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Review Article

**COMMON ANTIUROLITHIATIC MEDICINAL PLANTS IN PERSIAN
MEDICINE: A REVIEW**Mahdi Biglarkhani¹⁻³, Mohammad Ali Amir Zargar^{3,4}, Fataneh Hashem-Dabaghian^{1,2}, Farshad Amini Behbahani^{1,2}, Azam Meyari³, Omid Sadeghpour^{1,2*}¹Research Institute for Islamic and Complementary Medicine, Iran University of Medical Sciences, Tehran, Iran.²School of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran.³Department of Persian Medicine, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.⁴Urology and Nephrology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran.**Abstract:**

Urolithiasis is a common urological disease with considerable recurrence and morbidity which has affected human science ancient to now. Persian Medicine, an indigenous system of Iranian Traditional Medicine, offers vast herbal list for treatment of urinary stones. This review focuses on the most common antiurolithiatic medicinal plants mentioned in four major Persian literatures and their supporting new evidence and mechanisms of action. Medicinal plants mentioned in four main traditional manuscripts of Persian Medicine, including the books of «Canon of Medicine», «Liber Continens», «Zakhire Kharazmshahi» and «The Royal Book» for treatment of urinary stones were elicited. Then common antiurolithiatic herbs in all these four books were selected and searched in electronic databases including PubMed, Scopus, Google Scholar, Cochrane library, Magiran and SID to find studies that confirmed their efficacy. The findings included over all 124 plants with antiurolithiatic activities that 8 herbs were common among the all four major traditional resources of Persian Medicine. Scientific findings have revealed that these plants control urolithiasis through different mechanisms of action contain diuretic activity, antioxidant activity, inhibition of inflammatory process, inhibition nucleation, Inhibition crystallization, inhibition crystal aggregation, reducing hyperoxaluria, reducing stone size and reducing urine supersaturation. According to this study, all of the cited common medicinal plants have antiurolithiatic phytochemical reveals. Investigation of Persian Medicine literatures can lead to the identification of effective natural medicines for the management of urolithiasis; however, conclusive confirmation of the efficacy and safety of these treatments needs more evaluations especially by future clinical trials.

Key Words: *Urinary Stone, Antiurolithiatic, Persian Medicine, Traditional Medicine, Medicinal Plant, Herbal Medicine.*

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INTRODUCTION:

Urolithiasis is a common worldwide disease with considerable morbidity and recurrence [1, 2]. It is the third most common urological affliction after urinary tract infections and prostate disorders [3, 4]. This disease affected human both in antiquity and now [5]. The disease defined as formation of stones in the urinary system includes Nephrolithiasis (Renal Calculi or Kidney Stones), Ureterolithiasis (Ureter Calculi or Ureter Stone) and Cystolithiasis (Bladder Calculi) [6, 7]. Urolithiasis occur in around 12% of the global population and its occurrence rate in males is 70-81% and 47-60% in female [4]. The stones are made from polycrystalline aggregates consisting of varying amounts of crystal and organic matrix components [8, 9]. Of many types of stones that are formed, calcium oxalate and calcium phosphate are the most commons [7]. Urinary stone formation is a complex procedure that occurs due to imbalance between promoters and inhibitors in the kidneys [4, 10]. This formation encompasses several physicochemical events beginning with crystal nucleation, growth, aggregation, and ending by retention within urinary tract [7, 11]. Despite tremendous advances accomplished in understanding the mechanisms governing the formation of such concretion, The etiology of stones is remained speculative [3, 7]. Modern technologies such as X-ray, Computed Tomography, Ultra Sound, Intra Venous Pyelography is used to verify the diagnosis of urinary stones [4]. Interventional treatment options include Electro Shock Wave Lithotripsy (ESWL), Ureteroscopy(TUL), Percutaneous Nephrolithotomy(PCNL), and Open or Laparoscopic Stone Removal which are costly, painful and have several complications [4]. Many synthetic drugs like diuretics and narcotic analgesics are being used in treatment of renal stone but overuse of synthetic drugs, which can produce higher incidence of adverse drug effect and lack of their efficacy have forced people to return to nature for safe remedies herbal treatment [4, 11]. Humans have used plants as a source of drugs to combat diseases since ancient times and nowadays this consumption has been increased especially in chronic, recurrent and/or incurable diseases [12, 13]. According to the World Health Organization (WHO), more than three quarters of the world population trust in herbs as a traditional medicine for health care and there is an increasing interest in traditional herbal remedies due to their safety, efficacy, cost effectiveness, eco-friendly, readily availability, cultural acceptability and lesser side effects as compared to synthetic drugs [8, 11-13]. Many medicinal herbs have been used during the past many years to treat urinary stones [4, 14]. Persian Medicine or Traditional Iranian

