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A Comprehensive Review on Urolithiasis: Etiology, Clinical Management and Emerging Role of Bioactive Phytochemicals

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Calcium oxalate crystal

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Aggregation.

ABSTRACT:

The oldest and third most frequent painful urinary condition, urolithiasis, also referred to as kidney stones, is characterized by the development of calculi or stones in any part of the urinary system.The most prevalent kind of urinary stone, accounting for around half of all occurrences, is calcium oxalate.The prevalence and incidence, age, sex distribution, stone composition, and stone placement of urolithiasis vary by geographic region. Not all patients respond well to the synthetic medications used to prevent urolithiasis, and many of them have side effects that make long-term usage difficult. Because they are more effective, have fewer side effects, and lower the recurrence rate of stone development, herbal medications have become increasingly popular.Numerous phytoconstituents included in herbal remedies may help treat kidney stones. Phytochemicals such as flavonoids, alkaloids, polyphenols and saponins have demonstrated the ability to disrupt stone nucleation, growth and aggregation thereby facilitating the excretion of small, non-adherent crystals. More interdisciplinary research Preclinical studies need to be develop the efficacy of herbal extract inhibiting calcium oxalate crystallization and reducing oxidative stress. Standardized dose, safety profiles, and long-term efficacy of phytoconstituents must be established by extensive randomized controlled studies. The various medicinal plants and phytoconstituents used to cure kidney stones are covered in this review.

1. Introduction

Urolithiasis, commonly known as kidney stones, is the oldest and third most prevalent painful urinary condition in the world. Calculi or stones can occur in any part of the urinary system, including the kidney, bladder or ureter[1,2]. About 12% of people worldwide suffer from the excruciating urological condition known as stone formation, which has a recurrence rate of 72–81% in men and 47–67% in women[3]. It can occasionally cause more significant side effects including pyelonephritis or acute renal failure in addition to intense back pain. The most prevalent type of stone formation in the world is CaOx . urolithiasis.The Kidney stones are a global economic burden due to a combination of genetic and environmental factors[4]. The formation of urolithiasis stones is influenced by environmental factors such as nutrition, lifestyle, obesity, dehydration, and global warming. most of the drugs are generally used to restore metabolic abnormalities once they are detected Conventional therapy are medical expulsive therapy, dietary modification and standard surgical interventions such as Ureteroscopy, Percutaneous Nephrolithotomy and Extracorporeal Shock Wave Lithotripsy, are widely used to removal of stone rather than the long term prevention[5].

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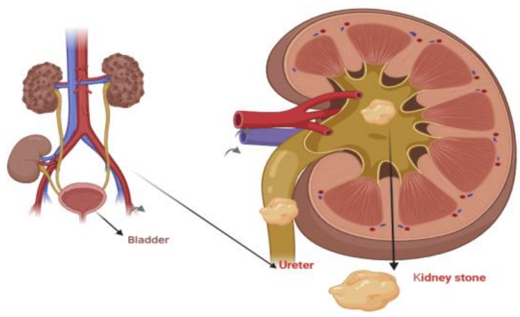

Figure 1: Diagrammatic view of kidney stone

1.1 Global Prevalence of Urolithiasis:

Every year, between 0.1 and 0.4% of people in the US and Europe get kidney stones. Additionally, it affects 2–5% of people in Asia, 8–15% of people in Europe and North America, and 20% of people in Saudi Arabia [6]. According to global epidemiological data, kidney stone disease is becoming more common, with a lifetime prevalence of about 14%. The prevalence and incidence of urolithiasis, age, sex distribution, stone composition, and stone placement vary by geographic region [7] . In 2021, the anticipated lifetime risk of urolithiasis was 62.95% worldwide, with the highest risks found in Central Asia (75.75%), Southern Latin America (80.34%), and Eastern Europe (89.20%).Male patients between the ages of 31 and 50 have an affect ratio of 46.4%, whereas female patients between the ages of 41 and 60 have an affect ratio of 47.1% [8].

