Review Article

Clinical studies of medicinal plants for their antiurolithic effects: a systematic review

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Background: Epidemiological studies indicate a surge in stone disease across the globe and climate change is making it worse. Current treatments for stones are expensive and not easily available to all people in all countries. As a result, there is a great interest in alternative medicines described in ancient texts of many countries and cultures. They are variously called as Ayurvedic and Unani medicine in Indo-Pakistan subcontinent, traditional Chinese medicine including Japanese traditional Kampo medicine in South-East Asia. These treatment options include herbal medicines, acupuncture, alkaline liquids, and others. Herbs being easily available at a relatively lower costs are most commonly used alternative medicines for stone disease. This interest has led to several *in vivo* and *in vitro* experimental scientific studies to understand the efficacy of herbs in reducing stone formation, however, the clinical data is limited. We recently performed systematic review of publications dealing with antiurolithic activities of various herbal treatments in rat models of calcium oxalate (CaOx) urolithiasis.

Methods: Here we present results of our systematic review of clinical studies. We adopted PRISMA guidelines and systematically reviewed PubMed/Medline for the literature up to May 2021, reporting results of various clinical studies of herbal products/medicine for the management of nephrolithiasis/urolithiasis.

Results: A total of 55 eligible clinical studies were retrieved from PubMed indexed with the (Mesh Term) "Urolithiasis" AND "Complementary Therapies/Alternative Medicine, "Urolithiasis" AND "Plant Extracts" and "Urolithiasis" AND "Traditional Medicine". Further screening resulted in the inclusion of 15 studies.

Discussion: Reduction in stone size, their number, and easy passage were considered favorable outcomes. According to our review of literature, scientific evidence of efficacy of herbal treatments is so far insufficient, but promising, underlining the importance of well-planned and well-defined clinical trials.

Keywords: Calcium oxalate; urolithiasis; nephrolithiasis; kidney stone; alternative medicine; medicinal plants; ayurveda; Chinese medicine; herbal medicine; traditional medicine

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Introduction

Urolithiasis, the development of stones/crystals in the urinary tract, is a common urological disorder and has been affecting humans since the dawn of history, as is evident from the finding kidney and bladder stones in Egyptian mummies (1). In 1998, Pak estimated lifetime risk of urolithiasis was considered around 2–5% in Asia, 8–15% in America and Europe, and about 20% in the Middle East (2). However recent estimations, considering the impact of climate change, predict that in the United States alone, the population living in high-risk zones for urolithiasis will grow from 40% in 2000 to 56% by 2050, and to 70% by 2095". In addition, the age of onset is decreasing (3) and the rate of recurrence is also increasing. After one year of the first episode, recurrence rate is around 10–23%, 50% within 5–10 years and around 75% in 20 years. After every stone episode the recurrence interval decreases and the subsequent relapse rate increases (4). Recent clinical and experimental data also show the involvement of urolithiasis in many other maladies such as hypertension, diabetes and cardiovascular diseases (5). These projections emphasize the need for development of better understanding the pathophysiology of urolithiasis and finding additional and better and cheaper means to reduce the recurrence of this disease and cheaper less costly tests and treatments.

Kidney stones are composed of a variety of crystals and a ubiquitous organic matrix and are named for their main crystalline constituents. Calcium oxalate (CaOx) alone or in association with calcium phosphate (CaP) is the major component of 75–80% of the kidney stones (6). Struvite, cystine, uric acid and ammonium acid urate are some of the other types of stones. Crystallization in the urine and kidneys is the initial event in the multi-step process of stone formation which starts with increased urinary supersaturation (SS) with stone-forming salts in the presence of lower crystallization inhibitory potential (CIP). Both supersaturation and reduced inhibition are a result of ineffective kidneys either through renal injury (7), or inheritances (8). Change in urinary pH and/or excretion of calcium (Hypercalciuria), oxalate (Hyperoxaluria), citrate (Hypocitraturia) and many other ions, that are involved in crystallization may be a result of genetic factors. Similarly, mutations in genes controlling urinary excretion of macromolecules that modulate crystallization, such as osteopontin (OPN), matrix-gla-protein (MGP), Tamm Horsfall Protein (THP) may lead to ineffective crystallization inhibition. Increase in urinary excretion of ions such as oxalate are damaging to renal epithelial cells with the production of reactive oxygen species and development of oxidative stress in the kidneys. Damaged cells can promote crystal nucleation, aggregation and retention within the renal tubules (9), plugging the tubules. Such tubular plugs or plaques in the terminal collecting ducts, through addition of more crystals, may act as sites for stone development. Ineffective renal immune response to abnormal conditions may start calcification in the renal interstitium leading to the formation of Randall's plaques, substrates for the growth of most common idiopathic CaOx kidney stones.

