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MOLECULAR INSIGHTS INTO OXIDATIVE STRESS–INDUCED CALCIUM OXALATE UROLITHIASIS AND EMERGING PHYTOTHERAPEUTIC TARGET

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Abstract

A common urological condition called urolithiasis is characterized by development of stones in urinary tract that are primarily made of calcium oxalate. Super saturation, crystal development, nucleation, aggregation, retention in renal tissues are some of the steps in the stone formation process. By causing damage to the renal epithelium and encouraging crystal adhesion, oxidative stress is a major factor in this illness. By this variety of molecular mechanisms, reactive oxygen species and inflammatory mediators further quicken the course of disease. The interest in plant based remedies as substitute treatments has grown. Pharmaceuticals and surgical procedures are current therapeutic approaches; however, they are frequently associated with side effects and recurrence. Therefore, interest in plant-based remedies as substitute treatments has grown. Through their diuretic, anti-inflammatory, and antioxidant properties, medicinal herbs have antiurolithiatic effects. Furthermore, they increase the composition of urine and lessen the production of crystals. In experiments, a number of herbal remedies have demonstrated encouraging outcomes. Phytopharmacological methods could therefore be safer and more effective ways to treat urolithiasis.

Keywords: *Urolithiasis, Calcium oxalate, calculi, supersaturation, struvite*.

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1. INTRODUCTION

Urolithiasis is a complex urological disorder derived from the Greek words 'ouron' (urine), 'oros' (flow), and 'lithos'(stone) [1]. It is condition characterized by calcifications in kidney, bladder, or urethra. Studies indicate that calcium oxalate (CaOx) is the most prevalent component of stone [2]. Urolithiasis, or the production of urinary stones, affects nearly all populations globally. It produces severe back pain and can lead to consequences including pyelonephritis or acute renal failure [3]. The incidence has grown during the previous 25 years. Poor eating habits (high in sodium and protein, insufficient fluid supply), obesity, hypertension, environmental pollution, accelerated life, and unregulated multivitamin and nutritional supplement use all contribute to increased morbidity [4]. Urolithiasis, or kidney stones, is a common urinary tract disease that causes significant morbidity. Stone formation is a painful urologic illness that affects around 12% of world's population, with a recurrence rate of 70-81% in men and 47-60% for women. It has been estimated that at least 10% of population in industrialized countries suffers from urinary stones [5]. Calculi in the urine can cause blockage, hydronephrosis, infection, and bleeding in the urinary tract system. Surgical procedures, lithotripsy, and high-power lasers were commonly utilized to remove calculi [6]. Even though urolithiasis has known since antiquity, many investigators continue to strive to understand how calcium oxalate forms renal stones. There is ongoing debate regarding the physiochemical processes by which different lithogenic salts in urine precipitate, grow, aggregate, and concretize to form stones. Additionally, recent studies have pointed out the role that crystals and renal tubular epithelial cells play in production of stones, in particular binding or endocytosis of crystals by cells [7].

This review comprehensively summarizes the epidemiology, pathophysiology, classification, particular emphasis on molecular mechanisms involved in stone formation and pharmacological evaluation of medicinal plants as potential antiurolithiatic agents.

1.1 Types of renal stones [8-10]

Urolithiasis is a common and recurrent urological disorder characterized by formation of solid crystalline calculi within kidneys or other parts of the urinary tract due to super saturation of urine with stone-forming

constituents. The process involves nucleation, crystal growth, aggregation, and storage in the tubules of the kidneys. Based on chemical compositions, kidney stones are broadly classified into calcium stones (calcium oxalate and calcium phosphate) and uric acid stones (shown in Figures 1 & 2). Among these, calcium stones account for approximately 70 – 80 % of cases. Each type is associated with specific metabolic abnormalities, urinary pH alterations, dietary factors, infections or genetic defects, which influence their formation, clinical presentation, and management.

Figure 01: Types of Kidney Stones

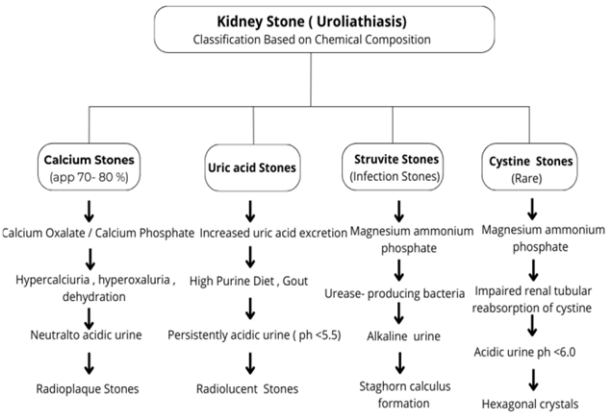

Figure 02: Classification of kidney stones based on chemical composition

1.2 Epidemiology of Uroliathisis

The epidemiology of urolithiasis varies by area and time due to socioeconomic factors that affect the site and physical-chemical composition of the calculi. Adult reno-ureteral calculosis with calcium oxalate and phosphate is more common in economically developed countries, where the prevalence rate is between 4% and 20% and the yearly hospitalization rate is 0.03 to 0.1% [11].

