Current Trends in Biotechnology and Pharmacy
Vol. 17 (4A) 141 - 150, October 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2023.4s.102

Molecular Mechanism of Phytochemicals for the Treatment of Urolithiasis

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Abstract

Kidney stone disease ranks as the world's third most prevalent urological condition, described by the formation of crystalline deposits within the urinary system due to dissolved minerals in the urine. These stone formations can be excruciatingly painful, causing urinary flow obstruction, urinary tract infections, swollen kidneys (hydronephrosis), excessive bleeding, and sometimes necessitate surgical intervention for their removal or fragmentation. While treatments like extracorporeal shock wave lithotripsy (ESWL) and pharmacotherapy are available, their utilization is limited due to high costs, the risk of residual stone fragments post-ESWL, and associated adverse effects such as acute kidney damage, impaired renal function, and increased stone recurrence. Recent studies have highlighted the potential role of plant-derived bioactive compounds, including polyphenols, flavonoids, phenolic acids, terpenes, and alkaloids, in the prevention and treatment of kidney stones. These phytochemicals exhibit diverse mechanisms such as diuretic properties, antioxidant effects, anti-inflammatory actions, inhibition of crystallization and aggregation, reduction of hyperoxaluria, diminishing stone size, and lowering urinary supersaturation. This paper aims to delve into the discussion of these anti-lithiatic phytochemicals and elucidate the mechanisms by which they function in preventing and treating kidney stones.

Keywords: Kidney stone, Phytochemicals, Crystal, Mechanism

Introduction

Phytochemicals refer to the materials obtained from plants that give biological actions. Kidney stones, which are also known as urolithiasis, nephrolithiasis, or renal calculi, are solid deposits composed of salts and minerals that develop within the kidneys. These formations can arise from various factors, such as dietary habits, overweight, underlying medical conditions, specific drugs and supplements. Generally, renal stones can have an impact on any region of the urinary tract, particularly from kidneys to bladder. Understanding the type of kidney stone can help identify its source and provides indications on how to reduce the likelihood of acquiring more kidney stones. In some cases, the stone consists of only one type of crystal, but often they are a combination. There are four main types of kidney stone: calcium stones, uric acid stones, struvite stones, and cystine stones (1). The main underlying mechanism of kidney stone formation is the buildup of calcium oxalate, a key factor in stone formation, that occurs in the supersaturation of urine with calcium salts. By altering the content and saturation of these stones, some metabolic abnormalities, such as hypercalciuria, decreased urine volume, hyperoxaluria, an adjustment in urine pH, hypocitraturia, gouty diathesis, and hyperuricosuria, promote stone

formation. Hence, it can be concluded that the main cause of urine crystallization is supersaturation. In general, nephrolithiasis (kidney stones formation) is a multistep process that has several events, including the nucleation of stone constituent crystals, growth and accumulation of stone which allows intrarenal structural interactions, the holding of stone within kidney, as well as the aggregation or secondary nucleation to form clinical nephrolithiasis. The renal tubular fluid of patients with kidney stones is usually more supersaturated with calcium salts than normal healthy adults, which favours crystal formation and growth. As noted previously, calcium oxalate supersaturation may be increased by low urine output, excessive calcium and oxalate secretion, or a combination of these factors. In addition, clinical stone formation is influenced by the long-term accumulation of other substances, whether crystalline or organic. Both hypercalciuria and hyperoxaluria may result from the interaction of environmental factors and genetic predisposition in varying proportions (1,2). However, the formation of kidney stones can be avoided by numerous bioactive substances present in plants (phytochemicals), including polyphenols, alkaloids, terpenoids, glycosides, polysaccharides, and fatty acids. These natural resources do, in fact, consist of a wide range of bioactive compounds, all of which have been proven to exhibit potent anti- nephrolithiasis activities by altering the ion composition of urine to decrease calcium ion concentrations or increase citrate and magnesium excretion (1,3). The aim of this review is to understand the causes of kidney stone, identify the phytochemicals for antiurolithiasis effects and mechanism of phytochemicals.

