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Review Article

UROLITHIASIS–AN UPDATED REVIEW OVER GENETICS, PATHOPHYSIOLOGY AND ITS CLINICAL MANAGEMENT

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ABSTRACT

Urolithiasis is the formation of renal calculi within the urinary tract of susceptible individual of various etiopathogenic factors with a complex pathogenic manifestation. It is a worldwide problem which was evident from the ancient times of Egyptian period. It is the third most urinary disorder with a lifetime risk of 15-25% and the prevalence rate of 3-5%. In the management of urolithiasis, the clinicians face a deprived status of mind with its multifactorial etiopathogenesis. Thus the exact therapy still remains to be debated with this modest understanding of pathophysiology and genetical aspects of urolithiasis. As a result of these poor understandings, an attempt was made to detail the multifactorial etiopathogenesis and genetical aspects of urolithiasis with a view to advancement in the clinical management. Moreover to this attempt, this review also summarized the updated clinical management in terms of specific and surgical measures along with its differential diagnosis to the extent of intending an immense sound over its management to the clinicians.

Keywords: Calculi, Diagnosis, Etiopathogenesis, Genetical, Management, Multifactorial.

INTRODUCTION

Urolithiasis also known as uroliths or calculi, the third most common prevalent urinary disorder that involves the process of stone formation in any part of urinary tract by the successive physiochemical events of supersaturation, nucleation, aggregation, and retention at the site of stone formation [1, 2]. It is a multifactorial disorder that results from multifactorial etiopathogenesis like epidemiological, biochemical, metabolic, nutritional, socio-economic, drug induced and genetical risk factors [3, 4].

The supersaturation of urine with stone forming elements like calcium oxalate, struvite, uric acid, and cystine tends to be a key pathological event in stone formation [5]. It affects about 13% in North America, 5-9% in Europe, 1-5% in Asia [6]. Globally it affects about 10-12% of the population especially in the industrialized countries. Besides that, in the last five decades the incidence has been increased along with economic development in the Western countries [7]. The recurrence rate was reported to be 40% within 3 years, 74% within 10 years and 98% within 25 years of the first incidence of urolithiasis [8]. Predominantly the incidence factor in the implication of urolithiasis is dependent greatly on age and gender factors [9]. But clinically the incidence was remained to be rare in children [10]. Urolithiasis often leads to other pathological implications like pyelonephritis, acute or chronic renal failure, pyonephrosis and perinephric abscess which can be life threatening complications [11].

Epidemiology

The intrinsic factors need to consider the epidemiology of urolithiasis are age. Sex and genetic perspectives of an individual. The incidence rate is very high at the age of 20-40 years; and in men rather than women due to increased testosterone induced hepatic oxalate production in men. While the extrinsic factors in epidemiology are geography, climate, season, diet, water intake, occupation and stress. Geographically the incidence is more in USA, Mediterranean countries, and Central Europe, whereas the lower incidence was reported at Central and South America and Africa. Hot climatic conditions tend to concentrate the urine which acidifies and saturates the crystal forming elements to precipitate. Increased intake of animal protein, salt and sugar causes increased excretion of urinary calcium, uric acid, and oxalate that predisposes to incidence of renal calculi. The other extrinsic factors like low fluid intake, sedentary occupation and stress can predispose to uroliths [12].

Types of stones

A. Physiologically

Physiologically the renal calculi differentiated as tissue attached and unattached.

1. Attached calculi tend to have the detectable site of attachment to papillae with the composition of calcium oxalate (CaOx) monohydrate.

2. While the unattached calculi distinguished by having different composition and lack of detectable site [13].

B. Clinically

Based on the composition of the stone forming element in the calculi, clinically these calculi are categorized as following types.

- Calcium stones (CaOx alone/with calcium phosphate)
- Struvite stones (Magnesium ammonium phosphate)
- Uric acid stones
- Cystine stones
- Drug induced stones
- 2,8-Dihydroxyadenine stones

Among the kidney stones, CaOx stones constitute about 75%, struvite stones of 15%, uric acid stones of about 6% and cystine stones of about 1-2% [14].

