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Urolithiasis (Kidney Stones): Current Pharmacological Diagnosis and Management

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ABSTRACT

Kidney stones are a common condition causing significant morbidity and economic burden. The prevalence of Urolithiasis (Kidney stones) is increasing from past 20 years, worldwide 5-15% of the population affected by Urolithiasis. The most common type of kidney stone is calcium oxalate formed in the renal surfaces. The mechanism of stone formation is a complex process which results from several physicochemical events including supersaturation, nucleation, growth, aggregation, and retention of urinary stone constituents within tubular cells. Obese people are known to have a higher risk of stone formation. Metabolic syndrome has resulted in an increasing rate of nephrolithiasis among women. The diagnosis and initial management of urolithiasis have undergone considerable evolution in recent years. This review article provides information about epidemiology, mechanism, diagnosis, and pathophysiology of kidney stone formation, and methods for the evaluation of stone risks for new and follow-up patients.

Keyword: Urolithiasis (Kidney stones), Calcium oxalate, Uric acid stone, kidney, Herbs, *In-vivo* and *in-vitro.*

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INTRODUCTION

Urolithiasis is the presence of calculi in the kidney and/or in any part of the urinary tract, including the ureters and bladder and may develop in one or both of the kidneys. Nearly about 80% of these calculi are composed of calcium oxalate and phosphate.[1] The lifetime risk of urinary stone disease is 12% in males and 6% in females.[2] Urolithiasis is a complex process that is a consequence of an imbalance between promoters (calcium, sodium, oxalate, urate, cystine, low urine pH, low urine flow) and inhibitors (citrate, magnesium, pyrophosphate, Tamm Horsfall protein, urinary prothrombin fragments, glycosaminoglycan osteopontin, and high urine flow) in the kidneys.[3] Calcium oxalate (CaOx) represents up to 80% of analyzed stone. Kidney stone formation is a complex process that results from a succession of several physicochemical events including supersaturation, nucleation, growth aggregation and retention within the renal tubules.[3]

What are kidneys?

The kidneys are two bean-shaped organs in the renal system. The kidneys extend from the level of the twelfth thoracic vertebra to the third lumbar vertebra. The left kidney is closer to the midline, longer and more slender than the right. They help the body pass waste as urine.[2] They also help filter blood before sending it back to the heart. The renal hilum, an entrance to the space in the kidney called the renal sinus, is a cleft lying at the concave medial margin of the kidney and is where the structures serving the kidney enter and exit.[2]

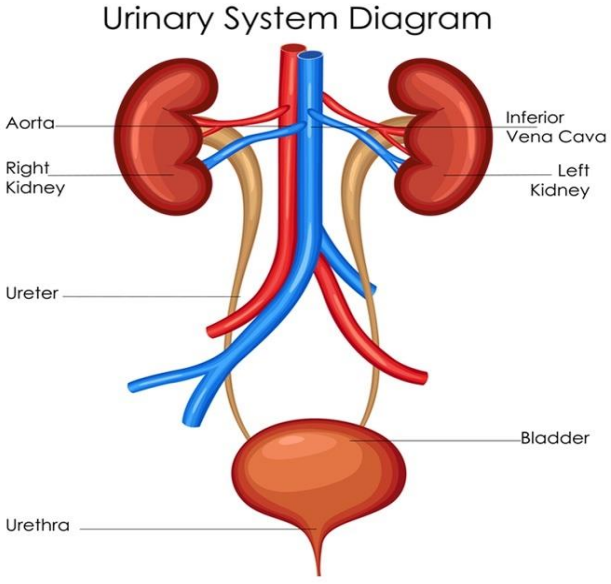

Fig.1: Urinary System Diagram

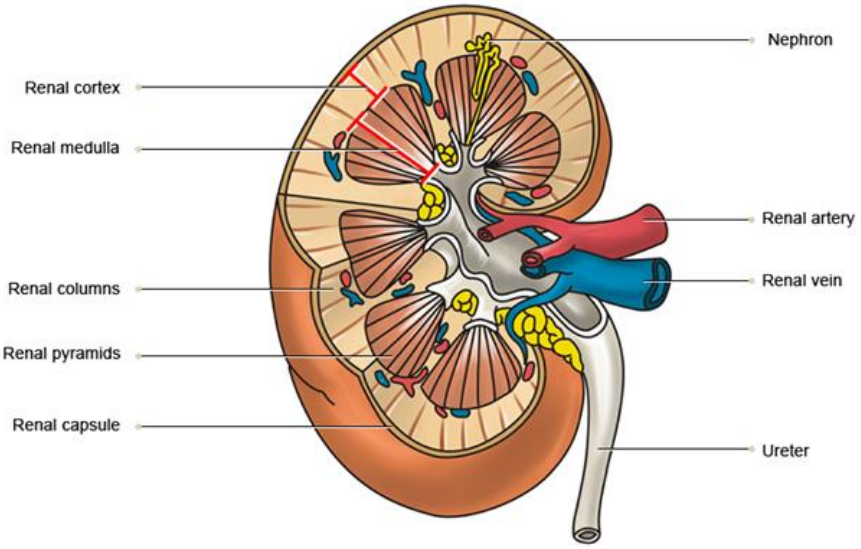

Fig.2: Structure of Kidney

The kidneys perform many crucial functions, including:

- ✓ Maintaining overall fluid balance
- ✓ Regulating and filtering minerals from blood
- ✓ Filtering waste materials from food, medications, and toxic substances
- ✓ Creating hormones that help produce red blood cells, promote bone health, and regulate blood pressure

Nephrons

Nephrons are the most important part of each kidney. They take in blood, metabolize nutrients, and help pass out waste products from filtered blood. Each kidney has about 1 million nephrons. Each has its own internal set of structures.

