Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/11515
DOI URL: http://dx.doi.org/10.21474/IJAR01/11515

REVIEW ARTICLE

SYSTEMATIC REVIEW OF MEDICINAL PLANTS AS POTENTIAL ANTI-UROLITHIATIC AGENTS

Diksha Sharma[1], Sushmita Dwivedi[2], Shweta Ranghar[3] and Mamta Baunthiyal[4]

1. M. Tech Scholar, Biotechnology Department, G.B.P.I.E.T Ghurdauri, Pauri Garhwal (246194) Uttarakhand India.
2. Ph.D. Research Scholar, Biotechnology Department, G.B.P.I.E.T Ghurdauri, Pauri Garhwal (246194) Uttarakhand India.
3. Assistant Prof. Biotechnology Department, G.B.P.I.E.T Ghurdauri, Pauri Garhwal (246194) Uttarakhand India.
4. Associate Prof. Biotechnology Department, G.B.P.I.E.T Ghurdauri, Pauri Garhwal (246194) Uttarakhand India.

Manuscript Info

Manuscript History
Received: 15 June 2020
Final Accepted: 17 July 2020
Published: August 2020

Abstract

Chemical compounds from different plant sources and plant products are referred to as 'Phyto-constituents'. These are mainly extracted from the plants either in fresh or dried forms. These bioactive compounds are necessary mediator in the pathophysiology of kidney stones. Unlike allopathic medicine that target only one aspect, most of plant-based therapies have been shown to be effective at different stages of stone pathophysiology. A number of ethno-medicinal plants from different countries are used against urolithiasis. However, the knowledge of health-promoting plants is limited to few elderly people of villages. This review aims to highlight the current trends in research of ethno-medicinal plants possessing potential anti-urolithiatic activity. The results as presented in this review demonstrate the promising role of phyto-extracts in the management and treatment of kidney stones. The study would help investigators to identify lead chemical compounds or formulate herbal products responsible for urolithiatic activity.

Introduction: -

Medicinal plants are an important herbal remedy of indigenous medical systems in India as well as in other countries. These beneficial sources are usually regarded as part of a culture's 'traditional' knowledge. Ethnobotanical plants comprise of complex mixtures of phyto-constituents that may be obtained from any raw or processed part of a plant. Urolithiasis or nephrolithiasis as kidney stones are the third most prevailing disorder of the urinary tract and nearly 80% of these calculi are made up of calcium oxalate (CaOx). Crystal formation, particularly of calcium phosphate (CaP) and CaOx, within the urinary tract is widespread. Humans excrete millions of urinary crystals daily indicating at least transient development of supersaturation. However, few develop kidney stones, probably because either the crystals do not form in the kidneys or the crystals that form do not stay there. The physiochemical mechanisms of stone formation via precipitation, growth, aggregation, and concretion of various lithogenic salts in urine are still in dispute [1]. Crystals can be retained at many sites in the kidneys and undergo the size-enhancing process of growth and aggregation. In order for stones to be formed, not only do crystals need to be retained within the kidney, but they must be located at sites from which crystals can cause ulceration at the papillary surface to form a stone nidus. The most important reason for the failure in the development of the anti-urolithiatic drug is due to the involvement of multiple mechanisms in the pathogenesis of urolithiasis [2]. Multiple constituents

Corresponding Author:- Mamta Baunthiyal
Address:- Associate Prof.Biotechnology Department, G.B.P.I.E.T Ghurdauri, Pauri Garhwal (246194) Uttarakhand India.

are possessed by plants that works in a synergistic manner in different stages of urolithiasis with no or less side effects and are available to a large population. Hence, compounds with properties such as antioxidant, anti-inflammatory and antispasmodic are an obvious choice for the development of antiurolithiatic drugs [3]. Unlike allopathic medicines which majorly target only one aspect of urolithiatic pathophysiology, most of the plant-based therapies have been shown to be effective at different stages of stone pathophysiology. Currently known extracts exert their anti-lithogenic properties by multiple mechanisms like: [4]

1. Spontaneously transit of calculi by enhancing urine volume, pH and anti-calcifying activity (Diuretic activity).
2. Balance the inhibitor and promoters of crystallization in urine and affects the crystal nucleation, aggregation and growth (Crystallization inhibition activity).
3. Relieve the binding mucin of calculi (Lithotriptic activity).
4. Improve renal function.
5. Regulate oxalate metabolism.
6. Regulate the crystalloid colloid imbalance and improve renal function, thus prevents recurrence of urinary calculi.
7. Improve renal tissue antioxidant status and cell membrane integrity and prevents recurrence (Antioxidant activity).
8. Relieve pain, burning micturition and haematuria (Analgesic and anti-inflammatory activity).

Current therapies, involve extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotomy which are costly and pose a threat of recurrence and have serious after effects. Few drugs available are Thiazides, allopurinol and potassium magnesium citrate which are useful in the secondary treatment of urolithiasis. Lithogenic substances can be prevented by Cystone drug which is marketed in herbal formulation. Cystone causes disintegration of urinary calculi, followed by antibacterial activity which is useful in the prevention of stone-associated urinary tract infections. Hence, compoundswhich directly inhibits CaOx crystallization in urine would represent a novel class of agents for the treatment of urolithiasis [5]. To determine the plant species acting as clinical diuretic, we reviewed all available literature with the intention of identifying these phyto-remedies with their beneficial traditional effect.

Epidemiology: -

Urolithiasis affects all ages, sexes and races; however, it mainly occurs in men than in women, about one out of 20 people at some time in their lives are affected with it. Nevertheless, lifetime recurrence rate is higher in males, although the incidence of nephrolithiasis is growing among females. Global data suggested that kidney stone disease is frequent in western hemisphere (5-9%) in Europe, 13-15% in USA, 12% in Canada) than eastern hemisphere (15%). Asian countries like Saudi Arabia ruled by the disease with 20% occurrence rate. Whereas other Asian countries like India, China, Pakistan, Myanmar, Thailand, Indonesia, Philippines shows overall (4-20%) of kidney stones occurrence rate [6]. In Indian 13-14% of the population are affected by kidney stones. There are two 'stone belts' more prone to kidney stones, one belt stretched from Amritsar to Uttar Pradesh via Delhi and Agra. Another belt starts from Gujrat to Jabalpur in central India. In south India, Kerala is leading with kidney stone disease with prevalence rate of 2643 per 100,000 adults. This significant increase is due to the fact that the life style diseases like obesity and diabetes are more common and steadily increasing with risk rate of 43% in Kerala. There is positive relation between diabetes and kidney stone [7].

