African Journal of Urology

REVIEW

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# Urolithiasis unveiled: pathophysiology, stone dynamics, types, and inhibitory mechanisms: a review

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**Abstract**

Urolithiasis is a multifaceted and common urological disorder characterized by the development of renal calculi. Calcium oxalate stones are the most prevalent type of calculi, forming when calcium and oxalate combine to produce crystalline structures in the urine. The incidence rates of urolithiasis exhibit geographical variations, which are determined by factors such as geographic location, age, sex, dietary habits, and genetics. The increasing trend of urolithiasis has emerged as a noteworthy public health issue, potentially attributed to shifts in dietary and lifestyle habits. In response to this challenge, various inhibitors of calcium oxalate crystal formation, including small molecules, peptides, and proteins, have been developed. Moreover, substances such as citrate, magnesium, inter-alpha-trypsin inhibitors, phytate, potassium, and pyrophosphates show promise in preventing kidney stones. A comprehensive metabolic assessment is crucial, customized for each patient, to effectively manage and avoid the recurrence of urolithiasis. Although specific pharmacological treatments for urolithiasis are currently unavailable, some drugs can reduce pain. Some drugs, including calcium channel blockers like nifedipine, phosphodiesterase-5 inhibitors like tadalafil, and alpha-blockers like tamsulosin, are thought to lower ureteral contractions by making the ureteral smooth muscle relax. In acute and severe pain cases, intravenous administration of narcotic analgesics and anti-inflammatory agents may be employed in emergency medical settings. To enhance therapeutic approaches, it is essential to gain more knowledge about the pathophysiology of renal calculi. The development of inhibitors targeting calcium oxalate crystal formation offers a promising avenue for urolithiasis prophylaxis. Identifying and investigating potential inhibitors lays the framework for the creation of more effective and targeted therapeutic options.

**Keywords** Urolithiasis pathophysiology, Stone types, Kidney stones, Calculi inhibitors, Stone promoters

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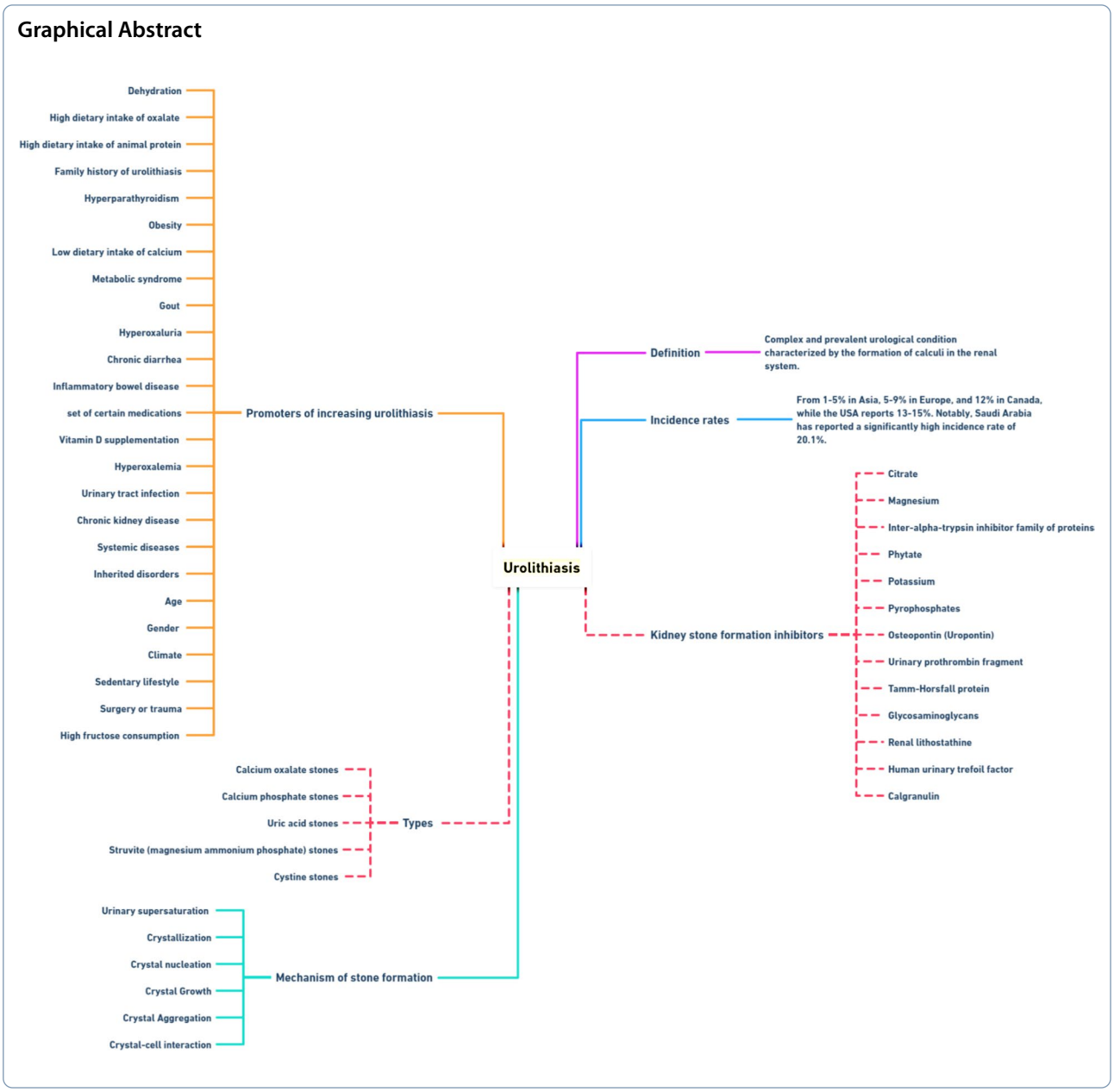


