

Phytomolecules investigated for the prevention and treatment of urinary stones

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Abstract: Urolithiasis is a recurrent pathology manifested by the stone formation in the urinary system; it has long been treated in traditional medicine by plant remedies. Several studies have provided the efficacy of medicinal plants as well as their chemical compounds against stone formation. The present work aims to summarize the antiurolithiatic effect of phytochemicals, including quercetin, rutin, catechin, diosmin, and thymoquinone. In this context, various databases, including PubMed, Science Direct, Scopus, and google scholar, were searched using keywords like antiurolithiatic bioactive molecules and chemistry of phytomolecules.

The results confirmed that phytochemicals, including particularly flavonoid molecules, could be effective against lithogenesis via different strategies such as decreasing the binding between crystals and cells, decreasing the growth of crystals, and increasing magnesium level. Nevertheless, more studies are required, such as determination of toxicity and clinical studies. This review may help researchers achieve more results about the mechanism and the side effects of phytochemicals administration.

Keywords: Urolithiasis; phytomolecules; lithogenesis; toxicity.

1. Introduction

Urolithiasis, a recurrent disease known as urinary calculi or urinary stones, are hard deposits of minerals and salt formed anywhere in the urinary tract. We can distinguish 3 terms; nephrolithiasis term used to indicate stones formed in the kidneys. Ureterolithiasis refers to ureteral stones, and Cystolithiasis term means the bladder calculi ¹. This disorder is the outcome of physicochemical steps; the initial step is the nucleation, characterized by the association of free ions into micro-particles after urine supersaturation. The following event is crystal growth, making crystals grow by removing promoters of a stone formation such as uric acid and urate from the urine ². The aggregation is the last event, during which the crystals bind to those already established to form larger particles ³. The etiology of this disease consists of increased excretion of stone-forming components such as calcium, oxalate, urate, cystine, xanthine, and phosphate and decreased urine volume ⁴. An excess of vitamin D can cause it, vitamin A deficiency, hyperthyroidism, gout, intestinal dysfunction ⁵, and infection by bacteria such as *Klebsiella pneumoniae*, *Pseudomonas* and *Oxalobacter formigenes* ⁶. There are other etiological factors such as dietary risk, hot climate, and genetic factors ^{7,8}.

The treatment is medical or surgical; the medical one is mainly based on applying hygienic and dietary rules, surveillance, and stones' spontaneous expulsion. Among the prescribed drugs for treating stones, there are synthetic drugs like thiazide diuretics (hydrochlorothiazide), alkali (potassium citrate), allopurinol, sodium cellulose phosphate (SCP), penicillamine (Cuprimine), analgesic (diclofenac sodium), bisphosphonates, potassium, phosphate, and probiotics (*Oxalobacter formigenes*) ⁹. For the surgical treatment, among the techniques used, there are: percutaneous lithotripsy (PCNL), extracorporeal shock wave lithotripsy (ESWL), and transurethral lithotripsy (TL) ^{10,11}. These treatments can lead to a decrease in renal function, hemorrhage, and hypertension. Besides, they are expensive and do not prevent the recurrence of stone formation ^{12,13}. Moreover, till now, there is no satisfactory drug to treat and prevent urolithiasis.

Medicinal plants possess a wide range of biological activities, such as antidiabetic, anticancer, antiurolithiatic, and analgesic effects ¹⁴. Besides, it exhibits an antimicrobial property, including antibacterial and antifungal activities ¹⁵. In addition, it can also act as an anti-infertile agent ¹⁶.

In folk medicine, urolithiasis has been treated by different herbal formulations. The decoction was the

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commonly used mode of herbal remedies¹⁷. Dried powder, fresh leaves¹⁴, and juice were also used¹⁸.

The side effects of medicinal plants and natural molecules are lesser than conventional treatment; therefore, several studies have examined medicinal plants' anti-urolithiatic activity. Its effectiveness is due to its rich phytochemicals. The goal of this work is to summarize some chemical properties of phytochemicals and their antiurolithiatic effects.

