REVIEW ARTICLE

A REVIEW ON UROLITHIASIS: CURRENT MANAGEMENT CHALLENGES AND THE EMERGING ROLE OF PHYTOTHERAPY

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Abstract:

Urolithiasis, commonly known as kidney stone disease, is a widespread and historically significant medical condition, affecting an estimated 1–15% of the global population. Its prevalence is notably increasing among working-age individuals, particularly in hot and arid regions. Documented as early as 4400 BC, urolithiasis involves the formation of crystalline stones within the urinary tract. Kidney stones are primarily classified based on their mineral composition. Calcium oxalate (CaOx) stones are the most prevalent, accounting for approximately 65.9% of cases. Struvite stones, comprising 2.7% to 15% of cases, are more common in females due to their association with urease-producing bacterial infections. Other types include uric acid, calcium phosphate, and rarer forms such as cystine or drug-induced stones. The pathogenesis of urolithiasis is multifactorial, involving urinary supersaturation, crystal nucleation, growth, and aggregation. Contributing factors include Randall's plaques, hormonal imbalances, the human microbiome, and immune responses. Current treatment strategies include pharmacological interventions (e.g., potassium citrate, thiazide diuretics) and surgical procedures such as extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS). Despite these options, recurrence remains a major challenge, with rates estimated at 30–50% within 5 years and 50–60% within 10 years. Moreover, conventional therapies can be costly, may induce acute kidney injury, and often fail to prevent future stone formation. This article evaluates phytotherapy as an alternative approach for managing urolithiasis. Plant-derived phytoconstituents—such as polyphenols, flavonoids, and terpenoids—exhibit diuretic, anti-lithic, antioxidant, and anti-inflammatory activities. These natural agents may inhibit crystal nucleation and aggregation, reduce oxidative stress, and facilitate stone dissolution. Medicinal plants such as *Alcea rosea* L. and *Bergenia ligulata* are among those showing promising potential.

In conclusion, despite therapeutic advancements, the high recurrence rate of urolithiasis underscores the need for a comprehensive understanding and personalized treatment strategies. Further research is essential to validate emerging treatments, including phytotherapy and probiotics, in order to reduce the global burden of this condition.

Keyword: Urolithiasis, Calcium Oxalate, Uric Acid, Calcium Phosphate, Flavonoids.

Introduction:

Urolithiasis, widely recognised as kidney stone disease, is a pervasive and ancient medical condition, impacting an estimated 1-15% of individuals globally during their lifetime. This condition is characterised by the presence of one or more stone-like structures, or calculi, within the urinary tract, which can include the kidneys, ureters, or bladder. The term "urolithiasis" itself is derived from the Greek words "oûron" (urine) and "lithos" (stone), directly referencing the formation of these solid structures within the urinary system. Its prevalence and incidence are currently on the rise worldwide, particularly affecting working-age adults in hot and dry climates. In 2019 alone, global incident cases of urolithiasis reached 115,55,2140, with India accounting for over one-fifth of these cases. (1)

Historically, the presence of urinary stones has been documented across ancient civilisations. The earliest recorded stones were found in Egyptian mummies, dating back to approximately 4400 BC. Early medical texts from Mesopotamia (3200-1200 BC) describe symptoms and treatments for stones. Ancient Hindu writings, notably the "Sushruta Samhita" by physicians Charaka and Sushruta (around 600 BC), detailed causes of stone formation and surgical procedures, including perineal lithotomy (2,3).

The renowned Greek physician Hippocrates famously cautioned against performing lithotomy in his oath. The practice evolved through figures like Ammonius of Alexandria (276 BC), who first suggested crushing stones, and Abulcasis (936-1013 AD), who refined lithotomy techniques and was possibly the first to crush stones in the urethra. Kidney stones are primarily categorised by their mineralogical composition (4). Calcium oxalate (CaOx) stones are the most common, making up approximately 65.9% of cases, often appearing alone or combined with calcium phosphate. Other significant types include carbapatite (15.6%), urate (12.4%), struvite (magnesium ammonium phosphate, 2.7%), and brushite (1.7%) (5). Struvite stones are notably more prevalent in females due to their strong association with urinary tract infections caused by urease-producing bacteria (6)

Urolithiasis Types:

Urolithiasis, or kidney stone disease, is a condition where stones form within the urinary tract. The main types of kidney stones include Calcium Oxalate (CaOx) Stones, which account for 65.9% of cases, and Struvite Stones (Magnesium Ammonium Phosphate), which account for 2.7% to 10% or 10-15% of all cases.

