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# Revolutionizing Urolithiasis Management: A Paradigm Shift through Nutraceutical Interventions, Fluid Therapy and pH Maintenance - A Comprehensive Review

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## ABSTRACT

Urolithiasis is characterized by the formation of mineral stones within the urinary tract, is a significant global health concern impacting millions worldwide. This review article examines the multifaceted nature of urolithiasis, encompassing its epidemiology, etiology, diagnosis, and management strategies. Key factors influencing stone formation include biochemical changes, dietary habits, hydration levels, genetic predispositions, and environmental factors. Diagnostic imaging methods such as ultrasonography and computed tomography aids in accurate diagnosis, while treatment options range from extracorporeal shock wave lithotripsy to dietary modifications and fluid therapy. Nutraceuticals, particularly phytoconstituents rich in polyphenols and alkaloids, offer promising avenues for managing urolithiasis by inhibiting crystal formation and supporting kidney function. Moreover, optimizing fluid intake and maintaining urinary pH levels play pivotal role in preventing stone recurrence. Prospects lie in the refinement of nutraceutical formulations, the integration of wearable technology for monitoring, and comprehensive clinical investigations to establish safety and efficacy. Ultimately, this review underscores the importance of holistic approaches to mitigating the burden of urolithiasis and improving patient outcomes.

***Keywords:*** Extracorporeal Shock Wave Lithotripsy, Epidemiology, Fluid Therapy, Nutraceuticals, Urolithiasis.

## INTRODUCTION

Urolithiasis, a prevalent global health issue, involves the formation of mineral stones within the urinary tract, typically starting with the crystallization of oxalates in the nephrons[1]. This condition, also known as urinary calculi or urinary stones, encompasses three distinct terms: nephrolithiasis; referring to stones formed within the kidneys, renal lithiasis; resulting from conditions favoring crystallization in the urinary tract, and urolithiasis; representing the overall formation of urinary stones[2]. Biochemical changes, including the generation of reactive oxygen species (ROS), can lead to tissue damage and facilitate the idiopathic accumulation of calcium oxalate crystals[3]. Urinary pH plays a crucial role in kidney stone formation, with a pH below 5.5 increasing the risk of uric acid stone formation and a pH above 6.0 elevating the risk of calcium stones[4]. Despite variations in urinary pH, the formation of calcium oxalate crystals appears largely unrelated to pH levels, suggesting a heterogeneous nucleation process influenced by the

presence of specific crystal types[5]. The condition affects approximately 5% of the global population annually[6] and comprises a complex interplay of factors such as lifestyle choices,[7] including diet and hydration levels,[8] along with the interaction of epidemiological, biochemical, and genetic predispositions[9]. The alarming recurrence rate of urolithiasis, exceeding 50% relapses within a span of 5 to 10 years, poses a significant challenge[10]. Management strategies have evolved, with surgical approaches aiming for complete stone removal such as Extracorporeal Shock Wave Lithotripsy (ESWL), ureteroscopy (URS), and percutaneous nephrolithotomy (PNL) or by consuming synthetic drugs, although these procedures can be intricate, costly, and do not guarantee prevention of recurrence[11]. The antioxidant properties of phytochemicals have been extensively documented, offering potential benefits in managing stress and inflammation often associated with conditions like urolithiasis. The properties highlight the potential of plant-derived compounds and enzymatic biomarkers in the prevention and management of urolithiasis[12]. The report obtained from the magnetic resonance shows that heightened levels of BMI, Triglycerides, Adiponectin, waist circumference, body fat percentage and alcohol consumption are associated with an augmented vulnerability to urolithiasis[13]. The etiology of this disease involves various factors contributing to increased excretion of stone-forming components such as calcium, oxalate, urate, cystine, xanthine, and phosphate, coupled with decreased urine volume[14]. Excessive vitamin D intake, vitamin A deficiency, hyperthyroidism, gout, intestinal dysfunction, and bacterial infections by Klebsiella pneumoniae, Pseudomonas, and Oxalobacter formigenes can all contribute to its development[15]. Among kidney stones, those containing calcium are the most prevalent (75–90%), followed by magnesium, ammonium, phosphate (struvite) (10–15%), uric acid (3–10%), and cystine (0.5–1%)[16].

Nutrition plays a fundamental role in maintaining overall health, and imbalances in nutrition often lead to various health issues. In India, a significant portion of the population, nearly 20%, and a concerning 44% of young children under the age of 5, suffer from malnutrition, resulting in underweight conditions[17]. In recent years, there has been increasing interest in exploring the potential of nutraceuticals in urolithiasis management. Nutraceuticals, encompassing herbal extracts, vitamins, minerals, and probiotics, are gaining recognition for their ability to support urinary health and potentially mitigate urolithiasis risk. These substances offer various benefits, including inhibiting crystal formation, balancing urine pH, decreasing urinary calcium excretion, and support kidney function. Moreover, nutraceuticals may assist in alleviating symptoms like pain and inflammation associated with urolithiasis[18].

