Natural Products in treatment of Urolithiasis

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Abstract

Urolithiasis, also known as urinary lithiasis or nephrolithiasis; is formation of stony concretions (calculi) or formation of mineral salts in the body, most often found in the gall bladder or urinary system. Formation of kidney stone is a complex event which includes supersaturation, aggregation, nucleation, development and withholding of calcium-containing stones within the kidneys or bladder. Around 75-90% cases of urolithiasis have calcium oxalate (monohydrate and dehydrate) and calcium phosphate which results in formation of hard calculi. It is estimated that 12% of global population experiences renal stone disease in which 70-80% are male and 47-60% are female. Risk Factors like dietary habit i.e. less fluid intake, climatic factor i.e. more exposure to hot & sunshine and diseases like metabolic syndrome contribute to renal stone formation are the causative factors for it. The patients suffering from urolithiasis is mainly recommended to change their lifestyle, however; also suggested medication for pain until the stones passes by its own. Recent studies confirm that herbs are very helpful in the prevention and treatment of urinary stones. Most of the plant based therapy shows its effective action on various stages of pathophysiology of stone formation. New diagnostic methods along with various treatment approaches helps in removing stones, thereby; improve management of urolithiasis.

Keywords

Urolithiasis; nephrolithiasis; mineral salts; medicinal herbs.

Introduction

Urolithiasis (formation of stones in urinary bladder) and nephrolithiasis (formation of stones in kidney) is the major occurring diseases in US [1]. Stones or calculi in the urinary tract which causes pain & bleeding, and may lead to further secondary infection [2]. It is associated with various lifestyle factors like less intake of fluid or more exposure to sun or dietary intake or some genetic or metabolic disorder [3]. Calculi are composed of mineral salts like calcium oxalate, magnesium ammonium phosphate, uric acid or cystine in the body organs that's further cause severe pain [4].

Calculi in the renal can be divided into two groups: one is tissue attached and another is unattached. COM renal calculi can be used to integrate attached calculi as it carries detectable site to which renal papilla is attached and also consist of core near attached site and use to concentricate radically in the form of peripheral layers. Renal cavities is the site of development of unattached calculi and does not carry detectable site to papilla and can exhibit diverse composition and also can exhibit diverse composition and structures [5].

Renal stones can vary in size from micrometers to centimeters in diameter. The options for the management of urolithiasis relays on the size & site of the stone where it has been formed. The following strategies may be adopted for prevention and care of urolithiasis [6]

- ✓ Conservative treatment
- ✓ Extracorporeal shock-wave lithotripsy (ESWL)
- ✓ Ureterorenoscopy (URS)
- ✓ Percutaneous nephrolithotomy (PCNL)
- ✓ Laparoscopy
- ✓ Open surgery

Risk factors

Risk factors related with the formation of urinary stones may vary with age (30–60 years and decreased afterwards) and gender (female to male ratio ranging from 5 to 1.3). However, ethnic and familial backgrounds are also one of the major causes of urolithiasis. Along with, climate and environmental factors such as prevalence and incidence of urolithiasis in summer and autumn are higher than that in spring and winter, lifestyle, dietary habits (precursors of oxalate i.e glycine, hydroxyproline and vitamin C in foods), occupation and level of educations are other causative agents [7].

Epidemiology of urolithiasis

Kidney stone is one of the most obiquitous urologic diseases in Asia. Due to various changes in economics and social lifestyle, the incidence and prevalence varies from country to country [8]. According to data obtained from the Urological Diseases in America Project (UDMP), the total cost involvement in treatment of urolithiasis in the US in the year 2000 was found to be $5.3 billion [9]. The **Figure 1** represents the prevalence of urolithiasis among various countries.