Improvement in therapy of kidney stones with extracorporeal shock wave lithotripsy (ESWL), ureteroscopy (URS), percutaneous nephrolithotomy (PNL) etc. has greatly improved the treatment and management of kidney stones, however, the recurrence rate of kidney stone has not been significantly altered. ESWL is less effective in cystine stones and calcium oxalate monohydrate (COM) than uric acid and calcium oxalate dihydrate (COD) stones (10). Moreover, the side effects including ESWL induced hypertension, renal damage, renal Impairment (11), steinstrasse, sever hematuria, infection, pancreatitis and persistent residual fragments as potential nidus for new stone formation are still there. While the complications can lead to large perfusion of the collecting system, urosepsis, extravasations of irrigating fluid, ureteral injury and delayed bleeding (12). Pharmacological agents include a limited choice like citrate and thiazide diuretic, and issues of side effects and tolerance (13). Oral citrate is commonly used due to its effect on urinary pH, however, it cannot be tolerated by all the patients and patients have been reported to form stone during therapy (14). On the other hand, there is growing public interest in herbal medicine, partly because of limited choice in the pharmacotherapy and high cost of the available stone removal techniques like URS, ESWL, PNL etc., apart from their serious side effects as mentioned above. In addition, herbal remedies are known to contain multiple constituents and acting through multiple pathways, offer therapeutic potential especially in urolithiasis, where multiple target therapy like, antispasmodic, antioxidant, diuretic, pain relieving, is used (15,16). Herbs have, since antiquity, been a source of medicine and their use is based upon local knowledge and belief systems and are a part of the so-called Traditional medicine (TM), often termed as "complementary", "alternative" or "non-conventional" medicine (11). Complementary and Alternative Medicine (CAM) has seen tremendous growth globally and is a

multibillion-dollar industry (17). Easy and economical access to herbal medicine, particularly in poorer countries and for poorer people has led to a remarkable increase in support for, and its usage (18). According to the World Health Organization (WHO), three-quarters of the World population is dependent upon herbal medicine as an economical and affordable source of drugs (15,19). The annual sale of herbal medicine is around 7 billion USD in Europe. The sale of herbal medicine is also increasing in United State. The sale of herbal products increased from $200 million in 1988 to >$3.3 billion in 1997 (20).

The interest in herbal medicine has led to research in the use of herbal medicine for various human maladies including kidney stones (21,22). Investigations have been focused on establishing the active ingredients of herbal extracts that control various steps of crystallization and mechanisms of their actions in inhibiting crystal formation and retention within the kidneys. Both *in vitro* cell cultures and crystallization systems and *in vivo* animal models have been utilized. Several reviews have been published in the past few years on herbal and traditional medicines for urolithiasis (11,23-26), summarizing the results of research articles and commenting on both the potential and challenges. We have recently reviewed the literature about the use of the rat as a model to study herbal treatments for, mostly the most common, calcium oxalate kidney stones (27). We surveyed the approaches utilized by different researchers to prepare herbal extracts and deliver them to rats with experimentally induced hyperoxaluria and CaOx urolithiasis. Most studies involved induction of hyperoxaluria by delivering ethylene glycol (EG) to male rats. Aqueous, alcoholic, or hydro-alcoholic extracts of various plant parts including leaves, stems, fruits, seeds, or a combination thereof were given to determine their efficacy in reducing renal crystal deposition and urinary, oxalate, crystals etc. All studies did not study same anti-urolithic activities of the herbal treatments. Changes in lithogenic factors such as change in urinary pH, urinary excretion of calcium, oxalate and reduction in CaOx crystal deposition in the kidneys were however, considered satisfactory outcomes. Few studies examined the antioxidant and diuretic actions of the herbal extracts and considered them as the basis for herbal treatments' anti-urolithic activities.

Animal model studies can provide the basis for the use of various herbal medicines in treating human diseases. But models can provide limited information. We still need to perform clinical studies to determine the efficacy of drugs. Many studies, albeit limited in numbers, have been performed to determine the value of herbal treatments. We decided to perform systematic review adopting PRISMA guidelines (28) and systematically reviewed PubMed/Medline for the literature, reporting results of various clinical studies of herbal products/medicine for the management of nephrolithiasis/urolithiasis. We present the following article in accordance with the PRISMA reporting checklist (available at https://lcm.amegroups.com/article/view/10.21037/lcm-21-51/rc).

Methodology

Literature search

All publications were retrieved from PubMed in May 2021, with Medical Subject Heading (Mesh) Terms; a new and thoroughly revised version of lists of subject headings compiled by National Library of Medicine (NLM) for its bibliographies and cataloguing. The Mesh term "Urolithiasis" (Mesh Unique ID: D014545) was used with Boolean operator "AND" and other related Mesh Terms "Complementary Therapies/Alternative Medicine; Mesh Unique ID: D000529", "Plant Extracts; Mesh Unique ID: D010936, "Traditional Medicine; Mesh Unique ID: D008519, were used to search all the records available up to date, i.e., "Urolithiasis" AND "Complementary Therapies/Complementary Therapies", "Urolithiasis" AND "Plant Extracts", "Urolithiasis" AND "Traditional Medicine". Endnote software was used to combine and sort out the duplicated articles. Both authors have reviewed the retrieved articles and included only those articles which were fulfilling the following conditions.

