BAGHDAD JOURNAL OF BIOCHEMISTRY AND APPLIED BIOLOGICAL SCIENCES
2022, VOL. 3, NO. 02, 69-98, e-ISSN: 2706-9915, p-ISSN: 2706-9907
https://doi.org/10.47419/bjbabs.v3i02.133

REVIEW ARTICLE

Therapeutic potential of medicinal plants for the management of renal stones

Mohammed I. Rasool[1], Tariq H. Mousa[2], Hayjaa M. Alhamadani[3] and Ahmed H. Ismael[4]

[1]Department of Pharmacology and Toxicology, College of Pharmacy, University of Kerbala, Kerbala, Iraq
[2]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Kerbala, Iraq
[3]Medical Technical College, Alfarahidy University, Baghdad, Iraq
[4]Department of Clinical Pharmacy, College of Pharmacy, University of Kerbala, Kerbala, Iraq

ABSTRACT

Kidney stone disease is the third most common urological ailment worldwide, people. The mechanism of stone formation includes: urine supersaturation, aggregation, retention, nucleation, and growth of crystals in the cells of the renal tubular epithelium. Kidney stones may cause extreme pain and blockage of urine flow. They are usually treated with conventional drugs and extracorporeal shock wave lithotripsy (ESWL) as well as a variety of medications that may cause several adverse effects. The remaining stone fragments and the risk of infection following ESWL are major challenges in the treatment of kidney stones. Recently, despite the emergence of modern drugs, medicinal plants have been recognized and utilized in many nations clinically due to their safety profile, efficiency, cultural acceptance, and fewer side effects than approved drugs. Medicinal plants are used in different cultures as a reliable source of natural remedies. The aim of this review is to provide comprehensive information about traditionally used antiurolithiatic plants as well as their scientifically proven pharmacological activities, their primary chemical ingredients, and potential mechanisms of action, such as analgesic, astringent, demulcent, diuretic activity, antioxidant activity, inhibition of the inflammatory process, nucleation inhibition, crystallization inhibition, inhibition of crystal aggregation, reducing hyperoxaluria, reducing stone size, and reducing urine supersaturation.

Keywords alkaloids, flavonoids, kidney stones, nephrolithiasis, phytochemicals, phytomedicine

Received 19-05-2022
Revised 27-06-2022
Accepted 28-06-2022
Published 30-06-2022

Corresponding Author
Mohammed I. Rasool
mesihani@gmail.com

Department of Pharmacology and Toxicology, College of Pharmacy, University of Kerbala, Kerbala, Iraq

DOI https://doi.org/10.47419/bjbabs.v3i02.133

Pages: 69-98

INTRODUCTION

Nephrolithiasis (also known as kidney stones, urolithiasis or renal calculi) is the presence of stones (hard mass) in kidneys. Kidney stones are mainly caused by a disruption in the equilibrium between solubility and precipitation of salts in the urinary system and kidneys.

Kidney stone disease affects people between the ages of 20 and 60, and it is more common in hot environments. It affects roughly 10% of people in their lives, with the occurrence rising with age; 50% of individuals might have a recurrence within 5–10 years, and 75% within 20 years.[1–3] Kidney stones is nearly three times more prevalent in men than in women, due to men's lower stone inhibition levels; although, stone inhibitor levels begin to fall after menopause, which might indicate why kidney stone development is equally common in both sexes as they get older.[4,5] Nephrolithiasis is also more prevalent in wealthy countries like hypertension, obesity and type 2 diabetes.[6,7] Patients who experience severe colic pain caused by kidney stones are not often completely relieved by traditional painkiller medications. Additionally, severe urinary tract blockage, infection, hydronephrosis and significant urinary tract hemorrhage might commonly occur in individuals with kidney stones. One of the most well-known approaches for managing very large stones is the renal stone open surgery. Nowadays, due to the confirmed side effects of conventional drugs, the tendency of consuming medicinal plants has increased.[8–10]Figure 1 shows the mode of action of medicinal herbs against urolithiasis.

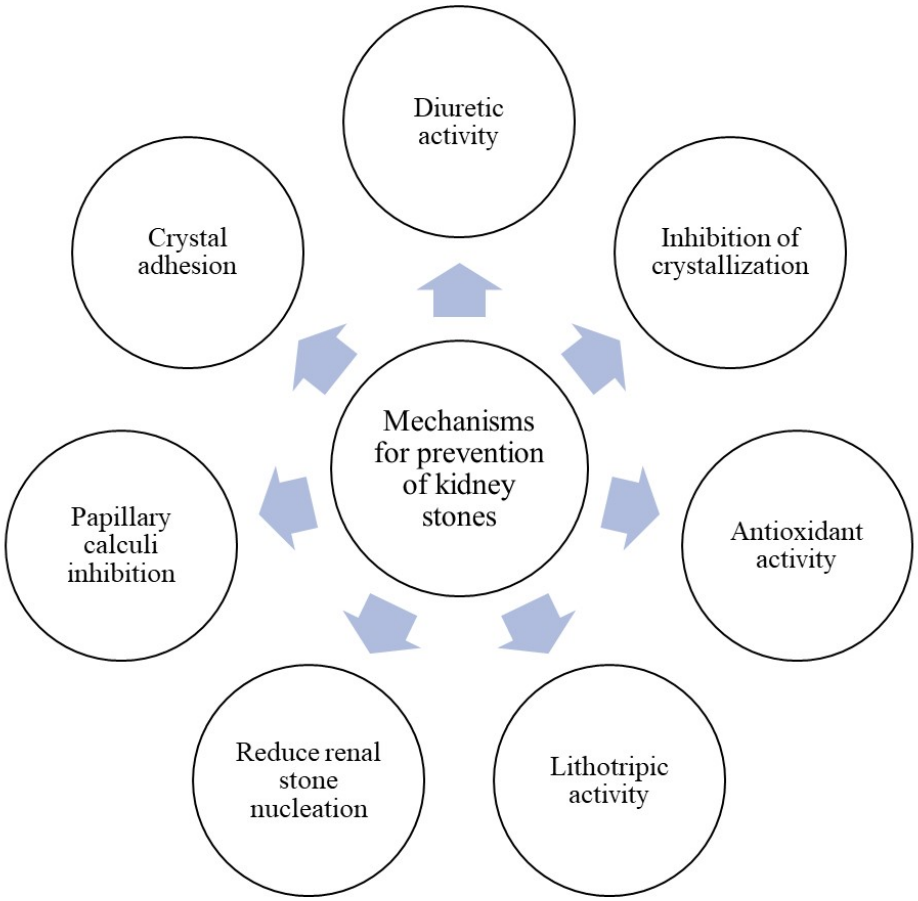


Figure 1 **The reported ways of phytochemical molecules against kidney stone formation.**[11,12]

LITERATURE SEARCH STRATEGY

The focus in this study was on the most frequent antiurolithiatic medicinal herbs, as well as new findings and mechanisms of action that support them. The surveyed literature was within the period from 1980 to 2021. The searched keywords (and phrases) were "urinary stone", "urolithiasis", "renal stone", "renal calculi", "antilithic", "calcium oxalate stones", "kidney stone", "dietary herb", "dietary plant", "fruits", and "phytochemical" in the title and abstract, as well as the name of each herb in the entire text. Each of keywords/phrases and herbs were searched in online electronic databases of PubMed, Scopus, and Google Scholar. All retrieved articles were screened for any *in vitro*, *in vivo*, or clinical evidence about the efficacy and pharmacological mechanisms related to urinary stones. The included papers were further assessed for the feasibility of the plant to be employed as a nutritional product, phytochemical composition, and the type of renal calculi that the plant or its compounds are effective on as well as the underlying modes of action.

RISK FACTORS OF KIDNEY STONE DEVELOPMENT

Several factors have been stated to influence the formation of renal stones. Excessive consumption of salt and animal proteins, as well as inadequacies in chelating agents such as alkali foods, fiber, and citrate are among the lifestyle habits and nutritional factors. Urinary stone production can also be aided by metabolic abnormalities such as hyperuricosuria (high amount of urinary uric acid excretion), hypercalciuria (excess calcium in the urine), hyperoxaluria (elevated excretion of oxalate in urine), hypocitraturia (low urinary citrate excretion), and a history of gout (defective uric acid biotransformation). Primary hyperparathyroidism (excessive parathyroid hormone production via the parathyroid gland) and hypercalcemic disorders as well as other calcium abnormalities may be considered as a risk factors. Other risk factors include metabolic urine composition, such as the high excretion of urinary crystallization promoters and the lower amounts in urine of inhibitory substances. Additionally, decreased volume of urine, insufficient water intake (dehydration and supersaturated urine) can contribute to urinary stone formation. Other factors include frequent urinary tract infections (UTIs), aberrant urinary pH, alkalinization of urine by bacterial urease [like that of *Proteus mirabilis*, which frequently causes catheter-associated UTIs that may be accompanied by urolithiasis (the formation of struvite or apatite stones)], renal tubular acidosis, as well as genetic susceptibility (family history of stones) and monogenic illnesses which are examples of genetic inherited/predisposition conditions. Furthermore, hypertension, obesity, and climate change (global warming), occupation, geographic conditions, and seasonal variations (higher in summer than winter) can have a role in nephrolithiasis. Inflammatory bowel disease and other intestinal malabsorption or other associated disease states of absence of intestinal oxalate-degrading bacteria can be a risk factor. Furthermore, there are certain types of drugs that could promote the development of renal calculi these include sulfonamides (sulfadiazine), protease inhibitors, indinavir, ceftriaxone

(high dosage for lengthy periods of time), and uricosuric agents.[13]

SYMPTOMS OF KIDNEY STONE

Kidney stone symptoms vary depending on whether the stone it is in the urinary bladder, kidney, or ureter. At first, stone development is not associated with any symptom. Later, the stone disease's clinical manifestations may include renal colic, oliguria (low amount of urine due to a stone obstruction of the urethra or bladder), hematuria (bloody urine), dysuria (burning on urination). These conditions may result in nausea, vomiting, UTIs or obstructive uropathy (urinary tract disease), pyuria (pus in the urine), and hydronephrosis (dilation of the kidney).[14]

TYPES OF KIDNEY STONES

The abnormalities of urine chemical composition are the main factors that determine the type of stone. The stones distribution and frequency depend on geographical location.[15] The ability of various components in humans to stimulate or inhibit the production of stones is referred to as promoters and inhibitors (Table 1).