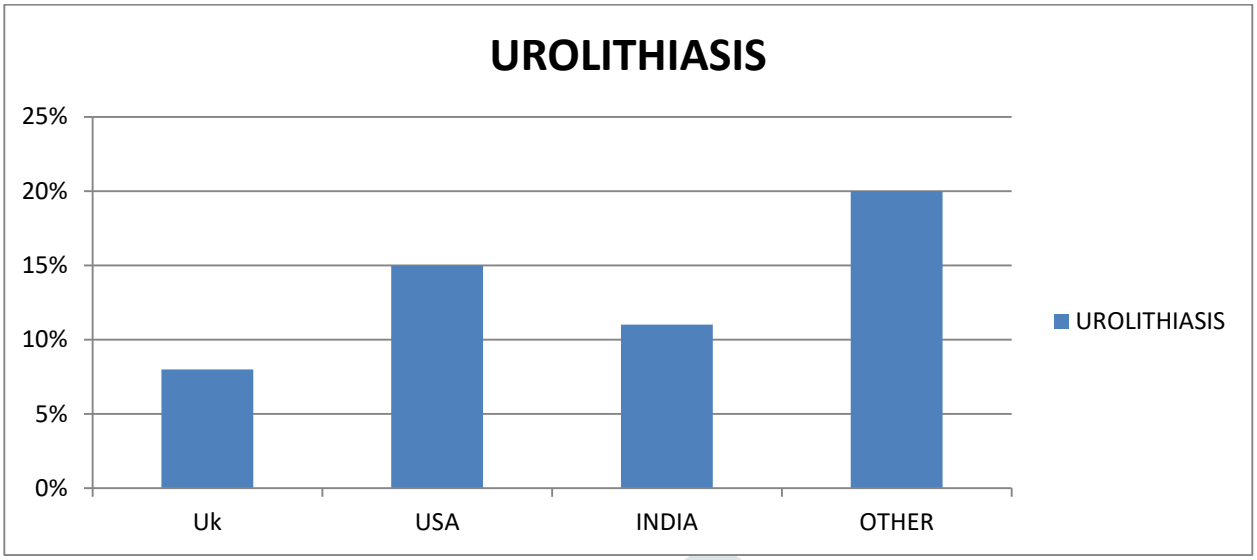

Figure 1 : Prevalence of urolithiasis

Pathophysiology of urolithiasis

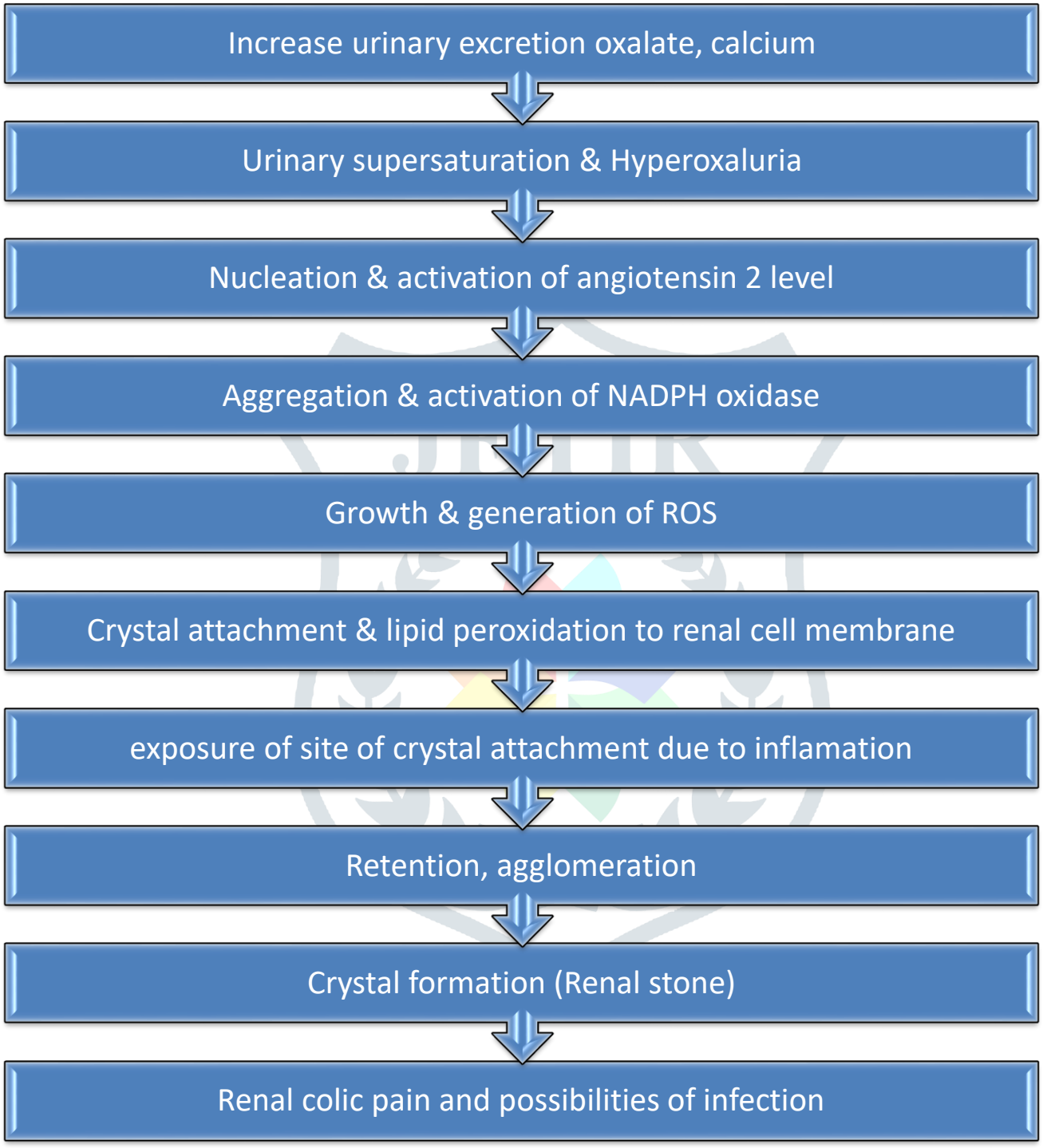

Figure 2: Pathophysiology of Urolithiasis

Conventional agents used in urolithiasis

The goal of currently available antiurolithiatic drugs is to passage of calculi by increasing urine volume, balance the inhibitory and enhancing factors involved in crystallization in urine and regulation of oxalate

metabolism. The various classes of drugs used for treatment of urolithiasis along with their class and complications have been summarized in the **Table 1**.

Table 1: Conventional treatment of urolithiasis and their complications

Pharmacological class	Drugs	Side Effects	References
Calcium-channel blocker	nifidipine	dizziness, headache	[10]
α_1-Selective α blocker	tamsulosin, terazosin, doxazosin	dizziness, hypotension, headache, and ejaculatory dysfunction	[11]
Corticosteroid	deflazacort	diabetes, weight gain, osteoporosis, glucoma	[12]
Glucocorticoid	methylprednisolone	unwanted hair growth, vertigo, mood swings, increase cholesterol	[13]
Thiazides	trichlormethiazide	hyperglycemia, hyperlipidemia, glucose intolerance	[14]

Herbal products