## 1 Background

Urolithiasis, derived from the Greek 'ouron' (urine), 'oros' (flow), and 'lithos' (stone), is a complex urological disorder characterized by the production of calculi in the kidneys, bladder, and urethra. Despite its long-standing prevalence in humans, urolithiasis poses significant medical and public health challenges [1]. The most common type of calculi in urolithiasis are calcium oxalate (CaOx) stones, which form when calcium combines with oxalate in the urine, resulting in crystalline structures. Other forms of calculi include uric acid, cystine, struvite, xanthine, ammonium acid urate, drug-induced stones, and dihydroxyadenine stones [2].

The geographical incidence of urolithiasis displays fluctuation, with generally greater rates in Western countries compared to the Eastern hemisphere. The incidence rates are approximately 1–5% in Asia, 5 to 9% in Europe, and 12% in Canada, with the USA reporting rates between 13 and 15%. A notably high incidence rate of 20.1% has been recorded in Saudi Arabia [3, 4]. Influencing factors include age and sex, with a larger prevalence in males compared to females [5], and the condition is most commonly observed in individuals in their thirties and forties

[6]. The growing trend of urolithiasis over time is likely linked to changes in diet and lifestyle [7]. Since 1990, there has been a global increase in urolithiasis cases, disability-adjusted life years, and mortality rates [8]. In 2007, the estimated cost of treating urolithiasis in the United States was $3.79 billion, with forecasts showing a yearly increase of $1.24 billion by 2030 [9]. The chemical composition of organic components, such as phospholipids and albumin, contributes to the formation of CaOx and calcium phosphate calculi, influencing the development of various types of urolithiasis [10]. Factors affecting incidence rates include geographic location, climate, ethnicity, dietary habits, and genetics [11].

Managing urolithiasis requires comprehensive metabolic evaluation to prevent recurrence, with treatments tailored to individual patient needs [12]. While specific pharmacological treatments remain unavailable, some medications can alleviate pain. For instance, alpha-blockers like tamsulosin, particularly when combined with dutasteride, aid in the passage of calculi, reducing discomfort by relaxing the ureteral smooth muscles [13]. Calcium channel blockers such as nifedipine and phosphodiesterase-5 inhibitors like tadalafil are also effective in reducing ureteral contractions [14]. In severe cases, intravenous narcotic analgesics and anti-inflammatory agents are administered in emergency settings [14]. Developing inhibitors that target CaOx crystal formation is a promising approach to preventing urolithiasis. A comprehensive, multidisciplinary approach, integrating various treatment modalities, is essential for the successful management and prevention of urolithiasis recurrence.

## 2 Methodology of literature searching

We searched electronic databases including PubMed, ScienceDirect, and Scopus to gather information on the prevalence of urolithiasis, the different types of stones, inhibitors, and promoters. The search covered the period from 2000 to August 2023. Keywords used in the search were "kidney stone", "urolithiasis", "nephrolithiasis", "renal calculi", "renal stone", "kidney stone inhibitors", "kidney stone promoters", "kidney stone types", and "kidney stone formation mechanisms".