2. Search Methodology

PubMed, Science Direct, Scopus, and Google scholar databases were searched for bioactive phytochemicals investigated to prevent and treat urolithiasis. For searching, we have used keywords like urolithiasis, anti-urolithiasis, antiurolithiatic bioactive molecules, the chemistry of phytochemicals. We considered that the studies are valuable if they include *in vitro*, *in vivo* studies for anti-urolithiatic effects, review, and research articles for bioactive molecules' chemistry. Concerning the selection, collection, and synthesis of data, we have based on the articles' title and abstracts; then, we extracted a standard data form based on the first author's last name and year of publication.

3. Phytochemicals with anti-urolithiatic activity and its Chemical properties

Many diseases can be prevented and/or treated by phytochemicals, among them urolithiasis; within this context, multiple studies were carried out for the antiurolithiatic effect of phytoconstituents (Table 1).

Quercetin (pentahydroxyflavone) is one of the phytochemicals investigated for anti-urolithiatic effect. It is a lipophilic molecule with five hydroxyl groups (Figure 1), categorized in flavonol class, synthesized in leaves, flowers, or fruit plant parts, and found in many dietary plants such as Onions¹⁹, Blueberry²⁰, and Mango²¹. Due to the presence of free hydroxyl groups, quercetin has exhibited a strong anti-oxidant activity²². Additionally, it is effective against inflammation and diabetes²³. In an *in vitro* study, the result showed that the decrease in MDCK (Madin–Darby canine kidney) cell viability and lipid peroxidation were inhibited in the presence of quercetin²⁴. Quercetin and hyperoside were studied using Ethylene Glycol Induced calcium oxalate kidney stones in a rat model. The result showed a significant increase in superoxide dismutase and catalase levels; the histopathological examination showed a significant decrease of crystals in the kidneys of quercetin-hyperoside treated group²⁵. Additionally, the co-administration of quercetin and betulin (isolated from *aerva lanata* L.) reduced the risk of stone formation by decreasing oxalate excretion, nucleation, and growth of crystals as well as increasing magnesium level²⁶.

Rutin or 3, 3', 4', 5, 7-pentahydroxyflavone-3-Rhamnoglucoside is a derivative of quercetin also named quercetin 3-O-rutinoside, it is a bioactive

phytochemical substituted with two sugars: glucose and rhamnose³⁴ (Figure 2), it has been studied for several biological activities among them, antihypercholesterolemic³⁵, anticancer³⁶, antidiabetic³⁷, and antimicrobial activity³⁸. In addition, rutin exhibits a nephroprotective effect against nephrotoxicity by diminishing the levels of MDA, urea, and creatinine and increasing glutathione peroxidase and superoxide dismutase^{39,40}. Rutin has been found to be capable of inhibiting calcium oxalate formation. Additionally, administration of rutin and curcumin has been found to be capable of restoring the normal urinary levels of calcium and oxalate and inhibiting aggregation and growth of calcium oxalate monohydrate crystals⁴¹. Catechin is another nutraceutical bioactive chemical, chemically named (2S,3R)-2-(3,4 dihydroxyphenyl) chroman-3,5,7-triol, has 4 enantiomers which are epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (EGCG) (Figure 3), those molecules have been found in many dietary plants such as green tea, blackberries, and apricot. Various studies have demonstrated the antiviral, anti-oxidant, and anti-inflammatory activities of catechin^{42,43}. Additionally, epigallocatechin gallate (EGCG) has been reported to protect kidneys against acute kidney injury caused by cardiopulmonary bypass operation⁴⁴. Similarly, and regardless of the cause, EGCG exerts a protective effect against AKI⁴⁵. Anti-urolithiatic effect of catechin against stone formation suggested inhibiting renal papillary calcification⁴⁶. In another study, catechin has shown a significant decrease in the number of crystals induced by melamine-cyanuric acid mixture; this effect could be attributed to its inhibitory effect of reactive oxygen species, phospho-P38, and apoptosis⁴⁸. In addition, EGCG has been found to be effective in the prevention of stone formation via inhibiting the expression of alpha-enolase protein and thus decreasing the binding between crystals and MDCK cells⁴⁹.