Medicine (TIM) roots back to nearly 10,000 years ago and it has a great potential for solving some of the present medical problems, as shown in some recent researches in the field [15-17]. In Iran, since ancient times, based on advices by great and famous scientists of Persian medicine, medicinal plants have been used to treat the urinary stones [18]. The golden era of medical sciences in the Islamic civilization spanned from the 9th to the 11th century. Medicine flourished through contributions from prominent Persian scholars such as Avicenna, Rhazes, Jorjani and Holy Abbas during this period [19]. Avicenna or Ibn-e-Sīna (980–1037 AD), the most famous Iranian physician that his works had a crucial impact on the modern medicine[20]. So he is called as the father of modern medicine and Clinical Pharmacology. He is known as the most influential medical writers in the medieval period and held a high place in Western medical studies, ranking as an acknowledged supremacy [20]. He was arguably one of the most outstanding medical scientists and practitioners ever, and had a deep influence on medical science in the golden ages of Islamic medicine (9–12th century AD) and in Europe as well. So he was called “Sheikh-al-Ra’eis” in Persia and ‘Prince of Physicians’ in the West. His masterpiece, The Qanun of Medicine also named Canon of Medicine and Al-Qanon-fi-al-Tibb, for centuries, was a major encyclopedia for practicing and teaching medicine in Islamic territories and Europe. It was translated in Latin by Gerard of Cremona in the 12th century AD. This book was regarded as the most important reference of medical sciences in most of European universities from 13th to 18th century. Sir William Osler, one of the four founding professors of Johns Hopkins Hospital, noted the Canon as "the most famous medical textbook ever written; a medical bible for a longer time than any other work" [20-23]. Abubakr Muhammad ibn Zakariyya al-Razi (865–925 AD) is known in the western world as Rhazes. He is surely famous as one of the most prominent medical scientists of the Islamic golden age. One major medical contribution has been preserved, Kitab al-Hawi or AlHawi (a comprehensive textbook of medical practice and treatment), also known as Liber Continens in a Latin translation of the 13th century and repeatedly reprinted in Europe in the 15th and 16th centuries belongs to him. This reference is an immense compendium containing 26 books on different medical issues. This book forms a synthesis of Persian, Greek, Indian, and Arab medical knowledge, including his own observations and around 900 case reports, touching on almost every conceivable topic [24]. Ali ibn Abbas Majusi Ahvazi(949-982 AD), also known as Haly Abbas in the west, was another renowned Persian physician of this era. He is

regarded as the first scientist who rejected ancient Galenic principles of medicine and who tried to present a new kind of medicine, based on observational data. He wrote a large medical encyclopedia entitled *Ka-mil al-Sina'a fi al Tibbiya* (The Perfect Book of the Art of Medicine) or *al-Maliki* (The Royal Book). And the last but not the least's scholar is theologian Seyed Esmaeel Jorjani (1041-1136 AD), titled Zeinoddin and known as Jorjani. More than one thousand years ago, he did valuable compilations in the history of medicine and many of his medical views are, to a great extent, in line with the recent views. His innovations and practices in various branches of medical sciences are quite novel and unique. His most famous book is *Zakhireh Kharazmshahi* which is one of the most complete, significant and comprehensive Persian medical texts that truly must be recognized as an integrated medical encyclopedia which covers all aspects of medical subjects and branches, including general medicine, anatomy and physiology, etiology of disease, description of health, hygiene, nutrition, health care duties of everyday life, medical procedures such as blood sampling, surgical procedures, disease symptoms and their treatments, pharmacology and pharmaceuticals. This book contains nine volumes plus a chapter exclusively about herbs; so, altogether, they amounted to ten volumes. *Zakhireh* has made an astonishing summary of the world of medicine and it seems this book is created as a relatively easy and clear medical source and standardized medical terms. So his works are complete examples of medicine [25]. In the writings of Avicenna, Rhazes, Haly Abbas and Jorjani there are real descriptions of the urinary stone disease, its etiology, management, indications for treatment and beneficial medicinal herbs [26-29]. So this study designed to review the new evidence about antiurolithiatic effect of common medicinal herbs mentioned in all these major Persian medicine resources.