Prevalence ranges from 7% to 13% in North America, 5% to 9% in Europe, and 1% to 5% in Asia [12]. The incidence, composition, and prevalence of calculi vary globally and have evolved over the past few decades. Several factor influences the uroliathiasis, including as age, gender, dietary habits, fluid consumption, climate, occupation and education level, socioeconomic situation, racial or national distribution, hereditary and metabolic diseases, are reflected in the variations across nations [13]. In India, urolithiasis affects about two million people annually, and certain regions have been dubbed "stone belts" [14].

The prevalence of kidney stones varies by gender and ethnicity, with Asian women having the lowest prevalence. Uranium workers in eastern Tennessee (18.5%) and adults in northeast Thailand (16.9%) have high prevalence rates, indicating that exposure to high-risk conditions can lead to kidney stones. Adolescent females have a higher frequency of kidney stones than boys, indicating a different gender trend in pediatric nephrolithiasis. Prepubertal children do not show significant sex-based variations in incidence [15].

1.3 Pathophysiology of Calcium Stone Formation

There is ongoing discussion over the physiochemical processes by which different lithogenic salts in urine precipitate, develop, aggregate, and concretize to create stones. Additionally, the "interaction among crystals and renal tubular epithelial cells - comprising adhesion or endocytosis of crystals by cells- has been emphasized in recent research as an important element in development of stones. Furthermore, a number of studies have shown that damage to renal tubular epithelial cells in crystal-cell contacts is caused by pre-existing cell injury easier to occur.

In accordance with current studies, nephrolithiasis should be recognized a systemic disease owing to how multiple risk variables interact. Modifiable risk factors for nephrolithiasis involve body mass index (BMI), hydration and calcium intake, and intake of sugar-sweetened beverages. The study suggests that central obesity, type 2 diabetes, gout, dietary sodium, fructose intake, and higher temperatures are risk factors for nephrolithiasis. The researchers identify potential protective variables for nephrolithiasis, including coffee/alcohol/beer intake, dietary calcium, and the DASH" diet. To offer an epidemiological basis for treating and preventing nephrolithiasis [16].

Theories of fixed and free particles: It is believed that for kidney stones to grow, crystals must first form in the tubular fluid, then they must be retained and accumulate in the kidney. There are currently three stone creation and growth pathways under investigation. The free particle model is the first hypothesis; the fixed particle model is the second; and Randall's plaque hypothesis is the third pathway [17].

1.4 Mechanism of uroliathiasis

1. Pathway of Free Particle Formation (Free-Particle Theory)

Through homogeneous nucleation, crystals are directly formed in supersaturated tubular fluid in the free particle pathway. Nucleation happens spontaneously without a pre-existing substrate when the concentration of urine solute surpasses the formation product (FP). These free-floating crystals grow and aggregate as they migrate through aggregation of the nephron.

The crystals can expand substantially to become clogged in the distal nephron segments or renal collecting system prior to being flushed out, blocking the flow and functioning as a nidus for further crystal aggregation. Diseases including cystinuria, enteric hyperoxaluria, and medullary sponge kidney have a particular connection with this mechanism [15].

2. Fixed-Particle: Plaque Mechanism

Randall Plaque Pathway: The main mechanism in idiopathic calcium oxalate stone formers is Randall plaque route. It starts when crystals of calcium

phosphate as or apatite, become embedded in the basement membrane of thin loops of Henle thin loops of Henle's basement membrane. Randall plaques are created when these interstitial deposits grow and spread into the papillary interstitium beneath the urothelium. Urine might reach the plaque when the urothelium is damaged. Amorphous apatite and urinary proteins (such osteopontin and uromodulin) cover the plaque, encouraging further mineral deposition. On this plaque surface, calcium oxalate crystals then develop and eventually enlarge into stones that are clinically noticeable [17].

3. Plug Formation Pathway (Fixed Particle: Intratubular Plug Mechanism)

Crystals occur within the nephron lumen via the plug pathway, generally at epithelial damage sites. These crystals bind to tubular epithelial cells and form intratubular plugs, especially in the inner medullary collecting ducts (IMCDs) and Bellini ducts. Over time, these plugs clog and widen tubules, extending into the renal collecting system and acting as attachment points for stone development. This mechanism is commonly observed in calcium phosphate stone formation (brushite, carbonate apatite), cystinuria, primary hyperparathyroidism, and after obesity bypass surgery.

Elevated urine pH leads to calcium phosphate super saturation, which promotes plug growth. Tubular blockage can prevent urine acidification, creating a vicious cycle that accelerates calcium phosphate crystallization and stone development [18].