Struvite stones are more prevalent in females due to their association with urinary tract infections caused by urease-producing bacteria. (7)

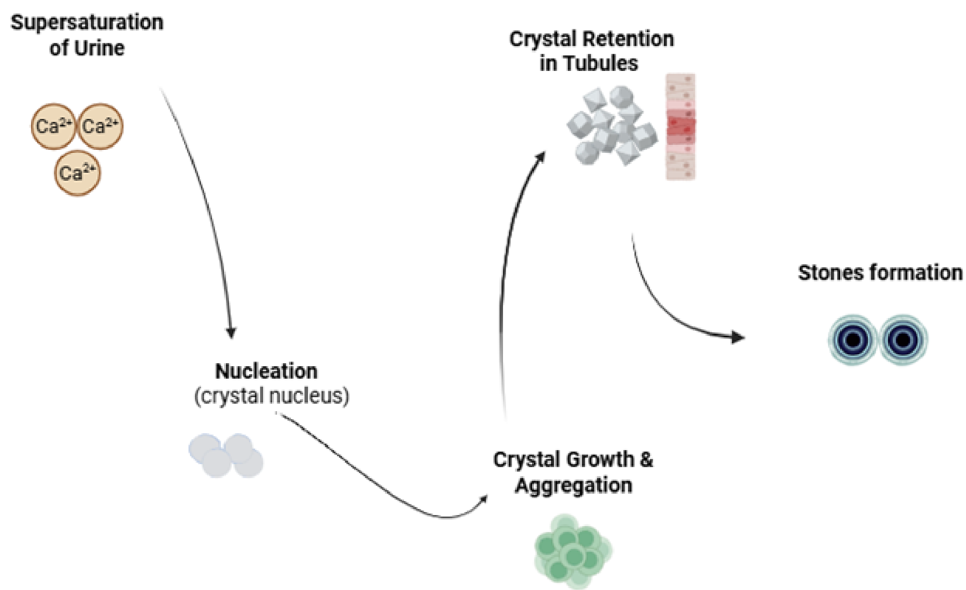
Uric Acid Stones, composed of uric acid, constitute approximately 10% of all urinary calculi. Factors contributing to their formation include high purine diets, low urine volume, and a consistently low urine pH. Calcium Phosphate Stones, composed of calcium and phosphate, constitute about 10-20% of all urinary stones and are associated with conditions like hyperparathyroidism and renal tubular acidosis (RTA). Carbapatite, a type of calcium phosphate stone, makes up 15.6% of cases. (8).

Cystine Stones, an uncommon form of kidney stone, account for less than 1% or 1-5% of cases. They arise from an inherited metabolic disorder called cystinuria, leading to an elevated concentration of cystine in the urine due to improper reabsorption of dibasic amino acids in the proximal tubule. Low solubility in urine at normal pH contributes to their formation. Medication-Induced Stones, accounting for less than 1% of stones, form due to the presence of pharmaceutical or herbal components. Prolonged high-dosage drug treatment can lead to stone formation from drug crystallisation or excretion of poorly soluble metabolites. Urine pH and diuresis also play a role in this type of stone development. (9)