MATERIALS AND METHODS:

This study is literature research, investigating four major and important Persian Medical and pharmaceutical manuscripts from the ninth to the eighteenth century AD. The manuscripts were composed of the book of *Al-Havi* (The Liber Continens, written by Rhazes) [27], *Ka-mil al-Sina'a fi al Tibbiya* (written by Haly Abbas) [28], *Al-Qanoon fi al-Tibb* (The Canon of Medicine, written by Avicenna) [26] and *Zakhireh Kharazmshahi* (written by Seyed Ismail Jorjani) [29] which are determined as Persian traditional references in medicine and pharmacy and nowadays are used as references for the Iranian Ph.D program in Persian Medicine and Persian Pharmacy. Then we selected plants used in

treating all types of the urinary stones. Consequently, common herbs mentioned in the four above mentioned books were extracted. Also, effects of these plants on related subjects were considered through a search in Physician's Desk Reference for Herbal Medicine (PDR) [30]. In order to make relationships between traditional data and current findings, electronic databases including PubMed, Scopus, Cochrane library and Google Scholar, Magiran and SID were explored for each of these herbs and all retrieved articles were evaluated to achieve any in vitro, in vivo and clinical evidence for their efficacy and pharmacological mechanisms related to urinary stones. Studies demonstrate both direct and/or indirect efficacy of these medicinal herbs in mechanisms involved in urinary stones were considered. Data were collected for the years 1980 to October 2017. The search terms were "urinary stone" or "urolithiasis" or "renal stone" or "kidney stone" or "ureter stone" or "bladder stone" in title and abstract and the name of each herb in the whole text. Results from primary search were screened by two independent Investigators. References of finally included articles were reviewed for more relevant studies. Included articles contain phytochemical investigations, in vitro, in vivo and human studies were reviewed to extract plant's scientific name, medicinal part, phytochemical compounds, active components (if mentioned) and drug effectiveness and efficacy.

FINDING:

Overall, 124 Medicinal herbs were determined as antiurolithiatic plants from the mentioned major traditional reference of Persian Medicine. Of this plants, 8 herbs were common in all these four books. Results are shown in Table 1. Below, these eight common medicinal herbs and all evidence confirming their efficacy on urinary stones are described individually.

Tribulus terrestris

In an in vitro study, *Tribulus terrestris* extract exhibited a concentration dependent inhibition of nucleation and the growth of Calcium Oxalate crystals. It has been shown that the aqueous extract of *Tribulus terrestris* inhibited Calcium Oxalate crystallization. The study data suggested that *Tribulus terrestris* extract not only has a potential to inhibit nucleation and the growth of the calcium oxalate crystals but also has a cytoprotective role. This study suggests the possibility of using *Tribulus terrestris* as a therapeutic agent to treat urinary calculi [9]. Furthermore, in an in vivo study, *Tribulus terrestris* significantly reduced the excretion of oxalate, calcium, and phosphate along with decreased

levels of blood urea nitrogen, uric acid and creatinine in serum in rats. *T. terrestris* also reduced hyperoxaluria- caused oxidative stress, and restored antioxidant enzyme activity and their expression profile in kidney tissue. Histological analysis depicted that *T. terrestris* treatment decreased renal epithelial damage, inflammation, and restored normal glomerular morphology [31]. Also in a randomized clinical trial about using *Tribulus terrestris* and placebo in the management of Nephrolithiasis in total 60 patients, it has indicated that this medicinal herb has excellent diuretic, analgesic, relieved burning micturition effect with statistical significance in group of drug. Further, it is observed during the 90 day study period, the extremely significant mean reduction size of the stone in Ultra-Sonography and Kidney-Ureter-Bladder X-ray studies. This study suggests *Tribulus terrestris* as an effective and safe treatment in renal calculus as it expels the stones and brings about the significant reduction of stone size and symptoms associated with Nephrolithiasis. In addition, no significant adverse reactions were reported or observed during the entire study period [32].

Adiantum capillus-veneris

In an in vitro investigation, extract of *Adiantum capillus-veneris* inhibited the crystallization in solution; less and smaller particles were observed in the presence of extract. These results were further confirmed in the nucleation assay, though the rate of nucleation was not inhibited but number of crystals was found to be decreased which showed that the extract contains nucleation preventing agents. Hydro alcoholic extract of the test drug at different concentrations decreased number of crystals in solution there by reduced supersaturation and the size of the particles. The test drug also inhibited crystal aggregation. It can be concluded therefore, that the test drug possesses significant antilithiasic activity. It was observed that test drug reduced mainly the amount of Calcium Oxalate Monohydrate crystals, which is responsible for higher potential risk for stone formation. The study interfered that the test drug possesses significant antilithiasic effects [34]. In vivo study of *Adiantum capillus veneris* efficacy in chemically induced urolithiasis in rats showed significant reduction in the number of crystals in Urine microscopy. Serum levels of calcium, phosphorous, and blood urea were found to be decreased significantly. Histopathology of kidney showed almost normal kidney architecture in treated animal groups. A significant decrease in the size of urinary stone was observed in animals treated with the extract of *Adiantum capillus veneris*, too. It is supposed in this study that antiurolithiasic activity of

Adiantum capillus veneris may also be due to its flavonoids constituent [33].