1.5 Stages of stone formation

The development of crystalline particles that follow elevated urine super saturation leads to the development of renal stones, formation of stone mainly follows six steps mainly: Urinary super saturation, crystal nucleation, crystal growth, crystal aggregation, crystal cell interaction, crystal retention [19].

1) Urinary Super saturation

When a solvent has dissolved a solute up to a given concentration but is no longer able to dissolve it, the solution is said to be saturated. Adding more solute than the solvent can dissolve creates a supersaturated solution, leading to crystallization at the same temperature and pH. The thermodynamic solubility product (Ksp) is the concentration at which a solution becomes saturated and crystallization begins. Super saturation in stone formation refers to ratio of urine calcium, uric acid, oxalate, cystine concentration to solubility. Ratio of urine calcium, oxalate, uric acid, or cystine concentration to its solubility is a representation of super saturation, the force that propels more crystallization and following stages of stone formation. For the nucleation and growth of crystals to generate calculi, the super saturation level must be greater than 1; otherwise, crystals will dissolve and no stone formation will take place. Patients with frequent episodes of stones likely to discharge more supersaturated urine than those without stones (Shown in Figure no 3) [20].

2) Crystal nucleation

The first step in crystallization is nucleation, which can happen homogeneously or heterogeneously and is the process by which solute molecules scattered in a solvent start to group together. A high level of super saturation relative to the mineral in concern is needed for homogeneous nucleation; in vitro, this happens usually in a pure solution free of particles and in a chemically inert container. In contrast, much more plausible process for crystal initiation in urine is heterogeneous nucleation. Within containers lined with chemically active cell surfaces, the activity can take place in presence of particles made up of proteins, other organic polymers, crystals of another mineral. In comparison with homogeneous nucleation, heterogeneous nucleation requires less super saturation to initiate crystals (Shown in Figure no 3) [21].

3) Crystal growth

After a certain size, adding crystal components to a crystal nucleus lowers its free energy and relative super saturation remains above. We refer this crystal growth. Crystal growth is necessary for particle and stone production. Every stage of stone production involves crystal growth and aggregation. Human serum albumin, a1-acid glycoproteins like a1-microglobulin, 2-HS glycoprotein, retinol binding protein, transferrin, and CaOx crystals made from entirely human urine have a crystal surface binding material that inhibits CaOx crystal growth (Honda et al.). Prothrombin and Tamm-Horsfall glycoprotein. However, for CaOx, most common stone component, importance of crystal formation is questioned. Even at an unrestricted rate of 2 mm/min, it is improbable that single particle can reach pathophysiologically relevant size through crystal development alone due to the sluggish rate of CaOx crystal growth as well as short tubular fluid transit time through kidney. Because of its regular excretion, fibronectin (FN), a multifunctional a2-glycoprotein present in extracellular matrix and body fluids, has a slight inhibitory effect on CaOx crystal formation. FN suppresses CaOx crystal formation by 9.9% at dose of 0.5mg/mL ((Shown in Figure no 3) [22].

4) Crystal Aggregation

Urinary stones are formed when many crystals come together. This process is known as aggregation. Researchers think that aggregation is a significant step in creating these stones, but they do not know exactly how it works. When tiny particles get smaller the forces that keep them stuck together become more important than gravity. Intermolecular forces dominate over gravitational at microscopic scales, significantly influencing crystal aggregation. This means that whether or not the tiny crystals in our urine stick together or stay separate depends a lot on these forces. There are six ways that these tiny crystals stick together and they range from weak to strong. These are: Attraction, Vander Waals forces, Liquid bridges, Capillarity, Viscous binding, Solid bridges.

Liquid bridges and capillarity are probably not that important in our urine because the particles are completely covered in fluid. Electrostatic forces actually

push the crystals apart in our urine because of the charge on the surface of the crystals. Proteins in our urine can coat the crystals and act like a kind of glue sticking them together with viscous binding. Solid bridges are the way that crystals can stick together but they can only form when the crystals are really close to each other and are stuck together with other forces.

Another important thing to know is that urinary stones are just as dense, as crystals. This means that the crystals cannot just be loosely stuck together to form a stone. After the crystals aggregate, they have to become more compact and solid over time, which is called densification. This process makes the aggregate become more dense and solid. Urinary stones and aggregation are still not fully. Researchers are still trying to figure out how aggregation and densification work together to form urinary stones (Shown in Figure 03) [23].

5) Crystal cell interaction

The process "of crystal-cell interaction" is intricate and involves numerous unidentified mechanisms. Crystallization may result from urinary super saturation. Renal tubular epithelial cells form and absorb crystals. Attachment of crystals to renal tubular cells through endocytosis is referred to as "crystal-cell interactions." COM crystals rapidly adhere to microvilli on cell surface and are subsequently absorbed, according to research on crystal-cell interactions in culture. According to Khan et al., development of urinary stone disease is significantly influenced by crystal-cell interaction.

