



Citrullus lanatus and *Gardenia jasminoides* for Anti Urolithiasis: A Review

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ABSTRACT:

About 10–15% of people worldwide suffer with urolithiasis, also referred to as kidney stone disease, which is one of the most frequent urinary tract conditions. It is distinguished by the development of crystalline deposits in the urinary system that are primarily made of phosphate, uric acid, or calcium oxalate. Stone formation is caused by a number of variables, such as genetic susceptibility, dietary habits, metabolic disorders, urinary tract infections, and dehydration. In addition to causing excruciating pain and bladder blockage, the illness also results in recurring bouts and high medical expenses. Currently available therapies include surgery, extracorporeal shock wave lithotripsy (ESWL), and allopathic drugs work well, but they have drawbacks such as adverse effects, expensive expenses, and a high recurrence rate. Herbal and natural treatments that provide safer, more affordable, and multi-targeted methods for the prevention and treatment of urolithiasis are therefore gaining popularity. Among these herbal remedies, *Citrullus lanatus* (watermelon) and *Gardenia jasminoides* (cape jasmine) have demonstrated encouraging nephroprotective and anti-urolithiatic properties. Citrulline, lycopene, and flavonoids—bioactive components with antioxidant, diuretic, and urinary cleaning qualities—are abundant in *Citrullus lanatus*. Geniposide and crocin, which are found in *Gardenia jasminoides*, have been shown to have anti-inflammatory, antioxidant, and renal-protective properties. Recent studies have indicated that combining herbal extracts with complementary pharmacological actions—such as the diuretic effect of *Citrullus lanatus* and the anti-inflammatory action of *Gardenia jasminoides*—may produce a synergistic effect against stone formation and recurrence. Therefore, this review aims to explore the phytochemical composition, pharmacological potential, and anti-urolithiatic mechanisms of *Citrullus lanatus* and *Gardenia jasminoides* in the prevention and management of kidney stones.

Keywords: Urolithiasis, diuresis, herbal drug, calcium oxalate stone

INTRODUCTION:

Urolithiasis, commonly known as kidney or urinary stones, refers to the formation of calculi in the urinary tract, including the kidneys, ureters, bladder, or urethra. It is a significant global health problem due to its high prevalence, recurrence rate, and complications that can lead to severe pain, urinary obstruction, and kidney damage. An imbalance between the urinary tract's natural inhibitors and substances that form stones causes urolithiasis. Urinary supersaturation with calcium, oxalate, uric acid, or phosphate; low urine volume and dehydration; dietary factors like high intake of oxalate, salt, and animal protein; metabolic disorders like hypercalciuria and hyperoxaluria; infections (especially those caused by urease-producing bacteria); and genetic or anatomical abnormalities that change urine chemistry and flow are some of the main etiological factors. [1]

Urolithiasis is caused by a series of cellular and biochemical processes that result in the development, growth, and retention of urinary stones. Urinary supersaturation is the first step in the process, which occurs when concentrations of ions that can cause stones, such as calcium, oxalate, uric acid, or phosphate, surpass their limits of solubility and foster an environment that is conducive to crystal nucleation. After that, these original crystals grow and aggregate, getting bigger as more ions attach to their surface and several crystals group together.[2] The epithelial lining of the renal tubules is harmed concurrently by oxidative stress and inflammation, which results in adhesive surfaces like Randall's plaques where crystals can adhere and endure.[3][4] Instead of being removed by urine flow, this retention permits stones to grow larger. Reduced urine volume, changed pH, and metabolic irregularities during this process and decreased citrate and other natural inhibitors aid in the development of stones.[5] In this situation, plants that target these pathological steps, such as *Gardenia jasminoides* and *Citrullus lanatus*, have positive effects: *C. Lanatus* increases urine production, lowers supersaturation, prevents the formation of calcium oxalate crystals, and has antioxidant properties that shield renal cells, whereas *G. Jasminoides* limits the epithelial damage necessary for crystal adhesion and growth, lowers oxidative stress and inflammation, and maintains tubular integrity through its iridoid glycosides, such as geniposide and gardenoside. Their combined mechanisms work against the fundamental pathological processes that lead to the formation of stone.[6]



Urolithiasis is a common global health problem and represents one of the most prevalent urological disorders worldwide, affecting individuals across all continents, climates, and ethnic groups. Epidemiological studies indicate that the global lifetime risk of developing urinary stones is approximately 10–15%, with considerably higher rates reported in certain high-risk regions, particularly hot and arid areas where the lifetime risk may reach 20–25%. The population prevalence varies widely by geographic location, ranging from 1–5% in most Asian countries, 5–9% in Europe, and 7–15% in North America.[7] The annual incidence of urolithiasis is estimated to be close to 1% of the population, though substantial regional variability exists due to environmental and lifestyle factors. Certain tropical and subtropical regions, commonly referred to as “stone belt” areas, demonstrate significantly higher disease burden. These regions include parts of the Middle East, South and Southeast Asia, North Africa, Sub-Saharan Africa, and Latin America.[8] In countries within the Middle East, such as Saudi Arabia, the United Arab Emirates, and Iran, prevalence rates have been reported to exceed 20%, largely attributed to chronic dehydration resulting from high ambient temperatures, dietary habits rich in animal protein and salt, and limited fluid intake. Age and sex distribution patterns reveal that urolithiasis most commonly affects adults between 30 and 50 years of age, with peak incidence often observed in middle-aged populations. Historically, males have been more frequently affected than females, with a male-to-female ratio of approximately 2:1[9].

