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An Update on Urolithiatic Plant Drugs as Alternative Treatment Option for Mitigation of Kidney Stones

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Abstract:

Uro-lithiasis, a common health problem growing globally, is the formation of mineral stones in the urinary tract which starts with crystallization of oxalates in nephrons. Stone or calculi in the kidney or other parts of urinary system cause a variable degree of unbearable pain in different parts of abdomen and leading to various urinary tract infections. Uro-lithiasis is a complex urinary disorder involving various mineral crystal formations in the urinary tract. The present study is attempted to enlighten the knowledge of lithiasis formation, causes of stone formation, control measures, medicinal plants, available treatments, marketed formulations and patents. A large extent (12-15%) of global population is suffering from different kinds of lithiatic conditions. Various treatment therapies are available for the removal of stones like ESWL (Extracorporeal Shock Wave Lithotripsy), Precutaneous Nephrolithotomy & Ureteroscopy. Various studies revealed that Phytotherapeutics can be used as the part of treatment along with the surgical or radiation treatment as an adjunctive therapy to control and prevent recurrence of stone formation. Various medicinal plants are being used for lithiatic treatment from older times. This review provides an account on such plants and the type of research performed using them. Some potent indigenous herbs which are used in treatment of urolithiasis were discussed here. This review will give the

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opportunities for the future research and for the development of new antiurolithiatic therapeuticagents.

Keywords: Anti-lithiatic Medicinal plants, Urinary stone, Urolithiasis.

INTRODUCTION:

Uro-lithiasis, currently affecting a large extent of population estimated 12-15% worldwide and is a third most common health affliction to kidney (Abhirama et al. 2018). Formation of calculi (calcium oxalate or other mineral crystals) in kidney or other parts of Urinary system cause variable degree of pain in abdomen, urinary bleeding and may also leads to urinary tract infections (Rathod et al. 2014; Jijja et al 2017). Calcium oxalate crystals formation is most predominant component (~ 80%) along with calcium phosphate, sodium oxalate etc. which are found in lower composition (Goyal et al. 2017).

For the management of urolithiasis different surgical treatments like ESWL (extracorporeal shock wave lithotripsy), Precutaneous Nephrolithotomy & Ureteroscopy etc. are currently available. These treatments are a bit costly to the patients and having undesirable adverse effects ranging from hypertension, haemorrhage, tubular necrosis and injurious damage to renal cells leading to recurrence of lithiatic crystals. Presently various therapies along with the invasive methods includes some diuretics and alkali-citrates to prevent the recurrence of calcium and oxalate induced uro-lithiasis (Shafi et al. 2016).

The known mechanism of lithiasis is based on various events leading to crystal nucleation, aggregation of insoluble mineral particles and finally growth of calculus. Supersaturation of urine with lithiatic minerals leads to crystallization at the site of stone formation. Other suggested modes of stone formation include imbalance of lithiatic promoters-inhibitors in the body fluids, generation of free radicals (ROS). A promoter includes minerals salts like calcium, sodium, urates, oxalates and Tamm-Horsfall protein. Low urine pH also promotes lithiasis. Inhibitors composed of inorganic (citrates, glycossaminoglycans, pyrophosphates, magnesium) and organic components (protease inhibitors, nephrocalcin). A healthy individual possesses the natural occurring stone inhibition capacity failing which results in lithiatic stone formation. Damage to the renal epithelial cells also promotes crystal growth by providing suitable environment and surface for attachment of mineral crystals (Aggarwal et al. 2013).

Urolithiasis- The 3rd Most occurring Urological Disorder:

Urolithiasis, commonly known as renal stone formation, is the physiological condition occurring due to formation of hard, solid, non-metallic stone like aggregated mineral crystals in the renal tissue. The site of stone formation can be anywhere in the urinary system including the renal tissue and urinary bladder. Urolithiasis is a complicated health problem which is growing as the third most common urological disorder globally. Stone or calculi in the kidney or other parts of urinary system causes an unbearable pain in different parts of

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abdomen and may lead to various urinary tract infections. Currently, a large extent of the globe population approximately 12-15% is suffering from urolithiatic disorders (Abhirama et al. 2018). Various surgical therapies are available for the removal of the renal as well as gall stones. Renal calculi possess high risk of recurrence, so, along with the invasive treatment the complete therapy includes the administration of some diuretics and alkali-citrates to prevent the recurrence of crystal reformation. Studies revealed that phytotherapeutics can be the part of treatment as an adjunctive therapy. Various medicinal plants are being used for kidney stone treatment from ancient times, which have not yet been scientifically explored (Gürocak et al. 2006). Calcium oxalate crystals are more prominent (~ 80%) than other types of stone forming crystals. Stones along the urinary tract can be located in the kidneys, urethra and urinary bladder (Goyal et al. 2017).

Mechanism of Oxalate crystal formation:

It is suggested that stone formation is caused by a series of physiological responses occurring in the urinary system. Urine supersaturation due to imbalance of lithiatic promoters-inhibitors in the body fluids and generation of free radicals. A promoter includes mineral salts like calcium, sodium, urates, oxalates and Tamm-Horsfall protein. Low urine pH also promotes lithiasis. Inhibitors composed of inorganic (citrates, glycossaminoglycans, pyrophosphates, magnesium) and organic components (protease inhibitors, nephrocalcin). A healthy individual possesses naturally occurring stone inhibition capacity failing which results in lithiatic stone formation. Damage to the renal epithelial cells also promotes crystal growth by providing suitable environment and surface for attachment of mineral crystals (Liu et al. 2020; Yasui et al. 2017).

