An insight into development of Urolithiasis and its treatment strategies using Herbal plants

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Abstract
Urolithiasis is the process of formation of stone either in kidney or urinary tract. Urolithiasis is the found to be 3rd most prevailing ailment all over the world. Nearly 12% of world population is affected with urolithiasis. Medicinal plants are highly valued around the world due to rich source of their active constituents for the prevention and treatment of many ailments. Kidney stone, often referred to as a renal calculus, is a solid concentration or crystal aggregation that develops in the kidneys from dietary minerals in the urine. Urinary calculi often known as stone are a very ancient health issue, these can occur anywhere in the urinary tract, kidney or bladder. Urolithiasis is a complex process which involves series of physiochemical events such as supersaturation, nucleation, growth, aggregation and retention in the kidney. The current article discusses the causes, types, risk factors, diagnosis and treatment, as well as variety of herbal options for urinary stone treatment.

Key words: Urolithiasis, Renal stones, Herbal plants

Introduction

1.1 Overview of urolithiasis

With an estimated frequency varying from 1% to 13% in various parts of the world[1,2], urolithiasis is one of the most prevalent urologic illnesses globally. According to recent evidences, there are many factors which are affecting urolithiasis, such as changes in socioeconomic conditions, dietary habits, environment, and illness comorbidities [1,3,4]. As a result of this change, the prevalence of the disease is rising, as well as the costs of diagnosis and treatment in the healthcare system and urolithaisis has the negative effects on the economy. [3,5,6].

Urolithiasis can affect anyone, although males are far more prone develop it when compared to women (12 in 100 compared to 6 in 100), and those between the ages of 20 and 40 are the most vulnerable [8]. The calculi are eliminated and cleansed using surgical, lithotripsy, and high-power laser techniques. These techniques used to eliminate and clean urolithiasis when the stone size is large than 5mm or unable to pass through the urinary system [9]. A number of unfavorable side

effects from these medical treatments might have an impact on a person's state of health and may cause impairing of renal function, resulting in abrupt renal damage and intermittent kidney stone formation [7,4]. Because of this, alternative medicines made from traditional herbs are actively being researched in order to treat urolithiasis.

Numerous healing herbs have been employed for ages in ayurvedic and traditional medicine, as well as in standard medical procedures. The herbal drugs have shown beneficial effects on urolithaisis and they are found to be less toxic as compaired to synthetic analogues. Some therapeutic plants, including Tribulus terrestris [10], Herniaria hirsute [11], Bergenia ciliate [12], Bergenia ligulata [13], Dolichos biflorus [14], and Plantago major [15], have recently demonstrated a notable impact on *in vitro* and *in vivo* anti-urolithiatic activity.

1.2 Symptoms / diagnostic parameter

The clinical symptoms of urolithiasis include flank pain, urine retention, haematuria, and infection [16]. Calcium oxalate, calcium phosphate, uric acid, struvite, and cysteine are among the composition of kidney stones [17]. Reduced urinary pH and volume, urinary stasis, obstruction, metabolic abnormalities such as hypercalciuria, hyperoxaluria, and hyperuricosuria, disease states such as metabolic acidosis, cystinuria, and inflammatory bowel disease, as well as dietary factors such as a high protein diet, a high sodium diet, a high oxalate diet, and a low fluid intake are all thought to be risk factors for urolithiasis.

Prognosis of urolithiasis includes diagnosis by physical examination, urine analysis, biochemical analysis, haematological analysis, stone composition analysis and imaging by ultrasonography, intravenous urography, endovaginal and transperineal imaging, KUB (kidney-ureter-bladder) radiography and computed tomography [16].

1.3 Types of Urolithiasis

Various types of urolithiasis are categorized based on the composition and pathobiology. The most frequent sort of renal stones is calcium stone, which is developed when there is excess amount of minerals like calcium, oxalate, uric acid, cystine or phosphate in systemic circulation[21].

Uric acid or urate stones: uric acid stones contribute to 8-10% of total renal stones worldwide [22]. The formation of uric acid may be due to metabolic changes inside the human body. The causes of uric acid stones are resultant of hyperuricosuria with or without hyperureicemia, which is expected because of abnormalities in acid/base metabolism. This ultimately results in low urinary ph(less than 5.5), causing precipitation of uric acid crystals. This results in uric acid nephrolithiasis among 9% of the renal stone cases [23].

The renal stones are compact having pebble shape; they are loosely packed in the center because of aggregated uric acid crystals [24,25].

