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Nephrolithiasis: An exploratory review on its herbal treatment

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ABSTRACT: Nephrolithiasis is an urological disorder caused by the obstruction of crystals in kidneys (nephrolithiasis). Successive physicochemical events at the renal papillary surfaces result in the deposition of crystals. They also involve certain promoters and inhibitors. Etiological factors include several metabolic disorders such as hypercholesterolemia, hyperparathyroidism, and diabetes mellitus. Supersaturation of urine with nutrients such as calcium, phosphate, magnesium, oxalate, and uric acid provokes the formation of different stones, most common being calcium phosphate. To date, there is no formulation in the market capable of treating kidney stones of all sizes. We can expedite only stones below, 5mm out of the body with the help of marketed drugs. Urological interventional procedures such as ESWL, percutaneous nephrolithotomy (PN), and surgery remove large-sized kidney stones but impose the fear of renal injury, dysfunction, or recurrence of stones. The present review discusses the herbal drugs being investigated in recent years to treat nephrolithiasis. We can further study these drugs to develop any novel delivery form that would directly target the accumulated calculi and lead to its degeneration and prevent its recurrence.

KEYWORDS: ESWL (extracorporeal shock wave lithotripsy),Hypercholesterolemia,Hyperparathyroidism,Nephrolithiasis,Percutaneousnephrolithotomy.

I. INTRODUCTION

Nephrolithiasis is a common kidney condition due to the supersaturation of urine with some chemical constituents responsible for stone formation. Supersaturation of urine results because of reduced urine volume, unfavorable urinary pH, or modified excretion rate of stone-forming constituents. Kidney stones or renal calculi are of two types, simple renal calculi, and complex renal calculi. A simple renal calculus comprises stones less than 5mm whereas a complex renal calculus comprises stones greater than 10mm. We mostly find it is mostly in men than in women during the age of 20-40 in both the sexes.

Stones less than 5mm pass through the urinary tract easily within 40 days either by changing the dietary intake mostly hydration or by nutritional intervention. Urologists remove complex renal calculus with the mediation of specialized procedures such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, and percutaneous nephrolithotomy (PN).

The major disadvantage of nephrolithiasis is that the stones recur if the residue remains. The recurrence rates are about 21% to 53% in 3-5 years. [1]

Urine becomes “supersaturated” because of insoluble substances composed of calcium, oxalate, phosphate, uric acid, magnesium, ammonium, and cystine. Supersaturation results because of low fluid intake or other genetic or environmental factors responsible for restricted urinary excretion of ions.[2]

II. EPIDEMIOLOGY

According to a recent review, about 19% of the Asian population suffers from urolithiasis and they find globally the highest prevalence and incidence rates in Saudi Arabia [1]. About 12% of the Indian population suffers the same among which half of them finish up with kidney dysfunction [3]. Males above 30 years of age have the highest rate of incidence. Environmental factors such as exposure to the sun and low consumption of fluid can stimulate the formation of stones. Males have higher chances of stone recurrence almost twice that of females [4]. Dietary habits and lifestyle play a key role in the formation of stones. Reportedly, because of global warming, the incidence rates can reach up to 56% by 2050.

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TABLE 1: TYPES OF STONES

CHARACTERISTIC	TYPES OF STONE				
	CALCIUM		STRUVITE	URIC ACID	CYSTINE
	OXALATE	PHOSPHATE			
INCIDENCE RATE	75%	5%	15-30%	5-10%	1%
COMPOSITION	Whewellite-monohydrate crystals (COM) and whedellite-dihydrate crystals (COD).[5][6]	Apatite stones	Calcium magnesium ammonium phosphate or triple phosphate stone	Catabolic product of purine (an animal protein)	Cystine and other amino acids such as lysine, arginine, and ornithine.
MORPHOLOGY	Envelope	Amorphous	Coffin lid	Diamond	Hexagon
FAVORABLE pH	Acidic pH	Alkaline urine [7][8]	Alkaline urine	Acidic urine	Acidic urine
ETIOLOGY	Metabolic disorders such as i. Hyperparathyroidism, ii. Malignancy iii. Sarcoidosis iv. Excess of vitamin D[9][10]		i. Urinary tract infections because of urease-producing bacteria such as Proteus, Klebsiella, Providencia, and enterococci. ii. Frequent catheterization of the bladder[11][12][13]	Protein-rich diet (when the concentration exceeds 2.0g/kg.)	Dysfunction of dibasic amino acid renal transportation leads to increased free concentration of cysteine.
TREATMENT	i. Thiazide diuretics		i. Removal of stones by PN and ESWL. ii. Aceto-hydroxamic acid. (Urease inhibitor) iii. Antibiotic therapy[14]	i. Allopurinol ii. Alkali salts e.g. Potassium salts iii. Restricted protein diet.	i. Urine alkalizing agents. ii. Increased fluid intake iii. d-penicillamine iv. Tiopronin v. Other thiol binding agents[15][14]

