RESEARCHING MEDICINAL PLANTS FOR ANTIUROLITHIATIC ACTIVITY: A SYSTEMATIC REVIEW

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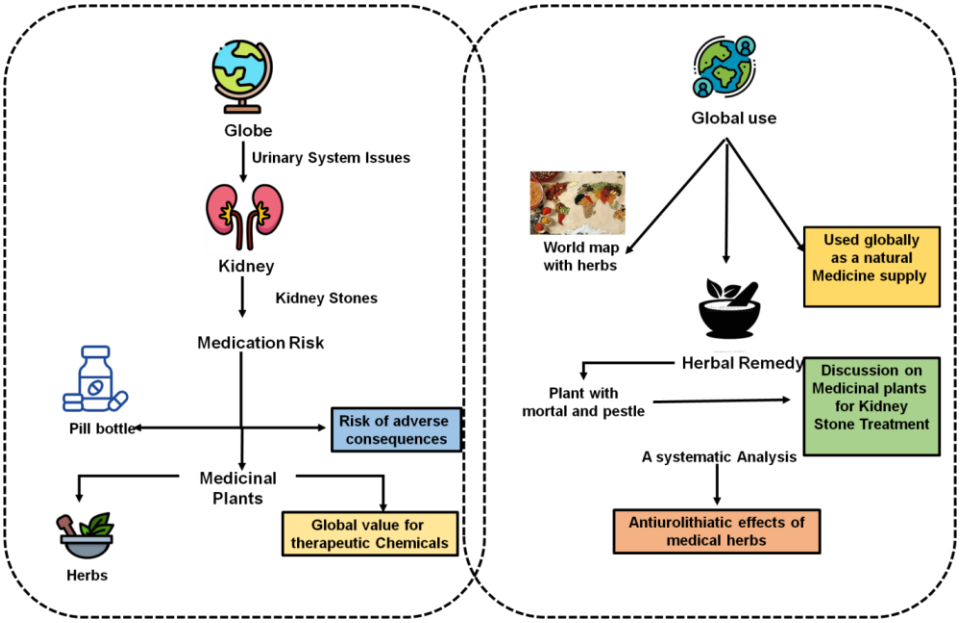
Graphical abstract



Abstract

Kidney stones are the most common urinary system issues, followed by UTIs and disorders related to the prostate. Kidney stones can obstruct the passage of urine and cause excruciating pain. Medication usage during treatment has a significant risk of adverse consequences. Throughout the globe, medicinal plants are highly valued for their abundant supply of therapeutic chemicals that can be used for illness prevention and therapy. Herbs have been utilized by many civilizations across the globe to cure a variety of illnesses. Despite the development of contemporary medications, medicinal plants have gained recognition and been used in many countries because of their effectiveness, safety record, cultural acceptability and inferior risks than authorized pharmaceuticals. Numerous cultures employ medicinal plants as a dependable natural medicine supply. The current article discusses the causes, forms, diagnostic and treatment options of kidney stones, including the use of several medicinal plants as an herbal remedy. This systematic review offers a thorough synthesis of the available data on the possible Antiurolithiatic effects of medicinal herbs.

Keywords: Antiurolithiatic Activity, Urinary System Issues Kidney Stone, Medicinal Plants.

1. Introduction

An integral component of routine urological care is the management of urinary stone disease. Between five and ten percent of people will develop stones throughout their lives. There is a discernible gender difference, with a high frequency in the age groups of four to five. Patients with stone illness must get treatment for recurrent stone development (Jebir and Mustafa, 2023). Three calcium-containing substances, basic calcium phosphate, calcium oxalate dehydrates and calcium oxalate monohydrate, are involved in 75–90% of occurrences of stones. Magnesium ammonium phosphate (Struvite) makes up 10%–15% of the mixture, uric acid makes up 3%–10% and cystine makes up 0.5–1% (Susilo et al., 2021). The most frequent kind of stones that occur is either calcium oxalate type 3 or magnesium ammonium phosphate type 2. Urinary stones have been treated using a variety of methods (Kuz'mina et al., 2020). Figure 1 depicts the kidney stone's anatomical location.

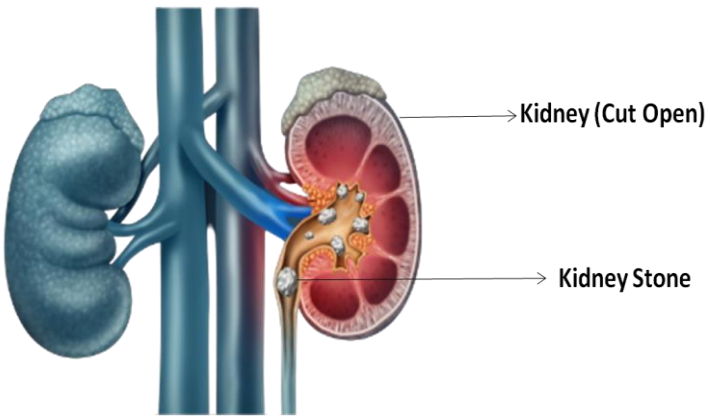


Fig: 1 Kidney Stone Formation

(van Wyk and Prinsloo, 2020)Over 5000 years have seen the use of natural plant products for a variety of reasons throughout human history; for a large portion of that time, herbal medicine was the exclusive form of treatment (Pengelly, 2020). Natural plant-based compounds called herbal medicines are used to either prevent or cure a variety of illnesses(van Wyk and Prinsloo, 2020). Any raw or processed portion of a plant might include complex combinations of organic compounds that are found in medicinal plants (Rao et al., 2022). Around the globe, plants constitute the source of 25% of prescription medications. Plants make up 11% of the 252 medications on the World Health Organization's (WHO) list of essential medicines (Sam, 2019). Herbal medicine, known as botanical medicine, is the use of flowers, berries, plant seeds, roots, bark and leaves for therapeutic effects (Parkash et al., 2018). Many experts are studying various medicinal plants to produce pharmaceutical medicines. The disorder known as Urolithiasis, or kidney stones, is characterized by the accumulation of urinary calculi inside the urinary system (Bencheikh et al., 2021). Chemicals in urine inhibit the formation of crystals. However, not everyone seems to benefit from these inhibitors and as a result, some individuals get stones (Daudon et al., 2018). The crystals will pass through the urinary system and exit the body in the urine undetected if they stay small enough.