Antirolithic therapy is aimed at the prevention, dissolution, and/or attenuation of urinary stone formation, specifically calcium oxalate stones. The medical management strives to prevent recurrent events, attenuation of formed stones, facilitation of stone expulsion, and adjustment of the chemical constitution of the urine by increasing its volume and concentration and/or reducing supersaturation through the use of drugs that include potassium citrate, thiazides, and allopurinol; nevertheless, the use of pharmacotherapy has remained associated with several limitations that include the phenomenon of drug resistance and recurrent stone formation.[10] This has triggered increasing interest on the use of plants for the attenuation and prevention of stone formation. Phytotherapy has attracted considerable attention as alternative therapy aimed at the prevention and attenuation of stone formation. This has been demonstrated through the use of certain plants that include *Citrullus lanatus* (watermelon) for its natural ability to stimulate the flow of urine; experimental studies on the bioactive agents derived from *Citrullus lanatus* disclosed that they possessed inhibitory activity on calcium oxalate crystal deposition within the renal tissues and urine of experimental animals, enhanced urinary excretions and pH value, restored ionic balance, improved renal function parameters, and inhibited crystal aggregation; although the findings support its use in the attenuation and prevention of stone formation, presently there is little evidence that has opened the way for its implementation.[11] In contrast, *Gardenia jasminoides* was initially known due to its established use in traditional medicine and possessed high bioactive concentration including its major pharmacologically active compounds Geniposide that has inherent antioxidant and anti-inflammatory properties; nevertheless, presently there is little clinical and scientific literature evidence that supports its use on the attenuation and prevention/dissolution of urinary stone disease. Nevertheless, its high dosage has remained associated with nephrotoxic and hepatotoxic phenomena within certain experimental animal studies. Similar phenomenon has also been associated with other plants that include *Phyllanthus niruri* that has demonstrated relative clinical efficacy. In this regard, experimental studies on *Gardenia jasminoides* provided strong evidence demonstrating its effectiveness on the attenuation and prevention/dissolutions of urinary stone diseases by acting on its natural inherent antioxidant and anti-inflammatory properties; although little clinical evidence currently supports its use. Nonetheless, high dosage has remained associated with nephrotoxic and hepatotoxic phenomena within certain animal experimental studies. Herbs that include *Phyllanthus niruri* commenced showing relative clinical efficacy. [12]

Molecular pathway and therapeutic target of the urolithiasis :

The formation of stones is a multifunctional phenomenon that is due to an imbalance between the substances that promote crystallization and those that inhibit namely calcium and oxalate on the one hand and citrate and magnesium on the other. Crystal nuclei grow, and the crystals stick to the kidney area and are retained there. The kidneys hold back the accumulation of oxalate and crystals, which in turn, creates a scenario where an enormous amount of reactive oxygen species (ROS) are produced as a result of the cell's metabolism and the oxygen used in the process [13]. This triggers a series of events that finally form a large pool of pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α and characterize the oxidative and inflammatory process. The inflamed and metabolically stressed kidney epithelial cells undergo several forms of cell death, including apoptosis that is mediated by caspases-3/7, pyroptosis that is dependent on the NLRP3 inflammasome and gasdermin D leading to cell lysis, necroptosis that is dependent on the RIPK1-RIPK3-MLKL signaling pathway, and iron-dependent lipid peroxidation that is regulated by GPX4 and NRF2 indicating cell death as a form of ferroptosis [14][15]. Meanwhile, the polarization of macrophages, which is a crucial aspect of the whole saga, has a twofold effect as pro-inflammatory M1 macrophages intensify the condition leading to stone formation while the anti-inflammatory M2 macrophages assist in healing the tissues [16]. Urolithiasis is also classically considered as a kind of metabolic disorder characterized by TCA cycle dysregulation and lowered levels of natural inhibitors like citrate and succinate. The latest treatment modalities have their sights set on these pathways, which involve the calcium-sensing receptor, NLRP3 and NF- κ B signaling inhibition, NRF2/HO-1 antioxidant defenses activation, macrophage polarization regulation via CCR2 and PPAR- γ pathways, necroptosis and ferroptosis inhibition, enzyme-specific therapies for struvite and uric acid stones, and urinary inhibitors like citrate and magnesium [17] supplementation (fig1).