A consumption of food rich in purines (present in red meat, poultry, fish, trout, herring, legumes and mushroom) causes hyperuricosuria. Purine breakes down to form uric acid stones by the enzyme xanathine oxidase (XO) converting hypoxanthine to xanthine as well Uric acid. The increase levels of uric acid results in Hyperuricosuric calcium urolithiasis and urate nephropathy, which is a purine end product [26]. Which is The production of acid is increased by a number of illnesses, including metabolic disorders, diabetes, and obesity, making the urine's pH more acidic. The increased production of H^+ ion-forming buffer into the urate, which results in the precipitation of uric acid stones, is caused by the deficiency or change of renal ammonium excretion [27].

Calcium stones: the calcium oxalate stones are the top-most found pathological anomaly which contributes to about 75% of the total renal stones [28]. The calcium stones are found to occur as either of the two forms, calcium oxalate or calcium phosphate crystals. Among these two forms of calcium stones, calcium oxalate is most extensive. The calcium oxalate exists as monohydrate or dehydrates, calcium oxalate monohydrates are thin and plate like or “dumb-bell” shaped. While calcium oxalate dehydrates has tetragonal bipyramidal shape [29].

The different factors which cause calcium stones are hypercalciuria, which is caused due to increased calcium absorption from gastro intestinal tract (GIT) or it could be resultant of some of the disorders like hyperthyroidism, hyperparathyroidism, hypercalciuria, and malignancy-related hypercalcemia. A significant threat for hypercalciuria is hyperoxaluria. The hyperoxaluria may be caused by either primary or secondary factors. Primary factors of oxalate pathogenesis which causes hyperoxaluria is due to the enzymatic defect (glyoxylate/hydroxypyruvate reductase and alanine-glyoxylate transaminase) [30]. While secondary factors can be because of diet rich in oxalate rich foods or other conditions like hypocitraturia, low urine volume forms the calcium stones [31]. Calcium phosphate is generally found as apatite (basic CaP), Brushite (calcium hydrogen phosphate dehydrate) and whitlockite(tricalcium phosphate). Calcium phosphate stones in pure form are rare [32]. The most common calcium phosphate stones among these are apatite, which grows in between the spaces of calcium oxalate crystals. Brushite occurs frequently in kidney stone which grows in between the spaces of thin blade like crystals. whitlockite condition is very rare in both kidney stones and urinary sedimentation [33].

The formation of renal stones is prevented by citrate and magnesium. In urolithiasis it is detected that there is low concentration of citrate and magnesium in the urolithiasis patients. Both the citrate and magnesium plays a major role in urolithiasis condition, citrate lowers the supersaturation of calcium salts and magnesium dissolves the crystal and enhances excretion in the urine. Therefore, metabolic changes elevate degree of stone promoters (hypercalciuria, hyperoxaluria), while diminishing levels of stone inhibitors result in supersaturation of crystal-forming stone [34, 35].

Cystine stones: less than 1% of the cystine stones contribute to the total renal stone formation**.** Compared to other stones, cystine stones are less common and form larger than calcium oxalate stones, eventually leading to chronic kidney injury [36]. The accumulation of cystine amino acid in the kidney and urine bladder is linked to the autosomal recessive inheritance of cystinuria [37]. The defective reabsorption of cystine in the proximal convoluted tubule results in the formation of excessive cystine amino acid in the urine develops aggregation of cystine forming crystal leading to stone formation in the kidney or urinary bladder [38]. The larger stones remain in the kidney, whereas the smaller stones find its way into the ureter and accumulate by blocking the urinary flow. The blocking builds up pressure on ureter and kidney. This ultimately results in urinary retention and urinary tract infection. Ultimately causes damage to kidney by urary infections.

Magnesium ammonium phosphate stones: Also known as struvite stones**.** Struvite stones contribute about 1% to the renal stone formation. The struvite stone are mainly composed of elements ammonia, magnesium, and phosphate, grows quickly within a month. Struvite stones are formed when urea is broken down to urine by the action of urease enzyme and also form ammonia and carbon dioxide, ammonia reacts with urine to form these stones [39, 40]. The increased ammonia production raises the pH of the urine, eventually resulting in formation of struvite stones by preventing the solubility of phosphates [41]. Furthermore, excessive generation of ammonia in urinary tract is due to bacterial infections caused due to staphylococci, proteus, and haemophilus bacteria. Whereas yeast, gram-negative bacteria, and gram-positive bacteria produce excess of urease what causes struvite stones [42].

