EJPMR, 2026, 13(1), 491-499 **Review Article** **Impact Factor 7.065**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

A REVIEW ON THERAPEUTIC POTENTIAL OF CITRIC ACID IN NEPHROLITHIASIS: MECHANISM OF STONE FORMATION AND PREVENTION

Diksha*[1], Preeti[2]

[*1,2]CT College of Pharmacy, Shahpur, Jalandhar, India, Pincode-144020.

***Corresponding Author: Diksha**

CT College of Pharmacy, Shahpur, Jalandhar, India, Pincode-144020.

https://doi.org/10.5281/zenodo.18205804

How to cite this Article: Diksha*[1], Preeti[2] (2026). A Review On Therapeutic Potential Of Citric Acid In Nephrolithiasis: Mechanism Of Stone Formation And Prevention. European Journal of Pharmaceutical and Medical Research, 13(1), 491–499.

Article Received on 05/12/2025 **Article Revised on 25/12/2025** **Article Published on 10/01/2026**

ABSTRACT

Nephrolithiasis is a frequently occurring urological problem worldwide. The worldwide prevalence of nephrolithiasis is at least 11% of the U.S. population and significantly greater than 11% of the world's population, with men being more frequently diagnosed than women. Its development is also affected by multiple mechanisms, including urinary supersaturation, crystal nucleation; crystal growth, and crystal aggregation; interaction of crystals with renal tubular epithelial cells; and retention of the stone in the renal tubular system. Several metabolic disorders also play a large role in nephrolithiasis development, such as hypercalciuria, hyperoxaluria, hyperuricaemia, and hypocitraturia; environmental factors such as obesity, diabetes mellitus, hypertension; and dehydration, as well as dietary habits, can all result in increased nephrolithiasis. Citrate is an important dietary precursor of citric acid and may help to protect against nephrolithiasis; increased consumption of citric acid results in increased urinary citrate excretion, and citric acid is a strong anti-lithogenic agent for calcium oxalate monohydrate crystals. In addition, citrate, an important endogenous inhibitor of urine crystallization, is able to reduce urine supersaturation by binding free calcium. The binding of free calcium to citrate also has the effect of directly inhibiting calcium salt crystal nucleation, growth, and aggregation, in addition to inhibiting the adhesion of renal tubular epithelial cells to calcium salt crystals. This review discusses the major risk factors, the potential therapeutic benefit of citric acid and citrate, and also outlines the current limitations of these treatments and future directions for research in this area.

KEYWORDS: Nephrolithiasis, Citric acid, citrate, Urinary crystallization.

INTRODUCTION

Nephrolithiasis is a widespread urological disease that has affected a significant population and is recognized in most parts of the world[1] about 1/10th individuals in the United States.[2] Approximately 10.6 percent of men and 7.1 percent of women in the United States are severely affected with nephrolithiasis. In china, men and women have been estimated to be 6.5 and 5.1, respectively.[3] Kidney stone disease is usually more common among the male gender than the female gender.[4] Kidney stones are hard mineral deposits generated owing to the synthesis, aggregation, and retention of urine crystals within the renal system, which are frequently enclosed in an organic proteinaceous matrix.[5]

Calcium-containing stones, particularly calcium oxalate and calcium phosphate, account for almost 80% of all kidney stones, with uric acid, struvite, and cystine stones accounting for around 9%, 10%, and 1% of cases, respectively.[6] Dehydration, eating habits, and genetic susceptibility are some of the variables that impact kidney stone development.[7] Obesity, diabetes, high blood pressure, and metabolic syndrome are risk factors for stone development, which leads to high blood pressure, chronic kidney disease, and end-stage renal disease.[8]

The urinary system, which includes the kidneys, ureters, urinary bladder, and urethra, is responsible for maintaining fluid and electrolyte homeostasis, controlling blood pressure, filtering metabolic waste, maintaining acid-base balance, and generating hormones involved in erythropoiesis.[7] The upper and lower urinary tracts (kidneys and ureters, and bladder and urethra) develop separately without relation to other germ layers, but are linked at mid-gestation as a result of a complex cascade of interactions known as ureter maturation. Errors in this connection that cause

Hydronephrosis.[9]

Stone formation is a complicated physicochemical process that includes urine supersaturation, nucleation, crystal development, aggregation, and retention within renal tubular cells. An imbalance between promoters and inhibitors of crystallization increases these processes, whereas epithelial cell damage promotes crystal adherence to renal papillary surfaces.[10] Dietary variables also play a crucial role in the production of kidney stones because they alter the content of urine. Reduced fluid consumption, excessive intake of sodium and animal protein, low intake of calcium and fruit, and high intake of oxalate-containing foods raise urine saturation, acidic pH, hypercalciuria, hypocitraturia, and hyperoxaluria, which favor nephrolithiasis.[11]

Citrate is a useful dietary and treatment agent in nephrolithiasis, a prominent endogenous inhibitor of the development of calcium stones. The nucleation, growth and agglomeration of the calcium oxalate crystals are also inhibited by citrate.[12-14] Citrate salts inhibit the formation of new stones and slow down the further stones.[15] Citrate also inhibits the formation of calcium oxalate monohydrate crystals by adsorbing to crystal surfaces and increasing the activity of inhibitory macromolecules such Tamm-Horsfall protein and osteopontin.[16] Citric acid is widely utilized in culinary, chemical, medicinal, and environmental applications because it is economically viable and environmentally compatible.[17] The paper will review the pathways in the pathogenesis of nephrolithiasis and the treatment potential of citric acid to reduce the formation and recurrence of the stone.