**Role of Phytoconstituents:**

The formation of kidney stones can be avoided by numerous bioactive substances present in plants (phytochemicals), including polyphenols, alkaloids, terpenoids, glycosides, polysaccharides, and fatty acids[19]. Phenolics flavonoids alkaloids terpenoids tannins saponins and sterols are a few of the diverse sorts of phytochemicals that have a place beneath the polyphenolic umbrella. These are primarily auxiliary metabolites the relationship between phytochemicals and their antioxidant adequacy has been altogether caught on advertising a chance to require utilize of this characteristic in arrange to check the aggravation and push that is regularly connected to urolithiasis separated from antioxidant phytochemicals enzymatic biomarkers such as catalase (CAT), superoxide dismutase (SOD), peroxidase (PER), glutathione S-transferase (GST), contribute against redox reaction, stress, and inflammation respectively. Besides, metabolic enzymes such as alanine-glyoxlate aminotransferase, oxalyl-coA decarboxylase, D-glycerate dehydrogenase, and lactate

dehydrogenase (LDH) regulate a crucial role in stone formation[13].

**Causes of urolithiasis:**

Factors in one's diet can elevate the occurrence of renal calculi which encompasses less drinking of fluids also more uptake of certain food elements like animal protein, sodium, refined sugars, and fructose particularly from sources like high fructose, corn syrup, oxalate grapefruit juice, apple juice and cola drinks. Stone occurrence commonly arises from factors like inadequate urinary drainage, presence of foreign bodies in the urinary tract, microbial infections and diets rich in oxalates and calcium. Additionally, abnormalities in vitamin levels such as deficiencies in vitamin A or excessive intake of vitamin D as well as metabolic disorders like Hyperthyroidism, Cystinuria, Gout and Intestinal dysfunction can also contribute to the likelihood of urolithiasis[20]. Which is a condition influenced by a combination of environmental and genetic factors making it a multifaceted disease, lifestyle choices, obesity, dietary patterns and inadequate hydration are among the environmental concerns linked to its development meanwhile hormonal imbalances genetic predispositions and anatomical variations are also believed to play significant roles in shaping the etiology of urolithiasis[21].

**Epidemiology:**

The epidemiology of renal calculi exhibits discrepancy over distinct geographical regions encompassing factors such as prevalence, incidence, age and gender distribution, socio-economic status report of stone composition, chemical-physical characteristics and locations of the stones indicating a wide disparity in the occurrence of kidney stones across various geographic locations with rates ranging from 8 to 19 in males and 3 to 5 in females in western countries[22]. Certain medications including Triamterene, Dyrenium, Indinavir, Crixivan and Acetazolamide, Diamox have been linked to urolithiasis in developing nations. The frequency of stones may be underestimated due to the possibility of silent and undetected kidney stones. Which were identified through renal sonography in 3 of asymptomatic individuals in children upper urinary tract anomalies and infections are typically associated with urinary tract issues rather than metabolic disturbances. While renal stones have historically been more common in men there has been a notable increase in adjusted discharge rates for stone disease in females in the us between 1997 and 2002 leading to a shift in the gender occurrence ratio from 171 to 131; male-to-female hypocitraturia, hyperuricosuria, hyperoxaluria, gouty diathesis and elevated sulfate levels are observed across various ethnic groups. The increased incidence of renal tubular acidosis in Indians may contribute to the increased frequency of kidney stone disease compared to other racial groups[23].

**Diagnosis:**

Depending on the patient's condition, diagnostic imaging methods to identify ureteral calculi include Ultrasonography, Plain radiography, Intravenous pyelography, and non-contrast helical computed tomography. Treatment options are Extracorporeal shock wave lithotripsy, Ureteroscopy, Ureterorenoscopy, and Percutaneous nephrolithotomy. Initial treatment focuses on addressing reversible factors, such as increasing urine volume to 2.5 L/d and implementing dietary restrictions, including sodium restriction with additional considerations for oxalate restriction in cases of significant hyperoxaluria, limiting sucrose/fructose intake, prescribing xanthine oxidase inhibitors if hyper uricosuric, and administering cholestyramine for fat malabsorption[24].

**INVESTIGATION PATHWAY:**

Cystone was chosen as the standard control in several studies due to its status as a polyherbal formulation widely utilized in clinical practice for treating kidney stone[s] [25].

Its effectiveness against calculi is attributed to various mechanisms including its ability to disintegrate crystals act as a diuretic and relax urinary smooth muscles by facilitating stone expulsion rate[26]. It has markedly diminished the necessity for concurrent symptomatic management with analgesics. Consequently, it offers multiple avenues for comparing the efficacy of the test drug and drawing conclusions about its mechanism of action [27].

**Effect of fluid therapy:**

Consistently low urine volume often stems from inadequate fluid intake or increased loss of water through respiration and skin. Research involving 708 patients at a metabolic stone clinic underscores the link between chronic dehydration and a heightened risk of urolithiasis, with 19% of cases attributed to this condition. Epidemiological studies further demonstrate that communities exposed to prolonged dehydration due to factors like high temperatures, vigorous physical activity, and insufficient replenishment of fluids tend to exhibit a higher incidence and prevalence of kidney stones[28]. Notably, higher fluid intake has been associated with a reduced risk of kidney stones, with men showing a relative risk of 0.71 and women ranging between 0.61 to 0.68 in the highest quintile of consumption compared to the lowest quintile[29]. However, the long-term effectiveness of specific fluids in preventing various types of stones remains uncertain. Emphasizing the significance of adequate hydration, achieving a urine volume of at least 2 liters per day is recommended for effective urine dilution. Depending on environmental conditions and activity levels, individuals may need to consume between 2 and 3 liters of fluids daily to maintain this urine flow. Furthermore, interventional studies have highlighted the effectiveness of increased water intake in reducing the recurrence of kidney stones[28].