It has been improbable that CaOx crystals could grow large enough to be retained in renal tubules, suggesting that crystal-cell interactions might be one of first steps in kidney stone formation. There were several published reports on crystal attachment. Crystals are held in kidneys via adhesion to renal epithelial cells, according to research utilizing tissue culture and animal models. Kok and Khan discovered crystal attachment to proximal tubule brush border in rats. The first phases of experimental induction of CaOx urolithiasis include crystalluria, hyperoxaluria, kidney deposition. Two specific urine macromolecules prevent the attachment of CaOx crystals. Urine contains a number of poly anionic compounds that stop COM crystals from adhering to the cell membrane, such as citrate, glycoproteins, and certain glycosaminoglycans. Compounds that inhibit COM crystal adhesion to cells frequently have polyanionic characteristics. They claimed that while polyanions in tubular fluid might cover crystals as well as stop them from sticking to tubular cells, the cells use a distinct set of signals to regulate their response to crystals that do" stick (Shown in Figure 03) [24].

6) Cell retention

Crystals must deposit and stay in the kidneys in order for stones to develop. This requires crystal interaction with the epithelial lining of the kidney tubules, which is dependent on interactions with the renal tubular epithelium rather than urinary crystallization inhibitors. Because of their antiadherent surfaces, distal tubules, collecting ducts, ureters, bladder, urethra usually prevent crystal adhesion. Damage to these surfaces, however, may encourage retention. Crystal attachment in injured kidneys may entail the expression of the CD44 receptor and its ligands, hyaluronic acid and osteopontin, on surface of epithelial cells (Shown in Figure 03) [25].

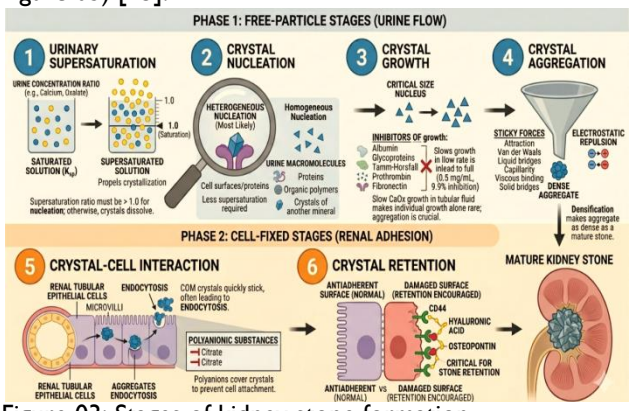

Figure 03: Stages of kidney stone formation

1.6 Promoters and Inhibitors of the kidney stone26-28

Molecules that raise SS required to start nucleation, slow down crystal development and aggregation, prevent secondary nucleation were known as inhibitors. Promoters, on the other hand, lessen the supersaturated solution's formation product. It has been suggested that an imbalance between elements that promote and hinder urination is more significant in development of urinary stones than disturbance of any one molecule. These materials consist of proteins, glycosaminoglycans, and inorganic compounds. Physiochemical conditions may be altered to encourage the production of stones due to improper functioning and/or concentration of these chemicals in the urine (Shown in Table 01).

Table 01: Promoters and inhibiters of kidney stones

Sl. No	Promotors	Pathophysiological mechanism
1)	Uric acid or urate	• Has an inhibitory effect on urine-based compounds. • Supports the heterogeneous nucleation of monosodium urate or uric acid. • There is an increase in calcium oxalate binding to cells.
2)	pH	• A highly acidic pH promotes calcium oxalate crystallization. • The formation of uric acid crystals increases. • Calcium phosphate precipitates are formed, which promotes the secondary nucleation of calcium oxalate.
3)	Volume	Increase crystal growth
4)	Hypercalciuria	• Reduced renal calcium reabsorption. • Increases calcium

		movement from the bones. • Increases urine super saturation, which leads to calcium crystallization.
Sl. No	**Inhibitors**	**Pathophysiological mechanism**
1)	Citrate	• Reduces calcium oxalate super saturation and prevents crystal • Aggregation and adhesion to the urinary epithelium by forming calcium complexes.
2)	Basic pH	• Decreases cysteine and uric acid stone elevation
3)	Magnesium	• Inhibits of growth (and presumably nucleation) of crystals and aggregation. While for attachment of calcium oxalate crystals, its supra-physiologic concentrations are required.
4)	Glycoprotein	• Inhibits spontaneous nucleation from metastable solutions and growth of preformed crystals.
5)	Pyrophosphate	• Both calcium oxalate and calcium phosphate crystals formation is inhibited.

1.7 Causes of Disease

Hereditary Causes of Kidney Stones and Chronic Kidney Disease [29].

1) Deficiency of adenine phosphoribosyltransferase (APRT): This leads to excessive production of 2, 8- dihydroxydenine 2, 8-dihydroxyadenine (DHA). It causes crystalline nephropathy and radiolucent kidney stones.