Drug-induced stones: Several drugs used for the treatment of gout like benzobromarone, salicylic acid and probenecid seem to increase the risk of kidney stones. Besides Other drugs like indinavir, atazanavir, sulphonamides, ceftroaxone etc., used for long term increases the risk of renal calculi forming stones as they are with poor solubility, high excretion rate of high dose. Normally, the proximal tubules of the kidney contain the nephrocalcin acidic glycoprotein protein, which prevents the formation of calcium oxalate crystals. However, when this protein is depleted, crystals are retained and form renal stones [43]. The other drugs also influence the formation of kidney stones like carbonic anhydrase inhibitors, laxatives either by altering the urine pH or metabolism of minerals which are responsible for renal stones [44, 45].

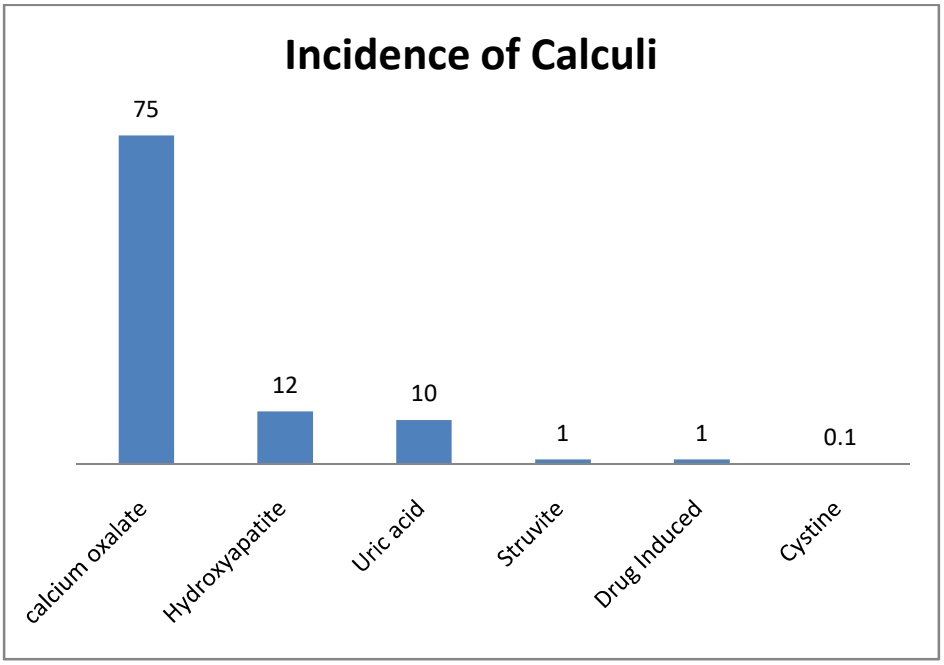
Table 1 List of kidney stone formation promoters:

Components	**Mechanism**
Uric acid or urate stones	It promotes diverse nucleation by uric acid or monosodium urate. Binding capacity of calcium oxalate to the cell is enhanced [25].
Urine pH	Higher Acidic pH increases calcium oxalate crystallization [10].
Urine volume	Assist crystallization [2].
Hypercalciuria	Enhanced intestinal calcium adsorption. Diminished renal calcium re-absorption. Calcium movement from the bones results in increased urine supersaturation and hence results in crystallization of calcium [26,13].

Hyperoxaluria	Due to inborn error in metabolism oxalate is produced in excess. Increased foods intake and bioavailability both have increased oxalate absorption through the gut. This has resulted in formation of calcium oxalate crystals and urinary supersaturation [27, 13].

Table 2 List of kidney stone formation Inhibitors:

Components	Pathological Mechanism
Alkaline pH	Obstruct the formation of cystine and uric acid [10].
Citrate	Citrate forms complex with calcium, therefore the concentration of calcium oxalate is decreased. This inhibits aggregation of calcium crystals and accoutrement of crystals to urinary epithelium[28].
Pyrophosphate	It interferes with formation of both calcium oxalate and calcium phosphate [29].
Phytate	Prevent calcium crystallization both in intra-papillary tissue and urine [30].
Magnesium	Inhibition of nucleation and aggregation of crystals [31].
Glycoproteins	Interferes nucleation in metastable form and effect perform of crystal growth [10].



