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A Narrative Review on an Insight of Herbal Origin Drugs and Their Traditional Medicine Formulations for the Treatment of Nephrolithiasis

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Abstract

Ethnopharmacological relevance. There is no satisfactory treatment at present to cure or prevent kidney stone recurrences using predictable medicines. There are several marketed formulations in Ayurveda, Unani and Homeopathic Traditional Medicines (TM) have potential lithotriptic effects and clinical applications. In India, prevalence rates of complementary and alternative medicine (CAM) for the treatment of nephrolithiasis are being estimated at 63.9%. Aim of the review This review article intended to scientifically documented reports on various herbal drugs and TM formulations with ethnopharmacological and clinical relevance for the treatment of nephrolithiasis ascertain in different books, literature and research articles belonging to the Asian continent. Materials and methods This review article was prepared by utilize several review articles, original research articles and related books from constant databases, such as ScienceDirect, PubMed, Wiley Online Library, SciFinder, ACS Publications, Web of Science, Springer, and Scopus between 1980 to 2021 and the literature exploration were carry out in English. In addition, traditional applications of herbal drug and formulations for the treatment of nephrolithiasis are discussed. Results The herbal drugs and formulations discussed here are affluent in phyto-constituents resembling Phenolic and flavonoid, tri-terpenoids, alkaloids and steroids, etc., liable for the nephrolithiasis effects. A lot of information recommends that reviewed plants and their traditional formulations have valuable role in dissolving the kidney stone. Conclusions In this paper, we have reviewed the pathogenesis, risk factors and management of nephrolithiasis with numerous herbals bioactive with Ayurvedic, Unani and Homeopathic drug formulations and assess the different kinds of herbal bioactive present in formulations which are responsible for management of nephrolithiasis.

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INTRODUCTION

The kidney is a vital organ, which serves purpose of purification and detoxification of the blood by filtration. Hence, this organ always exposes with toxins, heavy metals, chemotherapeutic agents, and other metabolites which could progress into events of different types of renal disease events. Nephrolithiasis, a complex process because of an imbalance between various promoters and

inhibitors in the kidneys [1]. In nephrolithiasis, individual small crystals function as nuclei to promote either growth into larger size crystals or eventually lead to secondary nucleation incidents. Such processes produce various small-sized intra-renal multi-crystalline aggregates/structures fixed within a different renal system region. Subsequently, these are clinically insignificant until subjected to be promotion, in terms of size and events of secondary nucleation (Figure 1).

However, here in this introductory review, our objective is towards more focused more approaches to enumerate those herbs which may interfere in the initiation and progression and nephrolithiasis. Subsequently, these herbs require validation of clinical performances via some indiscriminate clinical trials before their clinical translation. While owing to presence of different types of phytoconstituents in a single herb, which exerts different mechanism and act on, diverse targets so rather than focusing on these mechanisms, we are more focused on plants exhibit such protective actions.

PATHOGENESIS OF NEPHROLITHIASIS

Fate of nephrolithiasis directly depends on factors such as water excretion index, concentration and state of nuclei and crystals; localized *pH*; promoters, and inhibitor's presence [2]. Furthermore, nephrolithiasis may take place while one or more aggravating causes are present, leading towards a super sequential saturation of the urine. The development of crystals structure and further agglomeration in a stone [3]. Briefly, nephrolithiasis is continuous growth of stone, preferably of more than 5 mm (0.2 inches) in dimension, which either block passage in the ureter or their presence in the kidney may results into several symptoms such as bloody micturation, painful urination, severe pain in lower back or abdominal region of affected patients [4]. Subsequently tiny stones may block the flow of urine often; require prompt and urgent medical attentions, owing to severe pains [5].