Calcium stones

The Idiopathic causes are absorptive hypercalciuria, renal hypercalciuria and resorptive hypercalciuria. The metabolic causes are hypercalcaemia due to primary hyperparathyroidism, hyperoxaluria, hyperuricosuria, hypocitraturia and hypomagnesuria. In explaining the detail cause of each event- i. Hyperoxaluria arises due to primary hyperoxaluria of genetic disorder which enhances the hepatic oxalate production and enteric hyperoxaluria, where the colon is made to diffuse more oxalate. ii. Hyperuricosuria evident from excessive purine intake. iii. Hypocitraturia arises due metabolic acidosis induced by inflammatory bowel disease and chronic diarrhea. iv.

Hypomagnesuria be due to malabsorption of magnesium from gut because of inflammatory bowel disease and chronic diarrhea [15].

In hypercalciuria, calcium promotes the ionization and saturation of crystallization of calcium salts and also to bind with stone inhibiting substances such as citrates and glycosaminoglycans there by the events of hypercalciuria induced uroliths. The renal leak from kidney, resorption from bone and absorption from gut tends to be the key defects in implicating the hypercalciuria individually or in combination with each other [16]. In the other way, excessive dietary sodium intake predispose to uroliths by hypercalciuria and hypocitraturia. Moreover there exists a linear relationship between urinary sodium and calcium levels, which establish a strong relationship to confer risk of hypercalciuria induced uroliths [17, 18]. In addition to the above all etiological factors, protein overload and metabolic acidosis are the other possible etiological factors in the pathogenesis of hypercalciuria induced calcium nephrolithiasis. In metabolic acidosis, the high urinary pH favors the formation of calcium containing uroliths [19]. The excess protein intake can predispose to calcium nephrolithiasis which was evident from animal, metabolic and epidemiological studies [20-23].

Hypocitraturia corresponds about 20-60% of calcium nephrolithiasis. As it is a major inhibitory component of calcium oxalate and calcium phosphate, lowered levels of citrate favors the risk of hypercalciuria induced calcium uroliths. Furthermore, the citrate tends to complex with calcium to form a soluble complex to prevent the crystal growth [24]. Hyperoxaluria, the another etiological factor of equal importance with hypercalciuria in inducing calcium nephrolithiasis by promoting the CaOx supersaturation in urine [25]. It occurs as a result of dietary intake of oxalate rich foods of spinach, rhubarb, beetroot, Almond, nuts, etc. Hyperuricosuria, as a result of high dietary intake of protein can attribute CaOx uroliths by the heterogeneous nucleation of uric acid [26].

Struvite stones

These are also called as infectious stones, as a consequence of persistent urease producing bacterial infections. Generally these urease infections are caused by certain species of bacteria like *E. coli, P. mirabilus, Pseudomonas species, Staphylococcal species and Ureaplasma urealyticum* [27]. By secreting urease enzyme, these bacterial species hydrolyses the urea to carbon dioxide and ammonia which can raise the urinary pH to favor the struvite stones formation [28]. Infectious stones induced by these bacterial infections are caused by the urinary tract obstructions due to ureteropelvic junction stenosis, urinary catheters, the neurogenic bladder dysfunctioning, vesical ureteral reflux, medullary sponge kidney and distal renal tubular acidosis [29, 30].

Uric acid stones

Uric acid stones are clinically evident when there was increased hyperuricosuria, acidic urine and reduced volume of urine. Indeed the hyperuricosuria along with the aciduria clinically manifests the uric acid stones significantly. While the elevated levels of uric acid within normal pH can be tolerated. But hyperuricosuria seem to be a sole cause for uric acid uroliths in rare conditions [31]. The common etiological factors in inducing the uric acid uroliths are dietary intake of excess protein food, gout and recurrent monoarthritis along with acidic urine [32]. In addition, high body-mass index, type 2 diabetes and glucose intolerance are most commonly seen in patients of uric acid uroliths [33-35].

In particularly obesity and type 2 diabetes conditions, impaired renal ammonium excretion and increased net acid production resulting in aciduria can favor the uric acid uroliths formation when it is associated with hyperuricosuria. The other causative factors like chronic diarrhea, gastroenterostomy, exercise induced lactic acidosis and high consumption of animal protein can predispose to acidic urine. Reduced urinary volume occurs as a result of chronic diarrhea, excessive perspiration and intestinal ostomies can acts as contributing factors in attributing the uric acid uroliths. The congenital enzymatic deficiencies, uricosuric agents, gout, myeloproliferative disorders, hemolytic anaemia and chemotherapy induced tumor lysis acts as the risk factors of hyperuricosuria induced uric acid stones [36, 37].

