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REVIEW ARTICLE

Role of Flavonoids in the Treatment of Urolithiasis: A Challenging Herbal Approach

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Abstract

A common condition that puts a huge financial and morbidity burden is kidney stones. Throughout the past 20 years, the frequency of urolithiasis has increased; 5 to 15 % of people globally are affected. Calcium oxalate (CaOx) kidney stones, which form in the renal surfaces, are the most prevalent variety. Several physicochemical processes of urinary stone constituents within tubular cells lead to the complex process of stone generation. Obese people are known to be at an increased risk of developing stones. Nephrolithiasis in women is becoming more common because of metabolic syndrome. Recent years have seen a significant change in the detection and initial treatment of urolithiasis. Calcium oxalate renal stones are the most typical type of stone proclaimed in India. Since medicinal herbs are safer, more efficient, more acceptable culturally, and have fewer side effects than produced pharmaceuticals, they have been used for treatment for millennia. Patients are recommended to follow a low-fat diet and take herbal remedies in addition to fibre from naturally occurring plants. Flavonoids are a type of plant polyphenol that has been linked to several health benefits. Recent research has revealed that plant flavonoids can significantly reduce the formation of kidney stones *in vitro* and *in vivo*, which correlates with their anti-inflammatory, antioxidant, diuretic, antibacterial, and other beneficial actions. Thus, the flavonoids or extracts of flavonoid-rich plants associated with anti-urolithiasis activity were evaluated. This article emphasises the use of flavonoid-containing plants or herbs and synthetic medications to cure kidney stones. The epidemiology, mechanism of action, pathophysiology, synthetic and natural treatments for kidney stone development, and ways to reduce stone risks are all covered in this review article.

Keywords: Flavonoid-Rich Plants, Pathophysiology, Risk Factors, Synthetic Treatment, Urolithiasis

1. Introduction

Urolithiasis is termed a widespread issue with a high recurrence across many years. 12% of the population is predicted to experience urolithiasis, which has a risk of relapse of 70–81 % in men and 47–60 % in women. It leads to serious health issues like infection, urinary tract blockage, and excruciating discomfort. The body's unbalanced system might also result in stone production. Urinary calculi include four primary categories: calcium-containing, cystine, struvite, and uric acid stones, as well as a few unique forms. Genetic history of kidney calculi and conditions like diabetes, obesity, hypertension, metabolic disorder, urinary tract infections and gout have all been linked to urolithiasis. Uric acid, calcium phosphate, struvite, cystine, calcium phosphate and oxalate are among the possible materials for the composition of the stones[1,2]. Since they are present in more than 80% of urolithiasis patients, oxalate stones are the most common. Surgery, ureteroscopy, open or laparoscopic stone removal and Percutaneous Nephrostolithotomy (PCNL) are among the unpleasant and expensive treatment options. Kidney stones after treated with numerous synthetic medications, such as narcotic analgesics, and diuretics, but excessive use of these medications, which increases the risk of serious adverse effects, has forced people to turn to natural therapies like herbal medicine. Numerous herbal preparations have been used since the dawn of time and may be effective in treating renal

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calculi[3]. Due to their low cost, lack of negative side effects, and presence of several phytochemicals that have positive effects on urolithiasis, medicinal herbs have traditionally been used to treat urolithiasis[4].

2. Hypothesis on Stone Generation

2.1 Free Particle Hypothesis

According to this hypothesis, as urine traverses through the kidney, crystals of one of the substances that makes up stones begin to freely precipitate from the super-saturated urine which starts to gather or enlarge in size in the nephron canal. There is a potential that one of these many crystals will become trapped in a distal or constrictive area of the nephron, where it will serve as a nidus for the growth of stones[5,6].

2.2 Fixed Particle Hypothesis

This theory states that crystals that precipitate from the super-saturated urine attach with the renal epithelial tissue to the location of renal tissue damage, which may be brought on by infectious pathogens or by the crystals. Once bound, these crystals act as foci for stone formation because the renal epithelium is frequently revealed to supersaturated urine[5,6].

2.3 Randall's Plaque Hypothesis

According to this hypothesis, the renal lesion location is where stones originate. More precisely, this hypothesis claims that calcium phosphate accumulations (apatite), a type of renal abrasions, begin along the basal cells of narrow loops of Henle, followed by the transitional epithelium, ultimately demolishing the same due to the milieu created by reduced urinary volume and pH and increased urine calcium levels. These apatite deposits, also known as Randall's plaques, are associated with exposure to calyceal urine because of the depletion of the urothelium, which attracts organic materials such as glycosaminoglycans, lipids and urinary proteins like Tamm-Horsfall and osteopontin protein. This creates a matrix on which apatite crystals accumulate, which are then covered with another layer of proteins present in urine and other organic materials, and so on. The calcium oxalate crystals that eventually develop and form stones adhere to these various levels to establish an attachment site[7-11].

2.4 Blocked Lymphatic Hypothesis

According to this theory, the renal lymphatic system empties the renal pelvis and avoids the deposition of precipitating salts from building up inside the kidney. However, if these renal lymphatics are damaged or destroyed, salt precipitates can become occluded at the folds of the calyx's exterior of the collecting duct, where they ultimately demolish the surrounding membrane and cause urine flow. The concretions then develop into bigger renal crystals by involving continuous interaction with the ions and different constituents present in the urine[12,13].

2.5 Vascular Hypothesis

Due to their frequent flow separation, the vasa recta along with other capillaries throughout the renal papillary region are vulnerable to an abrupt rapid shift in blood flow from smooth to turbulent, like those seen in split arteries. They are susceptible to diseases and damage because of these rapid changes in the circulation of blood, with their osmotic and oxygen-deprived environment. Like arteries, these blood supply changes and susceptible tissue structures cause atherosclerotic plaques to form in the renal papilla's vasculature, which is then accompanied by calcification. These calciferous materials may demolish their path into the papillary duct system of Bellini and renal interstitium, where they constantly encounter urine and develop into larger stones[13].

3. Types of Stones

3.1 Struvite Stones

A particular solid mineral accumulation that can develop in the kidneys is called struvite stone. When Ca^{2+} and PO_4^- crystallize inside the kidneys and adhere to one another, stones are created. The microbes in your urinary tract produce mineral struvite.

Struvite makes up ten to fifteen per cent of total kidney stones. Women are more likely than men to develop this kind of stone. Struvite stones have a rapid rate of growth. They may eventually damage your kidney by obstructing your ureter, bladder, or kidney[14].