Diosmin or 3',5,7-trihydroxy-49-methoxyflavone 7-rutinoside (Figure 4), is a flavone glycoside compound, belongs to the family of citrus flavonoid, exhibits several remarkable biological activities such as anti-inflammatory, antihypertensive, anti-oxidant, vascular-protecting activity and chemopreventive effect against colon carcinogenesis⁵¹. This nutraceutical agent exerts a nephroprotective effect by attenuating lipid peroxidation and modulating Bax and p53 protein expression⁵². In addition, diosmin has been reported to modulate capillaries and vessels diameter of the cortex; it could prevent urolithiasis by keeping the acidic value of urinary pH; its preventive property against stone formation could also be attributed to the decrease of urinary protein level and the increase of potassium and magnesium urinary levels^{53,54}. Thymoquinone (2-Isopropyl-5-methyl-1, 4-benzoquinone) (Figure 5) is a nonpolar bioactive phytochemical and a major compound of *Nigella Sativa* seeds that categorized in monoterpenes class; it

can be found in other plants like *Juniperus Cedrus* Webb & Berthel and *Tetraclinis articulata* (Vahl) Mast.³², it covers a wide range of pharmacological properties which include antioxidant, anti-inflammatory, anti-Alzheimer, hepatoprotective, neuroprotective, anticancer, and nephroprotective

activity⁵⁵. This phytochemical has been investigated on Ethylene Glycol-Induced urolithiasis in the Rats model. The result of this study indicated that a low dose of thymoquinone (5mg/Kg) could be more effective with a significant prophylactic effect against CaOx stone formation⁵⁶.

Table 1. Chemical properties of phytomolecules and their effect on calculi formation.

Phytochemical	Molecular formula	Molecular weight g/mol	Plant source	Effect on stone formation
Quercetin	C ₁₅ H ₁₀ O ₇	302.23	<i>Allium cepa</i> L., <i>Camellia sinensis</i> (L.) Kuntze, <i>Moringa oleifera</i> Lam., <i>Apium graveolens</i> L., <i>Prunus avium</i> (L.) L. <i>Coriandrum sativum</i> L... ²⁷	Inhibits the Decrease of lipid peroxidation and cell viability caused by oxalate ²⁴ . Decrease crystal deposition in kidneys and urine ²⁵ . Reduce oxidative damage and increase serum paraoxonase 1(PON1) which can protect kidneys against oxidative stress ³³ .
Rutin	C ₂₇ H ₃₀ O ₁₆	610.5	<i>Ruta graveolens</i> L., <i>Sophora japonica</i> L., <i>Canna indica</i> L., <i>Canna edulis</i> <i>KerGawl...</i> ²⁸	Decrease MDA, urea, and creatinine. Increase glutathione peroxidase and superoxide dismutase ³⁹ . Restores normal calcium and oxalate urinary levels ⁴¹ .
Catechin	C ₁₅ H ₁₄ O ₆	290.27	<i>Arrabidaea brachypoda</i> Bureau, <i>Rhizophora mangle</i> L. ²⁹ <i>Camellia sinensis</i> (L.) Kuntze, <i>Actinidia deliciosa</i> (A.Chev.) C.F.Liang & A.R.Ferguson, <i>Malus pumila</i> Mill... ³⁰	Decrease calcium oxalate crystals and reduce papillary calcification ⁴⁰ . Increase osteopontin (OPN), decrease malondialdehyde (MDA) and calcium crystallization ⁴⁷ . Decrease crystal deposition in kidneys induced by melamine-cyanuric acid mixture ⁴⁸ .
Epigallocatechin gallate	C ₂₂ H ₁₈ O ₁₁	458.4	<i>Camellia sinensis</i> (L.) Kuntze, <i>Theobroma cacao</i> L... ³¹	Decrease the binding between crystals and MDCK cells by inhibiting the expression of alpha-enolase protein ⁴⁹ . Reduce free radical production and oxalate excretion in urine ⁵⁰ .
Diosmin	C ₂₈ H ₃₂ O ₁₅	608.5	<i>Citrus lemon</i> (L.), <i>Citrus reticulata</i> Blanco, and <i>Citrus sinensis</i> (L. Osbeck) <i>Teucrium gnaphalodes</i> L'Hér... ⁵⁴ .	Increase urinary magnesium and potassium levels ⁵² . Prevent stone formation by attenuating lipid peroxidation and modulating Bax and p53 proteins expression ⁵³ .
Thymoquinone	C ₁₀ H ₁₂ O ₂	164.2	<i>Nigella Sativa</i> L., <i>Nigella arvensis</i> L., <i>Juniperus Cedrus</i> Webb & Berthel. and <i>Tetraclinis articulata</i> (Vahl) Mast. ³²	Reduce CaOx crystal deposition in the kidneys ⁵⁶ . Decrease serum creatinine and urea levels. Reduce lipid peroxidation, malondialdehyde (MDA) and 8-isoprostane ⁵⁷ .