Cystine stones

It constitutes of about only least amount in all types of stones which occurs in individuals having cystinuria, an autosomal recessive disease which affects proximal tubular absorption of cystine. The solubility of cystine is about 243mg/L in normal urinary pH, while the solubility greatly increased by increasing the urinary pH. Moreover cystine being as a poorly soluble amino acid form, it tends to form cystine stones more at lower urinary acidic pH [38]. It is also occurred as an autosomal recessive disorder of ornithine, arginine and lysine [39]. It affects about 1 in 20,000 individuals especially at an age of 20-30 years [40]. They are presented as staghorn stones which are multiple and radio-opaque.

Drug induced stones

These constitute the rare forms of stones which are drug induced forms that results from various drugs like indanavir, triamterine, flouroquinolones, primidone, tetracyclines, magnesium trisilicate and sulfonamides. In addition to this, other drugs like calcitriol, corticosteroids, furosemide and acidifiers can predispose the individual to hypercalciuria induced calcium uroliths. In other cases like ascorbic acid and allopurinol therapy, there exist implications of hyperoxaluria and hyperxanthuria induced lithogenesis [4]. Topiramate, a new anti epileptic drug also implicate the calcium uroliths by its renal tubular acidosis induced by its carbonic anhydrase enzyme [41]. HIV-positive patients are more prone to develop these drugs induced stones when they are treated with lithogenic drugs like indinavir and sulfamides (sulfamethoxazole and sulfadiazine) [42].

2, 8-Dihydroxyadenine stones

Rare form of stones that results from a very rare form of adenine phosphoribosyl-transferase (APRT) deficiency inherited renal stone disease, progressively ends with renal failure. In APRT deficiency condition, it accumulates large amounts of adenine which then metabolized to nephrotoxic 2, 8-dihydroxyadenine by xanthine oxidase enzyme. Since it is a life threatening, the early diagnosis and treatment with allopurinol is needed [4].

Risk factors

The potential risk factors in a susceptible individual for inducing the stone formation are characterized as follows:

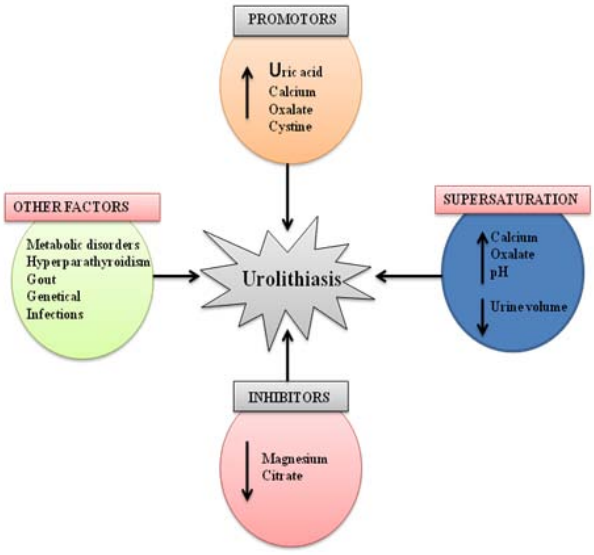

Fig. 1: Risk factors in inducing the stone formation.

- Metabolic disorders like hypercalciuria, hyperuricosuria, hypercalcaemia, hypocitraturia, hypomagnesuria.

- Gout.
- Genetical.
- Drug induced.
- Hyperparathyroidism.
- Dehydration.
- Hot climates.
- Anatomical abnormalities.
- Increased urinary pH.
- Lower urinary volume.
- Infections.
- Hypertension.
- Metabolic acidosis.

