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Exploring Plant Metabolic Products for Diuretic and Anti-Urolithiatic Properties: A Comprehensive Review

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A B S T R A C T

Plants have long served as a valuable inspiration for discovering new drug compounds. This is primarily due to the significant contributions made by plant-derived medicines to human health and overall well-being. Medicinal plants are widely utilized by various segments of society, either directly as traditional remedies or indirectly as components in modern pharmaceutical preparations. Natural products derived from plants offer several advantages, such as being non-toxic, having fewer side effects, and being accessible at affordable costs. Throughout history, plants have been a primary source of therapeutic agents for treating various human diseases. Both tribal communities and rural populations rely on the surrounding plant resources for their medicinal and other essential needs. Urinary bladder and kidney stones have remained a challenge within the medical field, prompting the exploration of alternative systems of medicine that prioritize natural sources with minimal to no side effects. The Fabaceae family, which consists of approximately 600 genera and 13,000 species, stands as the third largest family within the plant kingdom.

This current review aimed to enhance our understanding of plant metabolic products and to obtain results pertaining to their diuretic and kidney stone-related properties. The study involved conducting morphological and phytochemical screenings. The results revealed the presence of various phytochemical constituents in each sample. Pharmacological studies conducted on the samples demonstrated their effectiveness in terms of diuretic and antiurolithiatic properties during the preliminary stage. The response of the samples was evaluated both individually and in combination to determine any synergistic effects.

Keywords: Medicinal plant, anti-urolithiatic drugs, herbal medicine

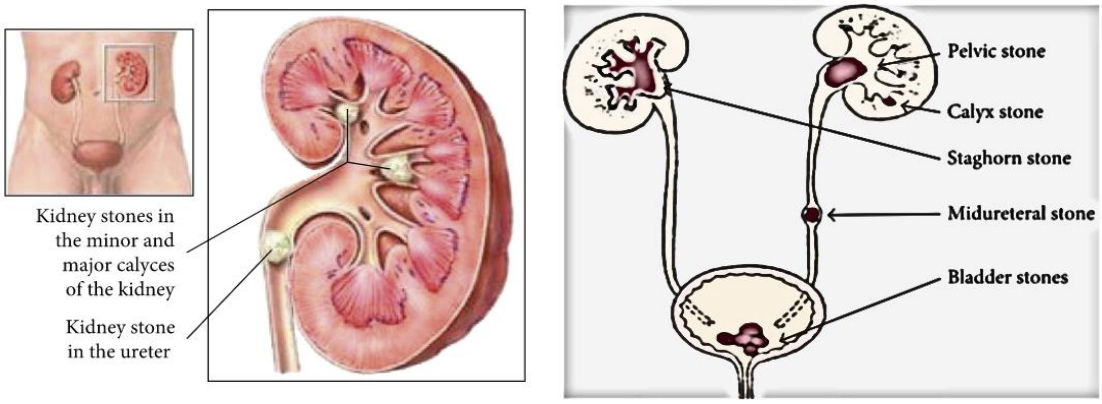
Introduction

Kidney stones develop as a result of the combination of organic and inorganic elements (such as crystalline salts and urine macromolecules) in the renal parenchyma or pelvicalyceal system (especially in the ureters, urinary bladder and urethra). Kidney stone disease (KSD), also known as nephrolithiasis or urolithiasis, is widespread throughout practically all of the world and is becoming more and more common in some areas [1]. It is one of the oldest, most prevalent, and most recurrent diseases, and the first evidence of it may be found in the tombs of Egyptian mummies from 4000 BC[2]. The prevention of stone recurrence requires better understanding of the mechanisms involved in stone formation[3]. Chronic kidney illnesses, end-stage renal failure, cardiovascular disorders, diabetes, and hypertension have all been linked to an increased incidence of kidney stones. Kidney stones may be a systemic condition connected to the metabolic syndrome, according to some research. If nephrocalcinosis is present, nephrolithiasis accounts for 2 to 3% of instances of end-stage renal disease[4]. Whether a kidney stone is in the ureter, kidney, or urinary bladder, the symptoms depend on where it is[5]. Stones do not first manifest any symptoms. Later, renal colic (severe cramping pain), flank pain (pain in the back), hematuria (bloody urine), obstructive uropathy (urinary tract illness), urinary tract infections, obstruction of urine flow, and hydronephrosis (dilation of the kidney) are signs and symptoms of the stone disease. These disorders may cause nausea, vomiting, and other discomfort due to the stone occurrence[6]. As a result, the quality of life and economy of the country are negatively impacted by the cost of treatment and time missed from work[4]. Human kidney stones are too diverse and their creation is too complex for a single hypothesis of etiology to adequately explain them[7]. Kidney stones are intuitively thought to be a risk factor for chronic kidney disease (CKD). The kidney's function includes eliminating metabolic wastes like calcium and oxalate at supersaturated quantities while avoiding crystallization. As a result, the development of stones may be seen as a symptom of renal illness and a form of "impaired kidney function." It is standard of care to measure the serum creatinine level and check for acute kidney damage (AKI) caused by an obstructive uropathy in patients who report with symptomatic kidney stones. The blood creatinine level often returns to normal with the resolution of the AKI after surgical or non-surgical stone removal. The long-term effects of a kidney stone on kidney health are less certain[8]. The prevalence of kidney stones disease is higher in boys than in females among the adult population in the US, according to data studies utilizing information from the NHANES (National Health and Nutrition Examination Survey). However, the frequency has increased in women (from 6.5% in 2007-2008 to 9.4% in 2017-2018) while being consistent in men over the past ten years (11.6% in 2007-2008 and 11.9% in 2017-2018). KSD also affects people of all ages, including, adolescents, children and adults[9, 10].

