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Review

Kidney Stone Disease in the Modern Era: From Ancient Origins to Precision Medicine

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Abstract

Urolithiasis, a disorder characterised by the development of stones in the urinary tract, is still a major global health concern and is becoming more common, especially in developed countries and areas known as the "**stone belt**." The historical development, pathophysiology, etiology, clinical manifestation, diagnostic developments, therapeutic approaches, side effects, and preventative measures associated with urolithiasis are all thoroughly examined in this review. The majority of calcium oxalate and phosphate stones are caused by a complex etiology that includes genetic predispositions, anatomical abnormalities, metabolic disorders, and dietary practices. In order to improve diagnosis and treatment planning, diagnostic techniques have advanced from traditional radiography to high-resolution modalities, including dual-energy CT and non-contrast CT. The three main components of preventive strategies are metabolic evaluation, medication intervention, and lifestyle change. Artificial intelligence, nanotechnology, gene editing, and phytotherapy are the main areas of current research. Through their bioactive phytoconstituents, traditional medicinal plants, including *Bergenia ligulata* and *Phyllanthus niruri*, have shown their potential in antilithiatic action. In addition to highlighting potential future avenues for better care and prevention of recurrent stone disease, this study emphasizes the importance of a multidisciplinary approach.

Keywords: Urolithiasis, Kidney Stones, Calcium Oxalate, Nephrolithotomy.

INTRODUCTION

Urolithiasis is the third most prevalent condition affecting the urinary system, and its prevalence has been steadily increasing over the past few decades worldwide. There is significant regional variation in its occurrence; research has found that it is 5.7% in Iran, with a wider range of 0.9% to 8.2% based on the region and population factors (1). Notably, the illness is more prevalent in men and tends to peak between the ages of 40 and 60 in Iran, which is different from certain other countries' demographic patterns. [1]

Nephrolithiasis is caused by a variety of causes, such as poor fluid intake, dietary practices that include a lot of animal protein and oxalate, and exposure to heat in the environment. Furthermore, it is commonly linked to systemic comorbidities such as dyslipidemia, diabetes mellitus, obesity, and hypertension [1,2]. Approximately 11–32% of people with stones eventually experience clinical symptoms, despite the fact that many of them remain asymptomatic [1]. Recurrence is a major worry for patients who have symptoms; up to 50% of them experience a reappearance of stones within five years, underscoring the necessity of continuous care.

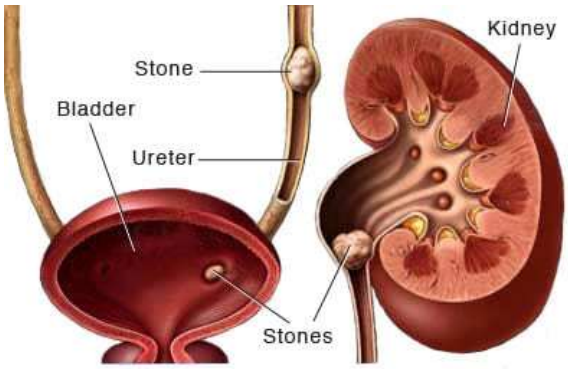

Fig 1: Kidney stones

Life-threatening effects, such as the development of end-stage renal disease (ESRD), chronic kidney disease (CKD), and links to prostate or renal cancers, can result from persistent and recurring stone formation. This has resulted in the creation of a number of therapeutic strategies, from non-invasive techniques like medication and nutrition to interventional techniques like surgical extraction and percutaneous nephrolithotomy [1,3].

Historical Background

Bladder stones found in Egyptian mummies from 4900 BC indicate that urolithiasis is one of the oldest known illnesses in medical history [4]. Early urinary stone treatments, such as herbal and diuretic regimens, were documented in ancient Egyptian and Mesopotamian medical books [5]. The 6th-century BC Indian surgical classic Sushruta Samhita described perineal lithotomy in detail, requiring the king's approval because of the high mortality risk [6]. During the Greco-Roman era, Aulus Cornelius Celsus recorded surgical methods for lithotomy in his treatise De Medicina [7], while Ammonius of Alexandria invented mechanical methods for stone breakup. In contrast, Hippocratic ethics recommended that doctors leave stone removal to experts [8]. During the Islamic Golden Age, Rhazes and Albucasis created specialized tools for stone extraction and enhanced surgical techniques [9]. Traveling lithotomists carried out these dangerous procedures in medieval Europe, especially after the Fourth Lateran Council of 1215 prohibited clergy from performing surgery [10]. Pierre Franco invented suprapubic lithotomy during the Renaissance, and William Cheselden improved perineal lithotomy by using quicker and more accurate methods [11].

