

Formulation of Ayurvedic Medicines and Extracts of Medicinal Plants as an Alternative Therapeutic Treatment Option for Nephrolithiasis

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Abstract

The incidence of nephrolithiasis, commonly known as kidney stone, is increasing worldwide with significant health and economic burden. Approximately 2 million people every year in India are affected by kidney stones. It affects all ages, genders, and races, but between the ages of 20 and 49 years, it affects most frequently in men than women. Different types of stones include calcium stones, cysteine stones, struvite or magnesium ammonium phosphate stones, uric acid stones, and drug-induced stones. This review article provides information about general pathophysiology, epidemiology, clinical presentation, and pharmacological treatment, which includes ayurvedic and herbal medicines for nephrolithiasis. Further understanding of the pathophysiological link between nephrolithiasis and systemic disorders is necessary for the development of new therapeutic options.

Keywords: Allopathic management, ayurvedic treatment, calcium stones, nephrolithiasis

INTRODUCTION

The kidney is an essential organ of the human body which performs various functions, i.e., regulates blood pressure by the renin-angiotensin-aldosterone system, controlling reabsorption of water, level of sodium, potassium, bone minerals, hemoglobin, and maintaining the correct pH of body fluid as well as chemical balance of the body. The most important function of the kidney is filtration and excretion of metabolic waste products in urine.^[1] Waste products of nitrogenous end products such as urea, uric acid, creatinine, and other toxins are not excreted from the body in kidney failure and accumulate in the body or organ in the form of crystals. These crystals attract other elements together to form a solid cluster that results in a kidney stone. The formation of the kidney stone is a complicated process that includes supersaturation of urine and various physicochemical changes. During supersaturation, nucleation occurs in the initial process of crystal formation in the urine. Moreover, a small number of ions, atoms, or molecules become forming a site, upon which additional particles are deposited as the crystal grows. The risk factors for crystallization include the level of urinary

saturation to the stone-forming constituents which include uric acid, calcium, phosphorous, cysteine, oxalate, and low urinary volume. After the crystal nucleation, the kidneys from the supersaturated urine and crystals present in the urine clump together to form a small hard mass of stone called crystal growth and this process is known as crystal aggregation.

Kidney stones are mainly formed in the kidney called the renal pelvis.^[2] It is a common cause of morbidity worldwide with an economic burden. It is the third most common disease followed by urinary tract infection (UTI) and prostate diseases.^[3] In the United States, the lifetime predominance of kidney stones is 12% among men and 7% among women.^[4] Depending on the

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location of the stone in the kidney whether it is located in the ureter, urinary bladder, or kidney, the symptoms developed. At the primary stage, there is no symptom of stone formation, but in later stages, signs and symptoms of nephrolithiasis develop which include flank pain (pain in the backside), renal colic (intense cramping pain), obstructive uropathy (urinary tract disease), hematuria (bloody urine), blockage of urine flow, hydronephrosis (dilation of the kidney), and UTIs. Nausea and vomiting result in these associated conditions suffering from the stone disease. In this manner, the treatment and time lost from work include the significant cost on the quality of life and the country's economy.^[2]

METHODS

We reviewed published studies on nephrolithiasis epidemiology, type of kidney stones, clinical presentation, and current allopathic and ayurvedic treatment for kidney stones. Our data collection strategy involved using a group of search terms in multiple languages. Search terms included the incidence of nephrolithiasis, categorization of nephrolithiasis, signs and symptoms, pathological conditions diagnosis, and pharmacological or surgical treatment of the stones. The literature database available in various peer-reviewed national and international journals such as PubMed, Scopus, NJLM, Medline, and Academic Journals Database was carried out electronically for the identification of potential studies related to nephrolithiasis. A professional network of scientists, researchers, and patent databases of the National International Intellectual Property was also considered.

