Current Trends in Biotechnology and Pharmacy
Vol. 17 (4A) 151 - 161, October 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.4s.103

Review on Phytochemicals for the Treatment of Kidney Stones

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Abstract

Urolithiasis, also known as kidney stones, is a common urinary tract problem that is caused by the deposition of hard crystals formed by mineral or salt accumulation in the urinary tract. It can cause pain and obstruct urine flow. Several studies have shown that certain natural plants and/or their constituents can help to treat kidney stones. The aim of this review is to review the natural plants used to treat the disease and investigate their pharmacokinetics profile, pharmacodynamic properties, and molecular mechanism of action in treating kidney stones. The study protocol was published in Web of Science, Scopus, PubMed, Embase, Cochrane Library and Google Scholar were searched up to May 2023. This review provided insight into identifying natural plants that can be used to treat urolithiasis. The report showed the primary underlying mechanism of these natural plants, as well as their isolated useful constituents. Our study showed that there are many natural plants that can treat urolithiasis. However, It is necessary to conduct research to assure the safety and effectiveness of these plants and their chemical compounds.

Keywords: Urolithiasis, kidney stones, natural plants, treatment, mechanism of action, main constituents.

Introduction

Urinary tract stones or kidney stones are hard crystals that form in the urinary system as a result of minerals or salts accumulation. Urolithiasis describes the condition in which the stone passes from the renal pelvis to the ureter, bladder, and urethra (1). Kidney stones are a common urinary tract problem all over the world, including Malaysia. According to the study, 10 to 20% of the general population in Malaysia develop kidney stones at some point in their lives. There are several types of kidney stones, but calcium stones are the most prevalent type. Other types of stones include uric acid, struvite, and cystine stones, which are far less common than calcium stones (1). Calcium stones are typically formed as calcium oxalate or calcium phosphate. Oxalate is a substance that the liver produces daily or that is obtained through foods such as spinach, chocolate, some nuts, coffee, and tea. Calcium phosphate stones, on the other hand, are commonly produced in metabolic conditions such as renal tubular acidosis. Therefore, having a high intake of oxalate and phosphate significantly increases the risk of developing the kidney stones.

Aside from high oxalate and phosphate intake, risk factors for stone formation include family history, particularly first-degree relatives, abnormalities in the kidney and/or urinary tract, relative dehydration, and the presence of medical conditions such as obesity, gout, hypertension, diabetes mellitus, and high salt intake. Stone formation begins with the formation of crystals in supersaturated urine, which adhere to the urothelium and serve as a point of origin for subsequent stone growth (2).

These salt crystals aggregate and grow in size, with the potential to migrate into the ureter and cause symptoms (1). For example, the person may begin to experience symptoms like body pain, dysuria, hematuria such as pink, red, or brown urine, cloudy or foul-smelling urine, frequent urination but in small amount, nausea and vomiting, and fever and chills if an infection is present. Urolithiasis is usually painless until the stone starts to move and enters one of the ureters, which are ducts that connect the kidney and bladder. If the stone becomes lodged in the ureters, it can block urine flow and eventually cause the kidney swell and ureter spasms, both of which can be excruciatingly painful. This is because the urinary duct is relatively narrow, which only has a diameter of 2 to 3 mm and a length of 10 to 12 inches. Large kidney stones cause friction as they travel down the ureters, thereby tearing and ripping the ureter wall. The intensity and location of the pain may also change as the stone moves through the urinary tract.

Medical therapies as well as surgical interventions are used in the treatment of kidney stone. The patient is treated based on the type of stone, the cause, and their acute presentation, primarily to relieve the pain (1). Although many synthetic drugs are available to treat patients in the clinical setting, natural plants are also widely used to cure the condition. Natural plants with pharmacological properties have been used for centuries. This is because they are inexpensive, readily available, and can occasionally serve as a safer source of the active ingredient in drugs (3). This report discusses natural plants and their therapeutic effects in the treatment of urolithiasis. The objectives of this review are to identify the natural plants for the treatment of urolithiasis and to understand the pharmacokinetics and pharmacodynamics of the natural plants in treating the medical condition.