Genetics of urolithiasis

In a multifactorial etiopathogenesis, genetic factors are known to play a significant role. Several studies were intended to discover the genetic linkage associated with this disease had succeeded in identifying the genes and their genetic polymorphism. The vitamin D receptor (VDR) gene confined to a region of chromosome 12 is greatly concerned with the functional aspects of calcium metabolism. But when the genetic polymorphism of FokI and TaqI VDR gene can results in hypercalciuria induced familial idiopathic CaOx urolithiasis [43, 44, 45]. Interleukin-1, pro-inflammatory and immunopathological cytokine also had an important role in inducing the bone resorption. Thus, induced bone resorption can results in idiopathic hypercalciuria which predisposes to calcium uroliths. Thus a genetic polymorphism of interleukin-1β (IL-1β) and interleukin-1 receptor antagonist (IL-1Ra) genes located on chromosome 2 are greatly concerned in idiopathic hypercalciuria implicated calcium uroliths [46, 47]. Calcitonin (CT), a polypeptide hormone of the thyroid gland is functionally associated with the inhibition of bone reabsorption thereby promoting the urinary calcium excretion. Therefore calcitonin receptor (CTR) gene located on chromosome 7 which is associated with calcium metabolism is found to be immensely associated with CaOx urolithiasis by its genetic polymorphism [48, 49].

Urokinase, a proteolytic enzyme involving in the fibrinolytic pathway also involved in the prevention of stone growth by its proteinase activity on the matrix protein which can influence the stone formation. However, a change in the protein structure can acts as a matrix protein in inducing the CaOx urolithiasis by its genetic polymorphism over the urokinase gene of 3′ untranslated region (3′-UTR) located in chromosome 10 [50, 51, 52, 53]. As the cellular injury along with the damage of cellular integrity is evident in stone formation, E-cadherin (CDH-1) which is an epithelial junction protein responsible for conserving the cellular integrity, epithelial cell development and organization is need to be considered in evaluating the etiological factor of stone formation. There exists a strong relationship with the CDH-1 gene (located on chromosome 16) 3′ untranslated region (3′-UTR) polymorphism in CaOx urolithiasis [54, 55]. Vascular endothelial growth factor (VEGF), a glycoprotein responsible for neovascularisation also associated with the CaOx urolithiasis by its VEGF gene polymorphism [56]. As the urinary stones are generally complied with the cell death, cyclin dependant kinase inhibitor that monitors the cell cycle is need to be considered in describing the genetic susceptibility of urolithiasis [57]. One such inhibitor is p21 protein, a downstream protein of p51 that inhibits G1/S phase of life cycle. The arginine form of p21 gene had less marginal susceptibility to CaOx urolithiasis [58]. The other genetic mutations of chloride channel (CLCN5) gene located on X chromosome generally linked with disorders of Dent's disease, X-linked recessive nephrolithiasis type I X-linked recessive hypophosphatemic rickets which are characterized by increased excretion of calcium that predisposes the patient to calcium uroliths formation [59].

Cystinuria induced urolithiasis is evident from the genetic mutations of genes responsible for the transportation of cystine from interstitial epithelium and proximal renal tubule. Genetic mutations of SLC3A1 and SLC7A9 genes are the known causes for type A and type B cystinuria which can predispose the cystinuria patients to cystine uroliths [60].

Table 1: Genetics of urolithiasis

Gene	Defect	Urolithiatic condition
FokI and TaqI VDR gene	Genetic polymorphism	Familial idiopathic CaOx urolithiasis
IL-1β receptor gene	Genetic polymorphism	Idiopathic hypercalciuria induced calcium uroliths
IL-1Ra gene	Genetic polymorphism	Idiopathic hypercalciuria induced calcium uroliths
CTR gene	Genetic polymorphism	Calcium Oxalate urolithiasis
Urokinase gene	Genetic polymorphism	Calcium Oxalate urolithiasis
CDH-1 gene	Genetic polymorphism	Calcium Oxalate urolithiasis
p21 gene	Arginine form of p21	Calcium Oxalate urolithiasis
CLCN5 gene	X-linked recessive allele	Hypophosphatemic rickets induced calcium uroliths
SLC3A1 gene	Genetic mutation	Type A cystinuria induced cystine uroliths
SLC7A9 gene	Genetic mutation	Type B cystinuria induced cystine uroliths
HPRT gene	Genetic mutation	Uric acid uroliths
PRPP gene	Genetic mutation	Uric acid uroliths
G6Pase gene	Genetic mutation	Uric acid uroliths
APRT gene	Autosomal recessive allele	2, 8 dihydroxyadenine induced urolithiasis