2. Modifiable risk factors

2.1. Dehydration

Dehydration is one of the most significant and well-established risk factors for nephrolithiasis. Reduced fluid intake or excessive fluid loss lowers urinary volume resulting in a supersaturated urinary environment that promotes nucleation, growth, and aggregation of crystalline particles[9]. Insufficient hydration also diminishes urine flow reducing the natural flushing of microcrystals that would otherwise be eliminated before they accumulate. These physicochemical changes create an optimal environment for stone development underscoring the critical role of adequate hydration in kidney stone prevention[10].

2.2 Dietary Habits

Another important factor in urolithiasis is dietary practices. People in underdeveloped nations consume vegetables, grains, and cereals that are high in oxalate and its precursors. Stone formation is a result of a westernized diet heavy in protein, fats, calcium, and sodium. Some dietary habits such as consumption of fruits, vegetables, meat, source of Potassium, Calcium and some vitamins play a vital role in urinary stone formation[11].

2.3 Obesity:

Numerous co-morbidities connected to an elevated risk of kidney stones are associated with obesity; these co-morbidities have been demonstrated to have some correlation with kidney stone formation. According to Eisner BH et al. (2010), an increase in BMI was linked to a number of risk factors for urinary stone disease, such as a drop in pH and an increase in salt and uric acid in men's urine, as well as a decrease in citrate [12]. The most common stones in obese persons are uric acid and calcium oxalate stones, with calcium oxalate stones remaining the most common in both obese and non-obese populations.

3. Non-Modifiable risk factors:

3.1 Cystinuria:

Defective reabsorption of cystine, lysine, ornithine, and arginine in the gastrointestinal tract's epithelial cells and the brush border membrane of the proximal renal tubule is the hallmark of cystinuria [13]. Due to its low solubility and low pH, urinary hyperexcretion of cystine causes precipitation in the distal tubule and the production of cystine stones even while all four amino acids reach high urine quantities. 17–25% of urine samples from patients with cystinuria show visible cystine crystals [14].

3.2 Metabolic disorders:

Hypercalciuria is a heterogeneous metabolic disorder which causes kidney stones**,** especially calcium oxalate and calcium phosphate stones. Several metabolic abnormalities can change the chemical composition of urine[15]. There is currently no reliable biomarker that predicts hypercalciuria severity, progression, or treatment response. By decreasing calcium solubility, hypocitraturia, a condition characterized by low urine citrate levels, further encourages the development of stones. Patients with metabolic acidosis, persistent diarrhoea, and high-protein diets typically exhibit the anomaly [16].

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4.Pathogenesis of urolithiasis

Urinary stones are caused by a variety of causes, and CaOx stone development differs from other stone forms. The presence of crystals, low urine pH, decreased urine volume, high urinary supersaturation, or other risk factors for stone development might cause nucleation and aggregation into bigger particles that may eventually form a stone[17].Urinary supersaturation, which happens when the concentration of some chemicals, like calcium, phosphate, and oxalate, in the urine beyond their solubility limit, is the first stage of stone formation. Kidney stones can form as a result of the excess solutes being unable to stay dissolved and starting to collect into tiny crystal particles. These particles can then merge and grow into larger crystals [18].When urine becomes oversaturated, solid crystals form as a result of the crystallization process. Urinary casts can occur as the crystals grow and aggregate, obstructing urine flow and encouraging the creation of more stones [19].

There are two main ways that nucleation can occur: heterogeneous nucleation, which happens on the surface of foreign particles or solid surfaces, and homogeneous nucleation, which happens spontaneously inside the solution.In order to create a stable nucleus that serves as the foundation for further crystal formation, solute molecules or ions must aggregate [20].Crystals expand by incorporating additional molecules into the crystal lattice following the creation of nuclei. By raising their surface charge and encouraging adhesion to other crystals or surfaces, the promoters of crystal development can aid in the aggregation and growth of crystals [21].Urine flow rates can affect the development of stones; faster flow rates encourage the flushing out of crystals, which prevents the aggregation, while slower flow rates allow for enhanced crystal aggregation and growth [22].Renal epithelial cells in urolithiasis are exposed to elevated CaOx concentrations, which can cause OS by increasing ROS generation and causing pathological biomineralization [23]. OS and stone illness may be caused by decreased antioxidant capacity or continuously supersaturated urine that increases crystallization [24]. The kidneys of stone-forming individuals produce ROS and develop OS, according to experimental and clinical research.