Inclusion criteria

Human clinical studies with English language, PubMed Indexed journals, indexed with Mesh terms as stated above.

Exclusion criteria

In vitro studies, mechanistic *in vivo* studies on antiurolithic effect, review articles, studies in languages other than English.

Results

A total of 252 articles were extracted by using Mesh terms "Urolithiasis" AND "Complementary Therapies" Or "Alternative Medicine" in advance search of PubMed (*Figure 1*) based on inclusion and exclusion criteria a

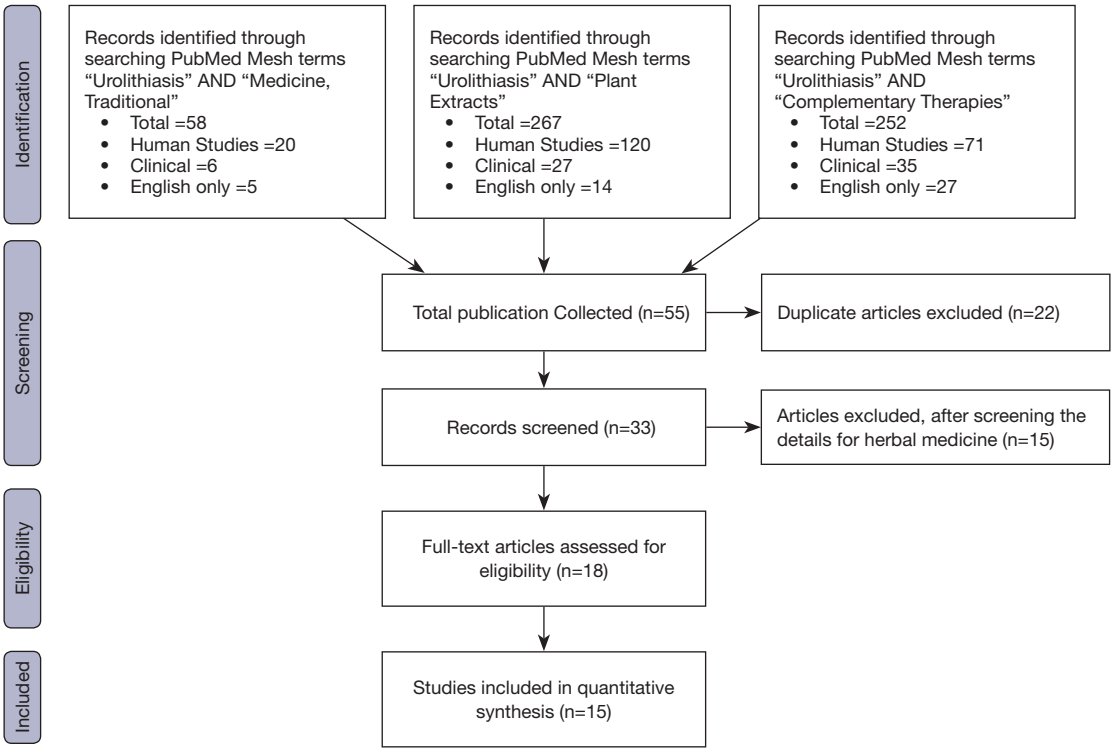

Figure 1 PRISMA 2009 flow diagram.

total of 27 clinical studies, were retrieved. A total of 267 articles were extracted by using Mesh terms "Urolithiasis" AND "Plant Extract" in advance search of PubMed. After selecting human clinical studies, a total of 14 were retrieved. A total of 58 articles were extracted by using Mesh terms "Urolithiasis" AND "Medicine, Traditional" in advance search of PubMed. After selecting human clinical studies, 5 were selected. A total of 55 studies were selected (*Figure 1*).

After combining all the articles and removing the duplicates, a total of 33 articles were left. After thoroughly screening and reading, another 15 articles were excluded after screening for herbal medicine only. A total of 15 publications were included in this systematic review as given in the *Table 1*. It provides information about the referenced study, year of study, common and scientific name of the plant, type of study, sample size, duration and outcome of the study i.e., reduced stone formation, improved lithogenic factors in urine such as calcium, oxalate, citrate, and signs of diuresis. Some studies used commonly available herbal products such as seeds, leaves, stems etc. Other studies used mixtures of specially made concoctions with known as well as unspecified proprietary herbal ingredients.

