75].

10.2.2. Anuria (Ihtibas al-bawl)

Also known as Asr al-bawl, it is a condition of complete retention of urine [69,75]. Both dysuria ('Usr al-bawl) and anuria (Ihtibas al-bawl) share a common principle of treatment which involves the use of deobstruents/dilators (Mufattihāt) [69]. Diuretics (Mudirrāt) are recommended only for incomplete obstruction, but are strictly forbidden in case of complete bladder outlet obstruction [69,75]. Medicines such as *C. pepo* (Maghz tukhm-i-kaddu shireen)

[66], *Linum usitatissimum* (Alsi) [65], *T. terrestris* (Khar-khask), *P. anisum* (Anisoon), *C. sativus* (Maghz tukhm-i-khyarein), and *M. recutita* (Babuna) are considered to be effective in alleviating these symptoms [64]. Most of these medicines were also found to have anti-inflammatory, 5alpha-reductase inhibitor, and anti-tumor properties [64]. In case of complete obstruction, catheterization or bladder incision has been advocated [76,77]. As per Galen, when anuria in elder males is because of hard fleshy swelling around the bladder neck, it is difficult to get rid of it completely [74].

10.2.3. Urine incontinence (Salas al-bawl)

Passage of urine without person's own will or, in other words, uncontrolled leakage of urine is called incontinence (Salas al-bawl). Retention of urine due to the bladder neck obstruction leads to over expansion and weakness of muscles of the urinary bladder. This gives a sensation of full bladder and desire to micturate frequently. With time, bladder sensations become weaker and weaker so that there is overflow incontinence. The medicines which are hot in temperament and strengthen the muscles and nerves of urinary bladder are recommended for this purpose [69,70].

10.2.4. Dribbling of urine (Taqtir al-bawl)

It is said to be a liminal state between dysuria and diuresis [69]. Passing urine repeatedly in small quantity but with definite will and control is known as dribbling (Taqtir), whereas when the same is not under one's control it is said to be incontinence (Salas al-bawl). Muhammad Akbar Arzani (–1772 CE), an influential Mughal physician, has mentioned that all the factors which produce dysuria can also produce dribbling,

for instance, bad humors (Akhlāt-i-ghaliz), impaired hot or cold temperament (Sū'-i-mizāj hārr or bārid), stones in urinary tract, swelling or extra muscular growth in urethra or in the neck of urinary bladder, and other forms of bladder outlet obstructions [70,75]. According to Rāzi (Persian scientist [854–925 CE]), dribbling of urine occurs mostly in elderly people due to impaired cold temperament (Sū'-i-mizāj bārid) [71]. The principle of treatment for dribbling is same as that of dysuria ('Ushr al-bawl) and anuria (Ihtibas al-bawl) [69,71].

A brief summary of the above facts has been provided in a tabular form (Table 2). This discussion clearly depicts the concept and appreciation of BPH in conventional and Greco-Arab (Unani) system of medicines. It also reveals that older Unani physicians managed the disease and its symptoms with a wide range of medicines, both internal and external. Little has been done to validate such medicines; however, the results achieved in some clinical trials are satisfactory. The rate of improvement and treatment success of Unani medicine for BPH can be seen in Table 3 and Fig. 3. Here three randomized controlled trials have been listed along with the percentage of improvement in each of their respective test and control groups.

- Trial 1—*C. pepo* seed vs. placebo [66]: This is a double-blind study comparing the effect of *C. pepo* seeds, their extract and placebo with each other, and our study has shown the comparison between pumpkin seed (*C. pepo*) and placebo only in order to simplify it. Five grams of seed was given twice a day for 12 months in test group against a placebo as control. Mean IPSS at the base line was compared with the mean IPSS obtained after the completion of treatment using last-observation-carried-forward approach.

Table 2 BPH in modern and Greco-Arab (Unani) system of medicine.