Several efficient treatments are being offered for KSD. The most popular techniques include surgical removal techniques such percutaneous nephrolithotomy, ureteroscopy, and extracorporeal shock wave lithotripsy. The size and position of the stone have a significant impact on the removal technique used. However, recurrence of the stone following removal continues to be a significant issue for surgical management of KSD. According to a recent data from Iceland, the recurrence rate in children after the removal of the stone varies from 26% at 5 years to 46% at 20 years[10, 11]. A decline in the number of patients with new and recurrent KSD (stone formers) would lower the total cost of KSD therapy because stone removal is an extremely expensive procedure. KSD places a heavy financial load on the stone formers in addition to heavy physical and mental demands[12]. Therefore, it is important to give significant thought to preventive measures for both new and recurring stone formation.

1. Urethral Stones and The Urinary System:

The glomerulus produces the urine filtrate, which then travels into the tubules where reabsorption or secretions change its amount and composition. The proximal tubules are where most solute reabsorption takes place, while the distal tubules and collecting ducts are where small modifications to urine composition are made. Urine that is 95 percent water, 2.5 percent urea, and 2.5 percent of a mixture of minerals, salts, hormones, and enzymes is concentrated via the Henle loop. The necessary nutrients such as amino acids, proteins, bicarbonate, calcium, phosphate, and potassium are also reabsorbed and returned to the blood stream in the proximal tubules along with glucose, salt, chloride, and water. The distal tubule controls the blood's salt and acid-base balance[4]. The position of the stones can differ as depicted in Figure 1.



(a) **(b)**

Fig 1: Kidney stones can be found in different locations within the urinary system, as illustrated in scientific diagrams (a) and (b) adopted from references [13] and [14].

2. Types of Kidney Stone:

The mineralogy of kidney stones is determined by the imbalances in the chemical makeup of urine. The chemical composition, size, and shape of the stones can vary depending on these abnormalities[15]. Kidney stones are categorized into different types based on their mineral composition and the way they form. There are five main types of kidney stones that are commonly recognized and classified accordingly[16].

2.1 Calcium stone:

Typically, kidney stones are categorized according to their primary crystalline structure. As depicted in Figure 1, numerous studies conducted across various regions have consistently indicated that calcium is the predominant inorganic composition found in kidney stones[17, 18]. The most frequent type of calcium stone is composed of calcium oxalate (CaOx), which can either be pure or mixed with other materials like calcium phosphate (CaP). CaOx comes in three crystalline forms, depending on its level of hydration: CaOx monohydrate (COM; $CaC_2O_4 \cdot H_2O$), CaOx dihydrate (COD; $CaC_2O_4 \cdot 2H_2O$), and CaOx trihydrate ($CaC_2O_4 \cdot 3H_2O$). Among these, COM (also known as whewellite) is the most commonly found form in clinical stones, followed by COD (also known as weddellite). The major risk factors for calcium stones are hypercalciuria, hyperoxaluria, hypocitraturia, and hypomagnesuria. Specifically, hyperoxaluria promotes the crystallization of urinary COM, while hypercalciuria favors urinary COD crystallization. That's right! Calcium phosphate (CaP) stones are commonly found in the form of apatite, which can be hydroxyapatite [$Ca_5(PO_4)_3OH$] or carbapatite (carbonated apatite) [$Ca_{10}(PO_4)_6CO_3$]. These stones are less common than calcium oxalate stones but can still be quite problematic. Unlike calcium oxalate stones, the formation of CaP stones is more dependent on urine pH. Low urine pH (acidic) promotes CaP stone formation, whereas high urine pH (alkaline) promotes the formation of other types of stones. Therefore, the treatment of CaP stones may involve adjusting the urine pH[17, 18].

2.2 Struvite stone:

The Struvite stone, also known as an infection stone, is composed of magnesium ammonium phosphate (MgNH4PO4·6H2O). This type of stone often forms in combination with calcium oxalate (CaOx) and calcium phosphate (CaP), particularly carbapatite, within the stone matrix[19]. The presence of urease-producing bacteria, including Proteus spp. and Klebsiella spp., is associated with the formation of this particular kidney stone type, which often occurs in conjunction with urinary tract infections (UTIs)[20]. An infection can cause more ammonium to be produced, which then leads to the urine becoming more alkaline. This makes it easier for struvite crystals to form in the kidneys. Recent research has shown that people who have struvite crystals in their kidney stones and have a high level of Proteus spp. in their urine cultures. In addition to bacteria that produce urease, other bacteria such as Escherichia coli and Enterococcus spp. have also been linked to the formation of struvite stones[19, 20]. In certain regions, it is noteworthy that this type of stone is more prevalent in females than males[21].