	Inhibitors	Promoters
Inorganic:-	Citrate Magnesium Pyrophosphate	Calcium Sodium Oxalate Urate
Organic:-	Tanm-Horsfa11 protein (THP) Glycosaminoglycans High urine volume	Low urine pH Low urine volume

Table 1: List of urinary lithiasis inhibitors and promoters

In urine, nuclei usually form on existing surfaces, a process called heterogeneous nucleation. Epithelial cells, urinary casts, RBCs, and other crystals can act as nucleating centres in urine.

Pathophysiology of Renal Stone:

Stone formation is caused by a series of processes taking place in the urinary system. Initiating by lithiatic promoters-inhibitors imbalance leading to generation of free radicals,

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inflammation and renal epithelial tissue injury which serves as site for crystal nucleation furthermore on supersaturation of urine aggregation of stone forming crystals and their growth and formation as renal calculi or kidney stone. Crystal nuclei starts to form on the site of tissue injury or inflammation, which act as crystal seed or centre of nucleation in urinary system for initiation of stone formation, a process called heterogeneous nucleation. Damage to the renal epithelial cells cause inflammation also promotes stone formation by providing suitable environment and surface for crystal nucleation.Next step includes supersaturation of urine with stone forming minerals such as calcium oxalate, sodium oxalate, which after nucleation start to aggregate and grow into larger size and results in generation of urolithiasis (Yasui et al. 2017; Miller et al. 2007; Smith etal. 1987).

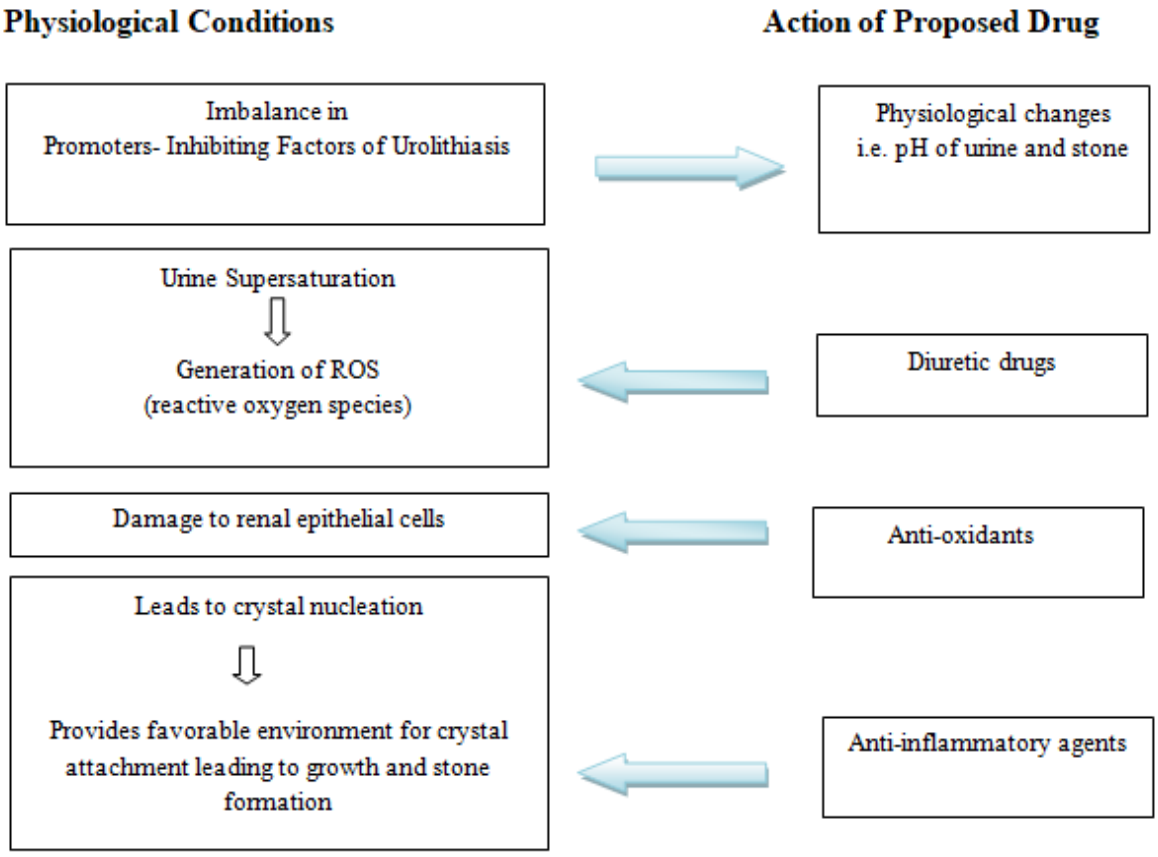

Figure 1: Representation of Renal Stone Pathophysiology

Plants for Antilithiatic Potential:

It has long been recognized that natural products represent the richest source of high chemical diversity, providing the basis for identification of novel scaffold structures that serves as starting points for rational drug design (Dhiman, 2020). Human civilization has used natural

