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Review

The Cause of Kidney Stone Formation and Treatment from the Perspective of Conventional and Traditional Persian Medicine

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Abstract

Urinary stone disease is the most common urinary tract disease that has caused human suffering since ancient times. The observation of a 7000-year-old bladder stone in an Egyptian skeleton proves this claim. This disease causes many complications for patients, but its pathogenesis is unclear. The knowledge about the cause of urinary stones formation and treatment recommendations from ancient physicians' perspectives is probably helpful in preventing and treating kidney stones. Data for this review were provided by search in five Traditional Persian sources available, including Canon of Medicine (Avicenna, 980-1037 AD), Kamil al–Sana al-Tibbiya (Majusi Ahwazi (Haly Abbas), died 982-994), Zakhire Kharazmshahi (Jorjani, 1042-1137 AD), Makhzan al Adviyeh (Mohammad Hossein Aghili Khorasani Shirazi in 18th AD), and Tib-e-Akbari (Mohammad Akbar Arzani-11th and 12th centuries AD) and Until January of 2023, all English publications in Science Direct, PubMed, Google Scholar and Scopus, using various search terms such as urolithiasis, lithiasis, and kidney stone. Some dietary recommendations in Traditional Persian Medicine (TPM) for treatment of urinary tract stones and 134 recommended plant species, in addition to studies of in vivo effects of some of them in conventional medicine have been described in this article. The TPM with long experience and special principles has good potential in the field of diagnosis and treatment in its own way and can act as a strong complementary treatment system for diseases that have challenging treatment. It seems using the experiences in the TPM sources and relying on today's knowledge can create a way to prevent the formation and recurrence of urinary tract stones.

Keywords: Urinary stones; Stone formation; Sand and gravel formation; Humoral medicine; Traditional Iranian medicine

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Introduction

Urinary stone disease (urolithiasis) is the most common urinary tract disease that has caused human suffering since ancient times. The observation of a 7000-year-old bladder stone in an Egyptian skeleton proves this claim [1-3]. In addition to causing many complications for patients, this disease imposes a heavy financial burden on health systems [4-6]. Kidney stones increase the risk of chronic kidney diseases [7-9], end-stage renal disease [8-11], cardiovascular diseases [12,13], diabetes, and hypertension [14-16]. Furthermore, kidney stones may be a systemic disorder associated with metabolic syndrome [17-20]. Obesity [14,21,22], diabetes [23-25], and hypertension [25-27] may be risk factors in stone formation. Stone formation is asymptomatic, but after formation, it causes symptoms such as renal colic, flank pain, hematuria, obstructive nephropathy, urinary tract infections, urinary obstruction, and hydronephrosis [28,29]. The disease affects both sexes, all ages, and all races [30,31], but is more common in men than women between the ages of 20-49 [32]. Despite significant advances in new treatments for urinary stone management, the incidence, and prevalence of urinary stones has increased worldwide in recent decades probably due to changes in diet, climate, and lifestyles [6,15,26,32,33]. Studies indicate that behavioral and nutritional interventions are potentially beneficial in patients with idiopathic urinary stones and should be the first step in preventing stones [34-37].

Urinary stones are a complex mass composed of organic compounds such as proteins, fats, polysaccharides, and cell debris [6,38-42], but the pathogenesis of urinary stone formation is unclear. Obviously, the primary crystal nucleus is formed [43,44]. When the crystal nucleus is formed inside the kidney [45-47], a hard coating is gradually formed around it and turns to stone under exposure to urine [48-50]. Identifying the first stage of crystal formation can increase the possibility of discovering methods to stop stone formation [51,52]. Therefore, the prevention of stone formation and its recurrence requires a better understanding of the mechanisms and primary factors involved in stone formation.

Traditional medicine has been fulfilling the medical needs of societies for thousands of years since the beginning of human existence [53-55], but many experiences and treatments relating to antiquity were lost or forgotten in the Renaissance in the transition from humoral medicine to conventional medicine models [56,57]. Like Greek medicine, the Traditional Persian Medicine (TPM) is an ancient model of medicine and a humoral medicine [58-60] based on four humors, namely phlegm, blood, yellow bile, and black bile. Each humor has the following characteristics: phlegm is cold and wet, blood is warm and wet, yellow bile is warm and dry, and black bile is cold and dry. Each humor is a substance resulting from the absorption and conversion of nutrients in the gastrointestinal tract. Based on humoral medicine and TPM sources, human health depends on the balance between these humors and the excessive amount of each one or the formation of abnormal humor leads to diseases [61-64]. The TPM with long experience and special principles and bases has good potential in the field of diagnosis and treatment in its own way and can act as a strong complementary treatment system for diseases that have challenging treatment [65-70].

Some studies have been done in TPM sources about the symptoms and treatment of urolithiasis. In these studies, the books of famous ancient physicians have been investigated like Rhazes' Al-Hawi, Avicenna's Canon of medicine, Majusi Ahwazi-Haly Abbas' Kamil al–Sana al-Tibbiya, Jorjani's Zakhire Kharazmshahi, Al-Akawayni's Hidayat al-Muallimin fi-al-Tibb. The authors have mentioned a number of common anti-urolithiasis herbs with analgesic, diuretic, relieved burning micturition, spasmolytic, and lithotriptic properties and also, the advised dietary for patients, in their manuscripts [71-75]. The present study investigated the cause of urinary stone formation using five TPM sources, two of which (Makhzan al Adviyeh written by Mohammad Hossein Aghili Khorasani Shirazi and Tib-e-Akbari written by Mohammad Akbar Arzani) were not explored in none of the described manuscripts. Also, in the present study, 134 recommended plant species with clinical trials and in vivo studies of some of them have been described in conventional medicine.

Materials and Methods

Data for this review were provided by search in five Traditional Persian sources available, including "Canon of medicine", volume 3 (Avicenna, 980-1037 AD), "Kamil al–Sana al-Tibbiya", volume 2 (Majusi Ahwazi-Haly Abbas-died 982-994 AD), "Zakhire Kharazmshahi", volume 2, 3 and 6 (Jorjani, 1042-1137 AD), "Makhzan al Adviyeh" (Mohammad Hossein Aghili Khorasani Shirazi in 18th AD), "Tib-e-Akbari", volume 1 and 2 (Mohammad Akbar Arzani 11th-12th AD). PubMed, Scopus, Science Direct, and google scholar electronic databases were searched for publications about the medicinal plants used for treatment of urinary tract stones using the search terms such as urolithiasis, lithiasis, and kidney stone. The articles in English language published till January 2022 were included.