By employing a lithotrite to perform transurethral lithotripsy in the 19th century, Jean Civiale significantly reduced operational mortality and established the foundation for evidence-based surgery by comparing results [12]. The first successful use of extracorporeal shock wave lithotripsy (ESWL) with the Dornier HM1 device in 1980 and percutaneous nephrolithotomy (PCNL) in 1976 were examples of modern advancements that made treating urolithiasis a non-invasive, outpatient procedure [13,14].

Etiology

About 80% of urinary stones are made of calcium oxalate or calcium phosphate, with lower amounts of uric acid, struvite, and cystine stones following. Urolithiasis has a complicated and multiple etiology. Low urine volume, hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia are the main causes of stone formation. These conditions are frequently paired with aberrant urine pH, which encourages crystallization. Thirty to sixty percent of calcium stone formers have hypercalciuria, which can be caused by idiopathic reasons or systemic

disorders such as sarcoidosis, renal tubular acidosis, primary hyperparathyroidism, excessive vitamin D, or extended immobilization. Supersaturation of urine calcium is promoted by increased intestinal calcium absorption, renal calcium leak, and bone resorption in idiopathic hypercalciuria, which is most likely polygenic.

A major effect is played by environmental and nutritional factors. Diets high in animal protein, sodium, foods high in oxalate (such as spinach, nuts, and chocolate), too much vitamin C, and high fructose increase the risk of stone formation by raising the excretion of calcium, oxalate, and uric acid in the urine while lowering inhibitory citrate levels. Insufficient hydration, especially in hotter regions, concentrates urine solutes and increases the risk of crystallization.

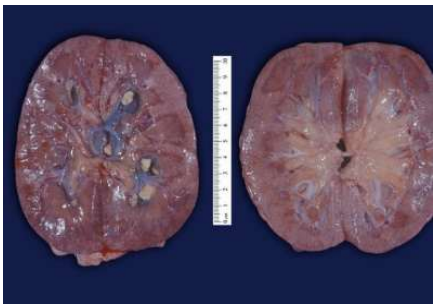

Fig 2: Urolithiasis

Fig 3: Kidney stones of varying sizes

Through metabolic changes, urolithiasis is linked to associated conditions like obesity, diabetes mellitus, hypertension, and metabolic syndrome. Insulin resistance encourages lower urine pH, higher excretion of uric acid, and decreased citrate levels, all of which contribute to the formation of uric acid and calcium stones. Additionally, by changing urine flow or solute handling, structural anomalies (such as medullary sponge kidney or ureteral strictures), inflammatory bowel illnesses, bariatric surgery, and cystinuria increase the chance of stone formation.

Randall's plaque, which serves as a nidus for calcium oxalate deposition, frequently forms in the renal papillae interstitium during the onset of crystal retention. Crystal nucleation, growth, aggregation, and retention occur when urine becomes supersaturated; these processes are influenced by promoters such increased calcium, oxalate, or uric acid, as well as inhibitors like citrate and magnesium. All things considered, urolithiasis is a systemic disease that results from the interaction of metabolic abnormalities, dietary and environmental exposures, urinary inhibitors, and genetic predisposition. [15-18]

Global burden of Urolithiasis

Despite a decrease in the age-standardized incidence rate since 1990, urolithiasis remains a major worldwide health concern, with over 115 million new cases recorded in 2019. [19] The prevalence varies greatly, ranging from 1–5% in low-income areas to over 15% in developed nations and up to 25% in the Middle East. [20,21] With the greatest burden in Eastern Europe and Central Asia, the disease is estimated to have caused 13,279 deaths and 0.6 million DALYs worldwide in 2019. [19] Although the gender difference is closing, the incidence is higher in men.[22] Low-SDI nations are experiencing rising rates of urbanization, dietary changes, and rising temperatures, especially in the "stone belt" regions of Asia and Africa.[23,24] These patterns show how important it is to develop prevention plans that are specific to local risk factors.

Pathogenesis

Physicochemical Basis: Super saturation and Crystallization

When urine gets supersaturated with ions that cause kidney stones, usually calcium with phosphate or oxalate, the ionic activity product surpasses the solubility product, which starts nucleation and crystal development. Nucleation, crystal growth, aggregation, and retention are among the processes. Nucleation is the clustering of free ions to create nuclei, which expand and combine into bigger crystals that can develop into clinically important stones if they are kept in the nephron.