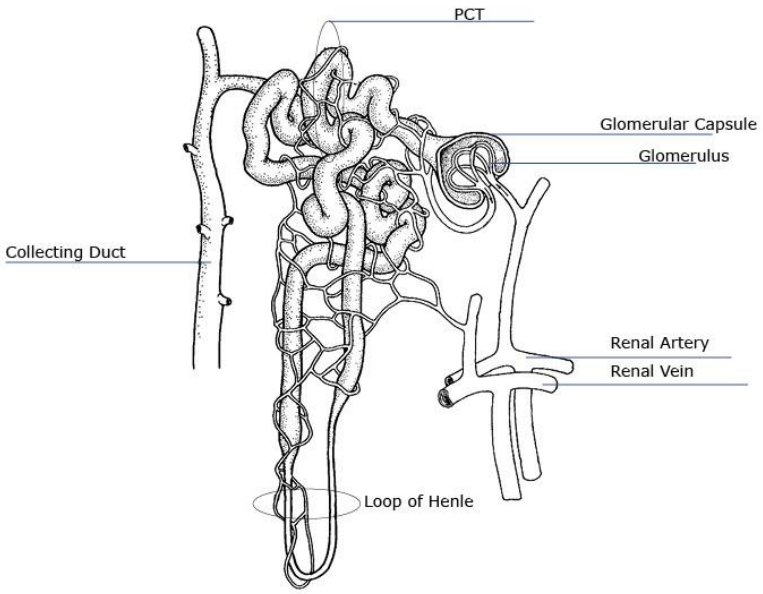

Fig.3: Nephron Anatomy

Epidemiology of Urolithiasis

The prevalence of urolithiasis is approximately 2 to 3 percent in the general population, and the estimated lifetime risk of developing a kidney stone is about 12 percent for white males. Approximately 50 percent of patients with previous urinary calculi have a recurrence within 10 years.[4] Stone disease is two to three times more common in males than in females. It occurs more often in adults than in elderly persons, and more often in elderly persons than in children. Whites are affected more often than persons of Asian ethnicity, who are affected more often than blacks. In addition, urolithiasis occurs more frequently in hot, arid areas than in temperate regions. Decreased fluid intake and consequent urine concentration are among the most important factors influencing stone formation. Certain medications, such as triamterene (Dyrenium), indinavir

(Crixivan) and acetazolamide (Diamox), are also associated with urolithiasis. Dietary oxalate is another possible cause, but the role of dietary calcium is less clear, and calcium restriction is no longer universally recommended.[5]

Presentation and Differential Diagnosis

Urolithiasis should always be considered in the differential diagnosis of abdominal pain. The classic presentation of renal colic is excruciating unilateral flank or lower abdominal pain of sudden onset that is not related to any precipitating event and is not relieved by postural changes or nonnarcotic medications. With the exception of nausea and vomiting secondary to stimulation of the celiac plexus, gastrointestinal symptoms are usually absent. The pain of renal colic often begins as vague flank pain. Patients frequently dismiss this pain until it evolves into waves of severe pain. It is generally believed that a stone must at least partially obstruct the ureter to cause pain. The pain is commonly referred to the lower abdomen and to the ipsilateral groin. As the stone progresses down the ureter, the pain tends to migrate caudally and medially.[4]

Table 1: Relationship of Stone Location to Symptoms[4]

Stone Location	Common Symptoms
Kidney	Vague flank pain, hematuria
Proximal ureter	Renal colic, flank pain, upper abdominal pain
Middle section of ureter	Renal colic, anterior abdominal pain, flank pain
Distal ureter	Renal colic, dysuria, urinary frequency, anterior abdominal pain, flank pain

Kidney stone (Urolithiasis) formation

When CaOx concentration is 4 times above the normal solubility a crystal starts to form. If the CaOx concentration is 7 to 11 times higher than normal solubility the nucleation begins. In low urine volume, the presence of high calcium, high oxalate the supersaturation (SS) of CaOx is increased. Citrate in the urine forms soluble complex with urinary Ca. If urine has low citrate concentration SS CaOx is promoted to form CaOx stone. If urine pH is > 6.5, proportion of divalent and trivalent ions are increased then SS CaP is favorable. The levels of urinary supersaturation of the different solutes determine the specific types of stones.[6]