Results

Traditional Persian medicine terms

Black bile (Soda): Black bile was believed that is pro-

duced in liver; while its storage and regulation is in the spleen. It is cold, dry, and sparse in the body. Natural black bile is the concentrated part of the blood and essential for the proper function of organs; it keeps bones, teeth, and tendons healthy and strong.
Material cause (sabab-e-māddi): the primary material from which something is made. For example, the material cause of a statue could be marble or bronze.
Efficient cause (sabab-e-fā'ile): a factor that acts on something and creates it. For example, the sculptor is the efficient cause of a statue, because he imposes the change upon the marble or bronze.
Phlegm (Balgham): Phlegm is cold and wet, high amounts of phlegm in the body will raise the coldness and humidity in the body. Phlegm is a slimy liquid very much like water (colorless, odorless and tasteless) and it can be found in body parts such as the dermis, adipose tissue (body fat), synovial fluid, and the mucus lining the lungs, throat, mouth, and nose, which require humidity and flexibility to function properly. Maintaining or improving flexibility is owed to the humor of phlegm.
Temperament (mizaj): it can be described as all aspect of personality which explains a person's morphological, physiological and psychological status.
Yellow bile (phlegm): Yellow bile is warm and dry, if it increases in the body, the body will become warmer and drier. It is the lightest of all humors. Yellow bile acts as a diluent and facilitates the transfer of blood and nutrients from capillaries to the remote body organs.

Urinary tract stones

Cause of stone formation
According to the Persian Medicine sources, a material cause and an efficient cause play roles in stone formation.

- Material cause
Refers to the raw viscous moisture from the phlegmatic materials caused by overeating and eating without discipline, exercise with a full stomach, and consumption of viscous and high-energy foods such as beef, ostrich meat, big fish, big ducks, roasted meat, milk, cheese, fried eggs, unleavened bread, white bread, totmaj (a soup with wheat flour), noodles, rice milk, haleem, Khash, very sweet and viscous sweets, bergamot orange, pear, raw fruit, melon with bread, especially Sheermal bread (bread that is produced from milk and oil and moderately baked) or oily bread, and eating melon after a meal. This viscous raw moisture accumulates in the kidneys or bladder and forms stones, especially if the digestive capacity of the stomach and liver is poor and the kidneys are warm. If this moisture is too concentrated, stones will form and if it has a low concentration, sand and gravel will be produced. However, pus and blood can rarely produce stones and gravel. Furthermore, a lot of semen, especially when lust is aroused, and the semen is not expelled, leads to pain in the testicles, swelling, and stone formation. Muddy water and concentrated wine can also lead to stone formation because their waste products are mixed with food but are not digested and eventually produce viscous and sticky substances that deposit in the bladder and form stones [76,77].

- Efficient cause
The strong heat absorbs this viscous moisture and waste products in the upper parts of the body before complete digestion and turns them into stones before excretion, and the weakness of the kidneys in excreting waste products is another factor [76, 78, 79]. This heat is either present, or it is the result of suffering, or the result of eating foods, with warm temperament or it is due to obstruction from complex wastes or simple hot swellings, or the involvement of nearby organs such as the intestines that put pressure on the kidneys and create an obstruction in them [77].

Stone formation

If the concentration and viscosity of the substance are high, it coagulates due to the heat when it enters the kidney space, and gradually turns to stone with the addition of materials and their coagulation. This is similar to the exposure of a clay pot to fire, which is cooked and hardened, or it is similar to a container in which water is constantly heated and water sediment gradually settles to the bottom of the container and coagulates and turns to stone due to the fire heat. Aelius Galenus says that the formation of stones may be due to a purulent wound in the kidneys that secrete pus and this pus is not excreted and gradually accumulates and freezes and causes kidney or bladder stones [78,79].

Sand and gravel formation

If the concentration and viscosity of the material are low, it gradually coagulates and the renal excretory force excretes it day by day with the urine and settles in the form of sand in the urine when it enters the kidney space [78,79].
In infants, milk types can play a role in the formation of stones: If it is choleric, it warms the baby's viscera and because the baby's urine is concentrated, it turns to stones sooner. If the milk is phlegmatic, the baby's urine becomes more concentrated, and the bladder heat causes coagulation of it and forms stones [77,78].

The stone formation place

Stones often emerge in the kidneys and bladder, but sometimes they may also be formed in other places, such as the colon. Zakariyyā Rāzī says 'I had a friend, who was obese, and there were always a lot of pebbles

in his urine, and once a large stone was excreted in the feces.' He also says 'that stones are often formed in the joints of those who suffer from joint pain.' Aelius Galenus says 'I saw a person who had pneumonia, and when he coughed, stones like dew came out of him.' [78]

Stone formation sign

If the urine is concentrated first and then dilute and clear, it is a sign that a substance remains in the kidneys and eventually produces stones. "Black urine without pain and disease is a sign of kidney or bladder stones, especially in old age," says Rufus. The presence of blood in the urine is another symptom of stone formation that is caused by scratches due to the stones, especially if the scratches are large [76-78].

Kidney and bladder stones difference

If there is a sharp pain with heaviness in the back, it is the reason for the formation of stones in the kidneys, and if this pain extends to the groin, it is because the stone is left in the urethra, and if the pain subsides, it is a sign that the stone has entered the bladder. In a person with kidney stones, overeating causes pain in the kidneys, especially when food enters the intestines and puts pressure on the kidneys. In this person, the pain disappears by emptying the intestine content. At the same time as kidney pain in men, there may be a pain in the testicles on the same side, as well as numbness in the thighs of the same side, and symptoms of colic may appear, and a deposit may be seen in the urine [76-78].

The difference between colic pain and kidney stone pain

Colic pain moves towards the umbilicus and front of the abdomen and sometimes affects the upper and sometimes the lower abdomen; while the kidney stone pain settles in the kidneys and the thigh numbness is seen on the same side [78].