Urinary stones that are up to 5 mm in diameter pass through the urinary system; however, stones bigger than 7 mm almost invariably need surgery (Das, 2019). It results in major health issues that have a negative impact on people's well-being, such as infection, urinary tract blockage and excruciating discomfort after urinating. Urolithiasis affects people of all ages, from newborns to those over seventy(Wróbel and Kuder, 2019) . Males are two to four times more likely than women to develop stones. Because males have more muscle mass than women, which increases testosterone's ability to produce stones and inhibits estrogen's ability to do so (Kittanamongkolchai et al., 2018). Additionally, the urinary system in men is more complex than in women. Because estrogen raises protective citrate levels and keeps urine alkaline, it aid in the anticipation of calcium stone development. Calculi are a common occurrence in the urinary system, with the highest prevalence of adverse medication responses occurring in the vesical, renal and ureteral regions (Dobrek, 2023). Shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy and open or laparoscopic stone removal are available treatments for kidney stones (Güler et al., 2019). However, many find these disagreeable and pricey treatment options to be inconvenient. Kidney stone illness can be effectively treated using a variety of medicinal herbs. The current article aims to highlight powerful medicinal herbs that are used to treat Urolithiasis.

2. Search Technique

In real-world scenarios, interviews were considered effective, but performing an intervention under perfect, controlled settings was considered successful. In 2018–2023, a comprehensive electronic search was conducted across a number of esteemed databases, including Embase, PsycINFO, Medline, Scopus and Web of Science, to find papers pertaining to the field of medicinal plant research. Among the crucial terms that were chosen were "urological therapy," "Medicinal plants, *antiurolithiatic*, stones, urinary stones, medical systems, urinary

tract problems and calcium phosphate. The search was restricted to studies that were published during the last three years, from 2018 to 2023, to assure the relevancy of the results. A comprehensive search strategy was created to gather the most recent and pertinent research contributions in the field of medicinal plants and their potential use in the treatment of urological problems.

3. Type of kidney stones

Renal stones come in a variety of forms with distinct etiology and composition. Included in an individual's typical diet, these substances constitute vital bodily components, including muscles and bones. Table 1 shows the classification of kidney stones.

Table 1: Different kind of kidney stone

Stone types	**calcium oxalate**	**calcium phosphate**	**Uric acid**	**struvite**	**cystine**	**Medication-induced stones**
Constituents	calcium oxalate	calcium, phosphate	uric acid	calcium, ammonia phosphate	cystine	indinavir, ephedrine, guaifenesin, silica)
% Incidence of all stones	70%	10%	5-10%	10%	Less than 1%	Less than 1%

3.1 Calcium stones

Calciuria brought by hyperparathyroidism is linked to calcium phosphate, calcium urate and calcium oxalate stones (Tavasoli and Taheri, 2019). Individuals with a history of illness have higher intestinal absorption of calcium, which results in calcium or phosphate leakage in the kidneys, as well as hypocitraturia, hyperuricosuria, hypomagnesuria and hyperoxaluria.

3.2 Struvite stones

Magnesium ammonium phosphate stones, sometimes known as partial or full staghorn calculi, expand to fill the collecting system to form Struvite (Nevo et al., 2019). This phase is brought by recurring infections of the urinary tract brought by Klebsiella, Pseudomonas and Proteus species, which are Gram-negative urea-splitting rods.

3.3 Uric acid stones

Uric acid stones can occur when gout patients take drugs that contain a lot of purines or have a fast rate of cell turnover (like cancer). Uric acid stones result from urine with a pH of 5.5 or

below. They can be seen in the natural world and they are radiolucent on X-ray film (Li et al., 2018).

3.4 Cystine stones

The inherited intrinsic metabolic disease known as cystinuria, which impairs the renal tubule's reabsorbing of cysteine, is the cause of cysteine stones (Siener et al., 2021). Because of their high sulfur content, these stones can be challenging to locate on X-rays. When drugs are used to produce stones, several drugs could have involvement in the production of renal stones.

3.5 Drug-induced stones

Kidney stones could result from some drugs, which can be used to treat other conditions (Daudon et al., 2018). These consist of silicate (antacids), triamterene, guaifenesin, atazanavir, indinavir and sulfa drugs. Radiolucent X-rays routinely reveal these very unusual stones.

4. Diagnosis

The assessment of clinical symptoms, including the kind and location of pain, is the basis for the diagnosis of Urolithiasis. Confirmatory imaging, such as computed tomography, ultrasonography and x-rays, is used to find out whether there are stones. In addition, a number of tests are carried out to identify probable sources and effects of the stones. Urine is examined under a microscope to detect proteins, germs, cellular casts, red blood cells and crystals. Blood tests are used to evaluate renal function; spot abnormally high blood calcium levels (hypercalcaemia) and detects a heightened white cell count (neutrophilia) suggestive of infection.

5. Medical Plants for Preventing Kidney Stone

Numerous therapeutic herbs shown in Table 2 have the potential to stop kidney stones from forming and even reverse the processes that lead to stone development.

Table 2: Medical plants and the mechanisms against kidney stone

Medical Plant	**Scientific name**	**Family Name**	**Part of Plant**	**Mechanisms**	**Reference**
Venus Hair	Adiantumcapillusveneis	Pteridaceae	Whole plant	Clitolytic Urolithiasis that resists calcium oxalate	(Dehdari and Hajimehdipoor, 2018)
Black seed	Nigella sativa	Ranunculaceae	Seed	Anti-inflammatory, antioxidant, and reduced CaOx deposition	(Ardakani Movaghati et al., 2019)
Thai green eggplant	Solanumxanthacarpum	Solanaceae	Root	Reduce the formation of CaOx stones, act as an antioxidant and reduce inflammation	(Zakaria et al., 2023)
Turmeric	Curcuma Longa L.	Zingiberaceae	Root	Lower the urine's calcium and oxalate levels. Lessen the quantity of stones that are abandoned.	(Antony et al., 2018)
Shatavari	Asparagus racemosus	Asparagaceae	Root	Antiurolithiatc, Diuretic,	(Bandarapalle et al., 2020)
Saffron	Crocus sativus L.	Iridaceae	Flower	Diuretic Renal excretion of oxalate is increased, whereas that of citrate and magnesium is decreased.	(Wani et al., 2022)
Rupturewort	Herniariahirsuta	Caryophyllaceae	Aerial part	Prevent the COM adherence and inhibit the aggregation of CaOx.	(Peeters et al., 2022)
Raspberry	Rubusidaeus	Rosaceae	Root	diuretics and	