## 3 Pathophysiology of urolithiasis

Environmental and genetic variables both influence the complexity and multifaceted nature of urolithiasis. The development of urinary stones involves various mechanisms, and the formation of CaOx stones differs from that of other types of stones. Impaired renal acidification, along with altered renal excretion or excessive absorption in the digestive tract, leads to the accumulation of stone-forming metabolites [15].

Among the distinct pathomechanisms of CaOx stone formation, Randall plaques and mineral deposits, play a critical role [16, 17]. However, the emergence and pathophysiology of CaOx stones are still poorly understood, necessitating further research to identify effective prevention and treatment strategies. Recent studies suggest that the formation of interstitial apatite crystals may be an initial step in the development of CaOx stones [18].

Reduced urine volume raises the concentration of stone-causing compounds, which in turn promotes crystallization and stone formation, making urine volume a critical factor in the pathophysiology of urolithiasis [19]. Kidney stones are more likely to form when urine volume is reduced, which can happen as a result of dehydration, some drugs, or medical issues that impact fluid balance or urinary function. One of the most prevalent causes of kidney stones is not drinking enough water [20].

Certain medical conditions can increase the risk of developing kidney stones. Renal tubular acidosis is a condition in which the kidneys are unable to eliminate acids from the blood into the urine, leading to an increase in blood acidity. Other conditions, such as cystinuria, hyperparathyroidism, and recurring urinary tract infections, can also increase the chance of kidney stone formation [21, 22]. Further research is needed to fully comprehend the pathophysiology of these disorders and develop effective preventive and treatment strategies for urolithiasis.

## 4 Mechanism of stone formation

In individuals with risk factors for stone formation, such as high urinary supersaturation, low urinary volume, or low urinary pH, crystals may nucleate and aggregate into larger particles, potentially forming a stone. Stone formation can occur in various locations within the urinary tract, including the kidneys, ureters, bladder, and urethra. The development of stones can be influenced by several factors, including genetics, diet, lifestyle, and medical conditions such as urinary tract infections or metabolic disorders [18, 23].

Once a stone has formed, it can continue to grow with the addition of new crystals and may also move within the urinary tract, leading to pain and other symptoms. The ability of a stone to move through the urinary tract can be influenced by its size and chemical makeup. While larger stones may require medical intervention for removal, smaller stones are more likely to pass spontaneously [24, 25].

### 4.1 Urinary supersaturation

The initial stage of kidney stone formation is urinary supersaturation, which occurs when the concentration of certain substances in the urine, such as calcium, oxalate,

and phosphate, exceeds their solubility limit. This leads to a state in which the urine becomes supersaturated, creating an environment conducive to the formation of crystals. Under these conditions, the excess solutes can no longer remain dissolved and begin to aggregate, resulting in the formation of small crystal particles [26]. These small particles can then combine and grow into larger crystals, eventually leading to the formation of kidney stones.

The degree of supersaturation, along with other factors such as urinary pH and the presence of inhibitors or promoters of crystal growth, can significantly influence the formation and growth of crystals, and ultimately the development of kidney stones. Understanding the factors contributing to urinary supersaturation and the subsequent crystal formation is important for the prevention and treatment of kidney stones [26, 27].

### 4.2 Crystallization

The process of crystallization occurs when urine becomes oversaturated, leading to the formation of solid crystals. The specific type and characteristics of the crystals depend on the substances present in the urine and the conditions prevailing during their formation. Kidney stones, are a common result of this process, with types including CaOx, calcium phosphate, and uric acid stones, which are caused by high concentrations of these substances in the urine [27].

The process of crystal formation is influenced by a multitude of factors, including the pH level of urine, the concentration of minerals that encourage stone formation, and the presence of inhibitors that hinder crystal growth. As crystals accumulate and grow, they can lead to the formation of urinary casts, which obstruct urine flow and promote further stone formation [28].

The development of effective strategies for the prevention and treatment of kidney stone disease depends on our understanding of the mechanisms that influence crystal formation and growth [29].

### 4.3 Crystal nucleation

The phenomenon of nucleation is a crucial aspect of crystal formation from a supersaturated solution. It involves the aggregation of solute molecules or ions to form a stable nucleus, which then serves as a basis for subsequent crystal growth. As a result, a crystal structure with a distinct lattice pattern is produced. Crystallization can occur in confined spaces within a solution, such as those present in certain regions of the nephron [30], and on surfaces such as cells and the extracellular matrix. Nucleation can occur through two main mechanisms: homogeneous nucleation, which arises spontaneously within the solution, and heterogeneous nucleation, which occurs on the surface of a foreign particle or solid surface [31].