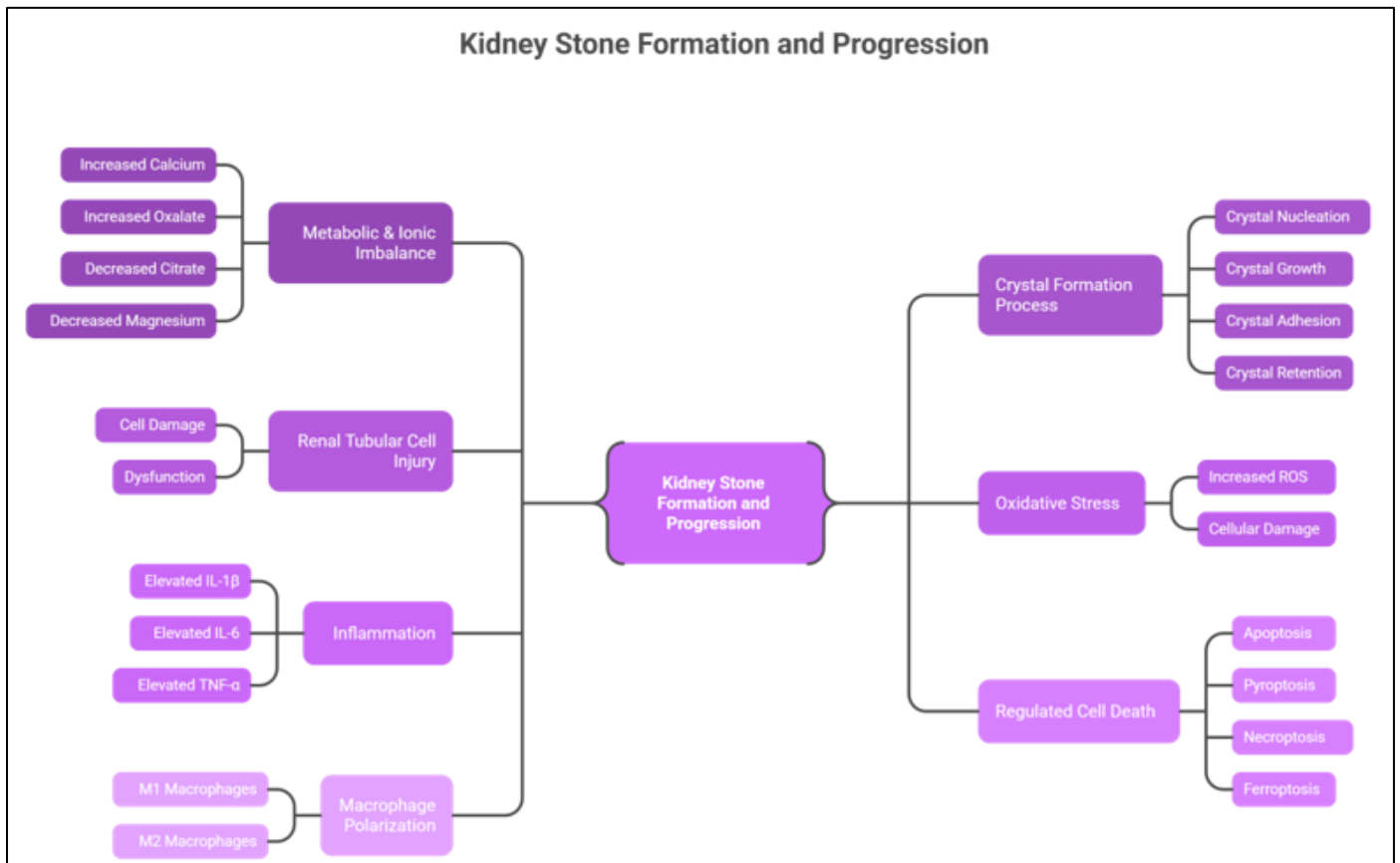


Fig: 1 kidney stone formation and progression

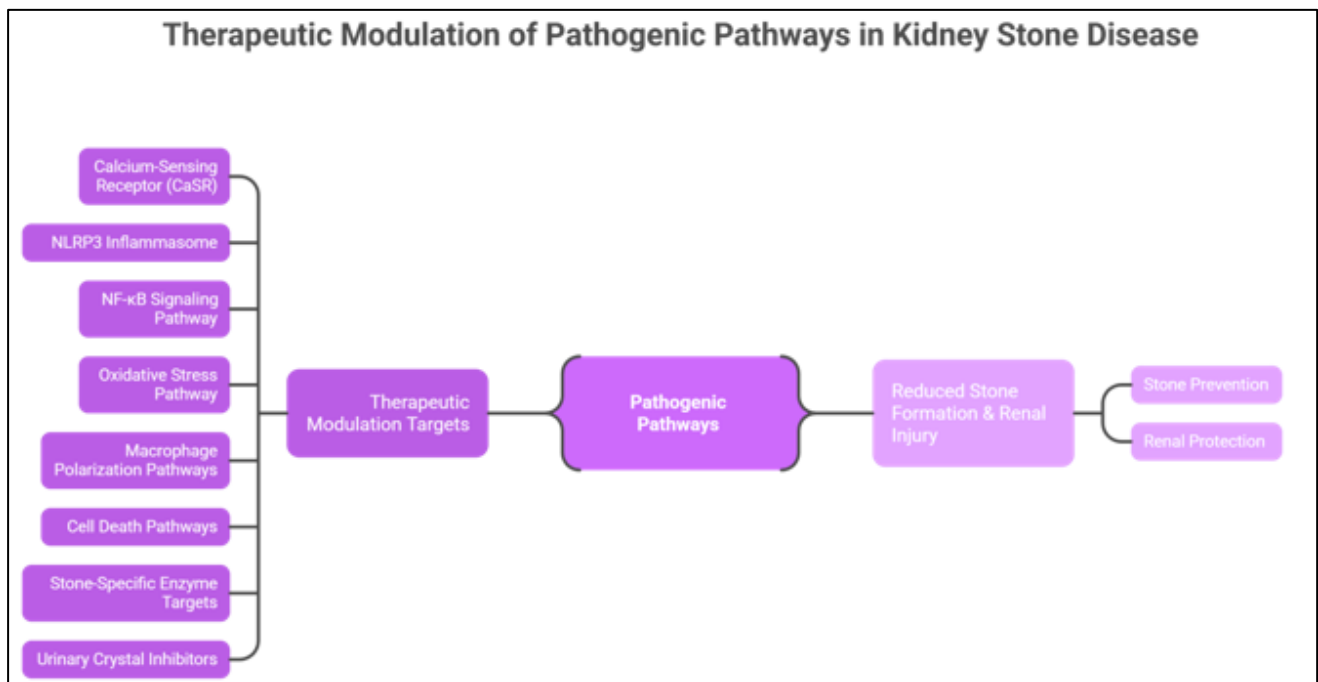


Figure 2. Therapeutic Modulation of Pathogenic Pathway in Kidney Stone Disease



Role of Citrullus lanatus and Gardenia Jasminodes in urolithiasis treatment.

The plant *Citrullus lanatus* is from the family *Cucurbitaceae* and is originally from Africa and Southeast Asia. The plant is cultivated for its edible water-rich fruit that is rich in vitamins C, potassium, lycopene, citrulline, and beta-carotene. The plant functions as a diuretic and antihypertensive because it is less fat, free from cholesterol, and very hydrated. This plant has long been employed in traditional medicine for renal ailments, with folkloric remedies advising a large consumption of watermelon fruits in the diet of a patient with kidney problems. The seeds are used in the management of hyperglycemia and have antimicrobial properties [18]. The juice of the plant is employed in *Gardenia jasminoides*. Characteristics : *Gardenia jasminoides* (cape Jasmine) - Family: *Rubiaceae*; native to China; growth habit: evergreen shrub (2–6 feet); dark green glossy leaves; white flowers with fragrance (4 inches in size); and reddish-brown ovate fruits (1.4–3.5 cm in size). Major active constituents: iridoid glycosides (geniposide: 5–6%), crocin, flavonoids, and triterpenoids; microscopic examination reveals: collenchyma, calcium. *Gardenia jasminoides* History : has been included in Chinese and Korean pharmacopoeias for thousands of years for its uses as a dye, flavoring agent, and medicine; traditional medicinal herb used in Traditional Chinese Medicine for treating oxidative stress, inflammation, and liver problems [19]. Regional names: Gandharaj (Hindi), Gandharaja (Sanskrit). *Citrullus lanatus*, the watermelon, is a fruit that has become common in many parts of the world with the traditional medicinal use ascribed to it being the fruit's diuretic property and urinary diseases treatment such as kidney stones (renal calculi). Also, several indigenous medical systems have recognized its use as such (Gupta, Singh, & Prasad, 2018; Hassan Abdullahi Dachia, 2020). It is composed of an array of bioactive compounds—citrulline, minerals, flavonoids, steroids, and other antioxidants—that are tieable to kidney health related physiological effects (Gupta et al., 2018; Dachia, 2020) [20].