Phytochemicals

Arbutin

Arbutin is a glycoside found in *Uva Ursi* which can be used to prevent urinary tract infection and inhibit the formation of calcium oxalate crystals, a type of kidney stone. Uva Ursi is a type of evergreen shrub that grows low to the ground and has a creeping stem, forming a carpet of dark green leaves. Arbutin has been found that both antioxidant and anti-inflammatory properties which may contribute to its benefits in the treatment of kidney stone. Arbutin contains hydroxyl groups that can form hydrogen bonds with other molecules which include the surface of oxalate-based crystals. The ability of arbutin to complex with two key components: calcium and oxalate that are involved in the formation of kidney stone. This may prevent the formation of kidney stone by reducing the concentration of calcium and oxalate ions in the urine that making them less available for forming crystals. Other than that, arbutin can bind to the surface of oxalate-based crystals and modified their structure, potentially reducing their contribution to the formation of kidney stones due to the hydrogen bonds between arbutin and crystals surface. The mechanism behind all of this is due to antioxidant activity of arbutin. It is able to scavenge free radicals which are highly reactive molecules that can damage cells and tissues of kidney through oxidative stress. The hydroxyl group of arbutin can donate electrons to free radicals to stabilize them and prevent them from causing damage and reduce inflammation in the urinary tract and kidney which may contribute to formation of kidney stone (4).

Phyllantin

Phyllantin is lignan found in *Phyllanthus niruri* which has been traditionally used for reducing stone risk and treatment of kidney stone. *Phyllanthus niruri* is also known as stonebreaker, which belongs to the Phyllanthaceae genus that has been used in traditional medicine system such as Ayurveda, Chinese and Malay for a significant period. It has a history of ethnomedical use in this culture for various purposes such as treating liver diseases, gastrointestinal tract disorder, kidney stones and others (5). Phyllantin is believed to be capable of inhibiting the formation of calcium oxalate crystals, which are the main component of kidney stones. The main target of calcium oxalate crystals' action is renal tubular epithelium which results in

damaging of the epithelium. This damage leads to further crystallization, crystal retention and the formation of stone. Renal tubular cells will undergo acquired renal cytoresistance to prevent this from happening. It is a reaction which accumulates cholesterol in cells, which increases the stability of plasma membrane and protects it from further damage. However, this beneficial effect may increase risk on kidney stones and progressive renal injury if left unchecked. Other than that, the crystals that interact with renal tubular epithelial cell may induce oxidative stress and inflammation (6). Phyllantin acts as an antioxidant agent by increasing the activity of superoxide dismutase (SOD) in the kidney. This may help to reduce oxidative stress and free radical damage which can contribute to the formation of kidney stone. Besides, SOD can also protect renal tubular cells from being damaged by calcium oxalate crystals. The antioxidant properties of phyllantin potentiate the activity of SOD in scavenge free radicals and reduce the oxidative stress (7).