Phytochemicals:

Asparagus Racemosus

Asparagus racemosus Willd. (Liliaceae) commonly known as satavar, a short-rooted undershrub with many succulent tuberous roots that are spiny. The plant can be found throughout India's tropical and subtropical regions up to an altitude of 1500 m. Its root is being used to treat various clinical conditions in addition to its antioxidant, antibacterial and diuretics property (4).

Shatavarins, a genus of steroidal saponins, make up the majority of asparagus' bioactive compounds. Beneficial in the treatment of diabetic retinopathy, these saponins have a broad range of biological activities, including those of antioxidants, immunostimulants, antihepatotoxicants, and antibacterials. Moreover, flavonoids, resin and asparagine are also the active principles of *Asparagus racemosus*. It has been noted from prior investigations that flavonoids and saponins have diuretic action. Additionally, polyphenols and flavonoids have antioxidant properties. Racemoside (A, B, C), Racemofuran, Asparagamine A, racemosol and sarsasapogenin are the active ingredients of *Asparagus racemosus* (5). In urolithiasis, the urine outflow blocked, and damaged renal parenchyma cause the glomerular filtration rate to decrease. Consequently, the toxic and waste products as well as some nitrogenous substances such as urea and uric acid remained and accumulated in the blood causing toxicity.

Solanum xanthocarpum

Solanum xanthocarpum, commonly known as yellow-fruit nightshade, is a member of the Solanaceae family. In India, it is used to treat a variety of urinary disorders, including urolithiasis, urinary retention, urinary tract infections, and nephrotoxicity. Solanum xanthocarpum decreases renal hyperoxaluria crystalluria and calcium oxalate supersaturation. The fruit of S. xanthocarpum is an abundant source of steroidal glycol-alkaloids, coumarins, triterpenes, as well as saponins. The fruit extract has a nephroprotective effect and reduces the nucleation and aggregation of calcium oxalate crystals in artificial urine solution. In ethylene glycol-induced urolithiasis, it inhibits polyuria, renal function impairment, oxidative stress, and

crystalluria. Lastly, it accelerates glomerular filtration and raises levels of the stone-inhibiting macromolecule glycosaminoglycan present in urine (6). Main constituents include solanacarpine and solamargine, caffeic acid, coumarins like aesculetin and aesculin, steroids carpesterol, diosgenin, campesterol, daucosterol, and triterpenes like cycloartanol and cycloartenol. Additionally, the fruit contains alkaloid saponins, and salasodine berries contain spiroketal alkaloid sapogenin with heterocyclic nitrogen atoms. The anti-inflammatory effect of salasodine is demonstrated by its ability to reduce the inflammatory response. It also contains N-analogue of diosgenin, a steroidal precursor typically used to produce corticosteroids, antifertility drugs, and anabolic steroids. (6).

Punica granatum

Punica granatum (pomegranate) is a strong, drought-resistant plant. The pomegranate, on the other hand, is classified as a berry, a member of the Punicaceae family. The trees can grow up to 30 feet in height. Edible fruit has a rounded hexagonal shape. Punica granatum seeds have been used to control urine flow and the burning sensation associated with it; its peel, oil, and juice are also used to treat kidney failure and to protect against nephrotoxicity including renal arteries (7).

Punica granatum has received a lot of interest for usage in the prevention of renal calculus development because of its anti-hypercalciuria and anti-urolithiasis properties; and also, its therapeutic phytochemicals' ability to relax the muscles in the biliary and urinary tracts, kidney stones can be removed with ease. The inflammation caused by ethylene glycol was dose-dependently decreased by the administration of the *Punica granatum* methanolic extract to individual with urolithiasis. Additionally, it was discovered that the methanolic extract was more protective than the chloroform extract, which may be related to the lipophilic nature of the *Punica granatum* components. Due to their antioxidants and anti-lipid-peroxidation properties, *Punica granatum* extracts and juice significantly reduced the amount of reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), nuclear factor-B (NF-B) and p38-mitogen-activated protein kinase (p38-MAPK) while also regulating urea, creatinine, and uric acid. Patients who received *Punica granatum* extract daily showed a substantial reduction in serum paraoxonase1 (PON1) arylesterase activity as well as a reduction in calcium oxalate supersaturation, showing that this intervention was effective in reducing the risk of kidney stone formation. Anthocyanins, glucose, ascorbic acid, ellagic acid, gallic acid, caffeine, catechin, Epigallocatechin gallate (EGCG), querticin, rutin, iron, and amino acids are all found in *Punica granatum* juice.