Nucleation Dynamics: Homogeneous vs. Heterogeneous

The direct formation of crystals (such as pure CaOx) by free ions in supersaturated urine is known as homogeneous nucleation. Using pre-existing surfaces as nucleating centers, such as **Randall's plaques** (interstitial calcium phosphate deposits at the papillae), urinary casts, or epithelial cells, heterogeneous nucleation promotes crystal anchoring and stone formation. Damage to the renal tubules makes crystals stick and stay in place, especially when the super saturation is lower. The direct formation of crystals (such as pure CaOx) by free ions in supersaturated urine is known as homogeneous nucleation. Using pre-existing surfaces as nucleating

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Inhibitors and Promoters: Molecular Modulators

By binding calcium/oxalate ions or inhibiting growth and adhesion, endogenous inhibitors (such as citrate, magnesium, pyrophosphate, nephrocalcin, osteopontin, uromodulin, and Tamm-Horsfall protein) prevent crystallization. Depending on the kind of stone, promoters include high levels of calcium, oxalate, urate, phosphate, and acidic/alkaline pH; proteins like CD44, nucleolin, HSP90, Annexin II, HA, and osteopontin may function as receptors for cell–crystal interactions, facilitating growth and retention.

Urine Volume and pH: Critical Physiochemical Modifiers

Low urine volume increases the risk of super saturation by concentrating solutes. Changes in urine pH affect the type of stone: High pH (>6.7) promotes the formation of struvite or calcium phosphate stones (e.g., alkali treatment, distal RTA). Low pH can decrease citrate excretion, which further promotes CaOx lithogenesis, and it also favors uric acid and cystine stones.

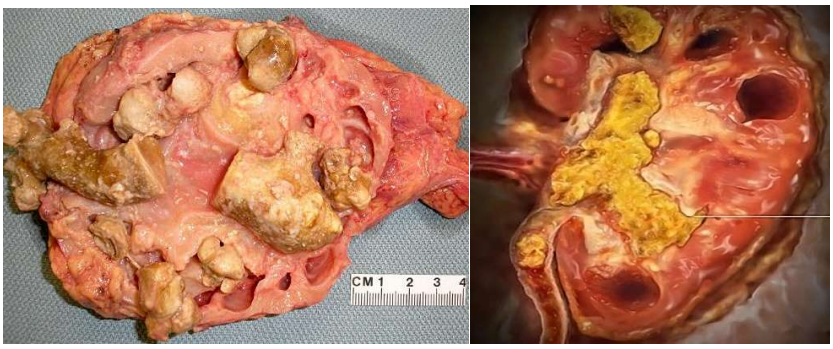

Fig 4,5: Gross specimen of a kidney with stones

Metabolic Abnormalities and Systemic Contributors

Dehydration, thiazides, sarcoidosis, or hyperparathyroidism can cause or cause idiopathic hypercalciuria, which raises the levels of free calcium. Urinary oxalate load is increased by hyperoxaluria because it can be primary (like AGXT, GRHPR, and HOGA1 mutations) or enteric (like Crohn's disease, malabsorption, post-bariatric surgery, and low Oxalobacter formigenes colonization). The impairment of ammonia genesis and acid excretion by hyperuricosuria and insulin resistance lowers urine pH and increases the danger of uric acid stones; urate crystals also encourage CaOx nucleation.

Dietary and Lifestyle Influences

These metabolic risk factors are made worse by obesity and insulin resistance. Consuming a lot of animal protein creates an acid load (from sulfur amino acids), which raises calcium and uric acid excretion while decreasing citrate. Sodium intake also exacerbates calciuria. Ironically, low dietary calcium promotes the absorption of oxalate; high quantities of vitamin C are converted to oxalate, increasing CaOx supersaturation.

Genetic and Anatomical Predisposition

Adenine phosphoribosyl transferase deficiency, cystinuria, Dent's disease, and different hyperoxalurias are monogenic stone illnesses that cause early, recurrent stone development. When there is an early onset or family history, these disorders may be candidates for genetic testing. Crystal retention and urine stasis are encouraged by anatomical anomalies such as polycystic illness, medullary sponge kidney, horse shoe kidney, or urinary tract blockages.