III. ETIOLOGY

Hypercalciuria

Hypercalciuria is a condition in which the concentration of calcium in the urine exceeds 200-250mg/d. Estimation of calcium concentration both in the urine and serum along with creatinine, uric acid, magnesium, oxalate, and volume of urine confirms the incidence of nephrolithiasis. One of the major determinants of idiopathic hypercalciuria is a high level of calcium in the urine. It enhances calcium absorption which increases the levels of

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unbound calcium ions. The feedback mechanism thus results in the reduced secretion of parathyroid hormone (PTH). All the above events potentially decrease the tubular reabsorption of calcium. We can improve this with the aid of 1, 25 dihydroxy vitamin D_3 [2][5]. Reducing the dietary sodium and concurrent administration of thiazide diuretics can increase the tubular reabsorption of calcium.

Hypocitraturia

Normally, urine remains supersaturated with solutes such as calcium and oxalate. However, an excess concentration of citrate does not lead to the formation of crystals, but reduced concentration leads to calcium oxalate crystallization. Urinary citrate must be greater than 450mg/d in males and similarly greater than 550mg/d in females. Calcium citrate, a soluble compound increases urinary pH. We thus recommend alkylating agents to treat hypocitraturia. The most common alkylating agent is potassium citrate. Other conditions that lead to hypocitraturia are diarrhea and renal tubular acidosis.

Hyperoxaluria

Reports confirm that the consumption of vitamin C alters the absorption of oxalate to a greater extent than the dietary oxalate [6]. However, some physicians restrict the dietary intake of oxalate to prevent its supersaturation. Patients diagnosed with inflammatory bowel disease (IBD) and diabetes also show a high incidence of hyperoxaluria [5][7]. IBD patients also exhibit hypocalciuria or negative calcium balance, a prominent symptom of hyperparathyroidism. Physicians recommend calcium supplements to improve the calcium balance in hyperparathyroidism. We should take a calcium supplement along with food so it can easily bind with the dietary oxalate. Restrictive bariatric surgery alters the absorption characteristic of oxalates by enhancing their reabsorption in the colon leading to hyperoxaluria [8][9]. Jiang et al. recommended the intestinal colonization of Oxalobacter formigenes, an oxalate degenerating bacteria. It can reduce oxalate levels in the body when given with a calcium supplement. [10]

Hyperuricosuria

Uric acid is insoluble in acidic pH, and thus pH remains its major determinant. Only 5% of the cases prevalent are of uric acid crystals. The normal uric acid excretion rate is 5.6mg/kg/d. The most important step to prevent hyperuricosuria is to limit the dietary intake of purines. Allopurinol also significantly reduces uric acid levels in the body.

Gouty diathesis

Around 10% of patients with gout develop kidney stones. Diet rich in purine, fructose, and alcohol increase the formation of uric acid in the body and lead to gouty diathesis. Alkaline pH favors the deposition of uric acid. [11]

IV. PATHOPHYSIOLOGY

Crystals form when urine becomes supersaturated with different salts such as calcium, oxalate, phosphate, uric acid, magnesium, ammonium, phosphate, or a non-essential amino acid such as cystine. We can group the mechanisms behind their crystallization into two categories. The first is the process of accumulation of crystal salts by combination with a non-crystalline protein matrix. Precipitation occurs by the aggregation of salts which progressively expand to a size capable of clinical detection. The second category of stones is responsible for the formation of Randall's plaque [12] or calcium phosphate nidus on the kidney. It exhibits this mechanism during the formation of calcium phosphate stones. However, this process remains unknown. [13]