3.2 Calcium Stones

The most frequent kind of kidney stones is CaOx stones. When there is an excess of calcium, cystine, oxalate, or

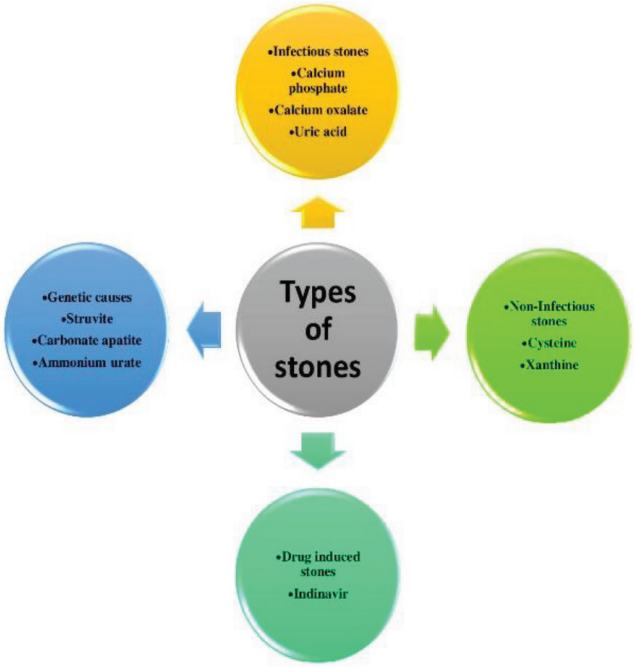

Figure 1. Types of stones.

phosphate and insufficient fluid, solid lumps called kidney stones develop in the kidney. Calcium oxalate is the main component of calcium stones, whether it is present alone or, far more frequently, in conjunction with calcium phosphate. Calcium stones are more likely to form when there is hypercalciuria, poor urine volume, and hypocitraturia. With conditions like hyperparathyroidism, cancer, sarcoidosis, and excess vitamin D, which are diseases linked to hypercalcemia, hypercalciuria is frequently present. Calcium phosphate stones are more likely to form in those with alkaline urine[15].

3.3 Uric Acid Stones

On simple radiographs, pure uric acid deposits are radiolucent; however, they are evident on ultrasound or Computerised Tomography (CT). People with hyperuricosuria are more likely to develop these stones. History of gout affects 15–25 % of people with uric acid stones. A diet heavy in animal protein may increase the possibility of uric acid stone development due to its elevated purine amount, which causes uric acid to be produced during catabolism. Urinary pH levels below 5.5 have a low solubility of uric acid, while pH levels above 6.5 have a higher solubility[16].

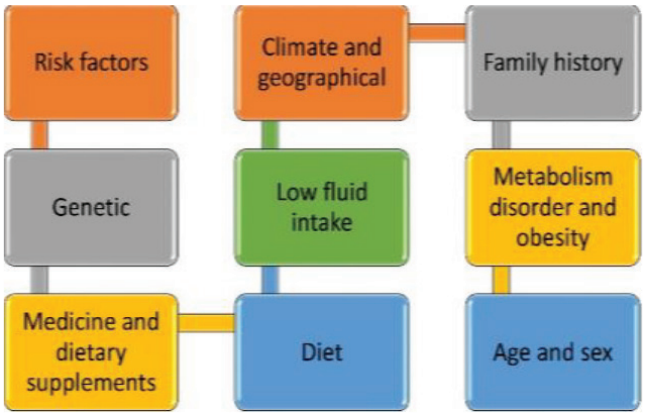

Figure 2. Risk factors associated with urolithiasis[18-20].

3.4 Cystine Stones

Cystinuria is an inherited (genetic) impairment of the transport of the amino acid cysteine, which caused an excessive amount of cysteine to accumulate in urine and the development of these types of kidney stones.

Cystinuria is the most prevalent issue with amino acid transit. Cysteine is not the only amino acid that is excreted abundantly in cystinuria; however, it is the least soluble of all naturally occurring amino acids. Cysteine has a propensity to precipitate from urine in the urinary system and form stones[17].

4. Pathophysiology

Renal stones develop as an outcome of a higher urinary supersaturation followed by crystalline particle formation. Most solid particles that crystallise in the urinary tract are emitted freely. However, if solid, rigid particles are held in the urinary system, they can develop into large stones. The next step, crystal-cell interaction, is also facilitated by renal tubule damage. Since crystalluria is a most common occurrence in human urine and is safe, kidney stones must develop when there is an unusual accumulation of formed particles. Crystal-cell interactions may therefore be very important. Renal calculi are generated because of the development and aggregation of internalized crystals in the interstitium. All forms of kidney stones are produced by crystal growth and nucleation which are essential factors[21-24].

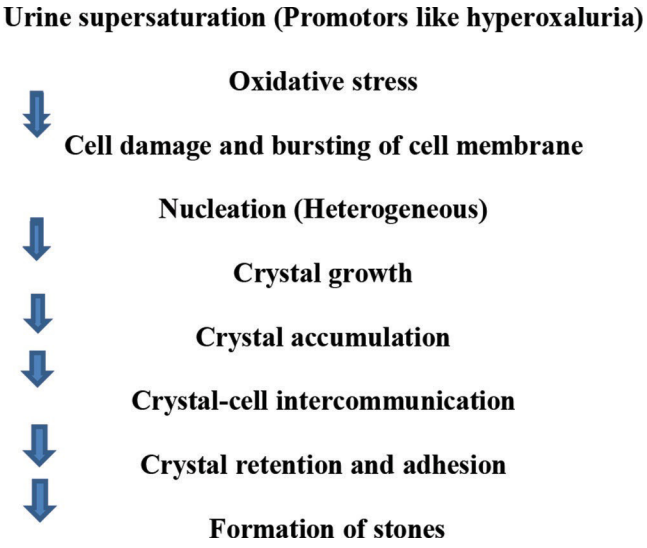

Figure 3. Flow chart of events leading to kidney stone generation.

5. Treatment of Urolithiasis[25]

5.1 Medicinal Treatment

Allopurinol, thiazide diuretics (for example, hydrochlorothiazide), penicillamine (cuprimine) sodium cellulose phosphate (SCP), analgesics (diclofenac sodium), potassium phosphate, bisphosphonates, and various probiotics (Table 1).