Apium graveolens

In an in vivo study conducted to evaluate the effect of *Apium graveolens* in reducing calcium deposits from renal parenchyma in rabbit models with induced nephrocalcinosis by a large dose of oxalic acid, it produced a significant reduction of blood urea nitrogen, serum creatinine and serum Na⁺ levels with non-significant reduction in serum K⁺. There was a significant reduction in calcium deposition in renal parenchyma in comparison to the control group after ten days of treatment which is due to its diuretic effect which may be related to its constituents, particularly allantoin that have diuretic action. So *A. graveolens* have a significant diuretic and attenuating effect in reducing calcium deposits from renal tissues [43].

Asparagus officinalis

In a study which investigated antioxidant and antibacterial activities of ethanolic extracts of *Asparagus officinalis* cv. Mary Washington and Compared in vivo and in vitro grown plant bioactivities, shown the antioxidant activities of *A. officinalis* as an effective antiurolithiatic factor differ between in vitro and in vivo grown plants. Total antioxidant capacity of in vivo grown plant was higher than in vitro grown plant, while the only antimicrobial activity was obtained from in vitro callus tissue against *B. cereus* [36]. In another study investigated the effect of ethanolic extract of *Asparagus racemosus*, another type of *Asparagus* species, on urolithiasis in Wistar albino rats, The extract significantly reduced their serum concentrations of calcium, phosphorus, urea, and creatinine. Consequently, it emphasized that the extract of *Asparagus racemosus* has protective effect against urolithiasis [44].

Commiphora mukul

A designed study to evaluate effect of Crashcal, a polyherbal formulation consisting of *Commiphora mukul*, *Tribulus terrestris* and some other herbs, in the treatment of renal calculi in rats, showed that the increased deposition of stone forming constituents was significantly lowered by Crashcal. The drug administration significantly reduced both calcium and oxalate levels in kidneys, which are known to prove beneficial in preventing calculi formation due to supersaturation of these lithogenic substances. Treatment of Crashcal restored phosphate level and decreased urinary phosphate, thus led to reducing the risk of stone formation. This study suggested that Crashcal possess significant antiurolithiatic and

antioxidant activity in rats. Thus, the results revealed that Crashcal has potent antiurolithiatic and antioxidant activity [38].

Commiphora opobalsamum

In an in vivo study on the pharmacological activities of an ethanolic extract of *Commiphora opobalsamum*, a significant increase in urine volume and urine PH of rats by Oral administration of Balessan extract was noted. The observations suggested that Balessan extract possesses diuretic, anti-inflammatory and analgesic activities in laboratory animals [39].

Cyperus rotundus

In an in vivo intervention a poly herbal suspension contains *Cyperus rotundus* roots, *Azadirachta indica* leaves and *Bryophyllum pinnatum* leaves was prepared for use in urolithiasis. Antiurolithiatic activity was studied in the ethylene glycol induced urolithiasis model in wistar rats. The polyherbal

suspension was found to be safe and effective in expelling excess urinary calcium, oxalate, phosphate, creatine, uric acid and urea resulting in antiurolithiatic effect. It was preventing and/or dissolving the formed stones. The results showed that the poly herbal suspension has prevented or decreased the super saturation of urine leading to prevention of stone formation and agglomeration. Thus the authors concluded that the formulated poly herbal suspension containing *Cyperus rotundus* has potential antiurolithiatic activity [40].

Laurus nobilis

In a phytochemical study to evaluate Phenolic content and antioxidant capacity of extracts of *Laurus nobilis*, the high antioxidant activity and four individual phenolic profile of *Laurus nobilis* extracts and infusions were determined. Now it is suggested that antioxidant and phenolic activities may partially contribute in the process of lithotriptic effect [33, 41].

Table 1: List of Common Antiurolithiatic herbal drugs in Persian Medicine with their related supporting evidence.