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sources for maintaining diverse health-related issues since time immortal by traditional healers (Dhiman et al., 2017)(Nandal et al., 2020) (Gupta et al., 2019). Literature revealed that the ingestion of bioactive compound from fruits and vegetables is associated with the reduced risk of many common forms of cancer and many other harmful diseases like tuberculosis (Garg V, 2019) (Jijja et al., 2019). The early symptoms developed can be characterized by dry cough, fever, lethargy and weight loss (Xu et al., 2021). Herbal remedies derived from plants and their products have been used since ancient times (Saini et al. 2020a; Saini et al. 2018) as therapeutic agents, attributed to various pharmacological activities v.i.z. antioxidant, anti-inflammatory, analgesic, anti-fertility, antimutagenic, larvicidal, anthelmintic activity etc. (Saini et al, 2020; Dhiman et al., 2017). Several medicinal plants are widely being used in Ayarvedic preparations (Shinvaikar et al. 2007) and contain a large number of secondary plant metabolites, which are of great therapeutic significance (Saini et al., 2016). Flavonoids are the main components of a healthy diet (Dhiman et al. 2016).
Alongwith herbal medicines, nutraceuticals and food supplements are claimed to be beneficial in several disease conditions which include cardiovascular disorder, neurodegenerative disorders, metabolic disorders and cancer prevention (Bansal & Dhiman, 2020). These may be explored for the production of natural medicinal formulations in pharmaceutical drug industries for several disorders on account of potential antioxidant activity (Bhilana et al., 2018). Due to fascinating properties and biomedical applications, there is an Immense necessity to explore newer prospective in the field of complementary and alternative medicine. This is one of the reasons that efforts have been directed to discover promising therapeutic agents from natural sources (Nandal et al., 2020).

Various medicinal plants were already studied for their medicinal properties by researchers. Various lists of such findings related to antilithiatic potential of medicinal plants (Gonzalezet al. 2020)are compiled along with their methods and observed outcomes are discussed below. The plants are categorized on the bases of type of research like in-vivoand in-vitro studies.

In-vivo Studies:

Table 2: List of some medicinal plants studied for theirin-vivo antilithiatic activity

S. No.	Common Name	Scientific name & Family of plant	Plant part used	Observed Outcomes

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1.	Galu Gasturi	*Abelmoschus moschatus* Malvaceae	Herbs	Urinary calcium, oxalate, phosphate decreased and magnesium increased (Christina *et al.;* 2013)
2.	Mountain knotgrass	*Aerva lanata* Amaranthaceae	Leaves	Correcting the promotor- inhibitor imbalance (Murugan *et al.*; 2001)
3.	Lavender	*Apium graveolens;* Apiaceae	Flowers	Protective effect against renal toxicity (Hegazy *et al.*2019)
4.	Asparagus	*Asparagus racemosus;* Asparagaceae	Roots	CaOx concentration decreased
5.	Ootang	*Bambusa nutans* Wall.; Poaceae	Shoots	Increased Diuretic action (Sohgaura *et al.; 2018*)
6.	Pasanabheda, Stone breaker	*Berginia ligulata;* Saxifragaceae	Rhizome	CaOx concentration decreased (Garimella *et al.;* 2001)
7.	Punarnava	*Boerhavvia diusa;* Nyctaginaceae	Roots	Hyperoxaluria prevented (Pareta *et al.;* 2011)

8.	Patharchata	*Bryophyllum pinnatum;* Crassulaceae	Fresh leaf juice	Reduction in elevated CaOx level (Shukla *et al*.; 2014)
9.	Papaya	*Carica papaya* Linn. ; Caricaceae	Roots	Preventive effect (Vijayakumar *et al*.; 2013)
10.	Bijoru	*Citrus medica* Linn. ; Rutaceae	Fresh fruits	Maintaining the promotor-inhibitor disbalance (Shah *et al.;* 2015)
11.	Lemongrass	*Cymbopogon proximus;* Poaceae	Whole plant	Reduction in lithiatic components (Ibrahim *et al.;* 2013)
12.	Sargassum seaweed	*Sargassum wightii;* Sargassceae	Brown macroalgae	Preventive effect on stone formation (Gilhotra *et al*.; 2013)
13.	Roselle	*Hibiscus sabdariffa* Linn*;* Malvaceae	Leaves	Decrease in concentration of promotor ions and increase of inhibitors (Gilhotra *et al.;* 2009)
14.	Apamarga, Puthkanda	*Achyranthes aspera* Linn. Amaranthaceae	Roots	Reducing renal tissue injury (Aggarwal *et al*.; 2012)
15.	Spirulina	*Cynobacterium*	Blue green	Provide nutritional balance as functional

			algae	food (Al-Attar *et al*.; 2010)
16.	Pepper elder	*Piper amalago* Linn*;* Piperaceae	Leaves	Increase in diuretic action (Silva *et al.;* 2014)
17.	Baby watermelon, ivy gourd	*Coccinia indica* Wight	Fruits	Dose-dependent lithiatic action (Kumar *et al*.; 2014)
18.	Shoeblack plant	*Hibiscus rosa sinensis* Linn; Malvaceae	Flowers	Reduction in level of urinary Calcium and oxalate level (Prasanna *et al*.; 2007)
19.	Varuna, sacred garlic pear	*Crataeva religiosa;* Capparaceae	Bark	Significant reduction in excretion of Calcium, oxalate, uric acid and phosphate ions (Siddarthan *et al*.; 2015)
20.	Wild sugarcane, Kans grass	*Saccharum spontaneum* Linn; Gramineae.	Roots	Reduction in calcium, phosphate and promoter ions (Sathya *et al*.; 2012)
21.	Wild carrot, Duqu,	*Peucedanum grande* C. B. Clarke; Apiaceae	Fruits	Significant decrease in level of CaOx crystals and promoting factors (Kumar *et al.; 2016*)