				antilithiatics	(Vogiatzaki and Ali, 2021)
Radish	Raphanussativus L.	Brassicaceae	Leaf	lithotriptic, diuretic, and decrease the crystallization of CaOx	(BAWARI et al., 2022)
Pomegranate	Punicagranatum	Lythraceae	Flower	Antioxidant, antihypercalciuric, anti-inflammatory, and muscle relaxation	(Kachkoul et al., 2023)
Oregano	Origanumvulgare L.	Lamiaceae	Leaf	Antispasmodics, diuretics, and antioxidants stop the production of CaOx.	(Mohamed and Alotaibi, 2023)
Olive	Olea Europaea	Oleaceae	Leaf	diuretics and antioxidants	(Babaeenezhad et al., 2019)
Ngingihel	Phyllantusniruri	Euphorbiaceae	Root	prevent CaOx stone-induced cytotoxicity, act as an antispasmodic, and prevent crystallization	(Garbens and Pearle, 2021)
Manjistha	Rubiacordifolia	Rubiaceae	Root	Reduce the kidneys' levels of calcium and oxalate to stop the formation of urinary stones.	(Nirumand et al., 2018)
Maize	Zea mays	Poaceae	Flower	Diuretics	(Bhandari et al., 2021)
Khellabalad	Ammivisnaga	Apiaceae	Fruit	Antioxidant, analgesic, diuretic, lithotriptic, relaxant of muscles	(Khalil et al., 2020)
Green tea	Camellia sinensis	Theaceae	Leaf	Diuretics antioxidant	(Nasrul and Sehgal, 2018)
Parsley	Petroselinum crispum	Umbelliferae	Seed	Lowering urinary calcium excretion	(Rahmat et al., 2019)

				and raising urine pH, volume, and diuresis.	
Barberry	Berberis vulgaris	Berberidaceae	Root	Diuretic, anti-inflammatory, and antioxidant	(Sumreen et al., 2021)
Roselle	Hibiscus sabdariffa	Malvaceae	Flower	Boost excretion of uric acid and prevent COM crystallization	(Ghazala Riaz and Rajni Chopra, 2018)

Adiantum capillus-veneris

A medicinal plant renowned for treating Urolithiasis (kidney stones) is Adiantum capillus-veneris, known as maidenhair fern. Pteridaceae is its family and it has been included in litholytic formulations. In rat experiments, the quantity as well as size of crystals was decreased by a hydroalcoholic extract of A. capillus-veneris along with serum levels of blood urea, calcium and phosphorus were lowered (Dehdari and Hajimehdipoor, 2018). Crystallization and crystal aggregation inhibition are the plant's anti-calcium oxalate Urolithiasis capability. It is advisable to exercise care, particularly if pregnant, since excessive use of the plant can induce vomiting and could cause splenic damage, especially in those who are vulnerable.

Fig 2: Adiantum capillus-veneris

Nigella sativa

The essential oil of Nigella sativa seeds, which belong to the Ranunculaceae family, contains healthy substances, including thymol, thymoquinone, thymohydroquinone and thymoquinone. A crucial ingredient, thymoquinone, has pharmacological properties that aid in the treatment of nephrolithiasis by minimizing the size and quantity of kidney stones (Ardakani Movaghati et al., 2019). During stone deposition, it functions as an antioxidant,

scavenging free radicals and superoxide anions. In addition to suppressing inflammation, thymoquinone blocks inflammatory pathways, including cyclooxygenase and 5-lipoxygenase. Although black seed is safe to eat during pregnancy, when taken medicinally, care should be taken because of possible effects on blood pressure, blood sugar, uterine contractions and coagulation.

Fig 3: Nigella sativa seeds

Solanum xanthocarpum

It is a nightshade with yellow fruits belongs to the family Solanaceae. The fruit extract, known as Solanum Xanthocarpum Fruit Methanol Extract (SXFME), is recommended for the handling of renal disease, urinary area infections and urolithiasis is difficulty urinating. By lowering crystallization, SXME has a diuretic effect that lowers urine super saturation and prevents Urolithiasis (Zakaria et al., 2023). It assists in keeping the ratio of stone promoters to inhibitors in check by lowering the excretion and deposition of calcium oxalate particles. Fruits of the plant contain high concentrations of alkaloids, phytosterols and saponins; derivatives of saponins have antiurolithiatic qualities. Furthermore, phytosterols have anti-inflammatory and antioxidant properties, which mean yellow-fruit nightshade, can be used as a prophylactic against kidney stone formation.

Fig 4: Solanum xanthocarpum

Curcuma Longa L.

The *Curcuma longa* is a tropical plant found in Southeast Asia and India that is a component of the family of ginger. Curcumin, the main ingredient in turmeric, has anti-inflammatory and antioxidant qualities. It has been shown that curcumin protects kidneys against kidney stones by bringing calcium as well as oxalate levels back to normal, avoiding kidney stone damage and helping to prevent kidney stones. But turmeric should be used with care since it might worsen liver problems, gallstones and bleeding disorders. Moreover, a high intake could decrease the absorption of iron, making it inappropriate for those who are iron deficient (Antony et al., 2018).

Fig 5: Curcuma Longa L

Asparagus racemosus

Asparagus racemosus, a plant belonging to the Liliaceae family, is used in traditional medicine. It is known by the popular name "satavari." It is made up of a variety of chemical components, including flavonoids, tannic acid, mucilage and volatile oil. According to research, A. racemosus can decrease the development of kidney stones or Urolithiasis. Its ethanolic extract decreased calcium, phosphate and oxalic acid levels in vitro research conducted on rats but also increased magnesium levels, a sign that prevents the formation of stones. A. racemosus has diuretic qualities that can help with kidney stone relief. It possesses Antiurolithiatic properties, speeding up the disintegration of stones and preventing their reappearance(Bandarapalle et al., 2020).

Fig 6 : Asparagus racemosus

Crocus sativus L.

More than 150 volatile chemicals can be found in the plant Crocus sativus L., which is well-known for its fragrant red stigma and yellow style(Wani et al., 2022). Plant parts include several bioactive chemicals, including safranal, crocin, picrocrocin and crocetin. Traditional medical practices have included the use of saffron to treat conditions including amenorrhoea, asthma, stomach illnesses and cardiovascular diseases. According to studies, it can be able to relieve kidney stones because of its active ingredient, crocin. Saffron extracts were successful in lowering oxalic acid levels in the urine linked to ethylene glycol-induced nephrolithiasis. However, excessive doses of saffron could have negative consequences; therefore, care is suggested, particularly for those who are pregnant or nursing, have low blood pressure, diabetes, or bipolar illness.