5.1.1 Calcium Channel Blocker and Alpha Blockers

Calcium channel blockers and α-adrenergic blockers, which block alpha receptors and inflow of calcium into the urinary tract, respectively, create outer ejection of the stones by retarding ureteral smooth muscle contraction, thereby enabling an increase in hydrostatic pressure close to the stone and offering relief from the pain of kidney stones. The preferred medication for medical expulsive therapy is tamsulosin because of its higher tolerability; however, doxazosin and terazosin are similarly effective. The combination of corticosteroids with tamsulosin has been proven to be quite effective since it reduces renal colic and acts as an anti-oedema agent[26-31].

5.1.2 Acetohydroxamic Acid

In cases of struvite stones, which are typically produced by or connected to the UTI brought on by microbes which produce urease, acetohydroxamic acid is given. As an inhibitor of urease, acetohydroxamic acid appears to help treat forms of infection stones, but the effectiveness of this treatment is called into question by its potential adverse reactions, which consist of alopecia, thrombosis, tremors, hemolytic anaemia and GI distress[32].

5.1.3 D-penicillamine

It is used to treat cystinuria in cases of cystine stones. By creating heterodimers of penicillamine-cysteine, it promotes the disintegration of cystine stones and reduces the concentration of cystine in the urine, which tends to have more solubility than cysteine-cysteine homodimers. However, due to its severe side effects, which include neuropathy, nephrotic problems, leukocytopenia, dermatitis, thrombocytopenia and pancytopenia, it is only useful in certain circumstances. A more well-tolerated substitute to D-penicillamine is alpha mercaptopropionylglycine (also known as tiopronin), although it has much lower potency and availability[33-35].

5.1.4 Thiazide and Other Diuretics

In cases of renal stone disease accompanied by idiopathic hypercalciuria, thiazide and similar diuretics are recommended. By promoting calcium reabsorption at the distal and proximal ends of convoluted tubules, they are associated with hypocalciuric action. The issue with using thiazide diuretics is their well-known potassium loss, which results in hypokalaemia and can eventually cause hypocitraturia, a feature that increases urolithiasis and can be treated with amiloride or potassium citrate administration. Triamterene, a potassium-sparing diuretic, also has the potential to treat hypokalaemia, however, due to its poor solubility, it can create triamterene calculi, a form of drug stones[36-39].

5.1.5 Sodium Cellulose Phosphate

It is well known that sodium cellulose phosphate binds to intestinal calcium and so prevents calcium absorption, lowering the high calcium excretion and preventing calcium stone accumulation. Although it is effective, it has the potential to lead to hypomagnesaemia and hyperoxaluria, both of which are crucial for aggravating renal calculi disorder. Furthermore, sodium cellulose phosphate might stimulate the parathyroid gland[40].

Table 1. List of synthetic medications used in the treatment of urolithiasis with their MOA and adverse effects

Drugs/class of drugs	Mode of action	Stones treated	Adverse effect	References
Alpha-blockers (Tamsulosin, doxazosin)	Inhibit contractions of ureteral smooth muscles	Ureteral stones	Tachycardia, syncope, collapse	26-31
Acetahydroxamic acid	Inhibit urease enzyme	Struvite stones	Haemolytic anaemia, GI distress, alopecia	32
D- penicillamine	Reduces cysteine levels in urine	Cysteine stones	Neuropathy, nephrotic syndrome	33-35
Potassium citrate	Increases level of citrate in the urine, its complex with Ca inhibits Ca crystals	Uric acid and calcium oxalate	GI upset	36-38
Thiazide and other diuretics	Promote Ca reabsorption at proximal and distal convoluted tubule	Calcium oxalate and phosphate stones	Hypokalemia, hypocitraturia	39
Sodium cellulose phosphate	Inhibits absorption of Ca thus reducing Ca stone formation	Calcium oxalate stones	Hypomagnesiuria, hyperoxaluria	40
Xanthine oxidase inhibitors (Allopurinol, febuxostat)	Prevent the formation of uric acid (lower urate levels)	Uric acid stones	Rashes and gout attacks	41-43
NSAIDs (diclofenac, indomethacin, ketorolac)	Blocks generation of prostaglandins and thromboxanes	All types	GI and renal side effects	44-47

5.1.6 Allopurinol and Febuxostat

For the therapy of uric acid and calcium oxalate stones, allopurinol is recommended. As an inhibitor of xanthine oxidase, it inhibited the formation of uric acid from xanthine and hypoxanthine, lowering the level of urate in the urine, and it has been again found to hinder the deposition of calcium oxalate. Allopurinol and febuxostat are both xanthine oxidase inhibitors, but febuxostat was previously shown to be more potent in the reduction of urine urate levels[41-43].

5.1.7 NSAIDs

Opioids and Non-Steroidal Anti-Inflammatory Medications (NSAIDs) are the two most often used pharmacological categories for treating urolithiasis-related pain. Opioid analgesics are recognised to produce nausea, vomiting, urine retention, bowel difficulties, and respiratory depression, whereas NSAIDs are recognised to have severe GI and renal adverse effects. Despite this, both drug categories have been determined to be similarly effective. Long-term use of opioids is also linked to an increased risk of addiction[44-47].

5.2 Surgical Treatment

It includes percutaneous nephrolithotomy, extracorporeal shock wave lithotripsy, and ureteroscopic stone removal.

5.2.1 Extracorporeal shock wave lithotripsy (ESWL)

Shock waves are used to disintegrate the stone during this procedure. 90% of patients are successful and it is typically well tolerated by the patient. Yet some stones continue to resist ESWL's ability to break them.

5.2.2 Ureteroscopy and Extracorporeal Lithotripsy

It is used to remove stones from the ureter. Once the stone has been located and its fragments removed, the ureter scope is inserted through the urethra into the ureter. Laser lithotripsy is the most contemporary approach.

5.2.3 Percutaneous Nephrolithotripsy

When extracorporeal lithotripsy fails to break large or/and dense kidney stones, Percutaneous Nephrolithotripsy (PNL) is used to remove them. The kidney stone is located using a nephroscope, which is introduced via the skin. The stone is then fragmented using specialised ultrasonic or ballistic equipment[48].

5.3 *Herbal Treatment*

Rencare Capsule, Cystone, Patherina Tablet Calcuri, Trinapanchamool, Chandraprabha Bati Ber Patthar Bhasma, etc. Numerous herbal traditional medicines have antiurolthiatic properties and are essential in illness prevention[49].