BPH	Modern concept	Greco-Arab (Unani) concept
Etiopathology (Asbāb-wa-mahiyate marad) [65]: It is also a double-blind	<ul style="list-style-type: none"> - Hyperplasia/enlargement of transitional zone of the prostate, surrounding the prostatic urethra - One major cause of BPH: Disturbed DHT and testosterone ratio (increased ratio of DHT to that of testosterone) 	<ul style="list-style-type: none"> - Waram-i-unuq al-mathāna/waram-i-zāghit (swelling/growth) at the neck of the bladder that compresses the majrā-i-bawl (urethra) or unuq al-mathāna (bladder neck) - One cause: Disturbed humoral equilibrium (Elevated level of balgham or phlegm).
Clinical features (Alāmāt)	<ul style="list-style-type: none"> - Partial or complete urine retention - Overflow incontinence - Increased frequency with urge incontinence - Dribbling of urine 	<ul style="list-style-type: none"> - 'Ushr al-bawl (dysuria) - Ihtibas al-bawl (anuria) - Salas al-bawl (urine incontinence) - Taqtir al-bawl (dribbling of urine)
Principles of management (Usūl-i-ilaj)	<ul style="list-style-type: none"> - Medical <ul style="list-style-type: none"> • To reduce the symptoms • To decrease the size of the gland - Surgical <ul style="list-style-type: none"> • Resection of the part or whole gland, such as open prostatectomy, transurethral resection, and transurethral incision of prostate. Surgery is needed if complications are developed. 	<ul style="list-style-type: none"> - Medical <ul style="list-style-type: none"> • Internal medicines to reduce the symptoms and decrease the overgrowth (swelling/growth) • External medicines for applying locally to reduce the waram (growth) - Surgical <ul style="list-style-type: none"> • Bladder incision for absolute urine obstruction was an age-old procedure.

BPH, benign prostatic hyperplasia; DHT, dihydrotestosterone.

Table 3 Intra- and intergroup comparison of test drug vs. control in three different clinical trials.

Trial	Duration and sample size (n=test+control)	Test ^a IPSS ^c		Percentage of improvement	Control ^b IPSS ^c		Percentage of improvement	Intergroup p-Value
		BT	AT		BT	AT		
1	12 months (n=475+474)	16.00±2.10	10.60±5.20	33.75	16.10±1.90	12.10±5.60	24.85	<0.001
2	4 months (n=25+24)	19.21±1.16	11.37±0.15	40.81	18.25±1.28	15.54±0.40	14.85	<0.001
3	3 months (n=40+33)	13.92±3.03	6.35±3.28	54.38	18.63±5.04	11.45±4.28	38.54	<0.001

AT, after treatment; BT, before treatment; IPSS, International Prostate Symptom Score; SD, standard deviation.

^a Test drug is a research drug to be evaluated for its efficacy in the disease treatment.

^b Control is a standard drug or placebo used to compare the efficacy of a research drug for treatment of the disease.

^c Mean±SD.

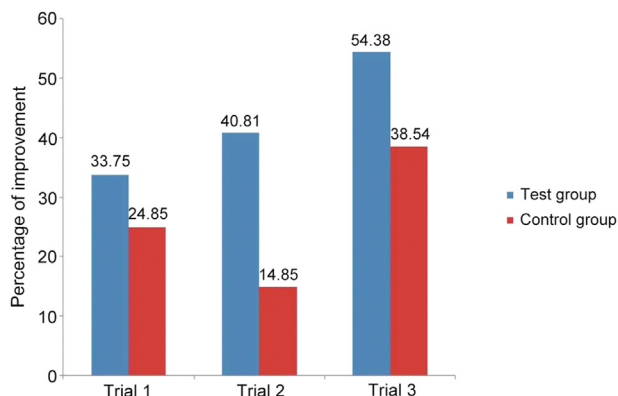


Figure 3 Percentage of symptom improvement with test drug and control in three different clinical trials.

✓ Trial 2—*Linum usitatissimum* extract vs. placebo [65]: It is also a double-blind placebo-controlled study where safety and efficacy of flaxseed extract, 300 mg and 600 mg per day for 4 months duration, was investigated against the placebo. To make the relation more comprehensible, here we have shown only the comparison between flaxseed extract (600 mg) and placebo.

✓ Trial 3—polyherbal Unani formulation vs. Urimax F, a standard control [64]: A single-blind, comparative, randomized study with a standard control was carried out to investigate the efficacy and safety of a polyherbal Unani formulation of 3 g in two divided doses per day against a standard control, Urimax F (finasteride 5 mg + tamsulosin 0.4 mg), for 3 months.

11. Conclusion

The scrupulous review of BPH in the modern medicine and its appreciation in Greco-Arab (Unani) system of medicine enlightens the disease awareness and its treatment in the Unani classical medicine. The discussion also reveals a close relation of the disease perception in both the systems of medicine. This encourages the discovery and validation of effective medicinal herbs and other natural ways of treatment for BPH and its associated symptoms. Unleashing the natural remedies will prove beneficial to decrease the burden of conventional medicines and need of the surgery with their different possible side effects.

Author contributions

Study design: Shabir Ahmad Bhat, Shameem Ahmad Rather.

Data acquisition: Shabir Ahmad Bhat.

Data analysis: Shabir Ahmad Bhat.

Drafting of manuscript: Shabir Ahmad Bhat.

Critical revision of the manuscript: Naquibul Islam, Shameem Ahmad Rather.

Conflicts of interest

The authors declare no conflict of interest.

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