If there is a stone in the bladder, the urine is white and its sediment is white or gray. In some cases, olive-colored deposits may accompany concentrated urine, but it is diluted in most cases, especially at first. Pain, itching, and heaviness are felt in the pubic and bottom of the penis so that the person constantly touches the sex organ, urinates with difficulty, and has frequent urination and sometimes urinary incontinence [76,77]. Bladder stones are large due to the width of the site; while kidney stones are small due to the narrowing of the site [76-79]. Bladder stones are painless unless they are placed in the opening of the bladder and prevent urine from coming out. It can cause numbness of the penis in men in walking. If urinary retention occurs, it is a sign that the bladder stone is not large and is located in the opening of the bladder. If there is more than one stone in the bladder, it will rub each other while walking, and as a result, sand will be seen in the urine. Furthermore, a lot of gravel in the urine is a sign that the stone is loose and small, and the absence of gravel indicates the stone hardness. Sometimes there is a deposit with sand relating to the bladder wall wear due to the large size of the stones. If the bladder stone is large and heavy, it can cause the rectal prolapse, especially if the anus is weak [76-78].

People at risk for urinary tract stone

Kidney and bladder stones are more common in children and from childhood to puberty. Stone formation occurs more in obese persons than slim persons [76,77]. In general, bladder stones are more common in children, young people, and slim persons, and kidney stones are more common in the elderly and obese persons [76,78]. In children, stones often form in the bladder for three reasons:

- Children have a higher ability to excrete waste from the kidneys to the bladder, and their urinary tract is wider too from the kidneys to the bladder due to their high body temperature.
- The more concentrated and darker the urine, the more stones will be produced. Due to consuming more food and lack of order in eating in children, urine is darker and more concentrated, and on the other hand, the bladder is warmer and bladder opening is narrower and causes urine more to stop in the bladder and thus produce stones.
- The amount of salt is higher in children's urine, and their urine is warmer that causes the formation of stones. Stone formation occurs most often in children as they have warm stomach and liver and a dry temperament because the dryness of temperament causes more water to be absorbed by the liver, which is excreted through the kidneys and bladder, and if the kidneys and bladder are warm, any concentration and turbidity will turn to stone [76,77,79].

In older people, most stones are formed in the kidney for two reasons:

- Lower body temperature and the formation of phlegm due to poor digestion.
- Narrowing of the urinary tract from kidneys to the bladder due to coldness of temperament in elderlies prevents the flow of concentrated materials from the kidneys to the bladder, and thus, the diluted materials flow and concentrated materials remain, then due to the high temperature of kidneys, lose their moisture and turn to stone [76-79].

In slim persons, stones are often formed in the bladder due to the dilation of pores and arteries. Due to the narrowing of arteries and pores in obese persons, most stones are formed in the kidney. Women compared to men rarely get bladder stones due to the short neck of the bladder and the wide opening of the bladder be-

cause any waste and humor, which enters the bladder, is excreted immediately [76-78]. Some people get kidney or bladder stones at certain times, for example, every few weeks or months or even once a year [79].

Treatment

Treatment recommendations

From the perspective of TPM, removal of stone formation factors that diet of the patient is the most important of them is the first step of urinary stone treatment. For this reason, the patient must be avoided eating some foods and replace another food in the diet [76-78].

If the patient feels faint, it is recommended easily digestible foods like small bird meat including partridge, francolin, common pheasant, swallows, fat chicken, yeanling meat, yolk of soft-boiled egg, and well-cooked whole grain bread.

If the patient was strong, food intake must be decreased and avoided from overeating. It was advised food like peeled mung bean, spinach, kashk-jo (the barley is cooked, then crushed and strained), Qalye Kadu and Qalye khiār (zucchini or cucumber cooked with oil, salt, pepper, turmeric, and fried onions), nokhodāb (chickpeas cooked with chicken or lamb meat, salt, turmeric, and some onions), soups with almond kernel or oil without meat. Also advised the patient to drink water between meals and sometimes on an empty stomach [76-78].

The patient should avoid eating viscous food like types of milk, camel and buffalo meat, fresh unleavened bread, white bread, haleem, and slow digestion fruits like apple and apricot [76-78].

Traditional herbal remedies

Several medicinal plants have been recommended for the treatment of urinary tract stones in TPM sources [76-80]. 134 plant species belonging to 58 families are listed in Table 1 that 51 species are from Apiaceae, Compositae, Lamiaceae, Leguminosae, and Rosaceae families.

Modern evidences of traditional herbal remedies

In this section, modern evidence of traditional herbal remedies has been investigated and summarized in table 2 and table 3.

Discussion

The properties and usage of 134 recommended plants in traditional medicine sources are summarized in Table 1, which are mostly related to Apiaceae, Compositae, Lamiaceae, Leguminosae, Rosaceae, and Cucurbitaceae, respectively, all of which are investigated in modern studies for antiurolithiatic properties as summarized in Tables 2 and 3. The results of Tables 2 and 3 show that most of the studies were carried out on animals. In the animal model, plants showed renal protective effects [86,90,94,96], increased urine volume [84,88,89,92,101,106,115,116], reduced calcium crystals deposition [106,108,109] and as a result, reduced calcium oxalate stone formation [82,87,98,100,113], along with decreasing the excretion of potassium [101,108], urea and creatinine in the urine [101,115,117]. A decrease in the amount of creatinine, uric acid and BUN in the serum was also observed [85,94,98,104,110].

The results of clinical studies (Table 3) show that the most studied plants have reduced the size of stones and their number, reduced pain, decreased the amount of uric acid, calcium, oxalate, and protein in the urine, and increased the amount of serum calcium. Globally, the recommended plants effectively reduced the calcium oxalate stone formation and excretion [121,123,124,127], which is prevalent in urinary stones [17,38,44].

Sadeq Pour and his colleagues, in their research on urinary tract stone treatment, extensively examined four prominent traditional Iranian medicine texts, including the Canon of Medicine, Kamil al-Sana al-Tibbiya, Zakhire Kharazmshahi, and Al-Hawi. From their investigation, they identified eight frequently utilized plants (Tribulus, Venus Hair, Celery, Asparagus, Muqul, Balasān, Nutgrass, Bay Laurel) that have also undergone scrutiny in contemporary medicine for their diuretic properties, stone formation reduction, promotion of urinary stone excretion, crystallization inhibition, and other factors linked to urinary stone development. These eight plants are also subjects of inquiry in our current study [71].