Aetiology: -

Stone formation is usually multi-factorial with more than one element increasing a patient's risk for stone formation. Hypertension and obesity increase rates are linked to nephrolithiasis which give rise to stone formation [8]. Stones are made up of multiple constituents but the first step in any stone formation is super-saturation of the urine. This result in crystallization of constituents and a nucleus for further stone growth and aggregation. This step is usually inhibited by compounds in our urine but in some patients, these are absent or defective. About 25% of patients with urolithiasis may be the result of a polygenic defect with partial penetrance. Several disorders that cause renal stones are hereditary and they are Renal Tubular Acidosis [9] and Cystinuria. Xanthinuria and dihydroxyadeniuria are rare hereditary disorders. Recent evidence has shown an increase in paediatric cases [10]. Increase, in water intake and urinary output decreases the incidence of stone formation in patients who are suffering from the disease.

Dietary intake of various foods and fluids that result in greater urinary excretion of substances that produce stones has a significant effect on incidence of urinary calculi. The risk of formation of urinary calculi was increased in most

affluent countries, regions, societies and individuals. These inhabitants have more disposable income to spend on animal protein, which leads to increased urinary concentrations of calcium, oxalate and uric acid [11].

Material and Method: -

The present review involves the studies related to the urolithiasis and work carried out to understand the pathophysiology of kidney stones with possible activities of compounds to inhibit stone formation. Regular Collection of data was done by studying various research papers, PUBCHEM and Ayurvedic literature. In order to explore indigenous and traditional knowledge of people, questionnaire on documented plants for nephrolithiasis was used to understand more about plant properties, their secondary metabolite's structures. Functional properties were determined on the basis of GC-MS and HPLC analysis data which is already reported in literature.

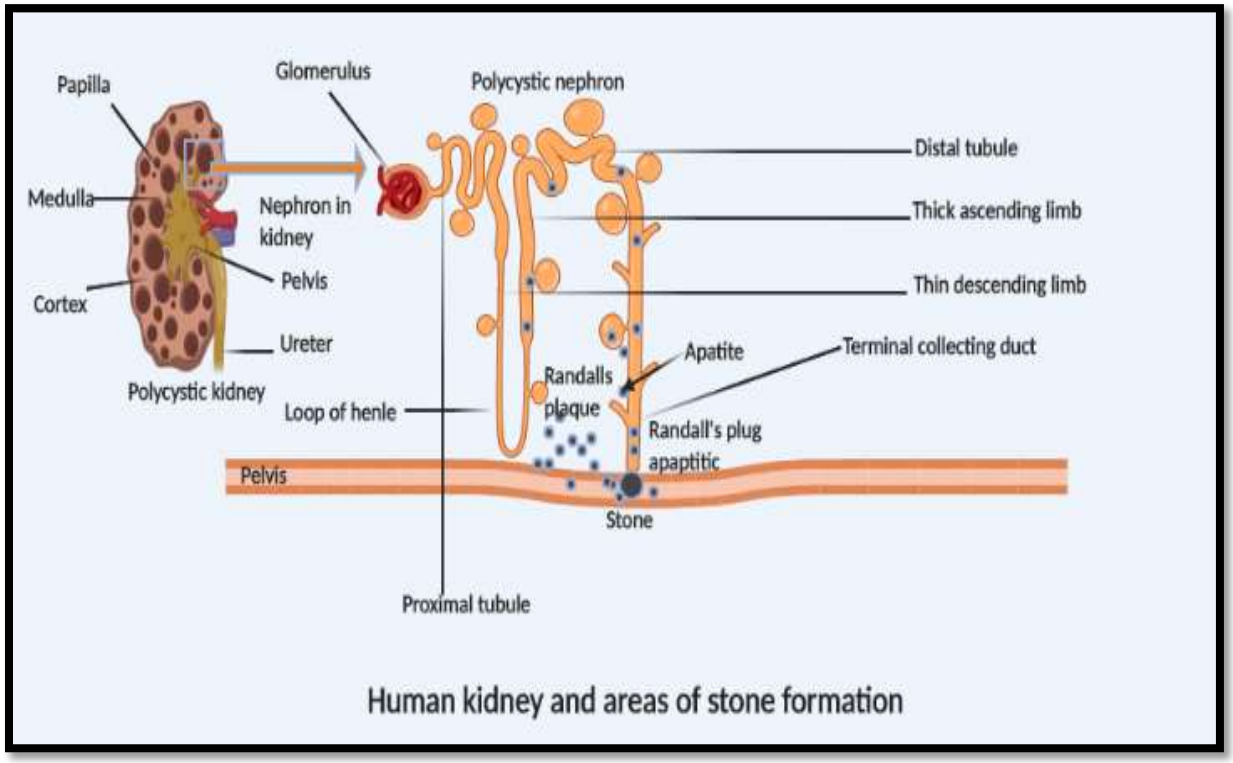

Figure1:-Morphology of human kidneys and areaof stone formation.According to the fixed-molecule component, stones start as statements of calcium phosphate (CaP) in the interstitial (apatite), become outwards arriving at the renal papillary surface, become presented to the pelvic urine and set up a core for the testimony of calcium oxalate (CaOx), prompting the development of CaOx stones joined to a CaP base, known as Randall's plaques. By differentiate, in the free-molecule instrument, for instance, CaP, uric acid orcystine crystal structure in the renal tubules, move with the urine, aggregate and attach to the terminal collecting duct. These plugs, called Randall's attachments or plugs, are presented to the pelvic urine. Accumulation of CaOx crystal on the CaP plugs prompts the arrangement of CaOx kidney stones [12] (constructed in biorender.com).