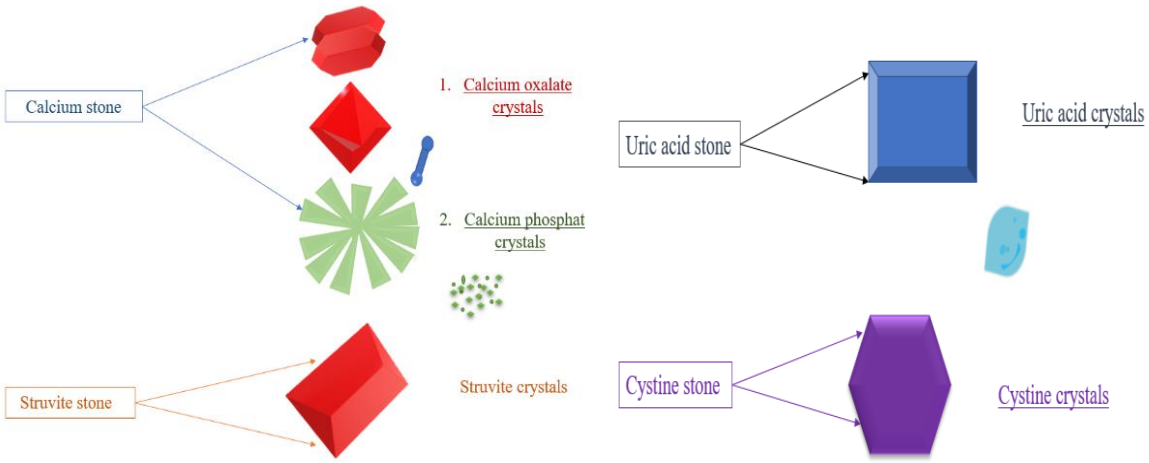


Fig 2: The classification of kidney stones is typically determined by their primary crystalline makeup. These various stone categories share some risk factors while also possessing distinct ones.

2.3 Uric acid stone:

The uric acid stone is composed of crystals of uric acid that typically form in urine with an acidic pH. The majority of these crystals exist in the dihydrate form[18]. Patients diagnosed with type 2 diabetes and obesity are more prone to this type of stone formation. The occurrence of uric acid stones appears to have been on the rise in male patients in recent years[21]. The combination of uric acid crystals with other crystal types is more common, according to research. The major contributing factors to the formation of uric acid stones are hyperuricosuria and chronic low urinary pH, which causes the urine to become more acidic[21].

2.4 Cystine stone:

Cystine stone is an uncommon kind of kidney stone that is linked to cystinuria, a genetic condition. The cause of this stone is due to an autosomal recessive gene, like SLC3A1, which controls the renal cystine transporter[22]. When someone has a genetic disorder that affects cystine transport, the body can't properly reabsorb cystine from urine. This leads to higher levels of cystine in the urine, a condition known as cystinuria[23]. Normally, urine with a pH below 6.5 helps keep cystine soluble. However, when cystine levels are too high, it can't stay dissolved and instead forms crystals that can clump together and create cystine stones[23].

2.5 Drug-Induced Stones:

About 1% of all stone kinds are represented by this. These stones are brought on by medications like triamterene, atazanavir, guaifenesin, and sulfa medicines. As an example, those who consume indinavir sulphate, a protease inhibitor, are at risk of developing side effects from an HIV medication[16]. Renal calculi the metabolites of such lithogenic medicines may deposit on existing renal calculi or to produce a nidus present. On the other side, these medications might cause they interfering with the metabolism of calcium oxalate or purines, it can cause calculi to develop[24].

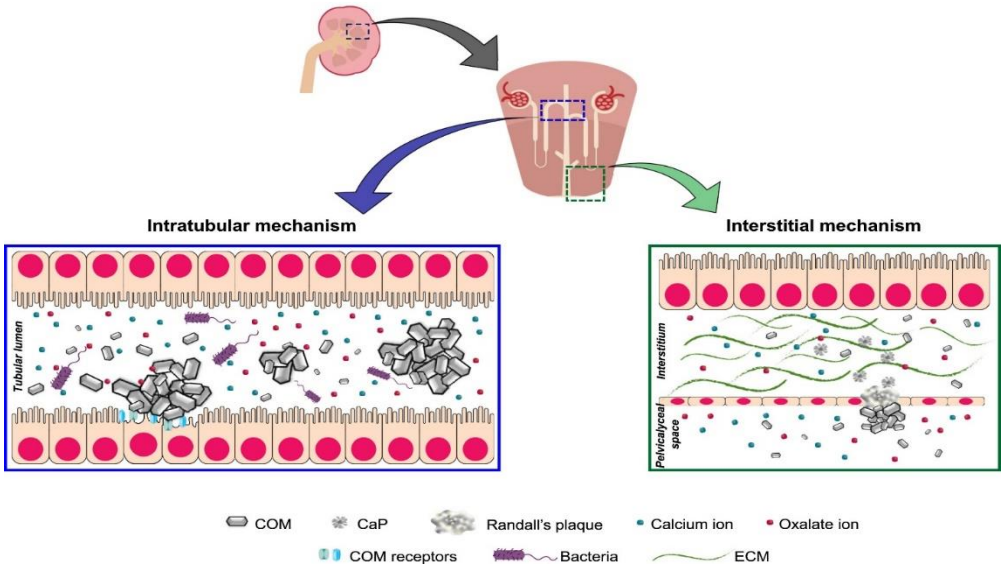
3. ETIOLOGY:

The causes of kidney stones are intricate, and the likelihood of getting the condition is influenced by a mixture of genetic, metabolic, and environmental factors. Certain dietary habits are linked to kidney stones, including insufficient fluid intake, excessive salt consumption, high intake of oxalate-rich foods, limited calcium intake, and excessive consumption of animal proteins[25]. Research has indicated that individuals who have diabetes mellitus,

hypertension, obesity, or chronic kidney disease have a higher probability of developing kidney stone disease[26]. Residing in regions with high average yearly temperatures and distinct seasonal changes, as well as having employment that entails exposure to heat, restricted access to restrooms or water, or direct occupational contact with nephrotoxic substances (such as cadmium, trimethyltin, or oxalic acid), can also make one more susceptible to developing kidney stones[27].