**Effect of pH:**

Urinary pH significantly influences the formation of kidney stones. When the pH falls below 5.5, insoluble uric acid crystals tend to develop, leading to the formation of uric acid renal stones, even in individuals with normal uric acid excretion rates. Conversely, a urinary pH exceeding 6.0 promotes the formation of calcium phosphate crystals, such as hydroxyapatite or brushite. Like many other health conditions, nephrolithiasis results from a complex interplay of genetic and environmental factors. Among these factors, dietary habits play a crucial role in the development of urinary stones. Additionally, fluid therapy is recommended as the primary treatment approach for all stone cases due to its safety, affordability, and effectiveness. Traditionally, the standard method to prevent renal lithiasis has involved alkalinizing the urine. However, an innovative domiciliary pH control system now enables patients with renal lithiasis to self-monitor and manage their urinary pH values. This system, comprising a pH meter and two nutraceuticals - an alkalinizer or an acidifier supplement - allows patients to regulate their urinary pH using dietary supplements. The alkalinizer supplement contains magnesium and potassium citrate, cocoa dry extract (theobromine), zinc, and vitamin A, while the acidifier supplement comprises l-methionine, calcium magnesium phytate, zinc, and vitamin A. Patients with previous uric acid stones and a urinary pH below 5.5 receive the alkalinizer supplement (1 capsule every 12 hours), while those with prior calcium oxalate stones and/or a pH above 6.2 are prescribed the acidifier supplement (1 capsule every 12 hours), along with specific dietary instructions during the study. Research indicates that this combined approach, utilizing a pH meter alongside nutraceuticals, effectively normalizes urinary pH in patients with a history of renal lithiasis. Uric acid stones are influenced by three key factors: acidic urine pH, reduced urine volume, and hyperuricosuria. Management of non-obstructing uric acid stones involves

alkalinization to maintain urine pH above 6, increasing urine volume, and decreasing urinary uric acid excretion[5]. This conservative treatment strategy has demonstrated success, resulting in elevated urinary pH levels up to 7.0 and total urine output exceeding 2 liters per day[30].

**The Nutraceuticals in the treatment of Urolithiasis:**

The significance of including fruits and vegetables in the diet to mitigate the risk of kidney stone formation has gained prominence in recent times. Fruits and vegetables contribute alkalizing agents to the diet, which counterbalance the acidic load typically associated with protein-based diets, thus mitigating the effects of heightened urinary calcium and reduced urinary citrate. Furthermore, certain fruits, notably citrus fruits, possess a naturally high citrate content, further augmenting urinary citrate levels. Additionally, fruits and vegetables are rich sources of magnesium, which promotes increased urinary magnesium levels, thereby exerting inhibitory effects on urinary crystallization[31].