6. Flavonoid-Rich Plants for Treatment of Urolithiasis (Table 2)

6.1 *Copaifera langsdorfii*

The family Fabaceae and the subfamily Detarioideae include the genus *Copaifera*. From the standpoint of ethnobiology, chemistry, and pharmacology, this plant group is among the most studied. This is most likely related to the existence of significant chemical elements, including alkaloids, flavonoids and coumarins, along with other metabolites, which prevent or cure disorders.

After solvent removal, the crushed and infused leaves of *Copaifera langsdorfii* yielded a 16.8% crude extract, with the main flavonoids identified by HPLC analysis as quercitrin with 5.4% and afzelin with 7.4% in the extract. After ravaging the extract to rats (which were provided with a CaOx pellet into the bladder for 30 days to induce urinary stones), it was discovered that sodium, potassium, and creatinine levels in urination, as well as plasma of plant extract-treated animals, were in their usual ranges, while the average number and weight of calculi were noticeably lowered compared to animals that were only treated with CaOx pellet[50] (Figure 4).

6.2 *Hypericum perforatum*

The most well-known plant is *Hypericum perforatum*, popularly known as St. John's Wort, which is particularly well-known for its uses in human medical treatment, which are connected to numerous phytochemicals found in this species' aerial portion. The primary active ingredients in this herb, naphtodianthrones (also known as hypericin), have undergone extensive pharmacological research.

It was discovered that the leaf extract contained glycoside flavonoids like quercetin and quercetin-3 and was beneficial in the treatment of renal calculi[51,52] (Figure 5).

6.3 *Flos carthami*

The traditional Chinese herb *Flos carthami* contains the active ingredients neocarthamine, carthamin and kaempferol 3-rhamnoglucoside. *Flos carthami* was first utilised to improve the effects of blood circulation due to its anti-coagulation properties. Similarly, it had been demonstrated in earlier studies that *Flos carthami* flower extracts can successfully ward off stone disease.

Table 2. Recent flavonoid containing medicinal plants for the treatment of urolithiasis

Name of Plant	Plant Parts from where flavonoid is isolated	Isolated flavonoid	Reference No.
Copaifera langsdorfii	Leaves	Quercitrin, afzelin	50
Hypericum perforatum	Leaves	Quercetin, quercetin-3	51,52
Flos carthami	Flowers	Carthamin, neocarthamine, kaempferol 3-rhamnoglucoside	53
Helichrysum plicatum	Flowers	Helichrysins A, helichrysins B, luteolin, apigenin	54
Pinus eldarica	Fruits	Quercetin, pinene, myrcene	55
Punica granatum	Fruits	anthocyanin	56-59
Desmodium stryracifolium	Leaves	Vicenin 1, vicenin 2, schaftoside	60,61
Urtica dioica	Leaves	Luteolin, rutin, gossypetin	62
Clerodendrum inerme	Leaves	apigenin, luteolin, hispudilin, chalcone	63,64
Hybanthus enneaspermus	Leaves	2H-Pyran	65,66

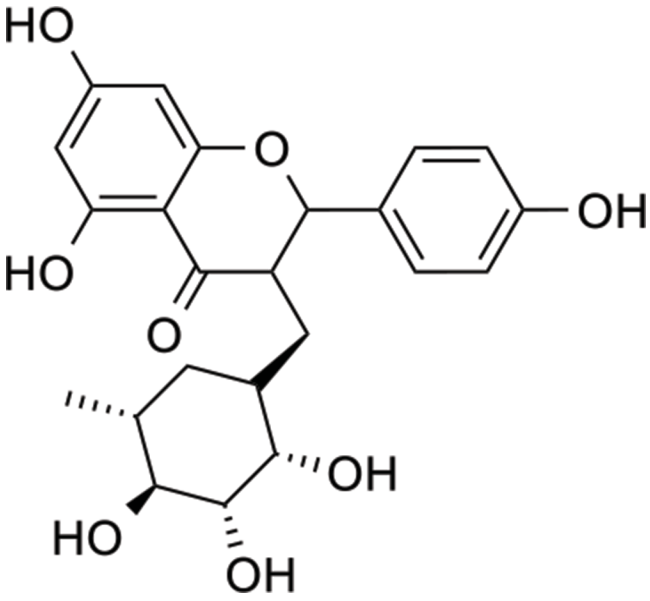

Figure 4. Afzelin.

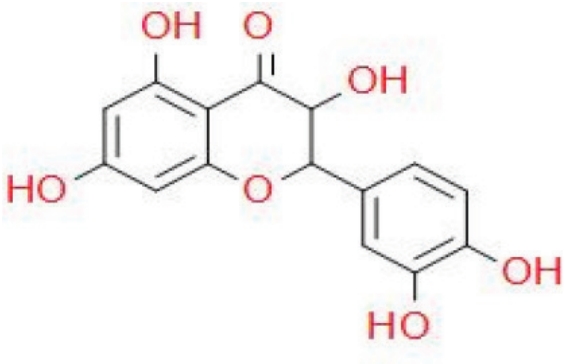

Figure 5. Quercetin.

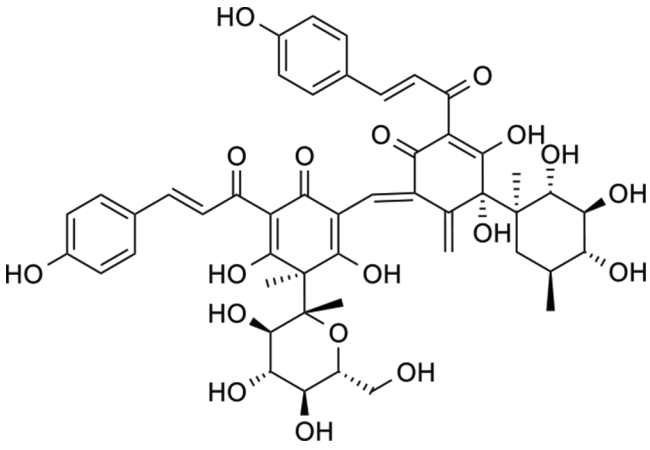

Figure 6. Carthamin.

After a 4-week experiment, the group that received starch and 0.75% EG intragastrically each day had a higher score for crystal deposition than the group that was 0.75% ethylene glycol and floral extract preparation each day[53] (Figure 6).