4. Pathophysiology:

The most frequently occurring type of kidney stone is the CaOx stone, which can form through two primary mechanisms based on its location**(figure3)**. These mechanisms are the intratubular mechanism that originates within tubular lumens and the interstitial mechanism that primarily occurs within interstitial space. The intratubular mechanism begins with the supersaturation of crystalline salts, which is followed by crystallization within the renal tubular lumens[28]**.** Afterwards, the crystals grow, clump together, and stick to the outer surface of tubular epithelial cells, causing them to remain within the tubular lumens. The attachment of crystals to the membrane is made easier due to the heightened surface presentation of specific proteins that are capable of binding with the crystals[29].Various research studies have stated that increased surface expression of crystal-binding proteins can occur due to various factors such as overexpression of annexin A1 induced by calcium, overexpression of α-enolase induced by oxalate, and overexpression of heat shock protein 90 induced by uric acid[30]. The crystals that have attached themselves can continue to increase in size and stick to each other, eventually becoming too large to pass through the narrow tubes. This causes them to accumulate within the renal tubules, blocking the flow of fluid through them[28].



(Figure 3): The formation of CaOx stones occurs through two mechanisms. The first mechanism involves supersaturation of crystalline salts, crystallization, growth, self-aggregation, and adherence on tubular epithelial cells within tubular lumens. Bacteria, both urease-producing and non-urease-producing groups, also contribute to this mechanism. The second mechanism occurs in the renal interstitium where interstitial hydroxyapatite CaP crystal deposition and tissue inflammation result in the formation of Randall plaques. Some of these plaques erode into the pelvicalyceal system, where CaOx is commonly supersaturated and crystallized. CaOx crystals then deposit on the eroded Randall plaque, which serves as the stone nidus, initiating stone formation[10]**.**

The second mechanism starts in the renal interstitium and involves the formation of Randall plaques, which are caused by the deposition of interstitial hydroxyapatite CaP crystals and inflammation of tissue. In an environment with high supersaturation, CaP typically crystallizes at the basement membrane of the thin limb of Henle loop in the renal papillary interstitium[31]. The build-up of CaP crystals in the interstitial area stimulates inflammation, resulting in the creation of Randall plaques. These plaques are primarily located at the papillary tip and surrounding areas, and some of them can wear away into the pelvicalyceal system, where CaOx is typically concentrated and crystallized. Following this, CaOx crystals accumulate on the eroded Randall plaque, which serves as a site for the formation of the stone nidus, initiating the formation of the stone[28, 31].