2) Cystinuria

Inadequate tubular reabsorption of cysteine and it causes the development of recurrent cystine stones.

3) Dental illness

An X-linked tubular disease linked to calcium stones, nephrocalcinosis, and hypercalciuria

4) Nephrocalcinosis, hypercalciuria, and familial hypomagnesemia (FHHNC)

Hypercalciuria and renal magnesium wasting. It causes kidney stones and nephrocalcinosis.

5) Hyperoxaluria primary (PH).

Overproduction of oxalate because of enzyme flaws. It Causes kidney damage and the development of calcium oxalate stones.

Other causes [30-33]

1) Low urine volume

Dehydration might result in less urine which Increases the risk of kidney stones

2) Diet

Eating a diet high in animal protein causes the body's acid levels and urine to rise. An atmosphere that is highly acidic can facilitate development of calcium oxalate and uric acid stones.

Caffeine is one of the primary ingredients in caffeinated drinks, including tea, coffee, soft drinks, and energy drinks. It has conflicting effects on kidney stone risk, according to earlier retrospective and prospective investigations.

3) Bowel Conditions

Prolonged diarrhoea and operations such as gastric bypass surgery increase risk of developing calcium oxalate kidney stones

4) Medical conditions

Obesity increases risk of kidney stones. Gout, Chronic diseases: diabetes and hypertension, Cystinuria, Distal renal tubular acidosis, aberrant parathyroid gland etc.

1.8 Role of oxidative Stress on uroliathiasis

The imbalance between ROS and the body's antioxidant defence systems is referred to as oxidative stress (OS), and it plays a role in development and progression of several kinds of ailments, including kidney stones. Analytical analysis of urine from kidney stone patients points to a possible connection between idiopathic stone development and ROS-induced renal cellular damage and inflammation. NADPH oxidase is main source of "reactive oxygen species (ROS)" in kidneys during pathophysiology of nephrolithiasis, but mitochondrial ROS production is a major secondary cause of renal damage linked to kidney stone formation [34].

These molecules are essential for a number of signalling cascades and regulatory functions, including activation or inactivation of regulatory biomolecules and their proliferation. ROS regulates NF-jB, AP-1, and c-fos, c-myc, and c-jun transcription. The primary ROS in cells are superoxide anion, hydroxyl radical, hydrogen peroxide. Most superoxide anions are produced by NADPH, xanthine, and heme oxygenase in the mitochondrial respiratory chain. When oxygen is sequentially reduced, superoxide anion, a precursor to hydrogen peroxide and hydroxyl radical, is produced initially. Increased ROS generation and/or decreased endogenous antioxidant capacity are the causes of oxidative stress (OS) that can lead to inflammation and damage [35,36].

Animal studies show that hyperoxaluria causes ROS generation, oxidative stress, and tubular epithelial damage. This involves mitochondria, endoplasmic reticulum, and activation of NADPH oxidase. Increased expression of immune and inflammation-related genes and proteins, comprising osteopontin and monocyte chemoattractant protein-1 (MCP-1) [37]. Oxidative stress is present in all CVDs, comprising diabetes, hypertension, atherosclerosis, and myocardial infarction. Oxidative stress inactivates NO, which pericytes need for endothelial function. This disrupts arterial relaxation, promotes endothelial transcytosis, and up-regulates pro-inflammatory molecules and pathways including

MCP-1, NF-κB, TGF-β, and MAPK. Oxidation of NO leads to the production of highly active ONOO−, leading to increased oxidative stress. Ang II primarily activates the AT1 receptor to activate kidney ROS-generating NADPH oxidase [38].

According to Khan, ROS are created during contacts among crystals and renal cells and can trigger numerous cellular responses. Renal epithelial cells exposed to crystals produce more bikunin, OPN, heparin sulfate, MCP-1, prostaglandin E2, all of which contribute to inflammation and extracellular matrix creation. Calcium oxalate crystal formation in rat kidneys stimulates renin-angiotensin system39. Research suggests that OPN, a highly phosphorylated protein, contributes to stone formation by promoting adhesion, aggregation, and nucleation. OPN is a pro-inflammatory factor that activates mast cells, macrophages, and T cells. These inflammatory cells can cause kidney damage and stones. OPN, which is primarily phosphorylated in kidney stones, plays a significant role in their production and could be a potential target for pharmacological therapy40. Vitamin E antioxidant therapy has been shown to reduce calcium oxalate precipitation in rat kidneys and decrease urinary oxalate excretion in people having kidney stones. Oxalate challenge dramatically lowered the levels of kidney antioxidants vitamin E, ascorbic acid, and glutathione. Vitamin E supplementation after surgical stone removal improved antioxidant levels and reduced oxalate and calcium excretion in the urine. A prior study on antioxidant enzyme levels in rats with stone formation found that all enzyme activity were reduced except for catalase [41].