Fig 7: Crocus sativus L.

Herniaria hirsute

Native to North Africa and Eurasia is this plant. It is referred to as hairy rupturewort. Two monodesmosidic saponins, flavonoids, phenolic and flavanols, were found in the aerial section of Herniaria. The Herniaria plant's has many pharmacological properties, including its antibacterial, antioxidant and anti-urolithiatic properties, are made possible by these active ingredients. The crude extract from the plant directly affects CaOx crystals by promoting the development of tiny, expelled CaOx dihydrate crystals. Moreover, the extract stopped CaOx aggregation. Furthermore, the H. hirsuta supplement reduced the quantity of crystal deposition in the kidneys and above all evidenced its antilithiatic activity by averting the development of kidney stones. CaOx crystals' interaction with renal epithelial cells was a critical stage in the development of kidney stones (Peeters et al., 2022). A solution of H. hirsuta is applied on the COM crystals, which keeps it from adhering to the cell, which has an effect on COM adhesion. Information on rupturewort's safety and potential negative effects is insufficient. When used with lithium, there are mild interaction warnings. Eating rupturewort could reduce the excretion of lithium since it can have a diuretic effect. Because lithium builds up throughout the body, this consequence might result in significant negative effects from the drug. If lithium is to be taken with rupturewort, the dosage needs to be adjusted.

Fig 8 : Herniaria hirsute

Rubus idaeus

A popular remedy for kidney stones in the Middle East is Rubus idaeus, a medicinal plant of the Rosaceae family. Its nutritional components include dietary fibres, anthocyanins, ellagitannins, minerals, vitamin C and flavonoids. Raspberry root has anti-Urolithiasis properties by reducing calcium and oxalate levels in the urine and inhibiting the formation of calcium oxalate (CaOx) stones (Vogiatzaki and Ali, 2021). By preventing crystal development, the aqueous extract encourages the evacuation of tiny particles. Raspberry vitamin E protects the kidneys. Because it disrupts sodium channels, methanolic extract has a diuretic effect. Nonetheless, it is important to use care and seek medical advice during the last trimester of pregnancy. Due to possible estrogenic effects and blood sugar decrease, raspberry ingestion should be used with caution in those with diabetes or hormone-sensitive disorders.

Fig 9: Rubus idaeus

Raphanus sativus

Raphanus sativus is utilized globally and it is available in a range of sizes, forms and colors. Its leaves offer therapeutic properties and they were once used to cure kidney stones and illnesses (BAWARI et al., 2022). Chemical components found in radish, such as flavonoids,

have been shown to be able to lessen the crystallization of CaOx in human urine. Radish saponins prevent crystallization by breaking down mucoproteins, which are known to be promoters of crystallization. R. sativus leaf extract in aqueous solution reduces crystal density, inhibits CaOx crystallization from nucleating and aggregating as well as facilitates the dissolution of CaOx crystals in vitro. However, those with diabetes and gallstones should use care while consuming radishes. Women who are nursing or pregnant should restrict their radish consumption to serving sizes of typical dishes.

Fig 9: Raphanus sativus

Punica granatum

The fruit pomegranates, Punica granatum (P. granatum), are recognized for a variety of bioactive substances, such as punicalagin, ellagic acid and alkaloids. P. granatum is a member of the Punicaceae family of plants and it was first cultivated by seed propagation in the Middle East. The plant has antiurolithiatic and anti-hypercalciuric qualities that are helpful in avoiding calcium oxalate (CaOx) stones in the kidney. Kidney stone removal is facilitated by phytochemicals found in P. granatum flower juices and methanolic extracts, which function by calming the biliary and urinary system's muscles(Kachkoul et al., 2023). Due to their ability to lower reactive oxygen species, pomegranates' flavonoids and anthocyanins, which are known for their antioxidant qualities, are essential in avoiding oxidative damage to renal tubules. Pomegranate aids in the control of uric acid, creatinine and urea levels.

Fig 10: Punica granatum

Origanum vulgare L

The Lamiaceae family's oregano (O. vulgare) has been used in folk medicine for its antispasmodic, lithotriptic and diuretic qualities(Mohamed and Alotaibi, 2023). Abundant in phytochemicals, including tannins, coumarins, saponins, alkaloids, flavonoids, terpenes and sterols, it has been linked to a number of therapeutic benefits, including anti-inflammatory, anti-cancer, antioxidant and stimulant properties. Oregano can help to prevent kidney stones by acting like a diuretic, which increases urine quantity and decreases crystal super saturation, according to research. It relieves pain by acting as an antispasmodic as well. Because of its antioxidant qualities, oregano helps to prevent and dissolve calcium oxalate stones while providing defense against oxidative stress.

Fig 11: Origanum vulgare L

Olea europaea

Olea europaea, a member of the Oleaceae family and a common plant in the Mediterranean area, has a number of historical applications in medicine. In particular, it has been shown that olive oil made from Olea europaea possesses antiurolithiatic qualities, which inhibit the development of kidney stones(Babaeenezhad et al., 2019). Urinary crystal formation is inhibited by the flavonoids in olive oil, which counteract the peroxidative stress brought by hyperoxaluria. It is possible that the oil's diuretic action comes from reducing glomerular filtration and blocking carbonic anhydrase. Olive oil's antioxidant qualities can hasten the breakdown of existing stones and stop the development of new kidney stones. However, owing to possible adverse effects such as headaches, nausea, coughing and dizziness, vigilance is suggested. People who are allergic to olive tree pollen can have adverse effects. Olive leaf extracts could potentially affect blood pressure and blood glucose levels; if used with hypoglycemic or hypertension medications, careful monitoring is necessary. Furthermore, it is advised to stop using olive oil two weeks before surgery to prevent any possible impacts on blood sugar regulation during and after the treatment.

Fig 12: Olea europaea

Phyllanthus niruri

The Euphorbiaceae family includes the therapeutic plant Phyllanthus niruri, sometimes referred as "stone breaker," which is found all over the globe. Brazilian folk medicine uses it extensively, particularly for urolithiasis patients(Garbens and Pearle, 2021). Triterpenes, in particular, are very useful in preventing cytotoxicity induced by calcium oxalate (CaOx). The plant includes alkaloids, flavonoids, lignans and triterpenes. Additionally, the kidneys' excretion of substances that cause stones and indicators of crystal formation is decreased by these substances. Furthermore, Phyllanthus demonstrates uricosuric activity by the extraction of methanol from its leaves. In hyperuricemic rats, this activity qualified to substances like phyllanthin and lignans was shown to be advantageous. Phyllanthus alkaloids contain antispasmodic qualities that relax smooth muscles, especially in the urinary tract, making it easier to remove kidney calculi. Together, these benefits support Phyllanthus niruri's capacity to fend against kidney stones. Phyllanthus niruri can be dangerous to use during pregnancy and breastfeeding. Thus, individuals with diabetes should take it with caution.