5.Classification of urinary stones

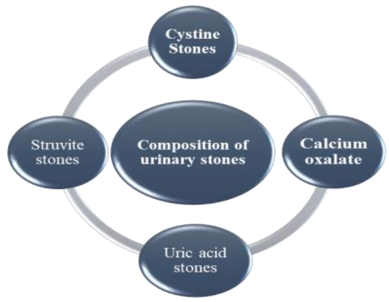

Figure 2: Classification of kidney stones

5.1 Calcium oxalate stones

The most prevalent kind of urinary stone, accounting for about half of all occurrences, is calcium oxalate [25]. The degree of urine supersaturation and the imbalance between urinary CaOx stone promoters and inhibitors determine the development of CaOx stones. There are two types of calcium oxalate stone: calcium oxalate monohydrate and calcium oxalate dehydrate [26]. Hypercalciurea, hyperoxalurea and hypocitraturea are the major metabolic contributors to their Calcium oxalate stone formation. This kind of shape will be present in over 90% of the crystals found in urine sediment.

5.2 Uric acid stones

High purine intake medications and high cell turnover, both prevalent in gout patients, are the most prominent causes of uric acid stones [27]. About 5–10% of all urinary stones are caused by uric acid stones, which are mainly associated with hyperuricosuria and acidic urine pH. One important treatment method for uric acid calculi is alkalization of urine with potassium citrate or sodium bicarbonate [28].

5.3 Struvite stones:

Struvite stones, also known as infection-related nephrolithiasis, are a unique subset of urinary calculi that are distinguished by their huge size, complicated branching shape, and rapid growth. Struvite stones, which are made of magnesium ammonium phosphate, usually develop when urease-producing bacteria cause persistent or recurrent urinary tract infections. Additionally, they are observed in individuals with underlying metabolic conditions such gout, hyperparathyroidism, and idiopathic hypercalciuria [29]. Current antibiotics poorly penetrate stones and biofilms, Persistent alkalinization accelerates stone enlargement and raises recurrence risk.

5.4 Cystine stones

Less than 2% of all urinary calculi are cystine stones, which are uncommon and result from a hereditary condition called cystinuria that affects the renal tubular reabsorption of cystine and other dibasic amino acids [30]. Particularly at acidic to neutral urine pH (<7.5), cystine is weakly soluble. Supersaturation leads to crystal nucleation, growth, aggregation and eventual stone formation. Chronic cystinuria results in recurrent stones and progressive renal damage if untreated.

6.Rationale for the study

Not all patients respond well to the synthetic medications used to prevent urolithiasis, and many of them have side effects that make long-term usage difficult. Since the development of Extracorporeal Shock Wave Lithotripsy, which has almost become the standard procedure for removing kidney stones, open renal surgery is an uncommon and infrequently utilized method of managing urolithiasis [31].In addition to being expensive, therapeutic doses of shock waves may reduce renal function, increase the risk of stone recurrence, and cause acute renal damage. Herbal medications have been increasingly popular in recent years because they are more effective, have less side effects, and lower the recurrence rate of stone formation. Numerous phytoconstituents included in herbal remedies may have a positive impact on kidney stone treatment [32].Complex molecular structures found in phytochemicals function through a variety of metabolic pathways to produce the intended therapeutic benefits. Certain secondary metabolites exhibit great selectivity for biological targets and are bioactive [33]. Through cooperative mechanisms, phytochemicals can produce biological activity. By preventing crystal synthesis and agglomeration, phytochemicals prevent the production of stones.

7.Current Therapeutic and Management strategies

7.1. Medical Expulsive Therapy

For distal ureteric calculi, medical expulsive therapy is helpful. It has been demonstrated that alpha blockers like tamsulosin greatly enhance the transit of stones between the proximal and distal ureters by 5–10 mm. In order to lessen ureteral spasms and promote stone migration towards the bladder, the drug relaxes the smooth muscles of the ureter [34, 35]. According to meta-analysis, using alpha blockers has the benefit of increasing the spontaneous stone transit rate by 14–29%, which is statistically significant [36].

