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Urolithiasis: A systemic herbal approach on pathogenesis and treatment of calculi formation

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CONTENTS

ABSTRACT

When the kidneys produce a crystallized substance, it acts as a kidney stone. Usually, it is affected by various risk factors (obesity, diabetes, hypertension and age) and treatments are available. Even though renal stone disease occurs in the older people, but the precise mechanisms of kidney stone formation and growth are still not entirely understood. Urinary stones are formed by crystals of phosphate, uric acid, magnesium ammonium phosphate, apatite and struvite. This review describes the (i). Pathogenesis, (ii). Stone formation and (iii). Prevention approaches. It also compares the surgical, herbal and allopathic urolithiasis treatments. The minerals in the body are depleted by kidney stones. Patients who have higher blood lipid levels may be more likely to develop kidney stones than healthy people. The patients are advised to consume low-fat foods, plant-based fibers and herbal treatments. Many people seek herbal therapy, because plant-based medication has fewer side effects and more efficient. To remove any kidney stone-related issues, combining herbal remedies with allopathic treatment is best option.

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Keywords: Allopathic, kidney stones, Herbal treatments, pathogenesis, Uric acid, Urinary stones, Urolithiasis.

1. INTRODUCTION

One of the first illnesses to strike human being was urolithiasis, when plants were our food. Despite significant advancements in our knowledge of the pathophysiological mechanisms, there are currently few and sometimes expensive therapeutic choices available to the public. Consequently, there is a growing interest in using herbal treatments as an alternative therapy to treat urinary stones (32). In spite of substantial progress in understanding the pathophysiological mechanisms, treatment options are still limited, often expensive for common people. Hence, there is a great interest in herbal remedies to treat urinary stone disease as an alternative therapy (32). Due to food and lifestyle changes, stone formation is the most common and painful urologic condition. Nephrolithiasis and urolithiasis are two kinds of stone formations. Urolithiasis, refers to the production of calculi in any section of the urinary system other than kidney, is distinguished from nephrolithiasis by the presence of calculi in the kidney (15). The lower urinary tract calculus consists of bladder stone and urethral calculus, while the upper urinary calculi are comprised of renal stone and ureteral calculi (4). The urolithiasis is a intricate syndrome influenced by various factors (Age, sex, nutrition, place of residence, environment, and etiological factors including renal and intestinal tract metabolic diseases) which can cause the formation of urinary stones (74) and even affect their properties. With a prevalence of 19 % in males and 9 % in females, hence urolithiasis is more frequent in men than in women (84). The renal stone and high total plasma level and free testosterone levels are correlated (40,54). Oestrogen acts in an inverse way to testosterone, which promote stone formation by increasing urinary oxalate excretion and inhibiting osteopontin production in the kidneys (87). Glycolic acid oxidase (GAO), an essential enzyme in the pathway of metabolism that leads to urinary oxalate production and hyperoxaluria, increases the hepatic levels in response to testosterone (75).

2. MECHANISMS OF STONE FORMATION

Stone forming pathogenesis consists of mainly three process (9).

(i). First stage (Supersaturation): is the process, which results in the formation of small masses by precipitating the solute present in the urine prior to nucleation (1,66). The main cause of crystallization in solutions is supersaturation. When a salt is mixed with a solvent, it dissolves until a particular concentration, where it is insoluble at higher concentrations. The solvent looks to be salt-saturated at this stage. When saturation occurs and crystallization starts, the concentration is called as the thermodynamic solubility product (TSP). If crystallization inhibitors are absent or do not work, the result will be nephrolithiasis (12). Urine pH, solute concentration ionic strength and complexations also affects the supersaturation (10).

(ii). Second stage (Nucleation): It is a transition from solvent to solid particles during a phase of supersaturation, when the salts begin to combine and form crystals. The nucleus of created crystal does not dissolve and burst the renal tubule endothelial cells the, which encourages the crystallization of calcium oxalate (5,34,42).

(iii). Third stage (Crystal Growth and Aggregation): It starts after the crystal supersaturation and nucleation, another process known as crystal growth begins, in which additional crystal components are added to the nucleus, reducing free energy. Furthermore, a solution with crystals stays together and form cluster, resulting in the production of huge particles of crystallize stone known as renal stone (49,55,91).