Microbiome and Emerging Mechanisms

Urinary oxalate excretion is reduced by oxalate-degrading bacteria like *Oxalobacter formigenes*; if this colonization is lost (for example, after taking antibiotics), the risk of CaOx increases. Recent studies indicate that microbial networks including multiple species can be more significant than individual species. [15,25,26]

Risk factors

Modifiable and non-modifiable factors are major risk factors for urolithiasis. Recurrence risk is significantly raised by genetic predisposition and personal history of stones. Male sex, age between the 30s and 50s, and family history all give increased susceptibility. Among modifiable risks, dehydration and low fluid intake, particularly in hot climates, significantly raise urinary supersaturation. Consuming a lot of animal protein, sodium, sugars (especially fructose), and foods high in oxalate (like spinach and nuts) increases the excretion of calcium, uric acid, and oxalate and lowers citrate, which favors the formation of crystals.[27] On the other hand, a lower risk of kidney stones is linked to a higher intake of dietary calcium, potassium, magnesium, fiber, fruits, and vegetables. Obesity, elevated body mass index, and rapid weight gain also increase the risk of kidney stones through insulin resistance, acidic urine pH, hypercalciuria, and hyperuricosuria. Metabolic diseases such as diabetes mellitus (type 2), gout, and hypertension are also linked to kidney stones independently, often through mechanisms like hypocitraturia and altered urine acidity. Smoking has been identified as a contributing factor by decreasing urine volume and increasing oxidative renal injury. Finally, underlying metabolic disorders such as hyperparathyroidism, distal renal tubular acidosis, primary hyperoxaluria, and medullary sponge kidney are recognized etiologies in a subset of stone-formers.[28,29]

Clinical features

Although most patients with significant calculi present with the characteristic renal or ureteric colic sudden, severe, intermittent flank pain radiating to the groin (testicle or labium), abdomen, or lower quadrant due to ureteral hyperperistalsis and obstruction patients with urolithiasis can range in severity from asymptomatic to critically ill. When stones irritate the bladder or ureterovesical junction, colicky pain usually lasts for 20 to 60 minutes in waves and is frequently accompanied by nausea, vomiting, microscopic or gross hematuria in up to 90% of cases, and urgency, frequency, or dysuria in the urine. Physical examination reveals a soft abdomen, hypoactive bowel sounds, costovertebral angle tenderness, restlessness, and pacing to find relief; peritoneal signs are usually absent. A higher index of suspicion should be applied to older patients whose presentations may be unusual or painless and are frequently linked to recurrent UTIs or obstructive anuria. Systemic symptoms like fever, leukocytosis, pyuria, or sepsis indicate an infection-related complication and indicate a urologic emergency that needs to be decompressed right away. [30-32]

Investigation

Basic laboratory testing, such as complete blood count, serum creatinine, electrolytes (such as calcium and uric acid), inflammatory markers (such as CRP), and urinalysis with microscopy and culture, should be performed on patients who present with suspected urolithiasis, particularly if infection is suspected. Hematuria (~85–90%) is commonly detected by urine dipsticks, and microscopy can reveal nitrites or pyuria. Imaging is crucial. For infants, pregnant women, or those who need repeated evaluation, preliminary radiation-free modalities such as renal ultrasound which is frequently paired with KUB X-ray to increase sensitivity while reducing exposure are favored.

The gold standard for diagnosing urinary calculi, however, is non-contrast enhanced computed tomography (NCCT), which has a sensitivity of 95% and a specificity of 96%. It provides precise evaluation of the size, location, burden, and degree of obstruction of the stone, as well as the estimation of its density and composition using dual-energy CT or Hounsfield units. KUB radiography is nevertheless helpful for detecting radiopaque stones and for monitoring known stone formers, even though its sensitivity is decreased (about 45–60%).

Although it is mostly out of date, intravenous urography can still be useful in some situations to evaluate anatomy and function (1). Cutting-edge techniques like dual-energy CT help with treatment planning by revealing information about the chemical makeup of stones. When renal function is questioned prior to procedures such as percutaneous nephrolithotomy, functional renal imaging (e.g., DTPA or MAG3 renography) may be taken into consideration.[33,34]

Diagnosis

Urolithiasis is mainly diagnosed clinically, with laboratory and radiographic evaluations supporting the diagnosis. In addition to nausea, vomiting, and occasionally hematuria, patients usually arrive with acute onset colicky flank discomfort that frequently radiates to the groin. Microscopic hematuria is detected in about 85% of patients, but its absence does not rule out stones, making urinalysis an extremely important first test. Serum creatinine, electrolytes, calcium, uric acid, and urine pH are among the other labs that aid in determining renal function and evaluating metabolic reasons. The use of imaging is essential:

NCCT: The gold standard for detecting urinary calculi of all compositions and sizes is non-contrast computed tomography (NCCT) of the abdomen and pelvis, which offers excellent sensitivity (>95%) and specificity (>96%).

