



An update on natural bioactive components of traditional preparations for the treatment of nephrolithiasis; a review

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ARTICLE INFO

Article Type:
Review

Article History:

Received: 29 Sep. 2022

Accepted: 22 Oct. 2023

ePublished: 24 Jun. 2024

Keywords:

Hajrul yahood

Jawakshar

Kidney stone

Herbal

Formulation

Nephrolithiasis

Pashanabheda

Traditional medicine

ABSTRACT

Nephrolithiasis is a condition characterized by the formation of crystal concretions within the kidneys or urinary tract. This urological disorder is on the rise globally, affecting both male and female populations. Unfortunately, conventional medicines used in the treatment of nephrolithiasis often lead to certain complications, eventually resulting in end-stage renal disease. As a result, there has been a growing interest in seeking risk-free therapies from nature to address this issue caused by the undesired effects of synthetic drugs. Evidence-based traditional medicine has emerged as a significant approach to treating nephrolithiasis, gaining recognition within the scientific community. In this review, we summarize recent scientific reports on various herbal drugs with clinical relevance in the treatment of nephrolithiasis, utilizing them as part of traditional medicine practices in the Asian continent. Additionally, several traditional medicine formulations from Ayurveda, Unani, and homeopathic systems, known for their potential lithotriptic effects and clinical applications, are highlighted. The primary focus of this review is to explore the mechanisms involved in the formation of kidney stones and provide a concise compilation of therapeutically effective herbs used in nephrolithiasis treatment.

Implication for health policy/practice/research/medical education:

Nephrolithiasis, also known as stone disease, is a common renal illness characterized by the accumulation of crystals in the renal medulla. Both adults and children are susceptible to this condition, with a majority of stones being composed of calcium oxalate, often combined with calcium phosphate. In recent years, traditional medicine has gained recognition for its use in treating nephrolithiasis within the scientific community.

Please cite this paper as: Singh P, Sabir Alam M, Arif M, Usmani S, Meraj Anjum M, Bhalla V, Garg A. An update on natural bioactive components of traditional preparations for the treatment of nephrolithiasis; a review. J Nephroarmacol. 2024;13(2):10545. DOI: 10.34172/npj.2024.10545.

Introduction

The kidney is a vital organ, which serves the purpose of purification and detoxification of the blood by filtration. Hence, this organ always is exposed to toxins, heavy metals, chemotherapeutic agents, and other metabolites, which could progress into events of different types of renal diseases events. Nephrolithiasis is a complex process because of an imbalance between various excitatory and

inhibitors in the kidneys (1). In nephrolithiasis, individual small crystals act as nuclei to promote either growth into larger size crystals or eventually lead to secondary nucleation incidents. Such processes produce various small-sized intra-renal multi-crystalline aggregates/structures fixed within a different renal system region. Subsequently, these are clinically insignificant until subjected to promotion, in terms of size and events of

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secondary nucleation (Figure 1).

However, here in this introductory review, our objective is more focused more towards approaches to enumerate those herbs, which may interfere in the initiation and progression and nephrolithiasis. Moreover, these herbs require validation of clinical performances via some indiscriminate clinical trials before their clinical translation. On the other hand, owing to the presence of different types of phytoconstituents in a single herb, exert different mechanisms and act on, diverse targets so rather than focusing on these mechanisms; we are more focused on plants exhibiting such protective actions.

Pathogenesis of nephrolithiasis

The fate of nephrolithiasis directly depends on factors such as water excretion index, concentration and state of nuclei and crystals; localized pH; promoters, and inhibitor's presence (2). Furthermore, nephrolithiasis may result from one or more aggravating factors, leading to a successive saturation of the urine, and crystallization. After crystallization, they further aggregate into larger ones called kidney stones and are clinically detectable. Those individuals, not detected with nephrolithiasis, can excrete crystals (3). Briefly, nephrolithiasis is the continuous growth of a stone, preferably of more than 5 mm (0.2 inches) in dimension, which either blocks passage in the ureter or presence in the kidney may result in several symptoms such as bloody micturition, painful urination, and severe pain in lower back or abdominal region of affected patients (4). Subsequently, tiny stones may block the flow of urine often; require prompt and urgent medical attention, owing to severe pains.

Types and classification of nephrolithiasis

According to *Ibn Sina*, the nature and constituents of renal and bladder stones are not the same. For example, Calculi of renal systems are tiny and soft with reddish, but the

bladder's monolith is relatively more prominent, robust, and sandy-white/black in appearance (5). Subsequently, crystals of calcium oxalate and phosphate, uric acid, struvite, proteins, and blood as non-crystalline materials are usually the component of kidney stone. Crystals of calcium oxalate crystals are the prime component of kidney stone. Around 75-85% of calcium oxalate is present as the monohydrate (Whewellite) and di-hydrate (Weddellite) form. In kidney stones, approximately 10-15% calcium phosphate is present as a combination of calcium oxalate or struvite (Figure 2). Crystalline calcium phosphate appears in the form of amorphous dark matter in the urine. When urate crystallizes in the kidney, it produces 5-10% of uric acid and 0.5-1% cysteine (6). Around 75 % of patients with kidney stones have calcium stones constituting chiefly calcium oxalate as a major component; however, in some cases, calcium phosphate is a major component. However, in contrast to this, only >10% of the population suffers from stones carrying uric acid constituents (7).

Reasons and risk factors of nephrolithiasis

Kidney stones may also be considered an inherited disease, so some specific sets of populations are relatively more vulnerable to the development of kidney stones. Nevertheless, the most common cause of nephrolithiasis is less consumption of drinking water. This may cause more retention of calcium and oxalate and low that of citrates in urine. This is the major risk factor directly responsible for the development of calcium oxalate crystals (8). The elevated concentration of calcium in the urine is the condition of hypercalciuria. Chronic diseases of hypercalciuria may lead to damage to renal function, renal insufficiency, and nephron calcinosis. The patients with hypercalciuria put out higher levels of calcium than usual through the kidney. Calcium may come through the gut, where abnormal calcium levels are absorbed

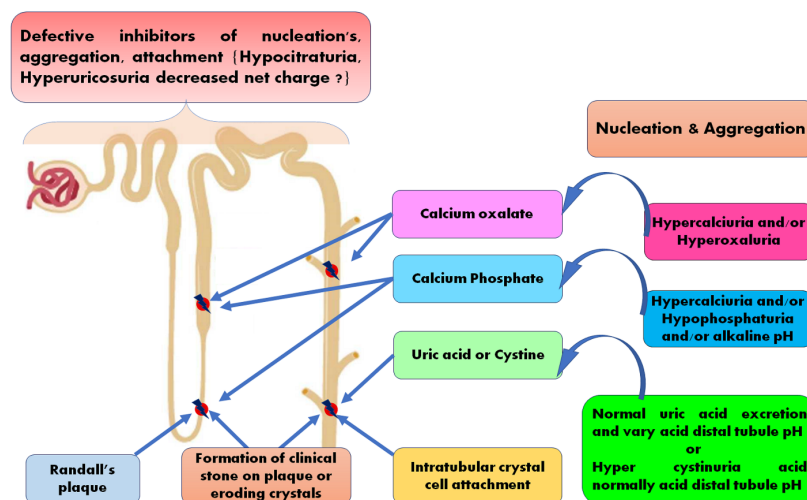


Figure 1. Mechanism and putative sites for oxalate crystal formation.