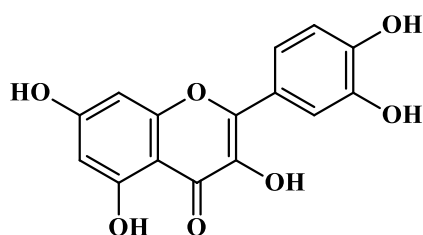


Figure 1. Chemical structure of quercetin

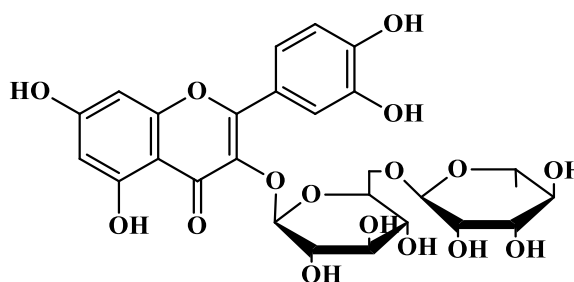


Figure 2. Chemical structure of rutin

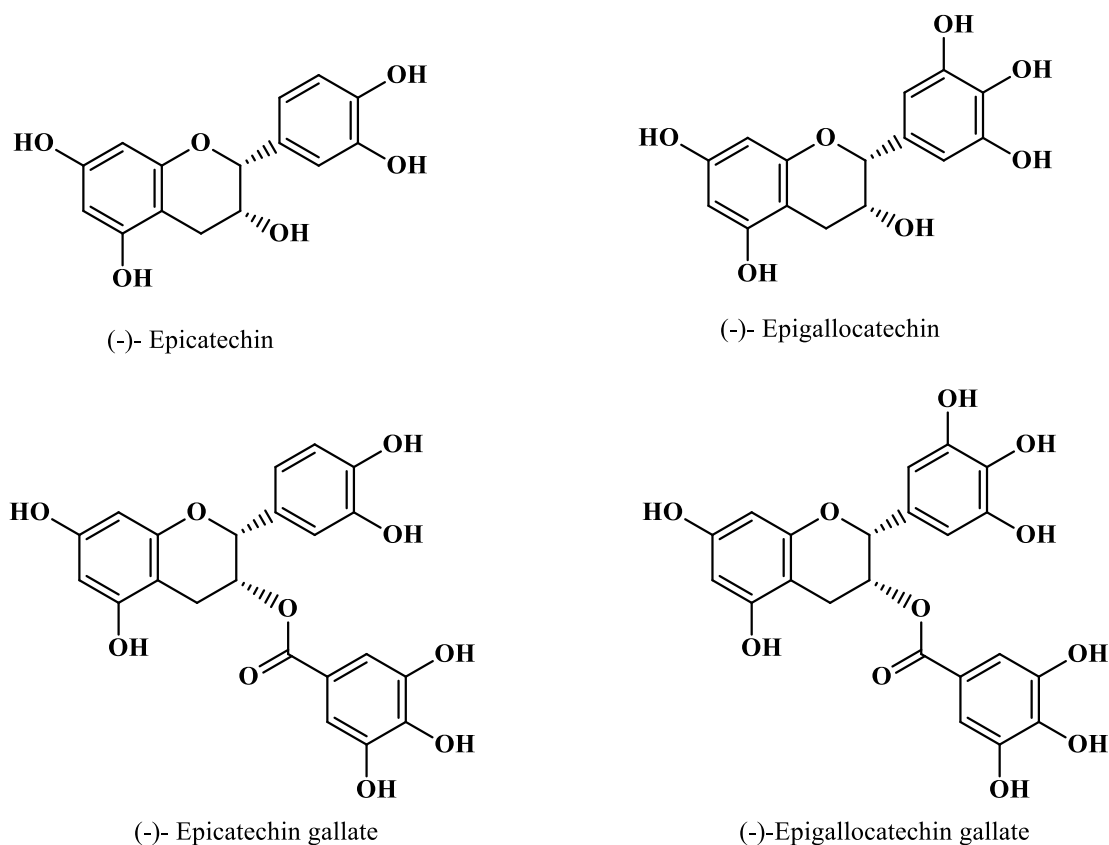


Figure 3. Chemical structure of the four enantiomers of catechin

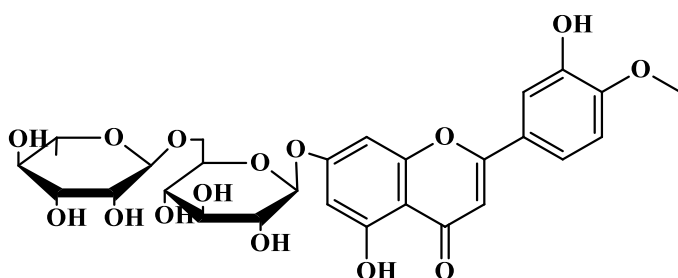


Figure.4 Chemical structure of Diosmin

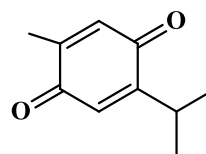


Figure.5 Chemical structure of thymoquinone

Urinary stones are a recurrent disorder that can lead to chronic kidney diseases (CKD) and acute kidney injury (AKI) ⁵⁸. The actual treatments (medical or surgical) described to patients with urinary calculi are quite restricted. Some drugs like alkali-citrate are described to patients to prevent calculi formation, but their efficacy is low. Thus, they are not entirely preventing urolithiasis ⁵⁹. Medicinal plants represent an essential source of prophylactic and therapeutic remedies to treat several disorders, including urinary stones.

In vitro and *in vivo* studies on the preventive and therapeutic effect of phytomolecules revealed that the mentioned chemicals could inhibit stone formation using various mechanisms, including decreasing crystal deposition in the kidneys and increasing glutathione peroxidase superoxide dismutase, and cell viability ^{24,58}. Phytochemicals also use other strategies to prevent urinary stone formation, such as

suppression of the bond between crystals and tubular epithelial cells, Decreasing MDA, and regulation of serum PON1 ^{33,47}. The mechanism by which thymoquinone can manage kidney stones is still unknown. But as some studies have demonstrated it, thymoquinone can probably inhibit urolithiasis by decreasing lipid peroxidation and MDA, as well as reducing the serum levels of creatinine and urea ⁵⁷.