Genetic mutations of hypoxanthine guanine phosphoribosyltransferase (HPRT) gene (Lesch-Nyhan syndrome), Phosphoribosyl-pyrophosphate synthetase (PRPP) gene (Phosphoribosyl-pyrophosphate synthetase super activity) and Glucose 6 phosphatase (G6Pase) gene (Glycogen storage disease type 1) can predispose the patient to uric acid uroliths [59]. In autosomal recessive fashion, the genetic defect of APRT gene located on chromosome 16 can ultimately lead to 2, 8 dihydroxyadenine induced urolithiasis [61]. While several other studies also found out the genetic polymorphism of androgen and estrogen receptor genes involvement in the urolithiasis especially in men [62].

Pathophysiology

The exact cascade of pathophysiological events in the pathogenesis of urolithiasis is still remained to be unclear. In general, the pathophysiology of urolithiasis largely depends on the phenotype of stone formed in the urinary tract. In CaOx urolithiasis, the nucleation of CaOx resulted from decreased solubility with the increase in uric acid levels [63, 64]. In addition to this, Randall plaques that are resulted from precipitation and accumulation of CaOx in the basement membrane and sub epithelial space of renal papillae that eventually lead to the calculi induction [65]. The other mechanism to adopt the pathogenesis of CaOx stone formation, when there is an imbalance in the promoters and inhibitors of crystallization compounds. However, the drug induced CaOx urolithiasis cannot be ruled out by the drugs like loop diuretics, acetazolamide, antacids, glucocorticoids and theophylline.

In particularly considering the crystal nucleation and aggregation aspects of CaOx urolithiasis, several theories like epitaxy, matrix and inhibitor theories have been proposed in order to hypothesize the exact events of crystal nucleation and aggregation of CaOx. Epitaxy theory proposed the heterogeneous nucleation of CaOxcan be induced by the supersaturation of sodium urate and uric acid crystals in urine epitaxially. Matrix theory assumes the role of some urinary macromolecules in the CaOx crystal nucleation and growth by acting as a matrix for stone induction. In inhibitor theory, the role of inhibitor substances like citrate, pyrophosphate, magnesium in inhibiting the nucleation and growth of CaOx has been described [66]. Stress induced secretion of vasopressin and Adrenocorticotropic hormone (ACTH) results in hypertonic urine and elevated serum calcium levels which explain the mechanism of stress as a pathophysiological factor in inducing the CaOx urolithiasis [67].

In struvite stone pathogenesis, the increased pH due to microbial conversion of urea to carbon dioxide and ammonia tends to be the key pathological event for the crystallization of struvite stones. The other non urease microbes like *E. coli* debated that the increased matrix production favors the adherence of struvite crystals at the site of calculi induction [12]. In uric acid stones, the pathological mechanisms seem to be very diverse in nature. It may be idiopathic, acquired and congenital mechanisms in inducing the pathogenesis. Clinically it was evident that the hyper uricosuria in uric acid stones pathogenesis that resulted from the high intake purine rich diet and drugs (losarton, probenecid) that impair the absorption of reabsorption of uric acid. More over to this, hyper uricosuria lowered the pH (<5.5) which favors the induction of uric acid nephrolithiasis. However, idiopathically there was uric acid nephrolithiasis even with normal urinary uric acid and pH levels, considered as idiopathic uric acid nephrolithiasis (IUAN) [68, 69]. In cystine stones, predominantly the autosomal recessive genetical abnormality of proximal tubule impairs the reabsorption of cystine by APRT deficiency. Thus developed cystinuria becomes a predisposing factor for cystine nephrolithiasis.

Despite of the phenotypic nature of uroliths, several other theories have been employed for the detailing the physiochemical process of stone formation irrespective of its phenotype nature. These are categorized as intracellular/interstitial theory and extracellular/intratubular theory. The intracellular theory primarily depicts the key pathological implicating event of renal lesion which potentiates the nucleation step of nephrolithiasis. The extracellular theory stated the importance of other intratubular factors in implicating the pathogenesis is presence of matrix components, alterations in urinary pH, alterations in urinary composition, lithogenic diet along with trigger factors like dehydration and rate of growth in crystallization [70].