A meta-analysis has shown that calcium channel blockers, such nifedipine, can effectively raise the 9% spontaneous stone passing rate. The combination of NSAIDs and corticosteroids, such as hydroxyprogesterone, can enhance the transit of stones and encourage ureteral relaxation and dilatation, which in turn can encourage the expulsion of stones by lowering inflammation and edema. lowering intrapelvic pressure and calming the smooth muscles of the pelviureteral wall [37].

7.2 *Pharmacological Management:*

Table 1**:** Pharmacological Management of Urolithiasis

Thiazides dervatives	Thiazides increase sodium excretion and decrease calcium excretion in the urine while stimulating calcium reabsorption in the distal nephron [38].
potassium citrate	In addition to thiazide diuretics, potassium citrate supplementation (40–60 mEq/day) is advised to reduce the rate of stone development and recurrence [39].
Allopurinol	Allopurinol reduces the generation of uric acid by blocking xanthine oxidase, which converts xanthine to uric acid.Consequently, the spontaneous nucleation of calcium oxalate is decreased [40].

8. Diagnostic and Imaging studies :

Diagnostic strategies combine clinical evaluation**,** laboratory testing**,** andimaging modalities**.** The choice of imaging depends on stone type, size, location, patient factors and the urgency of intervention[41].

8.1 Ultrasonography:

The main diagnostic imaging method for kidney stones should be ultrasonography. However, treating pain and stabilization the patient should never be delayed by

imaging assessments. Points of care The diagnostic accuracy of ultrasound for urolithiasis is moderate. For the evaluation of kidney stones, ultrasonography is still a reliable, accessible, and safe method. As a first-line imaging method for patients in emergency rooms, ultrasonography is still a safe, practical, and efficient way to assess kidney stones [42].

8.2 Non contrast computed tomography

For the diagnosis of urolithiasis, non-contrast computed tomography is regarded as the standard reference imaging test. When investigating a ureteral stone, NCCT has the best sensitivity and specificity (91–100% and 95–100%, respectively) [43]. With the primary exception of indinavir stones and pure matrix protein, which CT cannot detect, it can roughly identify all stones, independent of their location, size, or composition. CT is still the most effective way to find remaining stone pieces and evaluate post-treatment problems [44].

8.3 Kub Radiography

The additional advantage of CT KUB is that it can identify conditions other than urinary ones, such appendicitis, diverticulitis, or gynecological conditions like hemorrhagic cysts or ovarian inversion, which might mimic renal colic [45]. The presence of stones, their size, location, thickness, and the presence of hydronephrosis are all confirmed by CT KUB. KUB radiography has a sensitivity of 44–77% and a specificity of 80–87% for identifying stones [46].

9. Surgical interventions:

9.1 Extracorporeal shock wave lithotripsy

The overall number of shock waves every session is determined by the lithotripter model and shock wave strength. Vasoconstriction is achieved and renal damage is avoided by beginning on a lower energy setting with stepwise power (ESWL sequence). 1.0–1.5 Hz is the ideal shock wave frequency. The amount of time needed between repeated ESWL sessions is not well-established. To minimize movements during the session, pain management is essential. Ultrasonography and/or fluoroscopy are used to monitor the process [47].

9.2 Percutaneous Nephrolithotomy

For PCNL, a variety of rigid, semi-rigid, and flexible urologic endoscopes are available. For big renal calculi, PCNL is presently the gold standard procedure. The typical access tracts have a diameter of 24–30F. Longer OR times but fewer bleeding problems are associated with percutaneous nephrolithotomy [48].

9.3 Ureterorenoscopy for stone removal

The usage of URS was transformed by endoscopic mini-techniques, breakthroughs in deflection techniques, better lenses, and high-tech devices. Retrograde intrarenal surgery for renal and ureteral calculi. Calculi that cannot be immediately removed should be treated with intracorporeal lithotripsy [49].