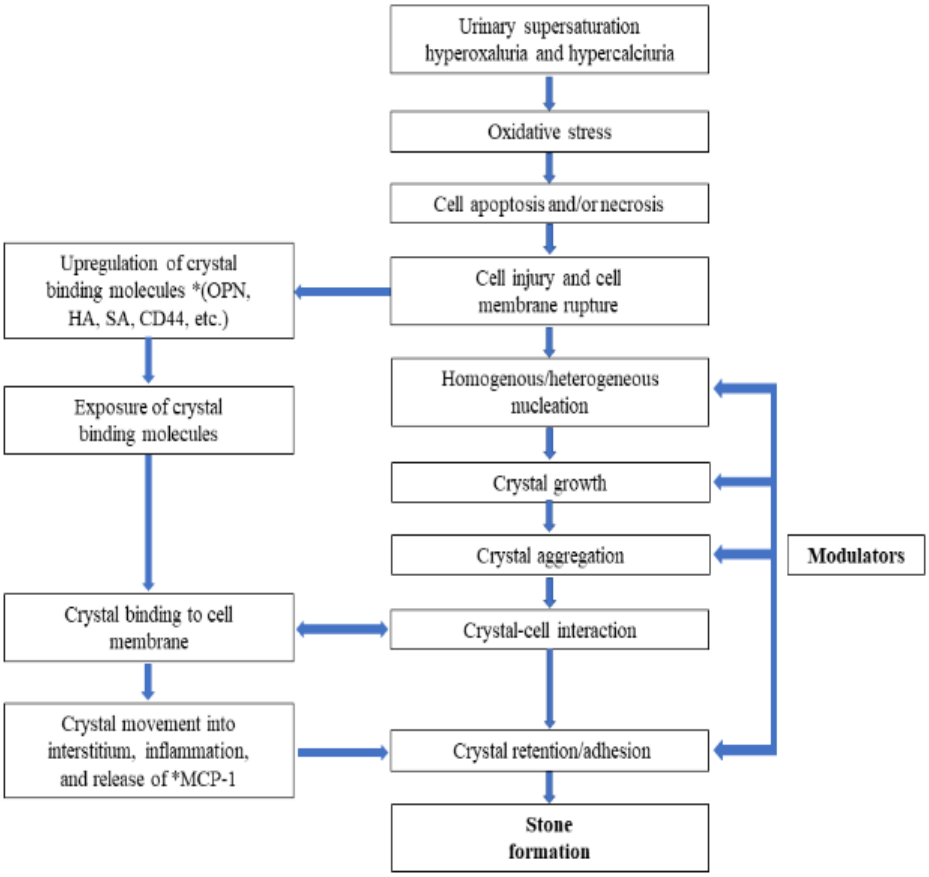


Figure 4: This diagram illustrates the different processes that occur within and outside the cells during the formation of urinary stones. The abbreviations used include OPN for osteopontin, HA for hyaluronic acid, SA for sialic acid, and MCP-1 for monocytic chemotactic protein-1[32].

5. Selecting specific kidney-targeting medication delivery locations:

5.1 Renal Glomerulus as a targeting site:

Due to its distinctive anatomical structure, the renal glomerulus is a favorable location for targeted drug delivery due to its enhanced retention and permeability effect. The glomerular mesangium can be directly reached through vascular endothelial fenestrations, which have a diameter ranging from 130-170 nm. The filtration slits on the glomerular basement membrane (GBM) have pore sizes ranging from 10-70 nm. To ensure drug delivery to the Renal Glomerulus, researchers have developed nanoscale delivery systems like polymeric nanoparticles and liposomes. The optimal size for these systems is between 70-130nm as it allows them to pass through the glomerular vasculature and reach the mesangium. Due to their size, they cannot pass through the GBM and instead accumulate and remain in the mesangial space, increasing their effectiveness in drug delivery[33]. Studies have shown that PEGylated gold nanoparticles, with a diameter of 75±25 nm, have the ability to accumulate in the mesangial space of mice kidneys. This indicates that the size of the nanoparticles plays a crucial role in their accumulation in the kidney. Research has also suggested that the renal glomerulus is a favorable site for targeted drug delivery using nanoscale delivery systems such as polymeric nanoparticles and liposomes, which are designed to pass through the glomerular vasculature and accumulate in the mesangial space[34].

Figure5: The anatomical structure of nephron and glomerulus

5.2 Renal tubular system as a targeting site

The cells found in the proximal tubules have various transporters and receptors that can be targeted for drug delivery. However, these transporters are not very efficient in delivering large drug carrier conjugates as they are primarily designed to uptake small endogenous compounds and small drug molecules. Additionally, many of these transporters are expressed in other organs besides the kidneys, which makes them unsuitable for targeted drug delivery to the kidneys. Therefore, they are not considered as an appropriate target for kidney-specific uptake of therapeutics[35, 36]. Targeting drug delivery to proximal tubular cells through receptor-mediated endocytosis appears to be a promising approach. Proximal tubular cells in the kidney have unique internalizing receptors that can take up small molecules and macromolecules that are filtered into urine. Since these receptors are exclusively found on

proximal tubular cells, using carriers that bind to these receptors to target drug delivery to tubular cells is the most appealing strategy for achieving efficient drug uptake[37-39]. Drug delivery to proximal tubular cells faces anatomical barriers on both the apical and basolateral sides of proximal tubules. To reach the basolateral side, drug delivery systems can penetrate the diaphragmed fenestrations (about 60-70 nm) of the endothelial cell layer of peritubular capillaries and tubulointerstitium positioned between the endothelium and tubular cells. On the other hand, to reach the apical side, a carrier system is required to get filtered through the endothelial layer of glomerulus, which has fenestrations of approximately 70-100 nm, followed by diffusion across GBM and the podocyte foot processes. (Refer to Figure 6 A and B).

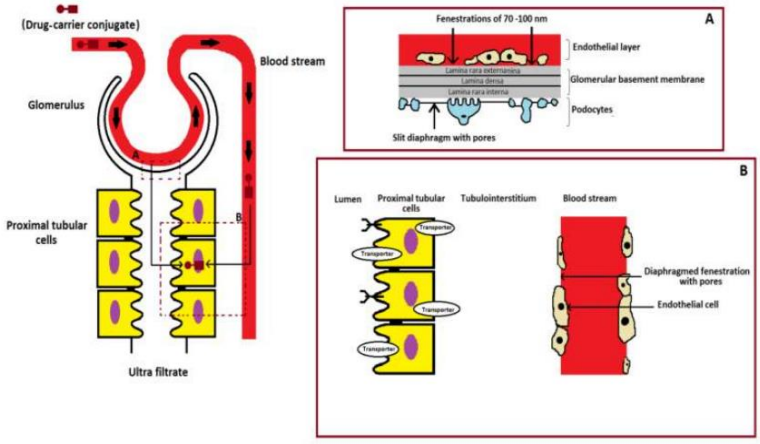
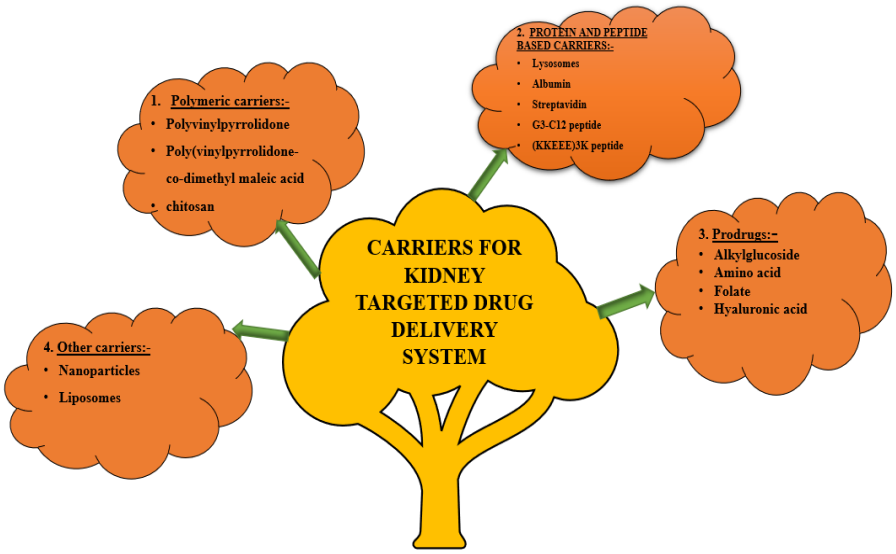