### 4.4 Crystal growth

After nuclei formation, crystals grow by adding new molecules to the crystal lattice. The rate of growth depends on various factors, such as the concentration of salts that form stones, urine pH, and the presence of inhibitors or promoters of crystal growth [32]. Inhibitors of crystal growth, such as citrate and magnesium, help prevent crystal aggregation and growth by binding to crystal surfaces and inhibiting their further growth [33]. Promoters of crystal growth, such as calcium and oxalate, can facilitate the aggregation and growth of crystals by increasing their surface charge and promoting attachment to other crystals or surfaces [32].

### 4.5 Crystal aggregation

Over time, crystals can aggregate to form larger particles, which may lead to the formation of stones. The aggregation of crystals can be influenced by several factors, including the concentration and composition of the stone-forming salts, the pH of the urine, and the presence of organic and inorganic molecules that can act as bridging agents or inhibitors of crystal aggregation [32, 34]. The formation of stones can also be influenced by urine flow rates; slower flow rates allow for increased crystal aggregation and growth, whereas faster flow rates promote the flushing out of crystals, thereby preventing their aggregation [35].

### 4.6 Crystal-cell interaction

The interaction between crystals and renal epithelial cells is a critical factor in the pathogenesis of kidney stones. When crystals adhere to the cell surface, they can cause injury and inflammation. This process can further promote crystal growth and aggregation, as well as the recruitment of immune cells and the release of inflammatory mediators. The attachment of crystals to renal cells occurs through various mechanisms, including electrostatic interactions, surface receptors, and extracellular matrix proteins. Once attached, crystals can cause cellular injury through multiple pathways, such as membrane disruption, oxidative stress, and mitochondrial dysfunction. These changes lead to the release of danger signals and the activation of inflammatory pathways, further exacerbating crystal-induced injury and inflammation. The interaction between crystals, renal cells, and immune cells can also lead to the formation of urinary casts, which may obstruct urine flow and promote stone formation. In addition to renal epithelial cells, immune cells such as macrophages and T cells can contribute to the progression of kidney stone disease by releasing