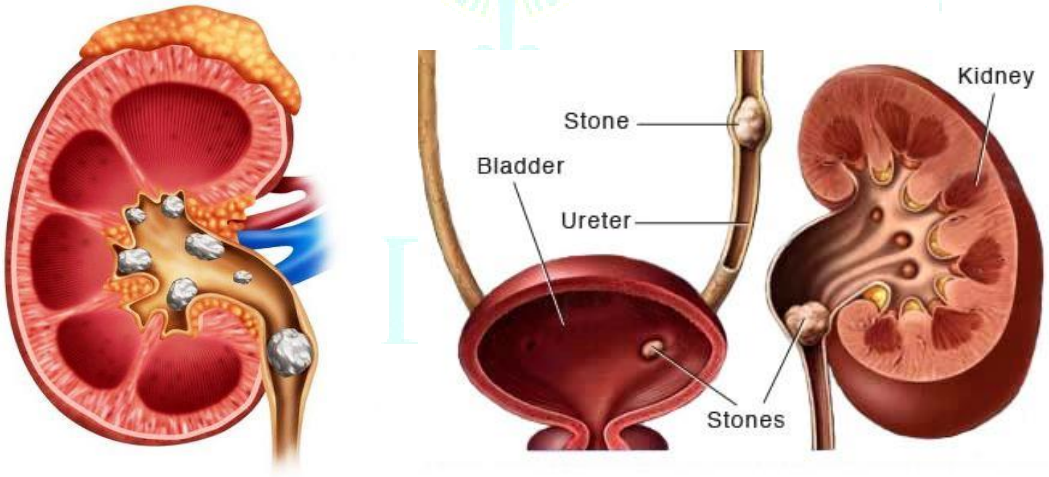

Fig. 4: Kidney stone formation

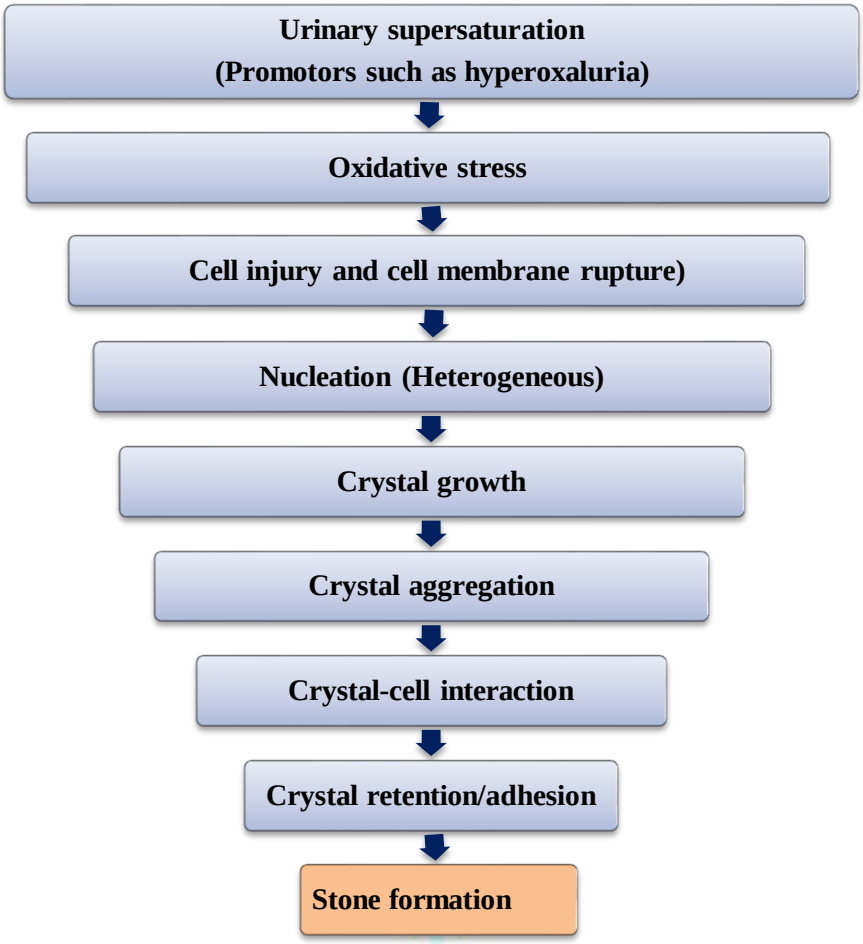

Fig. 5: Schematic representation of the various events of kidney stone formation.[7]

TYPES OF KIDNEY STONES (UROLITHIASIS)

Approximately 70-80% of kidney stones are composed of calcium oxalate and calcium phosphate. Of the rest, 10% are struvite, 10% of uric acid; and less than 1% are composed of cystine or are diagnosed as drug-related stones. Calcium and uric acid stones are more common in men; women have more struvite stones.[6]

Table 2: Type of stones

Type	Frequency (%)	Sex	Crystals	Radiography
Calcium oxalate/ mix	75	M	Envelope	Round, radiodense, sharply outlined
Calcium phosphate (brushite)	5	F>M	Amorphous: Alkaline urine	Small, radiodense, sharply outlined
Uric acid	5–15	M=F	Diamond; Acid urine	Round/ staghorn, radiolucent, filling defect
Struvite (Mg ammonium phosphate)	10–20	F	Coffin lid; Infection/ urea splitter	Staghorn, laminated radiodense
Cystine	1	M=F	Hexagon	Staghorn, radiodense