Punicic acid and sterols make up most of the components in *Punica granatum* seed oil. There are punicalgins, flavones, flavonones, and other flavanols in the pericarp (peel, rind). *Punica granatum* leaves include essential compounds such as tannins like punicalin and punicafolin as well as flavone glycosides like luteolin and apigenin. Ursolic acid, triterpinoids including maslinic acid and asiatic acid make up the *Punica granatum* blooms. *Punica granatum* roots and bark include piperidine alkaloids and ellagitannins. The main therapeutically useful *Punica granatum* ingredients, according to recent study, appear to include ellagic acid ellagitannins (including punicalagins), punicic acid, flavonoids, anthocyanidins, anthocyanins, and estrogenic flavone . Pomegranate flowers (gulnar) contain secondary metabolites such as polyphenol, gallic acid, ellagic acid and ethyl brevifolin-carboxylate. The polyphenol has strong antioxidant activity and ellagic acid has inhibitory effect on development of tumour. The appearance of the bright colour of its flower is due to anthocyanins. Lastly, the constituents enhanced nephro-protective effect by enhancing the detoxification process and ameliorating nephrotoxicity with its protective role (8).

Bergenia ligulate

Bergenia ligulate is a perennial herb native to the Himalayan region, specifically found in Nepal, Bhutan, and India (9). It belongs to the

family Saxifragaceae and is commonly known as "Bergenia" or "elephant ears" due to the large, thick leaves that resemble the shape of elephant ears (10). *Bergenia ligulata* has been utilised in Ayurvedic medicine for centuries due to its medicinal properties. According to the Ayurvedic system of medicine, Pashanbhed is a stonebreaker that is primarily used for the treatment of kidney and bladder stones due to its ability to break and disintegrate stones. The plant's roots and foliage are used to treat numerous conditions, including kidney stones, urinary tract infections, inflammation, and wounds. (10). *Bergenia ligulata* has been traditionally used in Ayurvedic medicine for various purposes. The main constituents of *Bergenia ligulata* are important because they are responsible for the plant's pharmacological activities and potential health benefits. The various active compounds present in the plant work together synergistically to provide a range of therapeutic effects, making *Bergenia ligulate* a valuable medicine plant (11).

The main constituents of *Bergenia ligulate* that are believed to be useful in the treatment of urolithiasis including bergenin, arbutin, gallic acid, catechins, tannic acid, and β-sitosterol (12). These bioactive compounds are presented in Table 1, are believed to be responsible for the therapeutic properties of plants. *Bergenia ligulata* has a diuretic like therapeutic effect that is useful in the treatment of urolithiasis. It increases the secretion of water and electrolytes (Na^+) resulting in an increase of urine production and excretion. This aids in flushing out stones that may have formed in the kidney or urinary tract and prevents the formation of new stones. Besides, it acts by inhibiting stone formation through binding to calcium ions. This may reduce the calcium ions availability to bind with oxalate. Thus, inhibit the formation of calcium oxalate crystals in the kidney, which are a common type of kidney stone (11). Moreover, *Bergenia ligulata* can reduce oxidative stress in the kidney and urinary tract that contributes to the formation and growth of kidney stones by promoting the production of reactive oxygen species (ROS). Bergenin is a type of glucoside, which is a C-glucoside of 4-O-methyl gallic acid. Bergenin has been found to have several biological activities, including anti-inflammatory, antioxidant, antipyretic, analgesic effects, and diuretic effects (11,12).

The anti-inflammatory properties exerted by Bergenin in *Bergenia ligulata* can reduce inflammation in the body. This is important for the treatment of many diseases, as inflammation is a common underlying factor in many health problems. In the treatment of urolithiasis bergenin can reduce inflammation in the kidneys and urinary tract, where the inflammation contributes to kidney stones formation and growth. Besides, bergenin has been found to have antioxidant properties by which it reduces oxidative stress in the body. When there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralise them, oxidative stress occurs. This can contribute to cell damage and is associated with the development of many chronic diseases. Bergenin also possesses analgesic and antipyretic properties that can reduce fever and pain which is one of the symptoms of urolithiasis.