Mechanism of kidney stone development: -

Stone development is brought about by a strange mix of elements that impact the thermodynamic main impetus (supersaturation) and the (motor rate-controlling) forms engaged with the crystallization of the different stone-framing minerals. The foremost thermodynamic main thrust for the two phases is the level of supersaturation of the liquid inside which inception happens. Regardless of whether this happens intracellularly or extracellularly, the laws of crystallization science ought to apply. The processes of stone formation encompass a number of steps as described in Figure 2

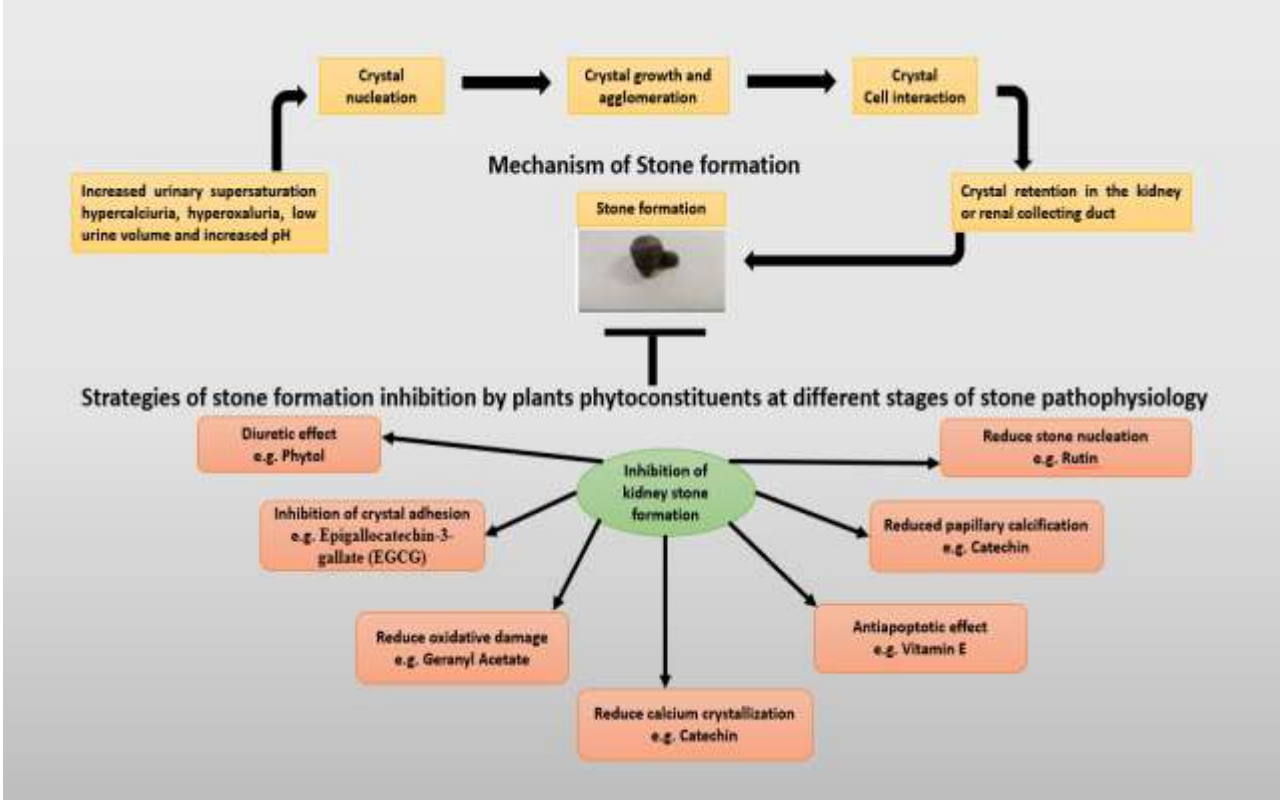

Figure 2:- Mechanism of stone formation and Strategies for stone inhibition used by plants and phytomolecules at different stages of stone pathophisiology.

Treatment and prevention of kidney stone: -

Sodium intake increases calcinuria due to competition between sodium and calcium for passive reabsorption along the nephron. Low dietary salt intake thus decreases urine calcium. A daily sodium intake less than 2-3 mEq/kg/day for young children or less than 2.4 grams in adolescents or adults is recommended for patients with hypercalciuria or calcium-based stones.

At the point when dietary alteration is ineffective, pharmacological treatment ought to be started. The principal compelling hypocalciuric specialists are thiazide diuretics whose hypocalciuric activity upgrades calcium reabsorption inside the distal renal tubules. However, because of side-reactions including weakness, discombobulation, feebleness, musculoskeletal indications, or gastrointestinal objections, these are banned [13]. Another confusion is thiazide-incited potassium exhaustion, which causes intracellular acidosis and may bring about hypokalaemia and hypocitraturia [14]. Natural drugs could close a spot during this respect.

In hyperuricosuric uric acid stones and moderate-to serious hyperuricosuria with calcium oxalate stones, allopurinol may be useful in re-establishing ordinary urinary uric acid [15]. The utilization of probiotic (colonization with the oxalate expending microorganisms Oxalobacterformigenes) has not been overwhelmingly fruitful. The way that it lessens oxaluria in patients with essential hyperoxaluria recommends that it may advance intestinal oxalate discharge.

The only available medical treatment for primary hyperoxaluria is pyridoxine, which promotes conversion of glyoxylate to glycine [16]. Pharmacological treatment of cystinuria depends on its severity. For moderate cystinuria (<500 mg per day), raising urine pH (>6·5) with potassium citrate or sodium bicarbonate, and fluid intake (>4 L per day) can suffice. In more severe cystinuria, chelating agents should be added (alphamercaptopropionylglycine or tiopronin, angiotensin converting enzyme inhibitors, and d-penicillamine) to promote formation of mixed disulfide-linked compounds with cystine [17].

Traditional medicinal plants: -
The advertised composite herbal formulations, Cystone (Himalaya Drug Company, India), Calcuri (Charak Pharmaceuticals, Bombay, India) and Chandraprabhabati (Baidyanath, India) have been broadly utilized clinically to break down urinary calculi in the kidney and urinary bladder. Pharmacological and clinical examinations completed on a composite natural plan, Trinapanchamool comprising of five herbal medications to be specific *Desmostachyabipinnata*, *Saccharum officinarum*, *Saccharum nunja*, *Saccharum spontaneum* and *Imperatacylindrica* was seen as compelling both as prophylactic in forestalling the arrangement and as remedial in dissolving the pre-shaped stones in rodents (albino rats). The anti-urolithiatic movement of this definition has been credited to its diuretic action. List of some chosen plants which have been utilized for the treatment of urolithiasis is given in Table 1 and Figure 3**.**

***Cynodon dactylon* (Gramineae):**
Cynodon dactylon (L.) Pers. (Fam: Poaceae) is normally known as "Doob" in India (Arugampul: Tamil). It is a weed and has shifted restorative properties. Leaf, root and rhizome of the plant have been utilized in people medication in various nations. In India the plants are utilized in the treatment of jungle fever, thirst, anorexia, consuming sensations in the body pruritus, unsuccessful labor and erysipelas, Ethanol extract of aerial parts of *C. dactylon* has marked CNS depressant and antioxidant activity [25-18].