Table 1 The inhibitors and promoters of nephrolithiasis.[11]

Inhibitors	**Role**
Magnesium (Mg)	Inhibition of crystal growth and aggregation.
Alkaline pH	Inhibits cystine and uric acid stone formation.
Citrate	Form complex with calcium (Ca) so, the calcium oxalate (CaOx) supersaturation decrease.
Promotors	
Urine volume	Low urine production promotes crystallization.
Urine pH	Highly acidic media enhance (CaOx) crystallization.
Hypercalciuria	Enhance urine supersaturation and hence crystallization of Ca.
Uric acid or urate	Promotes heterogenous nucleation and increase binding between cells and CaOx.

Calcium stones

Calcium stones include: calcium oxalate (CaOx), calcium phosphate, and calcium urate stones. Up to 80% of kidney stone are CaOx. The major contributor to CaOx stones formation is hyperoxaluria (high urinary oxalate content). The risk of kidney stones caused by CaOx was also influenced by the absence/decrease in the expression of several enzymes required for food degradation of oxalate as it seems to have a significant impact on how much oxalate is excreted in the urine.[14,16] Among calcium stone promoters, hypocitraturia a and hypercalciuria are two of the most prominent urinary disorders (Proofread and check,

please).[17] Citrate inhibits renal calculi development through binding to calcium (Ca), rendering it unable to combine to phosphate or oxalate and, thus; preventing the crystallization process.[18]

Struvite stones

Struvite stones also called infectin stones or triple phosphate stones. They are found in 10-15 % of the population. They and common among patients suffering from chronic urinary tract infections (UTIs) caused by bacterial species that produce urease (e.g. *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*).[19,20] Urease is cleaved into ammonia and carbon dioxide (CO_2) and elevate urine pH above 7.[21] This form of stones is more likely to occur in women than in men.[22]

Uric acid stones

It is 6 to 10% more common in men than women. Many factors may contribute to uric acid stones formation. High purine intake, especially diet containing high level of animal protein such as meat and fish, may trigger uric acid stone formation due to hypreuricosuric effect, low urine volume, and decreased the urinary pH (<5). Patients with gouty arthritis are also at risk for uric acid renal calculi. This type can usually be seen in the radiolucent on X-ray film.[23–25]

Cystine stones

They are associated with cystinuria which is a hereditary intrinsic metabolic defect that impairs cystine reabsorption in the renal tubule. X-rays can occasionally detect stones that are difficult to see. Cystine stones represent about 1-2% of renal stones.[26]

Drugs-induced stones

This type of kidney stones is rare. A variety of medications can contribute to the formation of renal stones such as, guaifenesin, sulfa drugs (sulfadiazine), indinavir, atazanavir, and other protease inhibitors, silicate (antacids), ceftriaxone, and uricosuric agents.[4,11]

SYNTHETIC NEPHROLITHIASIS MEDICATIONS

Thiazides diuretics

Thiazide diuretics are one of the most well-known medicinal treatments for renal stone prophylaxis. They decrease the Ca amount of urinary excretion and thus lower the amount of Ca in urine to form renal stones.[4,12]

Allopurinol

Allopurinol has many advantages against certain calcium renal stones. It intervenes with the uric acid hepatic production. The drug lowers the development of calcium stones in such individuals. Allopurinol is also employed for gout (or hyperuricemia) patients. Additionally, sodium bicarbonate, potassium bicarbonate or acetazolamide, citrate in the form of sodium citrate (Shohl's solution), potassium citrate also prevents the production of uric acid renal stones which are caused by urine alkalinization.[4,14]

NSAIDs

Analgesics or painkillers such as non-steroidal anti-inflammatory drugs (NSAIDS) are commonly utilized in emergency rooms. For less severe discomfort, oral drugs such as opioids are frequently beneficial. Acetaminophen used intravenously appears to be efficient as a pain-relieving agent.[4,12]

Tamsulosin

Tamsulosin, a selective alpha 1-adrenergic receptor blocker, may occasionally facilitate the passage of renal stones.[4,12]

MECHANISMS OF KIDNEY STONE FORMATION

Renal stones are formed as a result of increased urinary supersaturation, which leads to the formation of crystalline particles. Supersaturation is the determinant for crystallization in fluids like urine. When a solvent is introduced to a salt, the salt dissolves until it reaches a specific concentration, beyond which it is difficult for the salt to dissolve anymore. At this stage, the solvent is considered to be salt-saturated. As temperature and pH remain constant, more salt crystallizes in solution. If crystallization blockers are ineffective, nephrolithiasis will develop.[27,28] The steps of stone formation are as follows:

Nucleation

Nucleation refers to the first step in a supersaturated solution's transformation from a liquid to solid phase. This begins with the formation of loose clusters of stone salts in solution, which may grow in size as new components or clusters are added.[27,29]

Crystal growth

Crystal growth, which takes place after nucleation, is the next fundamental stage in renal stone formation. During this process, many molecules or atoms in a supersaturated solution begin to cluster. The supersaturation levels, shape/size of molecule, pH, physical properties of the materials, and faults that may emerge in the structure of the crystal, all may influence crystal growth.[30,31]

Aggregation

Aggregation is a critical step in the formation of stones. It is generally known as a step of crystal agglomeration and formation of large multicomponent particles.[32] A balance of forces determines particle aggregation in a solution, which includes both aggregating and disaggregating actions. Particle aggregation is aided by small interparticle distances, which increase attractive forces and enhance particle aggregation.[31,33]

PLANTS WITH ANTIUROLITHIATC EFFECT

Many medicinal plants listed in Table 2 could reverse the processes of stone formation and prevent the kidneys from stones.

Barberry (*Berberis vulgaris*)

It is a member of Berberidaceae family important in Iranian and Chinese traditional medicine over 3000 years ago for treating many diseases. The *B. vulgaris* contains a variety of active phytochemical compounds including ascorbic acid, more than 30 types of alkaloids, and phenolic compounds.[89] The most important alkaloids are the berberine that can exert many effects such as antioxidant, nephrolithiatic, and anti-inflammatory activities.[34] In kidney stones treatment, berberine shows effectiveness in the prevention and treatment of CaOx urolithiasis, these effects are due to their antioxidant, diuretic, hypocalciuric, and urine alkalinizing activities. The diuretics effect of berberine causes an elevation in the volume of urine by the saluretic effect also there will be a rise in urine pH and decrease in urine calcium content. The major risk of stone development is crystal deposition due to urinary supersaturation with presence of stone forming minerals. The high level of oxalate cause antioxidant imbalance results from greater production of superoxide and hydroxyl free radicals. Therefore, the antioxidant effect of berberine inhibit the retention of CaOx to renal tubules.[35,90–92] Berberine has the potential to induce rashes, constipation, and indigestion. It should be used be used with caution by pregnant or nursing women. Berberine can make newborns' jaundice worse, or it might induce a more serious illness that leads to a brain disorder. It can also interact with certain medications such as anticoagulants, blood pressure drugs, hypoglycemic medications, diuretics, as well as any other compounds metabolized by the liver.[40]

Table 2 **Medicinal plants and their medicinal activities against renal stones.**

Plant	Part of Plant	Mechanisms	Reference
Barberry (*Berberis vulgaris*)	Roots	Antioxidant, diuretic, anti-inflammatory	34
Black seed (*Nigella sativa*)	Seeds	Reduce CaOx deposition, antioxidant, anti-inflammatory	35–37
Celery (*Apium graveolens*)	Whole plant	Diuretics	38–40
Green tea (*Camellia sinensis*)	Leaves	Diuretics antioxidant	41,42
Khella balad (*Ammi visnaga*)	Fruits	Muscle's relaxant, antioxidant, analgesic, diuretic, antiurolithiatc, lithotriptic	43–46
Maize (*Zea mays*)	Flowers	Diuretics	47
Manjistha (*Rubia cordifolia*)	Roots	Decrease Ca and oxalate level in kidneys, inhibiting the growth of urinary stones	48,49
Ngingihel (*Phyllantus niruri*)	Roots	Inhibit cytotoxicity induced by CaOx stone, antispasmodic, inhibit crystallization	50
Olive (*Olea europaea*)	Leaves	Antioxidant, diuretics	51,52
Oregano (*Origanum vulgare* L.)	Leaves	Diuretics, antispasmodic, antioxidant prevent CaOx formation	53,54
Parsley (*Petroselinum crispum*)	Seeds	Increasing urinary pH, diuresis, and urine volume while decreasing urinary calcium excretion.	55
Pomegranate (*Punica granatum*)	Flowers	Muscle relaxation, antioxidant, anti-hypercalciuric, antiurolithiatc	11,56–59
Radish (*Raphanus sativus* L.)	Leaves	Diuretic, lithotriptic, reduce CaOx crystallization	60–63
Raspberry (*Rubus idaeus*)	Roots	Antilithiatic, diuretics	64–66
Roselle (*Hibiscus sabdariffa*)	Flowers	Increase uric acid excretion, and inhibit COM crystallization	67–70
Rupturewort (*Herniaria hirsuta*)	Aerial part	Inhibit CaOx aggregation, and prevent the COM adhesion.	71–74
Saffron (*Crocus sativus* L.)	Flowers	Diuretic, Increase oxalate renal excretion, decrease magnesium and citrate excretion.	75,76
Shatavari (*Asparagus racemosus*)	Roots	Diuretic, antiurolithiatc	77–79
Thai green eggplant (*Solanum xanthacarpum*)	Roots	Reduce CaOx stone deposition, antioxidant, anti-inflammatory	80–83
Turmeric (*Curcuma longa* L.)	Roots	Decrease the level of Ca and oxalate in urine. Decrease stones deposit	84–86
Venus Hair (*Adiantum capillus-veneris*)	Whole plant	The anti-calcium oxalate urolithiasis, litholytic	87,88

CaOx: calcium oxalate, **Ca:** calcium, **COM:** calcium oxalate monohydrate.