Arbutin is a glycoside of hydroquinone that is often referred to as p-hydroxyphenyl-β-d-glucopyranoside. It has been discovered to have anti-inflammatory, and anti-bacterial properties. Arbutin is present in high concentrations in *Bergenia ligulata* and has been shown to inhibit the formation of calcium oxalate crystals. In addition, gallic acid is a phenolic acid where catechins are a type of flavonoid that can be discovered in most plants. Both are secondary metabolites with anti-inflammatory and antioxidant properties (10). It has been demonstrated that they inhibit the formation of calcium oxalate crystals and reduce oxidative stress, both of which contribute to the formation of kidney stones. For β-sitosterol, phytosterol possesses several biological effect which are antioxidant, anti-inflammatory and analgesic effects (10). According to Sajad. T et al, β-sitosterol and its glucosides demonstrated that have an increase in vitro NK-cell activity, T-cell proliferative responses and the release of IL-2 and γ - interferon [Sajad et al., 2010]. This reduces

inflammation in kidneys and urinary tract which canleads to development of kidney stones and exacerbates symptoms.

***Crataeva nurvala* (varuna)**

Crataeva nurvala, commonly known as Varuna or Indian Elm, is a tree species belonging to the family Capparaceae. It is native to India and is typically found growing near streams and riverbanks throughout India. The tree is abundant in sub-Himalayan regions and is endemic to the states of Tamil Nadu, Kerala, and Karnataka. It is also found in plenty in other regions like Kerala, Madhya Pradesh, Bengal, and Assam. The flowering season of the plant is generally in March, and the fruiting season is in June. *Crataeva nurvala* has been used in traditional Ayurvedic medicine for centuries for the treatment of various health conditions, particularly those related to the urinary system (13). In ayurvedic medicine, various pharmacological activity has been exhibited by *Crataeva nurvala*. For instance, the bark and leaves of the tree are known for their diuretic properties and are commonly used for treating urinary tract disorders such as kidney and bladder stones, urinary tract infections, and prostate enlargement (13). The leaves pulp of the tree has activity on relieves of gastrointestinal disturbance like flatulence and abdominal pain. The leaves or bark also aid in wound healing on the (4). *Crataeva nurv*ala has been traditionally used in Ayurvedic medicine for the treatment of urinary stones. The antilithiatic effect of *Crataeva nurvala* is due to its ability to prevent the formation of calcium oxalate crystals, the main factor that cause urinary stones.

Studies have shown that *Crataeva nurvala* extracts can inhibit the formation and precipitation of calcium oxalate crystals. This is owing to the reason that the presence of certain compounds, such as lupeol, betulinic acid, quercetin, and beta-sitosterol, which have been shown to have anti-inflammatory, antioxidant, and anti-calcifying properties. *Cratave nurvala* increases the solubility of urinary stone components and decreases the supersaturation of calcium oxalate in the urine, which may prevent the formation of stones. Furthermore, *Crataeva nur*vala extracts have been shown to have diuretic and urinary alkalizing effects, which may help flush out stone-forming minerals from the urinary tract and prevent their precipitation. Besides, *Crataeva nurvala* bark decoction has been found to be effective in preventing the deposition of calcium and oxalate in the kidney by inhibiting the activity of the glycolic acid oxidase liver enzyme. Additionally, it has been reported that treatment with the decoction can reduce the levels of intestinal Na^+/K^+-ATPases and reduce the renal injury (14,15).

Studies on the phytochemical composition of *Crataeva nurvala* have revealed the presence of various compounds in different parts of the plant. For instance, the stem bark includes ceryl alcohol, friedelin, cadabicine diacetate, lupeol, betulinic acid, and diosgenin in addition to saponins, flavonoids, sterols and glucosilinates. Contrarily, glucocapparin, beta-sitosterol, triacontane, triacontanol, cetyl and ceryl alcohol are all present in the fruit. L-stachydrine, dodecanoic anhydride, methyl pentacosanoate, kaemferol-0-D-glucoside, and quercitin-3-0-D-glucoside are all abundant in the plant's leaves. The root bark, on the other hand, contains rutin, quercitin, lupeol, varunol and β- sitosterol. Alkaloids have also reportedly been found in the bark and stems of plants (13). Lupeol, a triterpene compound isolate from *crataeva nurvala.* According to Lakshmi. V, et.al, It has been shown to have various pharmacological activities, including anti-inflammatory, antioxidant, and anticancer properties and reduce the kidney stone (16).