Quercetin

Quercetin is a plant-derived flavonoid, more specifically a flavonol, that is primarily present in berries, grapes, onions, broccoli, cherries, and citrus fruits. It is a bitter ingredient used in foods, beverages, and dietary supplements (8). In a wide range of kidney diseases, quercetin may protect the kidney by minimizing nephrotoxicity, inflammation, fibrosis, and apoptosis. In other words, it is a potent antioxidant dietary phyto-phenol that has been shown to help prevent the process of kidney stone formation in the urinary tract (urolithiasis) (9). Kidney stone formation has been linked to the claudin family of tight junction proteins. In various models, flavonoid quercetin has been discovered to alter claudin expression and avoid kidney stone formation. The action of quercetin on claudin causes an increase in transepithelial resistance (TER) and a decrease in sodium and water potential, which can be attributed to the response of other claudins to compensate for Cldn2 removal. Generally, Cldn2 is a type of claudin that forms cation-selective pores and facilitates the transport of sodium, water, and calcium through the paracellular pathway. The localization of Cldn1, -3, -4, and -7 at the tight junction is expected to increase when levels of Cldn2 are decreased, effectively tightening the epithelial barrier and increases TER. This in turn blocks sodium, water, and calcium within the uterine from passing the epithelial barrier into interstitial space. Since the reabsorption of these substances is reduced, the transport of sodium and calcium in interstitial space will then be prevented, which could lead to stone formation (10). Moreover, quercetin has been found to be a potential therapy for reducing oxalate stone formation, particularly in those who have frequently develop stones due to high oxalate levels in the body (hyperoxaluria). Kidney stones consist of calcium oxalate and hyperoxaluria is a prevalent reason for the development of CaOx stones. Normally, oxalates are excreted by the body as a natural by-product of metabolism. In cases of hyperoxaluria, an excessive amount of urinary oxalate binds to calcium at physiological pH levels, resulting in the formation of calcium oxalate (CaOx) crystals that accumulate in the kidneys. These calcium oxide crystals can damage the tubular epithelial cells of the kidneys, leading to nephrolithiasis. However, studies have shown that urinary oxalate levels can be greatly reduced by quercetin (11).

Quercetin has shown great potential as antioxidants, diuretics, anti-inflammatory, and hypouricemics agents. Apart from being a potent reactive oxygen species (ROS) scavenger, quercetin also enhances the overall antioxidant activities of plasma. Numerous studies have highlighted the ability of flavonoids like quercetin to attenuate oxidative stress in renal tubular cells, inhibit the aggregation of calcium oxalate (CaOx) crystals, and decrease oxalate-induced lipid peroxidation in cell cultures (11). Together with hyperoside, they are considered effective phytotherapeutics for managing renal lithiasis due to their ability to inhibit the accumulation of calcium oxalate crystals, their antioxidant properties in protecting kidney tubular cell from

damage (by promoting the activities of SOD and catalase), and their anti-apoptotic effects. Furthermore, quercetin's ability to enhance serum PON1 provides an effective antioxidant effect in rats with hyperoxaluria (12).

Hyperoside

Hyperoside is a flavonoid compound that is found in a variety of plants as well as medicinal herbs such as *Ginkgo biloba*, *Hypericum perforatum*, and *Vaccinium myrtillus*. It has been investigated for its potential therapeutic effects on a variety of conditions, including kidney stones. There are several potential mechanisms in which hyperoside can help in the treatment of kidney stones (13). One of the main components of kidney stones is calcium oxalate. Hyperoside has been shown to inhibit the formation of calcium oxalate crystals in vitro, which helps in preventing the formation of kidney stones. Hyperoside binds to calcium ions and prevents them from combining with oxalate ions to form crystals. It can also inhibit the activity of certain enzymes, such as α-glucosidase, which are involved in the metabolism of oxalate. This leads to a decrease in the production of oxalate, which in turn reduces the formation of calcium oxalate crystals. Hyperoside also has diuretic properties, which will cause an increase in urine output. This will flush out the kidney stones and prevent their formation (14). Hyperoside has been shown to have antioxidant properties, which means it can help protect cells from oxidative damage. It enhanced SOD activity and decreased MDA, LDA, and ROS expression (15). This may be important in preventing or reducing the severity of kidney stone formation, as oxidative stress has been implicated in the development of kidney stones. Hyperoside is also shown to have anti-inflammatory effects, which may help reduce the inflammation and pain associated with kidney stones. Hyperoside prevented the inflammatory response that lipopolysaccharide (LPS) induced in HT22 cells (16). In a nutshell, hyperoside has beneficial effect in the prevention and treatment of kidney stones through a combination of its ability to inhibit calcium oxalate crystal formation, its diuretic, antioxidant, and anti-inflammatory properties.