Consumption of the commonly available bean, *Phaseolus vulgaris* (PV) has diuretic effects and its aqueous extract has been shown to reduce nephrolithic changes in a rat model of calcium oxalate urolithiasis. The effect of an aqueous extract of PV on various urinary factors related to stone formation was investigated in a randomized controlled study of 60 patients with kidney stones (size <10 mm). After 6 weeks of treatment, there was significant increase in urinary volume and potassium and significant decrease in urinary calcium, oxalate and uric acid, as compared to placebo control group, while urinary pH and magnesium increased slightly but not significantly. Renal ultrasound scan also showed significant reduction in stone size compared to placebo control group. Number of stones in the kidneys also decreased indicating their elimination (29).

Black seed (*Nigella sativa*) is a well-known medicinal herb in middle eastern medicine since the days of Hippocrates, Rhazes (al-Razi) and Avicenna (Ibn-Sina). Use of black seed along with water and honey was considered optimal for the treatment of kidney stones. Animal studies showed that aqueous-ethanolic extract of black seeds reduced the number of CaOx crystals deposits in hyperoxaluric rats (44). To determine the ability of black seed to dissolve and eliminate kidney stones a randomized, double blind, placebo-

Table 1 Selected clinical studies of herbal medicines

Reference, year, plant name	Common name	Dose and duration	Study design	Sample size	Urolithiasis risk factor correction				
					Reduction in size or number of stones	Increased urine citrate	Decrease in urine calcium	Decrease in urine oxalate	Diuresis/ increased urinary output
(29), 2020, *Phaseolus Vulgaris*	Beans	Extract. 250 g/2.2 Lit, thrice a week, for 6 weeks	Randomized controlled study	60 patients with kidney stones (size <10 mm)	√		√	√	√
(30), 2017, Unani medicine Renax®, Ingredients (*Cuminum cyminum* seeds, *Raphanus sativus* seeds, *Rheum officinale* seeds, *Citrullus lanatus*, Natrium phosphate and Potassium nitrate)	Renax. Ingredients Cumin, Radish, Chinese rhubarb (Phylum), watermelon	Renax 500 mg tablets twice daily for 3 weeks	Case control, randomized, double blind clinical study	100 patients, 50 of the test drugs and the 50 of control drug	√				
(31), 2018, *Nigella sativa L*.	Black seed	(500 mg) black seed capsule or placebo two times per day for 10 weeks	Randomized, triple-blind, placebo-controlled, clinical trial	60 patients with renal stones	√				
(32), 2012, *Agropyrum repens*	Couch grass	100 mg of dry extract, 5-month follow-up period	Prospective randomized controlled study	50 patients with nephrolithiasis	√	No effect	No effect	No effect	
(33,34), 2011, Cystone®	Poly herbal formulation	2 tablets twice a day, two phase study, 6 weeks and 52 weeks	Two phased study Randomized double blind and open label	10 recurrent cystine kidney stone formers and 10 calcium stone formers	Increase in stone burden	No effect	No effect	No effect	
(35), 2007, *Citrus limon*	Lemonade	Noncaffeinated fluid, with the exception of l emonade or other citrus drinks. For 5 days	Prospective cross-over trial	21 stone-forming patients, for 5 days		No effect	No effect	No effect	√
(36), 2013, *Rhizoma alismatis, Poria cocos Wolf, Polyporus umbellatus Fries, Rhizoma Atractylodis Macrocephalae* and *Ramulus Cinnamomi Cassiae*	Wu-Ling-San (WLS), Poly herbal powder	2 gm WLS formula three times daily for 1 month	Prospective, randomized and placebo-controlled clinical trial	39 recurrent CaOx stone patients were enrolled, and 28 patients completed the study					√
(37), 2003, *Vaccinium macrocarpon*	Cranberry juice	500 mL of cranberry juice diluted with 1,500 mL tap water for two weeks	Randomized cross-over trial	20 men with no history of kidney stones		√		√	

Table 1 *(continued)*

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Reference, year, plant name	Common name	Dose and duration	Study design	Sample size	Urolithiasis risk factor correction				
					Reduction in size or number of stones	Increased urine citrate	Decrease in urine calcium	Decrease in urine oxalate	Diuresis/ increased urinary output
(38), 2006, *Phyllanthus niruri*	Child Pick-A-Back, Gale Of Wind, Carry Me Seed	Uriston, a P. niruri extract (2 gm daily) for at least 3 months (group 1)		150 patients with renal stones, who received 1 to 3 extracorporeal shock wave lithotripsy	√				
(39), 2004, *Phyllanthus niruri*	Child Pick-A-Back, Gale Of Wind, Carry Me Seed	450 mg capsules, three time a day) or placebo (n=36) for 3 months	Randomized placebo control trial	69 calcium stone forming (CSF) patients		√			
(40), 2008, Ayurvedic drug "Herbmed", Ingredients *Crataeva nurvala* and *Musa paradisiaca*	Varuna and banana stem	2 Capsule of herbmed® two times a day	Prospective randomized, double-blind, placebo control trial	77 kidney stone patients were treated for 3 months	√				
(41), 2001, *Orthosiphon grandiflorus*	Java tea, kidneys tea plant	2 cups of Java tea daily using tea bags containing 2.5 g of tea leaves	Randomized control clinical trial	Forty-eight rural stone formers for a period of 18 months	√				
(42), 2011, Traditional Chinese medicines preparation containing 11 herbs	A decoction of 11 herbs	150 mL of decoction. twice daily for 7 days	Randomized control clinical trial	Sixty consenting patients with renal calculus					
(43), 2012, Seeds of *Celosia argental*	Sitivaraka, Cock's comb	Sitivaraka seed preparation (dose: 10 mg/kg body weight 3 times daily) for 1 month follow up for 6 months	Randomized, controlled, open-label trial	44 patients with renal stones	√			√	