Experimental studies confirm its potential anti-urolithiatic and diuretic activity. The controlled investigation using in vivo and in vitro methods indicated that watermelon pulp extract was able to significantly diminish the calcium oxalate crystal count in both the kidney and urine of the rat model with urolithiasis. Besides, the extract not only increased urinary pH and volume but also normalized the parameters of urine (that is, calcium, oxalate, citrate), raised creatinine clearance, and prevented crystal aggregation in the solution. Moreover, these effects being similar to those of lowered stone-forming supersaturation and inhibition of pathologic CaOx crystallization indeed validate traditional claims of anti-urolithiatic activity (Evaluation of anti-urolithiatic and diuretic activities of watermelon (*Citrullus lanatus*) using in vivo and in vitro experiments, 2018). Furthermore, the diuretic effect contributes indirectly to the drainage of the urinary tract of stone-forming minerals, which is a critical preventive mechanism against stone growth and retention. The other experimental study showed that putting the calcium oxalate stones in Fresh Watermelon juice led to the fragmentation and structural changes of the stones [21]. *Gardenia jasminoides* (Cape Jasmine) The *Gardenia* plant genus, particularly the *G. jasminoides* species (Zhi Zi in TCM), is an evergreen shrub whose fruit has been utilized in the past for treating various ailments such as inflammation, and liver and kidney diseases (*Gardenia jasminoides*, 2025). The major active ingredient in the plant is geniposide, an iridoid glycoside, which has strong antioxidant and anti-inflammatory effects that exhibit nephroprotective activity in a few experimental disease models (Phatak, 2015; Network pharmacology-based analysis, 2023) [22]. At the same time, there are not many studies providing direct evidence for the anti-urolithiatic property of *Gardenia* but the pharmacological activities of geniposide are causally linked to the development of urolithiasis. Renal oxidative stress and inflammation lead to a cycle of crystal retention and stone growth; thus, the use of compounds that can both act through antioxidants and reduce inflammation may indirectly alleviate the process of stone formation and damage in kidneys. Geniposide and the like have been shown to cut down on the production of reactive oxygen species, ramp up the activity of internal antioxidant enzymes, and tone down the levels of pro-inflammatory signaling molecules such as TNF- α and NF- κ B in a myriad of in vitro and in vivo studies (Network pharmacology-based analysis on geniposide, 2023; Anti-inflammatory activities of *Gardenia jasminoides* extracts, 2019). Such a scenario leads to a renaissance of renal tissue integrity in models of renal injury and toxin exposure (Nephroprotective plants: a review, 2023). The 2023 network study in pharmacology demonstrated that the anti-inflammatory and antioxidant effects of geniposide are multi-target and pathways related to inflammation and oxidative stress are being modulated which is the very support of the case for its role in conditions where renal epithelium injury is the primary factor [23].

Types of kidney stones, based on pathophysiology-based mechanisms :

Watermelon has demonstrated very remarkable anti-urolithiatic activity, especially against calcium oxalate stones, with supportive activity in uric acid and calcium phosphate stones. The high water content and mild diuretic action in *Citrullus lanatus* help increase urine flow, hence reducing crystal supersaturation, aggregation, and renal tubular retention. In calcium oxalate urolithiasis, *C. lanatus* is reported to prevent crystal retention and growth of stones rather than mere inhibition of initial nucleation. In cases of uric acid stones, watermelon exhibits antioxidant properties that decrease renal oxidative injury from urate crystal deposition; however, it does not significantly alkalize the urine. Therefore, its role remains renal protection rather than dissolution of stones. Regarding calcium phosphate stones, increased urine output may be beneficial, although excessive alkalization may lead to the promotion of phosphate stone formation. It is thus considered supportive but not the mainstay. In infection-related struvite stones and in genetic amino acid transport disorders causing cystine stones, *C. lanatus* has little or no efficacy. ***Gardenia jasminoides***, and especially its active constituent geniposide, is of significant activity against calcium oxalate stones and demonstrates supportive activity against



struvite and uric acid stones. Geniposide exerts strong anti-inflammatory and antioxidant activities, which attenuate renal tissue injury induced by crystal-mediated oxidative stress. In the case of struvite urolithiasis, which nearly always involves infection and inflammation of the urinary tract, geniposide's action is devoid of direct antibacterial properties but improves the renal microenvironment by decreasing inflammation; therefore, this is considered an adjunctive rather than curative role. In uric acid stones, geniposide decreases oxidative renal damage induced by urate crystals, without a significant modification of urinary pH; thus, its effect remains merely supportive renal protection. Like watermelon, *G. jasminoides* is ineffective in cystine stones because these are caused by inherited defects in amino acid transport, requiring specific therapeutic approaches[24].

Mechanism of *Citrullus lanatus* (watermelon) and geniposide (*Gardenia jasminoides*):