1.9 Phytochemical and Plant-based therapy for uroliathiasis

Ayurveda medicine in India suggests that "Pashanabheda" group herbs can help treat urinary stones. The Sanskrit term "Pashanabheda" refers to a collection of plants with diuretic and anti-urolithiatic properties. It is believed that 80% of world's population relies on traditional medicine to treat their illnesses. Medicinal plants have long history of utilise and are often safer than manufactured medications. They are trustworthy source for drug discovery [42]. Numerous drugs, such as alkali citrate and thiazide as a diuretic, are utilized to reduce the frequency of hypercalciuria and hyperoxaluria, which lead to the development of calculi; nevertheless, their low tolerability and limited efficacy make them insufficiently promising. It is worthwhile to examine novel pharmacological therapies for treatment of kidney stones due to the limitations of pharmacotherapy and the drawbacks of surgical methods. Urolithiasis can be treated using a variety of medicinal herbs that have diuretic, antispasmodic, antioxidant properties that inhibit crystallization, nucleation, and aggregation of crystals [43].

1.10 Plant with Proven Efficacy

1) *Phyllanthus niruri*: contains antispasmodic, decongestant, antimicrobial, and diuretic properties in addition to its primary litholytic function. Additionally, because it releases more glycosaminoglycans, which form a protein film around the stone, it can stop the enlargement of stones brought on by a continual crystal deposition on the surface. In patients with hyperoxaluria and hyperuricosuria, *Phyllanthus niruri* were reported to reduce urine oxalate and uric acid while increasing magnesium and potassium excretion [44].

2) *Avera lanata*: Male wistar albino rats that had been given calculi (ethylene glycol 0.75% v/v) have been utilised to test the antiurolithiatic potential of two isolated components from A. lanata, quercetin and botulin, by giving 2 mg/kg for 28 days, take b.w/day orally as a test dose, a notable decrease in calculi size and a notable increase in calcium, oxalate, and phosphate excretion. SEM of renal slices showed that treated mice had fewer calculi [45].

3) *Leucas aspera*: *Leucas aspera* (wild) in rat models of ethylene glycol-induced urolithiasis. To induce urolithiasis, rats were fed ethylene glycolated water (0.75% v/v) orally for 28 days. The high levels of ions in urine, blood urea nitrogen, serum creatinine, serum uric acid have been all significantly decreased by *Leucas aspera* (wild). Histopathological and radiological results also demonstrated improvement in kidney architecture following treatment with the plant extract because it contains one or more phytoconstituents, such as saponin and flavonoids, that may be responsible for the antiurolithiatic activity, which could reduce calcium and oxalate deposition in kidney. Traditional use of *Leucas aspera* (wild) as an anti-urolithiatic drug is supported pharmacologically by these findings [46].

4) *Rubia cordifolia*: Show that the HARC can guard against urolithiasis brought on by ethylene glycol since it decreased and stopped the development of urinary stones. Because HARC has an impact on the early phases of stone production, it is useful in preventing the disease's recurrence. This action may be mediated by an nephroprotection, antioxidant, its impact on concentration of risk factors and stone-forming components in the urine [47].

5) *Moringa oleifera*: Drumsticks (Moringaceae) are frequently utilized as phytotherapeutic agents in India. Male Wistar albino rats having calcium oxalate urolithiasis have been used to test the effects of hyperoxaluria and increased renal excretion of calcium and phosphate were outcomes of ethylene glycol feeding. Supplementing with an alcoholic and aqueous *Moringa oleifera* root-wood extract reduced urine oxalate, indicating a regulatory effect on endogenous production. Using aqueous and alcoholic extracts to treat and prevent calculogenic rats' kidney stone formation also significantly reduced [48].

6) *Chenopodium album Linn*: EG-induced increases in urine and plasma levels of calcium, uric acid, phosphorus, urea, creatinine as well as decreases in urine volume, pH, and oxalates were considerably reduced by the 28-day therapy with CAME or CAAE. Additionally, the EG therapy reduced oxalate crystal deposition in kidney and oxalate tissue. Effects of CAME and CAAE have been similar to those of cystone, a

common antilithiatic. Results show that CAME and CAAE have a preventative effect, which may be because they impede crystallization and stone disintegration. Phytochemicals including flavonoids and saponins were thought to be responsible for the impact [49].

7) *Mimusops elengi*: Curative and preventive treatment with "alcohol extract (AIE)" of M. elengi considerably ($P < 0.001$) reduced increased deposition of stone-forming components in kidneys of calculogenic rats. Additionally, it has been found that alcoholic extract of M. elengi significantly ($P<0.001$) reduced MDA while increasing SOD, GSH, CAT. Such findings support the strong antiurolithiatic activity of M. elengi's AIE [50].