Additional investigations, rooted in esteemed TPM sources, demonstrate that ancient physicians could diagnose and treat urinary tract stones solely by examining the physical attributes of urine and the symptoms exhibited by patients. This diagnostic approach was implemented without access to the modern laboratory facilities available today. Remarkably, the diagnostic symptoms and, at times, treatment recommendations for patients closely paralleled those of modern medicine [72,73,75]. All renowned sources of TPM underscore the importance of adhering to a specific diet for individuals suffering from urinary tract stones. This dietary regimen is a treatment method and preventive measure against stone recurrence. For instance, consuming dense and heavy foods such as milk, haleem, white bread, spinach, cheese, and similar items is discouraged. Instead, it is recommended to increase water intake and opt for light, easily digestible foods like small birds, nokhodāb, and soft-boiled egg yolks [71-75].

According to TPM practitioners, consuming heavy and

Table 1. Medicinal plants using for treatment of urinary tract stones in view of Traditional Persian Medicine references

Family	Scientific name	Traditional name	English Name	Part used	Application
Acoraceae	*Acorus calamus* L.	Waj	Sweet Flag	Root	Decoction
Alismataceae	*Alisma plantago-aquatica* L.	Mizmār al-rāei	European Water-Plantain	Root	Decoction
Amaranthaceae	*Atriplex hastata* L. *Atriplex hortensis* L.	Qataf	Garden Orache	Leaf	Extract
	Spinacia oleracea L.	Esfānakh	Spinach	Leaf	Decoction
Amaryllidaceae	*Allium cepa* L.	Basal	Onion	Bulb	Orally
	Allium sativum L.	Sum	Garlic	Bulb	Orally
Anacardiaceae	*Pistacia atlantica* Desf.	Botm, Bane, Habbah al-khadra	Atlas Pistachio	Fruit	Decoction
Apiaceae	*Ammi visnaga* (L.) Lam.	Bastiāj	Toothpick	Seed	Decoction
	Anethum graveolens L.	Shebet	Dill	Seed	Poultice
	Apium graveolens L.	Karasb	Celery	Root	Powder
	Carum bulbocastanum (L.) Koch	Jauz-e-arqam	Black caraway	Root	Decoction
	Carum ridolfia Benth. & Hook.f.	Hazā	Corn parsley	Leaf	Decoction
	Cuminum cyminum L.	Kammun	Cumin	Seed	Powder
	Daucus carota L.	Jazar, Gazar	Wild carrot	Root	Orally
	Dorema ammoniacum D.Don	Oshaq	Ammoniacum	Oleo-gum-resin	Infusion
	Eryngium caeruleum M.Bieb.	Qaras'ana	Sea holly	Root	Decoction
	Falcaria vulgaris Bernh.	trilalĀ	Sickleweed	Seed	Burning with glass and eating with honey
	Ferula gummosa Boiss.	Bārzad	Galbanum	Resin	With honey
	Ferula persica Willd.	Sakbinaj	Sagapenum	Root	Powder
	Foeniculum vulgare Mill.	Rāziānaj	Common fennel	Root	Extract
	Lagoecia cuminoides L.	Qardemānā	Wild cumin	Seed	Powder
	Malabaila secacul (Mill.) Boiss.	Jazar-e-barri	Arabian Hartwort	Seed	Decoction
	Opopanax chironium (L.) Koch.	Jāvshir, Gāvshir	Hercules' all-heal	Resin	Orally
	Peucedanum officinale L.	Bakhoor-al-akrad	Hog's-fennel	Resin, Latex	Powder
	Trachyspermum ammi (L.) Sprague	Nānkhāh	Ajwain	Seed	Powder
Arecaceae	*Phoenix dactylifera* L.	Tamr	Date palm	Fruit, Core	Decoction
Aristolochiaceae	*Aristolochia indica* L.	Zarāvand tawil	Indian birthwort	Root	Powder
	Asarum europaeum L.	sāronĀ	European wild ginger	Root	Infusion in grape juice
Asparagaceae	*Asparagus officinalis* L.	Halyun	Garden asparagus	Root	Decoction
	Ruscus aculeatus L.	Ās-e-bari	Butcher's broom	Leaf, Flower	Decoction
	Urginea scilla steinh.	Squill, Onsol	Red squill	Bulb	Powder