6.4 *Helichrysum plicatum*

Due to their diuretic qualities, *Helichrysum plicatum* (family: Asteraceae) flowers were frequently employed in herbal remedies to dissolve urinary stones. The *Helichrysum plicatum* (HP) subspecies Plicatum extracts were made by researchers using distilled water and ethanol in a ratio of 1:1 at 50–60 °C. Different dosages of HP extracts were administered by oral route for three weeks to animals who received 1% ethylene glycol and 1% ammonium chloride in drinking water, respectively, to evaluate the efficacy of HP as a preventive medication in a rat's urolithiasis model that was developed experimentally. The body weight increases of the three HP groups were discovered to be significantly larger than those of the urolithiasis group.

On the other hand, in HP groups, significant intratubular crystal accumulation and deteriorated tubular structures were not found[54] (Figure 7).

6.5 *Pinus eldarica*

The Tehran pine, *Pinus eldarica*, contains quercetin, myrcene, and pine, among other potent compounds. The beneficial properties of aqueous extracts of the berries of this plant on CaOx kidney stones in rats were examined in 2010. In the current investigation, the prophylactic and treatment groups were given the extract of the plant for 30 days initiated from the 14th day to the completion of

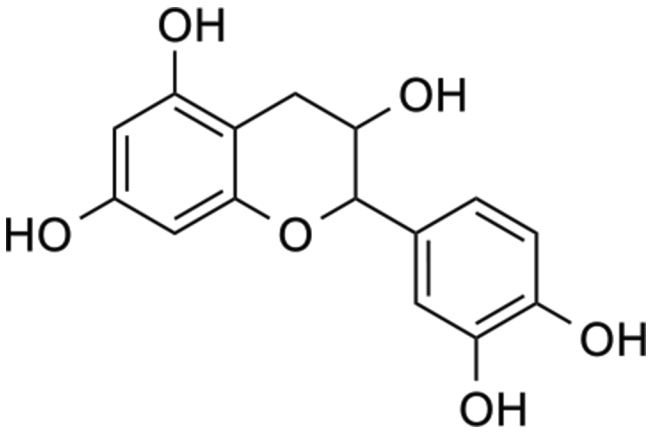

Figure 7. Luteolin.

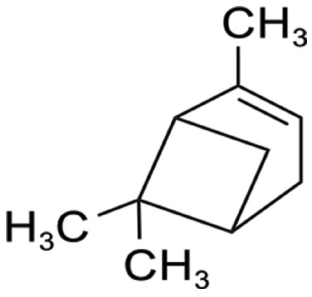

Figure 8. Pinene.

the trial, respectively, at doses of 500 and 1000 mg/kg body weight. Stone formation drastically declined in the prophylactic group after a one-month treatment period, but there was no significant distinction between the treatment group and the urolithiasis group. This finding revealed that the fruit extract of *Pinus eldarica* had a strong prophylactic impact on urinary stone disease. Probably, the anti-inflammatory, antibacterial and antioxidant properties of this plant extract reduced the stone formation[55] (Figure 8).

6.6 *Punica granatum*

Pomegranates have long been recognised as anthocyanin-rich plants. Numerous animal studies have demonstrated the protective effects of *Punica granatum* against urinary stones by lowering crystal accumulation, inducible oxide synthase, p38-MAPK, and p65-NF-B activity, as well as the number of oxidative stress indicators in the tissues of the kidney. To investigate how pomegranate extract affected human nephrolithiasis risk factors, researchers collected samples of blood and urine from individuals with and without recurrent kidney stones who had been taking the plant extract 1g each day for three months. The efficacy of *Punica granatum* extract supplementation to mitigate the risk of stone formation was not possible to determine in the preliminary research because the researchers were unable to demonstrate a beneficial or detrimental relationship between the administration of antioxidants with the extract and factors associated with the occurrence of kidney stones. Recurrent calculi formers were shown to have much greater initial levels of oxidative stress than non-stone formers[56-59] (Figure 9).

6.7 *Desmodium styracifolium*

Desmodium styracifolium has been utilised as a treatment for urolithiasis in ethnobotanical literature dating back

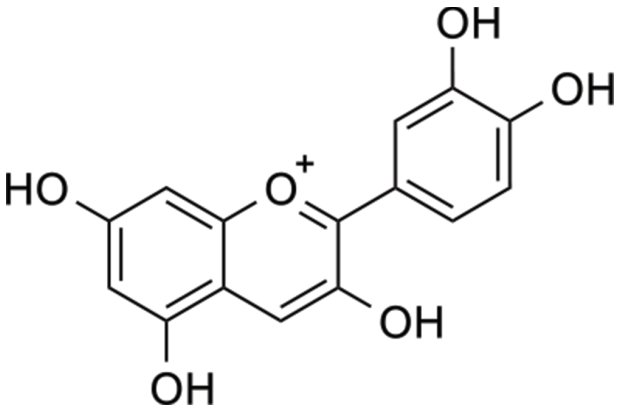

Figure 9. Anthocyanin.

to ancient China because of its capacity to eliminate heat and its diuretic effects. In one study, rats were given ordinary chow containing 5% w/w hydroxyl-L-proline to create animal models of CaOx urolithiasis. The crushed material from plants was extracted twice by the 50% ethyl alcohol for 90 mins each at 80°C. The primary flavonoids present in the *Desmodium styracifolium* leaf extract included vicenins, isoschaftoside, schaftoside and isovitexin which were beneficial for urolithiasis. The total amount of flavonoids in the extracts was 8 mg/mL[60,61] (Figure 10).