Black seed (*Nigella sativa*)

The plant *N. sativa* belongs to the Ranunculaceae family. The following ingredients have been reported in *N. sativa* seeds: alkaloids, saponin proteins, fixed oils, and essential oil. The main active ingredients in essential oil are thymoquinone, dithymoquinone, thymohydroquinone, and thymol.[93,94] Thymoquinone is a main constituent of *N. sativa* and responsible for its pharmacological actions especially for treating nephrolithiasis. In an earlier study, *N. sativa* had beneficial effect on CaOx stone deposited in rat kidneys by reducing the number and size of these stones.[36] Also, thymoquinone has a significant antioxidant effect by cleaning free radicals and superoxide anion when the stone is deposited in the kidney that leads to epithelial tissue damage and production of free radicals and superoxide anions. These products stimulate heterogenic crystal nucleation.[37] The thymoquinone can inhibit the cyclooxygenase and 5-lipoxygenase pathways resulting in the inhibition of the inflammatory process.[95] Black seed seems to be safe in food during pregnancy. However, taking larger medicinal amounts is likely unsafe. It can slow down or stop the uterus from contracting. Black seed might slow blood clotting and increase the risk of bleeding. Additionally, black seed might lower blood sugar and blood pressure levels in some people.[38]

Celery (*Apium graveolens*)

Apium graveolens L. is a herb that belongs to the family (Apiaceae). It is a flavonoid-rich herb that can dissolve calcium crystals. Because of its prevalence and abundance in celery, apigenin is regarded one of the most important flavonoids.[39] In an *in vivo* study conducted to evaluate the effect of *A. graveolens* in reducing calcium deposits from the renal parenchyma in a rabbit model with induced nephrocalcinosis by a large dose of oxalic acid, it resulted in a considerable decrease in blood urea nitrogen (BUN), serum creatinine, and sodium (Na^+) serum levels as well as a non-significant decrease in serum potassium (K^+) level. There was a notable reduction in calcium accumulation in renal parenchyma, which is attributable to its diuretic action, which may be connected to its contents. Therefore, *A. graveolens* reduces calcium deposits in renal tissues by acting as a diuretic and suppressing agent.[40] Celery oil and seeds, at the levels seen in medicine, are probably dangerous to ingest by mouth during pregnancy. This is because celery in large amounts might cause the uterus to contract, resulting in increased risk of an abortion. There isn't enough reliable evidence to determine whether celery is safe to consume during lactation. When taken at therapeutic doses, celery has been linked to an increased risk of bleeding. In case of kidney damage, celery should be avoided. It may also have the ability to lower the blood pressure.[96]

Green tea (*Camellia sinensis*)

Green tea is obtained from the leaves of *C. sinensis*. It belongs to the Theaceae family and used as a medical treatment from about 4000 years ago in the Asian region which include China and India for the treatment of many diseases such diabetes mellitus, obesity,

skin damage, and cardiovascular diseases.[97–99] Green tea acts as a protective agent towards kidney stone risk, and this activity is explained by two mechanisms. First, the diuretic and natriuretic effects of the tea due to presence of caffeine these effects together increase excretion of magnesium, calcium, chloride, and potassium. Second, the antioxidant properties of green tea which show direct inhibitory effect on CaOx stone formation, increases superoxide dismutase, and neutralize oxygen reactive species. These properties was ascribed to catechins such as, epigallocatechin gallate, epigallocatechin, epicatechin gallate, and epicatechin.[41,42] Furthermore, due to the presence caffeine in green tea, it used with caution in many cases such anxiety disorder, bleeding disorder, heart conditions, diabetes, diarrhea, glaucoma, irritable bowel disease, liver diseases, and weak bones. The large amount of green tea can worsen these conditions. Also, green tea can interact with amphetamine, cocaine, and ephedrine.[100]

Khella baladi (*Ammi visnaga*)

Ammi visnaga is a herb belonging to the family Apiaceae, an annual herb native to North Africa, Asia, European, and Mediterranean regions. The herb has a long history of usage in traditional medicine. The pharmacological actions are attributed to the plant's valuable chemical contents, which include essential oil, polyphenolic compounds such as flavonoids, and γ-pyrones, which are mostly represented by khellin and visnagin. Its flavonoid content is responsible for its antioxidant activity. And, its γ-pyrones component assists in the passage of kidney stones and relieves renal colic, as well as relaxing smooth muscle, including that of the coronary arteries.[43] Egyptian patients with renal stones have long utilized teas made from the fruits of *A. visnaga*.[44] This fruit's aqueous extract has been shown to hasten the breakdown of cystine stones. In a previous study, the fruit with its two main components, visnagin and khellin, were found to be effective in treating kidney stones produced by hyperoxaluria in male rats through reducing the risk of CaOx crystal formation, elevating citrate urine output while decreasing the oxalate excretion.[44] Khellin and visnagin, both isolated from *A. visnaga*, were thought to have pleiotropic effects on urolithiasis which include smooth muscle relaxation, diuresis, and the effects on urinary citrate.[45] Khellin has the ability to disrupt citrate metabolism. Because calcium oxalate urinary stones have been described as the most prominent type of urinary stones (up to about 80%) as well as citrate is a known inhibitor of crystallization of calcium oxalate, urinary citrate plays a key role in preventing calcium oxalate stone recurrence.[46] Khella baladi is unsafe during pregnancy and lactation and it is used with caution for patients with liver disease.[101]

Maize (*Zea mays*)

It also called corn silk (*Stigma maydis*). It belongs to Gramineae family. This plant is found widely in India, China, North America, and Malaysia. *Zea mays* hair is frequently chosen and used as an old folk therapeutic agent due to its effectiveness in treating a variety of ailments. This is because *Zea mays* contains a variety of bioactive constituents such as

flavonoids, tannins, terpenoids, cardiac glycoside, and phenols.[102,103] The reason why *Zea mays* is utilized in the treatment of renal calculi is the natural diuretic effect of this herb. This activity is attributed to the tannins and saponins found in the fibers. The kidneys are induced to generate more urine volume, resulting in a decreased urine salt content. This elevated amount of urine also eliminates small pieces of stones that have recently been developed in the urinary tract or may have broken off from bigger calculi fragments, allowing them to be discharged in the urethra and bladder. *Zea mays* might be useful in the management of UTIs. Large amount of maize should be avoided because it may affects patients such as those with hypokalemia, unstable blood pressure, diabetic ones, and pregnant women.[47]

Manjistha (*Rubia cordifolia*)

Rubia cordifolia, sometimes known as common madder or Indian madder, is a flowering plant belonging to the Rubiaceae family of plants. *Rubia cordifolia* roots are also used to produce medications.[104] Roots have tonic, antidysentery, astringent, and antiseptic properties.[105] The roots of manjistha are effective in preventing the kidney stones. They function by lowering the calcium and oxalate level in kidneys and inhibit the formation of urinary stones. This is attributed to the roots antioxidant and kidney protecting properties of the roots.[106] A previous *in vitro* study showed the impact of the hydro-alcoholic extract of *Rubia cordifolia* roots (HARC) on urolithiasis provoked by ethylene glycol. The ethylene glycol feeding resulted in hyperoxaluria and hypercalciuria as well as increased renal excretion of phosphate. Supplementation with HARC significantly suppressed changes in urine oxalic acid, phosphate, and calcium excretion in a dose-dependent manner. This indicates that the HARC can protect against urolithiasis stimulated by ethylene glycol through the suppression and/or prevention of urinary stones development. Therefore, HARC is helpful to prevent the recurrence of the disease as it showed its effect on early stages of stone development. These effects may be mediated by its antioxidant and nephroprotection properties as well as its influence on urinary stone-forming constituents and risk factors.[48] Its extract is used with caution in pregnant and lactating women.[49]

Ngingihel (*Phyllanthus niruri*)

It is commonly called "stone breaker", belongs to the Euphorbiaceae family which is distributed worldwide. *P. niruri* is a safe medicinal plant, efficacious, and culturally acceptable as an alternative treatment for a variety of human diseases such as jaundice, scabies, and cancer. It is widely used by urolithiasis patients as part of Brazilian folk medicine.[107,108] Alkaloids, flavonoids, lignans, and triterpenes were among the phytochemicals evidenced in *P. niruri*. From these compounds, triterpenes have been found to block the cytotoxicity stimulated by CaOx. They also lower the stone forming constituents excretion and crystal deposition markers in the kidneys. Furthermore, a uricosuric activity was demonstrated in hyperuricemic rats by an extraction of methanol from the *P. niruri* leaves containing phyllanthin and lignans.[50] Alkaloids derived from the *Phyllanthus* exhibit antispasmodic

activity, resulting in relaxation of smooth muscle, most notably in the urinary tract system, which in turn would aid in the removal of renal calculi. As a result, all of these effects are linked to *P. niruri*'s preventive ability.[109] *P. niruri* is possibly unsafe during pregnancy and lactation and should be used with caution for diabetic patients.[110]

Olive (*Olea europaea*)

Olea europaea belong to Oleaceae family, it is widely distributed in Mediterranean region. The majority of *Olea europaea* plant parts are used in traditional medicine around the world. For examples decoction of dried leaf and dried fruit used to treat UTI and extract leaves used to induce diuresis. Additionally, it has several medicinal uses such as the treatment of gall stones, diabetes mellitus, hair loss, and cardiovascular disorder.[111] Previous investigations confirm the antiurolithiatic activity of olive oil due to its content of flavonoids. The flavonoids prevent renal stone formation by numerous mechanisms. Hyperoxaluria causes the urine to contain calcium oxalate which results in peroxidative stress and the formation of urinary crystals. Due to its antioxidant properties, olive oil may have the ability to prevent renal stone formation by inhibiting renal tubular membrane damage induced by hyperoxaluria.[51,52] The diuretic activity of olive oil could be attributed to the inhibition of carbonic anhydrase and the improvement of glomerular filtration. Due to the synergistic activity of vitamin C with flavonoids, oil from leaves methanolic extract show good effect on reduction of Ca serum level.[112] Olive oil may cause dieresis and accelerate the preformed stone-dissolving process and also may prevent the formation of new renal stones in the urinary system.[113] Side effects include stomach pains, headaches, coughing, and vertigo. Some individuals are sensitive to the olive trees pollen and consuming the extract of olive leaf may cause them to experience an allergic response. Blood glucose levels and blood pressure may be reduced by using olive leaf extracts. Therefore, if hypoglycemic or antihypertensive drugs are to be administered, they should be done so under the supervision of medical staff and not as self-medication. Since olive oil might affect blood sugar, using olive oil might affect blood glucose control during and after surgery. Hence, olive oil should be discontinued two weeks before surgery.[113]

Oregano (*Origanum vulgare* L.)