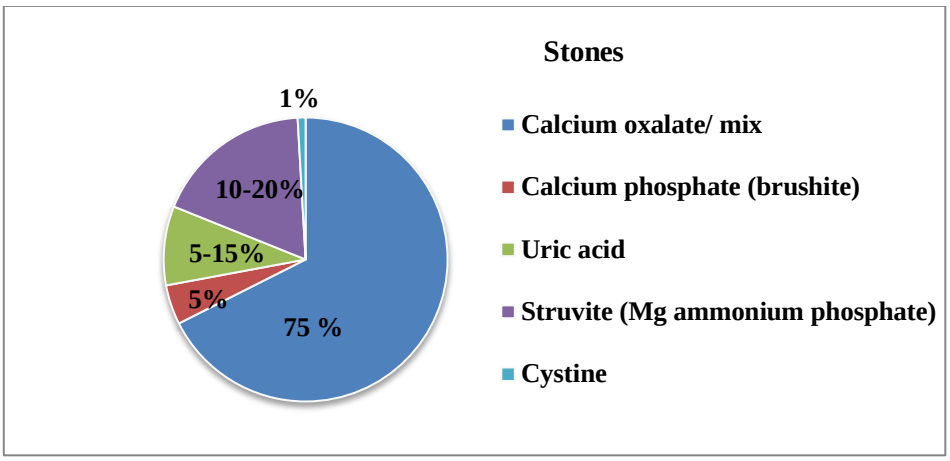

Fig.6: Chart showing % of Stone formation

Kidney stones tend to recur approximately 50% people who form one stone form another within 10 years. The risk of recurrence ranges from 30-50% at 5 years in observational studies. The control groups in recent randomized controlled trials have a 2-5% annual recurrence rate after an incident calcium oxalate stone. Recurrence rates also depend on the stone type. When nuclei of uric acid form, they lower the metastable limit (e.g. susceptibility to perturbation) and favor further stone precipitation. Decreased supersaturation of the urine filtrate will decrease the risk of recurrence of kidney stone.[8]

• Calcium stones

Calcium oxalate stones are the most common type of kidney stone. Kidney stones are solid masses that form in the kidney when there are high levels of calcium, oxalate, cystine, or phosphate and too little liquid. Calcium stones are composed of calcium oxalate, either by itself or much more commonly in combination with calcium phosphate or calcium urate.[9] Hypercalciuria, low urine volume and hypocitraturia all predispose to the development of calcium stones. Hypercalciuria often occurs with diseases associated with hypercalcemia like hyperparathyroidism, malignancy, sarcoidosis and vitamin D excess.[10] Alkaline urine is a risk factor for the development calcium phosphate stones. Another risk factor for calcium oxalate stone is hyperoxaluria, which occurs due to bowel disease (enteric hyperoxaluria) and genetic disorders of oxalate metabolism (primary hyperoxaluria).

Dietary oxalate may be important in stone development; spinach, beets and rhubarb in particular, contain large amounts of oxalate and they may increase urinary oxalate excretion and predispose to the development of calcium oxalate stones. High dose vitamin C therapy can also lead to increased oxalate generation as vitamin C (ascorbic acid) is metabolized. Oxalate reabsorption in the colon is reduced by the formation of insoluble calcium oxalate. [11]

Diarrheal losses cause volume depletion and decreased urine volume. Bicarbonate loss in the stool can cause a metabolic acidosis which can in turn lead to a low urinary pH and hypocitraturia (due to enhanced proximal reabsorption) which will predispose to the development uric acid and calcium oxalate stone formation. [12]

Fig. 7: Calcium stones

Symptom:

A kidney stone may not cause symptoms until it moves around within your kidney or passes into your ureter the tube connecting the kidney and bladder. At that point, you may experience these signs and symptoms:

- ✓ Severe pain in the side and back, below the ribs
- ✓ Pain that radiates to the lower abdomen and groin
- ✓ Pain that comes in waves and fluctuates in intensity
- ✓ Pain on urination
- ✓ Pink, red or brown urine
- ✓ Cloudy or foul-smelling urine
- ✓ Nausea and vomiting
- ✓ Persistent need to urinate
- ✓ Fever and chills if an infection is present
- ✓ Urinating small amounts

• Uric acid stones

Pure uric acid calculi are radiolucent on plain radiographs but visible on ultrasonography or computerized tomography (CT). These stones tend to form in individuals with hyperuricosuria. Approximately 15-20% of patients with uric acid stones have a history of gout. A diet rich in animal protein, because of its high purine content, which produces uric acid in its catabolism, may increase the risk of uric acid stone formation. At a urinary pH of less than 5.5, uric acid is poorly soluble, but solubility increases at a pH greater than 6.5.[13]

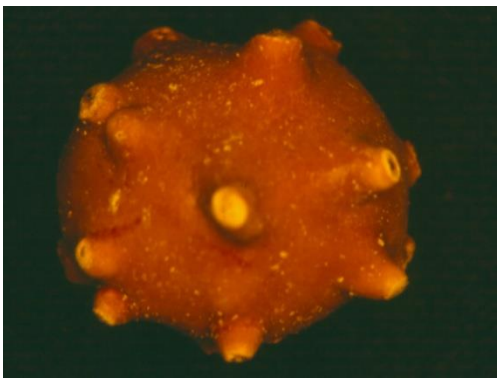

Fig.8: Uric acid stones

- ## Cystine stones

Cystine kidney stones are due to cystinuria, an inherited (genetic) disorder of the transport of an amino acid (a building block of protein) called cystine that results in an excess of cystine in the urine (cystinuria) and the formation of cystine stones.