In addition to the above stated multifactorial pathogenesis, the role of several proteins in the pathogenesis cannot be ruled out. Nephrocalcin from renal tubular origin inhibits the CaOx crystallization by impairing the aggregation of CaOx crystals. Inhibitory effect on the lithogenesis was reported with Tamm-Horsfall protein (THP) of the thick ascending limb of loop of Henle and early distal convoluted tubular origin. It was reported that the crystal matrix protein of the thick ascending limb of loop of Henle and early distal convoluted tubular origin can retard the CaOx crystallization [71]. Several studies also demonstrated that the damaged cellular membrane, damaged proximal tubules or loop of Henle, injured urothelium after treatment with nephrotoxic agents such as gentamicin, induce nucleation of CaOx crystals at a lower supersaturation [72].

In conclusion with the above stated possible pathophysiological mechanisms, the pathophysiology of urolithiasis is evident from multifactorial complex cascade of pathogenic events.

Clinical presentation

The majority of clinical symptoms seem to be asymptomatic and they are noticed in investigations of other conditions.

- Sudden renal colic or ureteric colic.
- Radiating pain towards the groin and testicular region.
- Intermittent biliary or intestinal colic.
- Dysuria.
- Oliguria.
- Haematuria
- Urinary retention.
- Rigors and fever.
- Nausea and vomiting.
- Pyonephrosis [73].

Diagnosis

General diagnosis

- Physical examination of any tenderness at the affected site.
- Electrolyte and urea level analysis in urine
- Dipstick analysis for the detection of Haematuria.
- pH of the urine.

- When pH > 7.5 in urine indicates the infection (infection stones).

- When pH <5.5 in urine indicates the presence of uric acid stones [73].

- Haematuria.
- Renal and biliary colic.
- Investigating the X-ray of urinary tract for the presence of stones.

Differential diagnosis [73]

- Urologically

- Pyelonephritis.

- Stricture.

- Renal infarction.

- Retroperitoneal fibrosis.

- Testicular torsion.

- Tumor.

- Necrosis of renal papillae.

- Non-urologically

- Biliary colic.

- Abdominal aortic aneurysm.

- Appendicitis.

- Ovarian cyst torsion.

- Fallopian tube Infection and inflammation, clinically called as salpingitis.

- Pouches in colonic region which leads to a painful condition of diverticulitis.

Clinical management

Management of acute stones

Acute therapy of nephrolithiasis mainly intended to manage pain, forcing the diuresis and hydration. In acute conditions non steroidal and narcotic analgesics seems to be prominent therapeutic choice in the management of pain. In conditions where the opoids are contraindicated, a combination of dextropropoxyphene and paracetamol is used in acute setting [71]. But the cyclo oxygenase inhibitors should be avoided in renal insufficiency conditions [74]. Elimination of the stones can be managed by inducing diuresis very

effectively by the increased fluid intake of at least >2L daily. But forced diuresis induced worsening pain, ureteral pain and hydronephrosis need to be monitored very carefully.

Management of Chronic stones

A. Specific measures

In calcium stones-hypercalciuria, thiazide diuretics administration can enhance the tubular reabsorption of calcium and ablate the intestinal calcium absorption [71]. In recurrent idiopathic conditions of calcium stones-hypercalciuria, indapamide stood to be as a best choice for its management [75]. Alternative to this, the usage of potassium sparing diuretics can spare the potassium in order to replace the phosphorous loss. Potassium citrate supplementation also acts as an additive therapy in order to inhibit the crystal aggregation by the citrate excretion. In calcium stones-hyperoxaluria, the effective management includes fluid intake, alkalinisation of urine and restriction over the intake of foods rich with high oxalate content. Clinically the therapeutic choice is the combinational therapy using calcium carbonate along with potassium citrate/ along with magnesium gluconate [76]. In calcium stones-hypocitraturia, the pathological intervention can be made by the supplementation with potassium citrate. This supplementation effectively replaces the loss citrate levels in order to form a complex with calcium to eliminate it [71]. In the management of calcium stones-hyperuricosuria, the treatment should include the restriction over the dietary purine intake and increased water uptake along with allopurinol supplementation [77].