***Asparagus racemosus* (Liliaceae):**
Parts utilized are roots. Regular name is Nunggarei-angouba. Its compound phyto-constituents are tannic acid, unpredictable oil, adhesive, saponin, flavonoids, asparagine, sitosterol, sapogenin, and asparagine. It is valuable in removing stones from the urinary tract. *A. racemosus* was explored for its inhibitory impact on stone development. Lithiasis was incited by controlling 0.75 % ethylene glycolated water to grown-up male albino rats (rodents) orally for 28 days. Ethylene glycol changed the urine science by raising the degrees of phosphate, oxalate, and calcium that are answerable for kidney stones. Raised degrees of phosphate, calcium, and oxalate were diminished by utilization of ethanolic concentrate of *A. racemosus*. Creatinine level was likewise decreased by this concentrate and magnesium level was expanded that is inhibitor of stone arrangement. Histological discovering gives that *A. racemosus* improves indications of disintegration incited by ethylene glycol. These perceptions show that *A. racemosus* represses ethylene glycol-incited stone development [19].

***Cedrus deodara*:**
This is the plant of Pinaceae family having very good medicinal value. In old ancient medicinal system, it was used as diuretic and for the treatment of kidney stones reported the petroleum-ether concentrate of the heart wood (PECD) for its diuretic and hostile behaviour to urolithiatic movement. The urolithiasis was tentatively incited by managing sodium oxalate (70 mg/kg, i.p) for 10 days. PECD (100 and 200 mg/kg) was orally gavaged every day 1 h before sodium oxalate (NaOx) organization for 10 days. In NaOx rewarded rodents, crystal was seen in urine under light microscope and rise of serum boundaries demonstrated the improvement of nephrolithiasis in the benchmark group. Associative organization of PECD for 10 days alongside NaOx forestalled raised serum biochemical levels because of the disposal of these in urine. Histology of the kidneys likewise showed that PECD treatment had secured against NaOx actuated nephroliathiasis. These outcomes acquired, affirmed the recipient impact of *C. deodara* in urolithiasis [20].

***Macrotyloma uniflorum*:**
It is a leguminous plant belonging to the family Fabaceae (alt. Leguminosae). It is an excellent source of iron and molybdenum and proteins. The seeds are ovoid and colour differs from light red, brown, or black sometimes with small, scattered black spots. Its therapeutic uses are known to Ayurveda and Uttarakhand conventional doctors for quite a long time. Different therapeutic arrangements are for the most part utilized as a tonic, astringent, diuretic and furthermore suggested in stiffness, neuralgia and other a few infections. Urolithiasis is a multifaceted procedure that happens from arrangement of many physicochemical occasions including super immersion, nucleation, development, total and maintenance inside the kidneys. Natural foodstuffs are more useful for livings because they encourage the repair mechanism in natural way [21].

***Urtica dioica*:**
U. dioica (stinging nettle) belongs to family Urticaceae and is native to Europe, Asia, Northern Africa and America. It is an herbaceous perennial flowering plant and encompasses a long history as herbal remedy and nutritive addition in diets. For hundredsof years *U. dioica* has been used to treat a variety of disorders ranging from allergic rhinitis to

hypertension. *U. dioica* has been utilized in conventional Austrian medication inside (as tea or new leaves), just as for the treatment of kidney, urinary plot, gastrointestinal lot and locomotor issues. Study done by Zhang et al.,2014 uncovered that the methanol concentrate of *U. dioica* productively breaks up calcium oxalate renal stones in male Sprague-Dawley rodents (rats). The concentrate indicated a portion subordinate corrective impact on urinary and renal boundaries, including calcium oxalate renal stone development. These discoveries bolster past reports that the concentrate can be utilized for the treatment of kidney and urinary parcel issues [22].

***Raphanus sativus*:**
Radish, biologically known as *Raphanus sativus* linn belongs to Brassicaceae family. It is an annual herb and used as a vegetable commonly known as Mooli. Radish is called by various names in many states, such as Mullangi, Moolika, Mooli etc. The fresh juice which is extracted from the leaves have properties like diuretic, laxatives, etc. The extract from the root has been stated to have antiurolithiatic property. Ascorbic acid, folic acid, and potassium are rich sources and fine source of vitamin B6, riboflavin, magnesium, copper, and calcium are found. They are very low in cholesterol because they are low in saturated fat. Researches have been done on the antimicrobial prospective in Raphanus sativus. "Raphanin" is a constituent which is present in seeds and leaves has already been reported for its antibacterial and antifungal activities. Radish is good source of vitamin C. Approximately all parts of the plant along with leaves, seeds and roots are also used in medicines for a variety of ailments including liver dysfunction and poor digestion, radish is used as medicinal food [23].

***Chenopodium album* L:**
Chenopodium album L. (family: Chenopodiaceae) is an herbaceous vegetable plant privately known as Bathua. The therapeutic property of this plant is basically present in leaves and seeds. The leaves are utilized in ethno-restorative practices for treatment of kidney infections and urinary stones. Ethnobotanical investigations of Aravalli area of Rajasthan (India) report the people restorative employments of cooked leaves of *C. album* in kidney stones and urinary plot inconveniences. Cooked leaves of *C. album* are utilized as conventional medication in the Shekhavati district of Rajasthan for treatment of urinary difficulties and colic. In Ladakh, leaves are additionally utilized customarily for controlling difficult urine. *C. album* is a significant restorative weed of Moradabad helpful in the treatment of urinary maintenance and kidney diseases [24].

Table 1:- Plants have potential to work as anti-urolithiatic agent with specific parts and uses.