Herbal products are used for various disorders worldwide. Around 65% of the global populations have access to local herbal plant knowledge system. Herbal products are mainly plant secondary metabolites such as flavonoids, saponin, tannin, alkaloid, steroid etc. Various plant extracts have been recommended as a safer remedy in treatment of urolithiasis and contains diverse types of biologically active principles such as khellin, kaempherol, bergenin, afzelechin, quercetin, betulin and lupeol which shows its action by inhibition of crystallization activity and its growth or may be diuretic in nature. The other possible mechanism involved may be oxalate metabolism regulation, improvement of antioxidants status in renal tissue and various symptoms related to urolithiasis.

Rutin

Rutin; *Herniaria hirsute* (Caryophyllaceae), a natural herbal source which is commonly used in Morocco is reported to be used to treat kidney stones and act by progressively decreases the adhesion of calcium oxalate crystals to kidney cells by coating themselves at the surface of crystal. It also decreases the size of crystals, therefore helps to eliminate their urinary route. It has been further reported that The extract of *H. hirsute* also helps to break and prevent the retension of crystals thus shows its antilithiatic potential [15].

Khellin

Khellin, a chemical constituent obtained from *A. visnaga*, is used as a smooth muscle relaxant and found to have significant effects on urinary citrate, smooth muscle relaxation & diueresis. Khellin also act as antiurolithatic agent by interfering with the citrate metabolism [16].