Rutin

Rutin (3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucoside) also known as rutoside and quercetin 3-rutinoside, is a citrus flavonoid glycoside mainly found in citrus fruit, berries like *Morus alba*, buckwheat or *Fagopyrum esculentum* (one of the best sources of dietary rutin), tea, and passionflower (17, 18). It is also present in several anti-urolithiatic plants such as *Hibiscus sabdariffa*, *Alcea rosea L*, and *Asparagus racemosus Willd*. Rutin exhibits a wide array of pharmacological-important activities, including anti-urolithiasis, antioxidant, antiradical, anti-inflammatory, antibacterial, antitumoral, cytoprotective, antispasmodic, antithrombic, and antiulcerogenic. Among all these biological activities, the effects of antioxidant, anti-inflammatory, diuretic, and anti-urolithiasis by preventing the crystallization of calcium oxalate are particularly essential in treating and preventing kidney stones (18). This is because the pathogenesis of nephrolithiasis is closely related to several factors, such as lipo-peroxidative and epithelial-damaging properties of reactive oxygen species (ROS). One study has discovered that the calculi-induced animals pre-treated with ethylene glycol and ammonium chloride have elevated calcium and oxalate levels in the urine and caused lipid peroxidation in renal tissues. It was found to have abundant and large depositions of calcium oxalate in the kidney tubules. However, the number and size of crystals formed and the risk of kidney interstitial fibrosis in calculi-induced rats were minimized after the administration of rutin. This study also found that co-treatment with rutin and curcumin to calculi-induced animals not only prevented the significant increase in calcium and oxalate levels, but also restored these values nearly to normal. Several studies have suggested that the inhibitory effects of rutin on calcium oxalate urolithiasis could be attributed to rutin's remarkable antioxidant and anti-inflammatory effects (19).

ROS are free radicals that can react quickly with lipids and proteins, making them unstable. Hence, excessive ROS generation harms and damages renal epithelial cells. Transition metals like copper and iron play a crucial part in inducing the production of free radicals that results in lipid peroxidation (14). Rutin is a potent and good antioxidant due to its capability to bind free radicals and chelate iron ions with II and III valences, thereby reducing the generation of free radicals. Besides, rutin also exerted its antioxidant effect through another mechanism—by suppressing induced nitric oxide synthase (iNOS) expression, which plays a key role in forming nitric oxide (NO) and superoxide anions. In addition, it was demonstrated that rutin is a scavenger of xanthine oxidase, an important mediator of oxidative stress (20). Therefore, it can be concluded that rutin can inhibit lipid peroxidation as a result of its high radical-scavenging activity.

Cyclooxygenase (COX-1 and COX-2), lipoxygenase (LOX), and protein kinases that are involved in the synthesis of inflammatory mediators (e.g., leukotrienes and prostaglandins). Rutin has been shown to reduce the activity of PLA2, an enzyme that catalyzes the initial step of the arachidonic acid cascade. Studies have reported that rutin inhibits the migration and degranulation of neutrophils, which are accounted for in parts of its anti-inflammatory activity. Furthermore, rutin's anti-inflammatory response can be shown by the downregulation of the expression of NF-κB and TNF-α, which are the key mediators of the inflammatory cascade [26]. These results proved that rutin has a protective role against urolithiasis in light of its excellent inflammatory properties.

On the other hand, drugs that have been utilized in treating urolithiasis also include diuretics such as thiazide medication. Increasing the amount of fluid passing through the kidney helps reduce the saturation of salts and flush out the salt deposits to prevent the aggregation of crystals (21). Rutin has been suggested to possess diuretic properties. The reason may lie in its metabolite derivative, quercetin, which can act on endothelium to cause NO release, leading to vasodilation and increased renal filtration rate (22). Therefore, it can be concluded that rutin may be effective in preventing stone formation and treating calcium oxalate urolithiasis.

Epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate (EGCG) is a type of natural polyphenol that is found in green tea (23). There are studies shown that EGCG has beneficial effects and can be used for the prevention and treatment of kidney stones. There are several potential mechanisms in which EGCG can be used to prevent or treat kidney stones, which are primarily composed of minerals such as calcium oxalate. Studies have suggested that EGCG may inhibit the crystallization process of calcium oxalate in urine, potentially reducing the risk of stone formation (24). EGCG can prevent the attachment of calcium oxalate crystals to the surface of kidney cells, thereby inhibiting their growth and aggregation (25). EGCG can also inhibit the formation of calcium oxalate crystals by modulating the activity of various enzymes involved in crystal formation, including oxalate oxidase, alkaline phosphatase, and calcium ATPase. Moreover, EGCG can also reduce the production of reactive oxygen species (ROS) in the kidney, which are known to promote calcium oxalate crystal formation.

EGCG has been shown to reduce the expression of several ROS-generating enzymes, such as NADPH oxidase, and to enhance the activity of antioxidant enzymes, such as superoxide dismutase and catalase, which can scavenge ROS. EGCG has also been shown to have antioxidant and anti-inflammatory properties, which may help to reduce oxidative stress and inflammation in the kidneys. This could potentially have a protective effect on the kidneys and reduce the risk of stone formation (26). In conclusion, EGCG can inhibit calcium oxalate crystal formation, preventing crystal attachment to kidney cells, modulating the activity of

enzymes involved in crystal formation, and reducing ROS production in the kidney. EGCG also exerts antioxidant and anti-inflammatory properties. These properties of EGCG make it a potential therapeutic agent for the prevention and treatment of kidney stones.

Tannin

Tannins, also known as tannic acids or gallotannins, are a group of astringent phenolic chemicals found in woody flowering plants that serve as major herbivore deterrents and have a variety of commercial uses. Gallotannin belongs to the hydrolyzable tannins, characterised by their glycosidic core and galloyl units. As a natural product, it has the potential to avoid kidney stones by inhibiting the attachment and accumulation of COM crystals in the nephrons. Calcium oxalate monohydrate (COM) crystals are tightly bound to the endothelial cell surface in kidney, and the pre-oxidative stress caused by oxalate can stimulate the binding of crystals to renal epithelial cells, which may be a key step in the formation of kidney stones. A significant build-up of COM crystals in renal tissues can result in tubular necrosis, leading to renal failure. In this case, gallotannins help prevent nephrolithiasis by inhibiting the binding of COM and expression of MCP-1 and OPN, as well as increasing antioxidant activity through direct action. In an in vitro wound healing assay, gallotannins considerably suppressed growth of COM crystal and their attachment to MDCK I kidney epithelial cells under non-toxic concentrations, and delayed renal cell migration, suggesting that gallotannins may be beneficial in vivo to prevent stone formation. In human primary renal epithelial cells (HRCs), reverse transcription polymerase chain reaction (RT-PCR) analysis showed gallotannins. substantially reduced oxalate-associated mRNA as well as protein expression of osteopontin (OPN), monocyte chemoattractant protein 1 (MCP-1), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunit p22phox and p47phox. Moreover, both malondialdehyde (MDA) and reactive oxygen species (ROS) produced by HRC were reduced by gallotannins. In response to oxalate, it also makes the antioxidant enzyme superoxide dismutase (SOD) more active. The antioxidant properties of gallotannins are expected to inhibit the formation pathways that could result in the retention of crystals in the kidney (27).

Thymoquinone

Thymoquinone is often extracted from *Nigella Sativa*, a plant that is essential to treat various disorders like asthma, bronchitis, headache, eczema, dizziness, hypertension, diabetes and inflammation. *Nigella Sativa* seed, which is also called black seed, consists of alkaloids, saponin proteins, fixed oils and essential oils (28). Thymoquinone acts as the major constituent of *Nigella Sativa* and is known as 1,4-bezoquinone. However, methyl and isopropyl groups are present to replace the hydrogens at position 2 and 5. In fact, this phytochemical compound possesses analgesic, antipyretic, antioxidant, anti-inflammatory, antiurolithic and anticancer effects (28).

