

Efficacy and Safety of Herbal Medicine for Urolithiasis- A Systemic Review

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Abstract:- The process of formation of stones in the kidney, bladder, and/or urethra (urinary tract) is known as Urolithiasis. According to WHO, urolithiasis covered 12 % of the total population and its proportion in males is 70-81% and in females 47-60% and their ratio is 2.4:1. Traditional plants had various chemical constituents which show constructive effects on lithiasis by numerous molecular mechanisms. A number of medicinal plants possessed antiurolithiatic effects include *Moringa oleifera*, *Crataeva magna*, *Aerva javanica*, *Peperomia tetraphylla*, *Terminalia bellirica*, *Ipomoea eriocarpa*, *Punica granatum*, *Hibiscus rosa-sinensis*, *Costus spiralis*, *Herniaria hirsuta*.. The present review is to provide the information and highlights in the present trends in research of medicinal plants with antiurolithiatic activity. This review may help to identify lead compounds or herbal products responsible for urolithiatic activity.

Keywords:- Urolithiasis, Molecular Mechanism, Traditional Plants, Lead Compound.

I. INTRODUCTION

Urolithiasis is a process of forming stones in the kidney, bladder, and/or urethra (urinary tract) [1]. In urinary system, urolithiasis (Greek- ouron, “urine” and lithos, “stone”) is the condition where urinary stones are formed or located. The terms nephrolithiasis (or “renal calculus”) are stones that are present in kidney, while ureterolithiasis are stones that are in the ureter and cystolithiasis (or vesical calculi) are stones which form or have passed into the urinary bladder [2].

The classification of Stones are based on their location or by their chemical composition. Calcium oxalate is the major constituent is present in urinary stones. According to survey, about 80% of kidney stones are in men when compared to women and they experience their first episode between 20-30 years of age, while for women it occurs later. [3]. Over their lifetime urinary stones affect about 10% of people and prevalence increases with age, recurrence of 50% in 5-10 years and 75% within 20 years. Over the past 30 years a rapid increase have seen in women which is almost equal to that of men [4].

❖ PATHOGENESIS [5]:

The volume of urine consists certain amount of calcium, phosphate, oxalate and sodium ions which is reason for formation of stones. The formation of urinary calculi is due to low urinary volume, low pH, high ion levels, and low citrate levels. The pathogenesis of stone formation includes various step physicochemical processes [6].

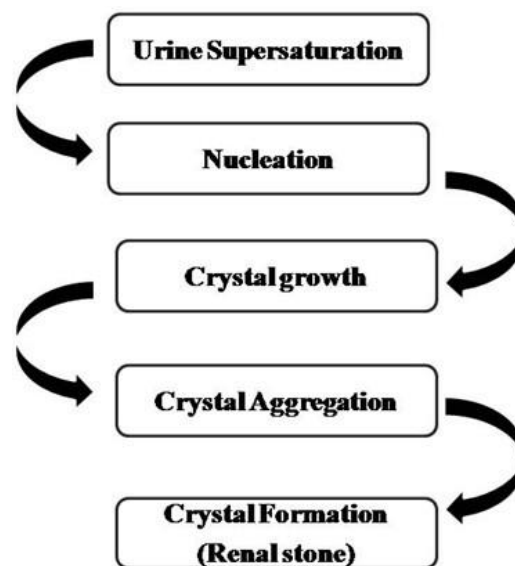


Fig 1. Pathogenesis of renal stone formation

➤ Nucleation

Nucleation of crystal occurs in unstable zone of supersaturation which is the starting stage in formation of stone due to homogeneous nucleation of a salt. Promoters induce heterogeneous nucleation leads to formation of stone and crystalluria. The reduced energy required for crystallization is provided by the promoters. Crystal components are formed due to reduced energy of solution and become part of the crystal structure. As the crystal components formed, the other crystalline particles can bind to each other and forms either an oriented or random growth pattern and then grow into a larger particle [7].

➤ Crystal growth

In crystal growth process, the crystals can grow up by epitaxially (overgrowth of one crystalline material on to another or a substrate crystalline lattice) mediated crystal growth. Further growth of crystals is followed by

monoepitaxial growth which is adsorption of the molecules or ions individually on the crystal surface from supersaturated urine leads to direct growth of one crystal on a surface of different composition or the surfaces of crystal or substrate. The growth of crystals is determined on the basis of molecular size and shape components, the physical properties, pH, and defects that may form in the crystals structure. Crystal growth is one of the major step for stone formation^[8].