ULTRASOUND: Although less sensitive for ureteral stones, ultrasound is helpful in preventing radiation exposure in children and pregnant women.

KUB X-ray: Due to its low sensitivity (between 45 to 60 %), KUB X-ray is not very useful, but it can help track radiopaque stones.
DUAL-ENERGY CT SCAN: When obstruction is suspected, functional imaging such as MAG3 or DTPA scans can evaluate differential renal function, and dual-energy CT can occasionally be used to characterize the composition of stones.[14,15,17,25]

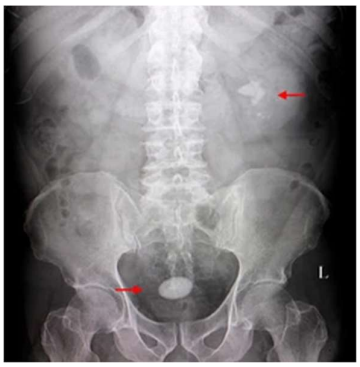

Fig 6: X-ray image of Urolithiasis

Treatment

The treatment of urolithiasis depends on the size, location, composition, presence of infection, and renal function of the stone.
MET: For distal ureteric stones ≤10 mm, conservative management with medical expulsive therapy (MET) using alpha-blockers such as tamsulosin, is effective, promoting spontaneous passage in up to 80% of cases.
Analgesia: Hydration is recommended but has not been proven to speed up stone passage. Stones larger than 10 mm, those causing obstruction, intractable pain, infection, or renal impairment, usually require intervention.
Extracorporeal shock wave lithotripsy: When ESWL fails or is not appropriate, ureteroscopy (URS) combined with laser lithotripsy is the preferred approach to treating mid-to-distal ureteric stones.
PCNL: For staghorn calculi, large renal stones (>20 mm), or lower pole stones that are not responding well to ESWL, percutaneous nephrolithotomy (PCNL) is the gold standard.
Decompression: Before definitive stone removal in infected obstructive urolithiasis, decompression must be performed immediately by ureteral stenting or percutaneous nephrostomy.
Metabolic evaluation and prevention strategies: Recurrent stone formers, metabolic assessment and preventative measures, such as medication (e.g., thiazides, citrate, allopurinol) and dietary changes, are essential.[35]

Complications

Complications from urolithiasis can range in severity from minor to fatal. Urinary flow obstruction is a frequent outcome that can lead to acute kidney injury (AKI), chronic kidney disease (CKD), or hydronephrosis, particularly when bilateral obstruction or just one kidney is functioning. If ureteral stenting or percutaneous nephrostomy is not performed immediately, infected obstructive uropathy a condition in which a urinary tract infection and blockage coexist can result in pyonephrosis, urosepsis, and septic shock. Long-term consequences for cardiovascular health and death may arise from the loss of renal function caused by persistent blockage and infection. Other risks include stone-induced ureteral damage, which can result in strictures, ureteral perforation, or the formation of urinoma, and hematuria, which can be severe or persistent. In a few cases, fistulae, xanthogranulomatous pyelonephritis, or emphysematous pyelonephritis may occur, especially in patients with diabetes or impaired immune systems. Around 50% of patients will acquire new stones within 5–10 years, making recurrent stone development a serious problem.[36] This is especially true if metabolic evaluation and preventative measures are not implemented.

Prevention and Management

Recurrence, which affects up to 50% of patients after 5–10 years, can be decreased with targeted medical therapy, metabolic evaluation, and risk factor adjustment as the mainstays of long-term urolithiasis prevention. Recommendations for lifestyle changes should be given to all patients. These include reducing animal protein and sodium intake, maintaining a balanced calcium intake, and increasing fluid intake to reach urine output >2.5 L/day, since both high and low calcium diets can raise the incidence of stones. To detect metabolic abnormalities like hypercalciuria, hyperoxaluria, hypocitraturia, or hyperuricosuria that direct pharmacologic interventions, a 24-hour urine analysis is crucial for high-risk individuals or recurrent stone formers.[3]

While potassium citrate helps with hypocitraturia and prevents calcium oxalate and uric acid stones by alkalizing the urine, thiazide diuretics are used to lower urinary calcium excretion in hyper-calcemic individuals.[16] Allopurinol or febuxostat may be recommended to reduce serum and urine uric acid levels in cases of uric acid stones. Recurrence risk is further decreased by dietary oxalate reduction, increased consumption of citrate-rich fruits and vegetables, and maintaining a normal body mass index. In order to prevent new stone formation and maintain renal function, follow-up involves routine imaging, laboratory testing, and reevaluation of adherence to dietary and pharmacologic regimens.[17]

Current Research

The new minimally invasive technologies, creative pharmacotherapies, and precision diagnostics are being investigated in urolithiasis research.