Nucleation, growth, and aggregation

The first step in the formation of crystals is **nucleation** technically referred to as "nidus formation". Nidus formation occurs in a supersaturated solution enclosed within the kidneys [14][15] where the concentration of promoters exceeds that of the inhibitors [16]. Supersaturated urine comprises atoms, ions, and molecules in the free state which combine to form microscopic aggregates or clusters. Bulk free energy of the aggregates is less than the urine in the supersaturated state [16]. The chemical pressure required for the nucleation process is more than required for the process of crystallization. The epithelial cells and erythrocytes found on the lining of the renal tubule may act as centers of heterogeneous nucleation. The mucopolysaccharides obtained from the organic matrix enhance the binding of the crystals [17]. Nanobacteria mostly gram-negative organisms form the basis of crystallization for the apatite structures. [18]

The growth of crystals is a slow and tedious process. It forms a hard mass from the microscopic aggregates already present in the urine, or it forms a secondary nucleus on the matrix surface of the crystal [19]. Certain proteins boost

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the formation of CaOx crystals such as Tamm-Horsfall protein and osteopontin [20]. When the crystals grow by the accumulation of preformed crystals on the nidus or the nucleus, the free energy of the crystal structure consequently decreases.[16]

The most prominent step is the **aggregation** of grown crystals into large masses. In all the cases of calcium oxalate stones, it retains the aggregated crystals within the kidneys.[21]

Figure 1 Pathophysiology of kidney stone formation

Crystal cell interaction

As the name suggests, in this process interaction occurs between the preformed crystals and the epithelial cells present in the lining of the renal tubules [21][22]. Hyperoxaluria plays an important role in triggering the crystal cell interaction. It injures epithelial cells of the renal region when the oxalate concentration exceeds the normal range leading to the formation of COM crystals in the basolateral region [23][24][25]. The crystals wander until they bind to the basement membrane and progressively take part in the development of renal stones [25]. It raises the force of retention between the injured cell and the crystal.[26]

Endocytosis

Calcium oxalate crystals have more affinity for the renal tubular cells and can easily attach themselves to the binding site. Renal epithelial cells readily internalize calcium oxalate dihydrate crystals as they are more innocuous than calcium oxalate monohydrate crystals. The polyanion molecules present in the urine coat the COM crystals and restrict its binding property, examples include glycosaminoglycans and glycoproteins [21]. Similarly, the THP protein plays an important role in crystallization but it's reported that it exists in two forms firstly as desialylated THP which stimulates crystallization, and secondly, as normal THP which prevents crystal formation [27]. Monocyte chemoattractant protein I, osteopontin, and sialic acid are some major binding spots on the renal cells.[21]

Cell injury and apoptosis

Hyperoxaluria leads to the production of highly reactive free oxygen species, which promotes lipid peroxidation leading to cell injury [28]. Injured cells develop nidus which stimulates the accumulation of crystals, mainly calcium oxalate crystals [29]. The clusters of CaOx promote the synthesis of mediators of inflammation [30]. The increased oxalate concentration inhibits the enzymes responsible for the deterioration of oxygen species and signals the initiation of apoptotic pathways.[31]

Genetic basis

Some genetic defects are also responsible for the formation of stones. These factors combine with the environmental factors to induce the crystallization process [32]. VDR (Vitamin D receptor), CASR (Calcium-sensing receptor), CLDN16 (Tight junction protein) are some genes involved in the pathogenesis of stone formation.