9.4 Dietary and Lifestyle Modification:

It is recommended to tailor the dietary treatment to each patient's metabolic risk profile in order to reduce the likelihood of recurrent kidney stone formation [50]. The risk of urolithiasis recurrence can be decreased by maintaining a high total fluid intake and aiming for a urine volume of more than 2.0 to 2.5 L/day [51,52]. For patients who are susceptible to calcium oxalate stones, meals high in calcium are recommended, whereas those high in oxalate, such as spinach and almonds, are restricted [53]. Long-term stone prevention has been shown to benefit from education initiatives that focus on dietary compliance. To help patients follow their treatment goals, innovative methods like smartphone apps for monitoring food and fluid consumption are being used [54].

10.Promising medicinal plant involved in urolithiasis

Table 2: Promising medicinal plant involved in urolithiasis

Plant name	Family	Part of plant	Phytoconstitue nts	Mechanism of action	Pharmacological action	Referen ce
Moringa Oleifera	Moringacea e	Root	Quercetin, Caffeic acid,		Antmicrobial,	**[55]**

			Gallic acid, Chlorogenic acid and Vanillic acid	Modulation and Inhibition of crystallization process and crystal morphology of calcium oxalate monohydrate	Antifungal, Antibacterial, Antiinflammatory Antioxidant, Antioxidant and Antiulcer.	
Celosia argentea	Amaranthaceae	Root	Quercetin, celosin, rutin, gallic acid.	c. argentea reduces urinary stone formation by inhibiting calcium oxalate crystallizationpromoting urine output	Diuretic, Antioxidant, antinflammatory and nephroprotective properties	**[56]**
Citrus medica linn	Rutaceae	Unripe fruits	Citricacid, limonoids, caffeic acid, citrusin	Apparently related to increased, lowering of urinary concentration of stone forming constituents	Anti-inflammatory, Antioxidant, Anti biotic	**[57]**

Glochidion velutinium	Euphorbiaceae	leaves	Phyllanthin, niranthin, ellagitannins	Inhibition of CaOx crystal formation	anti-cancer, hypotensive, diuretic, wound healing.	**[58]**
Pergularia deamia	asclepediaceae	Whole plant	Lupeol, ursolic acid, stigmasterol, pergularinine	It lowered oxalate level in urine and kidney.	Diuretic, antioxidant and anti-inflammatory.	**[59]**
Didymocarpous pedicellata	Gesneriaceae	leaves	didymocarpene, didymocarpen-A, isodidymocarpin, pedicin, methyl pedicinine, isopedicine, methyl pedicine, pedicellin, pashanone	showed less renal tissue damage and no crystals, guarding against urolithiasis and nephrotoxicity.	Nephroprotective, lithotriptc and diuretic properties	**[60]**
Equisetum L.	Equisetaceae	Aerial part of plant	Quercetin, luteolin, vitexi, chlorogenic acid.	preventing stone formation by protecting endothelial cells against oxidative damage	Antioxidant, anti-urease anticholinesterase, Anti-crystallization	**[61]**
Grewia flavescens	Tiliaceae	Root	catechin, rutin, gallic acid, and quercetin	helps prevent the creation of new CaOX nuclei by flushing away stone promoters in urine and lowering the super-saturation level of ions in urine.	Antioxidant activity, Hepatoprotective activity, antiurolithiasis.	**[62]**

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Hygrophila spinosa	Acanthaceae	Whole part of plants	Apigenin, stigmasterol, hispidulin, vitexin.	It considerably decreased the high amounts of protein and ions (calcium, oxalate, and inorganic phosphate) in urine.	demulcent, aphrodisiac, diuretic, urinary tonicand hepatoprotective sub stance	**[63]**
Macrotyloma uniflorum	Fabaceae	seeds	Caffeic acid, p-coumaric acid , vanillic acid ,sinapicacid , chlorogenic acid	Inhibit the formation of calcium oxalate	Anti-urolithaisis , Diuretic activity anti oxidant activity	**[64]**
Mimosa pudica	Mimosaceae	Leaves	Mimosin, tryptamines,caffeic acid, ferulic acid.	It decreased the quantity to calcium oxalate deposited	Anti inflammatory activity antioxidant anticancer anti urolithisis	**[65]**
Momordico charatin	cucurbitaceae	fruit	Charantin, momordicosides, momordicins.	Urinary stones are prevented by it. Lowering the urinary concentrations of sone forming constituents.	Antiurolithiasis, anthelmintic, anti-inflammatory	**[66]**