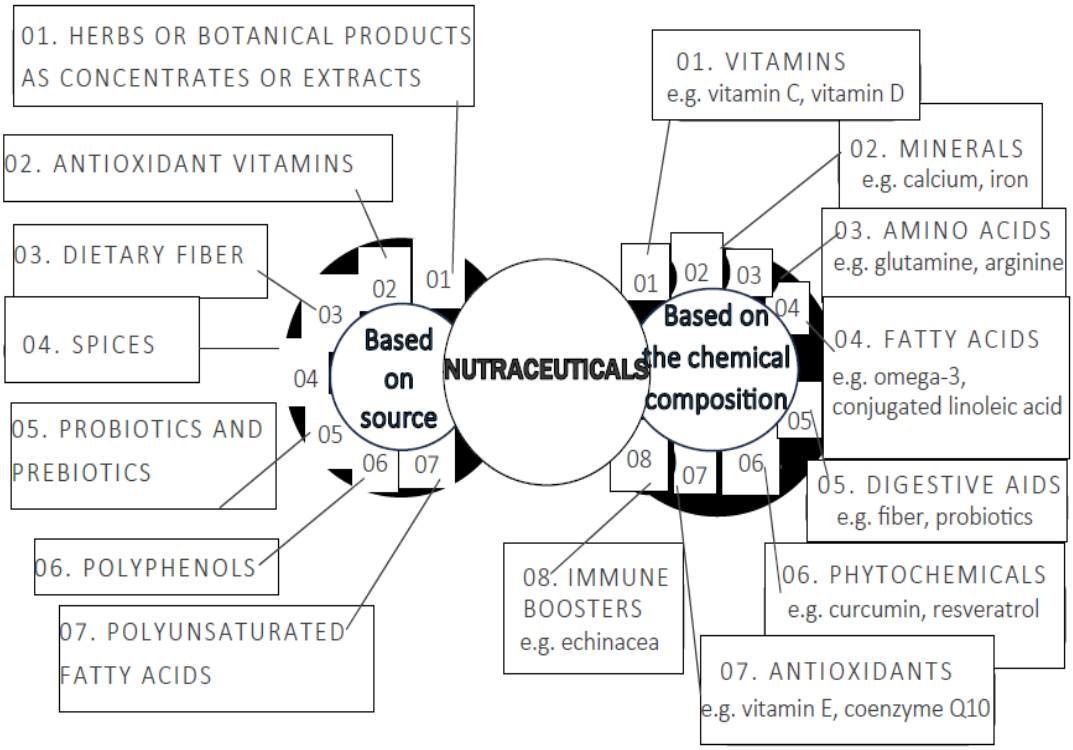


**Fig1: Classification of nutraceuticals**

**1. Aspargus (*Asparagus racemosus)*:**

The study investigates the potential antiurolithiatic effects of the ethanolic extract derived from *A. racemosus* in rats with experimentally induced urolithiasis. Parameters such as body weight, serum levels of calcium, phosphorus, urea, and creatinine, along with kidney histopathology are examined. A potential mechanism of action for *A. racemosus* could involve either enhancing the secretion or reducing the urinary concentration of salts, thus preventing the supersaturation of crystallizing salts. Previous research has suggested that flavonoids and saponins present in *A. racemosus* exhibit diuretic properties[32]. Additionally, another potential mechanism could stem from its antioxidant effects, attributed to phytoconstituents like flavonoids and polyphenols. Studies have shown in vivo evidence suggesting that hyperoxaluria-induced peroxidative damage to the renal tubular membrane surface creates a conducive environment for the attachment of individual calcium oxalate crystals, leading to the formation of kidney stones.

Furthermore, the antibacterial activity of the active principle 9,10-dehydrophenantherene found in *A. racemosus* may also contribute to its antiurolithiatic properties, as bacterial infections have been associated with promoting urolithiasis[33].

**2. Fenugreek (*Trigonella foenum graecum*):**

*Trigonella foenum graecum* is an annual plant belonging to the leguminosae family and is renowned for its culinary use as a spice. Alongside its culinary applications, fenugreek possesses a spectrum of medicinal properties including hypocholesterolemic, antibacterial, gastric stimulant, appetite stimulant, antidiabetic, galactogogue, hepatoprotective and anticancer[34]. This study examines the prophylactic potential of fenugreek seeds in preventing renal stone formation in rats. Fenugreek shows promise as a treatment for patients with calcic urolithiasis specifically the therapeutic efficacy of a standardized extract of fenugreek seeds termed standardized fenugreek seed extract-Test (SFSE-T) 60mg/kg containing trigonelline is evaluated in male rats with renal calculi induced by the 0.75% ethylene glycol (EG) and 1 % w/v ammonium chloride (AC) treatment is observed to decrease oxalate supersaturation and maintain urinary pH demonstrating its potential preventive effect against stone formation. Furthermore, subacute administration of the extract results in beneficial effects on the urinary excretion of oxalate citrate and chloride. Although not for sodium and potassium this treatment regimen not only aids in the prevention of recurrent stone formation but also improves kidney function as evidenced by histopathological analysis, which revealed fewer crystal deposits in the kidneys of rats treated with SFSE-T at a dosage of 60mg/kg compared to EG+AC control rats overall SFSE-T a trigonelline-based extract of fenugreek seeds exhibits significant therapeutic effects against EG+AC-induced urolithiasis as indicated by improvements in solute balance urinary pH creatinine clearance, total daily excretion and the number of calcium oxalate crystal deposits[35].

**3. Dwarf pineapple *(Ananas nanus* L.):**

The antiurolithiatic properties of *Ananas nanus* dwarf pineapple fruit extracts were investigated through in vitro assays. The aqueous extract of ananas fruit was obtained using the decoction method a traditional approach established in folk remedies for urolithiasis. Malaysia is known for its diverse array of medicinal plants including ananas species which have long been utilized as remedies for urolithiasis saponins exhibit anti-crystallization properties by breaking down mucoprotein suspensions, which are components that promote the crystallization process additionally phenols and flavonoids found in ananus extracts may enhance their antiurolithiatic activity. These compounds possess antioxidant properties that can mitigate reactive oxygen species (ROS)-mediated oxidative stress thereby aiding in the management of urolithiasis. Moreover, traces of alkaloids in ananus contribute to its antispasmodic effects leading to smooth muscle relaxation in the urinary tract and facilitating the expulsion of stones. The presence of saponins, phenols and terpenoids in ananus extracts strongly suggests the promising result in dissolving and inhibiting the occurrence of calcium oxalate (CaOX) making them comparable to the standard drug cystone[36].

**4. Papaya, (*Carica papaya* Linn.):**

In this study, rats induced with EG exhibited significantly lower body weight gain compared to the control group. Notably, the administration of aqueous and alcoholic extracts derived from the fruit of *Carica papaya* demonstrated a protective effect on body weight gain. Following treatment with Carica papaya, there was a notable reduction in the levels of these ions, indicating a potential protective role against urolithiasis. Conversely, treatment with Carica papaya significantly elevated urinary magnesium levels. Existing literature supports the inhibitory effect of magnesium on urine

crystallization and the formation of calcium oxalate crystals, as magnesium can form soluble complexes with free oxalate in the urine, thus reducing the availability of free oxalate to bind with calcium. Additionally, the extract induced diuresis and decreased serum levels of blood urea nitrogen (BUN), creatinine, and urea, which are nitrogenous waste products. The enhanced glomerular filtration rate (GFR) and anti-lipid peroxidation properties of *Carica papaya* fruit extracts may contribute to their protective effects against urolithiasis[37].