In particular, lupeol has been found to have anti-inflammatory effects by inhibiting the activity of various inflammatory mediators, such as prostaglandins, cytokines, and nuclear factor kappa B (NF-κB). It has also been shown to have antioxidant properties by reducing oxidative stress and lipid peroxidation in cells. It has also been shown to have potential antilithiatic effect that prevents the deposition of calcium and oxalate in the kidney by exhibit antioxaluric and anticalciuric effects

(14). Betulinic acid is a triterpenoid compound that exhibits various pharmacological properties such as antibacterial, antiviral, anti-inflammatory, anticancer and antidiabetic effect (17). In addition, constituents that are found in the leaves of *crataeva nurvala* are kaempferol, a tetrahydroxyflavone and quercetin, a flavonoid. Both show the effect of antioxidant and anti-inflammatory. β-sitosterol, a phytosterol, also shows anti-inflammatory and antioxidant effect that are responsible in treating urolithiasis.

Boerhaavia diffusa

Boerhaavia diffusa, also known as Punarnava or Spreading Hogweed, is a herbaceous plant belonging to the family Nyctaginaceae. It is a small, perennial, creeping herb that grows extensively throughout India and many other countries. The plant has long been used to cure a variety of illnesses in Ayurveda medicine, including diabetes, stress, dyspepsia, abdominal pain, inflammation, jaundice, spleen enlargement, congestive heart failure, and bacterial infections (17). *Boerhaavia diffusa* has been found to possess various activities including anti-inflammatory, anticonvulsant, antifibrinolytic, diuretic, hepatoprotective, and immunomodulatory properties.

Boerhaavia diffusa, commonly known as Punarnava, is an Ayurvedic medicinal plant widely used in India for the treatment of various ailments, including urolithiasis. Studies have shown that the extract of *Boerhaavia diffusa* exhibits antilithiatic effects by inhibiting the deposition of calcium and oxalate in the kidney. Besides, *Boerhaavia diffusa* has been reported to have a beneficial effect on urinary stone problems.

The ethanolic extract of BD was found to reduce the size of crystals and promote the formation of calcium oxalate dihydrate (COD) crystals more than monohydrate (COM) crystals. *Boerhaavia diffusa* contains various active constituents that are responsible for its medicinal properties. The major constituents present in *Boerhaavia diffusa* include alkaloids, flavonoids, glycosides, phenolics, steroids, terpenoids, and fatty acids. The alkaloids present in *Boerhaavia diffusa* include punarnavine. Punarnavine has been reported to have diuretic and anti-inflammatory effects. Punarnavoside, on the other hand, has been shown to possess anti-inflammatory, anti-fibrotic, and anti-cancer activities. Flavonoids are also present in *Boerhaavia diffusa* and include kaempferol, quercetin, and rutin. These compounds are known for their antioxidant and anti-inflammatory effects. Glycosides such as boeravinone, the member of rotenones also present in *Boerhaavia diffusa*. Boeravinone possesses an antilithiatic effect, antioxidant and anti-inflammatory effect. Phenolics and tannins, which are also present in Boerhaavia diffusa, have antioxidant and anti-inflammatory effects. Steroids such as stigmasterol and campesterol have been shown to possess anti-inflammatory and immunomodulatory effects (18).

Herniaria hirsute L.

Herniaria hirsuta L, commonly called hairy rupturewort, a somewhat inconspicuous, low-growing annual. *Herniaria hirsuta* is a species of flowering plant in the family Caryophyllaceae. Herniaria species have roots that are thin and thick, stems that are procumbent, prostrate, or ascending, branching from the base, caespitose, angular and occasionally woody. The general habit for the *Herniaria hirsute* is in the temperate Himalayas. The global distribution is at India, Europe, North America, and Pakistan. Aseptic, mildly spasmolytic, and highly effective in treating inflammations of the urinary system, kidneys, and gallbladder are some names for *Herniaria hirsuta L* (19).