RESULTS

Epidemiology of kidney stones

Nephrolithiasis is a worldwide issue that affects the globe in all geographical regions. Over the past 5 decades, the prevalence and incidence of nephrolithiasis is reported to be increasing across the world. Throughout the globe, the risk rate of epidemiology in Saudi Arabia is highest (20.1%) followed by the USA (13%–15%), Canada (12%), and Europe (5%–9%).^[5] About 12% of the total population is affected with kidney stones throughout their lifetime at some phases. It influences all ages, genders, and races, but between the ages of 20 and 49 years, It affects most frequently in men than women.^[2] The adults in the Western region have a higher incidence of nephrolithiasis as compared to the Eastern region of the world. Estimated 2.9 lakhs cases of nephrolithiasis were diagnosed including children below the age of 3 years in the year 2008. Every year in India, approximately 2 million people are affected by kidney stones. The rate of kidney stones is higher in some parts of the country, such as Maharashtra, Gujarat, Delhi, Rajasthan, Punjab, Haryana, and some other parts of the North Eastside. Approximately half of the population in India affected with nephrolithiasis may be suffered from kidney damage or loss of kidney function. A high occurrence rate is associated with dehydration and a hot atmosphere. The prevalence and

frequency of kidney stone disease are increasing with confined alternatives of effective drugs all over the world.^[5]

Types of nephrolithiasis

Depending upon the composition of abnormal urine constituents, nephrolithiasis is categorized into five types which are as follows:

- a. Calcium stones
- b. Cysteine stones
- c. Magnesium ammonium phosphate stones or struvite stones
- d. Uric acid stones or urate
- e. Drug-induced stones.

Calcium stones

Approximately 80% of kidney stones consist of calcium oxalate and calcium phosphate. The percentage of pure calcium oxalate stone is 50%, calcium phosphate is 5%, and a combination of both, i.e., calcium oxalate and calcium phosphate, is 45%. Hydroxyapatite and brushite (calcium hydrogen phosphate) is the main component of calcium stones.^[2] Oliguria, low urinary citrate excretion, and hypercalciuria associated with hypercalcemia like excessive Vitamin D and hyperparathyroidism are the known risk factors for the development of calcium stones. Another risk factor for the formation of calcium oxalate stone is the presence of excessive oxalic acid in the urine due to genetic disorders of oxalate metabolism and bowel disease while the risk factor for the formation of calcium oxalate stone is alkaline urine.^[6]

Cysteine stones

It is a hereditary disorder of the transportation of cysteine and amino acid which results in excretion of excessive amounts of cysteine in urine and it occurs in <2% of all types of stones. More than 600 millimoles of insoluble cysteine are excreted per day by the people who are homozygous for cystinuria.^[2,6]

Magnesium ammonium phosphate stones or struvite stones

It is also called triple phosphate stones or infectious stones. It occurs in approximately 10%–15% of all the stone types. This type of stones is formed in the presence of urinary tract disease with urease-producing bacteria. The pathogen most commonly included is *Proteus mirabilis* while less common pathogens include *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter*.^[2] As UTI is more common in women, so these types of stones are three times more common in women than men. This type of stone may be big enough as they fill the area at the center of the kidney and grow more rapidly.^[7]

Uric acid stones or urate

Uric acid stones occur to an extent of 3%–10% of all stone types and this type of stones developed in those patients who have a history of gout. High purine diet, especially the diet rich in animal protein like fish and meat; low urinary pH (pH < 5.05); and oliguria may increase the risk of uric acid stone formation. This type of stone occurs more frequently in men than women.^[2]

Drug-induced stones

Various drugs are used to treat various disease conditions that can cause kidney stones. Drug-induced calculi can be formed by the urinary supersaturation of the drug or its metabolites.^[8] These types of stones occur to the extent of 1% triamterene, guaifenesin, atazanavir, and sulfa drugs.^[2]

Clinical presentation of nephrolithiasis

As kidney stones are mostly asymptomatic, but in later stages, it causes symptoms which are as follows:^[5,9]

- Severe flank pain radiating to the groin (presence of a stone in the urinary system), frequent urination (e.g., once every hour or two), lower abdominal cramps, despite a severe sense of urgency, painful discharge of urine caused by spasm of the bladder and urethra.
- Extreme pain originates from the flank region. The pain usually occurs only on the side of the kidney stone and does not cross over to the other side
- Nausea and vomiting
- Blood infection (septicemia) and blood in the urine (hematuria)
- UTI (maybe as a result of struvite stone or infection)
- Chills, fever, or pus formation (commonly associated with infection stones).