3. COMPOSITION OF STONES

The urinary stones contain many chemical components viz., phosphate, oxalate, apatite, struvite, cystine and uric acid (63). Calcium-containing calculi [Calcium Oxalate (CaOx), Calcium Phosphate (CaP) stones and Calcium oxalate monohydrate], account for 70-80 % of all stones (22), with Struvite accounting for 10- 15 %, uric acid accounting for 3-10 %, and cystine accounting for 0.5-1 % (6,8,51)

3.1. Calcium Stone

Calcium oxalate, either by itself or in combination with calcium urate or calcium phosphate, makes up the majority of calcium stones (26). Calcium oxalate is the main component, followed by calcium phosphate levels varying from 1 % to 10 % (37). when concentration of calcium phosphate is more than 50 % in stone, then stone is called calcium phosphate stone (14). CaP is most commonly encountered as basic CaP brushite, apatite and whitlockite. Presence of pure calcium phosphate is rare in stone formation of calcium phosphate (35). Apatite is most common in calcium phosphate stone. Typically, brushite appears in kidney stones as rosettes of thin blade-like crystals scattered radially. High urine pH, hypocitraturia, and hypercalciuria all hasten the development of CaP stones (25,73). Hypercalciuria can be caused by (i). increase in calcium absorption in the gastrointestinal tract (GIT), (ii). illnesses such as hyperthyroidism, hyperparathyroidism, hypercalciuria, and cancer-related hypercalcemia (16), besides secondary causes are: high dietary oxalate consumption, decreased urine volume and less concentration of citrate, trigger the formation of calcium stone (50).

3.2. Uric Acid/Urate stones

Urate calculi develop in humans due to precipitation of uric acid in urine, dehumidification, anuria and acidic urine pH value (69). The majority of gout patients have high purine consumption medicines or high cell turnover (such as malignancy), which are associated with the development of uric acid stones. These are radiolucent on X-ray film (67). Additional contributing variables are: use of medications that prevent uric acid from being reabsorbed by the kidneys and accelerate purine breakdown, in people with blood cancer or those taking chemotherapy during cancer treatment (23,33). Hyperuricosuria calcium urolithiasis and urate nephropathy are caused by an increase in uric acid, which is a purine end product (86). A urine uric acid excretion level of more than 750 mg/dL in female and 800 mg/dL in male is considered hyperuricosuria (25,36). Hyperuricosuria is developed in 10 % people with calcium stone due to the increase in uric acid salts and created the nidus for Ca^{2+} and oxalic acid deposition (36).

3.3. Cystine Stones

The development of kidney or bladder stones is caused by the dysfunctional absorption of cystine through the (PCT) proximal convoluted tubule, this causes a surplus

of cystine amino acid in urine (11). Cystine levels in the urine > 250 mg/dL are indicative of cystinuria (68). Cystinuria is an autosomal recessive inheritance disorder (78), it inhibits the reabsorption of cystine amino acid and causes the formation of cystine-forming stones by mutations of genes like SLC7A9 or SLC3A1 which encode for a glycoprotein RBA, (neutral and basic amino acid transport protein), and increase the concentration of cystine in urine (56,77).

3.4. Struvite Stone

Within a month, the struvite stone, (containing NH^4, Mg^{+2} and PO_4^{+}), grows quickly. The urine's urea is broken down by the enzyme urease to produce ammonia and carbon dioxide, which combine with the urine to form these stones (3,65). There is a strong chance that the struvite stones will reoccur. These "infection stones" are a complication of typical calcium stones, particularly in men (38). This stage is brought on by recurrent UTIs brought on by Proteus, Pseudomonas and Klebsiella species, which are Gram-negative urea-splitting rods (39).

3.5. Drug Induced Stone

Less than 1 % of stones are drug-induced calculi (Triamterene, Indinavir, etc.) (43). The kidney stones increase with the use of many different gouty arthritis medication, including salicylic acid, benzbromarone, and probenecid. Long-term therapy drugs including Indinavir, Sulphonamides, Atazanavir, Ceftriaxone and others have limited solubility, high excretion rates, or high dosages that trigger crystallization and increase the risk of renal calculi (65). These stones are uncommon and never seen X - Radioactive (83).