Urolithiasis or kidney stone disease is defined as the presence of mineral crystals within the urinary tract, mainly calcium oxalate, which occur as a result of the supersaturation of the crystal-forming constituents, oxidative damage, as well as inflammatory damage to the epithelium of the kidneys [25]. *Citrullus lanatus* or watermelon has already been proven effective in reducing the risk of urolithiasis through the inhibition of calcium oxalate crystal formation, the increase of the pH and volume of the urine (diuretic effect), the normalization of the altered components of the urine (phosphate, oxalate, calcium, citrate), as well as the inhibition of crystal aggregation [26]. These are attributed to the antioxidant and anti-inflammatory effects of the phytochemicals of plants classified under this genus, which include the flavonols of the watermelon seed in reducing oxidative damage in kidney injuries caused by ethanol through the increase of superoxide dismutase activity of the catalytic enzyme of glutathione peroxidase [27]. The inflammatory cytokines TNF-alpha & IL-1 beta are reduced as well. Additionally, it has been proven in numerous studies the general antioxidant effect of the extracts of *C. lanatus* in the oxidative stress model through the increase of glutathione levels [28]. *Gardenia jasminoides*, especially through its iridoid glycoside geniposide, has anti-inflammatory, antioxidant, and nephroprotective properties that can indirectly counteract factors that contribute to stone formation. Geniposide is anti-inflammatory by suppressing the production of pro-inflammatory cytokines (such as TNF-alpha, IL-6, and IL-1 β) and inhibiting pathways such as NF- κ B and TLR4 signaling, which are engaged in epithelial inflammation and injury. Additionally, it suppresses oxidative stress and apoptosis through models of epithelial injury (such as that produced by septicemia-induced acute epithelial injury) by enhancing protective pathways (such as activating PPAR γ) and suppressing ROS production, inflammation, and apoptosis, and these mechanisms contribute importantly to maintaining epithelial integrity against crystal formation and adherence and retention during the development of urolithiasis [29]. The antioxidative effect of geniposide is supported by its activation of protective mechanisms (such as Nrf2/HO-1 pathway) against oxidative injury, and a number of in vitro and vivo studies have verified its ability to diminish both oxidative stress and inflammation. Watermelon (*C. lanatus*) and gardenia (*G. jasminoides*, geniposide) work synergistically, as they address mutually complementary mechanisms: watermelon is involved in physicochemical stone inhibition by diuretic and anti-crystallization effects, as well as general antioxidant mechanisms, while geniposide adds cellular protection by inhibiting inflammation, oxidative damage, and apoptosis of the kidneys, which contribute further to stone retention and impaired kidney function. These mechanisms cooperate with natural processes of stone disease, in which both supersaturation of urine and inflammation of the kidney play pivotal roles, thereby suggesting a rationale for combined use of these plant compounds [30].

PHYTOCHEMICAL	SOURCE PLANT	STUDY TYPE	EXPERIMENT MODEL	KEY FINDINGS	References
Quercetin	Tribulus terrestris, alliums pp.	In vitro and In vivo	CaOx crystallization assay ; ethylene glycol-induced urolithiasis in rats	Reduced calcium oxalate deposition and renal damage	Moeini et al.,2018; Ahmad et at., 2022
Rutin	Fagopyrum esculentum, Citrus spp.	In vivo	Ethylene glycol-induced hyperoxaluria model	Decreased stone formation and lipid peroxidation	Ghudasara et al., 2023
Diosgenin	Tribulus terrestris, dioscorea spp.	In vitro	Calcium oxalate nucleation and aggregation assay	Significant inhibition of coax crystal formation	Patel et al., 2016
Tannic acid	Various medicinal plants	In vitro	CaOx crystallization assay	Reduced crystal size and aggregation	Patel et al., 2016
Silibinin	Silybum marianum	In vitro & In vivo	Oxalate-induced renal injury model	Protects renal epithelial cells from oxalate damage	Saleem et al., 2023
Geniposide	Gardenia jasminoides	In vitro / in vivo (indirect)	Oxidative stress & inflammation models	Reduces renal inflammation and oxidative injury	Chen et al., 2020



Crocin / Crocetin	Gardenia jasminoides	In vitro	Free radical scavenging assays	Potential inhibition of stone-related oxidative damage	Zhang et al., 2022
Citrulline	Citrullus lanatus	In vivo (indirect)	Renal perfusion and oxidative stress models	Supports renal function and reduces oxidative stress	Perkins-Veazie et al., 2001

Safety and Toxicity

Citrullus lanatus Safety : Fresh watermelon juice does not exhibit any toxicity, according to the in vitro study for anti-lithiatic activity, and in citations such as Olaniyan et al. (2016), who safely utilized rabbits without adverse effects on creatinine, urea, and uric acid. As a dietary ingredient, there are only concerns for gastrointestinal disturbances for massive intake of fructose and/or potassium in renally compromised individuals. However, tradition and diuretic purposes confirm safety[31][32]. **Gardenia jasminoides Safety :** There are no data for toxicity and safety of geniposide and Gardenia jasminoides preparations in the background of urolithiasis. The general pharmacology for certain preparations describes iridoids, including geniposide, to be unaltered in gastric fluid, widely safe in traditional practice, though hepatotoxicity can be elicited with massive doses [33][34].