6.8 *Urtica dioica*

The treatment of kidney, gastrointestinal, urinary system, and locomotor problems has long been practised using the extract of *Urtica dioica* leaves. The flavonoids rutin, kaempferol-3-O-rutinoside, kaempferol-3-O-glucoside luteolin and gossypetin were found in leaf extracts of *Urtica dioica*. Two doses

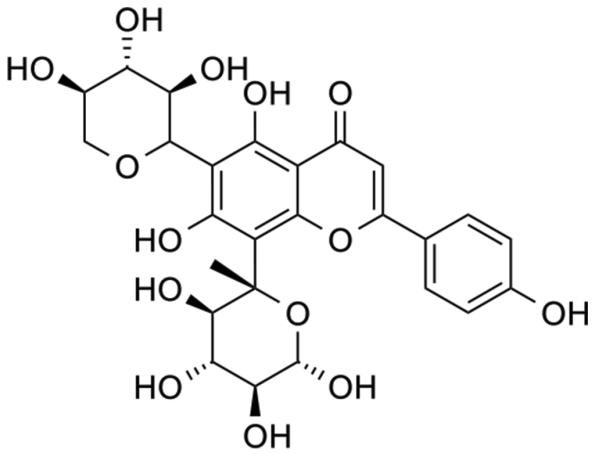

Figure 10. Vicenin.

of the extracts of the leaves (700 and 1400 mg/kg BW, 15 days) were administered by intubation of the gastric tract using a smooth catheter to the rats that had already been infused with 0.55% Ethylene glycol and 1% ammonium chloride in drinking water for a duration of ten days to assess the effects of the flavonoid-rich extracts on the formation of renal calculi. Rats in two extract groups were treated with methanol-extracted leaves of *Urtica dioica*, which significantly decreased the calcium and oxalate depositions in their kidneys. The disintegration of mucoproteins, which have a strong attraction for CaOx surfaces to encourage the formation and accumulation of crystals, was thought to be the mechanism by which the flavonoid-rich extracts would dissolve CaOx renal stones[62] (Figure 11).

7. Some Other Flavonoids and Their Effects on Urolithiasis

In rats, the preventive effect of various flavonoids like rutin, catechin, epicatechin, and diosmin on experimentally induced urinary stone development has been reported.

7.1 Rutin

Rutin has been used for centuries in traditional medicine to treat a wide range of illnesses because of its exceptional anti-inflammatory and antioxidant properties. Researchers examined how rutin affected the amounts of calcium and oxalate in the urine, the homogenate of renal tissues, and the pathology of the kidneys. They claimed that animals given rutin and drinking water with ethylene glycol and ammonium chloride had considerably lower calcium and oxalate amounts in their urine and renal tissue homogenate than rats that only received EG and NH_4Cl treatment. This is most likely a result of rutin's actions on oxalate synthesis inhibition and nitric oxide bioavailability enhancement that hold calcium via cGMP which is a 3', 5' cyclic guanosine monophosphate cycle process in calculus-induced rat models. The histopathological analysis also showed that rats receiving both rutin and drinking water comprising of EG and NH_4Cl had less harm to tissues as well as fewer CaOx deposits in their kidneys than animals that were only given EG and NH_4Cl. The researchers hypothesised that rutin, an anti-inflammatory and antioxidant molecule, might prevent epithelial cell damage brought on by CaOx crystals and have an anti-inflammatory impact[67] (Figure 12).

7.2 Catechin

Green tea is a good source of catechin and has a wide range of health benefits, including antimutation, antiatherosclerotic impact, and anticancer activity, thanks to the abundance of antioxidants it contains, including phenolic acids, flavonoids, and tannins. It

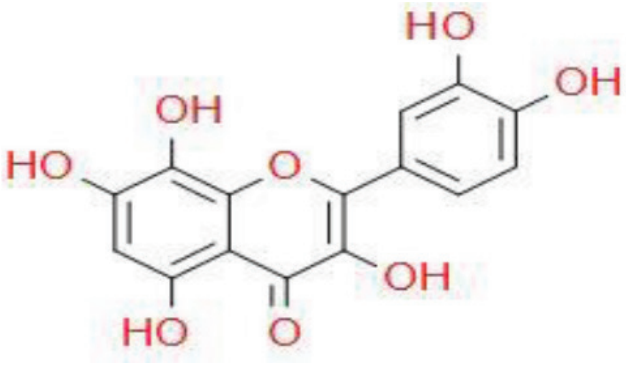

Figure 11. Gossypetin.

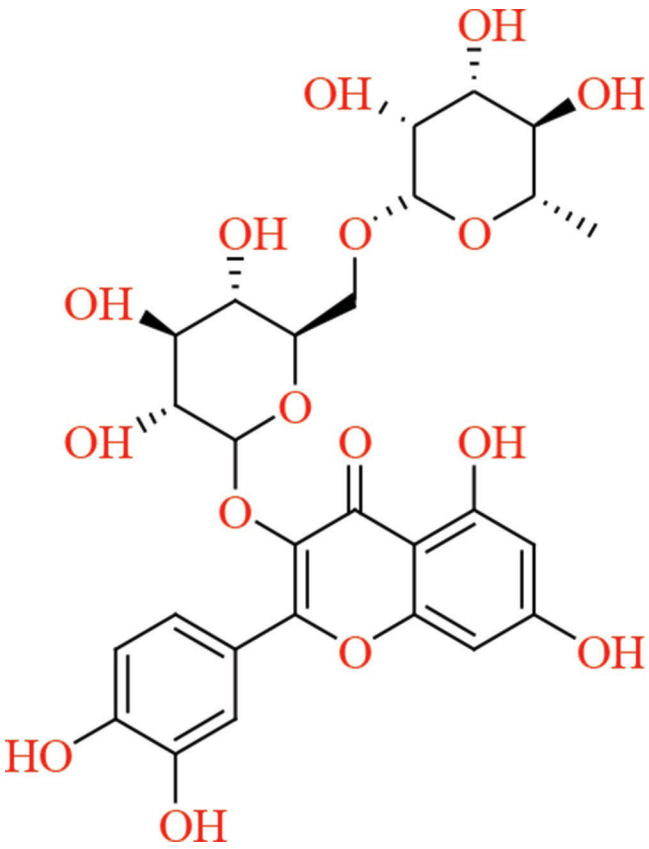

Figure 12. Gossypetin.

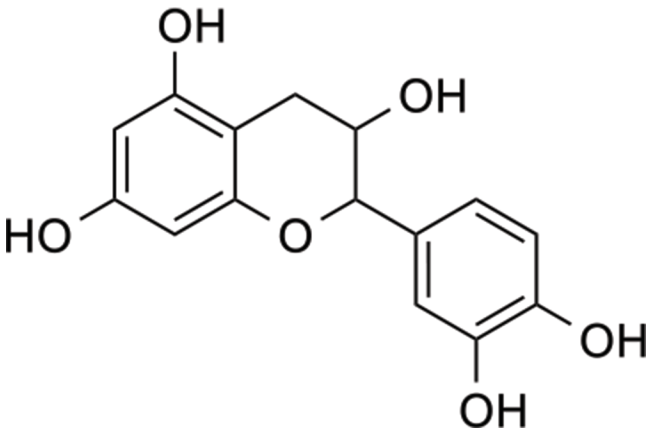

Figure 13. Catechin.