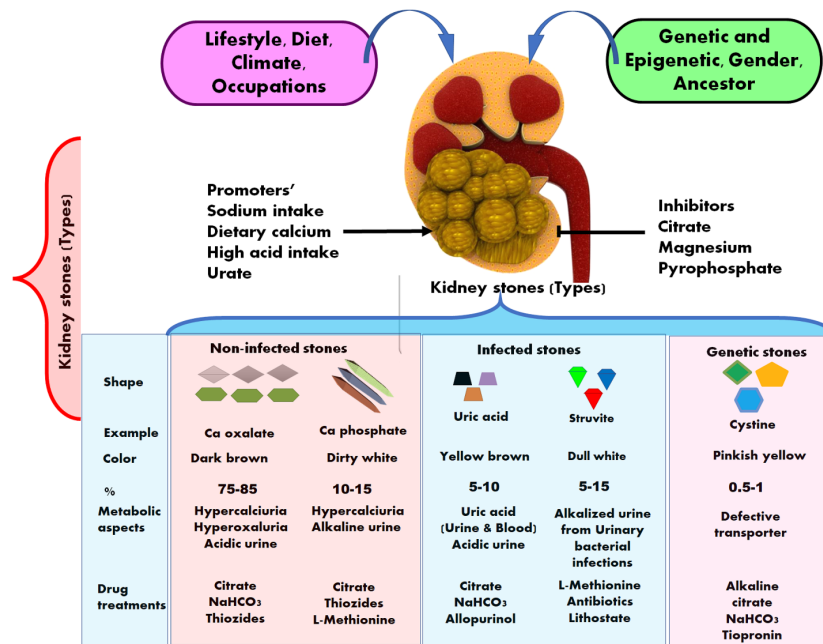


Figure 2. Factors influencing the formation of different stone types, their pathogenesis, and therapy.

from the bones. Furthermore, the oxalate excretion rate should not be more than 40 mg in a day. The risk factor of stone formation possibly depends more on the complete excretion of oxalate and concentration than on arbitrary average values (9). Citrate is under dissociated anion of citric acid, and functions as a weak acid. The source of citric acids is usually from either diet or endogenously being synthesized via tri-carboxylic acid cycles and being excreted out with a rate of <640 mg/d. Owing to the physiological role of citrate ions as an inhibitor of calcium salt crystals, hypocitraturia incidents, i.e., relatively lower amounts (>320 mg/d) of urinary citrate ions concentrations are considered significant risk factors for recurrent kidney stones. In, severe hypocitraturia, the excretion rate of citrates falls below 100 mg/d then which may lead to more severe consequences. Subsequently, hyperuricosuria, i.e., excessive uric acid concentration in the urine, is due to the direct dissolution of its crystals in the kidneys or urinary bladder (10). Congenital disorder of cystic dilatation in renal collecting tubules leads to a medullary sponge kidney, which is vulnerable to the development of kidney stones, followed by obstruction-mediated urinary tract infection. Here a very brief introduction to these metabolic abnormalities is reported in Table 1.

Epidemiology of nephrolithiasis

Among urinary tract diseases, nephrolithiasis is the third most common disease, creating primary medical problems for people worldwide (11). As per the national health and nutrition examination survey (NHANES), aged populations (~70 years) are highly vulnerable to incidents of kidney stones. As per the information available from

the 3rd NHANES, frequencies of such occurrences are continuously increasing not only from 5.2% during 1988-1994 to 2007-2010 but with more rapid rates are expected, in the future. Moreover, NHANES data established direct evidence of a relatively higher occurrence of kidney stones (8.8%) in the US population (12). In India, the prevalence rates of complementary and alternative therapies are estimated at 63.9%.

Conventional medicines in nephrolithiasis

There is no such specific treatment for nephrolithiasis in the allopathic system of medicine except surgical intervention. While surgery holds a lot of psychological and physical suffering for the patient, surgical intervention is often highly expensive and has complications (13).

Impacts of diets on nephrolithiasis

In both preclinical and clinical-based studies, however, a sufficient quantity of fluids and diet intake comprising of fruits, vegetables, low-fat food components, and calcium minerals but strict avoidance of high-calorie diet including sugar-sweetened beverages (SSB) are sufficient to reduce the level of kidney stone incidents. For example, the diet's required calcium level is proportionate to a 27-35% reduction in the development of risk of kidney stones, while SSB elevated risk factor by 30-40% stones (14).

Folklores approaches in nephrolithiasis

In India, different herbs are commonly used as an integral part, of the traditional system of medicines, for clinical management of various diseases. Therefore, in consequence of the above, many folklores are practicing these herbs to manage various ranges of clinical symptoms

Table 1. Metabolic abnormalities of kidney stones in detail with causes

Condition	Definition	Causes
Hypercalciuria	The elimination of calcium in the urine > 200 mg/d	Hypercalciuria due to absorption: ↑ GI calcium absorption Hypercalciuria of the kidneys renal impairment Calcium absorption hypercalciuria resorption: primary hyperparathyroidism
Hyperoxaluria	Oxalate excretion in the urine > 40 mg/d	Primary hyperoxaluria: genetic oxalate overproduction Dietary hyperoxaluria: excessive dietary intake Enteric hyperoxaluria: ↑ GI oxalate absorption
Hypocitraturia	Citrate excretion in the urine < 320 mg/d	Distal renal tubular acidosis: impaired renal tubular acid excretion Chronic diarrheal syndrome: GI alkali loss Thiazide-induced: hypokalemia Idiopathic hypocitraturia: high animal protein diet Excessive physical exercise, high sodium intake
Hyperuricosuria	Urinary acid excretion > 600 mg/d	Dietary purine excess, uric acid overproduction, or overexcretion
Hypomagnesuria	Urinary magnesium excretion <50 mg/d	Limited intake of magnesium-rich foods
Gouty diathesis	Urinary pH <5.5	Etiology unknown

Abbreviations: GI, Gastrointestinal; Ca, Calcium.

(15). In Ayurvedic, homeopathic, and Unani medicine, one can easily get rid of or control kidney stones through naturally occurring herbal medicines. The advantage of herbal medicine is that one can avoid surgery and nullify the body's tendency to form stones using herbal medicine. In Ayurveda, 'Pashanabheda' (stone dissolving) groups are containing a list of plants that claim to have usefulness in the treatment of urinary stones (16).

These herbs may contain several types of pharmacologically active phytoconstituents of different therapeutic classes such as acids (pedicellic acid), terpenes (cyperene, camphene, pinene), triterpenes (oleanolic acid, sarsasapogenin), and even alkaloids (berberine, lycopodine, lycodine). Most kidney stones-acting drugs are often effective, mainly due to diuretic properties, but not essentially. For example, lithotriptic (anti-nephrolithiasis) activities of many herbal drugs such as flavonoids (quercetin, kaempferol, pashanone, alizarin, astilbin, khellin, visnagin) and phenolic compounds (Bergin) type of phytoconstituents are being attributed with their potent antioxidant's characteristics. Briefly, these flavonoids, owing to strong antioxidant potentials, reduce inflammation, and inhibit glycolate oxidase (GOX) to adversely impact the synthesis of oxalate (17).