Urinary System

The urinary system is made up of the kidneys, ureters, bladder, and urethra[18] and is significant in the regulation of the fluid and electrolyte balance, homeostatic balance in the body. The urinary system is important in eliminating the waste products of metabolism in the blood. The other significant roles played by the system include the normalization of the concentration of the ions and solutes in the blood and the regulation of blood volume and the blood pressure.[19] It is a continuous hollow-organ system, the major role of which is to collect, transport, store and release urine at a certain time, and in a highly coordinated manner. By so doing, the urinary tract guarantees the removal of the metabolic products and the toxic waste produced in the kidney. The constant flow of the urine in the upper UTI and discontinuous flow of the urine in the lower UTI also serve a very vital role in cleaning the urinary tract by eliminating microbes that may have already found their way. The urinary tract is a closed system that is inaccessible to the microbes when they are not getting rid of urine. The urinary tract is made up of various structures, including renal papillae, renal pelvis, ureters, bladder, and urethra, which possess different anatomical structures and dissimilar functions.[20]

Anatomy of the Urinary System

Kidneys

Kidneys are bean shaped organs within the retroperitoneal cavity, which lie ventrolateral and adjacent to the lumbar vertebral bodies between the T 12 and the L3 vertebrae, with the right kidney being a little below the left kidney because of the liver.[21] The renal hilum is a medial concavity of each kidney that contains the renal artery and the renal vein and renal pelvis in an anteroposterior position vein artery and pelvis. Kidneys are surrounded by a fibrous capsule and surrounded by perinephric fat and renal fascia (Gerota fascia anterior and Zuckerkandl fascia posterior) that offer a protective quality and keep the kidney in an anatomical position.[24] The kidneys are related to the diaphragm, psoas major, and quadratus lumborum muscles in the posterior position and the colon, duodenum, and liver (right), and stomach, spleen, pancreas, and descending colon (left) in the anterior position.[22]

The kidney is made up of renal parenchyma and a collection system. The renal parenchyma is sub divided into an outer cortex and inner medulla. The renal cortex has renal corpuscles, proximal and distal convoluted tubules as well as cortical collecting ducts and it runs between the medullary pyramids in the form of renal columns. The medulla is structured into renal pyramids that consist of loops of Henle and medullary collecting ducts; a pyramid along with the cortex above the pyramid constitutes a renal lobe. The summit of every pyramid is a renal papilla, draining the urine into a minor calyx. Small calyces are joined to make bigger ones, which join to create renal pelvis which leads to ureter.

Functionally and histologically, the kidney consists of four main anatomic parts namely the glomeruli, renal tubules, interstitium and vasculature. The glomeruli along with the capsule of Bowman constitute the renal corpuscles that serve the purpose of filtration of blood.[23] The filtrate is modified in the tubular system which consists of the proximal, loop of Henle, distal tubule and collecting ducts where the filtrate undergoes reabsorption and secretion. Structural and metabolic support is ensured by the interstitium as well as the renal vasculature ensures adequate blood delivery and filtration pressure. The number of nephrons in each kidney is roughly 1-1.5 million, which combine these parts to form urine and fluid, electrolyte and acid-base homeostasis.

Ureters

Ureters are two fibromuscular tubes that carry urine from the renal pelvis to the urinary bladder. The ureters are around 22-30 cm long and pass through the retroperitoneum. They begin at the ureteropelvic junction (UPJ), which is situated behind the renal artery and vein and move inferiorly along the anterior surface of the psoas muscle. Upon entering the pelvic cavity, the ureters bend towards the middle and crosses the common iliac vessels in front of the bifurcation. The ureters

obliquely penetrate the wall at the ureterovesical junction (UVJ) and pass intramurally (approximately 1.5-2.0 cm) after which they open into the lumen of the bladder as ureteral orifices. This oblique intramural path allows compression of the ureter by the bladder wall during urine retention and micturition, thereby reducing vesicoureteric reflux. The ureters contain three physiological constrictions; one at the UPJ, one at the crossing of the common iliac vessels, and one at the UVJ. They are clinically significant constricted areas as they are the most frequent locations where ureteral stones tend to be trapped and result into urinary blockage.[24-25]

Urinary bladder & Urethra

Urinary bladder is a smooth muscular distensible, hollow sac found in the pelvic cavity, which acts as a temporary storage of urine. It has a tetrahedral shape and becomes ovoid when filled. The bladder wall is made up of smooth muscle and collagen, with a small amount of elastin added to help it expand when holding pee. The urachus is the fibrous remnant of the allantois that connects the superior surface of the bladder to the anterior abdominal wall. The bladder is situated between the rectum and the pubic symphysis in the male and it is situated between the rectum and the uterus or the vagina in the female. The bladder has three apertures; two ureteric openings, and one internal urethral opening. The trigone is a smooth triangle space in the bladder that is covered by the two ureteric openings at the top, and the internal urethral opening at the bottom. It is structurally differentiated as it has thickened bands of muscle and serves to guide urine to the urethra.[26] The bladder neck has internal urethral sphincter made of smooth muscle and is well developed in men but not so in women. The empty bladder has a length of about 5-7.5 cm and the full bladder can have a length of about 12.5 cm and a capacity of about 500 mL of urine, and can increase in volume to a very large extent.