**Table 1** Represents kidney stone inhibitors and their mechanisms

| Name of the inhibitor | Mechanism |
|---|---|
| Citrate | The effect of citrate on CaOx and calcium phosphate crystallization has been extensively researched. Citrate mostly binds to calcium ions in urine, resulting in a decrease in CaOx concentration. This effect is thought to occur due to crystal surface contact rather than a change in the availability of free calcium. As a result, citrate efficiently suppresses CaOx production and clumping [72].<br>Also, it has been shown that citrate stimulates the activity of large molecules in urine called Tamm Horsfall protein (THP), which inhibits CaOx aggregation. Likewise, citrate can inhibit the expression of osteopontin (OPN), a constituent protein in urinary stones. Finally, when excreted in the urine, citrate raises pH levels, which assists in the formation of complexes between calcium and phosphate [73]. |
| Magnesium | Magnesium, like calcium, has been shown to reduce oxalate absorption and excretion in the GI tract [74]. According to studies, individuals with magnesium deficiency who take magnesium supplements have higher amounts of citrate in their urine [75]. There is currently no evidence to support the use of magnesium treatment for patients with urolithiasis. |
| Inter-alpha-trypsin inhibitor family of proteins | The inter-alpha-trypsin inhibitor (IαI), also called bikunin, is a glycoprotein composed of a light chain and two heavy chains. It belongs to the Kunitz-type protein superfamily [76]. Some studies have proposed that this protein might alter how crystals adhere to and remain in tubules during urolithiasis [77]. These proteins have been shown in studies to reduce CaOx crystal formation and fragments of these proteins have effectively been found in urine. This shows a link between IαI and the development of CaOx stones [17]. |
| Phytate | Phytate, a naturally occurring compound found in plant-based foods, has shown promise in reducing the formation of calcium stones. It achieves this by binding calcium in the Gastrointestinal tract (GIT), preventing its absorption into the bloodstream. By limiting the availability of calcium for crystallization, phytate helps inhibit the development of calcium stones in the kidneys and urinary system [78]. |
| Potassium | It has been demonstrated that potassium may play a role in reducing the occurrence of kidney stones. This is achieved by decreasing the amount of calcium excreted through urine. By lowering the levels of calcium for crystallization, potassium helps to minimize the risk of stone formation [79]. |
| Pyrophosphates | Diphosphate and pyrophosphate have been shown to prevent the precipitation of calcium phosphate. Additionally, diphosphates have been discovered to inhibit the formation of crystals [80]. In contrast, pyrophosphate is known to reduce the absorption of calcium in the intestines. This effect is believed to be mediated by the production of 1,25-dihydroxy vitamin D [76]. |
| Osteopontin (Uropontin) | Osteopontin is a protein rich in charged aspartic acid. Research has shown that it has properties against the growth of CaOx crystals. In vitro studies have demonstrated that OPN plays a role in preventing the attachment of these crystals to epithelial cells, thereby reducing their ability to adhere to urinary tract surfaces and potentially decreasing the formation of kidney stones. This highlights that OPN can play a role in minimizing the formation, enlargement, and clumping of CaOx crystals [81]. |
| Urinary prothrombin fragment 1 | Prothrombin, a component in the clotting of blood, undergoes breakdown into three components: thrombin, fragment 1, and fragment 2. Among these fragments is Urinary Prothrombin Fragment 1 (UPTF1), which is released into the urine. UPTF1 has demonstrated properties in preventing the aggregation and attachment of CaOx crystals to kidney cells [82, 83]. |
| Tamm-Horsfall protein (THP) or mucoprotein | The presence of mucoproteins in urine, which are commonly known as uromucoid or uromodulin, has implications for understanding and preventing the formation of urinary stones. Several studies have demonstrated the effectiveness of uromucoid in preventing the clumping of COM crystals under conditions such as high pH levels, low ionic strength, and low concentrations of divalent ions and THP. In these conditions, uromucoid plays a crucial role in preventing the aggregation of crystals [84].<br>The ability of the uromucoid to inhibit crystal aggregation may be influenced by factors such as pH, elevated levels of calcium, sodium, and hydrogen ions, and low THP levels. This variation in the effects of uromucoid emphasizes how important it is to consider these factors [85]. |
| Glycosaminoglycans | Glycosaminoglycans (GAGs) are significant macromolecules present in the stone matrix that have significance for urolithiasis. Chondroitin sulfate, heparin sulfate, and hyaluronic acid are types of GAGs that are present in urine. These GAGs are thought to have a significant impact on CaOx crystallization. Studies conducted in vitro have shown that GAGs function as inhibitors for both the growth and aggregation of CaOx crystals [86]. |
| Renal lithostathine | Lithostathine is a protein present in pancreatic secretions and has been studied for its role in urolithiasis. Notably, lithostathine has been determined to inhibit calcium carbonate crystal growth effectively. Its presence regulates the growth of calcium carbonate crystals, which, in the absence of inhibitory factors such as lithostathine, can serve as a substrate for heterogeneous nucleation. This heterogeneous nucleation process can promote the formation of CaOx crystals in supersaturated urine, contributing to the development of kidney stones.<br>Lithostathine helps protect against the formation of CaOx crystals, which can lead to urolithiasis, by stopping the growth of calcium carbonate crystals [87, 88]. |

**Table 1** (continued)

| Name of the inhibitor | Mechanism |
|---|---|
| Human urinary trefoil factor | Human urinary trefoil factor, which is made by mucosal epithelial cells, is a potent inhibitor of CaOx crystal formation. This component, according to research, plays a key role in controlling CaOx crystal formation and development. As an inhibitor, the urinary trefoil factor is predicted to interfere with CaOx crystal aggregation and development. Thus, it should help prevent kidney stone formation [89, 90]. |
| Calgranulin | Calgranulin is present in both kidney and human urine. Its effectiveness as a strong inhibitor of COM crystal growth has been proven [91]. |

inflammatory cytokines and chemokines. This cycle of injury and inflammation can promote the growth and aggregation of stones, contributing to the development and progression of kidney stone disease [27].

## 5 Types of urolithiasis

Urinary stones are categorized into five major types.