TYPES AND CLASSIFICATION OF NEPHROLITHIASIS

According to *Ibn Sina*, the nature and constituents of renal and bladder stones are not the same. For example, Calculi of renal systems are tiny and soft with reddish, but the bladder's monolith is relatively more prominent, robust, and sandy-white/black in appearance [6]. Subsequently, crystals of calcium phosphate, calcium oxalate, uric acid, struvite, and proteins and blood as non-crystalline materials are usually present in kidney stones [7]. Calcium oxalate crystals are the most common component of kidney stones having around 75-85% of calcium oxalate and present in the form of monohydrate (Whewellite) and di-hydrate (Weddellite) [8]. In kidney stones, approximately 10-15% of calcium phosphate stones present in combination with calcium oxalate or struvite (Figure 2). Crystalline calcium phosphate appearsin forms of amorphous dark matter in the urine. When urate crystallizes in the kidney, it produces 5-10% of Uric acid and 0.5-1% cystine [9]. Around 75 % of patients with kidney stones have calcium stones constituting chiefly calcium oxalate as major components; however, in some cases calcium phosphate is major components. However, in contrast to this, only > 10% of the population suffers from stones carrying uric acid constituent [10].

REASONS & RISK FACTORS OF NEPHROLITHIASIS

Kidney stones, although may also be considered as an inherited disease, so some specific set of populations are relatively more vulnerable to the development of kidney stones [11]. Nevertheless, most common cause of nephrolithiasis is less consumption of drinking water. Higher concentration of calcium & oxalate ions and low fractions of citrates and urine are major risk factors directly responsible for the enlargement of stone [12]. Chronic diseases like *hypercalcinuria* may lead to damage of renal function, renal insufficiency, and nephron calcinosis. The patients with hypercalciuria put out higher levels of calcium than usual through the kidney. Calcium may come through the gut, where abnormal calcium levels are absorbed from the bones [13]. The risk of stone formation possibly depends more on complete excretion of oxalate and concentration than on arbitrary average values [14]. Citrate is under dissociated anion of citric acid, functions as a weak acid. Source of citric acids are usually from either diet or endogenously being synthesized via tri-carboxylic acid cycles and being excreted out with a rate of < 640 mg/d. Owing to physiological role of citrate ions as an inhibitor of calcium salt crystals,

hypocitraturia incidents, i.e., relatively lower amount (>320 mg per day) of urinary citrates ions concentrations is also considered as significant risk factors in the process of recurrent kidney stones growth. In, severe hypocitraturia, excretion rate of citrates if fall below the 100 mg/day then it may lead into more severe consequences [15-16]. Subsequently, *Hyperuricosuria*, i.e., excessive uric acid in the urine, is due to the direct dissolution of uric acid crystals in the kidneys or urinary bladder [17-18]. Congenital disorder of cystic dilatation in renal collecting tubules leads to a medullary sponge kidney (MSK), which is vulnerable to the development of kidney stones, followed by obstruction mediated urinary tract infection (UTI) [19].