S No.	Botanical Names	Common names	Part use	Folk use	References
1.	*Abutilon indicum*	Atibalaa	Leaf and Root	Cure urinary problems: used as diuretic.	[25]
2.	*Achyranthes asper* L.	Apamarga	Leaf and Seeds	Luteolytic property to cure urolithiasis.	[26]
3.	*Adiantum capillus-veneris* L.	Samalpatti	Leaf	Luteolytic properties and helps in menstruation problems. Leaves powder with Luke-warm water twice a day is beneficial in calculus.	[27]
4.	*Aerva lanata*	Weed, Kapoor Madhuri	Roots	Decrease urinary calcium oxalate uric acid, phosphorus excretion, diuretic	[28]
5.	*Adiantum venustum* D. Don	Hansraj	Leaf	Leaves powder with Luke water twice a day as a diuretic.	[29,26]
6.	*Artemisia arborescens* L.	Green ginger, vilayati	Whole plant	Luteolytic property and diuretic.	[25]
7.	*Asparagus racemosus* Willd.	Satavari	Root	Decoction of the	[26]

				roots alone with sugar is prescribed in urinary troubles due to stone.	
8.	*Begonia picta* Smith, *Bryophyllum pinnatum*	Patharchatta	Leaf and Tuber	Luteolytic properties and used to cure urolithiasis. Leaves decoction given twice a day after meal. Powder of tuber twice a day before meal cure nephrolithiasis.	[26]
9.	*Berberis aristata* DC.	Kingore	Roots	Crushed roots were allowed to secrete its phytochemicals in water for overnight and then consume the same twice a day for 45 days.	[30]
10.	*Bergenia ciliata* (Haworth) Sterbn	Pashanbhed	Tuber	Luteolytic properties. One tea spoon powder of tuber with luke lime water early in the morning empty stomach cure nephrolithiasis.	[25]
11.	*Boerhavia diffusa* L.	Punarvahava	Whole plant	Useful in all urinary troubles. Effective in case of uric acid stone. Decoction is also used to cure chronic renal problems.	[26]
12.	*Butea monosperma* (Lam.) Taubert	Dhak	Flower	Diuretic and used to get relief in case of burning sensations during passage of urine due to calculi.	[25]
13.	*Cedrus deodara* D. Don.	Deodara	Bark and Wood	Diuretic and used against urinary problems.	[30]
14.	*Chenopodium album* L.	Bathua	Whole plant	Diuretic and used to cure urinary problems caused by renal calculi.	[25]
15.	*Cichorium intybus* L.	Kasni	Leaf	Leaf extract is used in kidney troubles.	[25]
16.	*Coriandrum sativum* L.	Dhaniya	Whole plant	Diuretic and other urinary problems.	[25]
16.	*Costus spiralis*	Costus, strawberry bud	Whole plant	Decrease stone size	[28]
17.	*Cypreus rotundus*	Motha	Whole plant	Anti-urolithiatic	[30]

				activity	
18.	*Cucumis hardwickii* Royle	Kakdi	Seed	Urinary problem and used mainly as Diuretic.	[27]
19.	*Centella asiatica*	Gotu kola	Whole plant	Anti-urolithiatic activity	[31]
20.	*Cynodon dactylon* L.	Dhoob	Whole plant	Treatment of calculi.	[30]
21.	*Didymocarpus pedicellatus* R.Br.	Shilapuspha	Leaf and Root	Litholytic property, used to cure calculi, paste of leaves with luke water also reported to cure stone especially when stone is present in kidney. Root of plants along with leaves are used when stone is reduced in size and comes out in bladder.	[25]
22.	*Dryopteris cochleata* (Don.) Chr.	Fern	Areal Part	Cure gall and kidney stone.	[30]
23.	*Duchesnea indica*	Indian strawberry	Leaf	Diuretic and used to cure leucorrhea.	[31]
24.	*Echinops cornigerus* D.C	Gokhru	Root	Treat urinary problems mainly caused by urolithiasis.	[27]
25.	*Eupatorium birmanicum*	Langthrei	Leaves	Diuretic, antibacterial activity, prevent crystal formation, make urine alkaline	[31]
26.	*Flacourtia jangomas* (Lour)	Indian plum	Fruit	Diuretic in treating calculi problems.	[27]
27.	*Geranium nepalense* Sweet	Laljari, Ratanjot	Whole plant	Useful in both nephrolithiasis and other chronic renal problems.	[30]
28.	*Goodyera repens*	Dwarf rattlesnake	Whole plant	Anti-urolithiatic activity	[30]
29.	*Macrotyloma uniflorum*	Gaith	Seeds/leaves	Diuretics.	[32]
30.	*Micromeria biflora* (Buch. - Ham. ex D. Don) Benth.	Ban ajwain	Whole plant	Diuretic and used in urolithiasis.	[27]
31.	*Mimosa pudica* L.	Chui-mui	Root	Cure urine related problem generally due to calculus.	[26]
32.	*Ocimum basilicum* L.	Tulsi	Leaf	Treatment renal calculi	[25]
33.	*Oxalis corniculata* L.	Amrul	Leaf	Cure urinary troubles due to calculus.	[26]
34.	*Pyracantha crenulata* (D. Don)	Pheru, khemri	Fruit	Litholytic property	[27]

	M. Roemer			and used to cure calculi.	
35.	*Phyllanthus niruri*	Gale of wind, stone breaker, bhui amla	Seeds	Antispasmodic + relaxant, promotes glycosaminoglycans adsorption into calculi making them softer	[25]
36.	*Raphanus sativus*	Muli	Leaves	Treating calculi	[29]
37.	*Rubia cordifolia* L.	Majthi	Areal part	Cure urolithiasis.	[25]
38.	*Rubus niveus*Thunb.	Kala-hisalu, buglu	Fruit and Seeds	Used to cure calculi.	[29]
39.	*Sida acuta* Burn	Baraira	Root	Litholytic and used to cure urinary problem caused by calculus.	[27]
40.	*Solanum nigrum* L.	Makoi	Leaf	Diuretic, paste of leaves in very small quantity with luke water is used to treat calculi generally uric acid stone.	[25]
41.	*Smilax aspera*	Salsa, kalisar	Plant	Anti-urolithiatic activity	[25]
42.	*Solidago virgaurea* L	Pinjaphool	Leaf	Cure chronic renal problems caused by calculi such as hydronephrosis and also used as diuretic.	[27]
43.	*Taraxacum officinale* Weber.	Dudal, dudhi	Leaves & Roots	Leaf extract is used against kidney complaints, Root are diuretic and used in chronic renal disorders.	[30]
44.	*Thalictrum foliolosum* DC.	Kirmuri	Roots	Diuretic.	[30]
45.	*Trigonella foenum-graecum* L.	Methi	Seeds	Diuretic property and also used to cure calcium-based stone.	[27]
46.	*Uraria picta* Jacquin	Dabra	Root	Root of the plant is also used as one of the ingredients of Dasmularisht and also used to cure chronic renal infection or to recover kidney after calculus caused infection.	[27]
47.	*Urtica dioica* L.	Kandali	Leaf	Diuretic and used to	[26]