Anti-nephrolithiasis herbs; Ayurveda

The employment of traditional complementary and alternative therapies for primary health care among a population may vary from one country to the other. However, there are many evidence-based popular herbal plants mentioned in Ayurveda, which are available widely and show significant protection against this disorder. Some of these herbs may use either alone, but most commonly as a part of combination therapy.

Gokhru (*Tribulus terrestris L.*)

Tribulus terrestris L. of the family Zygophyllaceae are the fruits that come under the natural wild herb, commonly known as Gokhru, for a long time been used in Indian and Chinese medicines for curing various diseases. The anti-nephrolithiasis activity of Gokhru was due to the presence of flavonoid glycosides in the fruit such as kaempferol-3-glucoside and quercetin 3-O-rutinoside (Figure 2). These act by inhibiting the GOX and in turn causes oxalate synthesis inhibition. Gokhru is the main active component of Cystone tablets used for the cure of kidney stones, bladder, and other urinary tract infections. It helps to bring urinary tract health to normal by reducing dysuria (painful or bloody urination) and crystalluria. Gokhru prevents the concentration, supersaturation, and accumulation of carcinogenic chemicals in the urine (18).

Shilapushpa (*Didymocarpus pedicellata R.Br.*)

Didymocarpus pedicellata R. Br. (F. Gesneriaceae) is a valuable medicinal plant, commonly known as a stone flower, and Ayurveda, also known as shilapushpa, shantapushpi, and sometimes pasanbheda. Traditionally it is being utilized in the treatment of renal ailments, especially stones. Chemically, this plant contains flavonoids like chalcones (Figure 3) pashanone, didmyocarpin, isodidmyocarpin, dicarboxylic acid like α -methyl- α' -tridecyl succinic acid (Pedicellic acid). Shilapushpa is the ingredient of cystone tablets found helpful in regulating calcium absorption in the body. The plant is known for its diuretic properties, maintains a healthy urinary tract, and helps to dissolve kidney stones (19).

Pashanbheda (*Bergenia ligulata*)

Bergenia ligulata is commonly known as pashanbheda,

ashmabhid, ashmabhedi, nagabhid, upalbedak, pashana, zakhmehayat, asmaribheda, pa watched, and slashed (stone breaker) as it dissolves slabs. Chemically, the plant contains the phenolic compound trihydroxy benzoic acid glycoside (Berginin), tannic acids, β -sitosterol, and a new 4(4'- β -d-glucopyranosyloxy-1'-benzyloxy)-6-methyltetrahydropyran-2-one also termed as paashaanolactone (Figure 3). Pashanabheda is also the key ingredient of cystone tablets that possess diuretic effects, demulcent and antimicrobial activities. As it has a rich content of mucilage renders demulcent property to this herb. It also soothes and protects inflamed tissues. As a diuretic, this herb helps to excrete minor stones (20).

Apamarga (*Achyranthes aspera*)

Achyranthes aspera, known as apamarga, belonging to the family Amaranthaceae, is an herbal drug widely used in Ayurvedic medicine for ages. It can be found in many places growing as a common weed. It is an active component and typical ingredient of various drug formulations, including cystone (Himalaya), used to treat kidney stones. The plant has been scientifically proven for its anti-nephrolithiasis potency and ability to preserve renal functioning and protect it from renal injury. *A. aspera* contains triterpenoid saponins possessing oleanolic acid and alkaloids like acanthine and betaine (Figure 3) (21).

Gaozaban (*Onosma bracteatum*)

Onosma bracteatum, known as Gaozaban, is found in the Mediterranean regions, including Europe and Asia. *Onosma bracteatum* is also referred to as Gojihva, which belongs to the family of Boraginaceae. In Kashmir and

Kumaon region in India, it is sold as a medicinal herb in the local market. Small hair-like structures cover the leaves with small nodules giving it a rough appearance like a cow tongue. The leaves contain potassium, calcium with mineral acids, and pyrrolizidine alkaloids (glucosamine, and supindine viridiflorate) (Figure 3). The low concentration of alkaloids makes them less toxic. *Onosma bracteatum* is listed in the International Union for Conservation of Nature (IUCN) threat category as an herb used to alleviate pulmonary infections and kidney disease as a diuretic and spasmolytic (22).

Punarnava (*Boerhavia diffusa*)

Boerhavia diffusa is a flowering plant commonly known as punarnava belonging to the family Nyctaginaceae. Punarnava means to rejuvenate the body. Various part of the *B. diffusa* plant has reported a broad spectrum of antioxidant, diuretic, litholytic, and anti-cancer. It contains flavonoids (rotenone) and quinolone alkaloid luna marine (Punarnavin) (Figure 3) (23).

Giloy (*Tinospora cordifolia*)

Tinospora cordifolia is commonly called heart-leaved moonseed or Giloy et al. It is a herbaceous creeping plant indigenous to the Indian and also to Myanmar and Sri Lanka. It belongs to the family Asclepiadaceae. This plant extract has lipoxygenase inhibitory, lithotriptic, diuretic, and anti-inflammatory activity. It contains columbin, tinosporaside, palmatine, berberine, tembotrione, tinocordifolioside, choline, diasporic acid, tinosporal, and Inspiron (Figure 3) (24).

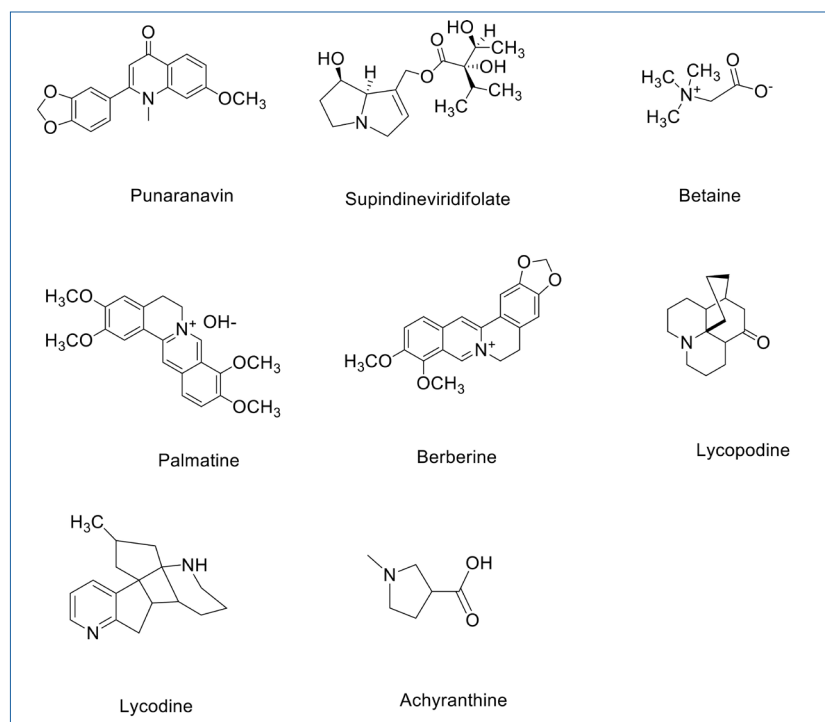


Figure 3. Chemical structure shows the active alkaloid with their anti-nephrolithiasis activity.