O. vulgare (family, Lamiaceae), it originated in mountainous areas of Asian and European, and Mediterranean regions. Its name is derived from an ancient Greek word that means "mountain joy." It was generally used in folk medicine as a diuretic, antispasmodic, and lithotriptic. It was also employed for additional pharmacological actions like as an expectorant, laxative, antioxidant, anticancer, antibacterial, anti-inflammatory, and stimulant. These medicinal activities are due to the presence of various groups of phytochemical compounds including coumarins, tannins, alkaloids, flavonoids, saponins, sterols, and terpenes that were determined in the crude extract of stems and leaves of the *O. vulgare*. Oregano has been used to treat kidney stones for centuries, according to research. It works

as a diuretic, increasing urine volume and decreasing crystal supersaturation, as well as an antispasmodic or pain reliever. Oregano aids in the dissolution of kidney stones as well as the breakdown and prevention of calcium oxalate stones. It possesses antioxidant properties that help in the scavenging of free radicals and the protection against oxidative stress. Oregano also protects kidney cells from calcium oxalate and other crystallization.[53,54] It may be harmful or unsafe during pregnancy if taken via mouth in medicinal amounts. There is a concern that ingesting oregano herb in quantities greater than those found in food may induce miscarriage.[114] People who are allergic to plants in the (Lamiaceae) family, such as mint, basil, marjoram, sage, and lavender may show allergic reactions to oregano as well. Oregano has been linked to an increased risk of bleeding during surgery. Thus, patients who consumed large doses of oregano should stop using it two weeks before surgery. Oregano might decrease body clearance of lithium. This could increase the risk of lithium serious side effects. Hence, the lithium dose might need to be properly adjusted.[115,116]

Parsley (*Petroselinum crispum*)

Parsley is a member of Umbelliferae family widely distributed in Europe, Mediterranean and Asian countries. For many years it has been used medicinally to a variety of diseases due to its antioxidant, anti-inflammatory, antihypertensive, antidiabetic and laxative activities.[117] Parsley seeds act as antiurolithiatic drug by reducing the urinary calcium, and thus CaOx, by either lowering serum Ca levels or increasing urinary citrate.[118] The favored pH for CaOx stone is between 4.5 and 5.5. Parsley could increase urinary pH close to 6 and act as a good anti-CaOx medication. In addition, parsley have diuretic activity due to its composition of various substances like flavonoids, organic acids or saponins.[119] Flavonoids may have diuretic properties because they bind to adenosine A1 receptors. The increase in urine volume results in a decrease in nucleation and supersaturation.[120] Parsley is used with caution for patients with edema, hypoglycemia, kidney disease, and high blood pressure. Parsley has moderate interaction with other drugs such as warfarin and diuretic drugs.[121]

Pomegranate (*Punica granatum*)

Also referred to as "a pharmacy unto itself".[122] *P. granatum* belongs to the Punicaceae plant family. It originated in the Middle East and spread to other parts of the world by seeds cultivation. Pomegranates contain a variety of bioactive compounds, including alkaloids, ellagic acid, and punicalagin, as well as other ellagitannins, anthocyanins, flavonoids, tannins, and other phytochemicals that may have a significant impact on human health and illness prevention and treatment.[123,124] *P. granatum* flower methanolic extracts and juices include a variety of useful phytochemicals that aid in the discharge of stones from the kidneys by relaxing the muscles of the biliary and urinary system. This demonstrates *P. granatum* antiurolithiatic and anti-hypercalciuric action, garnering considerable interest for its potential application in the prevention of renal CaOx stones. Pomegranate acts as an antioxidant due to the presence of flavonoids and anthocyanins in the fruit and other parts

of the plant, so it plays an important role in preventing oxidative renal tubular damage by reducing reactive oxygen species. Pomegranate also have a significant role in managing of urea, creatinine, and uric acid levels.[11,56–58] It should be used with caution for patients with hypotension.[59]

Radish (*Raphanus sativus*)

The radish is a root vegetable belongs to the Brassicaceae family. It is found and used all over the world. Depending on the season and duration of cultivation, it comes in a variety of sizes, shapes (round, long, oval), and colors (white, purple, red, pink, gray-black, green, yellow, and others). The leaves of this plant have therapeutic properties.[60] It has also been used traditionally to treat renal illness and urinary stones. Its chemical constituents, flavonoids, have been shown to reduce CaOx crystallization in human urine as well as saponins inhibited crystallization by disaggregating the suspension of mucoproteins, which are crystallization promoters.[61] Previous studies reported the effect of aqueous extract of the leaves of *R. sativus* on *in vitro* crystallization of CaOx crystals significantly reduced the crystal density and prevented the nucleation and aggregation of CaOx crystallization. It also reduced the growth and caused the dissolution of CaOx crystals.[62,63] Radish should be consumed cautiously with gallstone and diabetic patients. Pregnancy and lactating women should avoid using more than the amounts found in foods.[125]

Raspberry (*Rubus idaeus*)

It is a medicinal plant that is widely employed in the Middle East to treat kidney stones. It belongs to Rosaceae family.[126] The plant has a good nutritional and bioactive compounds' profile. They include a variety of critical minerals, dietary fibers, flavonoids, vitamin C, and polyphenolic components, particularly ellagitannins and anthocyanins, which give them their distinct red color.[127] *R. idaeus* root has anti-urolithiatic activity by preventing CaOx stone formation. This prophylactic effect is due to the decrease in the calculus promoter's excretion such as oxalate and Ca in the urinary tract, also it decreases the serum level of these chemicals. The aqueous extract of the plant acts as crystal growth inhibitors leading to formation of small particles that are easily excreted through the urine. The vitamin E in *R. idaeus* provides protection for kidneys from CaOx stone deposition.[64] The raspberry methanolic extract was reported to be a significant diuretic through disrupting the activity of epithelial sodium channels or aldosterone.[65,66] Although raspberry is unlikely to harm an unborn child, it should be avoided during the last trimesters of pregnancy due to a lack of safety information on organogenesis. Thus, for reasons of safety, it appears that pregnant women should avoid taking raspberry during their pregnancy. However, if needed to be used, it should only be taken under the guidance of medical staff and not as a self-medication. In hormone-sensitive conditions such as breast cancer, uterine cancer, ovarian cancer, endometriosis, or uterine fibroids, red raspberry might act like estrogen leading to worsening of these conditions upon exposure to red raspberry. Red raspberry might lower

blood sugar levels in people with diabetes. Thus, careful monitoring of blood glucose level should be considered in diabetic patients who consume red raspberry.[128,129]

Roselle (*Hibiscus sabdariffa*)

H. sabdariffa is commonly known as roselle. It is widely distributed in India and Africa. It is a member of Malvaceae family.[67] The primary active components of roselle have been identified as hibiscus anthocyanins, L-ascorbic acid, protocatechuic acid, quercetin, and polyphenols. Urinary calculi can be treated and prevented via *H. sabdariffa* in Thai traditional medicine and clinical trials revealed a uricosuric effect as well as a considerable rise in uric acid clearance and/or excretion. Also, there is a reduction in the retention time of oxalic acid in kidneys with an increase in urinary excretion.[66,68–70] Furthermore, the aqueous extract of *H. sabdariffa* flowers could inhibit the crystallization of calcium oxalate monohydrate (COM) crystals, which is a major component of kidney stones.[130] Roselle are likely safe for diabetic patient and pregnant women.[71]

Rupturewort (*Herniaria hirsuta*)

This plant is native to Eurasia and North Africa (family: Caryophyllaceae). It is commonly known as hairy rupturewort. The aerial part of *Herniaria* contained phenolic, flavanols, flavonoids, and two monodesmosidic saponin (*Herniaria* saponin E and F). These active compounds allow the *Herniaria* to have many pharmacological effects such as antioxidant, anti-urolithiatic and antibacterial effects. The plant's crud extract has a direct effect on CaOx crystals by encouraging the formation of small CaOx dihydrate crystals that are easily excreted from the urinary tract. Also, the extract effectively inhibited CaOx aggregation. Further, the *H. hirsuta* reduced crystal deposition in the kidneys and, more importantly, had an impressive prophylactic effect by removing preexisting kidney stones, confirming its antilithiatic effect. The interaction of CaOx crystals with renal epithelial cells is an important step in kidney stone development. The aqueous extract of *H. hirsuta* affects the adhesion of COM by coating the COM crystal and inhibited them from binding to the cell.[71–74] There isn't enough information available about he safety of rupturewort as well as the possible side effects. Moderate interaction cautions when used in combination with lithium. Since rupturewort might have a diuretic activity, consuming rupturewort could lower lithium excretion. This effect may lead to serious adverse effects of lithium due to its accumulation inside the body. Therefore, the lithium dose might need adjustment if intended to be used with rupturewort.[131,132]

Saffron (*Crocus sativus* L.)

Crocus sativus L. (family; Iridaceae). Commercial saffron is composed of the dried red stigma and a little portion of the yellow style. Saffron is made up of at least 150 volatile

and aroma-producing chemicals, the majority of which include terpene alcohol, terpenes, and associated esters.[133] Different plant parts like peels, fruits, seeds, and rind of *C. sativus* contain various biochemically active ingredients such as crocin, picrocrocin, crocetin, and safranal in different proportions. These constituents have demonstrated health promoting effect through the modulation of various biological and physiological processes.[134] Stomach disorders, asthma, coughs, cardiovascular ailments, and amenorrhea are among the health issues for which saffron is utilized as a herbal medication. Saffron's relaxing impact on smooth muscles might be the source of some of the plant's medicinal properties.[135] The antilithiatic potential of crocin, a pharmacologically active constituent of *C. sativus*, was evaluated against ethylene glycol (EG)-induced nephrolithiasis.[75] Saffron aqueous extractions (25, 50, and 100 mg/kg/day) were given via intraperitoneal route of administration in two protective or curative regimens. EG was found to cause urolithiasis. An increase in urine production and renal oxalic acid excretion as well as a reduce in citrate and magnesium excretion were all seen after ethylene glycol feeding. In curative (100 mg/kg) and preventive (50 and 100 mg/kg) investigations, saffron did not show any diuretic activity, but it considerably lower the high urinary oxalic acid levels.[76] There are special precautions and warnings for the use of large amounts of saffron in patients with bipolar disorder, diabetes, and low blood pressure. Larger amounts of saffron more than that in food can make the uterus contract and might cause a miscarriage so it is contraindicated for pregnant and lactating women.[136]

Shatavari (*Asparagus racemosus*)

Asparagus racemosus belongs to the family Liliaceae and commonly known as satavari. The dried roots of the plant are used as folk medicie.[77] The chemical constituents of *A. racemosus* are mucilage, volatile oil, tannic acid, sapogenin, saponin, asparagine, asparagenin, sitosterol, and flavonoids. *A. racemosus* was researched for its suppressive impact on urolithiasis. In a previous *in vitro* study that induced kidney stone to adult male albino rats by EG, the ethanolic extract of *A. racemosus* was able to decrease the levels of oxalic acid, calcium, and phosphate. Creatinine levels were also reduced by the ethanolic extract while the level of magnesium was elevated which was considered as a marker of stone development inhibition. Also, the ethanolic extract was beneficial in the excretion of calculi from the urinary tract. The investigation shows that *A. racemosus* inhibits EG-induced stone formation.[78] Because of diuretic properties of shatavari, it can show useful results in relieving kidney stones. Also, it may be considered as an antiurolithiasis herb that accelerates the dissolution of stones and prevents its recurrence.[79]

Thai green eggplant (*Solanum xanthocarpum*)

Yellow-fruit nightshade is another name for this plant. It is a member of Solanaceae family. In India, it is a well-known and commonly employed traditional plant. Fruit extract of this plant recommended for treating renal disease such UTI, urolithiasis, and urination

difficulty.[80,81] SXME (*Solanum xanthocarpum* fruit methanol extract) is useful in the treatment of urolithiasis. SXME produces its diuretic effect by the elevation of urine volume, which diminishes the supersaturation process that is considered as one of the favorable prerequisites for urolithiasis by crystallization. SXME may have effects such as reducing excretion and deposition of little CaOX particles from the kidneys, maintain a balance between stone inhibitors and promoters, reducing the chances of them being retained in the urinary tracts, and conserving the antioxidant environment. Several products and extracted compounds have been demonstrated to prevent kidney stone development. Alkaloids (including solamargine, solanacarpidine, solanacarpine, solasonine, and solasodine), phytosterols, saponins, as well as other phytoconstituents are abundant in the fruits of *S. xanthocarpum*. Saponin derivatives have been identified as components of a wide range of medicinal plants with antiurolithiatic properties. Phytosterols had anti-inflammatory and antioxidant properties as well.[82,83]

Turmeric (*Curcuma longa* L.)