4. MANAGEMENT OF STONES

4.1. Surgical Treatment

The best treatment of urolithiasis, depend on the number of critical variables including the location, size, makeup, and symptoms of the patient (85). As a result, unpromoted stone transit can be up to 80 % of individuals with stones less than 4 mm in diameter, whereas the likelihood of spontaneous transit is very low, for stones > 7 mm in diameter (45,47). The surgical management of kidney and ureter stones has significantly improved during the last two to three decades (70). Following are some reasons for stone removal.

(i). Whenever there is insufficient pain alleviation

(ii). When infection and stone blockage are present together

(iii). When pronephroses or urosepsis is a possibility

(iv). When one kidney is obstructed

(v). Bilateral obstruction (59)

Extracorporeal shock wave lithotripsy, Percutaneous nephrolithotomy retrograde intra renal surgery and Ureteroscopy are currently accessible as therapy alternatives (72). As the focus of surgery has shifted to less invasive procedures, these surgical techniques have improved with time (24). These techniques are expensive treatment options. Recurrence is also a common occurrence following these procedures, and the patient must undergo careful follow-up for a number of years (19). There's no proven

efficient remedy for urolithiasis, surgery is the ideal choice, if other options fail, however, it is bit costly (18).

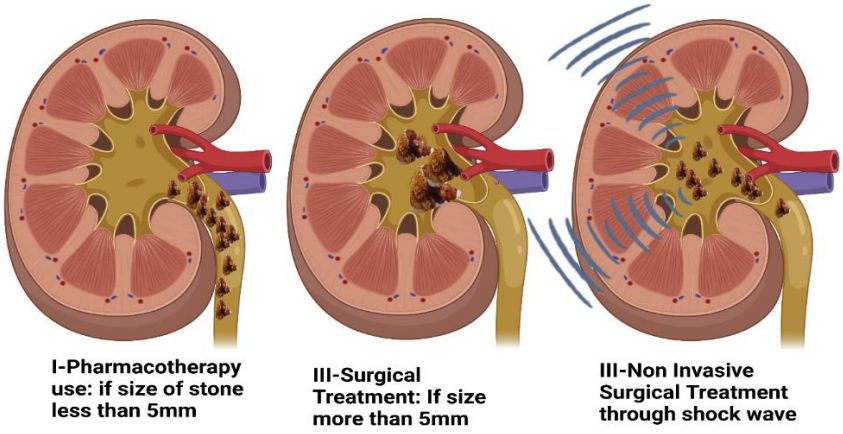

Figure 1. Various treatments of stones

4.2. Herbal Treatment

The rising occurrence of stone formation, accompanied by inflammation and intense pain, has sparked increased interest in herbal formulations to prevent lithiasis-related suffering. These formulations include extracts from various herbal plants containing active phytoconstituents (flavonoids, alkaloids, saponins, and sterols). These compounds exhibit bioactive properties including diuretic, anti-inflammatory, analgesic and antioxidant effects. Efficient healthcare is essential for disease prevention, diagnosis, treatment, and the maintenance of well-being in individuals and communities. As societies have progressed, diverse medical systems have developed to meet their unique requirements. Herbal and allopathic medicine represent two prevalent healthcare approaches utilized for these purposes.

Table 1. Comparative analysis of herbal remedies versus conventional allopathic treatments

Herbal Treatment	Allopathic Treatment
Mininmal or no side effect	Mild discomfort to severe complications
Addressing the root causes of illnesses, treat the underlying causes of illnesses	Focuses on alleviating symptoms, masking symptoms
Cannot become habitual	Become habitual
Cost effective and pocket friendly	Expensive
Herbal treatments utilize plant-based ingredients, such as roots, leaves, and flowers	Synthetic or isolated compounds
Herbal treatments often work synergistically with the body's natural processes, supporting self-healing mechanisms	Allopathic medications often target specific pathways or molecules to achieve their effects
Gradual and meticulous healing process	Offer immediate and transient respite (52)

In India, people have used plants for various purposes from ancient times. These are typically used to treat a variety of disorders (76). Western (allopathy) medicine and surgery are currently popular methods of treating kidney and urinary stone problems. However, due to the abuse of allopathic medications, which increases the likelihood of negative or severe side effects, the majority of respondents preferred plant-based (herbal) therapy (52). The current common perception is that herbal therapy is safer and more dependable (46). The World Health Organization estimates that 80 % of the population in underdeveloped nations takes herbal medications (80). A wide range of herbal medications are included as treatments for urolithiasis in several pharmacopoeia from different nations across the world (90,92). Increased consumption of fruits and vegetables, such *as Rubia cordifolia, parsley, pomegranate (Punica granatum), Pistacia lentiscus, Solanum xanthocarpum, Urtica dioica, Dolichos biflorus, Herbaceum vulgare, Ammi visnaga,* and *Nigella sativa,* may help prevent kidney stones (53).