Table 2: Herbal treatment of urolithiasis

Plant	Part used	Screening model	Reference
Achyranthes aspera (Amaranthaceae)	Roots	*In vitro* (Cell lines)	[89]
	Roots	*In vivo*	[90]
Aerva lanata (Amaranthaceae)	Leaves	*In vivo*	[91]
	Aerial parts	*In vivo*	[92]
Alcea rosea (Malvaceae)	Root	*In vivo*	[93]
Ammi visnaga (Apiaceae)	seeds	*In vivo*	[94]
Berberis vulgaris (Beriberidaceae)	Root	*In vivo*	[95]
Berginia ligulata (Saxifragaceae)	Rhizomes	*In vitro* and *in vivo*	[96]
Boerhavia diffusa (Nyctaginaceae)	Whole plant	*In vitro*	[97]
Bombax cieba (Malvaceae)	Fruit	*In vivo*	[98]
Bryophyllum pinnatum (Crassulaceae)	Whole plant	*In vitro*	[97]
Camellia sinensis (Threaceae)	Leaves	*In vivo*	[99]
Citrus limon (Rutaceae)	Juice	*In vitro* and *in vivo*	[100]
		In vivo	[101]
Citrus paradisa (Rutaceae)	Juice	*In vivo*	[102]
		Clinical trials	[103]
Commiphora wightii (Burseraceae)	Root	*In vitro*	[104]
	Herb	*In vitro*	[105]
Costus spiralis (Costaceae)	Whole plant	*In vivo*	[106]
Crataeva nurvala (Capparaceae)	Bark	*In vivo*	[107]
Cynodon dactylon (Poaceae)	Roots	*In vivo*	[108]
Herniaria hirsuta (Caryophyllaceae)	Herb	*In vitro*	[109]
	Herb	*In vivo*	[110]
	Aerial parts	*In vitro* and *in vivo*	[111]
Hibiscus sabdariffa (Malvaceae)	Calyces	*In vivo*	[112]
Lagenaria siceraria (Cucurbitaceae)	Fruit	*In vivo*	[113]
Leea macrophylla (Vitaceae)	Whole plant	*In vivo*	[114]
Moringa oleifera (Moringaceae)	Roots	*In vivo*	[7]
Musa paradisiaca (Musaceae)	Stem	*In vivo*	[115]
Nigella sativa (Rananculaceae)	Seeds	*In vivo*	[116]
Origanum vulgare (Lamiaceae)	Aerial parts	*In vitro* and *in vivo*	[117]
Orthosiphon grandiflorum (Lamiaceae)	Leaves	*In vivo*	[118]
Paronychia argentea (Caryophyllaceae)	Aerial parts	*In vivo*	[2]
Petroselinum sativum (Apiaceae)	Aerial parts and roots	*In vivo*	[119]
Phyllanthus niruri (Phyllanthaceae)	Whole plant	*In vivo*	[120]
	Whole plant	*In vivo*	[121]
	Whole plant	Clinical trials	[122]
Pinus eldarica (Pinaceae)	Fruit	*In vivo*	[123]
Plectranthus amboinicus (Lamiaceae)	Leaves	*In vivo*	[124]
Punica granatum (Lythraceae)	Juice/seeds	*In vivo*	[125]
	Fruits	*In vivo*	[126]
Quercus salicina (Fagaceae)	Leaves and branches	*In vitro* (cell lines)	[127]
	Leaves and twigs	*In vivo*	[128]
Raphanus sativus (Brassicaceae)	Tubercles	*In vivo*	[129]
Rotula aquatica (Boraginaceae)	Roots	*In vitro*	[104]
Rubia cordifolia (Rubiaceae)	Roots	*In vivo*	[1]
Salvadora persica (Salvadoraceae)	Leaves	*In vivo*	[130]
Sesbania grandiflora (Fabaceae)	Twigs	*In vivo*	[131]
Solanum xanthocarpum (Solanaceae)	Fruits	*In vivo*	[132]
Terminalia arjuna (Combretaceae)	Bark	*In vitro*	[133]
Terminalia chebula (Combretaceae)	Fruit	*In vitro* (Cell lines)	[134]
Tribulus terrestris (Zygophyllaceae)	Fruit	*In vivo*	[135]
	Fruit	*In vivo*	[136]
	Fruit	*In vitro*(Cell lines)	[137]
Trigonella foenum-graceum (Fabaceae)	Seeds	*In vivo*	[138]
Vaccinium oxycoccus (Ericaceae)	Juice	Clinical trials	[139]