Curcuma longa (turmeric or curcuma) is a member of the Zingiberaceae ginger family. It can be found in tropical and subtropical areas such as China, India, and Southeast Asia, where it is widespread. India is one of the main producers, users, and exporters of turmeric in the world. *Curcuma* comes from the Arabic term Kourkoum, which was the original name for saffron. The diferuloylmethane (flavonoid curcumin) and numerous volatile oils, such as zingiberone, atlantone, and tumerone, are the active ingredients in turmeric. Sugars, proteins, and resins are among the other components. Curcumin, which represents approximately 0.3–5.4 percent of crude turmeric, is the most well-studied active ingredient. It is known to have beneficial role in anorexia, diabetic wounds, cough, and hepatic disorders apart from its inherent antioxidant effects[84] Curcumin's anti-inflammatory and antioxidant capabilities are two of its most important pharmacological qualities that help with kidney stones. Curcumin is a kidney protector because of these qualities. Curcumin supplementation restored normal levels of calcium and oxalate in urine and kidneys, it can protect kidneys from damage and injury caused by kidney stones, and it can also help to prevent kidney stones deposition. It can also serve as a protective agent in lithotripsy.[85] Tumaric can worsen some conditions such as gall stone, bleeding, and liver diseases. Also, it has the ability to decrease the iron absorption when taken in large amounts hence it is contraindicated in patient with iron deficiency.[86]

Venus Hair (*Adiantum capillus-veneris*)

Adiantum capillus-veneris L. (Maidenhair fern) is a medicinal plant belongs to the family Pteridaceae. It is an important plant used in the treatment of urolithiasis and is found in many litholytic formulations. It was used either alone or in combination with other plants in multi-herbal preparations to treat a variety of diseases.[87] The anti-calcium oxalate urolithiasis property of a hydroalcoholic extract of *A. capillus-veneris* was studied in chemically

induced urolithiasis in rats demonstrated a considerable decrease in the number of crystals as well as lower calcium, phosphorous, and blood urea levels in the serum. Animals given the extract of *A. capillus-veneris* also showed a notable reduction in the size of urinary stones.[88] The plant inhibited the crystallization, crystal aggregation, and reduction in the number and the sizes of crystals. It was supposed that the antiurolithiatic activity of *A. capillus-veneris* may also be due to its flavonoids' content.[88] It is unsafe to use maidenhair fern during pregnancy. In large amounts, it can cause vomiting. According to studies, maidenhair fern could damage the spleen, so it should not be used in susceptible patients.[87]

Table 3provides more information on the pharmacological evidence of phytochemicals extracted from these plants.

Table 3 The effects of phytochemical constituents on the treatment of kidney stones.

Phytochemicals	Effect on kidney stones	References
Flavonoid	Antioxidant, free-radicals scavenging, prevent CaOx stone formation	137,138
Quercetin	Reduce the formation of crystals in the urine and kidneys, lower the oxidative damage	139
Tannin	Diuretic, anti-inflammatory, antioxidant	140
Catechin	Decreases CaOx crystals and reduce papillary calcification	139
Thymoquinone	Decrease the formation of CaOx crystals in the kidneys, lowers serum urea and creatinine levels	139
Alkaloid	Antioxidant, antilipid peroxidation	141
Saponin	Diuretic, stone dissolving agent, CaOx crystal inhibition	140
Phenol	Dissolve calcium phosphate stones	138
Glycoside	Prevent kidney damage and decrease urinary disorder	138

CaOx: calcium oxalate.

CONCLUSION

Kidney stones are one of the most prevalent urinary system disorders in different countries due to a multifactorial etiology, and higher recurrence rates. Despite the fact that most conventional drugs available to date are not totally successful, herbal therapy has been known as an alternative and effective technique for the treatment of kidney stones or urolithiasis. Also, these medications cause many of the undesirable side effects in patients. This supports the effectiveness of using the plant in remedy to treat urolithiasis. We have summarized the efficacy of certain herbal medications that have been studied for their usefulness in preventing and treating renal calculi. The results of the available investigations revealed that nearly all of the plants consumed on a regular basis include many nutraceuticals with beneficial effects, allowing them to be employed in the treatments and prevention of kidney stones. As a result, phytochemicals including thymoquinone, catechin, and quercetin have been highlighted as potential natural compounds for preventing and managing stone development. The plants can intervene at any step of the stone formation process by blocking the aggregation, nucleation, and development of CaOx crystals, and they can

utilize a number of strategies to prevent and treat urinary stones. Such methods include decreasing urinary calcium and oxalic acid levels, lowering free-radical generation, raising urinary magnesium levels, and weakening the crystal-tubular epithelial cell bond. As a result, these phytochemicals might be used to develop novel medications. Finally, by combining food and herbal remedies for the prevention of renal stones, it is possible to lower the risk of stone recurrence and enhance the quality of life.

There have been limited human studies on the effectiveness of medicinal herbs in the management of nephrolithiasis. Further investigations and research are needed to confirm the effectiveness and safety profile of these substances in individuals with nephrolithiasis through serious clinical trials.

ABBREVIATIONS

BUN, blood urea nitrogen; Ca, calcium; CaOx, calcium oxalate; COM, calcium oxalate monohydrate; EG, ethylene glycol; ESWL, extracorporeal shock wave lithotripsy; ESWL, extracorporeal shock wave lithotripsy; GP, general practitioner; HARC, hydro-alcoholic extract of Rubia cordifolia; HPLC, high performance liquid chromatography; Na, sodium; NSAIDS, nonsteroidal anti-inflammatory drugs; ROS, reactive oxygen species; SXME, Solanum xanthocarpum fruit methanol extract; UTI, urinary tract infection.

ACKNOWLEDGEMENTS

DECLARATIONS

Authors' contributions

All authors equally contributed, reviewed and approved this article before publication.

Conflict of interest

The authors declare no conflict of interest.

Ethical approvals

Not applicable for reviews.

Data availability

Not applicable.

Funding resources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Dawson CH, Tomson CR. Kidney stone disease: pathophysiology, investigation and medical treatment. Clin Med (Lond). 2012;12(5):467–71. Available from: 10.7861/clinmedicine.12-5-467.
2. Fakheri RJ, Goldfarb DS. Ambient temperature as a contributor to kidney stone formation: implications of global warming. Kidney Int. 2011;79(11):1178–1185. Available from: 10.1038/ki.2011.76.
3. Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006;367(9507):333–344. Available from: 10.1016/S0140-6736(06)68071-9.
4. Younis A, Radharikrishnan S. Kidney stone disease. Trends Urol Men's Health. 2011;2:15–20. Available from: 10.1002/tre.177.
5. Semins MJ, Shore AD, Makary MA, Magnuson T, Johns R, Matlaga BR. The association of increasing body mass index and kidney stone disease. J Urol. 2010;183(2):571–576. Available from: 10.1016/j.juro.2009.09.085.
6. Stapleton AE, Dziura J, Hooton TM. Recurrent urinary tract infection and urinary Escherichia coli in women ingesting cranberry juice daily: a randomized controlled trial. Mayo Clin Proc. 2012;87(2):143–150. Available from: 10.1016/j.mayocp.2011.10.006.
7. Han H, Segal AM, Seifter JL, Dwyer JT. Nutritional management of kidney stones (Nephrolithiasis). Clin Nutr Res. 2015;4(3):137–152. Available from: 10.7762/cnr.2015.4.3.137.
8. Mahmoud NAMRKNKSA, Bahmani. Medicinal plants for treatment kidney stones, An ethnobotany study in Shahrekord. Egyptian J Vet Sci. 2019;50(2):145–149.
9. Brikowski TH, Lotan Y, Pearle MS. Climate-related increase in the prevalence of urolithiasis in the United States. Proc Natl Acad Sci U S A. 2008;105(28):9841–9846.
10. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. Rev Urol. 2010;12(2-3):e86–e96.
11. Gupta S, Shamsher SK. Kidney stones: Mechanism of formation, pathogenesis and possible treatments. J Biomol Biochem. 2018;2(1):1–5.
12. Yadav RD, Jain SK, Alok S, Mahor A, Bharti JP, Jaiswal M. Herbal plants used in the treatment of urolithiasis: a review. Int J Pharm Sci Res. 2011;2(6):1412–1420.
13. Alelign T, Petros B. Kidney stone disease: An update on current concepts. Adv Urol. 2018;p. 3068365–3068365. Available from: 10.1155/2018/3068365.
14. Ankur C, Amarchand P, Aadarsh C, Deepa I, S PR, K PU. Potential of medicinal plants in kidney, gall and urinary stones. Int J Drug Dev Res. 2010;2(2):431–447.
15. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int. 2003;63(5):1817–1823. Available from: 10.1046/j.1523-1755.2003.00917.x.
16. Afkari R, Feizabadi MM, Ansari-Moghadam A, Safari T, Bokaeian M. Simultaneous use of oxalate-degrading bacteria and herbal extract to reduce the urinary oxalate in a rat model: A new strategy. Int Braz J Urol. 2019;45(6):1249–1259. Available