Talmakhana (*Asteracantha longifolia L.*)

Asteracantha longifolia L. F. of the family Acanthaceae is a component of the ayurvedic medicine, 'Kokilaaksha', and of 'Talmakhana' unani medicine. It is a spiky, stunted annual herb widespread in water-logged areas. The plant possesses certain pharmacological activities such as aphrodisiac, glucose lowering, antibacterial, antioxidant, anti-inflammatory, analgesic activity, and kidney problems. Seeds have been reported for their pharmacological activities. It contains lupeol, luteolin, stigmaterol, butelin, acids, and a few alkaloids (Figure 3) (25).

Cucumber (*Cucumis sativus L.*)

Cucumis sativus is a semi-woody, herbaceous creeping plant of the family of Cucurbitaceae. This plant is indigenous to the Indian tropical and sub-tropical, including Myanmar and Sri Lanka. The plant extract has shown many pharmacological properties such as refrigerant, anti-urolithiasis, free radical scavenger, and anti-inflammatory activities. The plant contains cucumegastigmanes I and II, cucurbitacins, vitexin, orientin, cucumerin A and B, and apigenin 7-O-(6"-O-p-coumaroyl) and 2"-O-(6"'-(E)-p-coumaroyl) glucosides (Figure 3) (26).

Anti-nephrolithiasis herbs; Unani systems

Several single and multiple Unani drug combination formulations have been used for the management of nephrolithiasis. It provides curative treatment using different drugs in irrigation, massage, poultice, sitz bath, and orally taken Unani drug formulations. Many of the abovementioned drugs are also used in Unani formulations. The different Unani drug formulations with pharmacologically established herbal drug ingredients used to expel kidney stones are summarized here. One of the potent drugs used in the clinical management of nephrolithiasis is Jew's stones (27).

Hajrul yahood (Jew's stone)

Jew's stone is the larger spines of normal echinoids, particularly cidaroids identified as *Lapis judicious* (English: Jews' stones; Arabic: Hajarul Yahud; Persian: Sang-e-Jahudan) and usually festooned by a series of longitudinal, delicately tuberculated striae. Hajrul yahud was grown in the late Jurassic period in North Africa, Europe, and the Middle East, and its spines have a short neck and a bulbous head festooned with beaded ribs. *Lapis judaicus* has been reported to be used for urinary infections by both Eastern and Western traditional medicine systems. Dioscorides Pedanius (first century AD) suggested the use of *L. judaicus* for dissolving kidney stones. Its fine powder has been used in different Ayurvedic and Unani formulations. Kushta and Majoon are two essential Unani formulations containing Hajrul yahood, a mineral-origin drug used in the calcinated form. The Kushta is prepared by putting *L. judicious* at a high temperature until fully

oxidized. However, other crude drugs are pre-treated (particular herbal extract/juice) to make them more efficient (28).

Anti-nephrolithiasis herbs; Homeopathy

In this system of medicine system, there are more than a hundred remedies listed which are used for treating kidney stones. The mechanisms of how the plants and natural products act for the prevention of kidney stones are shown in (Figure 4). The effectiveness of the above remedies has been established on healthy subjects and clinical trials on renal calculi patients. While many medicines can remove kidney stones or renal calculi, the homeopathy system also proves significant results in the treatment of urinary calculi. Homeopathic medicine in urinary calculi is valuable in all age groups, which will result in severe complications. The different homeopathic drug formulations with the pharmacologically established activity of herbal drug ingredients used to expel kidney stones are summarized here.

Barberry (*Berberis vulgaris Linn.*)

Berberis vulgaris Linn. (F. Berberidaceae), commonly known and called 'barberry', occurs mostly in Central and Southern Europe and the Northeast parts of the United States and South Asia Pakistan. The *B. vulgaris* is a more preferred remedy for the remove the stone located on the left side of the kidney. As per the homeopathic medicine system, *B. vulgaris* has been used for various urinary system abnormalities, including stones and other urinary tract ailments. Berberine an isoquinoline alkaloid is the main constituent with medicinal properties used in kidney stone disease (29).

Hydrangea root bark (*Hydrangea arborescens*)

Hydrangea arborescens is belonging to the family Hydrangeaceae is a flowering plant also known as smooth and wild hydrangea, or seven barks. *H. arborescens* is a deciduous herb of small to medium-sized, native to the eastern United States. The roots are a rich source of chemicals and minerals such as resins, soda, lime potassium, magnesia, sulphuric acid, phosphoric acids, and a proto-salt of iron. The root of *H. arborescens* plant was used for the cure of bladder and kidney stones by the Native Americans, and later by the early settlers also. It is indicated in genitourinary spasm, with khella, lobelia, kava, horse chestnut, and yucca root for acute pain due to kidney stones (30).

Lycopodium (*Lycopodium clavatum*)

Lycopodium belongs to a genus of clubmosses, referred to as ground pines or creeping cedar moss-like plants of the Lycopodiaceae family. These are flowerless, branched, erect, prostrate stems with needle-like leaves that cover the stem. *L. clavatum* is one of the pivotal homeopathic medicines of the ancient family with a long back

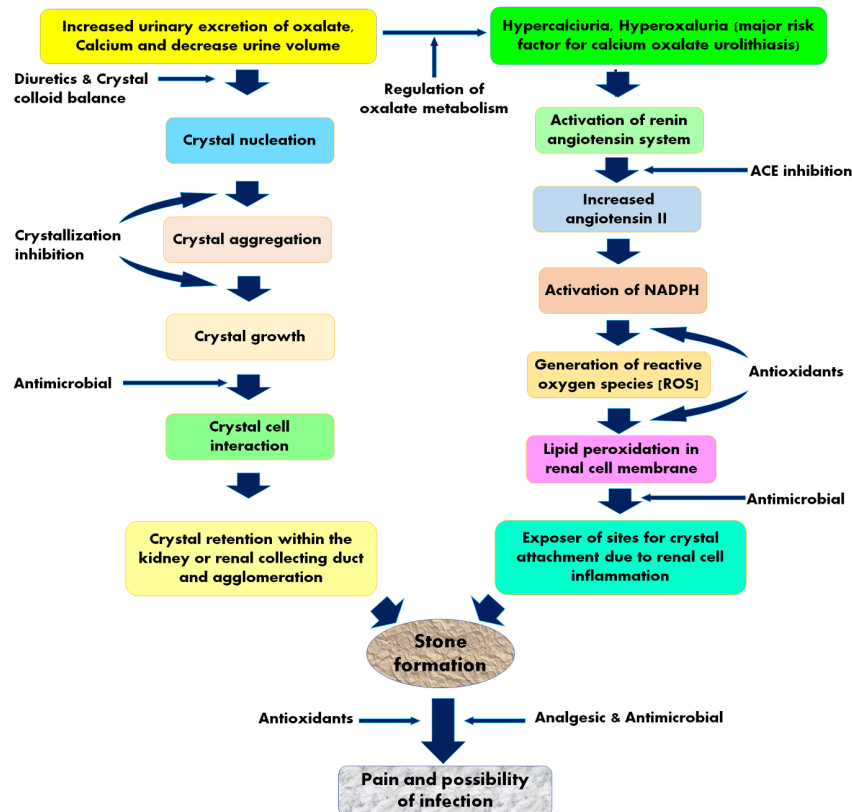


Figure 4. Mechanisms of plants and natural products in the prevention of kidney stones.