Randalls plaques

Acts as a precursor in some stone types [19] like apatite and purine crystals. The basement membrane or the interstitial region of the loop of Henle houses Randall's plaque [33][34] although its exact pathogenesis remains unknown[35]. Reportedly plaque comprises apatite and purine crystals majority being apatite [36]. Calcium phosphate deposits on the loop of Henle in combination with the mucopolysaccharide got from the organic matrix. Randall's plaque is the depositions that slowly move towards the interstitial space between the lining of ureters, urethra, and urinary bladder, namely urothelium [20]. The plaques come in contact with the supersaturated urine whenever there is renal cell injury. Injuries lead to the release of degradative entities that serve as heterogeneous nucleates. When the urine becomes supersaturated, the crystals easily fix themselves to the urothelium. Apatite crystals primarily serve as a nidus for the formation of calcium oxalate (CaOx) crystals [20]. The free radicals produced by oxidative stress precipitate the formation of Randall's plaque. The distal and the collecting region also help in the crystallization process by providing crystal attaching sites such as osteopontin, phosphatidylserine, hyaluronan, and

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CD44 [37][38]. Another mechanism involved in the development of Randall Plaque formation is the production of membrane vesicles from the epithelial cells of the nephron, mainly from the Henle's loop or collecting duct. [39]

Kidney stone inhibitors and promoters

Our body comprises both promoters (Figure 2) and inhibitors (Figure 3) and because of an abnormal proportion of these kidney stones precipitate. Inhibitors act by obstructing the pathogenesis of stone formation. [16][15][19][21][40]

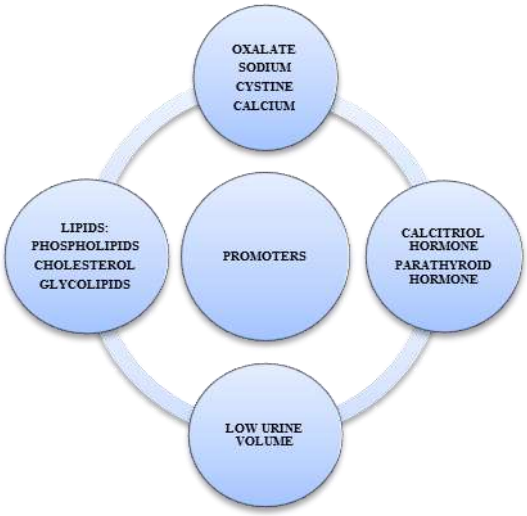

Figure 2 Promoters of stone formation

Figure 3 Inhibitors of stone formation

V. HERBAL TREATMENT OF LITHIASIS

Although herbal species are not fully effective for the complete treatment of kidney stones, we can use it as an alternative therapy to treat nephrolithiasis. Traditional literature available suggests the use of several herbal drugs alone or in combination with others to treat renal stones. The degenerative properties of the herbal sources were studied either by in-vitro crystallization systems which depict the physical chemistry of stones or culture of renal most commonly epithelial cells that display the pathophysiology of renal stone formation. The major drawback of herbal treatment is that it cannot prevent the recurrence of stones and in acute conditions, it is not the choice of treatment. Table 2 lists a few of the recently reported herbal drugs capable of improving the condition of the disease.

TABLE 2: PLANTS WITH REPORTED ANTILITHIATIC ACTIVITY

S.No.	Biological Name	Part used	Type of study	Reference
1.	Nigella sativa l.	Seeds	Randomized, triple-blind, placebo-controlled, clinical trial	[50]
2.	Daucus carota l	Roots	In-vivo study	[51]
3.	Phyllanthus niruri	Leaves	Clinical trial	[52]
4.	Ceterach officinarum	Leaves and aerial parts	In-vitro study	[53]

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5.	Pedalium murex (l.)	Whole plant	In-vivo study.	[54]
6.	Oxalis corniculata Linn.	Leaves	In-vitro study	[55]
7.	Duranta erecta	Leaves	In-vivo study	[56]
8.	Cichorium intybus l.	Flowers	In-vivo study	[57]
9.	Taraxacum officinale	Aerial parts	In-vitro study	[58]
10.	Blumea balsamifera extract	Leaves	In-vitro study	[59]
11.	Polygonum aviculare l.	Leaves	In-vivo study	[60]
12.	Biophytum sensitivum	Whole plant	In-vivo study	[61]
13.	Cerasus avium	Stem	In-vivo study	[62]
14.	Nigella sativa l	Seeds	In-vivo study	[63]
15.	Bryophyllum pinnatum	Leaves	In-vivo study	[64]
16.	Cynodon dactylon	Whole plant	In-vivo study	[65]
17.	Bergenia ligulata	Rhizome	In-vivo study	[66]
18.	Urtica dioica	Aerial parts	In-vivo study	[67]
19.	Capitulum of helichrysum graveolens (m.bieb.) Sweet (hg) and helichrysum stoechas ssp. Barellieri (ten.) Nyman (hs)	Flowers	In-vivo study	[68]
20.	Sargassum wightii	Brown algae	In-vivo study	[69]
21.	Terminalia arjuna.	Bark	In-vitro study	[70]
22.	Citrus limon peel	Peels	In-vivo study	[71]
23.	Crocus sativus	Stigma	In-vivo study	[72]
24.	Malva neglecta wallr	Leaves	In-vivo study	[73]