### 5.1 Calcium oxalate stones

Calcium oxalate urolithiasis is the most prevalent form of urinary stone, accounting for roughly 50% of all cases [36]. Hypercalciuria, a condition often associated with calcium kidney stones, has an etiology that is still not fully understood. In order to impede the formation of CaOx stones, it is advisable to regulate urine chemistry through controlled modification of sodium, citrate, oxalate, uric acid, calcium, and specific gravity levels [37]. By adhering to a straightforward dietary plan that targets five urinary parameters, patients with idiopathic CaOx stone formation may reduce their urinary supersaturation. This plan places emphasis primarily on dilute urine concentration, diminishing crystallization promoters (via lowering oxalate), and elevating crystallization inhibitors (through increased citrate). Absorption of intestinal oxalate can be reduced through higher fluid intake and calcium consumption during meals [38].

There is evidence that high dietary calcium intake can expedite kidney stone development, while consuming low-calcium foods alongside oxalate-rich ones may decrease this risk [39]. Additionally, the development of uric acid and CaOx stones is substantially correlated with obesity, unlike stones comprising calcium phosphate or cystine [40]. The development of renal papillary calcifications shows relevance in prognostic ability in CaOx urolithiasis cases. Further research into these facets is merited to inform effective preventative strategies against stone formation [41].

### 5.2 Calcium phosphate stones

Calcium phosphate stones, a type of urolithiasis stone, constitute approximately 10–20% of all urinary stones [36], representing a significant global urological concern. Recent research has demonstrated that calcium urolithiasis often arises due to renal phosphate leakage and concomitant phosphaturia. Individuals with abnormally elevated levels of phosphate in their urine (known as hyperphosphaturia) are at a heightened risk for the recurrence of these stones [42].

### 5.3 Uric acid stones

Uric acid stones, a specific type of urolithiasis, comprise approximately 10% of all instances of urinary calculi. These radiolucent stones can be efficiently treated using endoscopic and chemotherapeutic techniques, as well as surgical interventions such as percutaneous nephrolithotomy and extracorporeal shock wave lithotripsy [43]. The etiology of uric acid urolithiasis is still not fully understood despite intensive investigation. Hyperuricosuria, consistently low urine pH, and low urinary volume are risk factors for the development of these stones. Diseases such as uncontrolled diabetes mellitus, gout, and leukemia, which cause hyperuricosuria are known to predispose individuals to uric acid urolithiasis [44]. Additionally, dietary modifications, including reduced salt intake and limited consumption of animal protein, have been demonstrated to be effective in preventing uric acid stones [45].

### 5.4 Struvite (magnesium ammonium phosphate) stones

Urinary tract stones known as struvite or magnesium ammonium phosphate stones can develop in the urinary tract. These stones often occur in individuals with urinary tract infections caused by bacteria that produce urease, such as Klebsiella or Proteus [46]. Although not as common as CaOx stones, this type of urinary stones constitutes approximately 10–15% of all cases. They are more prevalent in females and individuals with a history of recurrent urinary tract infections [47, 48]. Struvite stones, composed of ammonium, magnesium, and phosphate can form when urease produced by bacteria breaks down urea in the urine, resulting in a rise in pH and the formation of struvite crystals that can aggregate and form stones [49]. The prevention of struvite stones involves treating and preventing Urinary tract infections (UTIs)