from: 10.1590/S1677-5538.IBJU.2019.0167.
17. Kreydiyyeh SI, Usta J. Diuretic effect and mechanism of action of parsley. J Ethnopharmacol. 2002;79(3):353–357. Available from: 10.1016/s0378-8741(01)00408-1.
18. Soni H, Thakkar T, Patel R, Patel G. Evaluation of acute toxicity and anti-urolithiatic activity of ural capsule. Int J Phytophar. 2014;5(1):15–20.
19. Barbas C, García A, Saavedra L, Muros M. Urinary analysis of nephrolithiasis markers. J Chromatogr B Analyt Technol Biomed Life Sci. 2002;781(1-2):433–455. Available from: 10.1016/s1570-0232(02)00557-3.
20. Coe FL, Evan A, Worcester E. Kidney stone disease. J Clin Invest. 2005;115(10):2598–2608. Available from: 10.1172/JCI26662.
21. Dursun M, Otunctemur A, Ozbe E. Kidney stones and ceftriaxone. Eur Med J. 2015;p. 68–74.
22. Ankur C, Amarchand P, Aadarsh C, Deepa I, S PR, K PU. Potential of medicinal plants in kidney, gall and urinary stones. Int J Drug Dev Res. 2010;2(2):431–447.
23. Safarinejad MR. Adult urolithiasis in a population-based study in Iran: prevalence, incidence, and associated risk factors. Urol Res. 2007;35(2):73–82. Available from: 10.1007/s00240-007-0084-6.
24. Khan F, Haider MF, Singh MK, Sharma P, Kumar T, Neda EN. A comprehensive review on kidney stones, its diagnosis and treatment with allopathic and ayurvedic medicines. Urol Nephrol Open Access J. 2019;7(4):69–74.
25. Kumar SBN, Kumar KG, Srinivasa V, Bilal S. A review on urolithiasis. Int J Univ Pharm Life Sci. 2012;2:269–280.
26. Scales CD, Smith AC, Hanley JM, Saigal CS. Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012;62(1):160–165. Available from: 10.1016/j.eururo.2012.03.052.
27. Aggarwal KP, Narula S, Kakkar M, Tandon C. Nephrolithiasis: molecular mechanism of renal stone formation and the critical role played by modulators. Biomed Res Int. 2013;p. 292953–292953. Available from: 10.1155/2013/292953.
28. Carvalho M, Nakagawa Y. Urinary supersaturation and recurrence in nephrolithiasis. Int Braz J Urol. 1999;25:475–479.
29. Boskey AL. Current concepts of the physiology and biochemistry of calcification. Clin Orthop Relat Res. 1981;(157):225–257.
30. Bihl G, Meyers A. Recurrent renal stone disease-advances in pathogenesis and clinical management. Lancet. 2001;358(9282):651–656. Available from: 10.1016/S0140-6736(01)05782-8.
31. Kasote DM, Jagtap SD, Thapa D, Khyade MS, Russell WR. Herbal remedies for urinary stones used in India and China: A review. J Ethnopharmacol. 2017;203:55–68. Available from: 10.1016/j.jep.2017.03.038.
32. Ratkalkar VN, Kleinman JG. Mechanisms of stone formation. Clin Rev Bone Miner Metab. 2011;9(3-4):187–197. Available from: 10.1007/s12018-011-9104-8.

33. Basavaraj DR, Biyani CS, Browning AJ, Cartledge JJ. The role of urinary kidney stone inhibitors and promoters in the pathogenesis of calcium containing renal stones. EAU-EBU Update Ser. 2007;5(3):126–136. Available from: 10.1016/j.eeus.2007.03.002.
34. Bhardwaj D, Kaushik N. Phytochemical and pharmacological studies in genus Berberis. Phytochem Rev. 2012;11:523–542. Available from: 10.1007/s11101-013-9272-x.
35. Thamilselvan S, Byer KJ, Hackett RL, Khan SR. Free radical scavengers, catalase and superoxide dismutase provide protection from oxalate-associated injury to LLC-PK1 and MDCK cells. J Urol. 2000;164(1):224–229.
36. Hadjzadeh MA, Khoei A, Hadjzadeh Z, Parizady M. Ethanolic extract of nigella sativa L seeds on ethylene glycol-induced kidney calculi in rats. Urol J. 2007;4(2):86–90.
37. Miyazawa K, Takahashi Y, Morita N. Cyclooxygenase 2 and prostaglandin E2 regulate the attachment of calcium oxalate crystals to renal epithelial cells. Int J Urol. 2012;19(10):936–943. Available from: 10.1111/j.1442-2042.2012.03060.x.
38. Edris AE. Anti-cancer properties of Nigella spp. essential oils and their major constituents, thymoquinone and beta-elemene. Curr Clin Pharmacol. 2009;4(1):43–46. Available from: 10.2174/157488409787236137.
39. Stiani SN, Syahidah FM, Fikriani H, Subarnas A, Rusdiana T. Anticalculi Activity of Apigenin and Celery (Apium graveolens L.) Extract in Rats Induced by Ethylene Glycol-Ammonium Chloride. J Pharm Bioallied Sci. 2019;11(4):556–561. Available from: 10.4103/jpbs.JPBS_202_19.
40. Al-Jawad FH, Al-Razzuq RAM, Al-Jeboori AA. Apium graveolens accentuates urinary Ca+2 excretions in experimental model of nephrocalcinosis. Int J Green Pharm. 2011;5(2):100–102. Available from: 10.4103/0973-8258.85160.
41. Shu X, Cai H, Xiang YB. Green tea intake and risk of incident kidney stones: Prospective cohort studies in middle-aged and elderly Chinese individuals. Int J Urol. 2019;26(2):241–246. Available from: 10.1111/iju.13849.
42. Musial C, Kuban-Jankowska A, Gorska-Ponikowska M. Beneficial properties of green tea catechins. Int J Mol Sci. 2020;21(5):1744–1744. Available from: 10.3390/ijms21051744.
43. Khalil N, Bishr M, Desouky S, Salama O. Ammi visnaga L., a potential medicinal plant: A review. Molecules. 2020;25(2):301–301. Available from: 10.3390/molecules25020301.
44. Vanachayangkul P, Chow N, Khan SR, Butterweck V. Prevention of renal crystal deposition by an extract of Ammi visnaga L. and its constituents khellin and visnagin in hyperoxaluric rats. Urol Res. 2011;39(3):189–195. Available from: 10.1007/s00240-010-0333-y.
45. Bhagavathula AS, Al-Khatib M, Elnour AJ, A A, Kalbani A, Shehab NM, et al. Ammi visnaga in treatment of urolithiasis and hypertriglyceridemia. Pharmacognosy Res. 2014;7(4):397–400. Available from: 10.4103/0974-8490.167894.

46. Byer K, Khan SR. Citrate provides protection against oxalate and calcium oxalate crystal induced oxidative damage to renal epithelium. J Urol. 2005;173(2):640–646. Available from: 10.1097/01.ju.0000143190.49888.c7.
47. Hasanudin K, Hashim P, Mustafa S. Corn silk (Stigma maydis) in healthcare: a phytochemical and pharmacological review. Molecules. 2012;17(8):9697–9715. Available from: 10.3390/molecules17089697.
48. Divakar K, Pawar AT, Chandrasekhar SB, Dighe SB, Divakar G. Protective effect of the hydro-alcoholic extract of Rubia cordifolia roots against ethylene glycol induced urolithiasis in rats. Food Chem Toxicol. 2010;48(4):1013–1018. Available from: 10.1016/j.fct.2010.01.011.
49. Verma A, Kumar B, Alam P, Singh V, Gupta SK. Rubia cordifolia-a review on pharmaconosy and phytochemistry. Int J Pharm Sci Res. 2016;7(7):2720–2731. Available from: 10.13040/IJPSR.0975-8232.7.
50. Murugaiyah V, Chan KL. Antihyperuricemic lignans from the leaves of Phyllanthus niruri. Planta Med. 2006;72(14):1262–1267. Available from: 10.1055/s-2006-947224.
51. Alenzi M, Rahiman S, Tantry BA. Antiurolithic effect of olive oil in a mouse model of ethylene glycol-induced urolithiasis. Investig Clin Urol. 2017;58(3):210–216. Available from: 10.4111/icu.2017.58.3.210.
52. Robertson WG, Peacock M. The cause of idiopathic calcium stone disease: hypercalciuria or hyperoxaluria? Nephron. 1980;26(3):105–110. Available from: 10.1159/000181963.
53. Escobar C, Byer KJ, Khaskheli H, Khan SR. Apatite induced renal epithelial injury: insight into the pathogenesis of kidney stones. J Urol. 2008;180(1):379–387. Available from: 10.1016/j.juro.2008.02.041.
54. Aihara K, Byer KJ, Khan SR. Calcium phosphate-induced renal epithelial injury and stone formation: involvement of reactive oxygen species. Kidney Int. 2003;64(4):1283–1291. Available from: 10.1046/j.1523-1755.2003.00226.x.
55. Al-Yousofy F, Gumaih H, Ibrahim H, Alasbahy A. Parsley! Mechanism as antiurolithiasis remedy. Am J Clin Exp Urol. 2017;5(3):55–62.
56. Tugcu V, Kemahli E, Ozbek E. Protective effect of a potent antioxidant, pomegranate juice, in the kidney of rats with nephrolithiasis induced by ethylene glycol. J Endourol. 2008;22(12):2723–2731.
57. Ilbey YO, Ozbek E, Simsek A, Cekmen M, Somay A, Tasci AI. Effects of pomegranate juice on hyperoxaluria-induced oxidative stress in the rat kidneys. Ren Fail. 2009;31(6):522–531. Available from: 10.1080/08860220902963871.
58. Rathod NR, Biswas D, Chitme HR, Ratna S, Muchandi IS, Chandra R. Antiurolithiatic effects of Punica granatum in male rats. J Ethnopharmacol. 2012;140(2):234–238. Available from: 10.1016/j.jep.2012.01.003.
59. Rababah TM, Banat F, Rababah A, Ereifej K, Yang W. Optimization of extraction conditions of total phenolics, antioxidant activities, and anthocyanin of oregano, thyme, terebinth, and pomegranate. J Food Sci. 2010;75(7):626–632. Available

from: 10.1111/j.1750-3841.2010.01756.x.