Management of nephrolithiasis

Medical care for the kidney stone is initiated after the diagnosis of the kidney stone, which includes the pharmacological treatment or surgical removal of the stones depending upon the type, location, size, shape, and other pathological conditions.^[9] A high amount of oral fluid intake must be advised in all kidney stone patients.^[10] According to the cohort study, approximately 2.5 L/day of urinary volume is associated with reduced urinary calcium oxalate saturation and reduction in kidney stone reoccurrence. Based on the literature, fluid intake such as orange juice is also effective in reducing urinary supersaturation with calcium oxalate and increased excretion of citrate.^[11]

Treatment of kidney stone patients in emergency conditions includes analgesics, antiemetics, and intravenous fluids.^[12] Several scientific strategies have been attempted to defeat colic (severe pain), which can be rationalized as ureteral spasm, even though narcotics including morphine, codeine, and meperidine are effective in suppressing pain but because of their negative effects such as dependence and disorientation effect. In view of these negative effects, physicians prescribe non-steroidal anti-inflammatory drugs (NSAIDs) including diclofenac, ibuprofen, and aspirin to handle the pain of renal colic. Out of these agents, ketorolac deserves special attention. According to one emergency department study, the effects of ketorolac were superior to the effects of meperidine.^[13]

NSAIDs and opioids are both categories of drugs used as analgesics. NSAIDs are known to cause GI and renal side effects whereas opioid analgesics are known to cause nausea and vomiting along with constipation, retention of urine, and respiratory depression. In an earlier published meta-analysis,

NSAIDs were better than opioids in terms of requiring lesser side effects. According to the European Association of Urology (EAU) guidelines, NSAIDs and intravenous opioids as the first-line treatment for renal colic pain during urolithiasis. Intravenous fluid is necessary to correct the reduced volume that may occur from vomiting, and it may also increase the chances of stone passage by increasing the production of urine. If the size of the stone is more than 5–6 mm, then there are fewer chances to pass the stone spontaneously.^[14]

Pharmacological treatment

Recurrent stone former patients need pharmacological treatment to treat the specific types of kidney stones, namely calcium stones, struvite or magnesium ammonium phosphate stones, uric acid stones, cysteine stones, and drug-induced stones, which are as under:

Treating calcium stones

In recurrent calcium stone formers, thiazide diuretics and their analogs are commonly used to lower the excretion of calcium in the urine. Thiazide diuretics are adequate in reducing the recurrence of kidney stones in several randomized controlled trials.^[15] The ideal impact of thiazides is achieved with a reduction in dietary sodium that is associated with a reduction in urinary calcium excretion. Thiazide diuretics are known to cause hypokalemia which can lead to hypocitraturia. Therefore, potassium citrate or amiloride supplementation is used to treat hypocitraturia.^[16]

Treating uric acid stones

Alkalinization of urine is necessary for the treatment of uric acid stones because uric acid is more soluble in alkaline urine. Diet less in purine is advised for patients who have increased blood uric acid levels. Allopurinol which is a xanthine oxidase inhibitor is the drug of choice for the treatment of calcium oxalate and uric acid stones. It was shown that allopurinol reduced the urate acid level and stone recurrence. It reduces urate levels in urine by inhibiting uric acid production from xanthine and hypoxanthine.^[9] Combination therapy of allopurinol with a thiazide diuretic is more effective in reducing stone recurrence as compared to single therapy with allopurinol. Supplementation therapy with bicarbonate or citrate (especially potassium citrate) is also effective in recurrent calcium or uric acid stone formers.^[17]

Treating cysteine stones

The aim for treating cysteine stones is to decrease the amount of cysteine in urine and solubility of cysteine is increased in urine. Patients with cystinuria should need to drink 3–4 L per day to achieve a urine cystine concentration of less than 243 mg/L and also educate the patient regarding diet restrictions (low meat protein, low sodium). Solubility of cysteine is increased with the alkalinization of urine by the oral administration of potassium citrate in the dose of 20 meq twice daily. Sodium citrate or sodium bicarbonate is the second-line choice of drug to increase the excretion of cysteine. Acetazolamide has also been prescribed to raise the urine pH. Cysteine-binding drugs are

recommended to those patients who are resistant to increased fluid intake and urinary pH and dietary restriction of salt and protein. D-penicillamine and alpha-mercaptopropionyl glycine or tiopronin are the drugs that are currently prescribed. Tiopronin is the first line of drug because the adverse effects associated with it are slightly lower as compared to D-penicillamine. Captopril is an angiotensin-converting enzyme that is also used as it is associated with increased solubility of cysteine.^[18]