Urethra is a tubular tract that extends into the bladder and is the last point of urine exit as it gets expelled through an external urethral orifice. It is characterized by eminent sexual dimorphism. In men, the urethra is around 15-25 cm in length and is subdivided into three, the prostatic urethra that runs through the prostate gland, the short membranous or perineal urethra which lies between the outer urethral sphincter, and the penile or spongy urethra, which is found in the corpus spongiosum and empties into the outer urethral meatus. In women the urethra is far shorter approximately 3-5 cm, follows the anterior vaginal wall, and is anchored at the end by the external urethral sphincter.[27]

Kidney's centrality is in their functions of ensuring homeostasis by balancing plasma osmolarity by changing water, solutes, and electrolytes in the blood. They maintain the long-term acid-base homeostasis and also play a role in the production of erythropoietin which promotes production of red blood cells. Renin is one of the prominent enzymes generated in the kidneys that regulate blood pressure and converts vitamin D into the active form, calcitriol, which helps in the metabolism of calcium. The kidneys functionally remove the water-soluble waste products and nitrogen toxins, the extracellular fluid volume and composition, and the electrolyte balance, including sodium and potassium. They control water status and urine concentration through vasopressin-mediated activities and produce medullary hypertonicity via the Henle loop and urine recycling systems. Also, the tubular reabsorbs solutes, electrolytes, and other nutrients, and the renin-angiotensin-aldosterone system helps in the regulation of the systemic blood pressure, which points out to the overall function of the kidneys in the fluid, electrolyte, and general metabolic homeostasis.[28]

Composition of kidney stone

When crystals formed and got grouped to form a hard lump in one of the two kidneys, they formed a kidney stone. They can be of different sizes ranging between a few millimetres and up to a few centimetres. Most of the stones will be evacuated by the urine without any assistance, yet others will need assistance in their extraction. The Urinary stone have been made using the crystal of phosphate, uric corrosive, magnesium ammonium phosphate containing apatite and struvite. Among the urinary stones, a mixture of the two mixes (45%), calcium-containing stones have been found to about 75% of every urinary analytics, which may be available as crystal of unadulterated calcium oxalate (50), calcium phosphate (5%) and a combination of the two mixes (45%). The 24-hour urine excretion of urine can be exposed to any of the specified properties at a higher risk of developing a stone.

I. Hypercalciuria (thickness of the bone mass)
II. Oxalate (hyperoxaluria) in high levels.
III. Uric acid (hyperuricaemia) levels are high.
IV. Reduced amounts of citrate (hypocitraturia).[29]

Table 1: Various categories of renal stones.

Composition	Frequency
Calcium oxalate	75%
Calcium phosphate	15%
Uric acid	8%
Struvite	1%
Cystine	<1%

Formation of Renal Calculi

Kidney stones have a complex pathogenesis associated with a complicated biochemical process of passing to the supersaturation of urine with solutes forming stones. Nucleation is encouraged with the help of supersaturation and the formation of crystals begins and they grow and congregate to become stones. Urine pH, elevated calcium, oxalate, uric acid, cystine, and low volume of urine are some of the factors that result in crystallization. Thermodynamic and kinetic processes affect both of them, which makes supersaturation the key element in the pathophysiology of renal calculi.[30]

Mechanisms of Stone Formation

Urinary Supersaturation

Uriinary supersaturation with lithogenic solutes (calcium, oxalate, phosphate, uric acid, and cystine) is the initial stage of kidney stones development. When the level of the solute surpasses its product of solubility, it causes supersaturation which permits crystallization to occur. The cause-and-effect factors that affect supersaturation are: urine volume, pH, ionic strength and temperature; low urine volume and abnormal pH increase the risk of stones.[31]

Nucleation

Nucleation: It is the process through which the solute molecules come together to create crystal nuclei and this process will shift a supersaturated liquid into a solid state. It can be homogeneous, where the solute molecules are the only molecules involved or heterogeneous, on surfaces like epithelial cells, urinary casts or Randall plaques. The calcium phosphate deposits in the renal interstitium in Randall are the calcium oxalate crystal overgrowth nidus. It can be homogeneous, where the solute molecules are the only molecules involved or heterogeneous, on surfaces like epithelial cells, urinary casts or Randall plaques. The calcium phosphate deposits in the renal interstitium in Randall are the calcium oxalate crystal overgrowth nidus.[32-33]

Crystal Growth

The crystals form after nucleation and then accretion of ions in the surrounding supersaturated urine occurs. The growth may take place through secondary nucleation on existing crystals or on matrix-coated surface, and crystal accretion is mediated by organic matrix components (proteins and lipids) that lower free energy. This is increased in urine where sustained supersaturation and low concentrations of urine inhibitors such as citrate and magnesium are maintained.[34]

Crystal Aggregation

Aggregation means the fusion of single crystals into bigger and clinically pertinent masses. To form a stone, aggregation can be considered a necessary step since microscopic crystals are usually excreted. Tamm-Horsfall protein and osteopontin are the examples of urinary macromolecule that affect aggregation positively or negatively depending on their concentration and conformation.[39-40] The last stone appears like a combination of crystals implanted into organic structure of proteins, lipids and polysaccharides.[35]

Crystal–Cell Interaction

Crystals can stick to or be absorbed by renal tubular epithelial cells, which is referred to as crystal-cell interaction. Anionic phospholipids are found in damaged epithelial cells, facilitating calcium oxalate monohydrate (COM) adhesion. Membrane vesicles and proteins, including renal prothrombin fragment-1, active as extra nucleation sites, are produced during cellular injury, and reactive oxygen species worsen the damage of epithelial cells and crystal retention.