Mimusops elengi	Sapotaceae	Bark	Taraxerone, ursolic acid betulinic acid	It decreased the renal content of components that produce stones.	Anti urolithiasis, antioxidant	**[67]**
Musa paradisiacal psudostem	Musaceae	Pseudostem	Luteolin, catechin, gallic acid, caffeic acid	In inhibit various pathway involuedin renal CaOx formation potential to inhibit biochemical markers of renal impairment.	Anti oxidant , anti urolithasis ,anti diabetes, anti hypertension.	**[68]**

10.1 Emerging role of phytochemical in urolithiasis

Many medicinal herbs are widely used to treat and prevent nephrolithiasis, and their bioactive components serve to enhance urinary function and prevent the production of stones (69). Phytochemicals such as flavonoids, alkaloids, polyphenols and saponins have demonstrated the ability to disrupt stone nucleation, growth and aggregation thereby facilitating the excretion of small, non-adherent crystals(70). The primary antioxidants found in a variety of fruits and vegetables are phyto-phenols, which have over 8,000 structural variants. These herbal medicines have shown notable inhibitory effects on oxidative stress-related kidney illnesses (71). Consuming plant-rich meals on a regular basis has been demonstrated to raise urine volume and pH as well as the levels of stone inhibitors such as potassium, magnesium, phytate, and citrate, which are associated with the excessive saturation of uric acid and CaOx (72). Urinary citrate levels can be raised by a plant-based diet that encourages alkali load, significantly lowering the risk of kidney stone development.

10.2 Bioactive Phytoconstituents in urolithiasis

Table 3: Isolated Phytoconstituents of urolithiasis

Phytoconstituents	Pharmacological properties	Mechanism of Action	Reference
Ellagic acid	Anti-oxidant, Anti-inflammatory and inhibit crystal nucleation.	Reduce oxidative stress. Polyphenols can interact with crystal surface to inhibit nucleation and aggregation of CaOxcrystals. suppress inflammatory factors including TNF-α and IL-1β.	**[73]**
Cinnamic acid	Anti-inflammatory, anti-oxidant, anti-diuretic activity.	Reduced urinary supersaturation. T-CA appears to reduce aggregation.	**[74]**
Curcumin	Anti-inflammatory, anti-aging and anti-neoplastic agent.	It stops the progression of ferroptosis in acute renal damage by inhibiting the	**[75]**

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		TLR4/NF-kB axis and activating HO-1.	
Ferulic acid	Anti-cancer,hepatoprotective, antiinflammatory,anti-diabetic, antiagingneuroprotective,anti-atherogenic, and radioprotective effects.	Increases the inflammatory mediators like TNF-α, 1L-6, IL-1β and CoX2.	**[76]**
Chlorogenic acid	Anti-oxidant activity	NF-kB/Runx2/AP-1/Osterix pathway inhibition	**[77]**
lupeol	Anti-crystallisation property	Reduce the amount of calcium oxalate, which has cytoprotective properties against damage caused by free radicals, and lower the kidney's cadmium levels.	**[78]**
Kaempferol	Anti-inflammatory and ROS-scavenging effects.	reduced adhesion, enhanced cell survival, and suppression of CaOx-induced HK-2 cell damage.	**[79]**
Saponin	Antilithiatic, diuretic and anti-crystallization property.	Saponins exhibit a greater rate of ionization and Ca2+ chelation, which increases the solubility of CaOx crystals and ultimately reduces the development of kidney stones.	**[80]**
Visnagin	Anti-inflammatory effect.	reduces gene expression and produces pro-inflammatory chemicals including TNF-α, IL-1β, and IFN-γ by inhibiting transcription factors like NF-kB.	**[81]**
Arbutin	Anti-oxidant and anti-inflammatory.	Because of the hydrogen bonds that occur between arbutin and the surface of oxalate-based crystals, it can attach to these crystals and change their	**[82]**