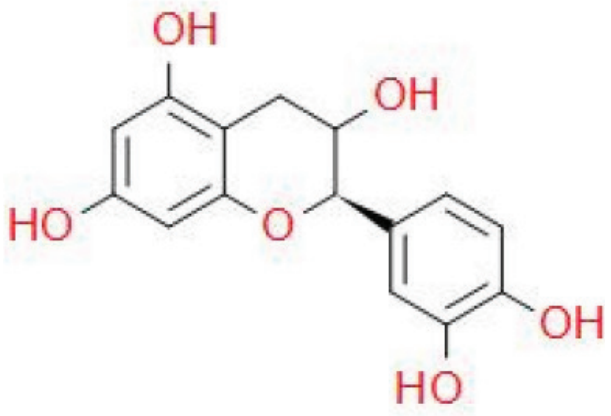

Figure 14. Epicatechin.

was important to remember that a prior study had also shown green tea›s anti-urolithiasis action to be effective against urinary stones. As compared to the stone group, green tea therapy significantly reduced the development of CaOx stones, osteopontin (OPN), a key soluble protein component of CaOx stones, and renal tubular cell death. It also boosted the Superoxide Dismutase (SOD) property in kidney tissues of rats[68] (Figure 13).

7.3 Epicatechin

Epicatechin can suppress renal calculi similarly to catechin because of the structural resemblance. The occurrence of squamous and intratubular calcium absorption in the kidneys of rats supplied with 0.8% v/v EG and 1% w/v NH_4Cl at the end of eight days was successfully halted by epicatechin administration (100 mg/L of epicatechin mixed with drinking water, for 24 days). The prevention of hyperoxaluria-induced peroxidative damage to the papillary tip epithelium and the renal tubular membrane surface by epicatechin may have contributed to the outcomes, which may have further suppressed kidney stone development[69] (Figure 14).

7.4 Diosmin

The citrus flavonoid family includes the naturally found flavonoid glycoside known as diosmin. Diosmin has been shown to have anti-inflammatory and anti-apoptotic properties in neural cells. Urinary volume, urinary sodium, potassium, magnesium, uric acid, creatinine, and calcium level in serum (inhibitors of stone formation) increased significantly in two diosmin groups (0.75% v/v EG with 2% w/v NH_4Cl and diosmin), whereas urinary pH, kidney weight, serum magnesium, sodium, potassium levels, total urinary calcium, phosphorus, proteins, and nitrogen levels of blood urea decreased. The team theorised that diosmin's anti-urolithiasis activity was comparable to that of the common medicine cystone due to its antioxidant and anti-inflammatory properties as well as its protective qualities of microcirculation[70] (Figure 15).

8. The Mechanism of Action of Polyphenols (Flavonoids) in Urolithiasis

In previous studies, caffeic acid[71], catechin[72], curcumin, rutin[73], diosmin[74], quercetin[75,76], and resveratrol[77] prevented ethylene glycol-induced calcium oxalate crystallisation in rats, but the mechanistic insights underlying these effects were barely explained. The anti-inflammatory, antioxidant, ACE-inhibitory, and diuretic activities of polyphenols (flavonoids) contribute to calcium oxalate calculi prevention[78].

8.1 Antioxidants

In vitro and *in vivo* studies suggest that the antioxidant property of natural polyphenols is important in preventing the development of calcium oxalate

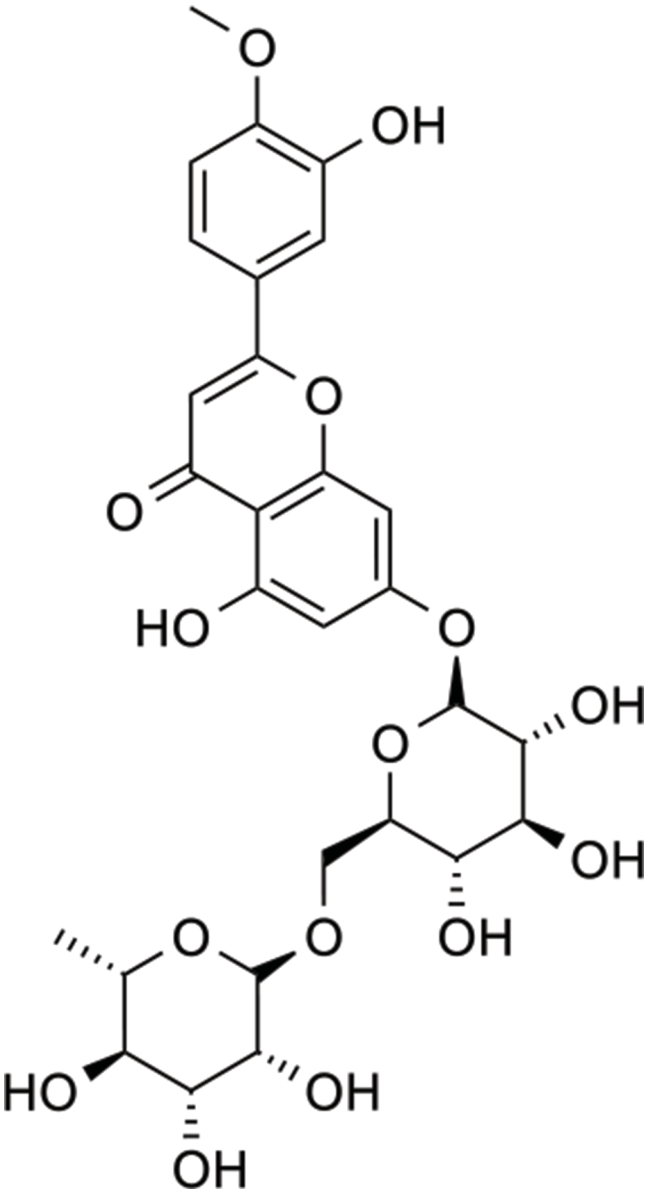

Figure 15. Diosmin.

monohydrate type urolithiasis, especially by preventing renal endothelial tissue injury triggered by cytotoxic compounds with oxidative capacity[79-81].