Stone Formation

The last phase is the formation of clinically significant stones which are the outcome of further crystal growth, aggregation and retention, as well as the addition of the organic matrix component Different stones react in different orders according to the chemistry of these urines with calcium oxalate, calcium phosphate, uric, cystine stones having the same fundamental mechanism but dissimilar in their nucleation and preservation details.[36-37]

Risk Factors for Nephrolithiasis

Environmental Factors-Warmer weather conditions cause dehydration that causes urine to become concentrated and thus an increased occurrence of kidney stones. The effects of global warming are linked to high cases of stone disease and other related problems of the kidneys.[38-39]

Dietary Factors-Animal based diet, high sodium, high fat and high sugar (particularly fructose) and low content of fiber, potassium and fluids in the western diet are a major contributor to the risk of stones.[40]

Hormonal Factors-Women with low estrogen levels in their postmenopausal stage and women who have oophorectomy are at increased risk of developing kidney stones.[41]

Lifestyle and Metabolic Factors-Urinary stones are highly related to obesity, greater BMI, and weight gain in both men and women. One of the major risks of renal calculi is obesity as it is related to insulin resistance and diabetes. Obesity is also a significant issue of public health concern in stone disease when it comes to kidney stones as obese persons are at greater risk of these stones as compared to normal weight people.[42]

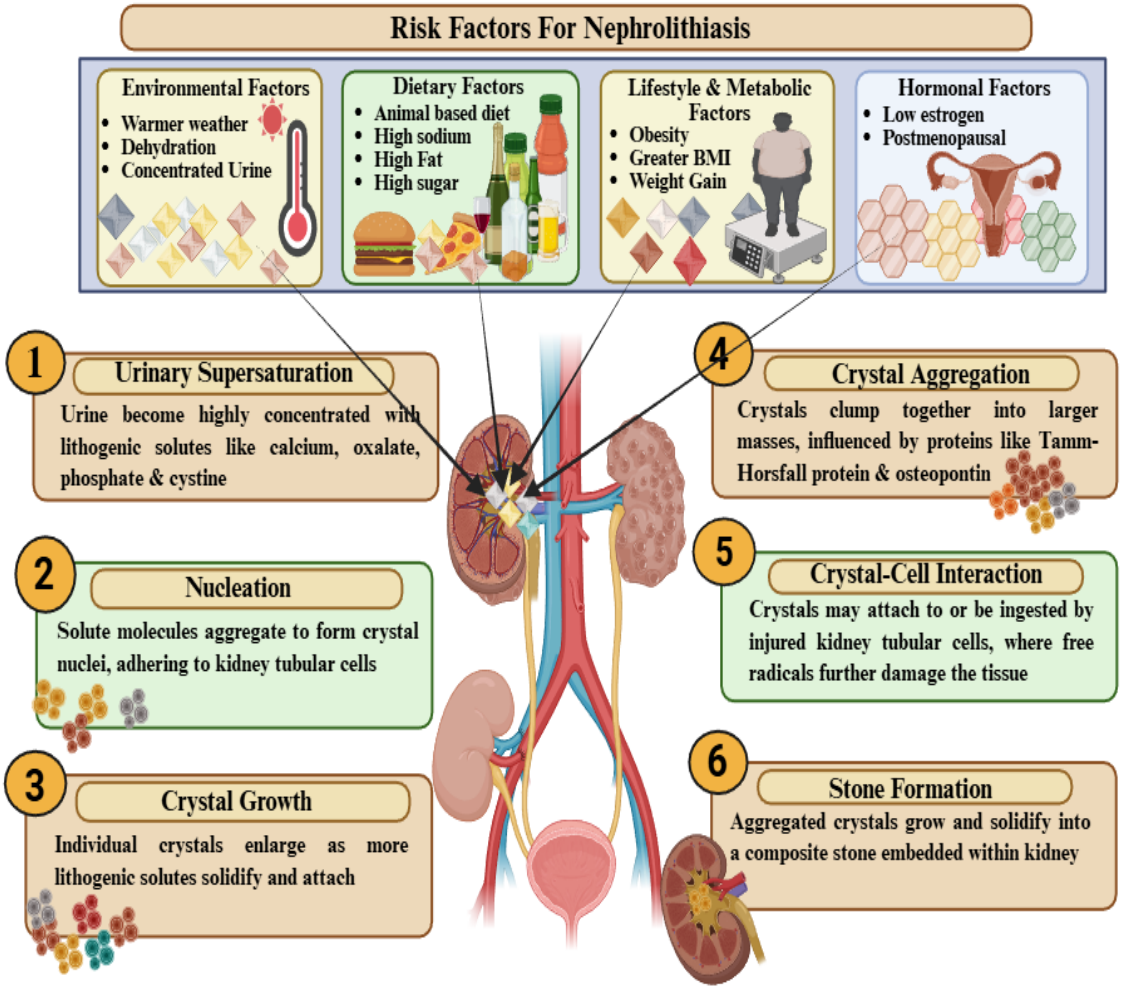

Figure 1: The image depicts the risk factors for nephrolithiasis, the sequential progression from urine supersaturation and crystal nucleation to crystal growth, aggregation, crystal-cell contact, and eventual stone formation.

