Therapeutic potential of medicinal plants for the management of renal stones

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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

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.\textsuperscript{1–3} Kidney stones are 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.\textsuperscript{4,5} Nephrolithiasis is also more prevalent in wealthy countries like hypertension, obesity and type 2 diabetes.\textsuperscript{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.\textsuperscript{8–10} Figure 1 shows the mode of action of medicinal herbs against urolithiasis.

![Figure 1](https://bjbabs.v3i02.133)

**Figure 1** The reported ways of phytochemical molecules against kidney stone formation.\textsuperscript{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), hypercalcuria (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, alkalization 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.\textsuperscript{13}

**SYMPTOMS OF KIDNEY STONE**

Kidney stone symptoms vary depending on whether the stone 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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. |

<table>
<thead>
<tr>
<th><strong>Promotors</strong></th>
<th><strong>Role</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume</td>
<td>Low urine production promotes crystallization.</td>
</tr>
<tr>
<td>Urine pH</td>
<td>Highly acidic media enhance (CaOx) crystallization.</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>Enhance urine supersaturation and hence crystallization of Ca.</td>
</tr>
<tr>
<td>Uric acid or urate</td>
<td>Promotes heterogenous nucleation and increase binding between cells and CaOx.</td>
</tr>
</tbody>
</table>

**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.\textsuperscript{14,16} Among calcium stone promoters, hypocitraturia and hypercalciuria are two of the most prominent urinary disorders (Proofread and check,
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.

**Struvite stones**

Struvite stones also called infectin stones or triple phosphate stones. They are found in 10-15% of the population. They are 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*). Urease is cleaved into ammonia and carbon dioxide (CO$_2$) and elevate urine pH above 7. This form of stones is more likely to occur in women than in men.

**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 hypouricosuric 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.

**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.

**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.

**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.
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.  

**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. 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.

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

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. 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. 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. The thymoquinone can inhibit the cyclooxygenase and 5-lipoxygenase pathways resulting in the inhibition of the inflammatory process. 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.

**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. 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. 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.

**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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{100}

\textbf{Khella baladi (Ammi visnaga)}

\textit{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 $\gamma$-pyrones, which are mostly represented by khellin and visnagin. Its flavonoid content is responsible for its antioxidant activity. And, its $\gamma$-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.\textsuperscript{43} Egyptian patients with renal stones have long utilized teas made from the fruits of \textit{A. visnaga}.\textsuperscript{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.\textsuperscript{44} Khellin and visnagin, both isolated from \textit{A. visnaga}, were thought to have pleiotropic effects on urolithiasis which include smooth muscle relaxation, diuresis, and the effects on urinary citrate.\textsuperscript{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.\textsuperscript{46} Khella baladi is unsafe during pregnancy and lactation and it is used with caution for patients with liver disease.\textsuperscript{101}

\textbf{Maize (Zea mays)}

It also called corn silk (\textit{Stigma maydis}). It belongs to Gramineae family. This plant is found widely in India, China, North America, and Malaysia. \textit{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 \textit{Zea mays} contains a variety of bioactive constituents such as
flavonoids, tannins, terpenoids, cardiac glycoside, and phenols. 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.

**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. Roots have tonic, antidysentery, astringent, and antiseptic properties. 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. 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. Its extract is used with caution in pregnant and lactating women.

**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. 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. 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.\(^9\) \(P. niruri\) is possibly unsafe during pregnancy and lactation and should be used with caution for diabetic patients.\(^10\)

**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.\(^11\) 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 diuresis 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, Lamiaeaceae), 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{121}

**Pomegranate (*Punica granatum*)**

Also referred to as “a pharmacy unto itself”.\textsuperscript{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.\textsuperscript{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.\textsuperscript{11,56–58} It should be used with caution for patients with hypotension.\textsuperscript{59}

\textbf{Radish (\textit{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.\textsuperscript{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.\textsuperscript{61} Previous studies reported the effect of aqueous extract of the leaves of \textit{R. sativus} on \textit{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.\textsuperscript{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.\textsuperscript{125}

\textbf{Raspberry (\textit{Rubus idaeus})}

It is a medicinal plant that is widely employed in the Middle East to treat kidney stones. It belongs to Rosacea family.\textsuperscript{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.\textsuperscript{127} \textit{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 \textit{R. idaeus} provides protection for kidneys from CaOx stone deposition.\textsuperscript{64} The raspberry methanolic extract was reported to be a significant diuretic through disrupting the activity of epithelial sodium channels or aldosterone.\textsuperscript{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.\cite{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.\cite{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.\cite{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.\cite{130} Roselle are likely safe for diabetic patient and pregnant women.\cite{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 crude 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.\cite{71,72,73,74} 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.\cite{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.\textsuperscript{133} Different plant parts like peels, fruits, seeds, and rind of \textit{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.\textsuperscript{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.\textsuperscript{135} The antilithiatic potential of crocin, a pharmacologically active constituent of \textit{C. sativus}, was evaluated against ethylene glycol (EG)-induced nephrolithiasis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{136}

### Shatavari (\textit{Asparagus racemosus})

\textit{Asparagus racemosus} belongs to the family Liliaceae and commonly known as satavari. The dried roots of the plant are used as folk medicine.\textsuperscript{77} The chemical constituents of \textit{A. racemosus} are mucilage, volatile oil, tannic acid, sapogenin, saponin, asparagine, asparagusin, sitosterol, and flavonoids. \textit{A. racemosus} was researched for its suppressive impact on urolithiasis. In a previous \textit{in vitro} study that induced kidney stone to adult male albino rats by EG, the ethanolic extract of \textit{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 \textit{A. racemosus} inhibits EG-induced stone formation.\textsuperscript{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.\textsuperscript{79}

### Thai green eggplant (\textit{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
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 phytococonstituents 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{85} Turmeric 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.\textsuperscript{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.\textsuperscript{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.\(^8\) 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.\(^8\) It is unsafe to use maiden-hair 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.\(^8\)

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

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

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