Asphodelaceae	*Asphodelus ramosus* L.	Khuntha	Asphodel	Root	Powder
Boraginaceae	*Alkanna tinctoria* (L.) Tausch	Ābukhalsa	Alkanet	Leaf, Root	Decoction
	Echium plantagineum L.	Lesān al-thaur	Paterson's curse	Flower	Herbal tea
	Lithospermum officinale L.	Qolb	Common gromwell	Seed	Powder
Brassicaceae	*Brassica napus* L.	Shaljam	Rapeseed	Root	Cooked
	Brassica pekinensis Skeels	Karnab	Chinese cabbage	Root	Ash
	Capsella bursa-pastoris (L.) Medik.	Tarāghiun	Shepherd's-purse	Whole plant	Powder
	Eruca sativa Mill.	Jerjir	Arugula	Seed	Decoction
Burseraceae	*Commiphora mukul* (Hook. ex Stocks) Engl.	Muqul	Guggul	Resin	Powder
	Commiphora opobalsamum (L.) Engl.	Balasān	Balm of Gilead	Resin	Powder
Caprifoliaceae	*Valeriana officinalis* L.	Sonbol	Garden heliotrope	Whole plant	Decoction
Caryophyllaceae	*Acanthophyllum squarrosum* Boiss.	Āzarbu, Artanithā	Not found	Root	Decoction
Compositae	*Achillea santolina* L.	Qaisum	Santolina yarrow	Flower	Decoction
	Arctium lappa L.	Luf	Burdock	Fresh raceme	Extract
	Artemisia vulgaris L.	Berenjasaf	Mugwort	Arial parts	Decoction
	Calendula officinalis L.	zarion Ā	Marigold	Flower	Herbal tea
	Centaurea behen L.	Bahman-e-sefid	White Behen	Root	Powder
	Centaurea solstitialis L.	Morrār	Yellow starthistle	Leaf	Powder, Extract
	Matricaria chmomilla L.	Babunaj	German chamomile	Flower	Herbal tea
	Chrysanthemum parthenium (L.) Bernh.	Oqhown	Feverfew	Flower	Decoction
	Chrysanthemum morifolium Ramat.	Dāvudi	Chrysanthemum	Flower	Powder
	Cnicus benedictus L.	Bādāvard	Blessed thistle	Leaf	Decoction
	Inula vulgaris (Lam.) Trevis. *Inula conyza* (Griess.) DC.	Barnuf	Ploughman's-spikenard	Flower	Decoction
	Statice limonium L.	Bahman-e-sorkh	Sea lavender	Root	Powder
Crassulaceae	*Umbilicus rupestris* (Salisb.) Dandy	Qutolidun	Navelwort	Root	Decoction
Cucurbitaceae	*Bryonia alba* L.	Fashrā	White bryony	Root	Powder
	Citrullus lanatus (Thunb.) Matsum. & Nakai	Betikh-e-hindi	Watermelon	Fruit	Orally
	Cucumis melo L.	Betikh, Qiththā	Melon	Fruit, Fruit skin	Orally, Powder
	Cucumis sativus L.	Qathad	Cucumbers	Fruit	Orally
	Ecballium elaterium (L.) A.Rich.	Qiththā al-himār	Squirting cucumber	Fruit	Extract
Cyperaceae	*Cyperus esculentus* L. *Cyperus rotundus* L.	So'ad	Chufa flatsedge	Rhizome	Powder
Ebenacea	*Diospyros ebenum* J.Koenig ex Retz.	bnusĀ	Ebony	Wood	Decoction
Ephedraceae	*Ephedra gerardiana* Wall. ex Stapf	Hum al-majus	Gerard jointfir	Flower	Decoction

Euphorbiaceae	*Chrozophora tinctoria* (L.) A.Juss.	Sāmariumā	Dyer's croton	Seed, Leaf, Root	Powder with fresh milk
	Croton tiglium L.	Dand	True Croton	Seed	Orally
	Euphorbia antiquorum L.	Zaqqum	Malayan Tree Spurge	Leaf	Juice of leaf
Haloragaceae	*Myriophyllum spicatum* L.	Hozonbul	Spiked water-milfoil	Root	Decoction
Hypericaceae	*Hypericum perforatum* L.	Heufāriqun	St. John's wort	Flower	Powder
Iridaceae	*Crocus sativus* L.	Za'farān	Saffron crocus	Red stigma	Powder
Lamiaceae	*Lamium purpureum* L.	Ghāghāles	Purple dead-nettle	Leaf, Branch	Decoction
	Ocimum album L.	Bādrooj	Sweet basil	Whole plant	Decoction
	Origanum dictamnus L.	Mushk tarāmashi	Dittany of crete	Arial parts	Decoction
	Rosmarinus officinalis L.	Eklil ol-jabel	Rosemary	Whole plant	Decoction
	Teucrium chamaedrys L.	Kamādharius	Wall germander	Root	Decoction
	Teucrium scordium L.	Joada	Water germander	Whole plant	Decoction
	Thymus serpyllum L.	Sisanbar	Wild thyme	Leaf	Decoction
	Thymus vulgaris L.	Sa'tar	Thyme	Arial parts	Decoction
Lauraceae	*Cinnamomum cassia* (L.) J.Presl	Salikhea	Chinese cinnamon	Bark	Powder
	Cinnamomum tamala (Buch. Ham.) T.Nees & Eberm.	Sādhaj	Indian bay leaf	Leaf	Decoction
	Laurus nobilis L.	Ghār	Bay laurel	Bark	Powder
Leguminosae	*Cercis siliquastrum* L.	Arjuan	Judas tree	Flower	Decoction
	Cicer arietinum L.	Black hemmas	Chickpeas	Seed	Decoction
	Dolichos biflorus L.	Hab-al-qolt	Horsegram	Seed	Decoction
	Lathyrus tuberosus L.	Balut-al-arz	Erthnut pea	Root	Poultice
	Lupinus angustifolius L.	Tormes	narrowleaf lupin	Seed	Powder
	Melilotus officinalis (L.) Pall. *Trigonella grandiflora* Bunge.	Eklil ol-malek	Sweet yellow clover Komeasarviapila	Fruit	Decoction
Linaceae	*Linum usitatissimum* L.	Katān	Flax	Seed	Decoction
Lytheraceae	*Lawsonia inermis* L.	Henna	Henna	Leaf	Powder, Infusion
Malvaceae	*Althaea officinalis* L.	Khatmi	Marsh mallow	Seed	Decoction
Melanthiaceae	*Veratrum album* L.	Kundus	White hellebore	Root	Decoction
Meliaceae	*Melia azedarach* L.	zad derakht Ā	Chinaberry tree	Leaf	Extract
Myrtaceae	*Myrtus communis* L.	Ās	Myrtle	Leaf	Decoction
Oleaceae	*Fraxinus excelsior* L.	Lisān al-asāfir	European ash	Flower	Decoction
	Fraxinus griffithii C.B.Clarke	Divdār	Griffith's ash	Wood	Powder
	Olea europaea L.	Zeitoon	Olea europaea	Oil	Orally
Orchidaceae	*Orchis mascula* (L.) L.	Tha'lab	Early purple orchis	Root	Decoction
Orobanchaceae	*Orobanche major* L.	Asadoladas	Broomrape	Whole plant	Decoction
Paeoniaceae	*Paeonia officinalis* L.	Fāvānia	Garden peony	Root	Powder
Parmeliaceae	*Usnea barbata* (L.) Ach.	Eshne	Beard lichen	Whole plant	Decoction