geological history of over 380 million years (31). The distinguishing symptom is the presence of red sand in the urine, and intense back pain, more provoked in the afternoon. Lycopodium is a profound-acting medicine frequently used as a legitimate. *L. clavatum* affects entire fat metabolism, a disturbing one in proving, regulates protein metabolism, and cures gout and kidney stones. In materia medica, the symptoms given are reddish-yellow sand in the urine with a strong smell. *L. clavatum* contains alkaloids like lycodoline, lucidioline, alpha-obscuring, lycopodine, lycodine, lycoposerramine-L, lycoposerramine-M, 11alpha-O-acetyl-lycopodine, des-N-methyl-a-obscuring, and clavonine (32).

Sarsaparilla (*Smilax sp*)

Sarsaparilla is the climbing or trailing tropical American plant belonging to the genus *Smilax*. Sarsaparilla is a lily family member that has alternate leaves, and umbels of flowers widely seen in temperate, swampy, and warm areas. In homeopaths, sarsaparilla is a right-sided medicine; the medicine could expel a left-sided stone and be equally effective based on the symptoms and used to treat rheumatism, leprosy, psoriasis, tumors, and cancer as traditional medicine. Sarsaparilla has anti-inflammatory, aphrodisiac, testosterone, and progesterone effects and is a male rejuvenator (33). The main chemicals constituents of sarsaparilla are flavonoids such as acetyl-parigenin, motilin, taxifolin, astilbin, isoastilbin,

kaempferol, dihydroquercetin, engeletin, isoengetitin (Figure 5), phenolic compounds like ferulic acid and resveratrol, and steroids like beta-sitosterol, diosgenin, parigenin, sarsaponin, sarsaparilloside, sarsapogenin, sitosterol-d-glucoside, smilagenin, smilasaponin, and stigmaterol (Figure 6). The use of sarsaparilla is much more appropriate for the white deposit in the urine. There is forceful pain at the cease of urination. There is also smoldering and acerbic in the urethra after urination. Urine exceeds a thin and shabby stream. Sarsaparilla roots have saponins known to help the body absorb other drugs more effectively (34).

Cantharis (*Cantharis sp.*)

The poisonous Spanish fly (*Cantharis sp.*) is superficially similar, sometimes called cantharis. Homeopathic medicine cantharis contains a terpene known as cantharidin. It shows the most desirable results in kidney stone cases where marked influential burning in the urethra during urination is a prominent symptom. Patients with kidney stones who suffer from burning in the urethra can benefit from cantharis and a marvelous homeopathic medicine used for kidney stones. However, it works exceptionally well in cases where burning micturition is the hallmark symptom (35).

Hairy rupture wort (*Herniaria glabra*)

Herniaria glabra, most commonly known as hairy rupture

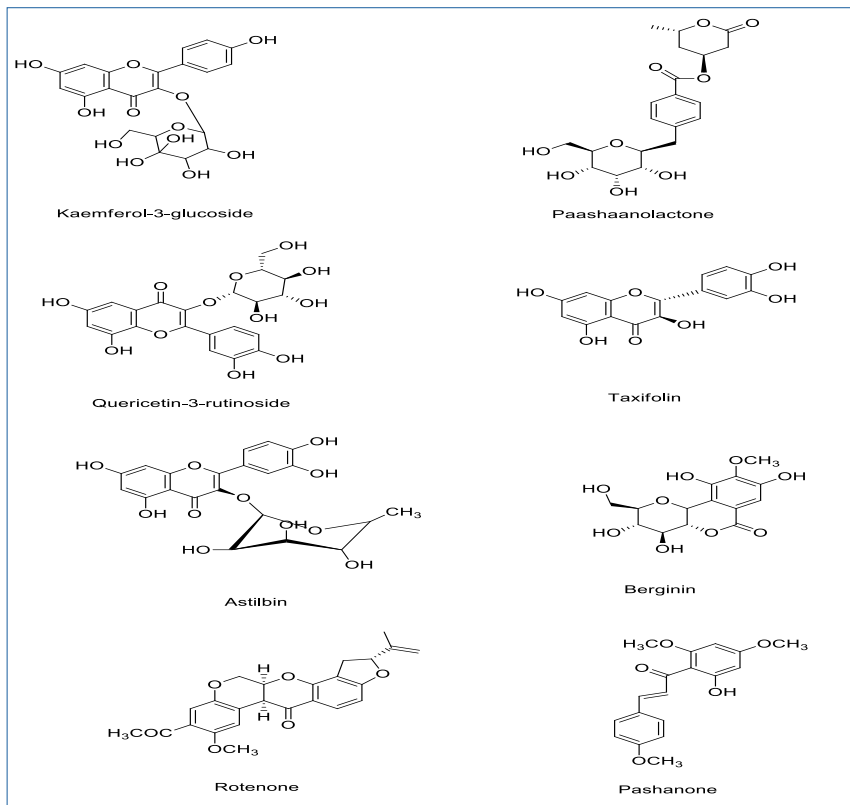


Figure 5. Active phenolic and flavonoids with anti-nephrolithiasis activity.