Figure 6: Accessing proximal tubules through the apical or basolateral side can be challenging due to anatomical barriers.

6. Drug targeting strategies for kidney

Different approaches have been used to develop drug delivery systems that specifically target the kidneys.



Throughout human history, herbal products have been the primary source of medicine in all cultures. Many different types of plants have been traditionally used to treat physical, mental, and social health issues. In India, the traditional systems of Unani and Ayurvedic medicine have relied on herbal drugs for centuries. These drugs are obtained from various parts of plants, including flowers, leaves, stems, bark, roots, and seeds. Herbal drugs, which have been used for centuries to treat various human illnesses, can be derived from plant excretory products like gum, resins, and latex. Due to the growing concern about the negative health effects associated with the unregulated use of synthetic medication, there is an increasing demand for plant-based drugs worldwide. There are numerous medicinal plants that have yet to be studied for their potential pharmacological properties, and pharmaceutical companies rely heavily on wild plant populations to obtain the raw materials needed to produce medically active compounds. For centuries, various communities across the globe have utilized herbs to treat a variety of ailments. Recently, a study was conducted in the forested regions of Nizamabad to explore the plants used by locals to treat diseases. The study found that kidney stones were the most common ailment in the area and that 20 different plant species from 13 Angiospermic families were utilized to treat it. Amaranthaceae had the highest number of species with four, followed by Fabaceae, Malvaceae,

Cucurbitaceae, and Padaliaceae with two species each[40]. The depletion of wild medicinal plants due to their commercial use has led to a reduction in their natural habitats. To ensure accessibility to pharmaceutical companies and individuals who rely on herbal medicines, cultivating herbal plants is necessary. Conserving natural sources alone cannot meet the increasing demand for pharmaceuticals. Therefore, it is important to develop cultural practices for cultivating these plants in suitable agro-climatic conditions. This will prevent the continued exploitation of wild sources and preserve rare natural wealth and biodiversity. Herbal remedies have been used throughout human history and are still important in both developing and developed countries. Medicinal plants are crucial for building primary healthcare systems in rural areas and have played a significant role in drug discovery[41].

Pharmacognosy:

The term "pharmacognosy" was coined by Prof. John Schmidt in his book "Lehrbuch der Materia Medica". It is derived from two Greek words, "pharmakon" meaning medicine and "gignosco" meaning to acquire knowledge of something. The term was introduced in the early 19th century to define the subject area of studying medicinal drugs obtained from plants[42]. Pharmacognosy was originally linked to botany and phytochemistry but with the progress of organic chemistry, a new dimension was added to the quality control and analysis of herbal drugs. As a result, the discipline has expanded to include the discovery of new chemical compounds with therapeutic properties from natural sources[43]. Pharmacognosy was initially linked to botany and phytochemistry, but as organic chemistry progressed, it added a new dimension to the examination and quality control of plant-based medicines. This has resulted in the identification of novel chemical compounds derived from natural sources with therapeutic benefits, expanding the scope of the field. Pharmacognosy also assists in verifying and validating plant material used in medication, and evaluating its pharmaceutical and other critical parameters[44]. The curative potential of a medicinal plant is indeed dependent on the quality and quantity of its chemical composition. The chemical constituents of a plant can vary based on factors such as climate, soil composition, and other environmental factors, which can affect the plant's growth and development[45]. It is crucial to assess the quality of the plant material to ensure that it is safe and effective for medicinal use. This involves identifying and quantifying the chemical compounds present in the plant and verifying its pharmaceutical and other critical parameters. Such precise identification and quality assurance of medicinal plants are essential for the reproducible quality of herbal drugs, which ultimately ensures their safety and efficacy[46]. Advancements in modern technology such as transcriptomics, genomic science, proteomics, nano-science, and synthetic biology have led to a significant transformation in medicinal plant research[47]. In some cases within traditional systems, different plant species may be given the same common name[48].

Treatment

The approach to treating kidney stones is individualized to suit the stone's type and size. The treatment possibilities include drugs, shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy[49-51]

a. Medicines:

If the renal calculi are small, drinking lots of fluids and taking pain relief medication can aid in flushing out the stone through the urinary tract. Various medications are recommended based on the type of stone, such as

- Allopurinol for uric acid stones,
- Thiazide diuretics and Phosphorus solutions to prevent calcium stone formation, and
- Sodium citrate or bicarbonate to reduce urine acidity.