➤ *Aggregation*

After crystal growth next step is aggregation, a process in which crystal nuclei form larger particles by cohering with each other. The attractive force, result of distance in inter-particles leads to rapid aggregation. The addition of desired salts also used for growth of initial nuclei. In stone formation crystal aggregation plays a major role and is a more significant step than nucleation and growth. In aggregation, particle in solution is determined by balance of forces between aggregating effects and disaggregation effects and also a small inter particle distance that prerogative particle aggregation^[9].

➤ *Retention*

The retention of crystal caused due to association of crystals within the epithelial cells lining. The steps in urolithiasis includes formation of crystals i.e nucleation, crystal growth followed by their retention and accumulation in the kidney. Crystal retention is one of the process for stone formation. The pathophysiology of urinary stone formation covers growth, aggregate and precipitation of crystal. The process of retention might also depend upon the composition of the renal tubular epithelial cell surface.

II. CLASSIFICATION

1. Calcium stones

About 80% of urinary calculi in renal stones contain major amount of Calcium^[10]. Calcium stones are mostly found in men between the 20 and 30 years of their age. Combination of oxalate, phosphate or carbonate with calcium leads to formation of stone^[11]. Oxalate content is high in food like spinach and even found in vitamin C supplements.^[12]

2. Cystine stones: Cystinuria occurs in people with high amount of cystine stones. This type of stones affects both men and women. Less than 2% of all stone types are present

in cystine stone^[13]. Combination and transport of amino acid and cystine results in a genetic disorder and results in an excess of cystinuria in urinary excretions^[14].

3. Struvite stones: These stones are mostly found in women with urinary tract infection and increases with extent of 10–15%. Struvite stones correlated with chronic urinary tract infection (UTI) with gram-negative, urease-positive organism that divide urea into ammonia, then the ammonia combines with magnesium and phosphate to crystallize into a calculus. Blockage of kidney, ureter or bladder occurs due to faster growth of struvite stone^[15].

4. Uric acid stones: They are more commonly seen in women than in men. Sometimes uric acid stones occur with gout or chemotherapy. Purines with high diet containing animal protein like meat and fish, results in hyperuricosuria, low urine volume and urinary pH (pH < 5.05) exacerbates uric acid stone formation^[16].

5. Protease-related stones: Stones of this type is usually seen in HIV positive patients due to usage of protease inhibitor indinavir sulphate drug^[17].

6. Silica stones: Some silica stones are formed due to some medications like Sulfa indinavir, acetazolamide, ciprofloxacin, triamterene, ephedrine, Zonisamide, guaifenesin, laxatives (when abused), , loop diuretics, topiramate have competence to induce silica stones^[18].

III. SIGN AND SYMPTOMS

Patients with Urinary calculi report pain, infection, or hematuria. People with non-obstructing stones, small or those with staghorn calculi experience average and effortlessly controlled symptoms. Some other symptoms such as following:

- Some symptoms like irritative voiding i.e. frequency, dysuria, suprapubic pain, urinary frequency and urgency, stranguria, bowel symptoms.
- Severe pain in lower abdomen that radiates to testicles or vulvar area, nausea with or without vomiting.
- Flank and lumbar are regions where pain radiates.
- Pain radiates anteriorly and caudally.
- Even there is pain in groin or testicle (men) or labia majora (women).
- Stones passed into bladder: Mostly asymptomatic; rarely, positional urinary retention^[19,20].