To put it simply, thymoquinone cures kidney stones since it minimizes the deposited calcium oxalate in kidneys and provides both antioxidant and anti-inflammatory actions. First and foremost, it decreases the quantity and size of calcium oxalate stones deposited in renal tubules. This is because those kidney stones accumulated in kidneys will destroy the epithelial tissues and yield free radicals and superoxide anions. Apart from that, thymoquinone gives the antioxidant activity to remove the free radicals and superoxide anions and therefore heterogenic crystal nucleation is unable to take place. On top of that, it inhibits the cyclooxygenase and 5-lipoxygenase pathways. The formation of inflammatory mediators including prostaglandins, thromboxane and leukotrienes from eicosanoids are eventually absent due to the inhibition of the COX and LOX enzymes by its anti-inflammatory effect. Besides, thymoquinone also inhibits proinflammatory cytokines IL-1β, TNF-α, IFN-γ, IL-6, and PGE2, blocking the synthesis of free radicals (29).

Berberine

Berberine is the isolate of *Berberis genus* and *Coptis chinensis*, a type of Chinese herb. Plus, it can also be extracted from *Hydrastis canadensis*. It is a pentacyclic benzylisoquinoline alkaloid to be orally administered. In general, it inhibits microbial growth, treats arrhythmia and cancer, prevents inflammation and brings down the level of cholesterol against eyes, skin, respiratory and digestive disorders (30). Furthermore, berberine provides renoprotective action to manage numerous renal diseases, which are renal fibrosis, renal ischemia, renal aging, renal stones and diabetic neuropathy. To add on, it gives effect against chemotherapy, heavy metal, aminoglycosides and NSAID-induced nephrotoxicity. Both acute and chronic renal disorders can be healed by this phytochemical compound (31).

Berberine acts as the primary constituent of several plants for the antiurolithic activity. To illustrate, the antioxidant and diuretic actions are involved to prevent and treat kidney stones *in vivo*. High levels of oxalate and calcium oxalate deposition in renal tubules will eventually lead to calcium oxalate urolithiasis. In this case, berberine's antioxidant activity reduces the enzymatic reactions present in the kidneys. At the same time, the levels of malondialdehyde and protein carbonyl are enhanced whereas GSH is depleted. On the contrary, its diuretic effect raises the urinary pH, resulting in the increased reabsorption of calcium ions and excretion of both sodium and potassium ions. Hence, the urine output is increased (32). This indicates that berberine incorporates the antioxidant, diuretic, urinary alkalinizing and hypocalciuric actions for the treatment of kidney stones.

Caffeic acid

Caffeic acid is an organic molecule categorized as a hydroxycinnamic acid and belongs to a vast chemical group called phenolic acids. All plant species synthesize it due to its role as an intermediary in the formation of lignin, one of the main constituents of woody plant biomass and its residues. It is found in the bark of *Eucalyptus globulus*, the grain of *Hordeum vulgare* (barley), *Ceylan cinnamon*, propolis, and in many beverages such as coffee, red wine, and plum. Caffeic acid is usually present as its precursor product in foods, for example, it occurs as chlorogenic acid in coffee (33). The chemical structure of caffeic acid can be described by a phenylpropanoid (C6-C3) moiety containing a carboxylic acid connected to a 3,4-hydroxylated aromatic ring via a trans-ethylene linker (34). The numerous physiological effects of caffeic acid include antibacterial, antiviral, antioxidant, anti-inflammatory, immunostimulatory, and anti-hepatocarcinoma activity. Among these activities, the antioxidant, anti-inflammatory, ACE inhibition, and diuretic properties of caffeic acid have been suggested to provide protective effects against urolithiasis. One study investigated how caffeic acid affects kidney stones induced by ethylene glycol in rats. The findings revealed that both the preventive and curative groups significantly controlled the abnormal biochemical parameters and decreased the accumulation of calcium oxalate in the kidney tubules. On top of that, the experiment analyzed the effects of caffeic acid treatment on the expression of several genes related to kidney stones. The results indicated that the osteopontin gene was downregulated by treatment with caffeic acid, whereas the prothrombin fragment 1, Tamm-Horsfall, and bikunin genes were up-regulated (35). An increasing amount of evidence suggests that ROS has played a vital role in kidney stone formation. It has been demonstrated that higher oxalate and calcium oxalate crystal concentrations can damage renal cells, raising ROS levels and lipid peroxidation. Therefore, antioxidants are well known to offer protection against free radical-induced damage and tissue injury. Like most other phenolic acids, caffeic acid has active ferrous ions chelation and free radical-scavenging action, which can enhance the antioxidant system. In addition, caffeic acid has also shown effective ABTS, DPPH, and superoxide anion radical scavenging activities (36). Due to its strong antioxidant properties, the generation of ROS and