S.No	Common Name	Scientific Name	Study Type	Part Used	Mechanism of Action/ Phytochemical compounds	Ref
1	Tribulus	<i>Tribulus terrestris</i>	In Vitro In Vivo(rat) RCT	plant fruit	inhibition nucleation inhibition growth of the CaOx reducing excretion of oxalate, calcium, and phosphate reducing hyperoxaluria reducing stone size restoring antioxidant enzyme activity	[31] [9] [32]
2	Venus Hair	<i>Adiantum capillus veneris</i>	In Vitro In Vivo(rat)	Whole plant	inhibition nucleation Inhibition crystallization inhibition crystal aggregation reducing supersaturation decrease the size of the stone decrease in Serum levels of calcium, phosphorous, and blood urea exist flavonoids constituent	[33] [34]
3	Celery	<i>Apium graveolens</i>	In Vivo (rabbit)	Whole plant	reducing calcium deposits from renal parenchyma reducing blood urea nitrogen, serum creatinine and serum Na+ exist allantoin constituents with diuretic activity	[35]
4	Asparagus	<i>Asparagus officinalis L</i>	Phytochemical Analysis	seed and Whole plant	antioxidant activities (in <i>Asparagus officinalis</i>) reducing serum concentrations of calcium, phosphorus, urea, and creatinine (in <i>Asparagus racemosus</i>)	[36] [37]
5	Mukul	<i>Commiphora mukul</i>	In Vivo (wistar)	Whole plant	reducing both calcium and oxalate levels in kidney decreasing urinary phosphate exist antioxidant activity	[38]
6	Balessan	<i>Commiphora Opobalsamum</i>	In Vivo (rat&mice)	aerial part	increasing urine volume (diuretic activity) anti-inflammatory activity analgesic activity increasing urine PH	[39]
7	Nutgrass	<i>Cyperus rotundus</i>	In Vivo (wistar)	root	expelling excess urinary calcium, oxalate, phosphate, creatine and uric acid decreasing super saturation of urine prevention of stone formation and agglomeration	[40]
8	Bay Laurel	<i>Laurus nobilis</i>	Phytochemical Analysis	Whole plant	Antioxidant activity and phenolic activity contribute in the process of lithotriptic effect	[41] [42]

DISCUSSION:

The present review covered scientific evidence about common antiurolithiatic medicinal plants mentioned in the four major Persian medicine literatures. Evidence prove that these eight common herbs have antiurolithiatic effects either in vitro and/or in vivo and/or clinically. These plants are world wild spread as are common in Iran and Asia. The Ethnobotanical and ethnopharmacological studies are effective ways to identify and prove plants with potential therapeutic effects on urinary stones in each traditional and complementary discipline in medicine [4, 5, 14, 18]. Some investigators have devoted their efforts to study their medicinal plants by using scientific methods and understanding the mechanism by which these herbal plants exert their effects and identify their action principles [7, 8]. Like other antiurolithiatic medicinal herbs, the above mentioned common herbs contain several phytoconstituent and exert their beneficial effects by multiple mechanisms and having ability to change some urine parameters contain: first, increasing the urine volume, pH and anti-calcifying activity (Diuretic activity) helps in spontaneous passage; Second, balancing the process of Inhibition and promotion of the crystallization in urine affects the crystal nucleation, aggregation and growth (Crystallization inhibition activity); third, relieving the binding mucin of calculi (lithotriptic activity); fourth, improving renal function; fifth, regulation of oxalate metabolism; sixth, regulating the crystalloid colloid imbalance and improve renal function, thus prevent recurrence of urinary calculi; seventh, improve renal tissue antioxidant status and cell membrane integrity, preventing the urolithiatic renal cell injury and prevent reoccurrence (Antioxidant activity); eighth, ACE and Phospholipase A2 Inhibition; ninth, exerting significant anti-infective action against the major causative organisms (Antimicrobial activity) and tenth, revealing marked improvement in symptoms of urinary calculi like pain, burning micturition and hematuria (Analgesic and anti-inflammatory activity)[4, 6, 14, 18, 45]. The current article only deals with articles published in English and Persian and this may ignores some studies published in other languages. This review can provide the opportunities for the future research and for the development of new antiurolithiatic compounds. Supplementary researches is needed to more identifying active principles from medicinal plants and evaluate their dosage and quality control, and investigate their interactions and adverse effects.

CONCLUSION:

The above mentioned eight common antiurolithiatic medicinal herbs in Persian medicine have antiurolithiatic supporting evidence. Scientific

evaluations of traditional documents in Persian medicine and doing all pharmacological studies on its antiurolithiatic plants can give considerable insights into the ideas of the past and be valuable in finding new data on clinical use of the antilithiatic herbs that should lead to future opportunities to investigate their potential medicinal use and this will be an important resource for the discovery of new effective drugs. In other word, Investigation of Persian medicine literatures can lead to the identification of effective and safe natural medicines for the management of urolithiasis; however, conclusive confirmation of the efficacy and safety of these treatments needs more evaluations especially by future clinical trials.

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