60. Karadi RV, Gadge NB, Alagawadi KR, Savadi RV. Effect of Moringa oleifera Lam. root-wood on ethylene glycol induced urolithiasis in rats. J Ethnopharmacol. 2006;105(1-2):306–311. Available from: 10.1016/j.jep.2005.11.004.
61. Joshi VS, Parekh BB, Joshi MJ, Vaidya AD. Inhibition of the growth of urinary calcium hydrogen phosphate dihydrate crystals with aqueous extracts of Tribulus terrestris and Bergenia ligulata. Urol Res. 2005;33(2):80–86. Available from: 10.1007/s00240-004-0450-6.
62. Kok DJ, Papapoulos SE, Bijvoet OL. Crystal agglomeration is a major element in calcium oxalate urinary stone formation. Kidney Int. 1990;37(1):51–56. Available from: 10.1038/ki.1990.7.
63. Akhtar SS, Mular SM, Khan ND, Khan ZH, Sohail S. In vitro study of aqueous leaf extract of Raphanus sativus var. for inhibition of calcium oxalate crystallization. Biosci Disc. 2017;8(2):153–157.
64. Ghalayini IF, Al-Ghazo MA, Harfeil MN. Prophylaxis and therapeutic effects of raspberry (Rubus idaeus) on renal stone formation in Balb/c mice. Int Braz J Urol. 2011;37(2):259–267. Available from: 10.1590/s1677-55382011000200013.
65. Zhang Y, Zhang Z, Yang Y, Zu X, Guan D, Wang Y. Diuretic activity of Rubus idaeus L (Rosaceae) in rats. Trop J Pharm Res. 2011;10(3):243–248. Available from: 10.4314/tjpr.v10i3.15.
66. Nirumand MC, Hajialyani M, Rahimi R. Dietary plants for the prevention and management of kidney stones: Preclinical and clinical evidence and molecular mechanisms. Int J Mol Sci. 2018;19(3):765–765. Available from: 10.3390/ijms19030765.
67. Prasongwatana V, Woottisin S, Sriboonlue P, Kukongviriyapan V. Uricosuric effect of Roselle (Hibiscus sabdariffa) in normal and renal-stone former subjects. J Ethnopharmacol. 2008;117(3):491–495. Available from: 10.1016/j.jep.2008.02.036.
68. Laikangbam R, Devi D, M. Inhibition of calcium oxalate crystal deposition on kidneys of urolithiatic rats by Hibiscus sabdariffa L. extract. Urol Res. 2012;40(3):211–218. Available from: 10.1007/s00240-011-0433-3.
69. Woottisin S, Hossain RZ, Yachantha C, Sriboonlue P, Ogawa Y, Saito S. Effects of Orthosiphon grandiflorus, Hibiscus sabdariffa and Phyllanthus amarus extracts on risk factors for urinary calcium oxalate stones in rats. J Urol. 2011;185(1):323–328. Available from: 10.1016/j.juro.2010.09.003.
70. Saleh DI, Mahmoud SF, Saleh ES. The rate of dissolution and crystallization of kidney stone in the presence of Hibiscus Sabdariffa extracts. Life Sci J;10(2):700–710.
71. Al-Snafi AE. Pharmacological importance of Herniaria glabra and Herniaria hirsuta- A review. Indo Am J Pharm Sci. 2018;5(4):2167–2175. Available from: 10.5281/zenodo.1214986.
72. Rovčanin BR, Tatjana, Steševi D, Keki D, Risti M. Antibacterial effect of Herniaria hirsuta, Prunus avium, Rubia tinctorum and Sempervivum tectorum plant extracts on multiple antibiotic resistant Escherichia coli. Biosci J. 2015;31(6):1852–1861.

Available from: 10.14393/BJ-v31n6a2015-29091.

73. Atmani F, Farell G, Lieske JC. Extract from Herniaria hirsuta coats calcium oxalate monohydrate crystals and blocks their adhesion to renal epithelial cells. J Urol. 2004;172(4):1510–1514. Available from: 10.1097/01.ju.0000131004.03795.c5.
74. Atmani F, Khan SR. Effects of an extract from Herniaria hirsuta on calcium oxalate crystallization in vitro. BJU Int. 2000;85(6):621–625. Available from: 10.1046/j.1464-410x.2000.00485.x.
75. Ghaeni FA, Amin B, Hariri AT, Meybodi NT, Hosseinzadeh H. Antilithiatic effects of crocin on ethylene glycol-induced lithiasis in rats. Urolithiasis. 2014;42(6):549–558.
76. Amin B, Feriz HM, Hariri AT, Meybodi NT, Hosseinzadeh H. Protective effects of the aqueous extract of Crocus sativus against ethylene glycol induced nephrolithiasis in rats. EXCLI J. 2015;14:411–433. Available from: 10.17179/excli2014-510.
77. Alok S, Jain SK, Verma A, Kumar M, Mahor A, Sabharwal M. Plant profile, phytochemistry and pharmacology of Asparagus racemosus (Shatavari): A review. Asian Pac J Trop Dis. 2013;3(3):4027291–4027291. Available from: 10.1016/S2222-1808(13)60049-3.
78. Christina AJ, Ashok K, Packialakshmi M, Tobin GC, Preethi J, Murugesh N. Antilithiatic effect of Asparagus racemosus Willd on ethylene glycol-induced lithiasis in male albino Wistar rats. Methods Find Exp Clin Pharmacol. 2005;27(9):633–638. Available from: 10.1358/mf.2005.27.9.939338.
79. Jagannath N, Chikkannasetty SS, Govindadas D, Devasankaraiah G. Study of antiurolithiatic activity of Asparagus racemosus on albino rats. Indian J Pharmacol. 2012;44(5):576–585. Available from: 10.4103/0253-7613.100378.
80. Kumar S, Pandey AK. Medicinal attributes of Solanum xanthocarpum fruit consumed by several tribal communities as food: an in vitro antioxidant, anticancer and anti HIV perspective. BMC Complement Altern Med. 2014;14:112–112. Available from: 10.1186/1472-6882-14-112.
81. Ranka D, Aswar M, Aswar U, Bodhankar S. Diuretic potential of aqueous extract of roots of Solanum xanthocarpum Schrad & Wendl, a preliminary study. Indian J Exp Biol. 2013;51(10):833–839.
82. Khan SR, Finlayson B, Hackett RL. Experimental calcium oxalate nephrolithiasis in the rat. Role of the renal papilla. Am J Pathol. 1982;107(1):59–69.
83. Patel P, Patel M, Saralai M, Gandhi T. Antiurolithiatic Effects of Solanum xanthocarpum Fruit Extract on Ethylene-Glycol-Induced Nephrolithiasis in Rats. J Young Pharm. 2012;4(3):164–70. Available from: 10.4103/0975-1483.100022.
84. Gandhi CN, Balaraman R. Effect of curcumin in the prevention of experimentally induced nephrolithiasis in rats by ethylene glycol and Vitamin D3. Orient Pharm Exp Med. 2009;9(3):259–267. Available from: 10.3742/opem.2009.9.3.259.
85. Tang M, Larson-Meyer DE, Liebman M. Effect of cinnamon and turmeric on urinary oxalate excretion, plasma lipids, and plasma glucose in healthy subjects. Am J Clin Nutr. 2008;87(5):1262–1267. Available from: 10.1093/ajcn/87.5.1262.

86. Azuine MA, Bhide SV. Chemopreventive effect of turmeric against stomach and skin tumors induced by chemical carcinogens in Swiss mice. Nutr Cancer. 1992;17(1):77–83. Available from: 10.1080/01635589209514174.
87. Dehdari S, Hajimehdipoor H. Medicinal Properties of Adiantum capillus-veneris Linn. in Traditional Medicine and Modern Phytotherapy: A Review Article. Iran J Public Health. 2018;47(2):188–197.
88. Al-Snafi AE. The chemical constituents and pharmacological effects of Adiantum capillus-veneris - A review. Asian J Pharm Sci Tech. 2015;5(2):106–111.
89. Rahimi-Madiseh M, Lorigoini Z, Zamani-Gharaghoshi H, Rafieian-Kopaei M. Berberis vulgaris: specifications and traditional uses. Iran J Basic Med Sci. 2017;20(5):569–587.
90. Wiessner JH, Hasegawa AT, Hung LY, Mandel GS, Mandel NS. Mechanisms of calcium oxalate crystal attachment to injured renal collecting duct cells. Kidney Int. 2001;59(2):637–644. Available from: 10.1046/j.1523-1755.2001.059002637.x.
91. Bashir S, Gilani AH. Antiurolithic effect of berberine is mediated through multiple pathways. Eur J Pharmacol. 2011;651(1-3):168–175. Available from: 10.1016/j.ejphar.2010.10.076.
92. Kim HH, Kwak C, Jeong BC, Kim SW. Effect of oxalate on the growth of renal tubular epithelial cells. J Endourol. 2002;16(4):261–264. Available from: 10.1089/089277902753752250.
93. Ragheb A, Attia A, Eldin WS, Elbarbry F, Gazarin S, Shoker A. The protective effect of thymoquinone, an anti-oxidant and anti-inflammatory agent, against renal injury: a review. Saudi J Kidney Dis Transpl. 2009;20(5):741–752.
94. Hayatdavoudi P, Rad K, Rajaei A, Hadjzadeh Z, A M. Renal injury, nephrolithiasis and Nigella sativa: A mini review. Avicenna J Phytomed. 2016;6(1):1–8.
95. Movaghati A, Yousefi MR, Saghebi M, Vazin SAS, Iraji M, Mosavat A, et al. Efficacy of black seed (Nigella sativa L.) on kidney stone dissolution: A randomized, double-blind, placebo-controlled, clinical trial. Phytother Res. 2019;33(5):1404–1412. Available from: 10.1002/ptr.6331.
96. Khalid Z, Osuagwu FC, Shah B, Roy N, Dillon JE, Bradley R. Celery root extract as an inducer of mania induction in a patient on venlafaxine and St John's Wort. Postgrad Med. 2016;128(7):682–683. Available from: 10.1080/00325481.2016.1218263.
97. Prasad K, D S, Bharathi K. Herbal drugs in urolithiasis - A review. Pharmacogn Rev. 2007;1(1):175–179.
98. Abbagani S, Gundimeda SD, Varre S, Ponnala D, Mundluru HP. Kidney stone disease: Etiology and evaluation. Int J Appl Biol Pharm Technol. 2010;.
99. Nasrul SI, Sehgal A. Green tea potential for prevention and managementof kidney stones. Int J Res Anal Rev. 2018;5(4):834–837.
100. Chou T. Wake up and smell the coffee. Caffeine, coffee, and the medical consequences. West J Med. 1992;157(5):544–53.
101. Haug KG, Weber B, Hochhaus G, Butterweck V. Pharmacokinetic evaluation of visnagin and Ammi visnaga aqueous extract after oral administration in rats. Planta