The principles of treatment for uric acid stones include effective alkalinisation of urine to 6.5 (pH), dietary restriction of purine rich foods and adequate water intake. Treatment options include potassium citrate and acetazolamide for effective alkalinisation; and administration of allopurinol and febuxostat to minimize the uric acid synthesis [78]. As the struvite stones are the infectious stones manifested by the bacterial infections, the antibiotic therapy should be recommended for a period of at least three months [30]. In specifically, the urease inhibition is preferred in certain cases of patients with acetohydroxamic acid or flurofamide [79, 80]. Where as in the cystine stones management, the approach is aimed at alkalinisation of urine by potassium citrate to pH >7.4, adequate water intake aimed to be more than 4L /day and administration of d-pencillamine [81]. The other treatment options include the therapy of tiopronin (α–mercaptopropionyl glycine), ascorbic acid and angiotensin converting enzyme (ACE) inhibitors [82, 83]. While the treatment option of captopril, an ACE inhibitor is still remains to be unclear. But it is used when the tiopronin therapy is unsuccessful [84].

B. Surgical procedures

Surgical procedures are adopted when the conventional system of therapy fails to eliminate the uroliths. Moreover it became an effective management application when the stones are larger than 5 mm in size and failed to pass by the conventional system of medicine [85]. Surgical procedures like Extracorporeal shock wave lithotripsy (ESWL), Percutaneous nephrolithotomy (PCNL), Ureteroscopy and open surgery are employed in the surgical management of nephrolithiasis. While laparoscopy equipment and instrumentation is under clinical consideration to evolve as a treatment option.

- In ESWL shock waves are used to break the stones which then they pass spontaneously.
- In PCNL, nephroscope is employed for the removal of stones especially for larger stones (>2 cm), cystine and Staghorn calculi.
- A laser beam is used in ureteroscope for the disintegration of stones. It is ideally best opted for the fragmentation of distal ureteral stones.
- Open surgery held to an effective choice when there is treatment failure of above surgical interventions, co-morbid with the other diseased condition and multiple stones.

The success rate of these surgical procedures greatly depends on the location, stone burden, composition and hardness of the calculi. But these surgical interventions are very expensive with high recurrence rate [86]. Despite of their highly targeted intervention, they were limited by renal damage, renal tissue necrosis and damage to the surrounding organs [87].

Prevention

The following measures are opted to be best suitable preventive measures in the management of urolithiasis.

- Increase uptake of water up to 2L daily.
- Maximizing the urinary output.
- Limiting the use of drugs that induce uroliths.
- Minimizing the intake of animal protein.
- Low intake of sodium.
- Lowering the dietary intake of purine and oxalate rich food.
- Limitation of dietary intake of calcium.
- Monitoring the body weight gain [71].

Herbal therapy

In the medical management of urolithiasis, phytotherapy opted to be an alternative or adjunctive therapy. Based on *in vitro, in vivo* and clinical studies, it was revealed that these phytotherapeutic agents acts by diuretic, antioxidant, increasing urinary citrate, antimicrobial, and other possible mechanisms [88]. The following plants are claimed to possess the antiurolithiatic activity.

CONCLUSION

The clinical management of urolithiasis is still remained to be unclear with the modest understanding of genetics and pathogenesis. Detailing the genetical, pathophysiological and management aspects will provide a treasure trove for the clinicians to manage urolithiasis very effectively. As the conventional therapy fails to meet the demands of management of urolithiasis, herbal therapy opted to be an alternative or adjunctive choice in its management. Hence this review also summarizes the potent herbal litholytic agents. But further extensive studies are needed in order to understand the exact cascade of pathogenesis, genetics and clinical therapy of urolithiasis.

CONFLICT OF INTERESTS

Declared None

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