				cure calculi.	
48.	*Valeriana hardwicki*i Wallich in Roxb.	Tagger asarun, shami	Root	Used in urinary problem and have litholytic property.	[27]
49.	*Vitis vinifera* L.	Angoor	Leaf, Fruit	Extract of leaves along with young twigs given as diuretic. Fruit juice increase urinary excretion	[25, 28]
50.	*Vaccinium Oxycoccus*	Cranberry	Cranberry juice	Increase urinary citrate excretion, decrease urinary calcium oxalate phosphorus excretion, diuretic	[28]
51.	*Xanthium strumarium* L.	Banokra	Roots	Diuretic &litholytic for curing calculi.	[25]

Figure 3:- Plants with reported anti-urolithiatic activity.

Phyto-compounds for prevention and treatment of Kidney Stones: -

The viability of a few dietary intercessions, as a great technique for assurance from kidney illnesses has been suggested by a few investigations either as a piece of, or separate from the acquired or hereditary elements. So as to limit the likelihood of kidney stone repeat alongside treating urolithiasis, a few wholesome plants and their phytochemicals can be utilized as dietary enhancements or included into the fundamental eating routine. In spite of the fact that there is an absence of information about the sub-atomic premise fundamental, the prophylactic impact of these phyto-therapeutics, various remedial spices and their parts are utilized for treatment of kidney issues. These phytomolecules also have specific mechanism of action (Table 2). With in excess of 8,000 basic variations, phyto-phenols have been found in a few vegetables and organic products that comprise the most plentiful dietary cancer prevention agents, which show prominent oppressive exercises against the oxidative pressure related kidney dysfunctions. The antioxidative impact of primary cell reinforcements, epicatechin and catechin found in plants sources like grape seeds and green tea [33] is licensed prevalently to either metal chelating and radical searching properties or to the patching up consequences for chemicals and interpretation factors, which gives protecting impact against arrangement of renal stones, oxidative pressure associated (with renal disappointment, and renal wounds) [34]. In COM-rewarded NRK-52E renal proximal cylindrical cell line, catechins restored the proteolysis of caspase 3 and mitochondrial layer potential as a result of its expanded SOD movement. This raised SOD action of catechins effectively delivered inhibitory impacts on the renal papillary calcification and improvement of COM papillary calculi [35]. A basic catechin, epigallocatechin-3-gallate (EGCG) intensely decreased the capacity of Madin–Darby canine kidney (MDCK) cells to tie to calcium oxalate monohydrate crystals which after organization, diminished the α-enolase protein articulation (liable for official) on the renal cylindrical cell surface which was chiefly liable for such a weakening response [36]. Dosmin, a flavonoid glycoside, shows defensive impacts in the kidney against oxidative pressure, nephro-poisonousness and diabetic nephropathy. Generally found in vegetables and citrus organic products, dosmin is a polyphenol with natural anti-urolithiatic action.

Table2:- Phytoconstituents with promising anti-urolithiatic activity and their possible activity.

S.No.	Compound names	Molecular formula	Possible Activities	References
1.	Catechin	$C_{15}H_{14}O_6$	Increases SOD activity. Decreases mitochondrial membrane potential (MMP), Caspase-3 activity, renal calcium crystallization. Renal papillary calcification, calcium oxalate monohydrate and papillary calculus formation	[35, 36]
2.	Epigallocatechin-3-gallate (EGCG)	$C_{22}H_{18}O_{11}$	Reduces free-radical production, crystal binding capability, urinary oxalate excretion, activities of urinary gammaglutamyl transpeptidase and N-acetylglucosamines and α-. enolase expression	[36]
3.	Octadecanoic Acid, Ethyl Ester	$C_{20}H_{40}O_2$	Antioxidant, Hypocholesterolemic, Nematicide, pesticide, Antiandrogenic flavour, Hemolytic, 5- α- Reductase inhibitor	[37]
4.	Hexadecanoic Acid, Methyl Ester	$C_{17}H_{34}O_2$	Lubricant, Antiandrogenic, Antioxidant, 5-Alpha-Reductase inhibitor	[37]
5.	Phytol (3,7,11,15 tetramethylhexadec-2-en-1-ol)	$C_{20}H_{40}O$	Antimicrobial, Antioxidant-inflammatory, Anticancer, Diuretic	[37, 38]
6.	Geranyl Acetate	$C_{12}H_{20}O_2$	Antioxidant	[37]
7.	Squalene	$C_{30}H_{50}$	Antibacterial, Antioxidant, Antitumor, Cancer Preventive, Immunostimulant	[37, 38]
8.	Octadecanoic acid (stearic acid)	$C_{18}H_{36}O_2$	Antioxidant, Anti-inflammatory, nemaicide, pesticde, Anti-androgenic flavor, hemalytic, 5- Alpha reductase inhibitor	[38]
9.	Pentadecanoic acid	$C_{15}H_{30}O_2$	Antioxidant	[37]
10.	9-Isopropyl-1-Methyl-2-	$C_{15}H_{24}O$	Antibacterial, Antitumor, Anti-inflammatory	[37]