controlled trial was performed. 500 mg of black seed powder was encapsulated. Sixty patients, 30 with intervention and 30 placebo controls, with kidney stones larger than 5 mm were recruited for the study. Patients used two capsules/day for 10 weeks. Sonography was used to determine the stone presence and size before and after the treatment. Stones were eliminated by 44.4% of the stone patients receiving the medicine. 57.6% of stone patients on medicine showed a decrease in stone size, while in the placebo group, 15.3% of the patients purged their stones completely, 11.5% had reduction in stone size, 15.3% had increase in stone size, and 57.6% had no change in their stone size. Black seed extract was also shown to contain antioxidative activity (31).

Ayurvedic medicine describes the use of *Celosia argentea* (Cock's Comb) seeds, the Sitivaraka, for kidney stones. A randomized, controlled, open-label pilot study was carried out to compare the efficacy of Sitivaraka with potassium citrate. Forty-four patients with stones approximately 8 mm in size based upon ultrasonography were selected. A group pf 21 patients received 10 mg/kg body weight seed preparation, three times a day. Another group of 23 patients received potassium citrate at 0.25 mL/kg body weight. A number of serum and urinary factors were determined at 1, 3 and 6 months. Stone size was determined at 3 and 6 months. The herbal medicine led to reduction in serum PTH, while citrate group didn't produce any significant change. Similarly, a significant reduction of stone size was observed after 3- and 6- months use of Sitavirika but no significant reduction was produced by citrate group. Urinary oxalate and uric acid however increased at 6 months (43).

Phyllanthus niruri is a common tropical plant with many medicinal uses. Tea made from whole plant has been traditionally used in many countries including Brazil for ailments such as kidney stones (45). In a randomized placebo control clinical study, sixty-nine patients with calcium stone disease were given capsules of 450 mg of lyophilized 2% aqueous extract, three times a day for 3 months. Serum and urine were analyzed for a number of biochemical factors. Overall, there were no significant differences between various biochemical parameters, before and after the treatments. However, there was a significant reduction in urinary excretion of calcium in hypercalciuric patients. Another prospective study was performed to determine the effect of *P. niruri* consumption on various lithogenic factors in patients with kidney stones (46). Fifty-six stone patients, with variety of abnormalities including hypercalciuria and hypocitraturia (42.8%), hyperoxaluria (8.9%), hypernatriuria (60.7%) were included in the study. The patients were advised to drink, twice a day for 12 weeks, a tea made by infusing 4.5 g of *P niruri* extract in 250 ml of boiling water. A number of urinary and serum elements were measured. There was a significant increase in urinary potassium, magnesium/creatinine ratio, and potassium/creatinine ratio from baseline to washout. There was a significant reduction in urinary oxalate in hyperoxaluric patients and uric acid in hyperuricosuric patients. Number and size of stones reduced in 67.8% patients. No alteration in size or number of stones was seen in 17.8% of the patients. 14.3% of patients showed an increase in upper stones. Some patients passed stones spontaneously while others reported sand in the urine.

In another study of *P. niruri*, capsules containing 225 mg of dried leaf extract mixed with, 152 mg magnesium stearate and 2 mg pyridoxine hydrochloride (vitamin B6), were given to 40 stone patients (47). The patients received one capsule twice a day for 3 months. Non-contrast enhanced computer tomography (CT) was used to determine the size and location of stones. Patients with ≤3 mm stones, located in middle or upper calyx became stone free after 3 months. Stones 3–4 mm in size showed a reduction in size. Bigger stones did not show any change in size.

A case control, randomized, double blind clinical study was performed using Unani herbal medicine (Renax, containing *Cuminum cyminum* seeds, *Raphanus sativus* seeds, *Rheum officinale* seeds, *Citrullus lanatus*, Natrium phosphate and Potassium nitrate), in comparison with allopathic medicine (Spironolactone + Furosemide) to treat urolithiasis in 100 kidney stone patients, where Renax completely eliminated kidney stones in almost 50% of the patients while success rate of allopathic medicine was 18% (30).