Treating struvite stones

As the struvite stones are also called infection stones. This type of stone is treated by antibiotic therapy which may also slow down the growth of stone. For choosing the particular antibiotic therapy, a culture of stone material is necessary. However, the surgical removal of the struvite stone is the preferred treatment. Diet less in sodium also helps to prevent struvite stones.^[19]

Ayurvedic treatment for kidney stones

Ayurveda has mentioned various methods of treatment of kidney stones by using the guideline of not only treating the disease but also preventing the recurrence of the disease. As overall population has a progressively positive perspective on plant-based drugs mostly as compared with modern medicine since they are evident as being safe and natural. The standard treatment of Ayurveda is to dilute the urine as the stone is formed due to concentrated urine. Increased fluid intake may help prevent the formation of stones by diluting urine concentration, decreasing urine acidity.^[20]

Ayurvedic drugs

Ayurveda illustrates various herbs having stone-breaking activity. Plants with stone-breaking agents are as follows:

Pashanabheda (Bergenia ligulata)

It is a well-known ayurvedic herb that belongs to the family Saxifragaceae, which is mainly used as a diuretic and lithotropic.^[21] The marketed formulation used as Pashanabheda is *Bergenia ligulata* (rhizomes), *Kalanchoe pinnata* (leaves), and *Coleus aromaticus* (leaves). These species are found in the vast majority of proprietary drugs, for example, Nieren syrup and capsule, Calcure tablets, Kid Clear capsule, Nefrol capsule and syrup, and Urotone tablet.^[22]

Varuna (Crataeva nurvala)

Crataeva nurvala is a deciduous tree that belongs to the family Capparaceae. Having the anti-lithogenic and anti-crystallization property, this drug prevents the formation of kidney stones.^[23,24]

Yava-Kshara (alkali preparation of barley)

In Ayurveda, Kshara is the most commonly used alkali herbal preparation obtained from the plant *Hordeum vulgare*. Yava-Kshara prevents the formation of renal calculi by neutralizing the acidic medium. As the pH of Yava-Kshara is 11.73, therefore it helps in the breakdown of the calculi and changes the pH of the urine.^[25]

Herbal extract treatment

As herbal extracts showed their effects such as adaptogenic, antimutagenic, and modification of the immune system, so

most people now preferred herbal treatment for the removal of kidney stones. Herbal drugs are free from any side effects; however, the treatment needs time to show their effects.^[26]

Trigonella foenum-graecum

Trigonella foenum-graecum, commonly known as fenugreek or methi, belongs to the family Fabaceae. Seeds and leaves of fenugreek are used across the world for their antidiabetic action, anticancer, antimicrobial, anti-urolithiasis, and antioxidant properties. According to the study conducted by Shekha *et al.*, the seeds of the fenugreek decrease the amount of calcium oxalate in the kidney, which reduces the formation of kidney stones.^[27]

Asparagus racehorses

Asparagus racehorses, commonly known as Shatavari or Shatamuli, belongs to the family Asparagaceae. The dried roots of the plant showed effects such as galactogogue effect, antitussive, antibacterial, antisecretory, anti-ulcer, antiprotozoal, anti-hepatotoxic, antioxidant, antineoplastic, adaptogenic, and anti-lithiatic effects. According to a preclinical study, the ethanolic extract of *Asparagus racehorses* reduces the elevated level of serum creatinine and increased the level of magnesium in urine.^[28]

Viratarvadigane

Viratarvadigana, commonly known as *Celosia argentea*, belongs to the family Amaranthaceae. The leaves and stem of the plant are used in the treatment of diarrhea, eye troubles, sore mouth, and urinary disorders. According to the Indian system of medicine, the aqueous decoction of *C. argentea* is utilized for the disintegration and passing of stones.^[26]

Boerhaavia diffusa

Boerhaavia diffusa, commonly known as punarnava herb or santhi, sanadika, gonajali, sanadika, sothaghna, etc, belongs to the family Nyctaginaceae. The major ingredients of punarnava herb are Punarnava contains Beta-sitosterol ester, palmitic acid, ester of b-sitosterol, tetracosanoic, hexacosanoic, stearic, arachidic acid, urosilic acid etc. The herb of punarnava is indicated in kidney and urinary disorders as it acts as a kidney remedial, which helps to excrete kidney stones.^[29]