**5. Bijoru, (*Citrus medica* Linn):**

The investigation on *Citrus medica* suggests that the extracted drug therapy could have prevented stone aggregation thereby alleviating pain and maintaining body weight in the animals. Normally urine tends to be acidic which helps prevent stone formation whereas alkalization of urine promotes stone aggregation. Treatment with both the standard and experimental drugs prevented the shift in urine pH towards alkalinity. In the model control group levels of oxalate and calcium excretion showed a progressive increase but treatment with cystone and *citrus medica* resulted in decreased oxalate and calcium levels. This reduction in oxalate and calcium excretion is advantageous in preventing stone formation or growth by reducing urine supersaturation. Furthermore, there was a significant increase in the excretion of inorganic phosphate and uric acid in both serum and urine in the model control group compared to the normal control group. However, treatment with the standard and experimental drugs significantly mitigated this treatment with the standard and experimental drugs led to an increase in magnesium concentration which decreases the growth and nucleation rate of calcium oxalate crystals by interfering with oxalate absorption. Additionally, there was an increase in citrate concentration which forms soluble complexes with calcium inhibiting the precipitation and aggregation of calcium oxalate and phosphate crystals. These mechanisms may contribute to the protective effects observed moreover administration of the standard and experimental drugs resulted in a significant decrease in lipid peroxidation and prevented a decrease in catalase levels in the kidneys compared to the model control animals. This suggests the efficacy of the treatment in preventing damage induced by free radicals[38].

**6. Black cumin (*Nigella Sativa* L.):**

The essential oil of black seed contains mono- and sesquiterpenes as well as fatty acids. A randomized double-blind placebo-controlled clinical trial was conducted to evaluate the efficacy and safety of *Nigella Sativa* L. in dissolving kidney stones. Compared with the placebo, *Nigella Sativa* L. demonstrated positive effects on the disappearance or reduction in size and the number of calcium oxalate deposited in the kidneys as evidenced in rat models. The ethanolic extract of *Nigella Sativa* L. decreased the number of calcium oxalate deposits and lowered the urine concentration of calcium oxalate. Previous studies have also reported on the effects of the methanol extract and essential oil of *Nigella Sativa* L. on kidney stones induced by ethylene glycol in rats it was concluded that the alcoholic extract of *Nigella Sativa* L. is more effective in preventing the accumulation of calcium oxalate crystals in the urinary tract and kidneys. Moreover, the antiurolithiasis effect of *Nigella Sativa* L. particularly in combination with other herbs such as *Butea monosperma* Lam. has been demonstrated in previous in vitro and in vivo studies. The study was done on the first human trial to evaluate the safety and efficacy of *Nigella Sativa* L. in dissolving renal stones by incorporating it into the diet compared to a placebo may help prevent kidney stones and dissolve early-forming stones however for the treatment of larger stones a concentrated extract may be necessary[39].

**7. Lemon (*Citrus limon*):**

A study investigated the impact of different concentrations of lemon juice on the formation of calcium oxalate (CaOx) crystals

in the kidneys of rats. Lemon juice exhibits a potent antioxidant capacity attributed to its constituents, including citrate, vitamin C, vitamin E, and flavonoids like eriocitrin, hesperetin, and limonoids. Vitamin E in particular, may hinder the deposition of calcium oxalate crystals in the kidneys by mitigating hyperoxaluria-induced peroxidative damage to the renal tubular membrane surface, thereby preventing lipid peroxidation. This protective action can potentially impede the attachment of calcium oxalate crystals and the subsequent development of kidney stones. A study revealed that lemon juice effectively inhibited the formation of urolithiasis in rats. These findings lend support to the utilization of lemon juice as an alternative therapeutic approach for the prevention of urolithiasis[40].

**8. Stonebreaker (*Phyllanthus niruri):***

The plant *Phyllanthus niruri* commonly known as the stone-breaker which belongs to the euphorbiaceae family boasts a rich history spanning over 2000 years in the treatment of urolithiasis. Within this plant lies triterpenes, believed to wield remarkable antilithogenic properties. Interestingly patients afflicted with calculi measuring 3mm particularly those settled in the middle or upper calyx showed notable efficacy in the elimination of stones. A course of treatment involving a standardized extract of *Phyllanthus niruri* administered over a span of three months, unveiled promising results a substantial reduction of 1.7mm in patients with the size of calculi ranging from 3-6mm. Extending the treatment duration is expected to yield even more favorable outcomes[41].