1.4 Mechanism of renal stone formation

We need to understand the molecular mechanism behind the renal stone formation to treat patients suffering from urolithaisis, as this will affect the morbidity and health Care cost (46). Renal stone genesis is complicated process which results because of succeeding physicochemical occurrences such as excellent saturation, growth, nucleation, retention and aggregation within the renal tubules.

1. **Urinary Saturation:** urine becomes highly saturated due to composition of various crystalloids and colloids. The stone forming inhibitors present in the urine prevent the precipitation in normal condition. If urine becomes supersaturated (when there is no space for any solute molecules to hold in the solution) with more than one crystal forming substances, a seed crystal may form through the process of nucleation [47].

2. Crystal nucleation: Nucleation describes the initial phase of the transition from a liquid to a solid phase in a supersaturated solution. Stone salts are first combined in solution to form loose clusters, which can then grow in size by adding additional clusters or components. Nuclei the earliest crystals that don't disintegrate and have a distinctive lattice pattern. Heterogeneous nucleation, which occurs when nuclei develop in urine typically on already-existing surfaces.

3. **Crystal growth**: the overall free energy decreases when a new crystal component is added to nucleus, this happen when the crystal has attained the critical size and the relative super saturation remains above one. This process is called crystal growth. Crystal growth is one of the important steps for particle formation and thus causes renal stone formation. The crystal growth and crystal aggregation are the major steps for stone formation [48].

4. **Crystal aggregation**: during this process crystals in the solution adhere together to form large particles. It is the stage of stone production that is the most crucial. Although crystal growth is undoubtedly a step in the formation of renal stones, the process of crystal growth is so slow that crystals do not grow large enough to obstruct the renal tubules. The viscous binding promotes crystal aggregation by abnormally self –aggregating Tamm-Horsfall glycoprotein or other macromolecules, which connect to crystal surface and function as glue [49].

5. **Crystal-cell interaction**: the mechanism behind the crystal-cell interaction is still unknown. Urinary super saturation is a major factor in crystallization. Once the crystals are formed, they adhere to and are absorbed by renal tubular epithelial cells.

1.5 Antiurolithiatic plants and plant products

Few marketed combination herbal formulations such as Chandraprabha bati (Baidyanath, India), Cystone(Himalaya Drug Company, India), and Calcuri (Charak Pharmaceuticals, Bombay, India) have often used in clinical settings to dissolve urinary calculi in renal stones.

Some of the marketed products have also been subjected to pharmacological screening and clinical studies to know their effectiveness both as a preventive measure to stop the formation of stone and treat or dissolve those stones which are already formed. Its diuretic properties are thought to be due to the active ingredients present in the herbal formulation. One such herbal formulation is Trinapanchamool composed of five herbal drugs listed *as Desmostachya bipinnata, Saccharun oficinarum, Saccharum nunja, Saccharum spontaneum* and *Imperata cylindrical* was found to be effective in prevention and treatment of renal stones [81].

Traditional medicines were the only choice in the ancient time; many medicinal plants have been used as anti-urolithiatic drugs belonging to the families such as Saxifragaceae, Amaranthaceae, Malvaceae etc. These medicinal plants consist of various active constituents like flavanoids, polyphenols, alkaloids and steroids having anti-urolithiatic activity [82]. These plants have been employed as mono or poly herbs in anti-urolithiatic formulations due to the presence of therapeutic activity such as anti-inflammatory, antioxidant, analgesic, diuretic or lithotripic action [83].

Figure 1 List of plants used in treatment of Urolithaisis

Name of plant	Family	Part of the plant used
Bergenia ciliata (Haw.) Sternb[50]	Saxifragaceae	Leaves
Costus arabicus L.[54]	Costaceae.	Stem & leaves
Herniaria hirsuta L.[55]	Caryophyllaceae	Herb
Terminalia chebula Retz.[56]	Combretaceae	Fruits
Tribulus terrestris L.[57]	Zygophyllaceae	Fruits
Acalypha indica L.[58]	Euphorbiaceae	Roots & leaves
Aerva lanata (L.) Juss.[59]	Amaranthaceae	Roots
Ageratum conyzoides (L.) L.[60]	Asteraceae	Leaves & roots
Alcea rosea L.[61]	Malvaceae	Ariel parts and flowers
Asparagus racemosus Willd.[62]	Liliaceae	All parts of the plants
Bombax ceiba L.[63]	Bombacaceae	Whole plant
Carthamus tinctorius L.[64]	Asteraceae	Flower
Cynodon dactylon (L.) Pers.[65]	Poaceae	All parts of plants
Helichrysum graveolens (M. Bieb.)[66]	Asteraceae	Flower
Hordeum vulgare L.[67]	Gramineae	Seeds
Hygrophila spinosa T.Anderson[68]	Acanthaceae	Ariel parts & roots