Pedaliaceae	*Sesamum indicum* L.	Samsem	Sesame	Seed	Orally
Piperaceae	*Piper cubeba* L.f.	Kabāba	Cubeb	Fruit	Orally
Poaceae	*Andropogon schoenanthus* L.	Ezkher	Camel grass	Root	Decoction
	Cynodon dactylon (L.) Pers.	Najm, Sil	Bahama grass	Root, Seed, Whole plant	Decoction, Juice
Polygonaceae	*Rheum undulatum* L.	Rāvand	Rhubarb	Root	Powder
	Rumex vesicarius L.	Hommāz	Bladder dock	Root	Decoction
Polypodiaceae	*Phyllitis scolopendrium* (L.)	Esqoloqandarion	Hart's Tongue Fern	Leaf	Powder
Portulacaceae	*Portulaca oleracea* L.		Purslane	Leaf, Stem	Juice
Primulaceae	*Androsace lactea* L.	Andarotalis	Rock Jasmine	Leaf, Seed, Stem	Decoction
Pteridaceae	*Adiantum capillus-veneris* L.	Barsiāoshān	Southern maidenhair fern	Frond	Decoction
Ranunculaceae	*Helleborus niger* L.	Kharbaq	Christmas rose	Root	Powder
	Nigella sativa L.	Shoniz	Black seed	Seed	Powder
Resedaceae	*Reseda luteola* L.	Wars	Dyer's rocket	Fruit	Powder
Rosaceae	*Cerasus vulgaris* Mill.	Qarāsia	Amarello cherry	Seed, Resin	Extract, Orally
	Prunus amygdalus var. amara (DC.) Focke	Lavz al-mur	Bitter almond	Fruit	Powder
	Prunus amygdalus var dulcis	Loze	Sweet almond	Oil	Orally
	Prunus armeniaca L.	Mishmish	Apricot	Bitter kernel oil	Orally
	Prunus domestica L.	Ijjās	Plum	Resin	Powder
	Rubus fruticosus G.N.Jones	Ollaiq	Blackberry	Root	Powder
Rubiaceae	*Gardenia jasminoides* J.Ellis	Jauz-al-kausal	Cape jasmine, Gardenia	Fruit	Decoction
Rutaceae	*Ruta graveolens* L.	Sodāb	Rue, Herb of grace	Leaf	Decoction
	Citrus aurantium L.	Nāranj	Bitter orange	Flower	Distilled water
Solanaceae	*Solanum dulcamara* L.	inab al-tha'lab	Bittersweet nightshade	Seed	Powder
Thymelaeaceae	*Aquilaria malaccensis* lam.	Ood-e-hindi	Eaglewood	Wood ash	Powder
Vitaceae	*Vitis vinifera* L.	Karm	Common grapevine	Branch, Tendril, Raisin	Ash, Juice of tendril, Orally
Zingiberaceae	*Amomum cardamomum* L.	Hamāmā	Cardamon	Seed	Powder
	Curcuma Zerumbet Roxb.	Jadvār	Bitter ginger	Root	Decoction
	Elettaria cardamomum (L.) Maton	Qāghola sighār	Cardamon	Fruit	Powder
Zygophyllaceae	*Peganum harmala* L.	Hormal	Syrian rue	Seed	Powder
	Tribulus terrestris L.	Hasak	Bindii	Leaf, Fruit, Root	Decoction

Table 2. Animal studies for the efficacy of medicinal plants for treatment of urinary tract stones

Family	Scientific name	Plant part	Form of use	Method	Results	References
Acoraceae	*Acorus calamus* L.	Rhizome	Ethanolic extract	250, 500 and 750 mg/kg oral dose in male Wistar albino rats	Antiurolithiatic and diuretic activity	[81]
Alismataceae	*Alisma plantago-aquatica* L.	Rhizome	Extract	800 mg/kg per day for 28 days in EG induced calcium oxalate deposits male Wistar rats	Prevent calcium oxalate stone formation	[82]
Amaranthaceae	*Spinacia oleracea* L.	Leaf	Extract	250 mg and 500 mg/day in male albino Wistar rats with minimal kidney damage	Hyperoxaluria and nephrocalcinosis	[83]
Amaryllidaceae	*Allium cepa* L.	Bulb	Hydroethanolic extract	40 ml/kg for one time in female Wistar rats	↑ Diuretic effect	[84]
	Allium sativum L.	Bulb	Aqueous extract	250 mg/kg/day orally for 21 days in adult male Wistar albino rats	Nephroprotective through significantly reducing serum urea	[85]
Anacardiaceae	*Pistacia atlantica* Desf.	Leaf	Hydroethanolic extract	200, 400, and 800 mg/kg/day for 7 days in gentamicin-induced nephrotoxicity male Wistar rats	Protective effects	[86]
Apiaceae	*Ammi visnaga* (L.) Lam.	Fruit	Aqueous extract	125, 250 and 500 mg/kg/day for 14 days orally in EG+ aluminum chloride-induced urolithiasis male Sprague-Dawley rats	↓ Calcium oxalate crystal deposition ↑ Urinary excretion of citrate ↓ Oxalate excretion	[87]
		Seed	Aqueous extract	500 mg/kg/day for 4 weeks orally in glycolic acid- induced oxalate nephrolithiasis male Wistar albino rats	Highly potent diuretic activity Inhibition of formation of calcium oxalate	[88]
	Anethum graveolens L.	Seed	Ethanolic extract and volatile oil	80 mg/kg intravenously in both sexes of mongrel dogs	Diuretic effect	[89]
	Apium graveolens L.	Seed	Powder	500 mg/kg and 1000 mg/kg/day in gentamicin induced nephrotoxicity male Wistar rats	Nephroprotective, Diuretic	[90]
	Daucus carota L.	Root	Ethanolic extract	200 and 400 mg/kg/day for 28 days in EG and (NH_4Cl) induced male and female Wistar rats	Normalization of creatinine and uric acid levels; and calcium, phosphate and oxalate deposition in kidney tissue, urinary levels of protein and uric acid, Diuretic activity	[91]
	Foeniculum vulgare Mill.	Root	Ethanolic extract, hydroethanolic extract	25, 50, 100 and 200 mg/kg/day, 200 mg/kg/day (both groups for 8 days in Sprague Dawley male rats)	↑ Urine flow except the lowest dose (25 mg/kg), ↑ Urinary sodium excretion at dose 200 mg/kg	[92]