H. histura can inhibit CaOx crystallization. An extract from the herb *H. histura. L* a plant that traditionally is used in Morocco for the treatment of lithiasis. The calcium oxalate crystallisation process may be aided by this plant. As a result, it may result in an increase in quantity or a decrease in size. Moreover, *H. hirsuta* can prevent crystal binding to renal cell cultures (20). Despite the presence of calcium oxalate monohydrate particles, it also encouraged the production of

calcium oxalate dihydrate crystals. Before causing crystallisation in a separate experiment, the herb extract was dialyzed and filtered to remove any fibrous particles and oxalate. As a result, the crystallisation of calcium oxalate is prevented. Certain characteristics of *H. hirsuta* may help to prevent kidney stone development. More crystallisation was encouraged by the treated herb extract, especially at high doses (21).

H. histura contains various active constituents that are responsible for its therapeutic qualities. The major constituents present in *H. histure* include flavonoids, and saponins. Herniaria saponins E, F, and G, three monodesmosidic derivatives of medicagenic acid, and herniariasaponin H, a bidesmosidic derivative, have all been identified in *H. hirsute. H. hirsuta's* saponins or their metabolites are thought to have antilithiatic properties. Several natural products known as prodrugs become active after undergoing biotransformation, as is widely known. The presence of several aglycones allowed for the detection of the saponins. The diverse sugar chain compositions and a variety of sugar moiety couplings.

As a result of fragmentation, product ions produced by the elimination of sugar moieties were presented in a distinctive way, showing glycosidic O-linkages [Peeters et al.,2020]. Flash chromatography and subsequent semi-preparative HPLC were used to separate the three flavonoids known as quercetin-3-O-(2″-O-L-rhamnopyranosyl)-D-glucuronopyranoside, rutin, and narcissin. These flavonoids were then identified using MS and 1D and 2D NMR spectroscopic methods. Most flavonoids found were glycoconjugates. the sugar moieties that are joined to the flavonoid aglycone. Product ions produced by the removal of sugar moieties during collision-induced fragmentation indicated the presence of glycosidic O-linkages. Other substances were also found, including free phenolic compounds and hydroxycinnamic acids. Using analytical standards, caffeic, p-coumaric, and chlorogenic acids were detected, among others (21).

Tribulus terrestris

Tribulus terrestris is a widely distributed annual plant belonging to the caltrop family that is used medicinally in the form of whole dried herbs and mature fruits. It is adapted to flourish in locations with a dry climate where few other plants can survive. It is indigenous to mild temperate and tropical regions in the southern regions of Eurasia and Africa. Tribulus terrestris is a Mediterranean plant that produces fruit and is clad in spines. Also known as perforation vine. The fruit, leaf, and rhizome of the tribulus plant are used medicinally. Modern pharmacological research has demonstrated that T. terrestris possesses neuroprotective, anti-inflammatory, anti-fibrosis], anti-cancer, and anti-lithiatic properties, highlighting its significant impact on the treatment of ischemic stroke, inflammation, pulmonary fibrosis, liver cancer, and urolithiasis. Steroids, saponins, flavonoids, sterols, Harman alka-loids, minerals, lignan amides, and cinnamic acid amides are the primary components of Tribulus terrestis.

The group of chemicals known as saponins has a variety of structures made up of hydrophobic aglycone and hydrophilic sugar residues. Typically, they are separated into triterpenoid, and steroid glycosides, or into triterpenoid, spirostanol, and furostanol saponins (22). The basic flavonoids in *Tribulus terrestis* which is kaempferol, astragalin, kaempferol-3-rhamnoglycoside, tribuluside, and rutin [Semerdjieva et al.,2019]. Due to their diuretic, antioxidant, anti-inflammatory, antibacterial and other preventive qualities, flavonoids can effectively prevent the development of CaOx stones. Hence, plant extracts high in flavonoids or flavonoid-containing compounds have anti-urolithiasis properties (23). The fruits of *Tribulus terrestris* include the tribulusamides A and B, lignan amides. These substances shield cells from cancers that are brought on by D-galactosamine or tumour necrosis factor α (22).

Terrestriamide and 7-methylhydroindanone-1 are two new compounds of the cinnamic acid amides found in fruits. From

the fruits of *Tribulus terrestis,* lignan amide known as tribulusamide, a feruloyl amide derivative, was discovered. To determine the inhibition of -glucosidase in the fruits of *Tribulus terrestis*, it differs from other lignan amides due to the presence of pyrrolidine-2,5-dione. Sitosterol, stigmasterol, and campesterol are the sterols that are provided (22).