The result obtained from the available literature showed that all of the phytochemicals are nutraceutical. They can be effective against stone formation through several mechanisms, among them the antioxidant activity. This later is strongly correlated to the anti urolithiatic effect. Unfortunately, the current results cannot confirm the effectiveness of these molecules without testing their toxicity and their effects on human health. Further research is needed to establish more results about the safety and efficacy of patients with urinary stones.

4. Conclusion

Many pharmaceutical drugs are used to treat urinary stones, such as potassium citrate and sodium cellulose phosphates. However, most of them are quite restricted and present many side effects; therefore, till now, there is no satisfactory drug to treat and prevent urolithiasis. Several studies have been demonstrated the efficacy of medicinal plants and their compounds on the prevention and management of urinary stones. In this work, we have summarized the efficacy of phytochemicals investigated to prevent and manage urinary calculi. The result obtained from the available literature showed that all of the phytochemicals are nutraceutical and can be found in many dietary plants. Therefore, phytochemicals such as quercetin, catechin, and thymoquinone have been considered as promising natural molecules for the inhibition and management of stone formation. It can use different strategies for preventing and treating urinary stones; it can act on all stone formation steps by inhibiting the nucleation, growth, and aggregation of calcium oxalate crystals. Other mechanisms are increasing urinary citrate and magnesium levels, decreasing urinary calcium and oxalate levels, reducing free-radical production, and diminishing the bound between crystals and tubular epithelial cells. A new drug can be developed from these phytochemicals. However, more studies are required to determine these compounds' validity and safety in patients with urolithiasis.

Conflicts of interest

The authors declare that no conflict of interest could influence the work reported in this paper.

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