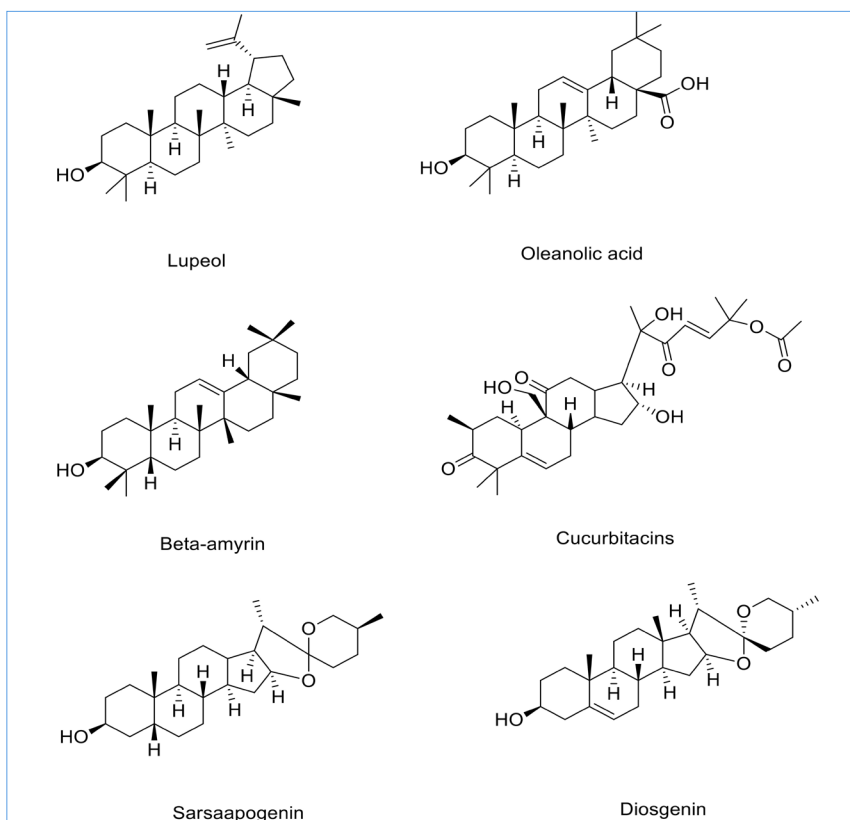


Figure 6. Active chemical structure of triterpenoids and steroids with anti-nephrolithiasis activity.

wort, is a flowering plant from the Caryophyllaceae family. Its species are native to Eurasia, also known in other continents, including North America. *H. labra* contained phenolics, flavonoids, flavonols, and saponins. *H. glabra* is evaluated in rat models of nephrolithiasis as a preventive therapy for the development of stones in the kidney. The experimental study was conducted in regular and the calcium oxalate nephrolithiasis rats and the results concluded that it enhances both the water intake and urinary volume in nephrolithiasis rats. However, their urinary pH decreased, especially in the third week of the treatment (36).

Visnaga (*Ammi visnaga*)

Ammi visnaga is a flowering plant of the Umbelliferae family. Many familiar names include toothpick-plant, toothpick weed, visnaga, and khella. It is a native plant of Europe, Asia, and North Africa. *A. visnaga* is widely used for the cure of several diseases, including kidney stones. The active chemical constituents are coumarin derivatives like khellin, visnagin, and visnadine obtained from *A. visnaga* seeds have anti-nephrolithiasis activity (37).

Apium (*Apium graveolens*)

Apium is a genus of nearly 20 species belonging to Apiaceae's flowering plant, distributed throughout Europe, Asia, South America, Australia, and Africa. These species grow up to 1 m in height in the wet soil of marshes. The plant has pinnate to bi-pinnate leaves and small white flowers in compound umbels. The active chemical constituents are volatile oil apiol, phenolic, apigenin, lunular, and apiin used to obstinate urine (38).

Poly-herbal clinical formulations

Different herb-based drug formulations clinically used to expel out kidney stones are summarized here (Table 2).

Cystone®

Cystone® is an Ayurvedic product by Himalaya Herbal and is used for kidney stones. In the clinical management of chronic urinary tract infection and prevention, Cystone has been prescribed for the recurrence of kidney stones. The medicine has some ingredients with the potential as a potent anti-lithiatic and lipotropic agent. The elements present in these formulations mostly act on all types of stones, helping to dissolve the stones and flush out the stone gravel through urination. This formulation contains *didymo carpus pedicellate*, *achyranthes Aspera*, *Onosma bracteatum*, *Bergenia ligulata*, *Rubia cordifolia*, *Cyperus scariosus*, *Vernonia cinerea*, and a purified form of Shilajit. Another ayurvedic formulation, "Gokshuradi," consists of five different medicinal plants, including dry fruits of *Tribulus Terrestris* L., seeds of *Hygrophila spinosa* T., roots of *Ricinus communis* L, *Solanum anguivi* lamk. and *Solanum surattense* burm. The individual plant components of gokshuradi are well known to possess several pharmacological effects, including removing the kidney stones (39).

Neeri KFT®

Neeri KFT is a natural kidney function toner, poly-herbal ayurvedic proprietary syrup. The phytoconstituents in the formulation work as a powerful antioxidant, nephroprotective, and immune-modulator, thereby multi-mechanism having a propensity to ensure further degenerative alterations. It also endorses restoring nephrons' functional capability and normalizes kidneys' digressed operational parameters like serum creatinine, serum proteins, and serum urea (40).

Crashcal®

"Crashcal" is a polyherbal tablet dosage form manufactured by Sampurna-Jeevan Pharmachem. Pvt. Ltd., India. It

Table 2. Some Ayurvedic, Unani, and homeopathic herbal bioactive marketed formulations for the treatment of kidney stone disease

Formulation	Contents	Activity
Cystone tablets: The Himalaya Drug Company Makali, Bengaluru, India	<i>Tribulus terrestris</i> (32mg), <i>Didymocarpus pedicellata</i> 130 mg, <i>Bergenia ligulata</i> 98 mg, <i>Rubia cordifolia</i> 32 mg, <i>Cyperus scariosus</i> 32 mg, <i>Achyranthes aspera</i> 32mg, <i>Onosma bracteatum</i> 32 mg and <i>Vernonia cinerea</i> 32 mg.	Anti-inflammatory, anti-microbial, spasmolytic, and diuretic activity.
Neeri-KFT Syrup AIMIL Pharmaceuticals Ltd, Street no. 17, Ranjeet Nager, Patel Nager, New Delhi-11008 (India)	<i>Boerhaavia diffusa</i> 1000 mg, <i>Cichorium intybus</i> 600 mg, <i>Tinospora cordifolia</i> 500 mg, <i>Nelumbo nucifera</i> 400 mg, <i>Albizia lebeck</i> 300 mg, <i>Tribulus terrestris</i> 300 mg, <i>Butea monosperma</i> 300 mg, <i>Pterocarpus santalinus</i> 200 mg, <i>Moringa oleifera</i> 200 mg, <i>Veteveria zizanioides</i> 150, <i>Amaranthus spinosus</i> 100 mg, <i>Coriandrum sativum</i> 100 mg, <i>Crataeva nurvala</i> 100 mg, <i>Cucumis utilissimus</i> 100 mg and <i>Carica papaya</i> 50 mg.	Antioxidant, anti-inflammatory, anti-lipoxygenase, diuretic, nephroprotective, and lipolytic activity. Prevents the accumulation and supersaturation of carcinogenic chemicals in urine and dissolves KS.
Lithocare capsules: Shakti Oils & Fats Shibpur, Howrah, (W.B), India	<i>Crataeva nurvala</i> 200 mg, <i>Boerhaavia diffusa</i> 200 mg and <i>Asteracantha longifolia</i> 100 mg.	Anti-inflammatory, analgesic anti-oxidant, antitumor, antibacterial, lipid peroxidation, and aphrodisiac.
Renovate tablets:	<i>Bergenia lingulata</i> 150 mg, <i>Tribulus terrestris</i> 100 mg,	Litholytic property.