Kaempherol

Kaempherol; (*Tribulus terrestris;* Zygophyllaceae), known by names *Gokshur* or *Gokharu* or puncture vine has been widely used in both the Chinese as well as Indian systems of medicine for treatment of numerous diseases. During the process of oxalate synthesis, glycolate oxidase (GOX) is required for converting glycolate to glycolate by the process of oxidation and then to oxalate for which GOX is the principle enzyme. The antiurolithic activity of *T. terrestris* is attributed to its GOX inhibition [17]. Recent studies shows that *T. terrestris* has the potential to normalize the peroxidant status and gene expression of antioxidant enzymes [18].

Bergenin & Afzelechin

Bergenin & Afzelechin are the active constituents of plant *Bergenia ligulata.* Various *in vitro* and *in vivo* models demonstrated that calcium oxalate aggregation and crystal formation of metastable solutions can be inhibited by alcoholic extract of *B. ligulata*. It further showed anti-oxidant potential against 1-diphenyl-2-picrylhydrazyl free radical and lipid peroxidation [19].

Quercetin

Quercetin; a chemical obtained from *Aerva lanata* (L); *Pashanabheda*, (Amaranthaceae), have been explored for its medicinal importance such as antiurolithiatic and diuretic. The other phytoconstituents present in *A.*

lanata includes alkaloids (ervine, methylervine, ervolanine, and aervolanine), flavanoids (kaempferol, quercetin, isorhamnetin, persinol, persinosides A & B), betulin, lupeol acetate benzoic acid, β-sitosteryl acetate and tannic acid [20]. The aqueous suspension of *A. lanata* is reported to possess potential of lowering enzymes required for oxalate synthesis, and further, causes the down-regulation of markers involved in crystal deposition in kidney [21].

Pyroglutaminylglutamine

Pyroglutaminylglutamin, obtained from hydroalcoholic extract of *Dolichos biflorus* is known from traditional times as medicinal plant which belongs from Fabaceae family, mainly possess pharmacological activities used as tonic, astringent, diuretic, and is also recommended in asthma, bronchitis, urinary discharges, hiccoughs, ozoena, heart trouble and other diseases of brain[22]. From different extracts of *D. biflorus* seeds aqueous fraction show highest dissolution calcium oxalate crystals [23]. It further reduces formation and deposition of the CaC_2O_4 crystal and is also reported to be an effective remedy in reducing the lipid peroxidation and therefore; helps to restore activity of the antioxidant enzymes [24].

Rutin

In the indigenous system of medicine, rutin (*Raphanus sativus*; Family -Brassicaceae) is demonstrated to possess efficacy in treatment and effective removal of urinary stones. Ritin act by causing a significant decrease in the weight of kidney stones and also increases increase in the urine volume. It lowers the urinary concentrations of constituents which form stones. The recovery of renal damage exhibited by rutin may be due to inhibition of lipid peroxidation [25].

Lupeol

Lupeol; derived from *Crataeva nurvala* (Capparaceae) is a high-value medicinal tree reported in traditional systems of medicine in the treatment of urinary disorders [26]. The mechanism of action includes the reduction in glycolate oxidase which is an oxalate synthesizing enzyme in liver and renal oxalate crystallization with elevated urinary magnesium [27].

Ecdysterone

Ecdysterone obtained from *Achyranthus Aspera*.(family: Amaranthaceae) commonly called as Putkhanda and Prickly chaff flower used in folk medicine for the treatment of urolithiasis having phytochemicals: 4-

methoxyheptatriacont-1-en10-ol & tetracontanol -2. The seed oil contains fatty acids such as lauric, myristic, palmitic, stearic, arachidic, behenic and linoleic acid [28]. The ethanolic extract of its leaves & aqueous extract of its roots were found to inhibit nucleation and growth of calcium oxalate crystallization and also provided protective effect against oxalate induced renal tubular epithelial cell injury [29].

Phyllanthin

Phyllanthin which is the compound of *Phyllanthus niruri*, popularly known as "stone-breaker" belonging to the family Euphorbiaceae has distribution in various countries and it is used in folk medicine in Brazilian system for patients suffering with urolithiasis. It act by lowering calcium oxalate induced cytotoxicity and further helps to eliminate stone making constituents. The pre-clinical study has proved usefulness of phyllanthin in hyperuricemic rats due to its urosoric activity [30]. The other part of this plant also increases urinary excretion of elements such as magnesium and potassium [31].