		structure, which may lessen their role in kidney stone formation.	
Hyperoside	Diuretics, anti-oxidant and anti-inflammatory.	Certain enzymes involved in oxalate metabolism, like α-glucosidase, are inhibited.As a result, less oxalate is produced, which lessens the formation of calcium oxalate crystals.	**[83]**
Epigallocatechin-3-gallate (EGCG)	Anti-oxidant and anti-inflammatory	By modifying the activity of several crystal-forming enzymes, including as oxalate oxidase, alkaline phosphatase, and calcium ATPase, it prevents the formation of calcium oxalate crystals. It can also lessen the kidney's generation of reactive oxygen species (ROS).	**[84]**
Tannin	Anti-oxidant properties	By preventing COM binding, MCP-1 and OPN expression, and boosting antioxidant action, it prevents nephrolithiasis.	**[85]**
Thymoquinone	Analgesic, antipyretic, antioxidant, antiinflammatory, antiurolithic and anticancer activity.	I It prevents the production of free radicals by inhibiting proinflammatory cytokines such as IL-1β, TNF-α, IFN-γ, IL-6, and PGE2.	**[86]**

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Rutin	Anti-urolithiasis, antioxidant, antiradical, anti-inflammatory, antibacterial, diuretic activity anti-tumoral cytoprotective, antispasmodic, antithrombic, and antiulcerogenic	The anti-inflammatory response can be demonstrated by downregulating the production of TNF-α and NF-κB, which are important mediators of the inflammatory cascade. These findings demonstrated a protective function against urolithiasis.	**[87]**
Berberine	Anti-urolithic, diuretic and anti-oxidant activity.	The kidneys' enzymatic responses are lessened by antioxidant activity.	**[88]**
Diosmin	Anti-urolithiatic activity	It inhibits lipid peroxidation, increases the activity of enzymes that scavenge radicals, and regulates the production of Bax and p53 proteins.	**[89]**
Isorhamnetin	Anti-cancer , anti-inflammatory and anti-oxidant.	By blocking the PI3K/AKT/NF-κB signaling pathway, it lowers inflammatory factors such as TNF-α, IL-1, and IL-6.	**[90]**
Puerarin	Anti-oxidant, anti-tumor and anti-inflammatory.	SIRT1/AKT/p38 pathway activation.	**[91]**
Vitexin	Anti-oxidant, anti-inflammatory and anti-tumor.	Activation of the SIRT1/AKT/p38 pathway.	**[92]**
Apigenin	Anti-oxidant properties	decreased crystal deposition due to TGF-β pathway suppression.	**[93]**
Catachin	Anti-oxidant	In NRK-52E cells exposed to COM,	**[94]**

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		decrease lipid peroxidation and suppress the expression of genes linked to apoptosis.	
Gallic acid	Anti-oxidant	In HK-2 cells treated with COM, the Nrf2/HO-1 pathway was activated, further suppressing crystal deposition.	**[95]**
Resveratrol	Anti-oxidant	It inhibited the expression of MCP-1, OPN, TGF-1, TGFR-I/II, and NADPH oxidase subunits (p22phox and p47phox).	**[96]**
Arjunic acid	Anti-oxidant Nephroprotective Anti-inflammatory.	It is inhibit the formation of kidney stones by reducing oxidative stress.	**[97]**
Arjungenin	Neproprotective Anti-oxidative Anti-inflammation.	It is capability to repair demand kidney cell and allivate to impact of oxidative stress caused by urolithiasis	**[98]**
Caffeic acid	antiviral, antioxidant, immunostimulatory, anti-inflammatory, antibacterial, and anti-hepatocarcinoma properties. These include the anti-oxidant, anti-inflammatory, diuretic, and ACE inhibitory properties.	TNF-α, IL-1β, IL-8, and IL-10 are among the pro-inflammatory and inflammatory cytokines that it reduces. It also modulates gene expression in the immune modulatory and anti-inflammatory response.	**[99]**
Theaflavin (TF)	Anti-oxidant Nephroprotective Anti-inflammatory.	By downregulating the expression of miR-128-3p, TF mitigated the suppression of SIRT1 and decreased oxidative stress damage and crystal deposition.	**[100]**
β-sitosterol	Anti-oxidantand Anti-inflammatory.	The antioxidant enzymes SOD and GPx were more active under OS.	**[101]**