Citric Acid

Citric acid (C6H8O7) is an organic acid naturally present, and a key metabolic intermediate that is present in plants and animals. It is weak organic carboxylic acid, very soluble in water and is well used as a preservative and antioxidant in a variety of edible foods. Of course, citric acid exists in high concentration in citrus fruits and is also found in various fruits and vegetables including lemons, oranges, tomatoes, and beets, but citrus fruits are the fruits that are the most concentrated with citric acid.[43]

There are a number of industrial assays that can be used to obtain citric acid, such as surface fermentation on liquid substrates, submerged fermentation, submerged fermentation on Aspergillus niger, submerged fermentation on yeasts and solid-state fermentation. The techniques enable massive and cost-effective citric acid production to be used in food, pharmaceutical, and industrial production. Citric acid diet has a positive effect in the prevention of renal calculi. Fruits and vegetables containing citric acid increase the levels of urinary citrate in addition to a sufficient intake of fluid. Citrate lowers urinary supersaturation by binding the calcium ions and preventing crystal nucleation and crystal growth, thus preventing the development of stones. Patients who have low citrate levels are advised to boost its intake by means of natural sources or lime juice.[44]

Citric acid is a major constituent of intermediary metabolism biologically as a constituent component of tricarboxylic acid (TCA) or Krebs cycle. Protective effect of citric acid against hepatic injury caused by toxicants like carbon tetrachloride (CCl4), lipopolysaccharide (LPS) and the organophosphorus insecticide malathion has been shown in experiments in rodents. Offering citric acid decreased hepatocellular injury through minimizing leaking of liver enzymes like alanine aminotransferase and aspartate aminotransferase, enhancing histology, and rectifying metabolic imbalances. Citric acid also was able to reduce the oxidative stress, decrease malondialdehyde levels, restore lost glutathione, increase antioxidant activity, inhibit caspase-3 activation and inducible nitric oxide

synthase (iNOS) expression. This evidence indicates that citrate has strong antioxidant as well as cytoprotective functions in that it inhibits excessive production of reactive oxygen and nitrogen species.[45]

Role of Citrate and Citric Acid in the Prevention of Kidney Stone

Citrate is one of the endogenous inhibitors of kidney stones and works in a variety of co-ordinated mechanisms. It has a major role of forming soluble complexes with urinary calcium that lowers the free ionic calcium, reduces supersaturation of calcium oxalate (CaOx) and calcium phosphate (CaP). Besides this chelating action, citrate has a direct interference with crystal nucleation, crystal growth, agglomeration and crystal aggregation by acting on crystal surfaces. It also plays an important role in the natural inhibition of the CaP precipitation and inhibits the heterogeneous nucleation of CaOx which is caused by monosodium urate. Citrate also influences urine crystallization by modulating the activity of Tamm-Horsfall protein (THP), a key stone matrix component. The THP activity is affected by the urinary pH and ionic strength and the presence of citrate is of great importance since the citrate can bind the calcium ions, decreasing the viscosity of THP. THP inhibits calcium oxalate aggregation in the presence of citrate, but in the absence of citrate, it can function as a crystal promoter. The major dietary and therapeutic source of citrate is citric acid, which as shown has strong antiurolithiatic effect specifically against calcium oxalate monohydrate (COM). At physiological pH, it lowers the concentration of free calcium that is needed to make the COM and calcium hydrogen phosphate dihydrate (CHPD). The antioxidant effect it possesses offers extra protection, in that oxidative stress-induced damage to cells in the renal tubules is limited by its presence.

nce, which otherwise promotes crystal retention and stone formation. Citric acid helps to get rid of crystals by urine excretion because it maintains the integrity of the membrane. Citric acid also contains numerous anionic groups which adsorb to positively charged surfaces of COM crystals concealing epithelial binding sites and creating electrostatic repulsions among crystals or between crystals and renal epithelial cells. This prevents the growth and aggregation of crystals and their attachment. Potassium citrate augments these advantages by boosting the concentration of urinary citrate and alkalinizing urine, which enhances the formation of calcium-citrate-phosphate complex, minimizes the availability of calcium and phosphate to crystalize, and elevates the solubility of uric acid and thus prevents urate-related calcium oxalate stone formation. Citrate and citric acid combined actions including calcium chelation and inhibition of nucleation and crystal growth, alleviation of oxidative damage, and facilitation of urinary clearance of crystals are key factors leading to the prevention of kidney stone formation.[46-47]