Fig 13: Phyllanthus niruri

Rubia cordifolia

Many people are aware of the therapeutic qualities of common madder, or Rubia cordifolia, particularly in relation to its roots. Supplements manufactured from these roots, called manjistha, had shown promise in preventing kidney stones by lowering the stage of calcium

and oxalate as well as preventing the formation of stones (Nirumand et al., 2018). Ethylene glycol-induced Urolithiasis was prevented in research using a hydroalcoholic extract from the roots. With its suppression of phosphate, calcium and oxalic acid excretion, the extract affects the components of urine yet can be useful in reducing the formation of urinary stones. Due to its nephroprotective and antioxidant qualities, it could have a preventative effect. Women who are expecting or nursing should use this extract with care, nevertheless.

Fig 14: Rubia cordifolia

Zea mays

Plants with medicinal qualities, called zea mays or maize silk, are found in places like Malaysia, China, India and North America. Because of its inherent diuretic action, this rich source of bioactive compounds such as flavonoids and tannins was well-known for treating kidney stones (Bhandari et al., 2021). Little pieces of stone are helped to pass through the urine by this diuretic action. People with diabetes, hypokalemia, irregular blood pressure and pregnant women should exercise caution. In spite of the possible advantages, moderation is essential while treating urinary tract infections and kidney stones.

Fig 15: Zea mays

Ammi visnaga

A member of the Apiaceae family, ammi visnaga is used in North Africa, Asia, Europe and the Mediterranean region for medical reasons. It contains flavonoids, essential oils and γ-pyrones such as visnagin and khellin. These ingredients support a number of kidney-related conditions and add to antioxidant qualities. Positive outcomes have been shown in studies using fruit teas from A. visnaga to treat renal stones in Egyptian patients. The aqueous extract of the plant hastened the disintegration of cystine stones (Khalil et al., 2020). Visnagin and khellin reduce the likelihood of calcium oxalate crystal formation, enhance citrate urine production and decrease oxalate excretion in male rats with hyperoxaluria-induced kidney stones. Because citrate prevents the crystallization of calcium oxalate urinary stones, which are common, khellin's capacity to interfere with citrate metabolism is essential for avoiding the recurrence of calcium oxalate stones. Due to its pleiotropic properties, such as diuresis, relaxing of smooth muscles and favorable effects on urine citrate, ammi visnaga can be used as a natural kidney stone preventive drug.

Fig 16: Ammi visnaga

Camellia sinensis

Asian medicine has been using green tea, which is derived from C. sinensis leaves, for 4000 years, mostly in China and India. By stimulating mineral excretion and having diuretic along with natriuretic effects (caffeine-induced), it avoids kidney stones. Reactive oxygen species were neutralized and stone formation was inhibited by antioxidants such as epigallocatechin gallate (Nasrul and Sehgal, 2018). People who suffer from anxiety, bleeding, heart difficulties, diabetes, diarrhea, glaucoma, IBD, liver disorders, or weak bones should exercise caution while consuming excessive amounts of green tea since these illnesses can deteriorate. It is important to think about possible interactions with drugs, including cocaine, ephedrine and amphetamines.

Fig 17: Camellia sinensis

Petroselinum crispum

Being an Umbelliferae family member, parsley is well-known for its therapeutic qualities, which include laxative, anti-inflammatory and antihypertensive, antioxidant as well as anti diabetic actions. Parsley seeds, in particular, had antiurolithiatic qualities that inhibit the production of calcium oxalate (CaOx) stones by lowering urine calcium levels (Rahmat et al., 2019). This is accomplished by either reducing serum calcium levels or raising urine citrate. Parsley is a possible anti-CaOx drug since it can elevate urine pH to around 6. CaOx stone formation prefers a pH range of 4.5 to 5.5. Furthermore, compounds such as flavonoids, organic acids and saponins that are responsible for parsley's diuretic action might increase urine volume while decreasing nucleation and super saturation. Those with edema, hypoglycemia, renal illness, or high blood pressure should exercise care, nevertheless. Some medications, such as diuretics and warfarin, can have mild interactions with parsley.

Fig 18: Petroselinum crispum

Berberis vulgaris

Chinese and Iranian traditional medicine has been using Berberis vulgaris, a member of the Berberidaceae family, for more than 3000 years. Packed with potent ingredients such as phenolic compounds, alkaloids, ascorbic acid and berberine, it has nephrolithiatic, anti-

inflammatory and antioxidant qualities. Berberine works well in the setting of kidney stones to prevent and cure CaOx Urolithiasis (Sumreen et al., 2021). Because of its diuretic impact, urine produces more pee, which raises urine pH and lowers calcium concentration, lowering the risk of stone formation. The antioxidant characteristics of berberine prevent CaOx retention in renal tubules by balancing the imbalance brought by excessive oxalate levels. However, owing to possible adverse effects, including constipation, indigestion and rashes, care is suggested. It can be utilized by women who are pregnant or breastfeeding since it could exacerbate neonatal jaundice and interfere with medicines.

Fig 19: Berberis vulgaris

Hibiscus sabdariffa

Members of the Malvaceae family of plants, hibiscus sabdariffa, or roselle, are plants that grow in Africa and India. Polyphenols, L-ascorbic acid, protocatechuic acid, quercetin and hibiscus anthocyanins are some of its active ingredients. It treated and prevented urinary calculi, or kidney stones, according to traditional Thai medicine (Ghazala Riaz and Rajni Chopra, 2018). Prolonged uric acid excretion and decreased renal oxalic acid retention are signs of a uricosuric effect shown by clinical research. Kidney stone formation's primary component, calcium oxalate monohydrate, is prevented from crystallizing by the aqueous extract of H. sabdariffa flowers. Rosabelle is thought to be safe for use by expectant mothers and diabetics.