**9. Horse gram (*Macrotyloma uniflorum):***

As a result of the extract's capacity to disrupt oxalate metabolism and decrease the saturation levels of calcium and oxalate ions in urine kidney stone formation is prevented. As evidenced by the decrease in calcium and oxalate excretion that occurs after therapy. The production of calcium oxalate crystals in the kidney was also prevented by the increased urine volume. Which also helped to lower the saturation of oxalate and calcium ions. The diuretic effect of the extract facilitated the flushing out of excessive ions and aided in the mechanical expulsion of stones. Furthermore, the extract was observed to lower serum urea levels and increase creatinine clearance levels alongside a significant rise in catalase activity indicating its antioxidant properties, these antioxidant effects can be attributed to the presence of flavonoids known for their remarkable anti-inflammatory and antioxidant activities. The scavenging of free radicals, anti-inflammatory properties, antimicrobial effects and antagonistic activity against AA1R receptors exhibited by flavonoids play pivotal roles in preventing the further formation and dissolution of crystals[42].

**10. Bottle gourd (*Lagenaria siceraria):***

In both the Cystone and *Lagenaria siceraria* fruit powder (LSFP) groups there was a decrease in oxalate levels. The suppression of oxalate production caused by LSFP therapy could be the cause of this decline. Furthermore, the LSFP -treated group exhibited significantly lower levels of uric acid in urine and serum indicating the mitigation of renal damage. Notably, the LSFP group did not show a decrease in $Mg_2$ levels possibly due to the protective effect of LSFP on the kidneys. Phytochemical constituents found in plants such as triterpenes and c-glycosylflavonoids have been shown to possess antiurolithiatic effects. Although the exact mechanism underlying this effect remains unknown it appears to be associated with the diuretic properties of these constituents and their ability to reduce urinary concentrations of stone-forming substances. The present investigation suggests that the presence of flavonoids and triterpenes in LSFP may have played a role in the observed decrease in kidney stone development and calcium oxalate crystal aggregation[43].

**11. Grapes (*Vitis vinifera*):**

Red and white grape seed extracts were employed as a pretreatment the kidneys of rats treated using ethylene glycol showed a significant decrease in calcium deposition. After both polyphenolic extracts were administered the results showed that diuresis has increased and renal function has improved because they can prevent damage to the papillary tissue from cytotoxic substances with oxidative capabilities. The antioxidant qualities of polyphenols extracted from red and white grape seeds may be particularly important in preventing the formation of calcium oxalate monohydrate papillary calculi by chelating metals and scavenging reactive oxygen species it has been shown that this antioxidant action helps to prevent oxidative damage to membranes and DNA[44].

**12. Carrot (*Daucus carota*):**

Rats treated with Daucus carota root extract (DCRE) showed a significant reduction in the presence of calcium oxalate dihydrate (COD) crystals in their urine compared to untreated rats. These crystals were notably smaller and less adhesive posing less harm to the renal epithelium compared to calcium oxalate monohydrate (COM) crystals. This underscores the anticrystallization properties of DCRE which can be attributed to its content of saponins, tannins and polyphenolic compounds as confirmed by phytochemical analysis. Treatment with both cystone and DCRE results a remarkable reduction in urinary levels of calcium phosphate oxalate, protein and uric acid. Additionally, it restored depleted urinary levels of magnesium and citrate thereby, rebalancing the disrupted equilibrium between promoters and inhibitors of stone formation. Furthermore, kidney homogenates from rats treated with DCRE and cystone showed a marked reduction in calcium phosphate and oxalate deposition compared to untreated rats moreover treatment with DCRE and cystone led to a notable decrease in serum levels of blood urea nitrogen (BUN), creatinine and uric acid indicating efficacy in improving renal function. And both treatments effectively inhibited renal tissue damage and inflammation, common occurrences associated with urolithiasis attributed to the generation of reactive oxygen species due to hyperoxaluria and crystalluria[45].

**13. Ivy gourd (*Coccinia indica Wight):***

The ethanolic extract of *Coccinia indica* (CIEE) when administered as a supplement, showed significant prevention of alterations in urinary levels of oxalate, calcium, phosphate, creatinine, and uric acid in a dose-dependent manner. Moreover, in rats subjected to diets high in magnesium along with CIEE supplementation, magnesium levels reverted to normal. This dietary combination has been identified to offer protection against the deposition of calcium oxalate in the kidneys, particularly in vitamin B6 deficient rats. Magnesium forms complexes with oxalate, thereby reducing the supersaturation of calcium oxalate and subsequently diminishing the growth and nucleation rate of CaOX crystals. In ethylene glycol-induced urolithic rats, treatment with CIEE led to a significant reduction in urinary magnesium, resulting in lowered uric acid excretion and a reduced risk of stone formation. Uric acid binding proteins present in CIEE have the capacity to bind to calcium oxalate and modulate its crystallization, thereby playing a crucial role in preventing stone formation. Furthermore, the administration of CIEE exhibited profound effects in minimizing the excretion of protein, potentially preventing the formation of a nidus for crystal nucleation. Overall, the results underscore the nephroprotective effects of the fruits of *Coccinia indica* wight & Arn. in an ethylene glycol-induced urolithiasis model[46].