Table 2. Phytoconstituents often linked to urolithiasis and their respective mechanisms of action

#	**Phytoconstituent**	**Mechanism of Action**	**Ref**
1.	Berberine	Prevent the formation of crystal due to its antioxidant effect	57
2.	Quercetin	Diminishes the formation of stones by reducing the excretion and nucleation of oxalate, as well as its diuretic and antioxidant properties. And enhancing the mg levels and lowering crystal-cell binding.	21
3.	Hydroxycitrate	Disintegrate the crystals of calcium oxalate	44
4.	Lupeol	Reduces cadmium levels in the kidney, lowers calcium oxalate levels, and possesses anti-free radical properties.	91
5.	Gallotannin	Decreased binding to renal epithelial cells and crystal formation. The mrna expression of monocyte chemoattractant protein 1, osteopontin, nicotinamide adenine dinucleotide phosphate oxidase, subunit p22phox, and p47phox on renal epithelial cells was drastically decreased by oxalate. Superoxide dismutase is activated by Gallotannin in exposure to oxalate.	41
6.	Curcumin	Beneficial effects in the initial stages of stone formation because of its strong anti-inflammatory and antibacterial properties.	61
7.	Catechin and Rutin	Retinal tubular cells decreased osteopontin expression as a result inhibits renal calcium crystallisation. It lowers the production of 4-hydroxynonenal, cytochrome c, superoxide dismutase and split caspase 3 in nrk-52e cells.	80
8.	β-Sitosterol	Lessens urinary tract and kidney inflammation. Enhanced SOD and GPX antioxidant enzyme activity under OS.	13
9.	Diosmin	Restoring the diameter of the capillaries and vessels in the cortex by capillary hyper-permeability degeneration of the glomeruli and tubules	64
10.	γ-Pyrones - visnagin	Guard the renal epithelial cell damage from oxalate and calcium crystals. Prevent the oxalate formation by increasing the level of urine pH. Additionally, this plant suppresses transcription factors like nf-κb, which lowers gene expression and produces chemicals that promote inflammation, including as tnf-α, il-1β, and ifnγ.	31

Commercialized composite herbal formulations have been used extensively in clinical practice to dissolve urinary calculi in the kidney and bladder. These formulations are called Calcuri (Charak Pharmaceuticals, Bombay, India), and Chandraprabha bati (Baidyanath, India) Cystone (Himalaya Drug Company, India) (88). Phytoconstituents are naturally occurring chemical compounds found in plants, and several have been studied for their potential effects on urolithiasis or kidney stone formation. These phytoconstituents may exhibit various properties that can influence the urinary system and help prevent the formation of kidney stones. Here are some key phytoconstituents associated with urolithiasis. Numerous phytoconstituents included in herbal treatments work in numerous ways to help with urolithiasis. These processes include changes in urine volume and pH as well as increase the levels of stone inhibitors such magnesium, potassium, phytate, and citrate diuretic, action, antioxidant activity, antispasmodic activity, inhibition of crystal growth and development (88).

Urinary stones are said to be treated using plants belonging to the "Pashanabheda" group in India's Ayurvedic medical system. The Sanskrit word "Pashanabheda" (Pashana = stone, Bheda = break) refers to a class of plants with diuretic and antiurolithiatic properties.