22.	Grapes	*Vitis vinifera* Vitaceae	Seeds	Renal function repair by antioxidant action (Grases *et al.*; 2014)
23.	Nigella, Kalonji	*Nigella sativa* L Ranunculaceae	Seeds	Significant nephroprotective effect (Benhelima *et al.*; 2016)
24.	Creeping launaea	*Launaea procumbens* Linn Asteraceae	Leaves	Antioxidant nephroprotection (Makasana *et al.*; 2014)
25.	Kurchi, Kutaja	*Holarrhena antidysenterica Linn* Apocynaceae	Seeds	Protective and preventive effects (Khan *et al.; 2012*)
26.	Golden dewdrop, Skyflower	*Duranta erecta* Verbenaceae	Leaves	Preventive and antioxidant action. (Agawane *et al.; 2019*)
27.	Patharchatta	*Kalanchoe pinnata;* Crassulaceae	Leaves	Reduction in calcium and oxalate level in urine (Gilhotra *et al.;* 2011)
28.	Bottle gourd, Lauki	*Lagenaria siceraria;* Cucurbitaceae	Fruits	Reduction in CaOx excretion and crystal deposition (Takawale *et al.;* 2012)

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29.	Bada gokhru	*Pedalium murex* L.; Pedaliaceae	Fruits	Promotor- inhibitor balance, diuretic action (Patel *et al.;* 2016)
30.	Yellow-fruit nightshade	*Solanum virginianum* L.*;* Solanaceae	Whole plant	Curative and preventive effects (Chinnala *et al.;* 2013)
31.	Vegetable hummingbird	*Sesbania grandiflora;* Fabaceae	Leaves	Significant antioxidant action (Doddola *et al.; 2008*)

In-vitro Studies:

Table 3: List of some medicinal plants studied for theirin-vitro Antilithiatic activity:

S. No.	**Common Name**	**Scientific Name and Family**	**Plant Part Used**	**Type of *in-vitro* Assay**	**Outcomes**
1.	Hairy rupturewort	*Herniaria hirsute* Linn*;* Caryophyllaceae	Fresh herb	Aggregation assay	Reduced CaOx crystalization (Atman *et al*.; 2000)
2.	Kulthi, Kultha, Horse gram	*Dolichos biflorus* Linn. ; Fabaceae	Seeds	Titrimetric and colorimetric analysis	Lowering of Calcium crystal formation (Garimella *et al*.; 2001)
3.	Stone flower or	*Bergenia ligulata* Wall.;	Rhizomes	Titrimetric and colorimetric	Lowering of Calcium

	Pashanbheda	Saxifragaceae		analysis	crystal formation (Garimella *et al*.; 2001)
4.	Hiranpug, Bindweed	*Convolvulus arvensis;* Convolvulaceae	Leaves, Flowers	Aggregation, Nucleation Assays, turbidity kinetic studies	Reduction in CaOx formation (Rajeshwari *et al*.; 2013)
5.	Sargassum seaweed	*Sargassum wightii;* Sargassceae	Brown macroalgae	Crystal nucleation	Preventing crystal growth, nucleation and aggregation (Sujatha *et al*.; 2015)
6.	Apamarga, Puthkanda	*Achyranthes aspera* Linn. Amaranthaceae	Roots	Nucleation and growth assays	Inhibition of crystal nucleation and growth (Aggarwal *et al.*; 2012)
7.	Moonseed vine	*Triclisia gilletii* Staner; Menispermaceae	Whole plant	Nucleation assay	Conc. Dependant prevention of crystal nucleation (Al-Attar *et al*.; 2010)
8.	Pepper elder	*Piper amalago* Linn*;*	Leaves	Turbidity analysis	Increase in diuretic action

		Piperaceae			(Silva *et al*.; 2014)
9.	Kurchi, Kutaja	*Holarrhena antidysenterica Linn* Apocynaceae	Seeds	Aggregation assay and LDH assay	Preventive and protective effects (Khan *et al.;* 2012)
10.	Golden dewdrop, Skyflower	*Duranta erecta* Verbenaceae	Leaves	Nucleation and synthetic urine assay	Inhibition of COM, COD formation (Agawane *et al*.; 2019)
11.	Cotton	*Gossypium herbaceum;* Malveceae	Leaves	Titrimetric testing	Calcium oxalate crystal dissolution (Niharika *et al.*; 2018.)
12.	Clearing-nut, Nirmali	*Strychnos potatorum* L.; Loganiaceae	Whole plant	Nucleation and aggregation assay	Significant CaOx dissolution (Binu *et al*.; 2016)
13.	Chikoo, Naseberry	*Manilkara zapota*	Seeds	Titrimetry analysis	Crystal dissolution (Sanjuna *et al*.; 2019)

Observed outcomes from the literature:

Agawane et al. (2019) investigated the antilithiatic effect of *Duranta erecta* extract in in-vitro and in-vivo urolithiatic models and observed significant antioxidant and protective action alongwith the repair of renal functions.