Cystinuria is the most common defect in the transport of an amino acid. Although cystine is not the only overly excreted amino acid in cystinuria, it is the least soluble of all naturally occurring amino acids. Cystine tends to precipitate out of urine and form stones (calculi) in the urinary tract.

Small stones are passed in the urine. However, big stones remain in the kidney (nephrolithiasis) impairing the outflow of urine while medium-size stones make their way from the kidney into the ureter and lodge there further blocking the flow of urine (urinary obstruction).

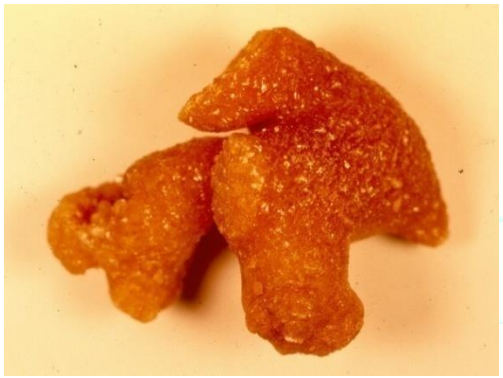

Fig.9: Cystine stones

Symptoms:

Cystinuria only causes symptoms if you have a stone. Kidney stones can be as small as a grain of sand. Others can become as large as a pebble or even a golf ball. Symptoms may include:

- ✓ Pain while urinating
- ✓ Blood in the urine
- ✓ Sharp pain in the side or the back (almost always on one side)
- ✓ Pain near the groin, pelvis, or abdomen
- ✓ Nausea and vomiting

- ## Struvite stones

Struvite stones are a type of hard mineral deposit that can form in your kidneys. Stones form when minerals like calcium and phosphate crystallize inside your kidneys and stick together. Struvite is a mineral that's produced by bacteria in your urinary tract.

About 10 to 15 percent of all kidney stones are made from struvite. This type of stone is more common in women than in men. Struvite stones can grow very quickly. Eventually, they can block your kidney, ureter, or bladder and damage your kidney.

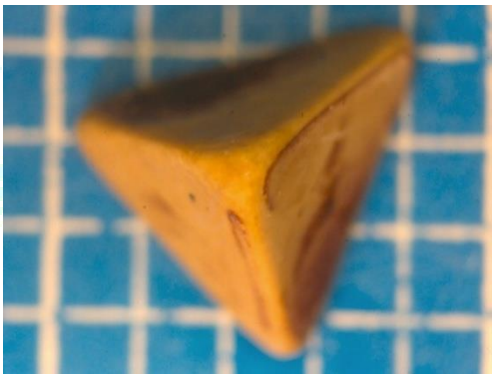

Fig.10: Struvite stones

Symptom:

Symptoms of struvite stones are similar to those of other types of stones, and can include:

- ✓ Pain in your side and back
- ✓ Fever
- ✓ Frequent need to urinate
- ✓ Pain when you urinate
- ✓ Blood in your urine

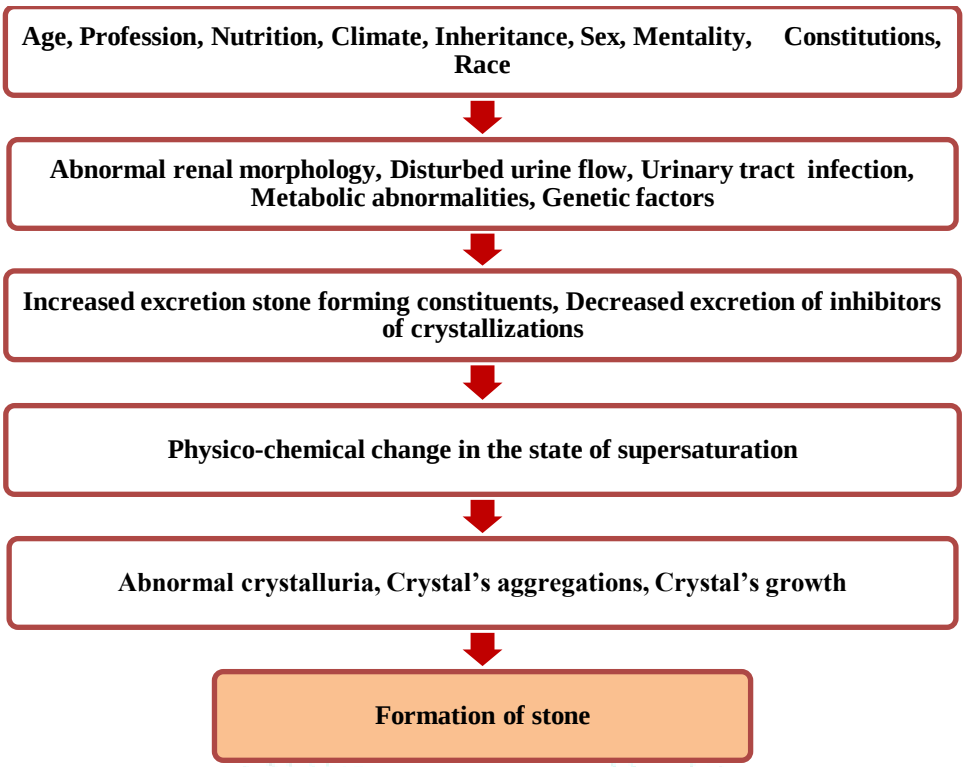

Fig. 11: Mechanism of stone formation[14]

Risk factors for kidney stones [15]

Factors that increase your risk of developing kidney stones include:

- **Family or personal history**.