Table 3. Herbs investigated for urolithiasis therapy and their principal phytochemical components

#	Scientific Name	Part Used	Main Phytoconstituents	References
1.	*Ammi visnaga (*L.) LAM.	Fruits	Furanochromone derivatives (e.g. Khellin and visnagin) coumarins and γ-pyrones	7
2.	*Citrus limon* L	Fruit rind	Coumarins, furanocoumarins, limonoids, terpenoids, Flavonoids and essential oils	7
3.	*Citrus sinensis* L	Fruit rind	Flavonoids (e.g. hesperidin), Essential oil (e.g. limonene)	7
4.	*Duranta erecta*	Leaves	Alkaloids, glycosides and saponin	2
5.	*Mentha piperita*	Aerial part	Chlorogenic Acid, epicatechin, quercetin, gallic acid, epigallocatechin, syringic acid, kaempferol and caffeic acid	2
6	*Moringa olifera*	Leaf, root	Quercetin, rutin, ascorbic acid, magnesium	82
7	*Pedalium murex L.*	Whole plant	Pedalitin	30
8.	*Piper cubeba*	Fruit	Phenolics, tannins, steroids, terpenoids and flavonoids	79
9.	*Hibiscus cannabinus* L	Leaves	Alkaloids, flavonoids, terpenoids, saponins, protein, glycosides, and phenolic compound	81
10	*Terminalia arjuna*	Bark	Tannin, terpenoids, saponin, flavonoids, glycosides, phenolic compounds, alkaloids	83
11.	*Boldoa purpurascens*	Leaves	Boldine, isoboldine, diterpenes, quercetin, kaempferol	65

4.3. Allopathic Treatment

Only after an in-depth medical assessment of the urolithiasis, the best pharmacotherapeutic strategy be determined. Medical expulsive therapy is advised to aid stone transit, when the stone is smaller than 5 mm in size and situated in the distal ureter

(29). The type of stone, its size, and any anomalies in the urine will determine the best course of treatment. The following drugs are used to treat stones (60).

4.3.1. Thiazide Diuretics: Thiazides are utilized to treat patients with increase amount of ca^{+} in urine nephrolithiasis due to their hypercalciuric effect. Indeed, when compared to a placebo group, thiazides, particularly hydrochlorothiazide, dramatically decreased the formation of stones (94). However, the side effects of thiazide medication are: fatigue, malaise, impotence and constipation to limit its use (89). Additionally, hypokalemia, hyperuricemia and hyperuricosuria might develop (58).

4.3.2. Sodium Cellulose Phosphate (SCP): Its main mechanism is to decrease the calcium reabsorption in renal site resulting in increase in calcium level in urine (27).

4.3.3. Potassium Citrate: Potassium citrate increases the pH the urine and decrease the acidity, which is beneficial for patients suffering from uric acid stones, cystine and calcium calculi, and low urinary citrate. This property of potassium citrate aids in the prevention of cystine and uric acid calculi and also decreased the occurrence of calcium stone formation by increasing the citrate level (20).

5. CONCLUSIONS

Urinary and kidney stones are chronic condition, affect around 10-12 % of population. The allopathic medicines and surgery are the most commonly used treatment methods. However, the conventional treatment methods are associated with some limitations including adverse effects or severe side effects, therefore researchers focused there compete interest on herbal medicines. The herbal medicines provide beneficial effects in clearance of stones, without producing any severe toxic effects. The treatment of stone depends on morphology and location. The possible mechanisms of action of herbal medicines include (increased excretion of urinary citrate, decreased excretion of urinary calcium and oxalate) and results in enhanced diuretic, antioxidant or antibacterial effects. If the stone size is progressively increased, results in urinary tract blockage, then it is necessary to remove the stone using ESWL or endoscopic intervention. Scientific literature clearly showed that pharmacotherapy is a reasonable first choice to treat urolithiasis, which are small-sized and do not significantly obstruct the urinary tract. Unfortunately, there is lack of scientific data documented regarding herbal medicines as the best option for stones treatment. In future, more scientific information required in preclinical and clinical studies to evaluate the efficacy of herbal medicines in kidney and urinary stone treatment.

AUTHOR'S CONTRIBUTION

In the present review, P. made a substantial contribution to concept of article on pathogenesis of urolithiasis and further compared the treatments. AM and SD performed the systematic evaluation and elaborated on the conclusion. All authors read and approved the final manuscript.

DECLARATION

We declare that all authors of this manuscript have made substantial contributions. We did not exclude any author who substantially contributed to this manuscript. We have followed our ethical norms established by our respective institutions.

CONFLICT OF INTEREST

The authors announce that they have no conflict of interest.

ETHICAL APPROVAL

The authors declare that the study was carried out following scientific ethics and conduct.

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