**14. Spirulina (*Arthrospira platensis*):**

Rats treated with a combination of ethylene glycol and spirulina exhibited statistically significant increases in the levels of sodium, chloride, BUN and ALT, while calcium levels were decreased interestingly. During

the final three weeks of the study, Rats induced with ethylene glycol and spirulina showed significant recovery from nephrolithiasis and within the initial three weeks, they showed complete recovery from hepatotoxicity induced by ethylene glycol. Although, the precise mechanism underlying the effect of spirulina on ethylene glycol-induced nephrolithiasis remains elusive, it appears to demonstrate increased diuresis and a reduction in the urine concentration of sodium, calcium, potassium, phosphorus, uric acid, creatinine and other substances that promote stone formation. This suggests a potential role for spirulina in mitigating the risk of kidney stone formation, thus further research is needed to fully understand its mechanisms of action[47].

**15. Sargassum seaweed (*Sargassum wightii*):**

In vivo studies have conclusively shown that the administration of PTSW effectively decreased the supersaturation with divalent cations in the urine, particularly calcium and oxalate. This promising intervention shows its potential to alleviate conditions marked hyperoxaluria and hypercalciuria. The mechanism underlying this reduction in calcium and oxalate levels can be attributed to PTSW's ability to impede the absorption of these substances from dietary sources and also effectively rectify enzymatic disturbances associated with idiopathic hyperoxaluria, as evidenced by decreased serum levels of calcium and oxalate. Furthermore, treatment with PTSW at various doses showed a significant reduction in the deposition of calcium and oxalate in the kidneys. Different concentrations of PTSW demonstrated a notable reduction in glomerular damage, membrane damage, and infiltration of inflammatory cells. most significantly the deposition of calcium oxalate was markedly diminished in both preventive and curative treatment groups[48].

**16. Chyawanprash:**

Several formulations of traditional herbal remedies with stone-breaking, stone-dissolving, and diuretic properties are commercially available in the market as Ayurvedic treatments for nephrolithiasis. One such formulation is Chyawanprash, which combines various traditional plants known for their antinephrolithiatic, nephroprotective, and diuretic effects to effectively and conveniently treat nephrolithiasis. Chyawanprash is prepared according to the instructions outlined in Ayurvedic texts such as the Charaka Samhita, an ancient Ayurvedic treatise.

Ingredients such as Varun moola (*Crataeva Nurvala*) and Palsahpushpa (*Butea monosperma*) are beneficial for urinary system complaints, including kidney stones, and possess analgesic, lithotriptic, and anti-inflammatory properties. Citron fruit (*Citrus medica*) is traditionally known for its ability to prevent crystal aggregation and also exhibits diuretic and antioxidant activities. Ashwagandha serves as an immunity booster and scavenges free radicals. Pomegranate juice contains bioactive compounds that mitigate the harmful effects of chronic heavy metal exposure. Horse gram extract is highly effective in dissolving calcium oxalate crystals and reducing their size significantly. Hydroalcoholic extracts of Gokhru (*Tribulus terrestris*) and Guggul (*Commiphora wightii*) possess anti-inflammatory, antihypertensive, diuretic, and urinary anti-infective properties. Basil leaves (*Ocimum basilicum*) act as nephroprotective agents, helping to mitigate the effects of nephrotoxic agents. Additionally, black pepper, nutmeg, cinnamon, and ginger possess chelating capacities and radical-scavenging properties[49].

**17. Green tea (*Camellia sinensis*):**

A Study revealed that treatment with green tea resulted in the reduction of accumulation of calcium oxalate deposits in the kidney tissue as well as a decrease in the expression of OPN and apoptosis while increasing SOD activity it is widely recognized that tea consumption can elevate urinary oxalate excretion this experiment is believed to hinge on mechanism wherein antioxidants block

NF-kB activation which has been proposed as an effective strategy for addressing urolithiasis and arteriosclerosis furthermore the antioxidative property of green tea were found to decrease the calcium oxalate stone formation, OPN expression and apoptosis while enhancing SOD activity in rat kidney tissues. The observed inhibitory effect of the tea on CaOx urolithiasis is likely attributable to its antioxidative properties[50].

**18. Parsley (*Petroselinum crispum*):**

In this investigation, results were observed the presence of CaOx crystals in the kidneys of EG/AC rats, primarily located within renal tubules exhibiting noticeable signs of tubular injury such as cloudy swelling and irregular luminal borders. Additionally, there was evidence of crystal encroachment upon the interstitium, particularly when compared to the kidneys of normal (negative control) rats. Tubular dilatation was also observed, although interstitial inflammation was only intermittently detected and not consistently associated with the presence of CaOx crystals. The presence of polymorphic irregular crystals within the tubules was found to contribute to the dilatation of proximal tubules and the occurrence of interstitial inflammation. This study demonstrated a significant decrease in the density of CaOx in renal tissue among rats administered parsley compared to those in the positive control group and those receiving cystone, which is consistent with previous findings. This decrease is attributed to parsley's ability to reduce oxalate synthesis, possibly by interacting with EG absorption in the intestine or with the enzyme responsible for oxalate synthesis in the liver. In conclusion, parsley exhibits antiurolithiatic properties by reducing urinary calcium excretion, increasing urinary pH to create an environment unfavorable for CaOx crystallization, promoting diuresis and increasing urine volume, thereby reducing urine supersaturation, and decreasing nucleation through the reduction of urinary protein excretion, ultimately demonstrating nephroprotective activity[51].