Tribulus terrestris

Tribulus terrestris, commonly known as Gokshura or Tribulus, belongs to the family Zygophyllaceae. The roots and fruits of *T. terrestris* are valuable in the treatment of kidney stones, impotence, and painful urination. It also shows antifungal, antibacterial, and anti-inflammatory activities. According to the study conducted by Azam *et al.*, after the administration of the extract of *T. terrestris* in albino rats, it inhibits stone formation and also reduces the elevated levels of serum urea levels and leukocytes.^[30]

Phyllanthus niruri

Phyllanthus niruri, commonly known as Chanca piedra or stone breaker, belongs to the family Euphorbiaceae. The extract of *P. niruri* shows antifungal, antibacterial, anti-inflammatory,

hypoglycemic, analgesic, hepatoprotective, and anti-lithiatic effects. The extract of *P. niruri* inhibits the growth and accumulation of calcium oxalate crystals in the early stages of kidney stones in the male Wistar rats and also the extract will change the shape and texture of the calculi.^[31]

Berberis vulgaris

Berberis vulgaris, commonly known as barberry, belongs to the family Berberidaceae. In the treatment of kidney stones, the root bark of *B. vulgaris* is used. The major constituents of *B. vulgaris* include alkaloid components such as berberine, berbamine, oxyacanthine, and palmatine. These constituents of *B. vulgaris* inhibit calcium oxalate crystallization and show antioxidant activity, thus preventing kidney stones.^[32]

Hibiscus sabdariffa

Hibiscus sabdariffa, commonly known as roselle, belongs to the family Malvaceae. The active principal constituents of the plant are polyphenols, L-ascorbic acid, hibiscus anthocyanins, quercetin, and protocatechuic acid. The aqueous extract of the plant is used for the prophylaxis and treatment of kidney stones by decreasing the deposition of stone-forming constituents in the kidneys.^[24]

Ammi visnaga

Ammi visnaga, commonly known as Khella, belongs to the family Apiaceae. Diverse kinds of tea arranged from the fruits of *A. visnaga* have been generally utilized by patients with kidney stones all over the world. The watery concentrate of this organic product quickened the disintegration of cysteine stones. The two major constituents of this fruit, namely visnagin and khellin, indicated the advantageous impacts in the management of kidney stone disease caused by hyperoxaluria.^[33]

Crataeva nurvala

C. nurvala, commonly known as Varuna bark or Varuna, belongs to the family Capparidaceae. The major chemical constituents of Varuna, lupeol, triterpenoids, and varunol were isolated from the root and bark system. Each part of the varuna tree, i.e., bark, leaf, and root, has many medicinal properties. According to Ayurveda, the herbs of the Varuna bark possess one of the best litholytic herbs. It has been indicated that the lupeol is the major component of *C. nurvala* deactivates the glycolate oxidase enzyme in turn reduces the body's production of oxalates combines with calcium to form kidney stones.^[34]

Oenothera biennis

Oenothera biennis, commonly known as evening primrose, belongs to the family Onagraceae. The seeds of the evening primrose contain about 14% fixed oil, which contains 65%–75% of linoleic acid, 7%–10% gamma-linoleic acid, with palmitic, oleic, stearic acids, steroids, campesterol, and beta-sitosterol. Daily intake of evening primrose seed oil in the dose of 1,000 mg/day increased the citrate level in the urine by inhibiting lipogenesis and decreased the oxalate level in the urine by altering the membrane debrane fatty acid, thus reducing the formation of kidney stones.^[26]

CONCLUSION

It is concluded from the above study that the formation of 80% of kidney stones consists of calcium oxalate and calcium phosphate. There are various treatment strategies for kidney stones which include ayurvedic, allopathic as well as herbal treatment. Among all of them, allopathic treatment is effective with an immediate response but with more side effects. Ayurvedic and herbal treatments are also effective in the treatment of urolithiasis with minimal side effects. Their efficacy varies from patient to patient and the recovery rate is slow. A clinical trial should be conducted for the combination of Ayurvedic and Allopathic treatment and their therapeutic efficacy may show fast recovery and reduces the chances of reoccurrence.

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Conflicts of interest

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