	Methylene-5-Oxa-Tricy			
11.	Vitamin E	$C_{29}H_{50}O_2$	Analgesic, Antidiabetic, Anti-inflammatory, Antioxidant, Antidermatitic, Antileukemic, Antitumor, Anticancer, Hepatoprotective, Antispasmodic	[37]
12.	9,19-Cyclolanost-23-Ene-3,25-Diol, (3.Beta.,23e)-	$C_{30}H_{50}O_2$	Antioxidant, Anti-inflammatory	[37]
13.	Benzenepropanol, 4-hydroxy-à-methyl-, (R)-	$C_{10}H_{14}O_2$	Antimicrobial, Antioxidant	[38]
14.	Ergost-5-En-3-Ol, (3.Beta.,24r)-	$C_{28}H_{48}O$	Antioxidant, Hypocholesterolemic	[37, 38]
15.	9(11)-Dehydroergosteryl Benzoate	$C_{35}H_{46}O_2$	Microglial anti-inflammatory Activity	[37]
16.	Gamma-Tocopherol	$C_{28}H_{48}O_2$	Antitumor, Antioxidant, Antimicrobial	[38]
17.	Tricyclo[6.3.0.0(2,4)] Undec-8-Ene, 3,3,7,11-Tetramethyl	$C_{15}H_{24}$	Antioxidant	[37]
18.	Thymol	$C_{10}H_{14}O$	Antimicrobial, Anti-inflammatory Analgesic, Antiseptic, Antioxidant Anticarcinogenic, Antiacne	[38]
19.	Quercetin	$C_{21}H_{18}O_{13}$	Antioxidant, Anti-inflammatory, Antibacterial, Antiviral, radical-scavenging, gastroprotective, and Immune-modulatory activities. Possesses hypo-uricemic, and anti-inflammatory activities. Exhibits inhibitory effect on the deposition of calcium oxalate crystal Decreases cell viability, lipid peroxidation, formation of urinary crystal deposit and oxidative damage. Increases Serum paraoxonase 1 (PON1)	[39, 36]
20.	2-Pentadecanone, 6,10,14-Trimethyl-	$C_{18}H_{36}O$	Cancer Preventive, Antibacterial, Antiavian Influenza A Virus	[37]
21.	Hexadecanoic Acid, Ethyl Ester	$C_{18}H_{36}O_2$	Lubricant, Antiandrogenic, Antioxidant, 5-α-reductase inhibitor	[37, 38]
22.	Rutin	$C_{27}H_{30}O_{16}$	Reduce stone nucleation	[39]
23.	Rutaecarpine	$C_{18}H_{13}N_3O$	Anti- anoxic, anti-obesity, cytotoxicity, vasorelaxaing	[40]
24.	Sweroside	C16H22O9	Antifungal, Anti-diabetic, Anti-inflammatory, Antitumor effects	[40]
25.	Calciferol	$C_{27}H_{44}O$	Hormonal properties	[40]
26.	Asperuloside-2	C18H22O11	Anti-obesity, Antimetabolic syndrome	[40]

Conclusion:-

Dietary plants have been proved to play major role in treating kidney stone diseases however the underlying mechanism used by these phytoconstituents is not well studied. Literature surveys provide evidence of the large number of *in vitro* and *in vivo* studies that were performed to analyze the effects of dietary plants extract in the management of kidney stone diseases. However, till date limited number of human studies has been done to establish the role of particular phytoconstituents from these dietary plants in the prevention of urolithiasis. Plants, fruits and vegetables whose efficacy have been confirmed by clinical trials were *Agropyron repens* L., *Dolichos biflorus* L.(horse-gram), *Hibiscus sabdariffa* L.(roselle), *Punica granatum* L.(pomegranate), and *Phyllanthus niruri* L. (bhui-aonla). Catechin, epicatechin, EGCG, diosmin, rutin, quercetin and hyperoside could be proposed as promising phytomolecules for the treatment of urolithiasis. From the literature it can be concluded that plants and their phytoconstituents can be useful in treating kidney stones. In future, preclinical and clinical investigations are

required to assess the efficacy of these plant derived phytomolecules in establishment of molecular and cellular mechanism.

References:-

1. Aggarwal KP, Narula S, Kakkar M, Tandon C. Nephrolithiasis: molecular mechanism of renal stone formation and the critical role played by modulators. BioMed research international. 2013 Oct;2013.
2. Jyothilakshmi V, Thellamudhu G, Chinta R, Alok K, Anil K, Debadatta N, Kalaiselvi P. Beneficial antioxidative effect of the homeopathic preparation of Berberis vulgaris in alleviating oxidative stress in experimental urolithiasis. Complementary Medicine Research. 2014;21(1):7-12.
3. Devkar RA, Chaudhary S, Adepu S, Xavier SK, Chandrashekar KS, Setty MM. Evaluation of antiurolithiatic and antioxidant potential of Lepidagathisprostrata: a Pashanbhed plant. Pharmaceutical biology. 2016 Jul 2;54(7):1237-45.
4. Pareta SK, Patra KC, Mazumder PM, Sasmal D. Establishing the principle of herbal therapy for antiurolithiatic activity: A review. J PharmacolToxicol. 2011;6(3):321-32.
5. Erickson SB, Vrtiska TJ, Lieske JC. Effect of Cystone® on urinary composition and stone formation over a one year period. Phytomedicine. 2011 Jul 15;18(10):863-7
6. López M, Hoppe B. History, epidemiology and regional diversities of urolithiasis. Pediatric nephrology. 2010 Jan 1;25(1):49
7. Atmani F, Slimani Y, Mimouni M, Hacht B. Prophylaxis of calcium oxalate stones by Herniariahirsuta on experimentally induced nephrolithiasis in rats. BJU international. 2003 Jul;92(1):137-40
8. Butterweck V, Khan SR. Herbal medicines in the management of urolithiasis: alternative or complementary?. Planta medica. 2009 Aug;75(10):1095.
9. Chaussy C, Schmiedt E, Jocham B, Brendel W, Forssmann B, Walther V. First clinical experience with extracorporeally induced destruction of kidney stones by shock waves. The Journal of urology. 1982 Mar;127(3):417-20.
10. Christina AJ, Ashok K, Packialakshmi M, Tobin GC, Preethi J, Murugesh N. Antilithiatic effect of Asparagus racemosusWilld on ethylene glycol-induced lithiasis in male albino Wistar rats. Methods and findings in experimental and clinical pharmacology. 2005 Nov 1;27(9):633-8.
11. Alok S, Jain SK, Verma A, Kumar M, Sabharwal M. Pathophysiology of kidney, gallbladder and urinary stones treatment with herbal and allopathic medicine: A review. Asian Pacific Journal of Tropical Disease. 2013 Dec 1;3(6):496-504.
12. Miller NL, Williams Jr JC, Evan AP, Bledsoe SB, Coe FL, Worcester EM, Munch LC, Handa SE, Lingeman JE. In idiopathic calcium oxalate stone-formers, unattached stones show evidence of having originated as attached stones on Randall's plaque. BJU international. 2010 Jan;105(2):242-5
13. Park S, Pearle MS. Pathophysiology and management of calcium stones. Urologic Clinics of North America. 2007 Aug 1;34(3):323-34.
14. Moe OW. Kidney stones: pathophysiology and medical management. The lancet. 2006 Jan 28;367(9507):333-44.
15. Ettinger B, Tang A, Citron JT, Livermore B, Williams T. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. New England Journal of Medicine. 1986 Nov 27;315(22):1386-9.
16. Milliner DS, Eickholt JT, Bergstralh EJ, Wilson DM, Smith LH. Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. New England Journal of Medicine. 1994 Dec 8;331(23):1553-8.
17. Pak CY, Fuller C, Sakhaee K, Zerwekh JE, Adams BV, With Investigators From Collaborating Units*. Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. The Journal of urology. 1986 Nov;136(5):1003-8.
18. Pal DK. Evaluation of CNS activities of aerial parts of Cynodondactylon Per. in mice. Acta Pol Pharm-Drug Res., 2008; 65: 37-43 20.
19. Akram M, Idrees M. Progress and prospects in the management of kidney stones and developments in phyto-therapeutic modalities. International journal of immunopathology and pharmacology. 2019 May;33:2058738419848220.
20. Ramesh C, Krishnadas N, Radhakrishnan R, Rangappa S, Viswanatha GL, Rajesh D, Gopal M, Talwar S. Anti-urolithiatic activity of heart wood extract of cedrusdeodara in rats. Journal of Complementary and Integrative Medicine. 2010 Apr 7;7(1).