Cystone®; an Ayurvedic poly herbal proprietary medicine is claimed to possess antiurolithic properties. According to the makers of the drug (http://himalayahealthcare.com/products/cystone.htm), it prevents stone formation by reducing supersaturation and disintegrates existing stones by acting on the "mucin" that binds the crystals together. The drug is available both as a syrup and tablet. Two products contain slightly different ingredients. Experimental *in vivo* ethylene glycol rat model of urolithiasis studies has shown Cystone's antiurolithic properties by effecting crystallization and crystal retention within the kidneys. The polyherbal formulation attenuates hyperoxaluria-induced oxidative stress and prevents subsequent deposition of calcium oxalate crystals and renal cell injury in rat kidneys (48). Rat study used Cystone syrup. The 5 mLs of the syrup contain extracts of Gokshura (Tribulus terrestris L.) 91 mg; Punarnava

(Boerhavia diffusa L.) 67 mg; Pashanabheda (Saxifraga ligulata Murray) 53 mg; Mustaka (Cyperus rotundus L.) 42 mg; Satavari (Asparagus racemosus Willd.) 21 mg; Kulattha (Dolichos biflorus L.) 21 mg; Ushira (Vetiveria zizanioides (L.) Nash) 21 mg; Karchura (Curcuma zedoaria Roxb.) 14 mg; and poweders of Trikatu (Mixture of Ginger, Piper nigrum, Piper longum) 14 mg; Saindhava (Rocl Salt) 50 mg; Suvarchika (Black Salt) 42.5 mg; Yavakshara (Hordeum vulgare) 5 mg; and Narasara (Ammonium Chloride) 2.5 mg (48).

The 2-phased; short (6 weeks) randomized double-blinded and long (one year) open label clinical trials were carried out on 10 calcium containing kidney stone patients, and 10 cystine stone patients. Patients received two 2 tablets of Cystone two times a day. Each tablet contains Shilapushpha (*Didymocarpus pedicellata*) 130 mg, Pasanabheda (*Saxifraga ligulata Syn. Bergenia ligulata/ciliata*) 98 mg, Manjishtha (*Rubia cordifolia*) 32 mg, Nagarmusta (*Cyperus scariosus*) 32 mg, Apamarga (*Achyranthes aspera*) 32 mg, Gohija (*Onosma bracteatum*) 32 mg, Sahadevi (*Vernonia cinerea*) 32 mg, Shilajeet (Purified) 26 mg, and Hajrul yahood bhasma 32 mg. There were no significant differences in urinary chemistries or stone burden in both calcium oxalate and cystine stone formers (33,34).

Similarly, in a prospective, randomized and placebo-controlled clinical trial on 28 patients another polyherbal formulation; Wu-Ling-San (WLS) formula was tested for its antiurolithic effect on recurrent stone former patients. Patients were given 2 grams of WLS formula three times daily for 1 month. WLS significantly increased the urine output as compared to placebo group, without any side effects or change in electrolyte imbalance (36).

Another Ayurvedic formulation "Herbmed", which is made up of *Crataeva nurvala* (Varuna) and *Musa paradisiaca* (banana stem), was tested in prospective randomized, double-blind, placebo control trial on 77 Kidney stone patients. Patients were given 2 capsules of Herbmed® two times a day for 3 months. In group A (stone size 5–10 mm), there was 33.04% reduction in the size of calculi in the active arm (Herbmed) while there was a 5.13% increase in the same group in the placebo arm (P=0.017). In the other group B (patients containing stone with size more than 10 mm), there was an 11.25% reduction in the active arm and a 1.41% reduction in the same group with placebo. Herbmed showed a promise for the management of upper urinary-tract calculi, especially renal calculi. It helped to dissolve renal calculi and facilitate their passage. In addition, it also helped in reduction of pain due to renal/ureteric calculus disease (40).