Kidney Stones: Mechanisms of Formation

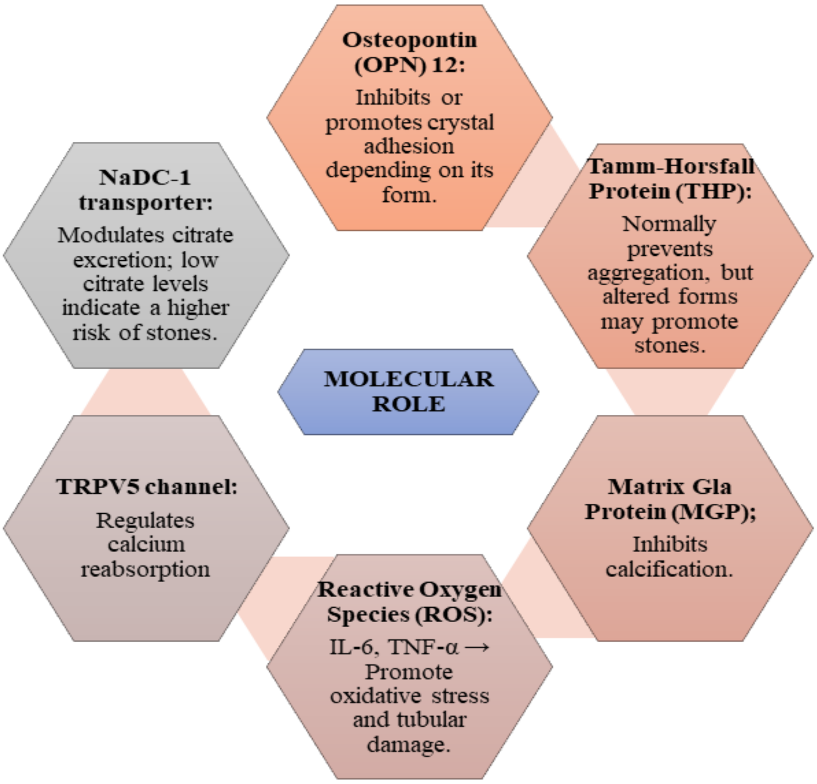
Kidney stones are a complex, multi-step process driven by various molecular and cellular mechanisms. The formation of calcium oxalate stones involves urinary supersaturation, crystal nucleation, growth, and aggregation. Crystal growth involves adding new components to the crystal nucleus once it reaches a threshold size, while crystal aggregation describes small, single-component crystals growing into larger, multicomponent objects or newly created crystals secondarily nucleating on existing ones. Crystal-cell interaction is critical, as crystals adhering to renal epithelial cells can cause injury and inflammation, further promoting crystal growth and aggregation. (10).

Kidney Stone Formation Steps Involved:



Randall's Plaques (RPs) are subepithelial mineralised tissues, primarily composed of calcium phosphate, located at the papillary tip. Factors such as vitamin D and calcium supplementation can accelerate RP formation, while long non-coding RNAs (lncRNAs), including H19 and MALAT1, have been implicated in mediating osteogenic differentiation and participating in RP formation. Sex hormones play a key role in nephrolithiasis development, with males having a higher incidence of calcium oxalate stones. (11). The human microbiome, including that in the kidney, urinary tract, and intestines, significantly influences urological health. Urease-producing bacteria, such as Proteus mirabilis and Klebsiella pneumonia, are strongly associated with struvite stone formation, particularly in females. Nanobacteria (NB), also termed calcifying nanoparticles (cNPs), have been isolated from kidney stones and RPs, potentially initiating pathological calcifications and stone formation. The immune response, especially macrophage differentiation, plays a crucial role in renal calcium oxalate crystal formation. Recruited macrophages can promote crystal development and secrete mediators, causing renal interstitial inflammation. Genetic factors also significantly influence the probability of developing urolithiasis, with specific gene mutations linked to cystinuria, a condition causing cystine stone formation due to reduced reabsorption of certain amino acids. (12,13).

Molecular Roles Involved:



Urolithiasis is caused by various molecular factors, including proteins like Osteopontin, THP, Matrix Gla Protein, reactive oxygen species, inflammatory cytokines, and calcium and citrate balance disruption, which contribute to crystal formation and retention (14).