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25.	Tragia involucrata.	Leaves	In-vivo study	[74]
26.	Chenopodium album Linn.	Leaves	In-vivo study	[75]
27.	Peucedanum grande c. B. Clarke	Fruits	In-vivo study	[76]
28.	Vernonia cinerea less.	Whole plant	In-vivo study	[77]
29.	Ipomoea eriocarpa	Leaves	In-vivo study	[78]

VI. DIAGNOSIS

Imaging

Computed tomography (CT) is the best method for the diagnosis of urolithiasis. Previously, medical practitioners relied on intravenous urography. The major symptom of renal calculi is acute pain in the renal region. If the pain is because of any other source, unenhanced CT, [41][42] can promptly identify except for the pain caused by drug-induced stones such as by indinavir.

24 hr urine collection

Physicians recommend 24hr analysis of urine for the identification of any sediment or crystals along with the determination which the levels of various constituents responsible for the development of calculus such as calcium, phosphate, magnesium, uric acid, oxalate, and citrate. [43][44][45]

Nutrition assessment

Nutrition plays an important role in the formation of renal calculus. We find all the constituents involved in the formation of crystals in our diet, and so its assessment could lead to the prevention of kidney stones. We can use a dietician for recommending the number of nutrient intakes such as sodium, calcium, and proteins. They maintain a record of the diet taken on the day of urine analysis along with the previous days. Methods of assessment include recalling the food taken by memory, maintaining a record, or filling questionnaires periodically. The nutrition got from food directly alters the composition of urine and the three major sources of nutrients are diet, beverages, and nutritional supplements.[2]

VII. INVASIVE PROCEDURES

It uses surgical or invasive procedures according to the condition of the disease or the symptoms it exhibits such as degree of pain, the position of the stone, obstruction of any kidney function because of large-sized stones. ESWL (extracorporeal shock wave lithotripsy) uses shock waves to smash down stones of large size into small pieces, which the body expels easily after some time in the urine. This method is not suitable for obese patients, and during the expulsion of cystine stones concerning its hardness.

Stones of large masses oblige the process of invasive methodologies of treatment. Percutaneous nephrolithotomy (PN) is the method of choice for large masses, although invasive. PN is opted when removal of stone is impossible cystoscopically. Nephrolithotomy is seldom carried out.

Invasive methods involve a flexible ureteroscopic method in which it completely removes the stones with no residual fragments. The major drawback of this method is that it may cause ureteral injury. Few of the invasive devices available are flexible ureteroscope of small diameter, stone baskets, ureteral access sheaths, and holmium laser lithotripsy.[2]

VIII. CONCLUSION

The major consequence of repeated episodes of kidney stones mainly because of metabolic abnormalities leads to morbidity and economic breakdown. Though progress in the medical field has led to the development of various interventional procedures and identification of chemical species effective to treat nephrolithiasis, its incidence rates are soaring high in the developing countries and thus its treatment requires a multifaceted approach. Early diagnosis and prevention strategies can only reduce the

complications of the disease. The major drawback of medical expulsive therapy is that it cannot prevent the recurrence of stones. The area of focus should be the development of novel entities derived from the biological species that would directly repress the process of stone formation or inhibit its pathogenesis. We can use these herbal sources as an alternative or adjunct therapy to treat kidney stones.

CONFLICT OF INTEREST

No conflict of interest.

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