Tribulus Terrestris can treat urolithiasis by having a diuretic impact. The muscles in the urinary system are relaxed because of its anti-spasmodic effects. This aids in easing the stomach pain that develops as the stone tries to pass through the urinary tract's constrained openings. Tribulus terrestris reduce the number of calcium oxalate monohydrate, but the CaOx dihydrate gradually rise as the concentration of little caltrops rises. Due to the presence of steroidal glycosides and steroidal saponins in *tribulus terrestris,* the majority of CaOx particles were seen as octahedral crystals of COD. As a result, these functional protein and acid groups could change the COM structure to COD. Following the reaction between $CaCl_2$ and $Na_2C_2O_4$, CaOx crystallised, with the stable COM being the predominant phase. Tribulus terrestris converts the majority of glycolate to glyoxylate by inhibiting the enzyme GAO at the second oxidation phase where glyoxylate is converted to oxalate, resulting in glyoxylate accumulation and its rapid removal via urinary excretion. Tribulus terrestris significantly decreased oxalate excretion by increasing glyoxylate excretion. Tribulus terrestris converts the majority of glycolate to glyoxylate by inhibiting the enzyme GAO at the second oxidation phase where glyoxylate is converted to oxalate, resulting in glyoxylate accumulation and its rapid removal via urinary excretion. Tribulus terrestris significantly decreased oxalate excretion by increasing glyoxylate excretion (23).

Trachyspermum ammi

Like cumin and caraway, *Trachyspermum ammi* is a plant that yields tiny, seed-like fruits. It belongs to the Apiaceae family of plants, which also contains parsnips, celery, caraway, coriander, fennel, and parsley. *Trachyspermum ammi,* also called ajwain or caraway, is a plant that originated in Egypt and is now widely cultivated in Iraq, Iran, Afghanistan, Pakistan, and India. In India and eastern Asia, the seeds of *Trachyspermum ammi* are commonly consumed and utilised in traditional medicine. It smells like thyme and has a strong, bitter flavour. The fruit seeds are usually dry-roasted or crushed and added to spice blends [Mushtaq et al., 2021]. In toothpaste and fragrance, it serves as a potent fungicide, antispasmodic and germicide (24). Fiber, carbohydrates, tannins, glycosides, moisture, protein, fat, saponins, flavones, and mineral matter are all present in *Trachyspermum ammi*. Thymol and carvacrol were the two main nonphenolic components identified in the ajwain essential oil, together with p-cymene and p -terpinene (25).

Thymol, a phenolic monoterpene molecule that is isomeric with carvacrol, is mostly present in *Trachyspermum ammi* essential oil. During aromization of -terpinene to p-cymene, thymol is employed as a stabiliser from the hydride of p-cymene (24). Aluminum, calcium, cadmium, copper, iron and lithium are among the minerals found in ajwain fruit. However, nitrates and nitrite have not been found in ajwain fruit. The fruits provided calcium, chromium, cobalt, copper, iodine, iron, manganese, phosphorus, zinc, riboflavin, thiamine, nicotinic acid and carotene (26). Like potassium citrate, *Trachyspermum ammi* exhibited diuretic properties that prevented the crystallisation of calcium oxalate (CaOx) in a concentration-dependent manner. The trachyspermum ammi can maintain renal functioning and reduce renal injury. So, it can maintain the retention in renal tissues.

Chanca Piedra (*Phyllanthus niruri* L)

Chanca Piedra, also known as *Phyllanthus niruri* L. is belong to Phyllanthaceae plant family and species of *Niruriamarus* [Beto et al., 2019]. It can be found in tropical areas all over the world, like Afrika, China and India. Its habitat is mainly in the rainforest and grows by spreading freely. So, it is called quinine weed which then

translated to Stone breaker as it can cure urolithiasis, which is also known as kidney stone disease in general (27). The whole part of the plant is used in plant extraction including leaves, bark and stems.

It is alkaline in nature, which interferes with calcium oxalate deposits by renal tubular cells (28). So, it acts as an alternative alkalizing agent to replace sodium bicarbonate and potassium citrate. It has been proved to have the ability to decrease kidney stone size by disrupting the complexing of calcium in the urine. Since it is alkaline, it increases the solubility of calcium in the urine therefore the concentration of free calcium be reduced. This causes the inhibition of the growth of calcium phosphate and also prevents the crystallization of calcium oxalate which forms kidney stones. Besides that, It also raises the urine pH in order to limit urine citrate uptake (29). There are dozens of commercial herbal products of *Chanca Piedra* selling in the market nowadays. The supplements are usually taken orally. The side effects include nausea and stomach pain. *Chanca Piedra* may increase the risk of bleeding as it might slow down the blood clotting process (30). The main contituents present in *Chanca Piedra* are Phyllanthin and quercetin.