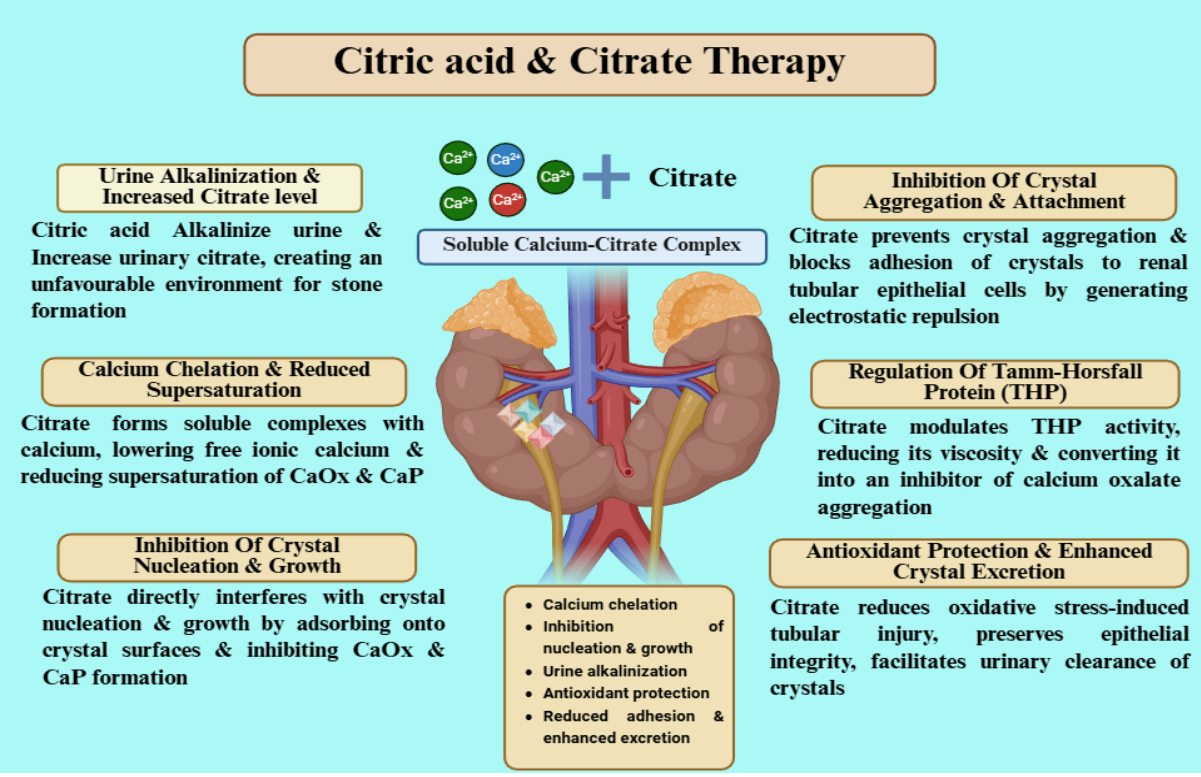

Figure 2: A schematic illustration of the therapeutic mechanisms of citric acid and citrate in the prevention of nephrolithiasis. The image depicts urine alkalinization, calcium chelation, suppression of crystal nucleation, development, and aggregation, modification of Tamm-Horsfall protein activity, antioxidant protection, and increased urinary crystal excretion.

Other Therapeutic Uses of Citric Acid

Lipid Control: Citric acid made significant contributions to the lipid profiles of hyperlipidemic rats by declining liver index, triglycerides, total cholesterol, and low-density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol. These actions suggest that it has a role to play in the regulation of blood lipids and reducing metabolic abnormalities caused by hyperlipidemia.[48]

Antioxidant Properties / Neuroprotection and Hepatoprotection: Citric acid (1-2 g/kg) reduced the development of LPS-induced oxidative stress and inflammation in the brain and liver, lowered MDA, nitrite, TNF-a, and liver damage markers, and boosted antioxidant defense (GPx and PON1). Greater doses (4 g/kg) enhanced fragmentation of DNA, in a dose-dependent manner.[49]

Intestinal Health and Antiviral Effects: Citric acid enhances the intestinal barrier strength, maintains gut health, improves the ratio of villus-crypt and the growth of IEC-6 cells, as well as the growth of beneficial bacteria such as Bifidobacterium and Lactobacillus. It elevates tight junction proteins (occludin, ZO-1, claudin-1), suppresses the inflammatory response, and prevents the copying of H9N2 avian influenza virus in intestinal cells, thus enhancing the intestinal immunity.[50]

Citrate Anticoagulation in CRRT: Citric acid enhances the intestinal barrier strength, maintains gut health, improves the ratio of villus-crypt and the growth of IEC-6 cells, as well as the growth of beneficial bacteria such as Bifidobacterium and Lactobacillus. It elevates tight junction proteins (occludin, ZO-1, claudin-1), suppresses the inflammatory response, and prevents the copying of H9N2 avian influenza virus in intestinal cells, thus enhancing the intestinal immunity.[51]

Antimicrobial / Anti-Biofilm Activity: Acinetobacter baumannii is a multidrug-resistant pathogen having high biofilm and capsule-mediated virulence. Anti- biofilm and anti-capsular effects of citric acid have also been demonstrated and this reduces bacterial virulence and provides a potential approach to treating MDR A. baumannii infections.[52]

Future Perspectives

Quality, Pragmatic Clinical Trials The large clinical trials badly needed include multi-center, long-term follow-up, randomized clinical trials (RCTs). Such trials must be low risk of bias and need to target hard clinical endpoints such as symptomatic stone recurrence, and not necessarily just surrogate measures (e.g., urinary citrate levels). Tailored Biomarker-Based Prevention: Future therapy cannot be limited to a one-size-fits-all approach. Multi-omics data (genomic, proteomic, metabolomic) must be incorporated in research to come up with predictive biomarkers of stone recurrence and treatment response. It will allow really personalized prevention programs specific to the risk profile of a biochemical and genetic profile.[53]

Emphasize Special Populations, in Particular CKD Patients One of the most important areas of research is to develop evidence-based guidelines on stone prevention in chronic kidney disease. This involves the study of the safety and effectiveness of different citrate preparations at different CKD stages, and the development of new treatment which is aimed at preventing stones as well as curing the CKD development.

Enhancement of Tolerability and Dietary Interventions Investigation To help with the adherence issue, research ought to be done to produce more tolerable formulations (e.g., delayed-release) of citrate salts. At the same time, further strict research on sustainable dietary interventions, including the use of lemon juice or other citrate-rich foods in a standardized form as first-line or complementary therapy, is justified, as it could be a more accepted long-term solution to a significant proportion of patients.