Treatment Options:

Pharmacotherapy for stone dissolution and prevention involves specific drugs targeting different stone compositions or metabolic abnormalities. These drugs include Potassium Citrate, Thiazide Diuretics, Allopurinol, Tiopronin and Penicillamine, and Bisphosphonates. Surgical procedures are often necessary for larger or more complex stones, such as Extracorporeal Shock Wave

Lithotripsy (ESWL), Ureteroscopy (URS), Percutaneous Nephrolithotomy (PCNL), and Open Surgery (15).

Urolithiasis is often a recurrent and lifelong disease, with a significant recurrence rate estimated at 30% to 50% within the first 5 years after the initial stone event and 50% to 60% within the next 10 years. A single treatment modality is not equally effective for all situations, emphasizing the need for differential indications based on stone size, localization, and composition. Pharmacological treatments for urolithiasis are currently unavailable, and evidence for the benefit of agents like alpha-blockers in ureteral stone treatment remains weak. Long-term use of urinary acidifiers and urease inhibitors for struvite stones is limited due to ineffectiveness and toxicity.

Surgical procedures, including ESWL and endoscopic techniques, can be costly, cause acute kidney injury, and do not prevent the probability of new stone formation. Potential complications of surgical procedures include haemorrhage, hypertension, tubular necrosis, subsequent kidney fibrosis, renal failure, steinstrasse, pancreatitis, infection, and persistent stone residue that can act as a nidus for new stone formation. (16).

Phytochemicals Treatment:

Alternative therapies include phytotherapy, which involves the use of herbs and herbal medicines with diuretic, antilithic, alkalizing, antispasmodic, and anti-inflammatory properties to prevent stone formation, promote dissolution, alleviate symptoms, and support kidney health. Phytoconstituents, also known as phytochemicals, are natural compounds found in plants that are increasingly being explored for their potential in treating urolithiasis. This approach, known as phytotherapy, leverages traditional knowledge of medicinal plants and is gaining attention due to the limitations of conventional treatments for kidney stones. Phytoconstituents and herbal remedies are believed to work through multiple mechanisms, including increasing diuresis, enhancing citraturia, decreasing calcinuria and oxaluria, inhibiting crystal nucleation and aggregation, promoting stone dissolution, and elevating glycosaminoglycan levels. Some specific phytoconstituents and plant-derived compounds have been reported to have mechanisms of action in urolithiasis treatment (17).

General categories of bioactive compounds include polyphenols, which are noted for their ability to reduce crystal formation through antioxidant activity, primarily by neutralizing Reactive Oxygen Species (ROS) and chelating metals like Fe^{3+}. They also inhibit pro-oxidant enzymes such as NADPH oxidase and interfere with the inflammatory cascade by inhibiting transcription factors like NF-κB and enzymes like cyclooxygenase (COX). Terpenoids, saponins, alkaloids, and sterols exhibit endogenous antioxidant activity by scavenging ROS or upregulating antioxidant enzymes like SOD, CAT, and GSH. They also act as anti-inflammatory agents by inhibiting macrophage proliferation, reducing inflammatory mediators, and decreasing levels of TNF-α and IL-6. (18)

Specific plants and their phytoconstituents/mechanisms include *Alcea rosea* L. (Roots), *Aerva lanata* (Whole plant), *Achyranthes aspera* L. (Leaves), *Asparagus officinalis* L. (Root) (19), *Azadirachta indica* A. Juss. (Leaves), *Basella alba* L. (Whole plant), *Bergenia ligulata Wall* (Rhizome), *Bombax ceiba* L. (Stem and bark), *Bryophyllum pinnatum* Lam (Leaves), *Cassia fistula* L. (Stem bark), *Celosia argentea* L (20), (Seed), *Daucus carota* L. (Seed), *Euphorbia hirta* L. (Leaves), *Herniaria hirsuta* L. (Whole plant), *Orthosiphon stamineus* (Leaves), and others (21,22).