But if the size of the renal calculi is large or if it's obstructing the urinary tract, additional treatment is necessary.

b. Shock wave lithotripsy (SWL): Shock wave lithotripsy is a treatment technique that involves using shock waves to fragment the renal stone into smaller pieces. This makes it easier for the stone to travel through the urinary tract and be eliminated from the body through urine.

These are the restrictions of the treatment method of SWL:

- It can cause discomfort to the patient
- General anesthesia is needed
- It may not be as effective for patients with hard stones or those who are morbidly obese
- There is a risk of ureteral obstruction due to stone fragments.

c. Ureteroscopy: During this process, a slender wire with an attached camera, referred to as a ureteroscope, is inserted through the urethra and into the urinary bladder. The objective is to locate and extract the stone that has become lodged in either the bladder or ureter.

Limitations:

- It requires general anesthesia
- It generally requires a postoperative ureteral stent
- Invasive
- Ureteral stricture/injury

d. Percutaneous nephrolithotomy:

This method of treatment involves making a minor cut on the back and inserting a tube into the kidney to extract the calculi. Surgery is performed through this tube to remove the stones.

Limitations:

- Invasive
- Bleeding
- Injury to nearby organs
- Injury to collecting system

Urolithiasis places a significant burden on the economy and healthcare system of the country. The estimated annual cost nationwide is over $70 million. Ureteroscopic stone removal and extracorporeal shock wave lithotripsy (ESWL) are commonly used methods to remove stones. However, ESWL has limitations such as the presence of residual stone fragments, potential traumatic effects of shock waves, and the risk of infection. It can also lead to acute renal injury, reduced renal function, and increased stone recurrence. These treatments are costly, painful, and require skilled professionals and specialized equipment. Surgery is often necessary for many patients to effectively treat this painful condition. Additionally, synthetic drugs used to prevent urolithiasis are not effective for all patients and may have adverse effects that limit their long-term use[52].

Despite significant advances in modern medicine, there are currently no highly effective drugs for the treatment of kidney stones. As a result, it is important to explore alternative treatments, such as phytotherapy, to replace the limitations of modern methods. The use of herbal drugs and extracts from medicinal plants has been well-documented as a successful remedy for urolithiasis. Traditional treatment systems, like Ayurveda, have utilized plants with components that exhibit antilithogenic effects by altering the ionic composition of urine, acting as diuretics, and possessing antioxidant and antimicrobial properties. Additionally, the therapeutic role of proteins derived from plants in the management of urolithiasis is gaining recognition. These plant proteins, which are rich in amino acids, have a unique ability to interact with calcium and render oxalate unavailable[52].

Herbal medicines have various active components that contribute to their effectiveness in treating urolithiasis through multiple mechanisms, including:

- Significantly increasing urine volume, pH, and anti-calcifying activity, which aids in the natural passage of stones (known as diuretic activity).
- Regulating the balance between inhibiting and promoting the crystallization of lithogenic substances in urine, thereby affecting crystal nucleation, aggregation, and growth (known as crystallization inhibition activity).
- Relieving the binding mucin of calculi, facilitating the breakdown of kidney stones (known as lithotriptic activity.
- By promoting better kidney function.
- By balancing oxalate metabolism.
- By regulating the balance between crystalloid and colloid substances and preventing the recurrence of urinary stones.
- By improving the antioxidant status and cell membrane integrity of renal tissues, thus preventing future occurrences.
- By inhibiting enzymes like Angiotensin Converting Enzyme and Phospholipase A2.
- By exhibiting strong antibacterial properties against the main bacteria responsible for urinary tract infections.

By significantly improving symptoms associated with urinary stones, such as pain, burning during urination, and blood in the urine, through its analgesic and anti-inflammatory effects[53]

The use of medicinal plants for the management and treatment of urolithiasis is common in different countries and cultures. [54]

Plants studied for antiurolithiatic property

Nature has endowed us with a plethora of medicinally important plants with enormous therapeutic potential. The clinically proven efficacy of these herbs has aroused a great deal of interest and hope in the treatment of kidney stones. Several medications are mentioned in Ayurveda has the capacity to dissolve kidney stones, relax the ureters, and reduce discomfort (Figure 1.5).

Figure 5. Probable mechanisms of plant based medicines

The medicinal flora's pharmacological properties are thought to be attributable to the presence of key phytochemicals such as alkaloids, phytosterols, saponins, flavonoids, carotenoids, prebiotics, tannins, fatty acids, terpenoids, phenolics, and dietary fibers [55, 56].Powered by plants Medicines have some advantages versus synthetic medications (see Figure 1.6).

Pashanbheda, an Ayurvedic drug, is used to break calculi and alleviate uncomfortable micturition. However, the plant's precise identity is uncertain, and several plants have been labeled as pashanbheda over time.

Figure 6. Benefits of using plant based medicines

Some of the plants explored for antiurolithiatic properties are discussed further below:

When tested using a spectrophotometric assay, ethanolic and aqueous extracts of Ipomoea batatas leaves and roots strongly reduced the nucleation and aggregation of calcium oxalate crystals in a concentration dependent manner[57].