8) *Olive oil*: Uric acid, serum urea, creatinine levels have been considerably higher ($p<0.05$) in-group II compared to groups III–VI and I. When olive oil was administered at varying dosages, groups IV and V's increased serum parameters were restored in comparison to group II. Compared to animals with EG-induced urolithiasis (group II), urine and kidney calcium, oxalate, phosphate levels in groups IV–VI have been considerably lower ($p<0.05$). When compared to group II, group V animals demonstrated a notable restorative impact on kidney, urine, and serum parameters [51].

9) *Alcea rosea*: Rats treated with hydroalcoholic extract of *Alcea rosea* roots in both preventive and curative protocols had considerably fewer kidney calcium oxalate deposits than the ethylene glycol group. The increased urine oxalate caused by ethylene glycol was similarly decreased by administering *Alcea rosea* extract. Effect may be caused by the plant's mucilaginous polysaccharides or by its diuretic and anti-inflammatory properties. It might also be connected to a decrease in the concentration of components that cause stones in the urine [52].

10) *Macrotyloma uniflorum*: In India, *Macrotyloma uniflorum Linn.* (Fabaceae) seeds are utilized extensively for their urolithiatic and diuretic properties. Current study examined impact of *Macrotyloma uniflorum* seed aqueous extract (AEMU) on rats' urolithiasis caused by ethylene glycol. 0.75%v/v ethylene glycol has been taken orally for 14 days in order to cause urolithiasis. From day 15 to day 28, curative doses of 400 and 800mg/kg have been given. Reduced the amount of calculus promoters including oxalate, calcium, uric acid, and urea while increasing volume of urine and levels of calculus inhibitors like magnesium and citrate. There was also a decrease in crystalluria in urine. Additionally, the AEMU supplement enhanced kidney's glomerulus activity and prevented degenerative alterations in the kidney [53].

1.11 Mechanism of treatment of phytochemical medicine54-56

The main way that phytochemical medications treat kidney stones is by preventing production, aggregation, retention of crystals in renal tubules. They have diuretic actions to remove stones and function as antioxidants and anti-inflammatory agents to lessen kidney damage. Common processes include decreasing amount of calcium and oxalate in urine, increasing excretion of citrate, decreasing size of stones.

Inhibition of Crystal Formation and Aggregation**:** Flavonoids, saponins, and tannins are examples of phytoconstituents that prevent calcium oxalate crystals from nucleating and growing. Antioxidant and Anti-Inflammatory Action: By lowering inflammation and oxidative stress, which are major causes of stone formation, phytochemicals like quercetin and rutin protect renal tissue. Diuretic Effect: Many plant-based medications enhance urine production, which helps remove small pieces of stone and lowers the concentration of salts that cause stones. Modulation of Urinary Composition: These medications increase inhibitors like citrate while decreasing the excretion of calcium and oxalate. Crystal Phase Modulation: Toxic calcium oxalate monohydrate can be changed into less toxic, more easily passed dihydrate forms by some substances, such as rutin (in nanorod form). Muscle Relaxation: Certain phytochemicals have spasmolytic properties that relax the smooth muscle in the urinary system to make it easier for stones as represented in Figure no: 04).

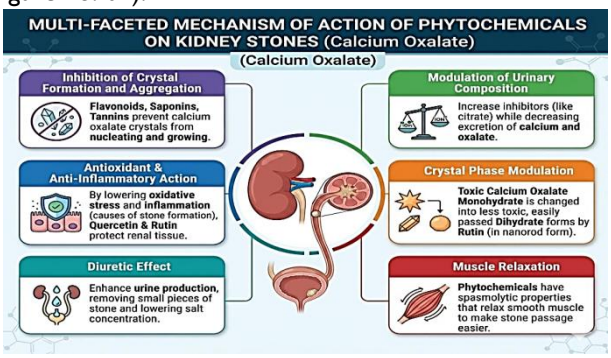

Figure 04: Mechanism of action of phytochemicals on kidney stones

1.12 Synthetic medication for Uroliathiasis For Stone Passage and Symptom Management

Painkillers: Ibuprofen and naproxen sodium are examples of over-the-counter medications that assist ease the discomfort associated with passing a stone.

Alpha-Blockers: Drugs like tamsulosin (Flomax) relax the ureter's muscles, facilitating a quicker and less painful passage of the stone [57].

Prevention and Stone Dissolution.

Alkalinizing drugs: such as potassium citrate and sodium bicarbonate, raise pH of urine that helps dissolve uric acid stones (the only kind that can occasionally be dissolved with medication) and stops new ones from developing. In India, there are several brands of these in syrup form, including Q Citra and Alkazip.

Allopurinol: Allopurinol (brand names include Lopurin and Zyloprim in various markets) is given to treat stones brought on by an excess of uric acid by lowering the body's uric acid production.

Diuretics with thiazides: Doctors may prescribe thiazide diuretics for calcium-oxalate stones in order to lower calcium in urine, hence preventing the formation of new stones [58].