8.2 Anti-Inflammatory

Pain and inflammation are closely linked to arachidonic acid, prostaglandin-E2, nitric oxide (NO), COX-2, and cytokines (IL-1, IL-6, and TNF-α)[82,83]. The oxidative stress-induced inflammation is caused by the production of reactive species[84]. Antispasmodic, analgesic, and anti-inflammatory properties are important in symptom alleviation. Apigenin[85], catechin, curcumin[86], cyanidin[87], ellagic acid, ferulic acid[88], gallic acid[89,90], luteolin[91], malvidin[92], p-coumaric acid, sinapic acid[93] and syringic acid[94] have shown anti-inflammatory activity by reducing PG-E2, cytokines IL-1β, IL-6 and TNF-α production.

8.3 ACE Inhibition

The Renin-Angiotensin-Aldosterone System (RAAS) stimulates the NADPH oxidase in kidney cells, which generates ROS. Angiotensin-converting enzyme inhibition (ACE-I) lowers calcium oxalate crystal deposition and renal inflammation by lowering ROS generation[95]. The free hydroxyl groups of phenolic substances chelate with the zinc atom found in the active centre of ACE, inhibiting it *in vitro*. Apigenin, kaempferol, luteolin[96], caffeic acid, chlorogenic acid, quercetin[97], catechin[98], cyanidin, delphinidin[99], daidzein[100], genistein[101], malvidin, and sinapic acid[102] inhibit ACE *in vitro* and play a significant role in preventing oxidative tissue damage and inflammation.

8.4 Diuretic

Polyphenols have frequently been reported to have diuretic properties. Traditional diuretics include extracts of *Opuntia ficus* indica fruit, *Camellia sinensis* (green tea), and *Hibiscus sabdariffa*. As a result of flushing away the salt deposits, the diuretic effect increases the amount of fluid going through the kidneys. As a result, increasing urine volume decreases salt saturation and hence prevents crystal precipitation at physiological pH. Diuretic action has been found for chlorogenic acid, cyanidin, delphinidin, quercitin[103], gallic acid[104], genistein[105], luteolin[106], protocatechuic acid, and rutin[107].

9. Potential Toxic Effects of Flavonoids

9.1 Carcinogenicity

Numerous research has found that flavonoids have a negative correlation with cancer[108,109]. A recent case-control study of 1522 Chinese women with breast cancer discovered an inverse relationship between the incidence of breast cancer and total flavonoid intake[110].

9.2 Renal Toxicity and Liver Toxicity

It was confirmed by many data that flavonoids have shown significant kidney-protection and

liver-protection activities *in vitro* and *in vivo*[111-114], a few research studies also demonstrated the potential liver toxicity and renal toxicity with epigallocatechin gallate intake[115,116].

9.3 Thyroid Toxicity

Many factors influence the effect of flavonoids on thyroid toxicity, including the length of consumption and realistic exposure settings. Even though numerous *in vivo* and *in vitro* studies have shown that various flavonoids may interact with the thyroid's activity and metabolism[117-120].

9.4 Affecting Microbiota of the Gut

Some flavonoids, particularly genistein and daidzein, have been shown in recent research to impact gut microbial ecology[121-123]. There are still numerous discrepancies between animal models and humans in research; nonetheless, evidence showed that there were clenched connections between diet-responsive intestinal metabolites and gut microorganisms in soy-fed neonate pigs[124].

9.5 Estrogen Activity of Phytoestrogens

Because of the diphenolic ring, phytoestrogens can bind ER receptors and so have potential hormone-like actions[125]. Daidzein and genistein are the two most common forms of soy isoflavones consumed regularly. Although daidzein and genistein with lightly estrogenic actions have been reported to be approximately 10-2 to 10-3 times less active than endogenous oestrogen[126], unnecessary or improper intake may also lead to hormone metabolism and endocrine function disorders[127].

10. Safety Guidelines of Flavonoids

Dietary flavonoids are typically recognised as safe in humans because they are naturally abundant in many foods and have a long tradition of use in the diet. Observational studies consistently show no link between daily intakes of up to 68 mg total flavonoids (mainly quercetin) from the regular diet and lung, breast, gastrointestinal system, respiratory tract, or all forms of cancer[128]. While such kinds of correlations provide the most robust evidence on the safety of current flavonoid intakes, adverse reactions are rarely documented using this research approach[129]. Hooper and colleagues conducted a systematic evaluation of the effects of various flavonoid subtypes and flavonoid-rich sources of food on cardiovascular disease and risk variables in a meta-analysis of 133 randomised controlled trials[130]. Flavonoid or flavonoid-containing food treatments are required to specify a source of flavonoids that would be found as normal dietary elements in their selection standards. The other 129 studies reported no adverse events directly connected to the consumption of the test foods or substances, except for an immediate elevation in blood pressure following black tea consumption recorded in four trials (probably due to caffeine intake).

Adherence with dietary guidelines suggests a higher intake of plant foods to boost health will result in a higher intake of flavonoids. However, the fascination with the purported health advantages of flavonoids has led to increased consumption of not only naturally flavonoid-rich foods and beverages but also foods fortified with flavonoids and nutritional supplements comprising these phytochemicals. Quercetin, for example, has been advertised as a nutritional supplement with suggested amounts surpassing 1000mg/day, but the daily consumption of this flavonol through food is estimated to be 10-100 mg. While there is no confirmation of the quercetin toxicity from supplementary ingestion, consumers may believe that because flavonoid supplements are 'natural,' they are safe for consumption[131]. It is vital to remember that elderly persons are more likely than their younger counterparts to utilise dietary supplements and are also more likely to use prescribed drugs. Thus, a study into the safety of high-dose flavonoids, particularly in older persons, is warranted.

11. Conclusion

The use of herbal remedies for the avoidance and therapy of illnesses is growing in popularity because of the potency and efficacy of the activities provided by natural components present in plants and the unfavourable adverse reactions of medical advances. The flavonoids and flavonoid-containing plant extracts that could be used to prevent urinary calculi were summarised. Research demonstrates that natural treatment is superior to other forms of treatment since

it has fewer side effects, is more cost-effective, and carries no risk of long-term infertility or recurrence. Herbal therapies are beneficial at various phases of stone pathology in modern medicine, which is why they are employed as additional therapy to provide better relief. Maintaining a healthy routine and eating a balanced diet are always good options, not just for preventing urolithiasis but for preventing any illness condition as well, as these are the indices that, if impaired, may result in one or more health impairments.

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