If someone in your family has kidney stones, you're more likely to develop stones, too. And if you've already had one or more kidney stones, you're at increased risk of developing another.

- **Dehydration.**

Not drinking enough water each day can increase your risk of kidney stones. People who live in warm climates and those who sweat a lot may be at higher risk than others.

- **Certain diets.**

Eating a diet that's high in protein, sodium (salt) and sugar may increase your risk of some types of kidney stones. This is especially true with a high-sodium diet. Too much salt in your diet increases the amount of calcium your kidneys must filter and significantly increases your risk of kidney stones.

- **Being obese.**

High body mass index (BMI), large waist size and weight gain have been linked to an increased risk of kidney stones.

- **Digestive diseases and surgery**.

Gastric bypass surgery, inflammatory bowel disease or chronic diarrhea can cause changes in the digestive process that affect your absorption of calcium and water, increasing the levels of stone-forming substances in your urine.

- **Other medical conditions.**

Diseases and conditions that may increase your risk of kidney stones include renal tubular acidosis, cystinuria, hyperparathyroidism, certain medications and some urinary tract infections.

Table 3: Stones classified according to their aetiology

Noninfection Stones	Infection stones	Genetic stones	Drug stones
Calcium oxalates	Magnesium ammonium phosphate (Struvite)	Cystine	Indinavir
Calcium phosphates	Apatite	Xanthine	
Uric acid	Ammonium urate	2,8-dihydroxyadenine	

Clinical presentation

Pain is produced as a result of stone obstruction usually at uretro-pelvic junction, pelvic brim and vesico-ureteric junction. Urolithiasis may exist asymptomatically, but it is often presented by excruciating pain that originates from the flank and radiates to the genitals. Stone obstruction also produces lower abdominal cramps, dysuria, urinary urgency and strangury and also promotes the elevation of intrarenal pressure that induces prostaglandin synthesis, which again causes ureteric smooth-muscle spasm. Renal colic is generally associated with nausea and vomiting. Haematuria

and infection are also common symptoms associated with renal stone disease. Urinary tract infection (UTI) may be a result of stone obstruction or may be the cause of magnesium ammonium phosphate (struvite) stones also called the infection stones. Fever, chills and pus formation are usually associated with infection stones.[16, 17, 18]

Diagnosis of Urolithiasis

Initial evaluation includes obtaining a non-contrast helical CT, which can accurately visualize the size and location of the stones. A kidney, ureter and bladder (KUB) film, although it is insensitive to uric acid stones since they are radiolucent and therefore are not visualized. However, it can visualize calcium containing, struvite and cystine stones in the kidney or ureter. Complete ureteral obstruction and upper urinary tract infection (UTI) are indications for stone removal by extracorporeal shock wave lithotripsy (ESWL) or surgery.[6]

Based on clinical symptoms of the location and severity of the pain diagnosis is done. Imaging like x-ray, computed tomography, ultrasound is used to confirm the diagnosis and a number of other tests can be undertaken to help establish both the possible cause and consequences of the stone.[19]

Other diagnostic methods

Other investigations typically carried out include:

- Microscopic study of urine, which may show proteins, red blood cells, bacteria, cellular casts and crystals.
- Culture of a urine sample to exclude urine infection (either as a differential cause of the patient's pain, or secondary to the presence of a stone).

Laboratory evaluation

The goals in this two-step process are to confirm the diagnosis of nephrolithiasis, then to identify the composition of the stones formed and the associated risk factors.

Initial Evaluation

Tests include dipstick urine assessment, serum chemistries, and a complete blood count (CBC). Urine dipstick assessment may be positive for blood, protein, or leukocyte esterase, indicating stones or fragments of stones present in the urinary tract. While nearly 10% of patients with stone disease exhibit gross hematuria, nearly 90% of patients have microscopic hematuria.

Radiologic Evaluation

Radiologic evaluation of stones is currently performed through plain x-rays, ultrasonography, and noncontrast spiral CT. When a patient presents with acute signs of nephrolithiasis, a plain film x-ray of the kidneys, ureters, and bladder (KUB) is acceptable as the first imaging study, as it is inexpensive and available in most areas.[20]

Management and Treatment of Kidney Stones

Pain relief. Provide analgesia, antiemetics, and intravenous hydration as needed at the evaluation. Nonsteroidal anti-inflammatories (eg, ketorolac 15 to 30 mg intravenously) can provide effective analgesia, with opioids administered either concurrently for rapid relief or if the nonsteroidal anti-inflammatory effect is insufficient. Use oral nonsteroidal anti-inflammatories with or without opioids for patients who are less symptomatic or for analgesia after discharge. [21, 22, 23]

If urgent intervention is not required, the treating physician needs to decide if the stone can be passed spontaneously. The likelihood of spontaneous passage decreases as the size of the stone increases and stones >5-6 mm are not likely to pass spontaneously. Patients who are having repeated stone attacks should be instructed to strain their urine and to submit the stone for composition analysis. Repeated imaging (plain abdominal radiography (KUB) for radiopaque stones and CT for radiolucent stones) is warranted to confirm stone passage. If follow-up imaging reveals no movement after a month, urologic intervention is generally warranted.[6]