1.13 Marketed products: [59-61]

Urinary Alkalinizing Agents (Prevent/Dissolve Stones)

- **Alkalinizing agents** for the urine that prevent or dissolve stones: Potassium citrate (Urocit-K, Cytra-K): Used to prevent uric acid and calcium stones by raising urine pH and citrate.
- **Sodium bicarbonate:** Used to dissolve uric acid stones and increase the pH of urine.
- **Thiazide Diuretics (Prevent Calcium Stones):** Hydrochlorothiazide (HCTZ): Lowers urine calcium levels to stop recurrence.
- **Alternative diuretics:** To lower calcium, excretion include chlorthalidone and Indapamide.

Uric Acid Reducers (Prevent Uric Acid Stones):

- Allopurinol (Zyloprim, Aloric, Lopurin): Reduces blood and urine uric acid levels to prevent uric acid stones.
- Alpha-Blockers (Aid Stone Passage): Tamsulosin (Flomax): Promotes faster stone passage by relaxing ureteral muscles.

Alpha-Blockers (Aid Stone Passage)

- Alternative alpha-blockers include doxazosin (Cardura) and terazosin (Hytrin).

Management of Specific/Rare Types:

1. Lithostat, or acetohydroxamic acid, is used to treat struvite stones caused by infections.
2. Nedosiran (Rivfloza): Approved to lower oxalate levels in primary hyperoxaluria type1 (PH1).
3. For cystine stones, use Tiola (Tiopronin)

2. CONCLUSION

A complex and recurrent urological condition, urolithiasis continues to be a major global health burden. Most renal calculi are calcium oxalate. They are created by a number of intricate physicochemical and biological processes, including crystal nucleation, urine super saturation, aggregation, growth, crystal–cell interaction, and retention within the renal tubules. There is growing evidence that oxidative stress contributes significantly to the pathophysiology of urolithiasis by causing renal tubular epithelial damage, inflammation, and crystal adhesion. Renal tissue injury and stone formation are facilitated by the overproduction of ROS as well as the activation of signalling pathways such as NF-κB, MAPK, and MCP-1. Although a number of synthetic treatments, including uric acid-lowering pharmaceuticals, thiazide diuretics, and alkalinizing agents, are available for treatment and prevention of kidney stones, their efficacy is frequently restricted and may have negative side effects. As a result, phytopharmacological methods for urolithiasis treatment and prevention are becoming more and more popular. Through a variety of mechanisms, including inhibition of crystal nucleation and aggregation, antioxidant and anti-inflammatory activities, modulation of urine composition, and diuretic effects, medicinal plants like *Phyllanthus niruri*, *Aerva lanata, Rubia cordifolia, Moringa oleifera*, and *Macrotyloma uniflorum* have shown significant antiurolithiatic potential, such as diuretic effects, antioxidant and anti-inflammatory properties, prevention of crystal nucleation and aggregation, and modification of urine composition.Due to their multi-target mechanisms and generally safer profiles, phytochemicals derived from plants provide intriguing therapeutic alternatives for the treatment of urolithiasis. To completely understand their modes of action and create efficient and standardized phytopharmaceutical formulations for therapeutic application, however, more experimental research, clinical trials and molecular studies are needed.

3. FUTURE PROSPECTS AND RESEARCH GAPS

There are still a number of gaps in our knowledge of the specific pathophysiology and efficient treatment of urolithiasis, despite a great deal of study on the condition. There is currently no evidence linking the amount of calcium oxalate crystal deposition in renal tissues to oxidative stress indicators such as SOD, CAT, GSH, and MDA. Furthermore, it is unclear how biochemical changes and renal histological changes relate to one another as the disease progresses. Few studies have examined the combined effects of medicinal plants on oxidative stress, urine parameters, and histopathological results in a single experimental model, despite the fact that many of them have shown antiurolithiatic activity. Furthermore, more research is needed to understand how ROS-mediated signalling pathways, such as NF-κB and MAPK, affect crystal-cell interactions and kidney damage. Limited evidence exists on phytochemical impacts on crystal phase change and retention in renal tubules. Furthermore, the lack of standardization in experimental design, extract characterization, and dosage selection restricts the reproducibility and therapeutic utility of findings. Future study should focus on integrated investigations that combine biochemical, molecular, and histopathological techniques to better understand the processes of urolithiasis. Well-designed experimental and clinical investigations are required to prove efficacy and safety of phytopharmacological therapies. It is also important to discover specific molecular targets and signaling pathways involved in oxidative stress and crystal formation. Standardization of herbal formulations and long-term toxicity testing are required for clinical adoption.

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5. CONFLICT OF INTEREST

All authors declare no conflict of interest.

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7. AUTHORS CONTRIBUTION:

Dr. Sowmya B A contributed to the conceptualization, literature survey, manuscript drafting, and preparation of the review article. Ms. Sinchana Hegde contributed to the literature collection and critical revision of the manuscript. Dr. Purnima Ashok contributed to the organization of content, interpretation of the literature, and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

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