Aggarwal et al. (2012) studied the preventive and curative antilithiatic effect of *Achyranthes aspera* Linn leaf extract and found the effectiveness in terms of reducing the renal injury and maintaining the promotor- inhibitor imbalance.

Al-Attar (2010) observed that spirulina have antilithiatic properties when administered as food supplement in solution form. The researcher concluded that the blue-green algae, possessing some nutritive properties that helping in control of lithiatic and other biochemical factors.

Atmani et al.(2000) estimated the antilithiatic activity of *H. hirsuta* extract using in-vitro aggregation assay and observed the reduction in CaOx crystal aggregation after the administration of different doses of the extract.

Benhelima et al. (2016) studied the nephroprotective effect of *Nigella sativa* L seeds in male wistar rats and observed a significant protective effect on urinary and serum calcium, phosphate and oxalate level.

Betanabhatla et al. (2009) observed the antilithiatic activity of *Hibiscus sabdariffa* using ethanolic extract of its leaves in ethylene glycol induced lithiatic model for rats and found the significant activity by decreasing the concentration of promotor ions and maintaining the inhibitors.

Binu et al. (2016) studied the in-vitro antilithiatic effects of *Strychnos potatorum* using calcium oxalate nucleation and aggregation assays and found it to be potential as it showed significant dissolution of CaOx crystals.

Chavada et al. (2012) observed that flavanoid rich fraction of *Citrus medica* significantly prevented EG induced lithiatic changes in experimentally induced urolithiatic model attributing to its diuretic action, decrease in promoters, increase in inhibitors level & antioxidant potential.

Chinnala et al. (2013) studied the effect of *Solanum virginianum* extract on ethylene glycol induced urolithiasis in rats and concluded the protective and curative properties for stone forming factors.

Christina et al. (2013) concluded that hydroalcoholic extract of the *Abelmoschus moschatus* Medikus was found effective against ethylene glycol induced nephrolithiasis. Urinary calcium, oxalate, phosphate level were decreased and increased urinary magnesium level. It also increased the urinary volume there by reducing the tendency for crystallization.

Da Silvaet al. (2014) studied the diuretic activity of *Piper amalago* in male adult wistar rats and suggested the antilithiatic potential on the basis of this study along with an in-vitro turbidity analysis using human urine samples.

Garimella et al. (2001) observed the in-vitro antilithiatic potential of rhizomes extracts of *Bergenia ligulata* Wall. and seed extracts of *Dolichos biflorus* Linn. also the combination of both and found the effectiveness of individual extracts as compared to the combination was significant in terms of formation of calcium crystal formation.

Ghaeni et al. (2014) evaluated the anti-lithiatic potential of pharmacologically active compound Crocin as curative as well as preventive dose regimen using EG induced lithiatic model in wistar rats and suggested that the compound, showing some antioxidant activity, can serve the role for adjunctive and alternative therapy in kidney stone management.

Gilhotra et al. (2011) studied the antilithiatic effect of *Kalanchoe pinnata* leaf extract in rats and observed the significant control of stone forming factors. They observed a significant reduction in the elevated level of ions such as calcium, oxalate, phosphate, protein, creatinine, unc acid in urine with treatment of *Kalanchoe pinnata* treated rats, it was also found to elevate the urinary magnesium level which helps in reducing the stone formation in the renal tissue.

Grases et al. (2015) studied the effects of polyphenols in lithiasis induced rats. The authors used EG + AC induced lithiasis model and observed the outcomes by antioxidant action of polyphenols, repairing the renal damage and regaining renal ftmctions.

Hegazy et al. (2019) evaluated the protective effects of *Apium graveolens* seed extract on liver and renal toxicity caused by gentamicin in wistar rats.

Ibrahim et al. (2013) concluded that the combination of *Foenicumum vulgare* and *Cymbopogon proximus* in beverage form efficiently reduced the level of risk factors promoting urinary stone. They also suggested that herbal beverage adjust the levels of urinary promotor- imbalance when taken in daily routine life.

Kalyani et al. (2010) observed that treatment with *Rubia cordiofolia* in the form of hydroalcoholic extract prevented the changes in urinary calcium, oxalate and phosphate excretion dose-dependently as well as revert the elevated calcium and oxalate level in lithiatic rats.

Khan et al. (2012) carried out in-vitro and in-vivo studies to investigate the antolithiatic potentioal of *Holarrhena antidysenterica* and observed the activity through CaOx aggregation and antioxidant actions.

Kumar et al. (2014) observed the antilithiatic potential of *Coccinia indica* W. and suggested the effective dose dependent antilithiatic activity using ethylene glycol induced lithiasis model on Wistar rats administering cystone as standard chug.

Kumar et al. (2016) performed in-vivo anti-urolithiatic studies of *P. grande* in rats and the outcomes suggested the lithotriptic action and the potential to prevent the growth of calcium oxalate crystals.

Makasana et al. (2014) investigated the anti-lithiatic effect of *Launaea procumbens* in rats and observed changes in urinary parameters through antioxidant nephroprotection and inhibition of stone formers.

Mekap et al. (2010) treated the lithiatic rats with ethanol extract of *C. magna* bark with a dose of 400 mg/ kg body weight and found that showing significant anti-urolithiatic activity than other grouped animals.

Murugan et al. (2001) reported that combination dosing of *A. Lanata* leaf extract and Vediuppu chunnam increases the urine volume, thereby reducing the solubility product with respect to crystallizing salts.