When compared to a typical polyherbal formulation, an ethanolic extract of Ipomoea aquatica caused substantial dissolution of calcium oxalate crystals in titrimetry [58]. In a study of 58 patients with hyperoxaluria and hyperuricosuria, Phyllanthus niruri increased urine excretion of magnesium and potassium while decreasing urinary oxalate and uric acid. The patients ranged in age from 18 to 60, and the kidney stones were less than 10 mm in size[59]. In vitro and in vivo, an ethyl acetate extract of Pedalium murex reduced the formation of struvite crystals. The extract also demonstrated a minimum bactericidal concentration against E. coli and Staphylococcus aureus[60]. The antiurolithiatic function of Ipomoea reniformis ethanolic leaf extract was demonstrated by a decrease in serum nitrogenous parameters in lithiatic rats[61]. Quercetin and Betulin, both extracted from Aerva lanata, have modest diuretic properties as well as antiurolithiatic activity, greatly lowering the size of renal calculi. Calcium excretion was dramatically reduced by the substances. Oxalate, and phosphate, but magnesium excretion increased[62].

Semicarpus anacardium, Tinospora cordifolia and Terminalia chebula showed significant antiurolithiatic property when studied by in vitro methods[63].

In an in vivo antiurolithiatic investigation in male sprague, an aqueous extract of the traditionally used Chinese herb Radix paeoniae was reported to generate a considerable reduction in renal crystallisation and pathological alterations sprague-dawley rats[64].

The antiurolithiatic effect of an aqueous-ethanol extract of Musa paradisiaca pseudostem (MUSA) was evaluated in ethylene glycol-induced urolithiatic animal models using urine and serum biochemistry, urine microscopy, oxidative/nitrosative indices, kidney calcium content, and histopathology and was found to be effective[65].

Biophytum sensitivum, a plant historically used in Ayurveda, was studied for its potential as an antiurolithiatic. It was discovered that supplementing with methanolic extract significantly improved glomerular filtration rate and protein excretion in urolithiatic mice with zinc disc implants[66].

Rats were employed in a zinc disc implantation paradigm to assess the protective effects of Abelmoschus moschatus extracts. The extracts significantly increased glomerular filtration rate and urine total protein excretion. The extract was also demonstrated as being promising by the decreased deposition of calculi around the implanted disc[67].

Male Wistar albino rats were used to study the effects of oral administration of an ethanolic extract of the Kigelia pinnata fruit on CaOx urolithiasis. Hyperoxaluria and an increase in the renal excretion of calcium, magnesium, and phosphate were both brought on by EG feeding. Intake of an ethanolic extract of the fruit of the Kigelia pinnata dramatically reduced the calculogenic rats' high levels of urine oxalate, uric acid, and phosphate as well as the deposition of substances that form kidney stones[68].

In laboratory experiments, it was discovered that the extract obtained from Lepidagathis prostrate, a plant known as Pashanabhed, showed effectiveness in inhibiting the formation and growth of calcium oxalate crystals. Furthermore, the analysis of the fraction using HPTLC (High-Performance Thin-Layer Chromatography) indicated the presence of two compounds, namely Lupeol and β-sitosterol[69].

In a study conducted on male Wistar albino rats using a model of ethylene glycol-induced lithiasis, the extracts obtained from Ageratum conzoides (also known as goatweed) in both ethanol and ethyl acetate forms demonstrated a significant reduction in the elevated levels of oxalate, calcium, and phosphate in urine[70].

The potential of the ethanolic extract obtained from the above-ground parts of Portulaca oleracea (commonly known as purslane) to inhibit the formation of urinary stones was investigated in albino rats using models induced by ethylene glycol and ammonium chloride. The extract exhibited positive effects by restoring various biochemical parameters, such as calcium, creatinine, and urea levels, in both serum and urine. Additionally, it significantly increased urine volume. Furthermore, treatment with the extract led to a decrease in the deposition of microcrystals in the kidney[71].

The effectiveness of standardized extracts derived from Fenugreek seeds (Trigonella foenum graecum) containing trigonelline as a marker was investigated in a study on male rats with experimental urolithiasis. Histopathological examination revealed a reduction in the number of crystals, as well as decreased cell damage and tubulointerstitial damage index, as evaluated by Kapase[72].

The analysis revealed that rats treated solely with EG (ethylene glycol) exhibited higher levels of calcium accumulation in their kidneys compared to the negative control rats. However, when lemon juice was administered, it effectively prevented the EG-induced increase in kidney calcium levels. Histological sections of the kidneys showed that rats treated solely with EG displayed substantial deposits of calcium oxalate (CaOx) crystals throughout all kidney regions. In contrast, rats treated with lemon juice had significantly fewer kidney calcifications, preventing the development of papillary and parenchymatous calculi, unlike the positive control rats[73].

Conclusion

Our study concluded that the different plant extracts posesses significant ameliorative effect on lithiasis, nephroprotective, antiapoptotic effects as well as antioxidant activity. The antiurolithiatic and antioxidant activity of the ethyl acetate extract may be due to the flavanoids and phenolic compounds which are known to posess inhibitory effects on the formation of calcium oxalate stones. The current review indicates the need for a comprehensive study

to gather information on various medicinal plants. This is essential for utilizing natural medicines effectively, achieving optimal results, and developing new formulations that can benefit humanity.

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