Fig 20: Hibiscus sabdariffa

6. Prevention and Management

The goal of recurrent urolithiasis prevention and treatment was to raise daily fluid intake to 2.5–3 liters (Kang et al., 2019; Kiremit et al., 2023) in addition to painkillers and medicines that track salts that might either promote or decrease the development of stones(Littlefield and Lenahan, 2019; Taguchi et al., 2019). Kidney stones were not treated by general practitioners instead;(Susilo et al., 2021) they manage the discomfort until the stones pass on their own. Kidney stone prevention and treatment can benefit from a vegetarian diet that emphasizes drinking plenty of water and herbs (Awuchi et al., 2020; Maqbool et al., 2023). The severity of renal colic has led to a decrease in the threshold for prescribing narcotic analgesics, thiazide-like diuretics, and potassium citrate. Many of the medications used to prevent Urolithiasis have side effects that make them unsuitable for long-term usage, and not all patients respond well to them (Tzelves et al., 2022). Nevertheless, the majorities of these conventional pharmacological treatments for Urolithiasis are not successful, expensive and prone to recurrence, have negative side effects, yet come with no guarantees. Medical or surgical procedures are used to treat Urolithiasis.

Surgical procedures such as:

- Shock wave therapy is the only non-invasive treatment available for stone disease.
- Stones may be effectively treated with endoscopic therapy, which includes both percutaneous nephrolithotomy and ureteroscopic procedures.

6.1 Medicinal plants as Antiurolithiatic agents

To prevent and cure Urolithiasis, controlling the crystallization event process is one of the best strategies. The most effective way to treat kidney stones is by the use of herbal extracts, which have been used widely in traditional medicine (Li et al., 2022). Herbal medicines are thought to be quite safe, have few or no negative effects and they are reasonably priced, easily accessible and widely available (Akram and Idrees, 2019).Table 3 Explore kidney stone prevention with medicinal plants: pre-clinical and clinical evidence.

Table 3 Medicinal plants studied for kidney stone prevention: clinical, pre-clinical evidence

Photochemical	In Vivo/In Vitro	Design	Results
Flavan (Di Pede et al., 2023)	In vitro	NRK-52E cells exposed to calcium oxalate monohydrate (COM).	↓ This is a crystal form of calcium oxalate, a compound that can form crystals in the urinary system and increase in the formation of kidney stones.

	In vitro	Nephrolithiasis induced by ethylene glycol in rats.	↑ Formation of papillary calculi through the crystallization of monohydrate calcium oxalate in the renal papillae.
Parsley, scientifically known as Petroselinum sativum Hoffm. (Slighoua et al., 2021)	In vitro	Feeding rats with ethylene glycol.	↓ The quantity of calcium oxalate accumulations.
	In vitro	Urolithiasis induced by ethylene glycol in a rat model.	↑ Reduced calcium oxalate supersaturation through the manifestation of renal hyperoxaluria and crystalluria.
Citrus aurantium L (González-Molina et al., 2010)	In vitro	Calcium oxalate crystallization induced by ethylene glycol.	↑ Halting the development of calcium oxalate nephrolithiasis and mitigating pathological changes in rats
Diosmin (Zheng et al., 2020)	In vitro	Nephrolithiasis induced the ethylene glycol on rats.	↑ The experimental induction of nephrolithiasis in rats through the administration of ethylene glycol is a focus of current research investigations.
Rutinoside (Dutta et al., 2021)	In vitro	Quercetin-3-rutinoside	↓ The rutinoside model yielded favorable outcomes, showcasing its potential efficacy in diverse applications.
	In vitro	Stone formation prevention model.	↓ Effective strategies prevent stone formation and inhibit calcium oxalate

			urolithiasis, yielding positive results in preventing kidney stone development.
Epigallocatechin gallate (EGCG) (Ahammed et al., 2018)	In Vivo	Hydroxyl (OH) groups attached to certain positions on the rings.	↑ Epigallocatechin gallate exhibits potent antioxidant properties, potentially benefiting cardiovascular health.
Quercetin flavonol (Gao et al., 2021)	In vivo	Inhibition of cell proliferation was observed in HepG2, PLC/PRF-5, and Hep3B cells.	In HepG2 cells: ↑ Upregulation of p53 and HO-1. ↓ Downregulation of Cyclin A and CHK1. No change in Cyclin E and SOD1 protein levels.

7. Conclusion

Medicinal plants have been widely accepted throughout history because of their many benefits, including low toxicity, safety, and affordability, decreased risk of illness recurrence and simplicity of use in remote places. There is no proven cure for Urolithiasis in allopathic medicine and the medications that are available have side effects. Although they are a possibility, surgical procedures have a greater risk of recurrence. As a result, using medicinal herbs to cure kidney stones becomes a good option. This study examines plants that have Antiurolithiatic qualities and compiles information on kidney stones. It seeks to assist scientists in discovering novel medication candidates to treat common human illnesses, reducing the difficulties encountered by a varied population and curing the illness.

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References

Ahammed, G.J., Li, Y., Li, X., Han, W.-Y., Chen, S., 2018. Epigallocatechin-3-Gallate Alleviates Salinity-Retarded Seed Germination and Oxidative Stress in Tomato. J Plant Growth Regul 37, 1349–1356. https://doi.org/10.1007/s00344-018-9849-0

Akram, M., Idrees, M., 2019. Progress and prospects in the management of kidney stones and developments in phyto-therapeutic modalities. Int J Immunopathol Pharmacol 33, 205873841984822. https://doi.org/10.1177/2058738419848220

Antony, A.S., Gomathy, S., Rajmohan, T.P., Anoop, P., Issaic, C., 2018. Pharmacological evaluation of curcumin for its nephroprotective activity in 5/6 nephrectomized rat model. Drug Invention Today 10.

Ardakani Movaghati, M.R., Yousefi, M., Saghebi, S.A., Sadeghi Vazin, M., Iraji, A., Mosavat, S.H., 2019. Efficacy of black seed (*Nigella sativa* L.) on kidney stone dissolution: A randomized, double-blind, placebo-controlled, clinical trial. Phytotherapy Research 33, 1404–1412. https://doi.org/10.1002/ptr.6331

Awuchi, C.G., Igwe, V.S., Amagwula, I.O., 2020. Nutritional diseases and nutrient toxicities: A systematic review of the diets and nutrition for prevention and treatment. International Journal of Advanced Academic Research 6, 1–46.

Babaeenezhad, E., Ahmadvand, H., Kkorramabadi, R.M., Bagheri, S., Khosravi, P., Jamor, P., 2019. Protective effects of olive in renal failure; a review on current knowledge. Journal of Nephropathology 8.

Bandarapalle, K., Yalavarthi, P.R., Bannoth, C.S.K., 2020. Evaluation of Antiurolithiatic Activity of Asparagus Racemosus on In Vitro Calcium Oxalate Crystallization Methods.(2020). Int. J. Life Sci. Pharma Res 10, P56-62.