Niharika et al. (2018) suggested the in-vitro studies of ethanolic and aquous extracts of *Gossypium herbaceum* using titrimetric method and observed the significant dissolution of CaOx crystals.

Pareta et al. (2011) stated that *Boerhaavia diffusa* extract inhibited in-vitro formation, nucleation and aggregation of CaOx crystals in the synthetic urine and cured polyuria, hyperoxaluria and impairment of renal function and CaOx crystal deposition in the renal tubules caused by EG intake was prevented by BDE treatment.

Patel et al. (2016) observed the antilithiatic activity of *Pedalium murex* fiuit extract and concluded that the activity might be because of maintaining balance in promoters- inhibitors and diuretic action.

Prasanna et al. (2007) studied the effect of *Hibiscus rosa sinensis* Linn on urolithiasis in albino rats in comparison with cystone as standard chug by reducing the level of urinary calcium and oxalate minerals.

Rajeshwari et al. (2013) observed the significant inhibition of CaOx crystal formation by the floral and leaf infusions of *Convolvulus arvensis* using in-vitro studies like inhibition, kinetic studies, nucleation, aggregation assays.

Sanjuna et al. (2019) studied the in-vitro antilithiatic activity of *Manilkara zapota* seeds and observed significant calcium oxalate crystal dissolution ability.

Sathya et al. (2012) studied in-vivoantilithiatic effects of root extract of *Saccharum spontaneum* in EG- induced urolithiatic rats and the finding suggests the lovering the level of stone forming factors and promotors in urine.

Shah et al. (2011) suggested that administration of Fruits extracts of *M charantia* Linn. in urolithiatic rats reduced and also prevented the formation of urinary stones.

Shah et al. (2015) observed the anti-urolithiatic activity of *Citrus medica* in caliculi induced rats by maintaining promotor- inhibitor imbalance.

Shukla et al. (2014) found that the treatment of *B. pinnatum* extract in different doses, significantly, reduced the elevated urinary oxalate concentration.

Siddarthan et al. (2015) studied the antilithiatic activity of *Cravaeva religiosa* bark extract with ethanolic extration on wistar rats and observed the significant reduction in calcium, oxalate, uric acid and phosphate ions as maintaining the promoter- inhibitor balance.

Sohgaura et al. (2018) found the diuretic potential of *Cynodon dactylon, Emblica officinalis, Kalanchoe pinnata* and *Bambusa nutans* as these helped in increasing the urine volume and excretion of sodium, potassium, chloride ions.

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 24, Issue 2, 2020, Pages. 507 - 537
Received 24 October 2020; Accepted 15 December 2020

Sujatha et al. (2015) studied the antilithiatic potential of *Sarghassum wightii* extract with *in-vitro* nucleation, aggregation and crystal growth assays and in-vivo studies in male Sprague Dawley rats and found the significance of plant in reduction of renal lithiasis.

Takawale et al. (2012) studied the effect of *Lagenaria siseraria* fruits in powder for treatment of lithiasis induced by sodium oxalate in wistar rats and found reduction in calcium oxalate excretion & prevention of crystal deposition.

Vijayakumar et al. (2013) found the preventive effect of methanolic extract of *Carica papaya* roots on CaOx crystal formation in the rat kidney.

Vyas et al. (2011) observedthe antiurolithiatic potentials of hydro-alcoholic extract of *Pergulia daemia* as reduction of stone-forming constituents in urine and their decreased kidney retention reduces the solubility product of crystallizing salts such as calcium oxalate and calcium phosphate.

Table5. List of allopathic formulations studied for antilithiatic activity:

S.No.	**Formulation/ Brand name**	**Generic name**	**Study type**	**Study type**	**Outcomes**	**Reference**
1.	Allopurinol	Allopurinol systemic	EG induced lithiasis	*In-vivo*	Reduction in oxalate formation	Yasui *et al.;* 2001
2.	Amiloride (Midamor)	Diuretics	Chemical induction	*In-vivo*	Na^+ reabsorption in late DCT and collecting duct	Bijauliya *et al.;* 2017; Mariano *et al.*; 2020
3.	Chlorthalidone	Thiazide-like diuretics	Patient study	NA	Reccurance prevention	Reilly *et al.*; 2010
4.	Crocin	Pure	EG- induced	*In-vivo*	Significant antioxidant	Ghaeni *et*

		compound	lithiasis		activity	*al.*;2014
5.	Digoxin (Lanoxin)	Cardiac glycoside			Inhibition of Na^+, K^+ ATPase	Bijauliya *et al.;* 2017
6.	Fennel, Cymbopogon	Herbal beverage	NaOx induced	*In-vivo*	Reduction in stone forming components	Ibrahim *et al.;* 2013
7.	Flomax/ Tamsulosin	Tamsulosin systemic	Patient study	NA	Effective and safe for treatment of stones size less than 10 mm	Thapa *et al.;* 2014
8.	Hydro-chlorothiazide (HCTZ)	Diuretic	Patient study	Non controlled clinical trial	Dose dependent hypo-calciuric effect	Naseri *et al.*; 2011
9.	Indapamide	Thiazide-like diuretics	Patient study	NA	Reccurance prevention	Reilly *et al.*; 2010
10.	*Kalanchoe pinnata, Rotula aquatica*	Formulation	Homogenous precipitation method	*In-vitro*	Inhibition of CaOx crystal formation	Gilhotra *et al.;* 2013
11.	Sodium bicarbonate	Oral formulation	Randomized clinical trial	NA	Increases citrate composition	Pinheiro *et al.*; 2013