Hypericum perforatum L.[69]	Hypericaceae	All parts of plants
Launaea procumbens L.[70]	Asteraceae	Leaves
Lygodium japonicum (Thunb.) Sw.[71]	Lygodiaceae	Leaves
Orthosiphon grandiflorus Bold.[72]	Lamiaceae	Ariel parts
Paronychia argentea Lam[73]	Caryophyllaceae	Ariel parts
Pedalium murex L.[74]	Pedaliaceae	Plant as whole
Pergularia daemia (Forssk.) Chiov.[75]	Asclepediaceae	Whole plant
Quercus salicina Blume[76]	Fagaceae	Leaves & shoots
Salvadora persica L.[77]	Salvadoraceae	Sticks
Selaginella lepidophylla (Hook. et Grev) Spring[78]	Selaginellaceae	Stem
Agropyron repens (L.) P.Beauv.[79]	Poaceae	Rhizome
Phyllanthus niruri L.[80]	Phyllanthaceae	Whole plant

Reducing the process of crystallization is one the best approach to prevent and treat urolithiasis. Herbal products are the most effective way to treat urolithiasis, as it is more convenient, economic and effective way as they were used since ancient time. Herbal medicines are viewed as being relatively safe, having few or no side effects and easily available.

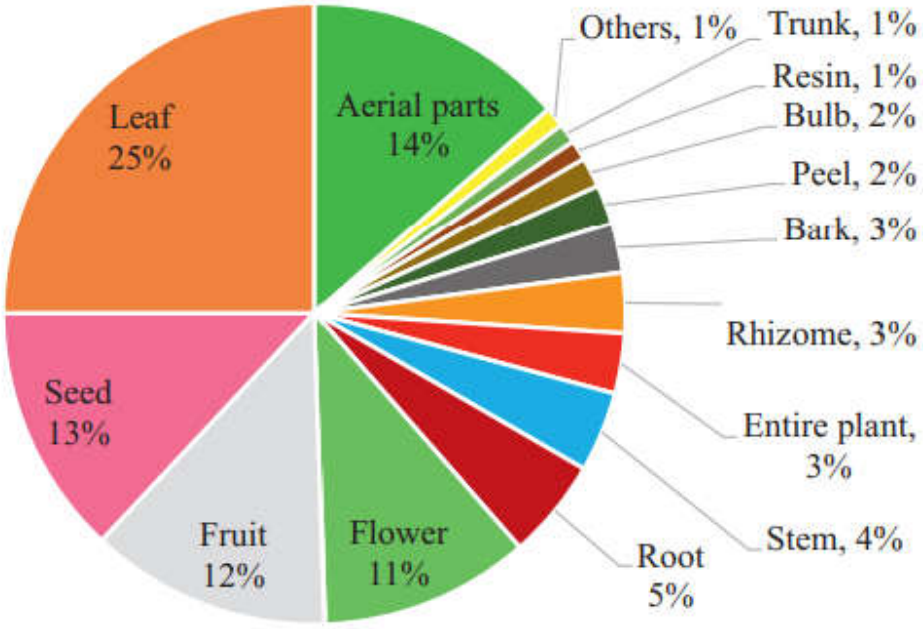


Figure 2 Frequency of plant parts used to treat urinary disease

1.6 Conclusion

The prevalence and incidence rate of urinary stone has increased in past few years, also in those places which had a low incidence of urolithaisis. The main causes in increase of urolithiasis may be due to change in the climate, food habits, genetics and lifestyle. Since folk times, medicinal plants has been used widely due to numerous benefits, including fewer toxic side effects, safety, effectiveness, affordability, a low risk of disease recurrence, and accessibility in remote areas. In allopathy, there is no effective medication for the treatment of urolithiasis, and the medications that are available have negative effects. Additionally, there is the option of surgery, but this has a higher risk of recurrence**.** The information in the current review, which includes information on kidney stones and plants used as antiurolithiasis agents, will help the researcher find new sources of drugs for this persistent human ailment to overcome the various drawbacks experienced by the wide range of people who suffer from this condition.

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