Research into Systemic and Long-Term Benefits Future study is needed to evaluate the potential pleiotropic advantages of citrate treatment beyond stone avoidance. It also incorporates its long-term impacts on cardiometabolic health, bone metabolism, and slows down the CKD progression, which might be a major change in its risk-benefit analysis.[54]

CONCLUSION

Nephrolithiasis is one of the most common types of urolithiasis that results in serious clinical and financial consequences for individuals worldwide. It is the result of numerous interdependent physical and chemical reactions, including those caused by dietary and lifestyle behaviours, as well as environmental exposure, metabolic disorders, and functional integrity of the renal tubular epithelium. The high prevalence of calcium-based stones indicates that regulating urinary calcium levels and controlling crystallisation are essential to developing effective preventative interventions. As one of the most critical endogenous inhibitors of kidney stones, citrate helps to mitigate urine supersaturation, chelate calcium ions, suppress nucleation, growth and aggregation of crystals, and prevent crystals from sticking to the renal epithelium. By increasing urine citrate excretion and providing antioxidant and cytoprotective properties, citric acid (which is a naturally occurring dietary source of citrate) enhances the protective mechanisms of citrate and decreases tubular injury due to oxidative stress. Thus, both citrate and citric acid are effective in decreasing the recurrence of stones, in addition to preventing crystal retention, Due to the advantages of citrate therapy (mechanistically) and clinically, there exist many limitations preventing widespread utilization of citrate therapy (e.g., variability of study quality, GI side effects, low long-term patient compliance) as well as a need for more evidence in

patients with renal impairment. To address these limitations, clinicians require well-designed long-term clinical studies and the development of more acceptable proprietary formulae for long-term use.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

1. Bargagli, M., et al., Kidney stone disease: risk factors, pathophysiology and management. Nature Reviews Nephrology, 2025; 21(11): 794-808.
2. Shastri, S., et al., Kidney Stone Pathophysiology, Evaluation and Management: Core Curriculum 2023. American Journal of Kidney Diseases, 2023; 82(5): 617-634.
3. Ma, Y., et al., Risk factors for nephrolithiasis formation: an umbrella review. Int J Surg, 2024; 110(9): 5733-5744.
4. Tamborino, F., et al., Pathophysiology and Main Molecular Mechanisms of Urinary Stone Formation and Recurrence. Int J Mol Sci, 2024; 25(5).
5. Baumann, J.M. and B. Affolter, From crystalluria to kidney stones, some physicochemical aspects of calcium nephrolithiasis. World J Nephrol, 2014; 3(4): 256-67.
6. Khan, S.R., et al., Kidney stones. Nat Rev Dis Primers, 2016; 2: 16008.
7. Ahmed, K., The Urinary System: Exploring the Anatomy, Function and Common Disorders RRJ Biol, 2023; 11(1): 005.
8. Khan, S.R., et al., Kidney stones. Nature Reviews Disease Primers, 2016; 2(1): 16008.
9. Finkelstein, J.B. and C. Mendelsohn, Chapter 19 - Vesicoureteral Obstruction and Vesicoureteral Reflux: Different Congenital Defects With a Common Cause, in Kidney Development, Disease, Repair and Regeneration, M.H. Little, Editor. 2016; 229-239.
10. Alelign, T. and B. Petros, Kidney Stone Disease: An Update on Current Concepts. Adv Urol, 2018; 3068365.
11. Ferraro, P.M., et al., Risk of Kidney Stones: Influence of Dietary Factors, Dietary Patterns, and Vegetarian-Vegan Diets. Nutrients, 2020; 12(3).
12. Phillips, R., et al., Citrate salts for preventing and treating calcium containing kidney stones in adults. Cochrane Database Syst Rev, 2015; 2015(10): 010057.
13. Doizi, S., et al., Impact of Potassium Citrate vs Citric Acid on Urinary Stone Risk in Calcium Phosphate Stone Formers. J Urol, 2018; 200(6): 1278-1284.
14. Zomorodian, A. and O.W. Moe, Citrate and calcium kidney stones. Clin Kidney J, 2025; 18(9): 244.
15. Miss. Telange – Patil P.V., M.G.S.S., Miss.Ubale.S.S, Mr.Pawar.S.M, REVIEW ON: Kidney Stone Dissolution For The Help Of Citric Acid. International Journal of Creative Research Thoughts, 2023; 11(12).
16. Zacchia, M. and P. Preisig, Low urinary citrate: An overview. Journal of nephrology, 2010; 23 Suppl 16: 49-56.
17. Peng, F., et al., Enhancing phosphorus release and recovery from waste activated sludge by citric acid treatment and cyclic extraction. Chemical Engineering Journal, 2024; 501: 157461.
18. Mancuso, G., et al., Urinary Tract Infections: The Current Scenario and Future Prospects. Pathogens, 2023; 12(4).
19. McLafferty, E., et al., The urinary system. Nurs Stand, 2014; 28(27): 43-50.
20. Hickling, D.R., T.T. Sun, and X.R. Wu, Anatomy and Physiology of the Urinary Tract: Relation to Host Defense and Microbial Infection. Microbiol Spectr, 2015; 3(4).
21. Grandmaison. D, G.L., I. Clairand, and M. Durigon, Organ weight in 684 adult autopsies: new tables for a Caucasoid population. Forensic Sci Int, 2001; 119(2): 149-54.
22. El-Reshaid, W. and H. Abdul-Fattah, Sonographic assessment of renal size in healthy adults. Med Princ Pract, 2014; 23(5): 432-6.
23. Garza, F.A. and S.W. Leslie, Anatomy, Abdomen and Pelvis: Kidneys, in StatPearls [Internet]. 2025; StatPearls Publishing.
24. Chesbrough, R.M., et al., Gerota versus Zuckerkandl: the renal fascia revisited. Radiology, 1989; 173(3): 845-6.
25. Coffin, A., et al., Radioanatomy of the retroperitoneal space. Diagn Interv Imaging, 2015; 96(2): 171-86.
26. Tirkes, T., et al., Peritoneal and retroperitoneal anatomy and its relevance for cross-sectional imaging. Radiographics, 2012; 32(2): 437-51.
27. Selcuk, I., et al., Basic clinical retroperitoneal anatomy for pelvic surgeons. Turk J Obstet Gynecol, 2018; 15(4): 259-269.
28. Fine, H. and E.N. Keen, Some observations on the medulla of the kidney. Br J Urol, 1976; 48(3): 161-9.
29. Zhang, J.L., et al., Functional MRI of the kidneys. J Magn Reson Imaging, 2013; 37(2): 282-93.
30. Bonsib, S.M., Renal Hypoplasia, From Grossly Insufficient to Not Quite Enough: Consideration for Expanded Concepts Based Upon the Author's Perspective With Historical Review. Adv Anat Pathol, 2020; 27(5): 311-330.
31. Breshears, M., W. Anthony, and A. Confer, Pathologic basis of veterinary disease. 2017; Elsevier: Amsterdam, The Netherlands.
32. Islam, O. and K. Islam, Fundamentals of Formation and Excretion of Urine: A Pictorial Review. Journal of Clinical Case Studies Reviews & Reports, 2024; 1-5.
33. Faris, M., R. Ibrahim, and S. Al-Mukhtar, Anatomy of the urinary system. 2021.
34. Hickling DR, Sun TT, Wu XR. Anatomy and Physiology of the Urinary Tract: Relation to Host Defense and Microbial Infection. Microbiol