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 24, Issue 2, 2020, Pages. 507 - 537
Received 24 October 2020; Accepted 15 December 2020

12.	Sodium-potassium Citrate (CG-120)	Sodium-potassium Citrate	Patient study	NA	Reducing the chances of recurrence	Suzuki *et al.*; 1991
13.	Tiopronin	2-mercaptopropionylglycine, 2-MPG	Patient study	NA	Renal function repair	Carlsson *et al.*; 1994
14.	Zonisamide	Sulphonamide derivatives			Inhibits the T-type Ca^{2+} channel	Bijauliya *et al.;* 2017

Table 6. List of Marketed Formulations Available for Treatment of Lithiasis:

S. No.	**Drug**	**Generic name or Composition**	**Route of Administration**	**Mechanism**
1.	Uro-Mag	Magnesium oxide systemic	Oral dosage	Mg suplementation
2.	Polycitra- K solution	Potassium citrate systemic	Oral dosage form	K^+ supply
3.	Bicitra solution	Sodium citrate systemic	Liquid Oral dosage form	Lessen the acidity of urine
4.	Oracit	Citric acid/ sod. Citrate systemic	Oral route	Reduce uric acid level

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 24, Issue 2, 2020, Pages. 507 - 537
Received 24 October 2020; Accepted 15 December 2020

5.	Cytra-2	Sodium citrate systemic	Oral	Reduce uric acid level
6.	Virtrate-2	Sodium citrate systemic	Oral dosage form	Lessen the acidity of urine
7.	Liqui-Dualcitra Solution	Potassium and sodium citrate	Oral liquid dosage form	Lessen the acidity of urine
8.	Potassium citrate ER	Potassium and sodium citrate	Oral	Reduce uric acid level
9.	Urosit- K	Potassium and sodium citrate	Oral route	Reduce uric acid level

Table 7. List of Herbal Formulations Available in Market for Kidney Stone Treatment:

S. No.	**Formulation**	**Dosage Form**	**Constituents**	**Mfg. Company**
1.	Cystone Syrup	Liquid Oral Dosage Form	*Bergenia ligulata/ciliate; Rubia cordifolia; Cyperus scariosus; Achyranthes aspera; Onosma bracteatum; Vernonia cinerea,* Shilajeet (Purified) and Hajrul yahood bhasma	Himalaya Herbals
2.	Cystone	Oral	*Bergenia ligulata/ciliate; Rubia cordifolia; Cyperus scariosus;*	Himalaya

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 24, Issue 2, 2020, Pages. 507 - 537
Received 24 October 2020; Accepted 15 December 2020

	Tablets	Tablets	*Achyranthes aspera; Onosma bracteatum; Vernonia cinerea,* Shilajeet (Purified) and Hajrul yahood bhasma	Herbals
3.	Neeri Tablets	Oral Tablets	*Bergenia ligulata; Boerhaavia diffusa; Butea monosperma; Swait Parpati; Yahood Bhasam; Crataeva nurvala; Vernonia cinerea; Achyranthes aspera; Tribulus terrestris; Mimosa pudica; H. vulgare;* Sudh Shilajeet	Aimil Pharma
4.	Kee Stone Capsules	Oral Capsules	*Crataeva nurvala; Ficus racemose; Boerhaavia diffusa; Tribulus terretris; lawsonia alba; Didymocarpus pedicellata; Achyranthes aspera; Raphanus sativus; Hemidesmus indicus;* Shilajit	Kee Pharma
5.	Ural capsule	Oral Capsules	Pashanbhed, punarnava Gokshurak, Kullthi, Varuna, Chandraprabha	Vasu Healthcare ltd.

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 24, Issue 2, 2020, Pages. 507 - 537
Received 24 October 2020; Accepted 15 December 2020

6.	Keva Stone Crush Tonic	Tonic Syrup	*Bergenia ligulata; Crataeva religiosa; Boerhaavia diffusa; Tribulus terrestris; Coriandrum sativum; Picrohiza kurroa; Cardamomum elettaria*; Processed potash alum; Yavakshara; Sodium chloride; Sodium bicarbonate	Keva S. Biotech (India), Punjab, India.
7.	Kapiva Stone Go juice	Liquid form	Pashanbheda, Harad, Baheda, Amla	Kapiva Ayurveda
8.	Alkaston B-6 Syrup	Liquid Syrup	Magnesium citrate, Potassium citrate and vitamin B6 (pyridoxine)	Ipca Laboratories Ltd.
9.	STON- 1 B_6 tablets	Tablets	Magnesium citrate, Potassium citrate and Vitamin B6	Cipla Ltd.