Intraoperative Endoscopic Video Processing: With the use of artificial intelligence in intraoperative endoscopic video processing, it is now possible to identify the morphology of different types of stones in real time with a high degree of accuracy (~88%), which could help guide treatment decisions without the need for manual sample analysis. On the basis of genetic risk profiles, deep learning models such as CNN-enhanced polygenic risk scores are being researched in parallel to predict an individual's susceptibility to stone disease.

Nanotechnology-Based Methods: In terms of treatment, new nanotechnology-based methods and experimental burst wave lithotripsy tools seek to break up and remove stones without causing pain or requiring stents or anesthesia.

Spinner-Assisted Fragment Removal Devices: Device technical advancements include spinner-assisted fragment removal devices that improve clearance efficiency during RIRS, catching dozens of pieces in a single pass and drastically cutting down on operative times.

3D-Printed: To improve accuracy in intricate renal anatomy, 3D-printed patient-specific PCNL puncture guides and robotic-assisted flexible ureterorenoscopy are being developed.

RNA Interference: Furthermore, RNA interference therapies and gene editing agents like lumasiran, nedosiran (RIVFLOZA), and early-stage CRISPR-based treatments like YOLT-203 are becoming available for primary hyperoxaluria. By inhibiting the production of oxalate, these treatments may provide a one-time, permanent cure.

Nutritional Research: Dietary niacin intake has also been linked in epidemiologic cohorts to a ~22% lower incidence of kidney stone development, according to nutritional research, which opens the door to preventative dietary measures.[25,37]

Traditional Medicinal Plants Used for Urolithiasis

Through the use of their bioactive components, a number of plants have shown antilithiatic, diuretic, anti-inflammatory, and antioxidant properties in a variety of traditional systems, including Ayurveda, Unani, Chinese, and Philippine folk medicine.[38-40]

Table 1: Traditional Medicinal Plants Used in the Management of Urolithiasis and Mechanisms of Action

Plant Name (Botanical)	Key Phytoconstituents	Mechanism of Action
Ammi visnaga (Khella)	Khellin, visnagin (furanochromones)	Increases urinary citrate, inhibits nucleation, protects renal epithelium
Bergenia ligulata	Bergenin, β-sitosterol, gallic acid	Antilithiatic, inhibits CaOx crystal formation
Dolichos biflorus (Horse gram)	Flavonoids (quercetin), β-sitosterol, alkaloids, saponins	Inhibits crystal aggregation, shows litholytic activity
Phyllanthus niruri ("Stone breaker")	Lignans, phyllanthin, hypophyllanthin, flavonoids	Inhibits CaOx crystallization, reduces oxalate/uric acid, increases urinary Mg^{2+} & K^{+}
Tribulus terrestris	Saponins (protodioscin), flavonoids, phytosterols	Inhibits nucleation, has diuretic and anti-inflammatory effects
Solanum xanthocarpum	Saponins, steroidal glycoalkaloids, triterpenoids	Prevents crystal aggregation, reduces hyperoxaluria, oxidative renal damage
Urtica dioica (Stinging nettle)	Flavonoids, anthocyanins, saponins	Diuretic, antioxidant, inhibits CaOx crystallization

CONCLUSION

Urolithiasis's high prevalence, recurrence, and related morbidity make it a persistent clinical and public health concern. Complex interactions between dietary, metabolic, genetic, and environmental factors lead to the

condition. The capacity to properly diagnose and treat urinary stones has significantly improved thanks to developments in imaging and minimally invasive surgery. Nonetheless, metabolic control, nutritional advice, and personalized risk assessment are still essential for preventing recurrence. Hope for focused interventions in the near future is given by encouraging advancements in gene therapies, AI-based surgical instruments, and precision diagnostics. Furthermore, a wealth of possible antilithiatic compounds can be found in traditional medicinal herbs, highlighting the importance of integrative approaches in the treatment of this ancient illness. Reducing the global incidence of urolithiasis requires a thorough, patient-centered approach that blends cutting-edge technology with preventative treatment.

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