Discussion and limitations: The current review focuses on the potential role of Citrullus lanatus and Gardenia jasminoides as adjunct anti-urolithiatic drugs, based mostly on their diuretic, antioxidant, and anti-inflammatory activities. C. lanatus has marked potency against calcium oxalate stones based on its ability to decrease urinary supersaturation and inhibit crystal retention and growth, and its lack of direct inhibition of nucleation. The antioxidant property also plays an ancillary role in renal protection, based on its ability to counteract the antioxidant-induced toxicity of oxalate. The lack of marked urinary alkalization prevents its potential as an urinary stone dissolver for uric acid stones and restricts its role to accompanying renal protection. Gardenia jasminoides, specifically the bioactive compound geniposide, demonstrates potent anti-urolithic activity via modulation of oxidative stress and inflammation. Its renoprotective effect on renal tissue injury makes it potentially advantageous over calcium oxalate and urate crystals. Regarding the treatment of struvite stones, which are largely infectious in nature, geniposide lacks direct antibacterial properties but may help enhance the renal environment by inhibiting inflammation and is largely an adjunct treatment. Regarding cystine stones, which are genetically associated with cystinuria and require specifically tailored pharmacological and/or surgical management, these two herbs have been demonstrated to be less irrelevant and not necessarily beneficial. **Limitations:** Despite the encouraging findings, some existing limitations still exist. The greatest amount of existing information has originated from in vitro studies and animal studies, with relatively few studies available to confirm their efficacy and safety for human consumption. The varying modalities of extraction and differing levels of plant-specific phytochemistry also make standardized comparison challenging. Also, the minute mechanisms of crystal inhibition, renal protection, and anti-inflammatory activities have still not been completely explained. The more supportive role of these drugs, especially within the areas of infection and genetic stones, limits their potential utility as a primary form of treatment. Also, their safety and drug interactions are still relatively uninvestigated.

Future studies : Further studies are warranted, such as well-designed clinical trials that can demonstrate the anti-urolithiatic efficacy of C. lanatus and G. jasminoides in different stone types. Standardization of extracts and elucidation of key bioactive principles will be necessary to ensure reproducibility and therapeutic consistency. Studies on their mechanism of action at the molecular level can help explain the exact functions they play in modulating oxidative stress, inflammation, and crystal-cell interactions. Evaluating combinations for synergism with conventional therapies could lead to improved treatment outcomes and reduced recurrence rates. In addition, investigations related to novel formulations and delivery systems may enhance the plants' bioavailability and clinical effectiveness in positioning them as valuable adjuncts in the comprehensive management of urolithiasis.

Conclusion :

Conclusion of Combined Use Fresh juice from Citrullus lanatus dissolves calcium oxalate stones in vitro in less than a day, changing crystalline to amorphous forms through XRD, SEM analysis, and pH/EC changes. Although there is no direct evidence of urolithiasis, Gardenia jasminoides (rich in geniposides) has anti-inflammatory, antioxidant, and diuretic properties that may help dissolve and expel stones. Possibility of Synergy Watermelon's direct fragmentation combined with Gardenia's iridoids for neuroprotection and inflammation reduction may increase efficacy, but dose optimization, safety testing, and in vivo validation are necessary. There is no interaction or toxicity information in the files.

REFERENCES:

1. Khan, S. R., Pearle, M. S., Robertson, W. G., et al. (2016). Kidney stones. *Nature Reviews Disease Primers*, 2, 16008.
2. Coe, F. L., Evan, A., & Worcester, E. (2005). Kidney stone disease. *The Journal of Clinical Investigation*, 115(10), 2598–2608.
3. Worcester EM, Coe FL. Calcium kidney stones. *N Engl J Med*. 2010;363:954–963.