Table 8: List of Patented Herbal Formulations Available For Treatment of Lithiasis:

S. No.	**Patent ID**	**Title of Patent**	**Date of Patent**	**Patent Authority**	**Ingredients**	**Refrences**
1.	US 9.259,441 B2	Herbal composition for the treatment of kidney stone	Feb.16, 2016	US patent	*Crataeva nurvala, Musa sapientum, Achyranthes*	Patankar; 2016

		and other urinary tract disorders			*aspera*, *Hordeum vulgare*	
2.	US 2013 0337057A1	Novel herbal composition for the treatment of kidney stone and other urinary tract disorders	Dec.19, 2013	US patent	*Crataeva nurvala*, *Musa sapientum*, *Achyranthes aspera*, *Hordeum vulgare*	Patankar; 2013
3.	US 9,233,135B1	Composition and methods to inhibit kidney stone growth	Jan.12, 2016	US patents	Citric acid, magnesium citrate, phytin, pyridoxine and *Musa paradisiacal*	Hayer *et al.*; 2016
4.	US 2013 OO64912A1	Formulation for alleviation of kidney stone and gallstone symptoms	Mar.14, 2013	US Patents	*Berberis vulgaris* and *Nux vomica*	Barron; 2013
5.	#5,137,722	Patent for extract and pharmaceutical composition for treatment	Aug.11, 1992	US patents	*Eriobotrya japonica*	Costello; 1992

		of calcium oxalate stone disease.				

Limitations of allopathic treatments for lithiatic disorders:

Kidney stone or urinary calculi are metabolically formed in urinary system due to the changes in urinary lithiatic promoter- inhibitor balance. As the known mechanisms suggest that stone formation starts with renal tissue injury and urine supersaturation. All such biochemical changes lead to formation and growth of mineral crystals into large sized stones which cause unbearable pain in the abdominal portion of body.

The treatment conditions includes various types of therapies like surgical removal of stone, radiation or laser therapy (ESWL) or endoscopic procedures like Ureterorenoscopy (URS) and Percutaneous nephrolithotripsy (PCNL). The large sized stones are broken into smaller size and removed from the body through urinary passage. Allopathic medications like diuretics, anti-inflamatry agents and mineral supplements are prescribed during or post surgical treatment for maintaining the normal physiological conditions. Urolithiasis has a high risk of recurrences and chugs like diuretics cannot be used for long term as they are known for causing renal damage and other side effects. Allopathic medicines are used to provide symptomatic treatments and provide quick action to suppress the symptoms rather than treating the actual cause of disease. Using diuretics or other such drugs for a longer period can cause toxicity and damage to the organs. Patients are prescribed alkalizers or renal tonics for maintaining the tonicity, mineral balances removal of stone and reduce the cellular toxicities. Nowadays herbal medications are being used widely for the treatment of lithiatic disorders (Gonzalez et al. 2020). Several medicinal plants that possess the potential to dissolve the stones and remove as already reported in the ancient literatures and are being investigated by the researchers these days. The plants like *Bergenia ligulata, Boerhaavia diffusa, Butea monosperma, Crataeva nurvala, Vernonia cinerea, Achyranthes asper, Tribulus terrestris, Mimosa pudica, H. vulgare* and others have been investigated for various pharmacological applications.

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 24, Issue 2, 2020, Pages. 507 - 537
Received 24 October 2020; Accepted 15 December 2020

Herbal drugs are being used by modern day physicians because of better results, long term relieves, very less account of side effects and long term use for permanent treatment of disease.

Various approaches that are required to be considered for development of a potent drug regimen for treatment of lithiasis:

Stone formation is caused by a series of processes taking place in the urinary system. Initiated with lithiatic promoters-inhibitors imbalance leads to generation of free radicals, inflammation and renal epithelial tissue injury which serves as site for crystal nucleation furthermore on supersaturation of urine aggregation of stone forming crystals and their growth and formation as renal calculi or kidney stone. Crystal nuclei starts to form on the site of tissue injury or inflammation, which act as crystal seed or centre of nucleation in urinary system for initiation of stone formation, a process called heterogeneous nucleation. Damage to the renal epithelial cells cause inflammation also promotes stone formation by providing suitable environment and surface for crystal nucleation. Next step includes supersaturation of urine with stone forming minerals such as calcium oxalate, sodium oxalate, which after nucleation start to aggregate and grow into larger size and results in generation of urolithiasis (Moe et al. 2011).

Properties of an Ideal Antilithiatic Medicine:

An ideal antilithiatic chug regimen is alone or in combination is required to provide the following qualities:

It should be able to maintain the promoter- inhibitor balance;

It should maintain the adequate pH and alkalinity of urine;

It should be able to repair the tissue damage caused by stone aggregation and should prevent further epithelial injuries;

It should provide significant diuretic action so that to prevent supersaturation and crystal accumulation;

It should possess significant anti-oxidant and anti-inflammatory potentials.

Conclusion:

Uro-lithiasis is a common health problem growing globally which starts with crystallization of oxalates in renal tissue. The present study was attempted to enlighten the knowledge of lithiasis formation, causes of stone formation, control measures, medicinal plants, available

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Received 24 October 2020; Accepted 15 December 2020

treatments, marketed formulations and patents. A large extent of global population is suffering from different kinds of lithiatic conditions. Various studies revealed that Phytotherapeutics can be used as the part of treatment along with the surgical or radiation treatment as an adjunctive therapy to control and prevent recurrence of stone formation. Various medicinal plants are being used for lithiatic treatment (Gonzalez et al. 2020). This review gives an account on such plants and the type of research performed using them. Some potent indigenous herbs which are used in treatment of urolithiasis were discussed. This review suggests ideas about the opportunities for the future research and for the development of new antiurolithiatic therapeutic agents.

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 24, Issue 2, 2020, Pages. 507 - 537
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