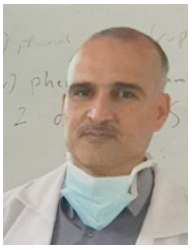
Med. 2012;79(3-4):1831–1836. Available from: 10.1055/s-0032-1315393.
102. Maksimović ZA, Kovacević N. Preliminary assay on the antioxidative activity of Maydis stigma extracts. Fitoterapia. 2003;74(1-2):144–147. Available from: 10.1016/s0367-326x(02)00311-8.
103. Solihah MA, Rosli WW, Nurhanan AR. Phytochemicals screening and total phenolic content of Malaysian Zea mays hair extracts. Int Food Res J. 2012;19(4):1533–1538.
104. Anand SP, Sati N. Artificial preservatives and their harmful effects looking toward nature for safer alternatives. Int J Pharm Sci Res. 2013;4:2496–2501.
105. Patil R, Mohan M, Kasture V, Kasture S. Rubia cordifolia: a review. Orient Pharm Exp Med. 2009;9(1):1–13. Available from: 10.3742/OPEM.2009.9.1.001.
106. Ahmed S, Mohtasheemul-Hasan M, Mahmood ZA. Antiurolithiatic plants in different countries and cultures. J Pharmacogn Phytochem. 2016;5(1):102–115.
107. Atmani F, Slimani Y, Mimouni M, Hacht B. Prophylaxis of calcium oxalate stones by Herniaria hirsuta on experimentally induced nephrolithiasis in rats. BJU Int. 2003;92(1):137–140. Available from: 10.1046/j.1464-410x.2003.04289.x.
108. Barros ME, Lima R, Mercuri LP, Matos JR, Schor N, Boim MA. Effect of extract of Phyllanthus niruri on crystal deposition in experimental urolithiasis. Urol Res. 2006;34(6):351–357. Available from: 10.1007/s00240-006-0065-1.
109. Boim MA, Heilberg IP, Schor N. Phyllanthus niruri as a promising alternative treatment for nephrolithiasis. Int Braz J Urol. 2010;36:657–664.
110. Pucci ND, Marchini GS, Mazzucchi E, Reis ST, Srougi M, Evazian D, et al. Effect of phyllanthus niruri on metabolic parameters of patients with kidney stone: a perspective for disease prevention. Int Braz J Urol. 2018;44(4):758–764. Available from: 10.1590/S1677-5538.IBJU.2017.0521.
111. Khan MY, Panchal S, Vyas N, Butani A, Kumar V. Olea europaea: A phyto-pharmacological review. Pharmacognosy Rev. 2007;1(1):114–118.
112. Al-Okbi SY, Hassan ZA, El-Mazar MM, Ammar NM, El-Kassem LA, El-Bakry HF. Potential diuretic activity of olive leaf extracts. Int J Pharmtech Res. 2016;9(9):519–533.
113. Lockyer S, Rowland I, Spencer J, Yaqoob P, Stonehouse W. Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: a randomised controlled trial. Eur J Nutr. 2017;56(4):1421–1432. Available from: 10.1007/s00394-016-1188-y.
114. Ciganda C, Laborde A. Herbal infusions used for induced abortion. J Toxicol Clin Toxicol. 2003;41(3):235–239. Available from: 10.1081/clt-120021104.
115. Benito M, Jorro G, Morales C, Peláez A, Fernández A. Labiatae allergy: systemic reactions due to ingestion of oregano and thyme. Ann Allergy Asthma Immunol. 1996;76(5):416–418. Available from: 10.1016/S1081-1206(10)63456-4.
116. Singletary KP, Oregano. Nutr Today. 2010;45:129–138. Available from: 10.1097/NT.0b013e3181dec789.

117. HA S, NA E, MS H. The ameliorative effect of Petroselinum crispum (parsley) on some diabetes complications. J Med Plants Stud. 2015;3:92–100.
118. Alyami FA, Rabah DM. Effect of drinking parsley leaf tea on urinary composition and urinary stones' risk factors. Saudi J Kidney Dis Transpl. 2011;22(3):511–514.
119. Patel U, Kulkarni M, Undale V, Bhosale A. Evaluation of diuretic activity of aqueous and methanol extracts of Lepidium sativum Garden cress (Cruciferae) in rats. Trop J Pharm Res. 2009;8(3):215–219. Available from: 10.4314/tjpr.v8i3.44536.
120. Al-Yousofy F, Gumaih H, Ibrahim H, Alasbahy A. Parsley! Mechanism as antiurolithiasis remedy. Am J Clin Exp Urol. 2009;5(3):55–62.
121. Arslan S, Ucar R, Caliskaner AZ. A cases of near-fatal anaphylaxis: Parsley "over-use" as an herbal remedy. Med Arch. 2014;68:426–433. Available from: 10.5455/medarh.2014.68.426-427.
122. Jurenka J. Therapeutic applications of pomegranate (Punica granatum L.): A review. Altern Med Rev. 2008;13(2):128–144.
123. Setiadhi R, Sufiawati I, Zakiawati D, Nur'aeny N, Hidayat W, Firman DR. Evaluation of antibacterial activity and acute toxicity of pomegranate (punica granatum l.) seed ethanolic extracts in swiss webster mice. J Dentomaxillofac Sci. 2017;2(2):119–123.
124. Melgarejo-Sánchez P, Núñez-Gómez D, Martínez-Nicolás JJ, Hernández F, Legua P, Melgarejo P. Pomegranate variety and pomegranate plant part, relevance from bioactive point of view: a review. Bioresour Bioprocess. 2021;8:2. Available from: 10.1186/s40643-020-00351-5.
125. Banihani SA. Radish (Raphanus sativus) and diabetes. Nutrients. 2017;9:1014–1014. Available from: 10.3390/nu9091014.
126. Anttonen MJ, Karjalainen RO. Environmental and genetic variation of phenolic compounds in red raspberry. J Food Compos Anal. 2005;18(8):759–709. Available from: 10.1016/j.jfca.2004.11.003.
127. Upton E, Halfacree G. Raspberry Pi® User Guide. John Wiley & Sons; 2012.
128. Nordeng H, Saboni M, Samuelsen AB, European Medicines Agency. EMA/HM-PC/44209/2012, Assessment report on Rubus idaeus L, folium; 2014. Commitee on Herbal medicinal products.
129. Simpson M, Parsons M, Greenwood J, Wade K. Raspberry leaf in pregnancy: its safety and efficacy in labor. J Midwifery Womens Health. 2001;46(2):51–59. Available from: 10.1016/s1526-9523(01)00095-2.
130. Frank T, Netzel G, Kammerer DR. Consumption of Hibiscus sabdariffa L. aqueous extract and its impact on systemic antioxidant potential in healthy subjects. J Sci Food Agric. 2012;92(10):2207–2218. Available from: 10.1002/jsfa.5615.
131. Czygan FC. Herbal Drugs and Phytopharmaceuticals. In: Wichtl M, Bisset NG, editors. A Handbook for Practice on a Scientific Basis Herbal Drugs and Phytopharmaceuticals. Medpharm GmbH Scientific Publishers; 1994. .
132. Gruenwald J, Brendler T, Jaenicke C. PDR for Herbal Medicines. In: Physician's desk reference (PDR) for herbal medicines the information standard for complementary medicine. Montvale NJ, Medical Economics Company Inc.; 1998. .

133. Srivastava R, Ahmed H, Dixit RK, Dharamveer, Saraf SA. Crocus sativus L.: A comprehensive review. Pharmacogn Rev. 2010;4(8):200–208. Available from: 10.4103/0973-7847.70919.
134. Rahmani AH, Khan AA, Aldebas YH. Saffron (Crocus sativus) and its active ingredients: Role in the prevention and treatment of disease. Pharmacognosy J. 2017;9(6):873–879. Available from: 10.5530/pj.2017.6.137.
135. Hajyzadeh M, Olmez F, Khawar KM. Chapter 5 - Molecular Approaches to Determine Phylogeny in Saffron. In: Saffron; 2020. p. 57–68. Available from: 10.1016/B978-0-12-818462-2.00005-X.
136. Pourmasoumi M, Hadi A, Najafgholizadeh A, Kafeshani M, Sahebkar A. Clinical evidence on the effects of saffron (Crocus sativus L.) on cardiovascular risk factors: A systematic review meta-analysis. Pharmacol Res. 2019;139:348–359. Available from: 10.1016/j.phrs.2018.11.038.
137. Pant A, Pandey R. Bioactive phyto molecules and aging in Caenorhabditis elegans. Healthy Aging Res. 2015;4. Available from: 10.12715/har.2015.4.19.
138. Nagpal G, Sharma M. Kalanchoe pinnata and its remedial properties to treat kidney stone- A lesser known plant. IntJ Biol Pharm Allied Sci. 2020;9(11):3016–3023. Available from: 10.31032/IJBPAS/2020/9.11.5259.
139. Chandel VK, Jain S, Choubey A. An overview on phyto-molecules and screening method of antiurolithiatic activity. J Drug Deliv Ther. 2019;9(4):848–857. Available from: 10.22270/jddt.v9i4-A.3709.
140. Swamy MK, Akhtar MS, editors. Natural Bio-active Compounds. vol. 2 of Chemistry, Pharmacology and Health Care Practices. 1st ed. Springer Singapore; 2019. Available from: 10.1007/978-981-13-7205-6.
141. Gupta S, Ss K. Phyto-molecules for kidney stones treatment and management. Biochem Anal Biochem. 2018;07:1–8.

AUTHOR BIOGRAPHY

Mohammed I. Rasool he received his Ph.D. in Pharmacology and Experimental Therapeutics from the University of Toledo (United States), and his M.Sc. in Pharmacology was from the University of Al-Nahrain (Baghdad, Iraq). His B.Sc. in Pharmaceutical Sciences was from the University of Kufa (Najaf, Iraq). He is now a faculty member at the Pharmacology and Toxicology Department, College of Pharmacy, University of Karbala (Karbala, Iraq).



Tariq H. Mousa he holds a master's degree in Pharmacy from the University of Baghdad (Baghdad, Iraq). His B.Sc. in Pharmaceutical Sciences was from the University of Baghdad too. He works as a faculty member at the Medicinal Chemistry Department, College of Pharmacy, University of Karbala (Karbala, Iraq).

Ahmed H. Ismael he got his Ph.D. in Pharmacology and Therapeutics from the University of Al-Nahrain (Baghdad, Iraq) and M.Sc. in Pharmacology from the University of Al-Nahrain (Baghdad, Iraq). His bachelor of medicine and surgery (M.B.Ch.B) was also from the University of Al-Nahrain (Baghdad, Iraq). He now works as a faculty member at the Clinical Pharmacy Department, College of Pharmacy, University of Karbala (Karbala, Iraq).