In another randomized control clinical trial, the protective effect of traditional Chinese preparation containing *Rhizoma*, *Rehmannia preparata* and supplements of a few traditional Chinese medicinal herbs, was investigated by Sheng *et al.*, on sixty consenting patients with renal calculus who underwent Extracorporeal shock wave lithotripsy (ESWL) treatment. The whole preparation comprises of 11 herbs with the following composition. Common yam rhizome (Rhizoma *Dioscoreae*, *Shanyao*, 24 g), *Rehmannia* dried rhizome (Radix Rehmannia, Shengdi, 15 g), Asiatic Cornelian cherry fruit *Cornus officinalis* (Fructus Corni, Shanzhuyu, 9 g), dried rhizome of *Alisma orientale* (Rhizoma Alismatis, Zexie, 9 g), Indian bread (mushroom *Poria*, Fu ling, 9 g), Root-bark of *Paeonia suffruticosa* (Cortex Moutan, Danpi, 9 g), roots of *Astragalus membranaceus* (Radix Astragali, huangqi, 18 g), dried plant *Plantago asiatica* (Herba plantaginis ceqiancao, 9 g), rhizome of *Imperata cylindrica* (Rhizoma Imperata, Baimaogen, 15 g), *Herba lysimachiae* (Christina loosestrife, Jin qian cao, 15 g) and spores of climbing fern *Lygodium haijinsha* (Spora lygodii, Hai Jin Sha 4.5 g). Each preparation was decocted to 300 ml and each participant received 150 mL orally twice daily. The results of the study indicate that the medication group has a significantly higher stone free rate after ESWL, as compared to control group. Also, the preparation significantly reduced the need for re-ESWL in the treatment group. decoction significantly reduced the renal tubular damage induced by ESWL and can shorten the recovery time of renal tubules in human subjects. The preparations exert their effects by improving renal resistance to oxidative stress, ameliorating circulatory disorders, and interfering with local inflammation (42).

Agropyron repens (Couch grass) is native of temperate Europe to Central Asia and traditionally used as soothing diuretic and for calming pain and spasm in the urinary tract (49). It's antiurolithic effect has been investigated in the animal models where its mixture with other herbs prevents deposits of calcium oxalate crystals and of microcalcifications in the kidney (50). In a prospective randomized controlled study of 50 patients with urolithiasis in the Hemodialysis Unit, Ospedale S. Donato, Arezzo, Italy, 100 mg of dry extract of couch grass, significantly reduced the total number of stones as compared to the potassium citrate group. No significate effects were noted in the two groups with respect to urinary oxalate, citrate calcium excretion and urinary pH (32).

Lemon (*Citrus limon*) juice has shown not only an antiurolithic effect but also improve renal function as compared to the disease control group in the ethylene

glycol rat model of urolithiasis (51). A prospective cross-over trial was conducted on 21 stone forming patients, to determine the effect of lemonade intake on a change in urinary pH and improvement of urinary stone risk factors compared with potassium. The results of the study showed that lemonade did not provide improvements in urinary citrate or pH levels as compared to citrate, however, it increased urine output as compared to potassium citrate group (35).

Vaccinium macrocarpon commonly known as American cranberry belongs to the family Ericaceae, has shown antiurolithic activity (52) and have interesting role in women with recurrent urinary tract infections and other health benefits (53). A randomized placebo control cross-over trial was conducted on men with no previous history of kidney stones, to see if cranberry juice reduces the risk factor for CaOx kidney stones. The study participants were given 500 mL of cranberry juice diluted with 1,500 mL tap water for two weeks and at the end of the study, the data showed that ingestion of cranberry juice significantly and uniquely decreased oxalate and phosphate excretion and increased citrate excretion, In addition, there was a decrease in the relative supersaturation of calcium oxalate, which tended to be significantly lower than that induced by water alone (37).

Java tea, infusion of finely powdered fresh leaves of the *Orthosiphon grandiflorum* (OG) has been reported to reduce the crystals deposition in the laboratory animals (54). In a randomized control clinical trial, results of the two cups of Java tea daily, each teacup made from an OG tea bag (contained 2.5 g dry wt.) were compared to the sodium potassium citrate, in forty-eight renal stone formers. Stones were identified by ultrasonography. After a period of 18 months. rates of stone size reduction per year (ROSRPY) from the recorded ultrasound images showed that the mean of ROSPRY of the java tea group was lower than sodium potassium citrate. In addition, 90% of the patients on Java tea reported relief from initial clinical symptoms such as, back pain, headaches and joint pain. while fatigue and loss of appetite were observed in 26.3% of sodium potassium citrate group (41).

Discussion

Formation of kidney stones is a complex process starting with changes in the urinary environment (2,55), involving a variety of participating ions and macromolecular crystallization modulators (56-59). Urinary supersaturation can change throughout the day leading to the formation of crystals which are regularly passed via urination. Abnormal conditions lead to the formation of larger in number and size and aggregated crystals which do not move with the urine and plug the tubules. Some of the stones develop on the plaque of crystals formed by plugging the terminal collecting ducts (60,61). In idiopathic CaOx stones, immunological responses of various renal cells, epithelial as well as vascular, lead to the formation of a sub-urothelial foundation of biological apatite, called Randall's plaque (RP), on renal papillary surface (61). Most idiopathic kidney stones develop attached to such plaques.