β-Sitosterol

β-Sitosterol is a steroidal compound, obtained from *Cynodon dactylon*(Poaceae) and is known for its pharmacological potential. The plant is a rich source of various types of elements and also contains proteins in high amount. C. dactylon possess various biologically active principles such as coumaric acid, sitosterol, syringic acid which is responsible for its biological activities. The plant has been used for treatment of diabetes, uresis, convulsions and nephrolithiasis [32].

Vanillic acid

Vanillic acid **(***Paronychia argentea*, Caryophyllaceae) is an important plant constituent which can be obtained from different genus and is used to treat number of diseases. *P. argentea* has been used as anti-oxidant and also possess xanthine oxidase inhibitory properties [33]. Various *in vitro* and *in vivo* methods have been used to prove anti-oxidant potential of *P. argentea [34]*.

α-Pinene

α-Pinene **(***Trachyspermum ammi*, Apiaceae) commonly known as ajwain is most commonly used as spices in various parts of the country. The fruit of plant is used as stimulant, anti-spasmodic and carminative. Medicinally, it is also used as antilithiasis, abotifacient, diuretic, bronchodilator, anti-tussive agent. It also contains β-pinene, limonene, dillapiole and thymol[35].

Isotrifolin

Isotrifolin is a flavonoidal compound obtained from leaves of *Moringa oliefera* (Moringaceae) and is reported to be used as diuretic, anti-microbial, anti-oxidant and for renal failure. The plant has high nutritional value and is native to India in tropical and subtropical regions of World. The plant also contains other chemical constituents which may be responsible for its biological activities are ferulic acid, gallic acid, ellagic acid, kaempferol[36].

Schaftoside

Schaftoside (*Costus spiralis*, costaceae; is a Brazilian folk medicine used for treatment of hypertension and cardiac hyperexcitability. The phytochemical assessment reveals presence of saponins, flavones, xanthone and tannins [37]. Anti-lithiasis activity of aqueous extract of C. spiralis was evaluated in CaOX monohydrate crystallization system and results have indicated that C. spiralis decreased crystal growth in dose dependent manner, therefore can be used in treatment of lithiasis[38].

The various herbal products and their molecular targets have been depicted in **Table 2.**

Table 2: Herbal products with antiurolithiatic potential along with their molecular targets

Component	Family	Chemical class	Source	MOA	References
Rutin	Caryophyllaceae	Saponins	*Herniaria hirsute*	lower crystal size & up regulation of COD, diuretic	[15]
Khellin	Umbelliferae	furanochrome	*Amni visnaga*	diuresis, inhibit renal epithelial cell damage	[16]
Kaempherol	Zygophyllaceae	flavonoid, glycoside, saponin & alkaloids	*Tribulus terrestris*	COM, decrease oxalate	[17, 18]
Bergenin & Afzelechin	Saxifragaceae	flavan-3-ol	*Bergenia ligulata*	COM, decreases calcium	[19]
Quercetin	Amaranthaceae	pentahydroxyflavone	*Aerva lanata*	Decrease crystal ppt	[20, 21]
Pyroglutaminylglutamine	Fabaceae	polysaccharides	*Dolichos biflorus*	oxalate crystals	[22-24]

Rutin	Brassicaceae	pyrrolidinethione	*Raphanus sativus*	diuretic	[25]
Lupeol	Capparaceae	pentacyclic triterpenoid	*Crataeva nurvala*	down-regulation of oxalate induced renal epithelial cell injury	[26, 27]
Ecdysterone	Amaranthaceae	flavonoids, alkaloids and saponins	*Achyranthus Aspera*	protect renal epithelial damage, diuresis	[28]
Phyllanthin	Euphorbiaceae	triterpenes	*Phyllanthus niruri*	Antispasmodic & relaxant	[30, 31]
Vanillic acid	Caryophyllaceae	methoxy benzoic acid	*Paronychia argentea*	Antioxidant activity	[39]
α-Pinene	Apiaceae		*Trachyspermum ammi*	Reduce renal injury and decrease crystal retention in renal tissues	[40]
Isotrifolin	Moringaceae	Flavonoids	*Moringa oliefera*	Diuretic, improved renal function	[41]
Schaftoside	Costaceae	Flavonol glycosides	*Costus spiralis*	Decrease stone size	[42]