BAWARI, S., Tewari, D., Sah, A.N., 2022. Ameliorative Effects of Raphanus sativus L., Nyctanthes arbor-tristis L. and Ficus palmata Forssk. on Calcium Oxalate Crystallization Events of Stone Formation In Vitro. Indian Journal of Pharmaceutical Sciences 84.

Bencheikh, N., Elbouzidi, A., Kharchoufa, L., Ouassou, H., Alami Merrouni, I., Mechchate, H., Es-Safi, I., Hano, C., Addi, M., Bouhrim, M., 2021. Inventory of medicinal plants used traditionally to manage kidney diseases in north-eastern Morocco: Ethnobotanical fieldwork and pharmacological evidence. Plants 10, 1966.

Bhandari, R., Panta, A., Panth, P., Aryal, D., Gautam, U., Joshi, D.R., Kumar, R., Rokaya, T.B., Pandey, J., Aryal, P., 2021. In-vitro comparison of anti-urolithiatic effect of Crataeva nurvala, Zea mays (corn silk) and ayurvedic formulation neeri tablet.

International Journal of Pharmaceutical Sciences Review and Research 66, 26–30.

Das, D.S., 2019. Comparative Study to Assess the Relationship between Renal Calculi, Thyroid and Parathyroid Hormones and Urinary Infections at Tertiary Care Centre (PhD Thesis). Sree Mookambika Institute of Medical Sciences, Kulasekharam.

Daudon, M., Frochot, V., Bazin, D., Jungers, P., 2018. Drug-Induced Kidney Stones and Crystalline Nephropathy: Pathophysiology, Prevention and Treatment. Drugs 78, 163–201. https://doi.org/10.1007/s40265-017-0853-7

Dehdari, S., Hajimehdipoor, H., 2018. Medicinal properties of Adiantum capillus-veneris Linn. in traditional medicine and modern phytotherapy: a review article. Iranian Journal of Public Health 47, 188.

Di Pede, G., Mena, P., Bresciani, L., Achour, M., Lamuela-Raventós, R.M., Estruch, R., Landberg, R., Kulling, S.E., Wishart, D., Rodriguez-Mateos, A., 2023. Revisiting the bioavailability of flavan-3-ols in humans: A systematic review and comprehensive data analysis. Molecular Aspects of Medicine 89, 101146.

Dobrek, L., 2023. Lower Urinary Tract Disorders as Adverse Drug Reactions—A Literature Review. Pharmaceuticals 16, 1031.

Dutta, A., Dahiya, A., Verma, S., 2021. Quercetin-3-rutinoside protects against gamma radiation inflicted hematopoietic dysfunction by regulating oxidative, inflammatory, and apoptotic mediators in mouse spleen and bone marrow. Free Radical Research 55, 230–245. https://doi.org/10.1080/10715762.2021.1914334

Gao, M., He, M., Xing, R., Wang, X., Wang, Z., 2021. Borate-modified carbon dots as a probe for quercetin in plants. Analyst 146, 590–596.

Garbens, A., Pearle, M.S., 2021. Causes and prevention of kidney stones: separating myth from fact. BJU International 128, 661–666. https://doi.org/10.1111/bju.15532
Ghazala Riaz, G.R., Rajni Chopra, R.C., 2018. A review on phytochemistry and therapeutic uses of Hibiscus sabdariffa L.

González-Molina, E., Domínguez-Perles, R., Moreno, D.A., García-Viguera, C., 2010. Natural bioactive compounds of Citrus limon for food and health. Journal of pharmaceutical and biomedical analysis 51, 327–345.

Güler, A., Erbin, A., Ucpinar, B., Savun, M., Sarilar, O., Akbulut, M.F., 2019.

Comparison of miniaturized percutaneous nephrolithotomy and standard percutaneous nephrolithotomy for the treatment of large kidney stones: a randomized prospective study. Urolithiasis 47, 289–295. https://doi.org/10.1007/s00240-018-1061-y

Jebir, R.M., Mustafa, Y.F., 2023. Kidney stones: natural remedies and lifestyle modifications to alleviate their burden. Int Urol Nephrol 56, 1025–1033. https://doi.org/10.1007/s11255-023-03764-1

Kachkoul, R., Touimi, G.B., Bennani, B., El Mouhri, G., El Habbani, R., Mohim, M., Houssaini, T.S., Boukansa, S., Tahiri, L., El Fatemi, H., 2023. In vivo Anti-lithiasis activity and antibacterial effect of hydroalcoholic extract and infusion of Punica granatum L. peel. Scientific African 22, e01918.

Kang, H.W., Seo, S.P., Ha, Y.-S., Kim, W.T., Kim, Y.-J., Yun, S.-J., Kim, W.-J., Lee, S.-C., 2019. Twenty-four-hour urine osmolality as a representative index of adequate hydration and a predictor of recurrence in patients with urolithiasis. Int Urol Nephrol 51, 1129–1135. https://doi.org/10.1007/s11255-019-02108-2

Khalil, N., Bishr, M., Desouky, S., Salama, O., 2020. Ammi visnaga L., a potential medicinal plant: A review. Molecules 25, 301.

Kiremit, M.C., Boyuk, A., Petkova, K., 2023. Fluid intake recommendations in urolithiasis and general advice to patients without metabolic risk factors. World J Urol 41, 1251–1259. https://doi.org/10.1007/s00345-023-04285-3

Kittanamongkolchai, W., Vaughan, L.E., Enders, F.T., Dhondup, T., Mehta, R.A., Krambeck, A.E., McCollough, C.H., Vrtiska, T.J., Lieske, J.C., Rule, A.D., 2018. The changing incidence and presentation of urinary stones over 3 decades, in: Mayo Clinic Proceedings. Elsevier, pp. 291–299.

Kuz'mina, M.A., Nikolaev, A.M., Frank-Kamenetskaya, O.V., 2020. The Formation of Calcium and Magnesium Phosphates of the Renal Stones Depending on the Composition of the Crystallization Medium, in: Frank-Kamenetskaya, O.V., Vlasov, D.Yu., Panova, E.G., Lessovaia, S.N. (Eds.), Processes and Phenomena on the Boundary Between Biogenic and Abiogenic Nature, Lecture Notes in Earth System

Sciences. Springer International Publishing, Cham, pp. 107–118. https://doi.org/10.1007/978-3-030-21614-6_6

Li, C.-C., Chien, T.-M., Wu, W.-J., Huang, C.-N., Chou, Y.-H., 2018. Uric acid stones increase the risk of chronic kidney disease. Urolithiasis 46, 543–547. https://doi.org/10.1007/s00240-018-1050-1

Li, S., Macaringue, E.G., Zhou, D., Shi, P., Tang, W., Gong, J., 2022. Discovering inhibitor molecules for pathological crystallization of CaOx kidney stones from natural extracts of medical herbs. Journal of Ethnopharmacology 284, 114733.