Results of experimental *in vitro* and *in vivo* studies; solution chemistry, cell culture and rat models, have shown that many of the herbal medicines influence stone formation by controlling crystal formation and their subsequent retention within the kidneys (55,62,63). Cell culture and animal model studies indicate that exposure of renal epithelial cells causes production of reactive oxygen species (ROS) by the renal epithelial cells and may be responsible for renal injury (7). When studied, clinical studies have also reported development of oxidative in the kidneys of stone (7,64). Production of various crystallization modulators which are involved in inhibition of crystal nucleation, growth and aggregation is also regulated by the ROS (65). ROS also regulate osteogenesis in both the renal tubular epithelial and vascular endothelial cells (66). Osteogenesis may play a significant role in the formation of Randall's plaque. Our studies have shown that specific antioxidants reduce hyperoxaluria, and CaOx crystal deposition associated injury (67) in both animal models and tissue culture studies.

Clinical investigations into herbal treatments of stone disease generally followed protocols that have been in practice since ancient times. Patients were advised to take the herbal extracts as teas, or juices, or lyophilized powders in capsule or tablet forms or simply consuming the seeds. Many of the medicines were a mixture of two or more herbs and even mixed with ingredients such as vitamins. Medicines were taken two or three times a day for a specified period. Patients were selected on the basis of stone presence detected by ultrasound, X-ray or computed tomography (CT) scanning. A variety of urinary and serum lithogenic factors, including calcium, oxalate, uric acid, creatinine etc., the elements with known impact on stone formation, were investigated before and after the treatments. All studies examined change in size and or movement or elimination of kidney stones. Few studies looked for change in urinary

volume and renal functions. A few studies determined urinary citrate and pH.

Clinical studies have mostly been concerned with determining change in the stone burden, i.e., reduction in number and size of kidney stones. Small stones were eliminated and large stones became smaller. Most studies reported herbs to have diuretic effects. Kidney stones are normally located within the renal pelvis and ureters. Increased urinary volume is most likely responsible for stone passage and their elimination. What caused reduction in size is unclear. Thus, even for studies with positive results, we do not understand how does a specific herbal treatment work.

Some of the treatments have been shown to increase urinary excretion of citrate and decrease that of urinary calcium, both impacting urinary supersaturation. Herbs inhibit crystal nucleation, growth and aggregation thereby preventing an increase in size of the embryonic stone and retention within the narrow renal tubules. Herbal treatments increase urinary volume promoting urinary flow through renal tubules and elimination of the incipient stone before it becomes too big to move and occludes the tubular lumens. They may stop the formation of reactive oxygen species in the kidneys and resulting injury to the renal epithelium which is known to promote crystal attachment and their retention within the kidneys.

Conclusions and future direction

Idiopathic CaOx kidney stone formation is a common urological disorder and generally starts as interstitial or tubular deposition of CaP within the renal papillae. Once these CaP deposits become exposed to pelvic urine, as Randall's plaques or plugs, they act as foundations for the formation of stones through continuous deposition of, mostly, CaOx crystals. Recurrency is common and the goal of treatments is to eliminate the existing stones and stop the formation of new stones. Clinical studies indicate that most herbal treatments have diuretic effects and help passage of at least small stones. Results of animal model studies would suggest that herbal treatments interfere with crystal deposition in the kidneys. Cell culture studies indicate that hyperoxaluria and CaOx crystals are injurious to renal tubular epithelial cells through the production of reactive oxygen species. Reactive oxygen species induce osteogenesis leading to the formation of plaques. Injured cells are prone to crystal adherence which promotes crystal retention within the renal tubules and may be responsible for plugging of the terminal collecting ducts providing a base/nidus/platform for stone development. Many of the herbs have antioxidant properties and most probably interfere with crystal retention and deposition by preventing injury to the renal tubular epithelium. Results of *in vitro* studies indicate that certain herbs stop the nucleation, and/or growth and/or aggregation of the CaOx crystals. These properties would influence crystal retention within the renal tubules.

Thus, results of experimental and clinical studies indicate that herbal treatments can impact stone formation through a variety of means and in general can produce positive outcomes. However, results of most clinical studies do not allow for understanding mode of action of the herbal treatment, which is important to determine their ability to stop recurrence. Studies follow different protocols for the preparation of the herbal extracts and delivery and look at different outcomes. Most studies do not identify the stone type that is being treated. There is limited knowledge of the bioactive components of the herbs and their safety profile. Some of the herbal medicines can be injurious to the kidneys (25,26). The effect of extraction and delivery protocol on the active ingredients is not well known. Do the ingredients determined to be active in *in vitro* studies, actually end up in the kidneys? We have suggested that clinical studies should include following measures (27). Future studies should determine the active compounds present in the herbal preparations and whether those compounds reach the kidneys and urine and are nontoxic and improve renal structure and function. Ingredients of polyherbal treatment should be individually tested for their non-toxic nature. Researchers should agree upon the outcomes to be investigated to determine the efficacy of a treatment. Is treatment stone specific or universally efficacious against all type and forms of stones. The outcomes should, in addition to change in stone size and presence, include change in urinary chemistry such as calcium, oxalate, citrate, pH and reactive oxygen species. Urine should also be analyzed for its crystallization inhibitory potential as well as crystalluria.

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