Nigella sativa

Nigella sativa, commonly known as black seed or black cumin, has been used to treat urolithiasis for centuries. It belongs to the Ranunculaceae family (28). It originated in Southeastern Asia. Its fruit has been used as food preservative and spice. While its seeds and oils are being extracted and studied. In traditional references, black seed can be used alone or by combination with water and honey which indicated for renal stone dissolution. The seed crude is found to contain the main constituent, thymoquinone, which plays an important role in kidney stone disease treatment. An active quinone interferes with the calcium oxalate deposits and prevents the calcium oxalate endocytosis. It has an anti-urolithiasis effect by preventing the accumulation of calcium oxalate crystal in the urinary tract by dissolving the kidney stones. This can reduce the size the number of kidney calcium oxalate deposits. Thymoquinone can minimize the oxidative and lipid peroxidation markers which significantly reduce the creatinine and urea concentration. Thymoquinone on the other hand has antioxidant and free radical effects inhibiting the cyclooxygenase and lipoxygenase pathways. This prevents crystal binding and inflammation in the kidney by inhibiting the regulation of COX-2 enzyme by oxalate (31).

However, black seed can only be used for early-stage kidney stone disease when the stones are smaller as the efficacy of the medication reduce as the increment of stone size. Black seed products may be topical or taken orally with food. Black seed may increase the secretion of serotonin which induce various side effects including vomiting and heart problems (32). Thymoquinone, Thymol, Hydroquinone is present in *Nigela sativa*.

Salvia hispanica L

Salvia hispanica L. can be found almost throughout the world. It belongs to Lamiaceae family from genus *Salvia*. It is widely used as raw material in preparation of medications, food, supplement due to it high nutritional value and multiple healing properties including anti-inflammatory, antioxidation and anti-urolithiasis effect. The seed of plant which is also known as chia seed is extracted to get quercetin and mycertin which perform anti-urolithiasis activity.

It is proved that chia seed extraction can reduce the levels of creatinine, urea, urea nitrogen and uric acid in the urine. It inhibits the initial stages of calcium oxalate crystal formation including nucleation and crystallization, aggregation and growth of kidney stone. The prevention of urolithiasis formation is due to the reduction of urinary calcium and phosphate levels. The precipitation of calcium oxalate stone is also inhibited by the antioxidant properties of quercetin which stimulate the secretion of antioxidant enzyme. It can absorb the toxins and heavy metals in the body thus the aggregation of calcium oxalate can be minimized. Chia seed is highly rich in fiber,

therefore excessive intake of chia seed may cause digestive issues such as abdominal pain, bloating, constipation and diarrhea. Chia seeds, which is rich in Omega-3 fatty acid often prepare as the meal replacement for patient suffering from obesity as it can create a feeling of satiety.

Conclusion

In conclusion, many natural plants and their phytochemicals may be useful in the prevention and treatment of urolithiasis. Natural plants are chemical complex that consist of essential compounds which capable of exerting the pharmacological action on the target tissues and/or organs and primarily used for health promotion and the treatment of chronic, rather than life-threatening condition. The use of natural plants as traditional remedies also comes into play when conventional medicine is ineffective in treating diseases such as advanced cancer or when new diseases emerge, therefore, it is crucial for health care professionals to understand pharmacokinetics, evidence-based knowledge about efficacy, pharmacological mechanisms, and side effects. Studying the pharmacokinetic effects and herb-drug interactions of the important compounds, as well as their associated mechanism of action at molecular level, help to maximise the therapeutic effect while minimising the toxic effect of herbal drugs, thus providing the safe and effective treatment to mitigate various kidney diseases such as urolithiasis.

Acknowledgement

The authors would like to thank UCSI University for the support provided by the Research Excellence and Innovation Grant (REIG) with code REIG-FPS-2022/063.

Conflicts of Interest

The authors declare no conflict of interest.

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