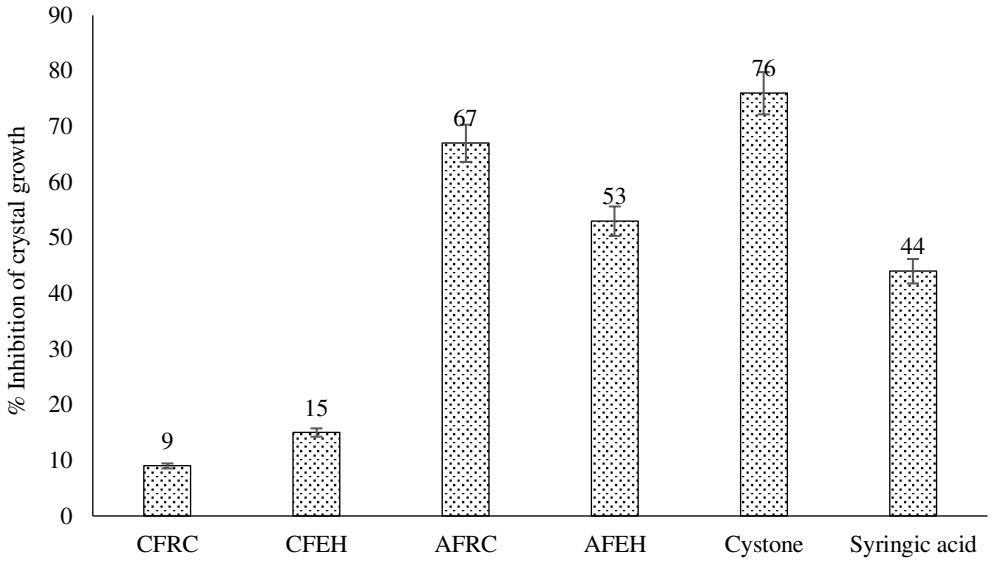

Figure 1. Effects of chloroform and aqueous fractions of *Ricinus communis* and *Euphorbiahirta* CFRC & AFRC; CFEH & AFEH, aqueous extract of cystone, and Syringicacid on calcium oxalate crystallization. The data represent the percentage of inhibition of crystal growth.

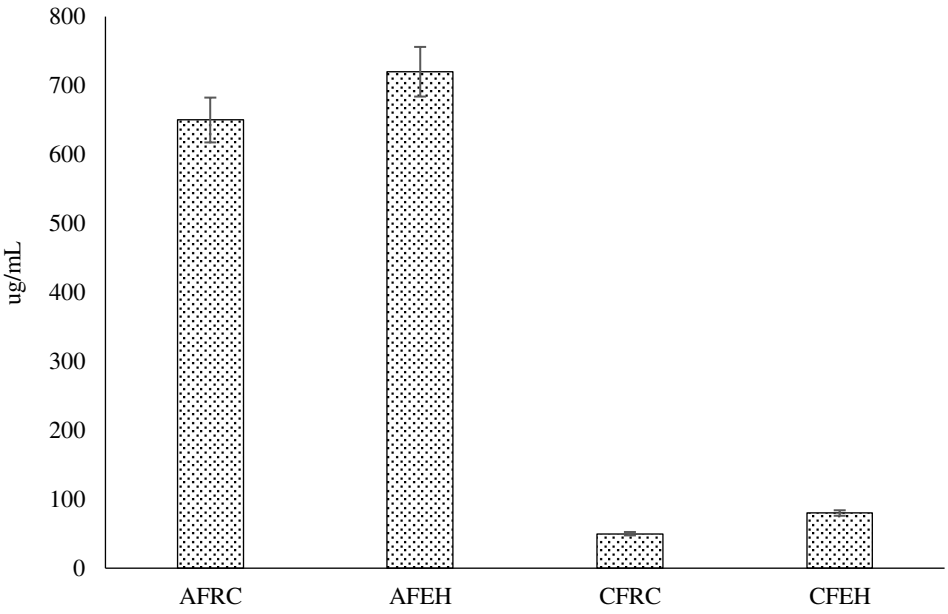

Figure 2. Total phenolic contents of chloroform and aqueous fractions of *Ricinus communis* and *Euphorbiahirta* CFRC & AFRC; CFEH & AFEHin respect of syringic acid.

Epidemiology of Nephrolithiasis

Among the urinary tract's diseases, nephrolithiasis is the third most common disease, which affects primary medical problems, peoples of all over the world [20]. According to the National Health and Nutrition Examination Survey (NHANES), aged populations (~70 years) are highly vulnerable with incidents of kidney stones [21]. As per the information available from the 3rd NHANES, frequencies of such occurrences are continuously increasing not only from 5.2% during 1988-94 to 2007-10 but with more rapid rates are expected, in future. Moreover, NHANES data also established a direct evidence of relatively higher occurrence of kidney stones (8.8%) in United States population [22].