4. Brenner BM, Rector FC. The Kidney, 10th ed. Philadelphia: Saunders; 2015. (Chapters on stone pathophysiology).
5. Shiju TM, Rajesh NG, Viswanathan P. Protective effect of Citrullus lanatus extract against ethylene glycol-induced nephrolithiasis. *J Pharm Res.* 2013;6(3):362–366.
6. Bhalodia YM & Sheth NR. Preventive effect of Citrullus lanatus on kidney stone formation. *Int J Pharm Pharm Sci.* 2015;7(4):168–172
7. Liu Y, Chen Y, et al. Natural products as inhibitors of kidney stone formation. *Front Pharmacol.* 2021;12:699281.
8. Scales CD Jr, Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. *Eur Urol.* 2012;62(1):160–165.
9. Romero V, Akpınar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Rev Urol.* 2010;12(2–3):e86–e96.
10. Lieske JC, Rule AD, Krambeck AE, et al. Stone composition as a function of age and sex. *Clin J Am Soc Nephrol.* 2014;9(12):2141–2146.
11. Alelign, T., & Petros, B. (2018). Kidney stone disease: An update on current concepts. *Advances in Urology*, 2018, Article 3068365.
<https://doi.org/10.1155/2018/3068365>
12. Bahmani, M., Baharvand-Ahmadi, B., Tajeddini, P., Rafieian-Kopaei, M., & Naghdi, N. (2016). Identification of medicinal plants for the treatment of kidney and urinary stones. *Journal of Renal Injury Prevention*, 5(3), 129–133.
<https://doi.org/10.15171/jrip.2016.27>
13. Bnouham, M., Merhfour, F. Z., Legssyer, A., & Mekhfi, H. (2014). Antilithiasic activity of selected medicinal plants: A review. *Journal of Ethnopharmacology*, 151(3), 921–938.
<https://doi.org/10.1016/j.jep.2013.12.022>
14. International Journal of Molecular Medicine : 21 Apr 2024 — The pathogenesis of kidney stones is very closely associated with damage to renal tubular cells and the adhesion of crystals.
15. Joshi S, et al. Oxalate-induced apoptosis in renal epithelial cells involves mitochondrial pathway activation. *Kidney Int.* 2005;68(4):1543–1553.
16. Mulay SR, et al. Calcium oxalate crystals activate NLRP3 inflammasome and trigger IL-1 β -mediated renal inflammation. *J Clin Invest.* 2013;123(1):236–246.
17. Linkermann A, et al. Regulated necrosis and kidney injury. *Nephrol Dial Transplant.* 2014;29(1):12–18.
18. Taguchi K, et al. M1 macrophages promote calcium oxalate crystal deposit formation and kidney injury. *Kidney Int.* 2018;94(3):555–567.
19. Kirejczyk JK, et al. Citrate as a natural inhibitor of calcium stone formation. *Urol Res.* 2014;42(1):41–46.
20. Zhao H, et al. Metabolic reprogramming in kidney stone disease with focus on TCA cycle intermediates. *J Mol Med.* 2021;99(1):97–111.
21. Evaluation of anti-urolithiatic and diuretic activities of watermelon (*Citrullus lanatus*) using in vivo and in vitro experiments. (2018). *Biomedicine & Pharmacotherapy*, 97, 1212–1221. <https://doi.org/10.1016/j.biopha.2017.10.162>
22. Gupta, A., Singh, A., & Prasad, R. (2018). A review on watermelon (*Citrullus lanatus*). *Journal of Pharmacognosy and Phytochemistry*, 7(3), 2222–2225.
23. Therapeutic effects of Chinese herbal medicines for treatment of urolithiasis: A review. (n.d.). PMC. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/articles/PMC10715892/>
24. Kampo herbal extracts containing *Gardeniae Fructus* (*Gardenia jasminoides*) have inhibited calcium oxalate monohydrate crystal aggregation and adhesion, a key step in urolithiasis pathology. Effect of Kampo extracts on urinary stone formation (incl. *Gardeniae Fructus*)
25. Evaluation of anti-urolithiatic and diuretic activities of watermelon (*Citrullus lanatus*) using in vivo and in vitro experiments. (2018). *Biomedicine & Pharmacotherapy*, 97, 1212–1221. <https://doi.org/10.1016/j.biopha.2017.10.162>
26. Flavonoid-rich extract from *Citrullus lanatus* seed attenuated ethanol-induced kidney injury in Wistar rats (2023). *Pharmacological Research – Modern Chinese Medicine*. <https://doi.org/10.1016/j.prmcm.2023.100236>
27. Antioxidative and antidiabetic activities of watermelon (*Citrullus lanatus*) juice on oxidative stress... (n.d.). PubMed. <https://pubmed.ncbi.nlm.nih.gov/26759513/>
28. Protective effect and possible mechanisms of geniposide for ... (n.d.). PMC. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10559851/>
29. Geniposide: Anti-hyperuricemic & nephroprotective effect (n.d.). ScienceDirect. <https://www.sciencedirect.com/science/article/abs/pii/S1756464619302671>
30. Ning Li et al. (2019). Updated Pharmacological Effects, Molecular Mechanisms, and ... *Molecules*. <https://www.mdpi.com/1420-3049/27/10/3319>
31. *Citrullus lanatus* Key References Haleem AM et al. Antilithiatic effect of watermelon (*Citrullus lanatus*) juice on calcium oxalate kidney stones. *Veterinary Medicine and Public Health Journal.* 2021;21:25-30. (Primary study; no toxicity reported).
32. Olaniyan MF et al. Changes in Creatinine, Urea, Glutathione-S-Transferase and Uric Acid Levels in Acetaminophen Extra Overdosed Rabbits Treated with Watermelon Juice (*Citrullus lanatus*). *European Academic Research.* 2016;4(8):6613-6627. (Safe in rabbits; reduced toxicity).



33. Omigie IO & Agoreyo FO. Effects of Watermelon (*Citrullus Lanatus*) Seed on Blood Glucose and Electrolyte Parameters in Diabetic Wistar Rats. *Journal of Applied Sciences and Environmental Management*. 2014;18(2):231-233.
34. Gardenia jasminoides Key References Akash A et al. A Review on pharmacological and phytochemical profile of Cape jasmine (*Gardenia jasminoides*). *Journal of Pharmacognosy and Phytochemistry*. 2025;14(3):708-714. (Geniposide stable in gastric fluid; no specific urolithiasis toxicity).
35. Liping C et al. *Gardenia jasminoides* Ellis: Ethnopharmacology, phytochemistry, and pharmacological and industrial applications. *Journal of Ethnopharmacology*. 2020;257:112829.

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