Significance of herbal therapy

Medicinal plants have been known for millennia and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention of various ailments. Today large number of population suffers from kidney stone, gall stone and urinary calculi. Stone disease has gained increasing significance due to changes in living conditions i.e. industrialization and malnutrition. Changes in prevalence and incidence, the occurrence of stone types and stone location, and the manner of stone removal are explained. Medicinal plants are used from centuries due to its safety, efficacy, cultural acceptability and lesser side effects as compared to synthetic drugs.[14]

Standard pharmaceutical drugs used to prevent and cure urolithiasis are not effective in all cases, costly, quite common reoccurrences, risks of long term fertility, potential side effects and no guarantee.[24, 25] Surgical treatment causes some problems like long term renal damage, hypertension and reoccurrence of stones. Extracorporeal shock wave lithotripsy is considered as a revolution in treating renal stones, but this treatment also causes some problems like long term renal damage, hypertension and reoccurrence of stones and so an approach is being extensively investigated to prevent or inhibit the stone reoccurrence, which resulted in treatment with hydrochlorothiazide, orthophosphate, alkali-citrates and magnesium to reduce the rate of stone reoccurrence. It is a well-known fact that glycosamino glycons and urinary proteins which are present in the matrices of the urinary stones are the strong inhibitors against CaOx crystal formation.[26] References prove that litholytic herbs for treatment of renal stones are used since ancient periods before inventing modern treatments. Standard pharmaceutical drugs used to prevent and treat urolithiasis are not effective in all cases and also produce many adverse effects.[24] Scientific studies are mostly focused on phytotherapy as it is proved to be vital in preventing reoccurance of stones. Herbal drugs are reported to be effective with no side effects. The drug for prevention of the disease or its reoccurrence is of great interest as no drug in clinical therapy is of satisfactory result.[24]

Table 4: List of plants used for the treatment of kidney stone and urinary tract troubles [27, 28, 29]

Sr. No	Name of Plants	Common name	Family	Part used	Medicinal uses
1	*Abutilon indicum* (L.) Sweet	Jhumka	Malvaceace	Seed and leaf extracts	Extract is given for urinary disorder
2	*Abutilon indicum* (Linn.)	Kanghi	Malvaceae	Leaves	Juice taken twice daily for two weeks
3	*Ageratum conyzoides* L.	Gana gaaju	Asteraceae	Leaves	Leaf extract given twice a day
4	*Amaranthus caudatus* L.	Love lies bleeding	Amaranthaceae	leaves	Extract is taken in kidney stone
5	*Aerva lanata* (L.) Juss. ex Schult	Pindikura	Amaranthaceace	leaves	Plant extract with *Cuminum cyminum* fruits and sugar is given for 10-15 days to cure kidney stone.
6	*Amaranthus spinosus* L.	Jangali chauli	Amaranthaceae	Root	Root paste use for reduces irritation in urinary duct
7	*Amaranthus viridis* L.	Piazi	Liliaceae	leaves	Decoction of leaves
8	*Azadirachta indica* A.Juss.	Kaduneem	Meliaceae	Stem bark, Leaves	Stem bark, Leaves
9	*Beta vulgaris* L.	Ullam gadda	Amarantrhaceace	Rhizome	Daily two glass of rhizome juice for seven days to cure kidney stone
10	*Bauninia racemosa* Lam	Apta	Caesalpiniaceae	Stem bark	Stem bark
11	*Bombex ceiba* Linn.	Silk cotton tree	Bombacaceace	Stem and bark	Given for urinary problems
12	*Butea monosperma* (Lam.) Taub.	Palas	Fabaceae	Leaves, seeds	• Leaves juice or decoction is useful. • Seed powder in one teaspoon after meals is taken.
13	*Ceropegia bulbosa* Roxb.	Khadula	Asclepidaceace	Tubers	Decoction of tubers orally to get rid of urinary bladder stone
14	*Chenopodium album* Linn.	Chilua	Chenopodiaceae	Leaves	Cooked leaves as a vegetable given in urinary trouble
15	*Costus speciosus* (Koen.) Sm.	Mahalakri	Costaceace	Tubers	Decoction of tubers orally for urinary complaints
16	*Cordia dichotoma* (L.)	Bhokar	Boraginaceae	Stem Bark, Fruits	Stem Bark, Fruits
17	*Digera muricata* (L.) Mart.	Lesua, Latmahuria	Amaranthaceae	Leaves	Once in a day
18	*Equisetum debile* Roxb.	Jod tod ki ghas	Equistaceace	All parts	Whole plants juice along with 1 gram *Piper nigrum* Linn. Twice a day for 7 days
19	*Gomphrena celosioides* Mart.	Gomphrena weed	Amaranthaceae	Whole plant	Juice along with *Piper nigrum* Linn. And lemon juice twice a day for 10 days
20	*Hemidesmus indicus* (L.) R. Br.	Anantmul	Apocynaceae	Root, leaf	• Root powder is given daily morning, afternoon and evening. • Leaf decoction is used in morning and evening
21	*Hygrophila auriculata* (Sch.) Heine	Talimkhana	Acanthaceae	Roots.	Roots are given
22	*Kalanchoe pinnata* (Lam.)	Panphuti	Craussulaceae	Leaf	Fresh leaves juice is given at any time.
23	*Lagenaria siceraria* (Molina) Standl.	Dudhi bhopla	Cucurbitaceae	Fruits	One cup of fruit juice is advised twice a day for seven days