21. Sharma N, Bisht SS, Gupta S, Rana M, Kumar A, Pathak R. in-silico study for antiurolithiatic activities of compounds extracted from horse gram (Macrotylomauniflorum) collected from Uttarakhand (India) as xanthine dehydrogenase inhibitor by molecular docking. 2019.
22. Zhang H, Li N, Li K, Li P. Protective effect of Urticadioica methanol extract against experimentally induced urinary calculi in rats. Molecular medicine reports. 2014 Nov 30;10(6):3157-62.
23. Sabishruthi S, Vedha Pal JS, Kavitha S, Deepak Paul DB, Ponsegaran V. An Illustrative Case Study on Drug Induced Steven-Johnson Syndrome by Ginkgo biloba. J Clin Res. 2018;2(105):2.
24. Chaudhary A, Singla SK, Tandon C. In vitro evaluation of Terminalia arjuna on calcium phosphate and calcium oxalate crystallization. Indian journal of pharmaceutical sciences. 2010 May;72(3):340.
25. Ahmed S, Hasan MM, Mahmood ZA. Antiurolithiatic plants in different countries and cultures. Journal of Pharmacognosy and Phytochemistry. 2016 Jan 1;5(1):102.
26. Pandey NC, Bhatt D, Arya D, Chopra N, Upreti BM, Joshi GC, Tewari LM. Diversity of ethno-medicinal plant: a case study of Bageshwar district Uttarakhand. J Med Plants Stud. 2017;5(2):11-24.
27. Kumar H, Khajuria AK, Bisht NS. Traditional phytoremedies used to treat urolithiasis in Pauri (Garhwal) Uttarakhand India. Journal of Pharmacognosy and Phytochemistry. 2018;7(3):2941-4.
28. Yadav RD, Jain SK, Alok S, Mahor A, Bharti JP, Jaiswal M. Herbal plants used in the treatment of urolithiasis: a review. International Journal of Pharmaceutical Sciences and Research. 2011 Jun 1;2(6):1412.
29. Mehra A, Bajpai O, Joshi H. Diversity, utilization and sacred values of Ethno-medicinal plants of Kumaun Himalaya. Tropical Plant Research. 2014;1(3):80-6.
30. Khajuria AK, Kumar G, Bisht NS. Diversity with ethnomedicinal notes on Orchids: A case study of Nagdev forest range, Pauri Garhwal, Uttarakhand, India. Journal of Medicinal Plant Studies. 2017;5(1):171-4.
31. Sharma G, Lamichhane G. A review of plant based medicine in treatment of Urolithiatic disorder. The Pharma Innovation. 2017;6(10):08-12
32. Chanchal DK, Niranjan P, Alok S, Kulshreshtha S, Dongray A, Dwivedi S. A brief review on medicinal plant and screening method of antilithiatic avtivity. International Journal of Pharmacognosy. 2016;3(1):1-9.
33. Khan SR, Canales BK. Unified theory on the pathogenesis of Randall's plaques and plugs. Urolithiasis. 2015 Jan 1;43(1):109-23.
34. Mendoza-Wilson AM, Glossman-Mitnik D. Theoretical study of the molecular properties and chemical reactivity of (+)-catechin and (−)-epicatechin related to their antioxidant ability. Journal of Molecular Structure: THEOCHEM. 2006 Mar 17;761(1-3):97-106.
35. Grases F, Prieto RM, Fernandez-Cabot RA, Costa-Bauzá A, Tur F, Torres JJ. Effects of polyphenols from grape seeds on renal lithiasis. Oxidative medicine and cellular longevity. 2015 Jan 1;2015.
36. Nirumand MC, Hajialyani M, Rahimi R, Farzaei MH, Zingue S, Nabavi SM, Bishayee A. Dietary plants for the prevention and management of kidney stones: preclinical and clinical evidence and molecular mechanisms. International journal of molecular sciences. 2018 Mar;19(3):765
37. Kalita BC, Das AK, Gupta DD, Hui PK, Gogoi BJ, Tag H. GC-MS analysis of phytocomponents in the methanolic extract of Gynocardiaodorata R. Br.-A poisonous plant from Arunachal Himalayan Region. Journal of Pharmacognosy and Phytochemistry. 2018;7(1):2458-63.
38. Kumar BV, Vijayendra SV, Reddy OV. Trends in dairy and non-dairy probiotic products-a review. Journal of food science and technology. 2015 Oct 1;52(10):6112-24.
39. Đurović S, Pavlić B, Šorgić S, Popov S, Savić S, Petronijević M, Radojković M, Cvetanović A, Zeković Z. Chemical composition of stinging nettle leaves obtained by different analytical approaches. Journal of Functional Foods. 2017 May 1;32:18-26.
40. Sharma N, Bisht SS, Gupta S, Rana M, Kumar A, Pathak R. in-silico study for antiurolithiatic activities of compounds extracted from horse gram (Macrotylomauniflorum) collected from Uttarakhand (India) as xanthine dehydrogenase inhibitor by molecular docking. 2019.