Spectr. 2015; 3(4).
35. Makanjuola, D. and M. Lapsley, CHAPTER 7 - The kidneys, renal function and kidney disease, in Clinical Biochemistry: Metabolic and Clinical Aspects (Third Edition), W.J. Marshall, et al., Editors. 2014; Churchill Livingstone. p. 124-151.
36. Raunak S, P.K.S., P.C. Gupta, Kidney stone: A clinical review. IOSR Journal Of Pharmacy And Biological Sciences, 2020; 15(5): 42-49.
37. Aggarwal R, Jain SK, Ritika S, Singh R. Renal Stones: a clinical review. European medical journal, 2017; 5[1]: 98-103.
38. Tamborino, F., et al., Pathophysiology and Main Molecular Mechanisms of Urinary Stone Formation and Recurrence. International Journal of Molecular Sciences, 2024; 25(5): 3075.
39. Allam, A.T., et al., A holistic guide to effective prevention and treatment for kidney stones: a systematic review exploring anti-urolithiasis approaches. Naunyn-Schmiedeberg's Archives of Pharmacology, 2025.
40. Ratkalkar, V.N. and J.G. Kleinman, Mechanisms of Stone Formation. Clin Rev Bone Miner Metab, 2011; 9(3-4): 187-197.
41. Nalini H.Sofia, M.K., Thomas M.Walter, Prevelance and risk factors of kidney stone. Global Journal for research analysis, 2016; 5(3).
42. Shamsuddeen, S., et al., Risk Factors of Renal Calculi. The Bangladesh journal of scientific research, 2013; 11: 90-95.
43. Kanse GN, Mokal D, Patil K,Bhandurge P, Prashant D,. REVIEW ON CITRIC ACID PRODUCTION AND ITS APPLICATIONS. 2018; 6(9): 5880-5883.
44. Gul, Z. and M. Monga, Medical and dietary therapy for kidney stone prevention. Korean J Urol, 2014; 55(12): 775-9.
45. Abdel-Salam, O.M.E., et al., Chapter 16 - Citric Acid an Antioxidant in Liver, in The Liver, V.B. Patel, R. Rajendram, and V.R. Preedy, Editors. Academic Press: Boston. 2018; 183-198.
46. Caudarella, R., et al., Citrate and mineral metabolism: Kidney stones and bone disease. Frontiers in bioscience : a journal and virtual library, 2003; 8: 1084-106.
47. Ahmed, S., M. Hasan, and Z. Mahmood, In vitro urolithiasis models: An evaluation of prophylactic management against kidney stones. Journal of Pharmacognosy and Phytochemistry, 2016; 28: 28-35.
48. Yadikar, N., et al., Exploring the mechanism of citric acid for treating glucose metabolism disorder induced by hyperlipidemia. J Food Biochem, 2022; 46(12): e14404.
49. Abdel-Salam, O.M., et al., Citric acid effects on brain and liver oxidative stress in lipopolysaccharide-treated mice. J Med Food, 2014; 17(5): 588-98.
50. Hu, P., et al., Citric Acid Promotes Immune Function by Modulating the Intestinal Barrier. International Journal of Molecular Sciences, 2024; 25(2): 1239.
51. Boer, W., et al., Unapparent systemic effects of regional anticoagulation with citrate in continuous renal replacement therapy: a narrative review. Annals of Intensive Care, 2023; 13(1): 16.
52. El-Soudany, I., et al., The Effect of Citric and Ascorbic Acids as Anti-Biofilm and Anti-Capsular Agents on Multidrug-Resistant Acinetobacter baumannii. Medical Principles and Practice, 2024; 33(3): 281-290.
53. Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Biyani CS. Citrate salts for preventing and treating calcium-containing kidney stones in adults. Cochrane Database Syst Rev., 2015; (10): 010057.
54. Gill D, Zagkos L, Gill R, et al. The citrate transporter SLC13A5 as a therapeutic target for kidney disease: evidence from Mendelian randomization to inform drug development. BMC Med., 2023; 21: 504.