11.Biomarkers role in urolithiasis

Table 4: Biomarkers role in urolithiasis

Biomarkers	Mechanism of action	Reference
Neutrophil Gelatinase Associated Lipocalin	NGAL is a 25kDa lipocalin secreted by neutrophil and renal tubular epithelial cells. NGAL binds matrix metalloproteinase stabilizing it and influenzing extracellular matrix remodeling during inflammation.	[102]
Carbohydrate Antigen 19-9	Potential indicators for kidney damage associated with blockage include serum and urine CA19-9 values. Patients with hydronephrosis and urolithiasis have higher levels.	[103]
OPN	Along with other positive effects, it is linked to kidney tubulogenic qualities. Kidney illness and urolithiasis are associated with elevated levels. Patients with abnormal urine dipstick results had greater amounts of OPN in their blood and urine, according to a study on acute leptospirosis.	[104]
Urinary Prothrombin Fragments-1	Urine contains thrombin fragments called UPTF-1. Studies conducted both in vivo and in vitro show that it inhibits crystallization. Individuals who have low UPTF-1 levels are more likely to develop stones.	[105]
Cystatin c	Cystatin C has undoubtedly become more crucial in the diagnosis of CKD and AKI. Serum levels of this tiny molecule, which the kidneys eliminate from the bloodstream, are a more accurate indicator of renal function than serum creatinine levels. In patients with diabetes, chronic kidney disease (CKD), and following kidney transplantation, cystatin C is a useful kidney biomarker.	[106]
Kidney Injury Molecule-1	Renal proximal tubular epithelial cells release KIM-1, which is barely expressed in healthy kidney tissue. Research has shown that urinary KIM-1 (uKIM-1) can predict long-term renal outcomes and differentiate between transitory AKI and permanent kidney injury with a ROC curve AUC of 0.703, sensitivity of 78.4%, and specificity of 60.8%. Levels above 2.37 ng/mg are linked to worse progress.	[107]
Urinary N- acetyl beta - D-glucosaminidase	The proximal renal tubule has a high concentration of NAG, a high molecular weight enzyme found in many tissues. In patients with leptospirosis in the emergency room, NAG was employed as a kidney damage biomarker.	[108]

12.Challenges and Future perspectives

Polyphenolic compounds from herbal sources exhibit unique anti-oxidative characteristics with their stability and bioactivity influenced by various factors such as heat resistance, pH stability and intestinal absorption(109). The microencapsulation techniques are employed to enhance thermal resistance and ensure stability during processing and storage. The heat stability of phytochemicals including polyphenols and flavonoids varies depending on their molecular structure. While some polyphenols exhibits moderate heat resistance and many degrade at high temperatures leading to diminished antioxidant activity and therapeutic efficacy[110]. The bioavailability of polyphenols is generally low due to poor absorption, rapid metabolism and fast excretion, necessitating advanced formulation strategies to optimize their therapeutic potential[111].

The future clinical research in urolithiasis prevention will focus on advancing evidence-based nutraceutical interventions particularly in the area of herbal medicine. While extensive preclinical and traditional medicine studies have demonstrated the efficacy of herbal extracts in modulating urinary biochemistry, inhibiting calcium oxalate crystallization and reducing oxidative stress, large-scale randomized controlled trials are necessary to establish standardized dosing, safety profiles and long term efficacy [112].

3. Conclusion

Based on this review urolithiasis remains a prevalent and recurrent urological disorder worldwide The substantial potential of bioactive phytoconstituents in the treatment and prevention of urolithiasis is highlighted in this review. Potential bioactive phytoconstituents involved in variety of mechanism including inhibition of crystal nucleation, growth, aggregation, and retention as well as antioxidant, anti-inflammatory, diuretic activity. Experimental and preclinical studies provide substantial evidence supporting the efficacy of these phytoconstituents in reducing stone formation and promoting stone dissolution, particularly in calcium oxalate–induced urolithiasis model. Bioactive phytoconstituents represent a promising and complementary approach for the management of urolithiasis. Continued systematic research and clinical validation may pave the way for the development of effective, safe, and affordable phytopharmaceuticals for long-term prevention and treatment of kidney stone disease.

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