subsequent oxidative stress in urolithiasis may be inhibited.

It has been documented that caffeic acid provides anti-inflammatory protection by reducing pro-inflammatory and inflammatory cytokines, including TNF-α, IL-1β, IL-8, and IL- 10, and by modulating the gene expression in immunomodulatory and anti-inflammatory response. One study investigated the effects of caffeic acid in the kidneys of diabetic mice proved that caffeic acid possesses significant anti-inflammatory activities because it could dose-dependently reduce the level of IL-6, IL-1β, TNF-α, and monocyte chemoattractant protein 1 (MCP-1) (33). Activation of the renin-angiotensin-aldosterone system produced ROS. By reducing ROS production, angiotensin-converting enzyme inhibition (ACE-I) considerably lowers calcium oxalate stone formation and inflammation in the kidney. When free hydroxyl groups from phenolic substances such as caffeic acid interact with the zinc atom in the active site of ACE, they generate a chelate that inhibits ACE in vitro. In other words, caffeic acid protects tissues from inflammation through ACE inhibition.

An increase in urine production was found in the ethylene glycol rat model treated with caffeic acid in a dose-dependent manner. Undeniably, diuresis helps remove kidney stone debris from the urinary tract and decreases stone formation risk. The same study also supported that caffeic acid significantly decreased oxalate excretion and induced urinary citrate, a compound that can inhibit crystallization by complexing with free calcium in the urine. The experiment showed that caffeic acid downregulated osteopontin, a compound believed to promote crystal attachment and formation by coating renal tissue surfaces. The three genes inhibiting calcium oxalate stone formation—prothrombin fragment 1, Tamm-Horsfall, and bikunin genes were found to be up-regulated after administrating caffeic acid to ethylene glycol-induced rat models. Hence, it can be concluded that caffeic acid can act as a regulator of kidney stone formation through a wide range of mechanisms to alter the constituents of urine and the gene expressions of various modulators related to kidney stone formation (34).

Conclusion

In conclusion, phytochemicals have shown promising potential in the treatment and prevention of kidney stones. Kidney stones have become one of the major health issues worldwide and pose a significant therapeutic challenge due to ineffective treatments and high rates of recurrence. Many studies have reported the beneficial effects of various phytochemicals, such as flavonoids, alkaloids, and terpenoids, in reducing the risk of kidney stone formation and helping to dissolve existing stones. However, additional investigations and research are required to validate the efficacy and safety of these compounds for individuals with kidney stones. There is limited human research available regarding the effectiveness of herbs in managing kidney stones. Therefore, further investigation and research are necessary to confirm the safety and effectiveness of these substances in individuals who have kidney stones. All herbs have potential benefits and risks, which can be balanced by using them properly and in moderation.

Acknowledgment

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

Conflicts of interest

The authors declare no conflict of interest.

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