Phytoconstituents and herbal remedies have been shown to have various effects on urolithiasis treatment (23). Polyphenols, including flavonoids and tannins, are noted for their ability to reduce crystal formation through antioxidant activity, primarily by neutralizing Reactive Oxygen Species (ROS) and chelating metals like Fe3+. Terpenoids, saponins, alkaloids, and sterols exhibit endogenous antioxidant activity by scavenging ROS or upregulating antioxidant enzymes like SOD, CAT, and GSH. They also act as anti-inflammatory agents by inhibiting macrophage proliferation, reducing inflammatory mediators, and decreasing levels of TNF-α and IL-6. Phytoconstituents and plant-derived compounds are effective in treating urolithiasis by reducing reactive stress, inhibiting pro-oxidant enzymes, and preventing the formation of kidney stones.

These compounds are effective in treating urolithiasis by reducing the formation of calcium oxalate stones, preventing the formation of calcium oxalate stones, and reducing the formation of kidney stones (24). In conclusion, phytoconstituents and plant-derived compounds have shown promising results in treating urolithiasis through various mechanisms. By incorporating these compounds into the diet and lifestyle, they can help prevent kidney stones and promote overall health (25).

Discussion:

Urolithiasis, a prevalent and historically significant urological disorder, involves the formation of calculi (stones) in the urinary tract. It affects 1–15% of the global population, with a rising trend due to changing diets, climates, comorbidities, and socioeconomic conditions. Countries like India, China, and Russia bear a significant burden, both in terms of cases and mortality. Urolithiasis results in high healthcare costs and disability-adjusted life years (DALYs), making it a substantial public health issue.

The disease is multifactorial in origin, involving complex mechanisms such as urinary supersaturation with stone-forming substances (e.g., calcium, oxalate, phosphate), formation of Randall's plaques, hormonal imbalances (notably testosterone and estrogen), dysbiosis in the gut and urinary microbiome, and immune responses involving macrophage-mediated inflammation. Stone formation progresses through stages—nucleation, growth, aggregation, and interaction with renal epithelium. Depending on mineral composition, stones are classified into calcium oxalate (most common), calcium phosphate, struvite, uric acid, cystine, and rare medication-induced forms.

Recurrence rates are high (50% within 5–10 years), often requiring lifelong management. Risk factors for recurrence include early onset, family history, specific stone types, metabolic and genetic conditions (like cystinuria and hyperoxaluria), diet, climate, and lifestyle factors. The disease also contributes to long-term complications like chronic kidney disease and cardiovascular risk.

Treatment approaches are diverse and depend on stone size, type, location, and patient condition. Pharmacotherapy includes NSAIDs, alpha-blockers, potassium citrate, thiazides, allopurinol, and cystine-binding agents. Minimally invasive procedures like ESWL, ureteroscopy, and PCNL are commonly used, with open surgery reserved for rare complex cases. Phytotherapy using herbal drugs (e.g., *Phyllanthus niruri*, *Tribulus terrestris*, *Bergenia ligulata*) is gaining popularity due to its antilithic, antioxidant, and anti-inflammatory actions. Probiotic therapy using oxalate-degrading bacteria (e.g., *Oxalobacter formigenes*, *Lactobacillus spp.*) is an emerging adjunct approach.

Prevention of recurrence is essential and involves adequate hydration (urine output >2.5 L/day), dietary modifications (moderating calcium, sodium, oxalate, and animal protein intake), metabolic evaluation, and regular imaging follow-up. Despite advancements, there remains a critical need for high-quality clinical studies to validate the efficacy and safety of phytotherapeutics and probiotics. Personalized, integrative strategies combining dietary, pharmacologic, surgical, and microbiome-targeted interventions represent the future of comprehensive urolithiasis management.

Conclusion:

In conclusion, urolithiasis is a multifaceted disease that demands a comprehensive understanding of its complex pathophysiology and individualized patient care. While significant advances have been made in diagnostics and treatment modalities, the high recurrence rates emphasize the need for effective preventive strategies, accurate metabolic assessments, and personalized dietary and lifestyle adjustments. Further research is essential to fully elucidate the underlying molecular and cellular mechanisms, validate emerging therapies like phytotherapy and probiotics, and ultimately reduce the global burden of this condition.

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Declaration of Competing Interest:

The authors declare that they have no competing interests.

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