Table 2. Continued

Formulation	Contents	Activity
Critical: Sampurna-jeevan Pharmachem Pvt. Ltd. Ichalkaranji, Maharashtra, India	<i>Bergenia ligulata</i> , <i>Dolichos biflorus</i> , <i>Boerhavia diffusa</i> , <i>Tribulus terrestris</i> , <i>Mimosa pudica</i> , <i>Crataeva nurvala</i> , <i>Asphaltum</i> : <i>Commiphora mukul</i> , <i>Hajrul Yahood</i> : <i>Lapis judaicus</i> .	Uterine complaints, inflammations, burning sensation, inhibitory effect on calcium oxalate crystallization, anti-oxidative, preventing initial stage of nidus formation.
Unex capsule: Unijules Life Sciences, Nagpur, India	<i>Boerhaavia diffusa</i> and <i>Tribulus terrestris</i>	Diuretic, anti-nephrolithiasis, and anti-inflammatory.
Nilstone: Domagk smith labs pvt. ltd. Balaji anchorage, gtm colony, Sirsa, Haryana, India	<i>Crataeva nurvala</i> 20 mg, <i>Bergenia ligulata</i> 50 mg, <i>Boerhavia diffusa</i> 20 mg, <i>Cucumis sativus</i> 40 mg, <i>Tribulus terrestris</i> 40 mg, <i>Picrorhiza kurroa</i> 40 mg, <i>Elettaria cardamomum</i> 20 mg and <i>Jawakshar</i> 70 mg.	Refrigerant, appetizer, stomachic, febrifuge, tonic, anti-urolithiatic, antioxidant, anti-inflammatory, and hepatoprotective activity.
Ural syrup: Vasu Healthcare Pharmaceuticals, Vadodara, Gujarat, INDIA	<i>Bergenia ligulata</i> 300 mg, <i>Tribulus terrestris</i> 300 mg, <i>Boerhavia diffusa</i> 200 mg, <i>Crataeva nurvala</i> 200 mg, <i>Vigna unguiculata</i> 50 mg, <i>Smilax china</i> 50 mg, <i>Hajrul yahood</i> bhasma 50 mg, <i>Jawakshar</i> 50 mg, <i>Tankana Bhasm</i> .	Antioxidant, antibacterial, useful in jaundice, KS, anorexia, constipation, and dissolved urinary calculi.
Calcury tablets: Charak Pharma Pvt. Ltd. 501/A, Dr. Annie Besant Road, Worli, Mumbai, India	<i>Tribulus terrestris</i> 80 mg, <i>Picrorhiza kurroa</i> 80 mg, <i>Moringa oleifera</i> 75 mg, <i>Hajarul yahood</i> 50 mg, <i>Bergenia ligulata</i> 15 mg, <i>Didymocarpus pedicellata</i> 10 mg, <i>Boerhaavia diffusa</i> 10 mg, <i>Butea monosperma</i> 4 mg, <i>Asphaltum</i> 6 mg, <i>Jawakshar</i> : <i>Elettaria cardamomum</i> .	Retentive, resolvent, hypertension, antiemetic, diuretic, antioxidant, antimicrobial, anti-inflammatory, refrigerant, tonic, and anti-urolithiatic.
Stonill: Satyam Health Care Makarpura GIDC, Vadodara, Gujarat, India	<i>Tribulus terrestris</i> 60 mg, <i>Boerhavia diffusa</i> 60 mg, <i>Vinga unguiculata</i> 60 mg, <i>Crataeva nurvala</i> 20 mg, <i>Raphanus sativus</i> 30 mg, <i>Bergenia lingulata</i> 60 mg, <i>Asphaltum</i> 40 mg, <i>Commiphora wightii</i> 30 mg, <i>Jawakshar</i> 30 mg, <i>Hajarul yahood</i> 30 mg, <i>Shwet Parpati</i> 80 mg.	Antioxidant, antibacterial, diuretic, lithontriptic, febrifuge, anti-flatulent, and useful in KS, increase the urine volume, anorexia, and constipation.
Kaltropsin syrup: United Pharmaceuticals Alwar, Rajasthan, India	<i>Cichorium intybus</i> , <i>Boerhavia diffusa</i> , <i>Tribulus terrestris</i> , <i>Achyranthes aspera</i> , <i>Bergenia ligulata</i> , <i>Glycyrrhiza glabra</i> , <i>Cedrus deodara</i> , <i>Saileya</i> : (Lichen), <i>Permelia perlata</i> , <i>Solanum nigrum</i> , <i>Phyllanthus emblica</i> , <i>Cucumis utilissimus</i> , <i>Asparagus racemosus</i> , <i>Tinospora cordifolia</i> , <i>Berberis vulgaris</i> , <i>Navasadara</i> , <i>Shwet Parpati</i> .	Treatment of cystitis, KS, diabetes, Addison's disease, stones in the kidney, urolithic infections, oxidative stress, hyperlipidemia and metabolic alkalosis, and hypochloremia states.
Unani formulations		
Majun Hajrul yahood: Hamdard Laboratories, Gaziabad, India	Maghz tukhm kadu: <i>Lagenaria siceraria</i> , Maghz tukhm khayarain: <i>Cucumis sativus</i> , Maghz tukhm kharbooza: <i>Cucumis utilissimus</i> , <i>Habbe kaknaj</i> : <i>Physalis alkekengi</i> and <i>Hijrul Yahood</i>	Anti-urolithiasis, antioxidant, anti-inflammatory, aperient, strongly diuretic, and lithotriptic.
Kushta Hajrul yahood: Hamdard2A/3, Asaf Ali Road, New Delhi, India	<i>Hajrul yahood</i> , <i>Shora Qalmi</i> <i>Aabe Mooli</i> (<i>Raphanus sativus</i>).	Dissolving urinary calculi.
Homeopathic formulations		
<i>Hydrangea arborescens</i> SBL Pvt Ltd. India	<i>Hydrangea arborescence</i>	Kidney pains, KS, enlarged prostate gland, pain and burning in the urethral region, and difficulty for urination to begin.
<i>Berberis pentarkan</i> Dr. Willmar Schwabe, Pvt. Ltd. India	<i>Berberis vulgaris</i>	Anti-inflammatory, treatment of kidney and bladder stones.
<i>Apium graveolens</i> : SBL Pvt Ltd. India	<i>Apium graveolens</i>	Used in obstinate retention of urine, throbbing headaches, and heartburn.
<i>Sarsaparilla</i> : SBL Pvt Ltd, India	<i>Smilax</i> sp.	Expel a left-sided stone effectively on a symptom basis.
Cantharis: Dr. Reckeweg & Co, India	Insects of <i>Cantharis</i> sp.	Severe burning and violent pain when passing and so passes it in drops. Strong desire to urinate.
<i>Herniaria glabra</i> : Dr Willmar Schwabe Pvt Ltd.	<i>Herniaria glabra</i>	Nephrolithiasis activity.
<i>Ammi visnaga</i> : SBL Pvt Ltd, India	<i>Ammi visnaga</i>	Increased frequency of urination, especially at night Increased urination KS.

effectively controls urinary disorders, and it has the best anti-calcifying lithotriptic effect. Crashcal tablets consist of *Bergenia ligulata*, *Dolichos biflorus*, *Boerhavia diffusa*, *Tribulus terrestris*, *Mimosa pudica*, *Crataeva nurvala*, Triphala, Asphaltum, *Commiphora mukul*, including Hajrul yahud bhasma (41).