**Table 2** Represents kidney stone promoters and their mechanisms

| Name of the promoter | Mechanism | Refs. |
|---|---|---|
| Dehydration | Dehydration can lead to more concentrated urine, consequently increasing the risk of the development of urinary stones. | [92] |
| High dietary intake of oxalate | Urinary stones made of CaOx are composed of oxalate. Eating a diet high in oxalate can increase the risk of developing these stones. This is because consuming a lot of oxalates can result in more excreted oxalates in the urine, leading to the formation of CaOx crystals in the urinary tract. | [93] |
| High animal protein dietary intake | Eating animal protein can lead to higher levels of calcium and uric acid in the urine, which can increase the risk of developing urinary stones. | [94] |
| Family history of urolithiasis | Urolithiasis has been recognized to be genetically linked, and those with a family history of the disease may have a higher probability of developing urinary stones. | [95] |
| Hyperparathyroidism | Hyperparathyroidism, a condition characterized by excessive secretion of parathyroid hormones, can lead to an increase in urinary calcium excretion, which can contribute to the formation of urinary stones. | [96] |
| Cystinuria | Cystinuria is a genetic disorder that affects the kidneys' capacity to reabsorb cystine, an amino acid, resulting in the formation of cystine stones. | [58, 97] |
| Hyperuricosuria | Hyperuricosuria is a condition characterized by increased levels of uric acid in the urine, which can significantly increase the risk of developing uric acid stones. | [98] |
| Obesity | Research has linked obesity to an increase in the amount of calcium passed through the urine, which can contribute to the creation of urinary stones. Having extra weight and being obese can cause changes in metabolic processes, including those related to bone and mineral metabolism. | [99] |
| Low dietary intake of calcium | Because oxalate is more easily absorbed in the GIT when there is low dietary calcium intake, this can increase the risk of stone formation. | [100, 101] |
| Metabolic syndrome | Metabolic syndrome refers to a cluster of metabolic disorders, including obesity, insulin resistance, and dyslipidemia. This complex condition can significantly increase the risk of stone formation by influencing urinary chemistry and promoting inflammation. | [102, 103] |
| Gout | Gout is a type of arthritis that is identified by hyperuricemia, which means that you have elevated levels of uric acid in your bloodstream. This condition can increase the chances of stone formation by encouraging the release of uric acid through urine. | [104] |
| Hyperoxaluria | Hyperoxaluria is a medical condition where there is an excess amount of oxalate excreted in the urine, resulting in an increased level of oxalate in the urine. This condition increases the likelihood of the formation of CaOx stones in the urinary tract. | [105] |
| Chronic diarrhea | Chronic diarrhea can increase the chances of developing stones in the body due to the poor absorption of minerals such as calcium. This leads to the discharge of these minerals into the urine in greater amounts. | [106] |
| Inflammatory bowel disease | Individuals diagnosed with inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, may be at increased risk of developing urinary stones due to alterations in urinary chemistry and a higher risk of dehydration. | [107, 108] |
| List of certain drugs | It is pertinent to acknowledge that specific medications, such as diuretics, calcium-containing antacids, and protease inhibitors, have the potential to modify the chemical composition of urine, thus increasing the vulnerability to urinary stone formation. It is advisable to be cognizant of the potential effects of these medications and respond appropriately to mitigate the risks associated with their use. | [109] |
| Vitamin D supplementation | High doses of vitamin D can enhance calcium absorption in the GIT and increase calcium excretion in the urine, thus promoting the development of stones. | [110, 111] |
| Hyperoxalemia | Hyperoxalemia is a medical condition characterized by elevated levels of oxalate in the blood. This condition can indeed increase the risk of stone development by encouraging the creation of CaOx stones in the urinary system. | [112] |
| Urinary tract infection | Urinary tract infections can result in an increased risk of kidney stone formation by affecting urinary chemistry and potentially aggravating dehydration. UTIs can cause alterations in the composition of urine, such as changes in pH and the presence of various substances, including bacteria and white blood cells. These changes can create conditions that promote the crystallization and aggregation of certain minerals, such as calcium or struvite, in the urinary tract. | [113, 114] |
| Chronic kidney disease | Chronic kidney disease (CKD) is associated with an elevated risk of developing kidney stones. This is due to the alterations in the composition of urine that CKD instigates, which can lead to the formation of crystals that eventually transform into kidney stones. CKD can impede the filtration and clearance of waste products from the blood, causing substances to accumulate in the urine and contribute to stone formation. These findings suggest that CKD can serve as a significant risk factor for kidney stone development, and further research is warranted to better understand this relationship. | [17, 115, 116] |
| Systemic diseases | Systemic diseases like diabetes and cardiovascular diseases can affect urinary chemistry and potentially raise the risk of kidney stone formation. | [27, 117] |

**Table 2** (continued)

| Name of the promoter | Mechanism | Refs. |
|---|---|---|
| Inherited disorders | Inherited conditions such as Dent disease and distal renal tubular acidosis can modify the urinary chemistry and increase the likelihood of developing kidney stones. | [118, 119] |
| Age | As individuals advance in age, they become increasingly susceptible to urolithiasis, commonly referred to as kidney stones. This increased risk can be attributed to altered urine composition and a greater propensity for comorbidities. | [120, 121] |
| Gender | Males have urolithiasis more frequently than females, which could be attributed to differences in urinary anatomy and hormonal factors. | [122–124] |
| Climate | It is plausible that hot and dry climates could elevate the risk of stone formation by promoting fluid loss through sweating and decreasing urine output. | [125, 126] |
| Sedentary lifestyle | A sedentary lifestyle and lack of physical activity may heighten the risk of urolithiasis by reducing urinary output and altering urinary chemistry. | [127] |
| Surgery or trauma | Urinary tract injuries or surgeries can increase the likelihood of developing stones and blockages due to altered urine composition. | [128] |
| High fructose consumption | Studies have shown a correlation between high fructose consumption and an increased risk of developing stones. This is due to the elevation of urinary excretion levels of uric acid and oxalate. | [129, 130] |

caused by bacteria that produce urease through antibiotic treatment and good hygiene practices [50]. Additionally, maintaining urinary tract health and adequate fluid intake can also help prevent the formation of struvite stones [51, 52]. Depending on their size and location, struvite stones require different treatments: small stones may pass spontaneously, whereas larger stones might necessitate medical intervention [53].