IV. MECHANISM OF ACTION

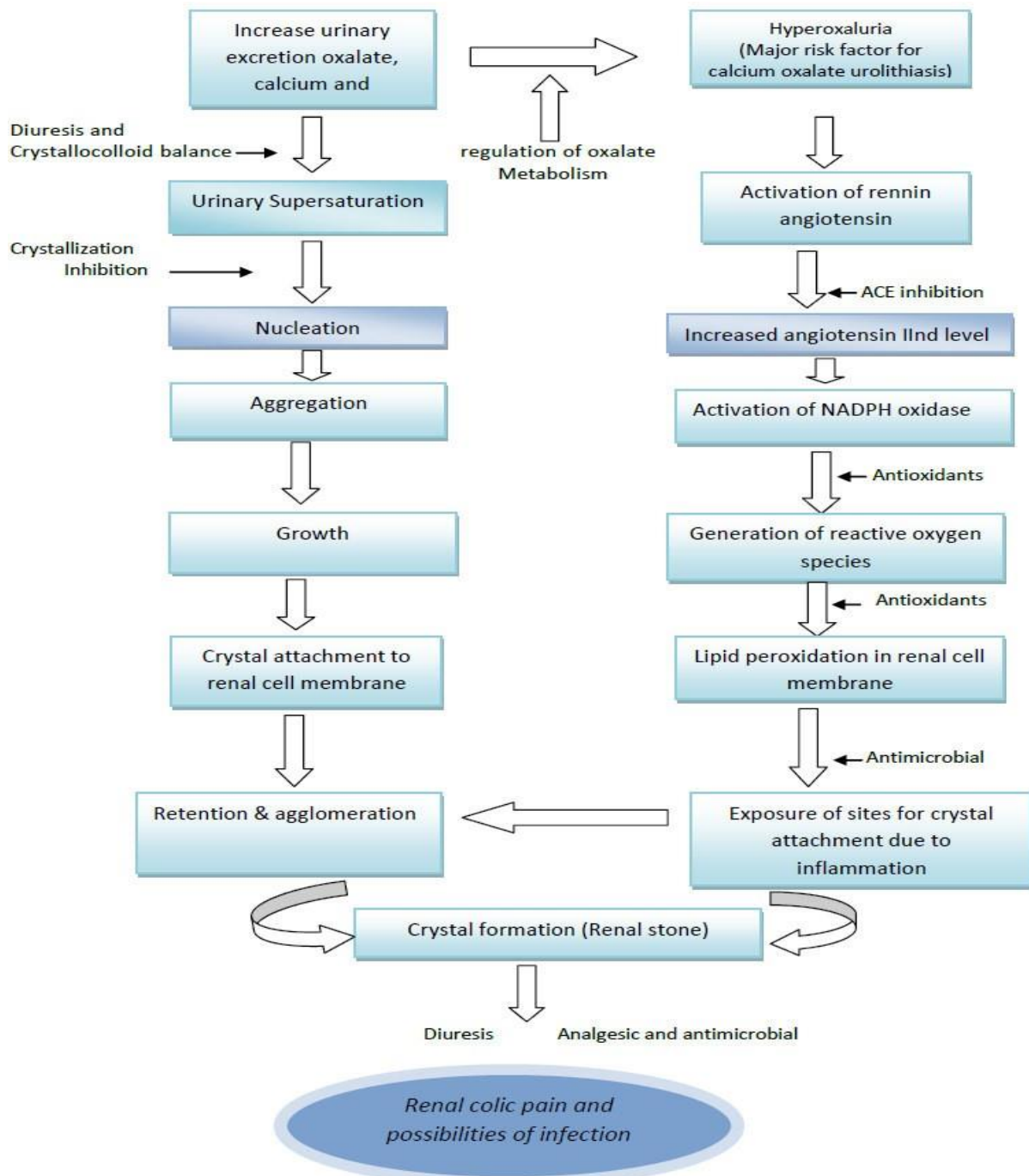


Fig 2. Mechanism of action of urolithiasis [21]

Formation of Uroliths is a **multifactorial process** correlate with urinary tract infection, diet, decreased urinary drainage and urinary stasis, altered urinary solutes and colloids, Randall’s plaque , prolonged immobilization and microliths etc. [22].

❖ **DRUG-INDUCED STONE DISEASE**

Medications that can precipitate in urine causing stone formation include the following [23,24,25]

- Indinavir
- Guaifenesin

- Triamterene
- Atazanavir
- Silicate (overuse of antacids containing magnesium silicate)
- Sulfa drugs, including sulfasalazine, sulfadiazine, acetyl sulfamethoxazole, acetylsulfadoxazole, and acetylsulfaguanidine
- Ceftriaxone (rarely) [26]

V. MANAGEMENT

The treatment for stones involves reassuring care and management includes agents such as the following^[27]:

- IV hydration
- NSAIDs (eg, ketorolac, ketorolac intranasal, ibuprofen)
- Nonnarcotic analgesics (eg, acetaminophen [APAP])
- Alpha blockers (eg, tamsulosin, terazosin)
- PO/IV narcotic analgesics (eg, codeine, morphine sulfate, oxycodone/APAP, hydrocodone/APAP, dilaudid, fentanyl)
- Antiemetics (eg, metoclopramide, ondansetron)
- Antibiotics (eg, ampicillin, gentamicin, trimethoprim-sulfamethoxazole, ciprofloxacin, levofloxacin, ofloxacin)

The following drug classes are used for stone prevention/chemolysis^[28]:

- Uricosuric agents (eg, allopurinol)
- Alkalinizing agents (eg, potassium citrate, sodium bicarbonate)
- Thiazide diuretics - help treat hypercalciuria

➤ Surgical options:

Stones with size of 7 mm and larger improbable to pass spontaneously that leads to serious condition which require some type of surgical procedure, such as the following:

- Stent placement
- Extracorporeal shockwave lithotripsy (ESWL)
- Ureteroscopy
- Percutaneous nephrostolithotomy (PCNL) or mini PNCL
- Percutaneous nephrostomy
- Open nephrostomy - largely supplanted by less-invasive techniques
- Anatomic nephrolithotomy - for large, complex staghorn calculi that cannot be cleared by an acceptable number of PCNLs; typically done via laparoscopic or robotic approach.^[29]

As we know synthetic drugs cause various side effects, to reduce or to overcome the side effects drugs synthesized from the traditional/herbal/higher plants continue to tenant major role in modern medicine which leads to introduction of new therapeutic agents^[30]. A number of medicinal plants possessed antiurolithiatic effects these include *Moringa oleifera*, *Crataeva magna*, *Aerva javanica*, *Peperomia tetraphylla*, *Terminalia bellirica*, *Ipomoea eriocarpa*, *Punica granatum*, *Hibiscus rosa-sinensis*, *Costus spiralis*, *Herniaria hirsuta*. This review discussed the antiurolithiatic effects of medicinal plants which has no or minimal side effects.

➤ *Moringa oleifera*:



Fig 3. *Moringa oleifera* Lam. root

Moringa oleifera Lam. used as a phytotherapeutic agent belonging to the family Moringaceae, well known as 'drumstick tree' or 'horse-radish tree'. The administration of Aqueous Extract and Alcoholic Extract of root-wood with ethylene glycol to rats induce lithiasis. The plant extract decreases the size and avert the expansion of urinary stones, and shows the antiurolithiatic activity. Urolithiasis mechanism is still unspecified, but it lowers the urinary concentrations of stones forming constituents and elevates diuresis.^[31]

➤ *Crataeva magna*:



Fig 4. *Crataeva magna* Lour. Bark

The ethanolic extract of *Crataeva magna* Lour. Bark which is known as Baruna, belonging to the family Capparaceae used against urinary stone and was investigated *in vitro* and *in vivo* method. The reduction in calcium, serum creatinine, urine oxalate and kidney weight significantly due to maximal dose of plant extract with a marked increase in urine volume output and final body weight when compared to toxic group. The standard polyherbal drug treated group was compared to plant extract group and thus posses potent antiurolithiatic activity.^[32]

➤ *Aerva javanica*:Fig 5. *Aerva javanica* whole plant

It is also termed as Tella burga which is assert to be useful for the treatment of renal calculi. The plant have chemical constituents alkaloid, flavonoids, phenol, tannin, proteins, amino acids, steroids, saponins and carbohydrates. The investigation on potential activity of various extracts of *Aerva javanica* against the renal calculi induced in rats. Hyperoxaluria resulted from administration of Ethylene glycol where as groups treated with ethyl acetate, aqueous and methanol extract of tella burga notable reduced the raised urinary oxalate. The increased accumulation of stone forming constituents in the urine and serum of calculogenic rats was also remarkably decreased. [33]

➤ *Peperomia tetraphylla*:Fig 6. *Peperomia tetraphylla* whole plant

Peperomia tetraphylla also called as Ala ala wai nu Kani comes under the family of Piperaceae and Tamil name is vanabhrami. On comparison with positive control rats, the animals treated with ethanolic extracts had far reduced kidney calcification and decreased renal tissue calcium levels. The *Peperomia tetraphylla* ethanolic extract has both inhibitory as well as therapeutic effects in urolithiasis of rats. [34]