**19. Pomegranate (*Punica granatum*):**

Rats administered ethylene glycol produce high levels of urinary calcium oxalate, leading to rapid crystal deposition and nephrolithiasis with corresponding elevations in lipid peroxidation, ROS-free radical generation, malondialdehyde (MDA; as measured by TBARS), and nitric oxide. Inhibition of this pathway through inactivation of nuclear factor κB (NF-κB) prevents CaOx precipitation in rats with kidney stones. Pomegranate plants, which are rich in multiple antioxidants, including polyphenols, hydrolyzable tannins, anthocyanins, and ellagic acid derivatives, have been shown to suppress NF-κB activation in vivo and inhibit lipid peroxidation. Pomegranate extract supplementation with 1,000 mg polyphenol extract daily may confer some modest benefit in lowering the supersaturation of calcium oxalate. The correlation between increasing serum PON1 activity with lower saturation of calcium oxalate may help explain the reduced risk of calcium oxalate stone formation with pomegranate shown in the animal studies[52].

**20. Oregano (*Origanum vulgare*):**

The research conducted on the plant extract revealed its ability to inhibit CaOx crystal nucleation and aggregation in a concentration-dependent manner, similar to citrate, a well-established inhibitor of CaOx crystallization commonly used in the clinical management of urolithiasis. Furthermore, in the incubation study, Ov.Cr demonstrated a reduction in crystal count and transformed COM to COD crystals, similar to the effects observed with citrate and $Mg^{2+}$. The presence of an antiurolithic effect in *Origanum vulgare* against renal calcium oxalate crystal deposits is likely mediated through a combination of actions, including CaOx crystal inhibition, diuretic activity, antioxidant properties, antispasmodic effects, protection of epithelial cells, reduction in urinary calcium levels, and increase in urinary citrate levels, thereby acting on multiple pathways[53].

**21. Vegetable hummingbird (*Sesbania grandiflora*):**

A study has demonstrated that S. grandiflora may affect calcium and oxalate excretion and deposition, potentially by breaking down mucoproteins, which are known to promote crystallization. The presence of polyphenols in *S. grandiflora* may aid in dissolving calcium oxalate and magnesium ammonium phosphate stones by forming complexes with divalent cations such as calcium and magnesium. Treatment with *S. grandiflora* leaf juice resulted in a significant decrease in malondialdehyde (MDA) content, suggesting a reduction in lipid peroxidation. This decrease could be attributed to a reduction in oxalate levels in the kidney and urine post-treatment, or vice versa. Reduced glutathione (GSH) serves as a sensitive marker of oxidative stress and is crucial for maintaining system integrity. The anti-urolithiatic activity of S. grandiflora may stem from the breakdown of mucoproteins by saponins and the formation of complexes between tannins and calcium. Both in vivo and in vitro antioxidant studies suggest that *S. grandiflora* has the potential to mitigate damage to renal membranes induced by gentamicin and hyperoxaluria caused by calcium phosphate deposition[54].

**22. Yellow-fruit nightshade (*Solanum virginianum*):**

In rats induced with ethylene glycol (EG), there was a notable increase in the urinary excretion of calcium and phosphate. This elevation in calcium and phosphate excretion might be attributed to impaired tubular reabsorption in the kidneys. However, treatment with standard, curative, and preventive regimens of *S. virginianum* significantly lowered the levels of these ions, indicating a protective effect against urolithiasis. The administration of ethanolic extracts of *S. virginianum* in both curative and preventive regimens induced diuresis, reduced kidney weight, and also decreased elevated serum levels of BUN, creatinine, and urea. Histopathological examinations revealed no microcrystalline deposition or kidney damage in the groups treated with *S. virginianum* extract. These findings collectively support the preventive and curative potential of *S. virginianum* against ethylene glycol-induced lithiasis in rats. In conclusion, the ethanolic extract of *S. virginianum* exhibits both preventive and curative properties in rat urolithiasis[55].

## CONCLUSION AND FUTURE PERSPECTIVE:

This review article delves into the efficacy of nutraceuticals, fluid intake, and maintaining pH levels in patients with urolithiasis. Urolithiasis presents a substantial burden on global healthcare systems, attributed to its widespread prevalence and recurrent nature. As a result, numerous nutraceuticals have been subjected to scrutiny for their potential in either preventing the formation of kidney stones or facilitating their passage. Besides, adequate fluid intake stands as a basic recommendation in the prevention of kidney stone recurrence. This suggestion is firmly rooted in the principle of urine dilution, which aids in preventing the supersaturation of substances prone to forming stones. The pivotal role of dietary factors, particularly acid-forming or alkalinizing foods, in modulating urinary pH and thereby influencing the risk of stone formation, remains an area open for further investigation. Understanding the complexity of these factors holds promise for refining preventive strategies and improving outcomes for individuals afflicted with urolithiasis.

In upcoming years, nutraceuticals, particularly dietary polyphenols, are poised to revolutionize urolithiasis treatment by offering tailored interventions. Innovations in formulations will improve effectiveness complemented by wearable technology for monitoring and enhancing patient involvement and adherence. However, challenges remain in establishing bioavailability, safety and mechanisms of action through thorough clinical investigations, imperative for their inclusion

in conventional treatment approaches. This integration method eventually reduces dependence on surgical intervention and enhancing patient outcomes.

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