### 5.5 Cystine stones

Cystine stones, an uncommon form of kidney stone, form due to an inherited metabolic disorder called cystinuria. This disorder leads to an elevated concentration of cystine in the urine, which can crystallize and form stones in the kidneys, ureters, or bladder [54, 55]. Characterized by their yellowish-brown color and hexagonal shape, they are typically larger and harder than other types of kidney stones. The prevalence of cystinuria, the underlying cause of cystine stones, is estimated to be around 1 in 7,000 to 1 in 20,000 individuals worldwide. However, it varies among different ethnic groups, with higher rates reported in certain populations such as Ashkenazi Jews, Libyans, and Cypriots [56, 57]. Cystine stones consist of cystine, an amino acid that contains sulfur. Due to its low solubility, cystine tends to precipitate and form crystals in urine, resulting in the formation of cystine stones [58, 59]. The primary prevention of cystine stones involves managing cystinuria through dietary modifications and medical interventions, including maintaining a high fluid intake, adhering to a low-sodium diet, and avoiding excessive intake of animal protein [60, 61]. Medical therapy for cystinuria involves the use of medications such as alpha-mercaptopropionylglycine (tiopronin) or D-penicillamine, which help to reduce cystine concentration in the urine by forming soluble complexes with cystine [62]. Conservative management, pain management, and surgical intervention may also be necessary for the treatment of cystine stones [63, 64].

## 6 Kidney stone formation inhibitors

Significant progress has been made recently in the creation of inhibitors that target the formation of CaOx crystals, such as small molecules, peptides, and proteins [65, 66]. These inhibitors play a crucial part in preventing the pathological crystallization of CaOx crystals (Table 1). Notably, growth-inhibiting compounds with acidic moieties, including carboxylates, phosphates, and sulfates, have demonstrated remarkable suppression of calcium oxalate monohydrate (COM) crystal expansion, attributed to their specific association with $Ca^{2+}$ ions on crystalline interfaces [65, 67, 68]. Moreover, synthetic peptides, polymers, and proteins have also exhibited significant COM crystal formation inhibition [67, 69]. However, it is noteworthy that the synthesis of these potent inhibitors primarily relies on synthetic methods, leading to substantial expenses and potential regulatory approval challenges [70, 71].

## 7 Promoters of increasing urolithiasis

Urolithiasis can emerge due to a diverse range of factors, involving genetic, environmental, and lifestyle influences. Some examples of these factors, along with their respective mechanisms of promoting urolithiasis, are provided in Table 2.

## 8 Conclusion

Urolithiasis presents a significant public health challenge, necessitating continued research to enhance our understanding and treatment of this condition. The pathophysiology of urolithiasis is a dynamic process involving a series of events, from supersaturation and nucleation to crystal aggregation and ultimately stone production. Numerous variables, such as the pH of the urine, crystal promoters and inhibitors, and anatomical variations, impact this condition. The exploration of potential inhibitors of calcium oxalate crystal formation shows promise in revolutionizing urolithiasis prevention strategies. Through a systematic approach that combines various modalities, we can effectively manage urolithiasis, thereby mitigating its impact on global health. The landscape of research is evolving, emphasizing the importance of genetics and molecular pathways, and opening exciting opportunities for future therapeutic approaches.

**Abbreviations**

| | |
|---|---|
| CaOx | Calcium oxalate |
| COM | Calcium oxalate monohydrate |
| THP | Tamm-Horsfall protein |
| OPN | Osteopontin |
| GAGs | Glycosaminoglycans |
| GIT | Gastrointestinal tract |
| UTIs | Urinary tract infections |
| CKD | Chronic tract infections |

**Acknowledgements**
Not applicable.

**Author contributions**
E A. H. A designed the structure of the paper, drafted the manuscript, performed the literature search, wrote, and revised the manuscript.

**Funding**
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Availability of data and materials**
The data supporting this study are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
All authors declare that they have no competing interests.

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Received: 19 October 2023 Accepted: 10 July 2024
Published online: 23 July 2024

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