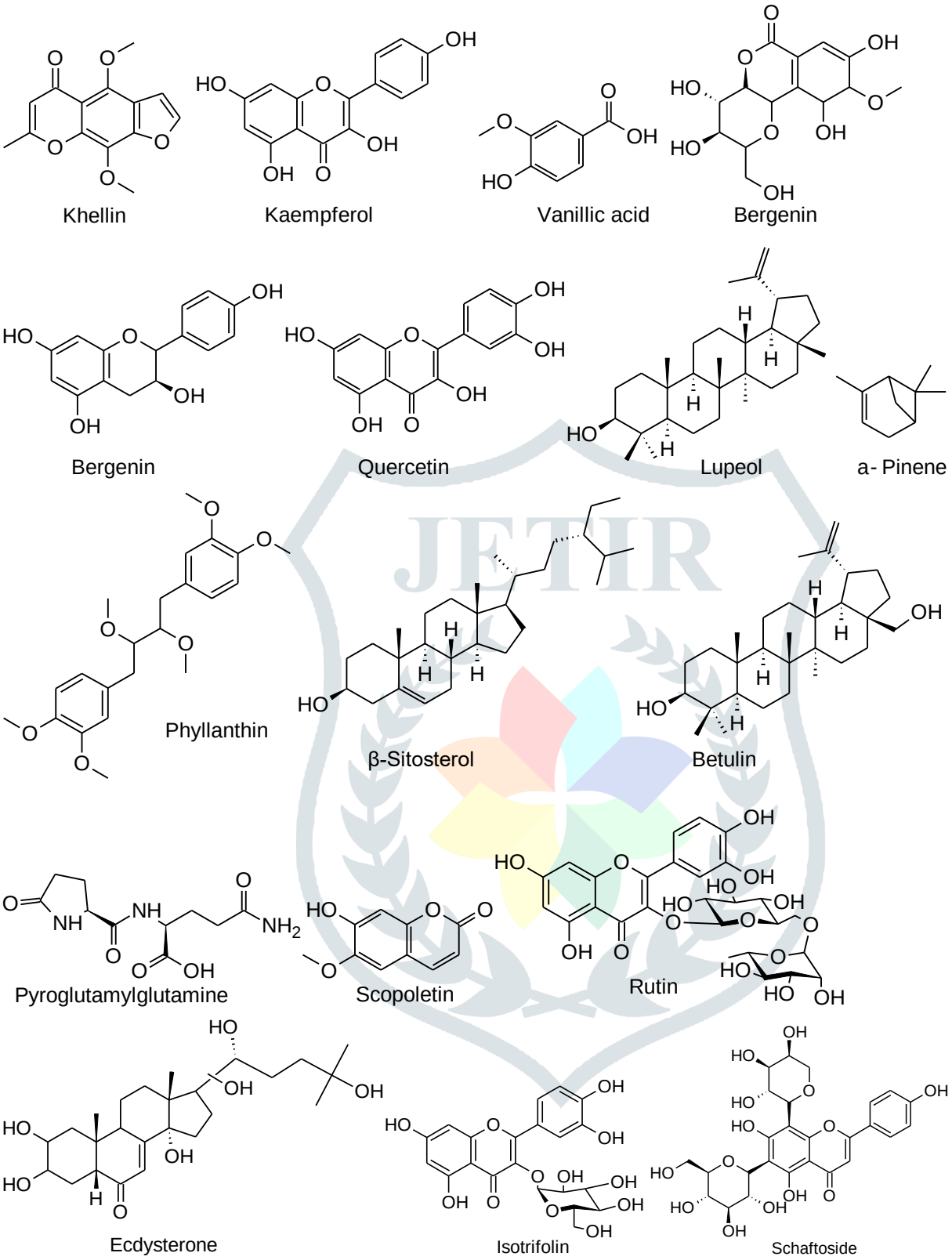

Figure 3: structures of chemical constituents of herbal product

Conclusion

Although many conventional and non-conventional treatments for urolithiasis have been identified, all of these are associated with few limitations such as long-term efficacy, safety, and cost. Herbal medicines relieve symptoms in urolithiasis patients as well as to overcome the drawbacks associated with present treatment

methods. Although a number of herbal medicines are recommended for urolithiasis, further research is required to investigate their safety, efficacy, and potential drug interactions.

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