Renomet®

“Renomet” is a polyherbal formulation manufactured by Matxin Labs Pvt. Ltd. It contains *Bergenia ligulata*, *Tribulus terrestris*, *Dolichos biflorus*, and *Crataeva nurvala*. Renomet formulation has proven to be safe and effective in reducing stones’ size and virtually eliminates them from the kidney (42).

Ural Syrup®

“Ural Syrup®” by Vasu Healthcare Pharmaceuticals, India. It has excellent lithotriptic properties, and it possesses alkalizing agents. Its lithotriptic action breaks down the stone into gravel, promotes diuresis, and treats burning micturition safely, even in pregnancy (43).

Unex Plus®

“Unex Plus®” recommends diuretic action, reduces painful micturition, and is sometimes used as an adjuvant to anti-hypertensive therapy. It helps the diseases of the genitourinary tract and urinary stones and kidney dysfunctions (44).

Stonill plus®

“Stonill plus®” syrup is a natural lithotriptic polyherbal formulation manufactured by Satyam Health Care, India, using high-grade, which requires the essential herbal ingredients that are beneficial to eliminating renal calculi. This syrup is useful for treating urinary tract infections, renal colic, urethritis, cystitis, recurrent stones, painful micturition, and dysuria.

Lithocare®

Lithocare is a research-based ayurvedic formulation containing anti-inflammatory, anti-infective, and diuretic herbal constituents. It promotes urine flow and tackles infection. It also clears urinary dumps and urinary pain in cystitis and inflammation. Lithocare is very helpful in preventing stone development and avoids the situation of surgery. Lithocare is also employed for other urinary symptoms with urinary incontinence, hypotonic, enuresis, and neurogenic bladder.

Kaltropsin syrup®

“Kaltropsin syrup®” is a safe, pleasant-tasting drug manufactured by United Pharmaceuticals. It has diuretic effects on various types of urinary disorders. Kaltropsin has Lithotriptic, antimicrobial, and nephroprotective actions.

Nilstone®

“Nilstone®” is also great ayurvedic therapy for renal stones. It breaks up the stones entirely and is best used for urinary tract infections, painful micturition, and cystitis.

Calcury®

“Calcury®” is a natural lithotriptic and diuretic polyherbal formulation manufactured by Charak Pharma Pvt. Ltd., India. Calcury is used as an alternative treatment therapy in discriminatory patients with negligible nephrolithiasis.

Challenges in herbal therapy

The presence of several phytoconstituents, their drug targets, and pathways are very complicated to decode and practice. Therefore, the elucidation of the exact mechanism of action of individual herbs is quite challenging and often misleading too. Due to the above-mentioned complicated issues with their mechanisms and pathophysiology of a disease, the prediction of the performance of these herbs in clinical patients could not be addressed (45). Consequently, based on an evidence-based long history of safe usage, integrating these phytoconstituents is useful for various proposes in reliable manners. However, due to possible toxicity and lack of specific actions on different targets, combined dosage form-based approaches provide overall better pharmacological responses (46).

Future scope and discussion

Presently, the management of kidney stones by surgical means and surplus bodily shock wave intervention (lithotripsy) are frequently employed. This way of treatment is threatening to the soft tissues of the kidney and sometimes leads to cancer. It may also be a sound approach to avoid surgical interventions for the treatment of renal calculi. Numerous researchers found that chemical molecules from the plant matrix may produce a synergist effect in combination with conventional medicine to decrease the side effects (47). Various herbal bio-actives were critically studied and compiled in the article to prevent and treat nephrolithiasis. Unfortunately, the documented info-chemical characterization of all herbal bio-actives and their single or combined preparations is inadequate. Researchers have further shown that in contrast to conventional medicines bearing many side effects such as head and visceral pain, fatigue, and stone recurrences, the integration of bioactive components not only ameliorated such side effects but also improve performances. These herbs are not only effective in the clinical management of nephrolithiasis and kidney stones but also to reduce other types of severe complications. Subsequently, this study’s findings revealed that the enhanced cost of lithotripsy and allopathic medicine and poor financial status leads people to rely on traditional medicine for their basic healthcare needs. Many marketed traditional medicine formulations in Ayurveda, Unani,

and the Homeopathic medicine system are used amongst the Asian country population due to its non-affordability and shortage of lithotripsy clinics. Hence, recently emphasis is given to the exploitation of traditional medicine and the promotion of their formulations as more effective and safer options (48). Therefore, the current review stressed the role of different types of herbs which increases the release of urinary citrate or enhances the retention of calcium and oxalate in the body, or due to diuretic and antioxidant properties. Ayurvedic, Unani, and homeopathic traditional medicine formulations are a choice to treat kidney stones without causing any side effects. As scientists are becoming aware of significant outcomes and distinctions of these herbs, mainly product-specificity; some more research is required to reveal the mechanism of action of the bio-actives substances. Future scientific studies in clinical settings on the efficacy of herbal bioactive components would be of great benefit by adequate phytochemical studies. So, it is the need of the hour to develop an acceptable and standardized herbal formulation for nephrolithiasis treatment. Usually, plenty of such herbs are being prescribed in poly-herbal-based natural therapy; but sometimes may also be prescribed with standard allopathic medicines, either to potentiate actions or to lower the adverse impacts of drugs. However, trends are also emerging toward the conceptualization of various dosage forms, to enhance solubility, potentiate actions, and reduce drug regimens. While different types of carriers such as polymeric, metallic, or lipids nanoparticles may be exploited for oral, parental depots, and transdermal delivery; for better bioavailability and desired patient convenience. Subsequently, some dosage forms also achieve a higher degree of selectivity owing to the presence of directing ligands over the carriers, which are usually some biocompatible biological macromolecules.

Conclusion

In this review, we collected and compiled the details related to the lithotriptic effects of many herbal medicines, including their poly-herbal formulations in India and other Asian countries. These herbal medicines could help the global community venture into the field of alternative and integrative medicine systems. Standardization of medicinal plants, along with systematic research, needs to be undertaken. Here an attempt was made to explore the traditional medicine for the treatment of nephrolithiasis. We conclude that more interdisciplinary research should be encouraged to develop newer high-quality plant-derived natural herbal products to prevent and cure kidney stones. Moreover, research needed to be done to search for the possible interactions between prescribed drugs and traditional medicine inside humans.

Acknowledgments

We want to express our sincere thanks to Prof. S.W.

Akhtar, Honorable Chancellor, Integral University, Dasauli, Lucknow, India for providing an excellent research atmosphere. The authors are also thankful to the Dean of R&D, Integral University, for technical support and assigning manuscript communication numbers for this review manuscript (IU/R&D/2018-MCN 000477). MSA and VB also thank fu to SGT College of Pharmacy for their support and increasements.

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Conflicts of interest

The authors declare that there is no conflict of interest, financial or otherwise.

Ethical issues

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, and redundancy) have been completely observed by the authors.

Funding/Support

None.

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