Arecaceae	*Phoenix dactylifera* L.	Fruit	*n*-Butanol and Aqueous extracts	200 mg *n*-Butanol or Aqueous extracts/kg/day for 28 days in EG induced calcium oxalate male Wistar Albino rats	Creatinine, urea↓ uric acid levels, n-butanol extract was more effective than aqueous extract	[93]
Brassicaceae	*Eruca sativa* Mill.	Seed	Aqueous infusion	150 mg/kg for 24 h in gentamicin-induced nephrotoxicity male Sprague Dawley rats	↑ Urine output, ↑ Urinary concentration of Na^+ and K^+, ↓ Elevated serum urea and creatinine	[94]
Compositae	*Arctium lappa* L.	Fresh raceme	Aqueous infusion	Replace water by infusion/for 12 days in female Wistar rats	Prevents kidney epithelium microcalculous retention	[95]
	Citrullus lanatus (Thunb.) Matsum. & Nakai	Fruit	Ethanolic extract	200 mg seed extract or pulp extract/kg/day for 21 days in EG induced calcium oxalate male Wistar rats	Improved renal functions ↓ Crystal deposition Improved renal architecture	[96]
Cucurbitaceae	*Cucumis melo* L.	Peel and pulp	Petroleum ether chloroform, methanol, ethanol and water hot extraction by Soxhlet	400 µg/g/day peel or pulp extract for 21 days in EG induced urolithiasis male mice	Chloroform and methanol extracts exhibited potent antiurolithiatic activity as evident from serum creatinine, uric acid and BUN levels	[97]
	Cucumis sativus L.	Fruit	Hydroethanolic extract	100, 200, and 400 mg/ Kg/day for 28 days in EG induced urolithiasis male albino Wistar rats	Dose dependent effect on lowering the concentrations of calcium, phosphates and oxalates, ↓ Levels of serum creatinine, BUN and uric acid	[98]
Cyperaceae	*Cyperus rotundus* L.	Rhizome	Decoction extract	5 and 10 g/kg, of plant dried weight before extraction, for 4 h in adult male Sprague–Dawley rats	Failed to demonstrate any diuretic activities	[99]
Hypericaceae	*Hypericum perforatum* L.	Flower	Hydroalcoholic extract	300 and 500 mg/kg/day for 28 days in EG and (NH_4Cl) induced calcium oxalate male Wistar rats	↓ Size and number of calcium oxalate deposits, ↓ Urine level of calcium and phosphorous	[100]
Iridaceae	*Crocus sativus* L.	Red stigma	Aqueous extract	60, 120 and 240 mg/kg in male rat	↑ urinary volume significantly ↑ Urinary sodium in 240 mg/kg group ↓ Urinary Potassium ↓ Urinary urea and creatinine	[101]
Lamiaceae	*Rosmarinus officinalis* L.	Whole plant	Aqueous extracts	10 ml/kg/day of %8 or 16% extract for 7 days in male Wistar rats	↑ At the dose of 8% the peak of urinary excretion of sodium, potassium and chloride, ↓ Creatinine clearance at the dose of 8%, Slight increases in urinary excretion of sodium and chloride at the dose of 16%	[102]

Leguminosae	*Dolichos biflorus* L.	Seed	Hydro-alcoholic extract	150 and 300 mg/kg/day for 28 days in EG induced calcium oxalate Wistar rats	↓ Crystal deposition Improved renal architecture	[103]
Linaceae	*Linum usitatissimum* L.	Seed	Aqueous extracts	400 mg/kg/day for 10 days in EG induced urolithiasis Albino Wistar rats	↓ Urine creatinine, uric acid, urea, and calcium (mg/dl) level, ↓ The serum creatinine, urea, uric acid and calcium (mg/dl) level	[104]
Lytheraceae	*Lawsonia inermis* L.	Leaf	Aqueous and ethanolic extracts	250 mg/kg and 500 mg/kg in male Wistar rats	↑ Dose-dependent in urine excretion, Comparatively the ethanolic extract produced more significant diuresis than aqueous extract underlying a more specific increase in water, sodium, potassium and chloride ion excretion	[105]
Meliaceae	*Melia azedarach* L.	Leaf	Aqueous extract	250 mg/kg/day for 28 days in EG induced nephrolithiasis male Wistar albino rats	↑ Urine volume, ↓ Urinary calcium, oxalate, phosphate, ↑ Urinary magnesium level	[106]
Myrtaceae	*Myrtus communis L.*	Leaf	Methanolic extract	300 mg/kg/day for 28 days in EG induced kidney stone model Sprague Dawley male rats	↓ Tissue degeneration, ↓ Number of stones	[107]
Oleaceae	*Olea europaea* L.	Oil	Oil	1.3 and 1.7 mL/kg/day for 28 days in EG induced calcium oxalate adult albino mice	↓ Urine and kidney calcium, oxalate, and phosphate levels Prevented the growth of urinary stones	[108]
Orobanchaceae	*Orobanche major* L.	Whole plant	Aqueous extract	3g/kg/day for 28 days in EG induced nephrolithiasis male albino rats	↓ Phosphorus, Calcium and Oxalate in kidney tissue	[109]
Piperaceae	*Piper cubeba* L.f.	Fruit	Ethanolic extract	100, 200 and 400 mg/kg/day from 15-28 days in EG induced calcium oxalate Wistar albino rats	↓ Levels of serum creatinine, BUN, uric acid, ↓ Levels of calcium, oxalate and phosphate in urine and kidney homogenate	[110]
Poaceae	*Cynodon dactylon* (L.) Pers.	Root	Aqueous extract	1 ml of aqueous extract (50 mg/ml)/day/orally for 21 days in EG induced calcium oxalate Wistar rats	↓ Oxalate excretion	[111]
Pteridaceae	*Adiantum capillus-veneris* L.	Leaf, Branch	Hydro alcoholic extract	127.6 mg/kg and 255.2 mg/kg/day for 21 days in EG induced calcium oxalate male Sprague Dawley rats	↓ Crystal deposition Improved renal architecture	[112]
Ranunculaceae	*Nigella sativa* L.	Seed	Aqueous-ethanolic extract, N-butanol fraction and N-butanol phase remnant	250 mg/kg/day in drinking water for 28 days in EG induced calcium oxalate Wistar rats	↓ Number and size of kidney calcium oxalate deposits ↑ Urinary concentration of oxalate ↓ Urine citrate concentration	[113]