24	*Lagerstroemia parviflora* L.	Lendya	Lythracea	Roots	Roots are crushed and 1-2 gms are swallowed once a day, till gets rid of kidney stone.
25	*Macratyloma uniflorum* (Lam.)	Kulthi, Kulith	Fabaceae	Fruits	Boiled Fruits with cold water is given thrice a day.
26	*Madhuka longifolia* (J.Konig)	Moh	Sapotaceae	Stem	2 cm stem bark powder is soaked in 1 glass of water overnight. In morning, a pinch of white pepper powder and cumin seed powder is added and taken at empty stomach. This is taken once in a week. Total 60 doses are required.
27	*Meyna laxiflora* Robyns, Bull. Jard	Alu, Helu	Rubiaceae	Seed	Five pinches of seed powder is mixed with water and given twice a day for 15 days.
28	*Momordica diocia* Roxb. ex. Willd	Kartoli	Cucurbitaceae	Roots, Fruits.	Roots, Fruits.
29	*Ocimum sanctum* L.	Tulas	Lamiaceae	Leaf	Leaves juice + Honey.
30	*Ocimum tenuiflorum* L.	Tulsi, Tulas	Lamiaceae	Leaf	Entire plant should burn and ash mixed with water is given thrice a day
31	*Pedalium murea* Linn. (Pedaliaceace)	Dakhigokhru	Pedaliaceace	Fruits	Decoction of fruits used for continuance of urine and other complaints of urinary system
32	*Punica granatum* L.	Anar, Dalimb	Punciaceae	Seed, fruits	Seed juice is given before breakfast
33	*Raphanus sativus* (L.) Domin	Mula	Brassicaceae	Root, leaf, seed	• Root juice is given after meals. • Leaf juice is given before breakfast. • Seed powder is useful before breakfast.
34	*Ricinus communis*	Arandi	Euphorbiaceace	Root	Root decoction along with half gram sunthi + one gm of heeng + common salt given twice a day for 7 days
35	*Solanum surattense* Burn.	Ber kaleli, neeli kateti	Solanaceace	Root powder	Root powder + curd given daily for 2 weeks
36	*Tephrosia purpurea* (L.) Pers.	Sharapunkha, Unhali	Fabaceae		• Root powder or juice is useful if taken morning and evening. • Leaf decoction (one glass) before breakfast is given. • Entire plant boiled and juice is given after particular intervals.
37	*Terminalia arjuna* (Roxb.)Wight & Arn.	Arjun, Sadada	Combretaceae	Bark	Bark powder is given after breakfast, lunch and dinner.
38	*Tinospora cordifolia* (Wild.L)	Gugul	Menispermaceae	Stem	Crushed stem is given orally to expel the stone.
39	*Tribulus terrestris* Linn.	Gukhru	Zygophyllaceae	Leaves	Used in treatment of kidney stone
40	*Tridex procumbens* L.	Molymehndi	Asteraceace	Leaves	Leaf paste is used taken for kidney stone
41	*Tridex procumbens* L.	Kambarmodi	Asteraceae	Leaf	Leaf paste is given.
42	*Tubiflora acaulis* (L.F.) Kuntze	Patta chatta	Acanthaceace	Leaf	Leaf powder with water
43	*Zea mays* L.	Maka	Poaceae		Paste given orally.

Herbal medicines act by multiple mechanisms like

- Helping in spontaneous passage of calculi by increasing urine volume, pH and anticalcifying activity (Diuretic activity).
- Balancing the Inhibitor and promoter of the crystallization in urine and affecting the crystal nucleation, aggregation and growth (Crystallization inhibition activity).
- Relieving the binding mucin of calculi (Lithotroptic activity).
- Improving renal function.
- Regulation of oxalate metabolism.
- Regulating the crystalloid-colloid imbalance and improving renal function, thus preventing recurrence of urinary calculi.
- Improving renal tissue antioxidant status and cell membrane integrity and preventing recurrence (Antioxidant activity).
- Exerting significant anti-infective action against the major causative organisms (Antimicrobial activity).
- ACE and Phospholipase A2inhibition.
- Relieving symptoms like pain, burning micturition and haematuria (Analgesic and anti-inflammatory activity).[29]

Methods of evaluation of Anti-Urolithiasis Activity[29, 30, 31]

Different screening model for urolithiasis and potential antiurolithiasis are divided in to in-vivo and in-vitro evaluation. This study will help scientist for selection of suitable model in search of antiurolithiasis compounds.

IN VIVO ANIMAL MODEL

- Ethylene glycol induced urolithiasis in rats.
- Ethylene glycol and ammonium chloride induced urolithiasis in rats.
- Sodium oxalate (NaOx) induced urolithiasis in rats.
- Calculi-Producing diet induced urolithiasis
- Glyoxylate induced acute lithiasis
- Zinc disc induced urolithiasis in rats

IN VITRO STUDIES ON UROLITHIASIS

- Calcium oxalate crystal assay
- Determination of effect on CaC_2O_4 crystallization
- Nucleation Assay
- Growth assay
- Calcium phosphate assay
- Lactate dehydrogenase leakage assay

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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