➤ *Punica granatum*:Fig 7. *Punica granatum* fruit

Also known Pomegranates belong to the family Punicaceae, it regulates urine discharge and prevents the burning sensation of urine. Decrease in urine oxalate, phosphate, calcium serum creatinine, urea, uric acid levels and renal tissue oxalates is due to administration of extract of *Punica granatum* chloroform extract and *Punica granatum* methanolic extract at 100, 200 and 400 mg/kg doses in observed in ethylene glycol induced rats. At the dose of 400 mg/kg of *Punica granatum* chloroform extract and *Punica granatum* methanolic extract reported more potential to reduce renal stones and decreases the renal tissue regeneration in male rats. [35]

➤ *Hibiscus rosa-sinensis*:Fig 8. *Hibiscus rosa-sinensis* flowers

Also known as china rose from Malvaceae family is a bald shrub mostly distributed in the tropics as an ornamental plant and has several diversity with different colors of flowers. The *in vitro* assays performed in the study revealed that the flower extract of at various concentrations exhibited a very good inhibitory effect against the various steps include in stone formation i.e nucleation, growth, aggregation, retention. It is clearly evident that the components present in the flower extract might be responsible for its preventive action against kidney stone formation. Therefore, the components present in the extract can very well be used for medicinal preparations for the treatment of lithiasis. [36]

➤ *Costus spiralis*:Fig 9. *Costus spiralis* whole plant

It is pre-owned in Brazilian folk medicine in throwing out urinary stones and used to prevent urinary infections. It belongs from the family Zingiberaceae. The stone formation in rats occurs either by calcium ox- alate crystal or zinc disc implants in the urinary bladder were inhibited by aqueous extract of *Costus spiralis* Roscoe. The plant extract have potential activity in both male and female rats at different doses, and that reduced growth of urinary stones. The aqueous extract was also tested for toxicity, it did not produce any change in the spontaneous motor activity or signs of toxicity up to 4 weeks of aqueous extract administration.^[37]

➤ *Terminalia bellirica*:Fig 10. *Terminalia bellirica* fruits

Popularly known as Baheda belonging from the family Combretaceae have potential effect in urolithiasis induced by ethylene glycol. In surface of renal tubular membrane, the deposition of CaOx crystal in the kidney is prevented by inhibiting hyperoxaluria. The early stages of development of various stones is prevented by *Terminalia bellirica* fruits. These fruits also reported with saponin and flavonoids in other studies which is found to be responsible for the anti-urolithiatic activity of herbal drugs. For the treatment CaOx stones *T. bellirica* are therapeutically effective and also have other potential effects that are high antioxidant, anti-inflammatory, and anti-microbial activity, which is one of the reason for its anti- urolithiatic activity.^[38]

➤ *Ipomoea eriocarpa*:Fig 11. *Ipomoea eriocarpa* leaves

Commonly known as Morning glory belongs to Convolvulaceae family. The histopathology examination under light microscope reveals the place of calcium oxalate crystals and kidney structure. The plant extract of *Ipomoea eriocarpa* crucially reinstate the measure of serum, urine and kidney homogenate to bring back to normal level. The deposition of calcium oxalate crystals in renal tubules and dilation and congestion of parenchymal blood vessels were reverted by *Ipomoea eriocarpa* extract treatment and it was revealed by histopathological examinations. The leaf extract of *I. eriocarpa* shows its antiurolithiatic activity by inhibiting and reducing the growth of urinary stones.^[39]

➤ *Herniaria hirsute*:Fig 12. *Herniaria hirsute* whole plant

Synonym as Hairy rupturewort belonging to the family Caryophyllaceae. The investigation was done in between calcium oxalate induced nephrolithiasic rats and normal rats in three weeks of duration. The evaluation of intake of water, pH, urinary volume, crystalluria and urinary chemistries. After treatment with plant extract, treated rats excrete small amount of CaOx dihydrate crystals while the untreated rats have high amount of CaOx monohydrate and few dihydrate crystals. After kidney examination, the final report shows that the plant extract of *Herniaria hirsuta* have antiurolithiatic effect and act as preventive agent for calcium oxalate crystals in the formation of urinary stones^[40].

VI. CONCLUSION

A number of medicinal plants possessed antiurolithiatic effects. This review highlights etiology, risk factors, epidemiology, symptoms, types of kidney stones, pathogenesis, some drugs with mechanism and the antiurolithiatic effects of medicinal plants to open the door for their clinical uses as a result of effectiveness and safety.

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