Rutaceae	*Ruta graveolens* L.	Leaf	Hot water infusion	9.00, 6.75 and 4.5 mg/ml in male albino rats	↑ Cumulative urine output, ↑ Specific conductivity Na^+ level, K^+ level, Na^+/H^+ ratio and Na^+/cl^- ratio of urine	[114]
Vitaceae	*Vitis vinifera* L.	Leaf	Hot Continuous Extraction (Soxhlet)	200 and 400 mg/kg in EG induced urolithiasis male Wistar albino rats for 21days	↑ Urine volume, ↓ Serum calcium levels, ↓ Serum uric acid, ↓ Retention or deposition of calcium levels in kidneys, ↓Deposition of uric acid levels in kidney, Less crystal depositions	[115]
Zingiberaceae	*Elettaria cardamomum* (L.) Maton	Fruit	Aqueous-methanolic (70%) extract	1, 3 and 10 mg/kg/day for 7 days in male albino rats	↑ Urinary volume ↑ Urinary excretion of Na+ and K+	[116]
Zygophyllaceae	*Peganum harmala* L.	Seed	Hydro-alcoholic extract	50 mg/kg in EG induced urolithiasis rats	↓ Creatinine, uric acid, urea, kidney injury molecule-1 (Kim-1), calcium, magnesium, phosphate, and oxalate levels ↑ Urine output and urine pH	[117]
	Tribulus terrestris L.	Fruit	Aqueous extract	5 g/kg/day for 30 days in male Wistar rats fed sodium glycolate	↓ urinary oxalate excretion ↑ urinary glyoxylate excretion	[118]

EG: ethylene glycol, NH_4Cl: ammonium chloride

Table 3. The list of medicinal plants used for treatment of urinary tract stones in human subjects

Family	Scientific name	Plant part	Form of use	Method	Results	References
Amaryllidaceae	*Allium sativum* L.	Bulb	Aqueous extract	900 mg per day in tree-divided capsules for 2 weeks in patient with kidney and ureteral stones less than 10mm	The pain level significantly decreased, Help the passage of stones	[119]
Apiaceae	*Apium graveolens* L.	Seed	Ethanolic extract	Triple-blind, placebo-controlled, cross-over, 4 capsules/day for 4 weeks in hypertensive patients	Beneficial effects on kidney functions	[120]
	Trachyspermum ammi (L.) Sprague	Seed	Powder in milk and sugar	15 gr (Total dose for each patient taken within 9 days-each 5-gr boiled with 150 ml cow milk and 25 gr sugar) for 9 days before breakfast in 350 patients with urinary stone	Good affectivity on ca-oxalate stones, lithotripsy effect	[121]

Leguminosae	*Cicer arietinum* L.	Seed	Aqueous extract	330 mg three times a day for 30 days in 74 patients with 6-10 mm renal stones	Complete stone dissolution occurred in 9 (23.7%) patients, ↓ Stone size was observed in 17 (44.7%) patients, ↑ Urinary magnesium, ↑ Urinary volume	[122]
	Dolichos biflorus L.	Seed	Aqueous extract	1-2 mg/day in 3 equally divided doses for 6 months in patients with diagnosis of calcium oxalate renal calculi	↓ Recurrence of calcium oxalate stone	[123]
Poaceae	*Cynodon dactylon* (L.) Pers.	Root	Hydroalcoholic extract	1,600 mg for 21 days in patients with urolithiasis	↓ Stone size, Effective on kidney stones excretion	[124]
Ranunculaceae	*Nigella sativa* L.	Seed	Ethanolic extract	Randomized block sampling method, 2 capsules (100 mg/day) for 12 weeks in patients with kidney stones	↓ Stone size ↓ Amount of urinary oxalate	[125]
Zygophyllaceae	*Peganum harmala* L.	Seed	Powder	Randomized clinical trial, 1 capsule (50 mg/kg/day) for 2 weeks in patients with kidney and ureteral stones	↓ Urinary stone size and numbers ↓ Pain score	[126]
	Tribulus terrestris L.	Leaf, flower, Fruit,	Aqueous extract	10 mL/day for 7 days in renal stone patients	↓ Uric acid levels in urine samples, ↑ Mean serum calcium level, ↓ Mean urinary calcium level, ↓ Mean citrate, oxalate and proteins in urine	[127]

↑: Increase; ↓: Decrease

dense foods is believed to contribute to the deposition of substances and the accumulation of viscous humors in the kidneys, leading to kidney stones [72,75]. In conventional medicine, these dietary items are similarly discouraged due to their high calcium and oxalate content [17,18]. Conversely, light and easily digestible foods are believed to aid in the breakdown of stones and ultimately facilitate their excretion or dissolution [73,74]. By adhering to a specific diet and incorporating diuretic herbs, which enhance the excretion of calcium, urea, and creatinine, as well as kidney-protective herbs, the excretion of urinary stones is improved and the likelihood of stone recurrence is reduced [75].

The results obtained from animal and human studies are a seal of approval on the herbal treatment recommendations of TPM, although more studies are needed in this field, especially on plants that have not been studied so far. The TPM with long experience and special principles has good potential in the field of diagnosis and treatment in its own way and can act as a strong complementary treatment system for diseases that have challenging treatment.

Conclusion

Kidney stone formation is a biological process that includes physicochemical changes and excessive saturation of the urine but the order of events leading to stone formation varies depending on the chemical composition of the stone and the urine. Many aspects of kidney stone formation are still unclear. However, the renal cell damage, crystal retention, cell apoptosis, and Randall plaque certainly play important roles in the formation of kidney stones.

Few urologists have a thorough understanding of the various mechanisms underlying urinary tract stone formation and the selection of the best method to combat stone formation. Understanding the pathophysiology and pathogenesis of kidney stone formation can lead to the discovery of new drugs and strategies for managing the disease in the near future.
Since the TPM physicians had explained the cause of kidney stone formation with complete reasons and based on the principles and foundations of the TPM about a thousand years ago without having the modern tools and technology so that they are often consistent with modern medicine information, it seems, using the experiences in the TPM sources and relying on today's knowledge can create a way to prevent the formation and recurrence of urinary tract stones.

Conflict of Interests
None.

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