Littlefield, A., Lenahan, C., 2019. Cholelithiasis: Presentation and Management. J Midwife Womens Health 64, 289–297. https://doi.org/10.1111/jmwh.12959

Maqbool, M., Dar, M.A., Ara, I., 2023. Planting a path to kidney health: The vegetarian diet and diabetic nephropathy. Open Health 4, 20230011. https://doi.org/10.1515/ohe-2023-0011

Mohamed, A.A., Alotaibi, B.M., 2023. Essential oils of some medicinal plants and their biological activities: a mini review. J.Umm Al-Qura Univ. Appll. Sci. 9, 40–49. https://doi.org/10.1007/s43994-022-00018-1

Nasrul, S.I., Sehgal, A., 2018. Green tea potential for prevention and management of kidney stones.

Nevo, A., Shahait, M., Shah, A., Jackman, S., Averch, T., 2019. Defining a clinically significant struvite stone: a non-randomized retrospective study. Int Urol Nephrol 51, 585–591. https://doi.org/10.1007/s11255-019-02117-1

Nirumand, M.C., Hajialyani, M., Rahimi, R., Farzaei, M.H., Zingue, S., Nabavi, S.M., Bishayee, A., 2018. Dietary plants for the prevention and management of kidney stones: preclinical and clinical evidence and molecular mechanisms. International journal of molecular sciences 19, 765.

Parkash, J., Prasad, D.N., Shahnaz, M., Dev, D., 2018. Herbs as traditional medicines: a review. Journal of drug delivery and therapeutics 8, 146–150.

Peeters, L., Foubert, K., Breynaert, A., Schreurs, G., Verhulst, A., Pieters, L., Hermans, N., 2022. Effects of medicagenic acid metabolites, originating from biotransformation of an Herniaria hirsuta extract, on calcium oxalate crystallization in vitro. Journal of Ethnopharmacology 285, 114860.

Pengelly, A., 2020. The constituents of medicinal plants: an introduction to the chemistry and therapeutics of herbal medicine. Routledge.

Rahmat, A., Ahmad, N.S.S., Ramli, N.S., 2019. Parsley (Petroselinum crispum) supplementation attenuates serum uric acid level and improves liver and kidney structures in oxonate-induced hyperuricemic rats. Orient Pharm Exp Med 19, 393–401. https://doi.org/10.1007/s13596-018-0353-7

Rao, K.S., Haran, R.H., Rajpoot, V.S., 2022. Value addition: A novel strategy for quality enhancement of medicinal and aromatic plants. Journal of Applied Research on Medicinal and Aromatic Plants 31, 100415.

Sam, S., 2019. Importance and effectiveness of herbal medicines. Journal of pharmacognosy and phytochemistry 8, 354–357.

Siener, R., Bitterlich, N., Birwé, H., Hesse, A., 2021. The impact of diet on urinary risk factors for cystine stone formation. Nutrients 13, 528.

Slighoua, M., Mahdi, I., Di Cristo, F., Amaghnouje, A., Grafov, A., Boucetta, N., Bari, A., Bousta, D., 2021. Assessment of in vivo estrogenic and anti-inflammatory activities of the hydro-ethanolic extract and polyphenolic fraction of parsley (Petroselinum sativum Hoffm.). Journal of Ethnopharmacology 265, 113290.

Sumreen, L., Tanveer, R., Shamim, T., 2021. Practice of Berberis vulgaris and Lycopodium clavatum in urolithiasis: A systemic review. International Journal of Homoeopathic Sciences 5, 136–40.

Susilo, J., Purwanto, B., Doewes, M., Indarto, D., 2021. Calcium Oxalate Crystals: Epidemiology, Causes, Modeling Of Crystal Formation and Treatment Management. Journal of Pharmaceutical Sciences and Research 13, 118–123.

Taguchi, K., Cho, S.Y., Ng, A.C., Usawachintachit, M., Tan, Y., Deng, Y.L., Shen, C., Gyawali, P., Alenezi, H., Basiri, A., Bou, S., Djojodemedjo, T., Sarica, K., Shi, L.,

Singam, P., Singh, S.K., Yasui, T., 2019. The Urological Association of Asia clinical guideline for urinary stone disease. Int J of Urology 26, 688–709. https://doi.org/10.1111/iju.13957

Tavasoli, S., Taheri, M., 2019. Vitamin D and calcium kidney stones: a review and a proposal. Int Urol Nephrol 51, 101–111. https://doi.org/10.1007/s11255-018-1965-z

Tzelves, L., Berdempes, M., Mourmouris, P., Mitsogiannis, I., Skolarikos, A., 2022. Optimal Delivery of Follow-Up Care for the Prevention of Stone Recurrence in Urolithiasis Patients: Improving Outcomes. RRU Volume 14, 141–148. https://doi.org/10.2147/RRU.S277498

van Wyk, A.S., Prinsloo, G., 2020. Health, safety and quality concerns of plant-based traditional medicines and herbal remedies. South African Journal of Botany 133, 54–62.

Vogiatzaki, E., Ali, A., n.d. Prevent and Treat Kidney Stones Naturally.

Wani, A.K., Singh, J., Shukla, S., 2022. Therapeutic application and toxicity associated with Crocus sativus (saffron) and its phytochemicals. Pharmacological Research-Modern Chinese Medicine 4, 100136.

Wróbel, G., Kuder, T., 2019. The role of selected environmental factors and the type of work performed on the development of urolithiasis–a review paper. International Journal of Occupational Medicine and Environmental Health 32, 761–775.

Zakaria, N.H., Majid, F.A.A., Helmi, N.A.N.M., Fadhlina, A., Sheikh, H.I., 2023. Medicinal potentials of Strobilanthes crispus (L.) and Orthosiphon stamineus Benth. in the management of kidney stones: A review and bibliometric analysis. Journal of Herbal Medicine 100773.

Zheng, Y., Zhang, R., Shi, W., Li, L., Liu, H., Chen, Z., Wu, L., 2020. Metabolism and pharmacological activities of the natural health-benefiting compound diosmin. Food & function 11, 8472–8492.