CONVENTIONAL MEDICINES IN NEPHROLITHIASIS

In India, prevalence rates of complementary and alternative medicine (CAM) for the treatment of nephrolithiasis are being estimated at 63.9% [23]. There is no such specific treatment for Nephrolithiasis in the allopathic system of medicine except surgical intervention. While, surgery rivets a lot of emotional and physical suffering to the patient, while surgical intervention is often highly expensive and complications [24].

IMPACTS OF DIETS IN NEPHROLITHIASIS

At both preclinical and clinical-based studies, however, a sufficient quantity of fluids and diet intake comprising of fruits, vegetables, low-fat food components, and calcium minerals but strict avoidance of high-calorie diet including sugar-sweetened beverages (SSB) are sufficient to reduce the level of kidney stone incidents [25]. For example, the diet's required calcium level is proportionate to a 27-35 % reduction in the development of risk of kidney stones, while SSB elevated risk factor by 30-40% stones [26].

FOLKLORES APPROACHES IN NEPHROLITHIASIS

In India, different herbs are commonly used as an integral part, in traditional system of medicines, for clinical management of various diseases [27]. So, in consequences to above, many of folklores are also practicing these herbs to manage various ranges of clinical symptoms [28]. In Ayurvedic, Homeopathic, and Unani medicine, one can easily remove or manage kidney stones naturally using simple herbal medicines [29]. The advantage of herbal medicine is that one can avoid surgery and nullify the body's tendency to form stones using herbal medicine. In Ayurveda, 'Pashanabheda' (stone dissolving) groups are containing list of plants which claim to have usefulness in the treatment of urinary stones [30].

These herbs may contain several types of pharmacologically active phytoconstituents of different therapeutic classes such as acids (Pedicellic acid), terpenes (Cyperene, Camphene, Pinene), triterpenes (Oleanolic acid, Sarsasapogenin), and even alkaloids (Berberine, Lycopodine, Lycodine) [31]. Most of kidney stones acting drugs are often effective, mainly due to diuretic properties, but not essentially [32]. For example, lithotryptic (Anti-nephrolithiasis) activities of many herbal drugs such as flavonoids (Quercetin, Kaempferol, Pashanone, Alizarin, Astilbin, Khellin, Visnagin) and phenolic compounds (Bergin) type of phytoconstituents are being attributed with their potent antioxidant's characteristics. Briefly; these flavonoids, owing to strong antioxidant potentials, reduce inflammation, inhibit glycolate oxidase (GOX) to adversely impact synthesis of oxalate [33].

Anti-Nephrolithiasis Herbs: Ayruveda

The employment of traditional complementary and alternative medicine (TCAM) for primary health care among a population although may vary from one country to the other. However, there are many evidenced based popular herbal plants mentioned in Ayurveda, which are available widely, and showing significant protections against this disorder (Figure 3). Some of these herbs may use either alone, but most commonly as a part of combination therapy.

Gokhru (*Tribulus terrestris* L.)

Tribulus terrestris L. of the family Zygophyllaceae are fruits that come under the natural wild herb, often referred as Gokhru, have been used for curing of various diseases [34]. Anti-nephrolithiasis

activity of Gokhru was the occurrence of flavonoid glycosides of kaemferol, quercetin and rutinoside [Figure. 4]. Gokhuru is an ingredient of Cystone tablets that helps to cure bladder infections and super-saturation of calculogenic chemicals in the urine [35].

Shilapushpa (Didymocarpus pedicellata R.Br.)

Didymocarpus pedicellata R.Br. (F. Gesneriaceae) is a valuable medicinal plant, commonly known as, shilapushpa, shantapushpi, stone flower and sometimes pasanbheda [36]. Chemically, this plant contains flavonoids like chalcones, pashanone, didmyocarpin, isodidmyocarpin, dicarboxylic acid like α-methyl-α′-tridecyl succinic acid (Pedicellic acid). Shilapushpa is the ingredient of cystone tablets found helpful in regulating calcium inclusion in the body [Figure. 4]. Shilapushpa is well known for its diuretic properties, maintains the healthy urinary tract, and helps to dissolve kidney stones [37].

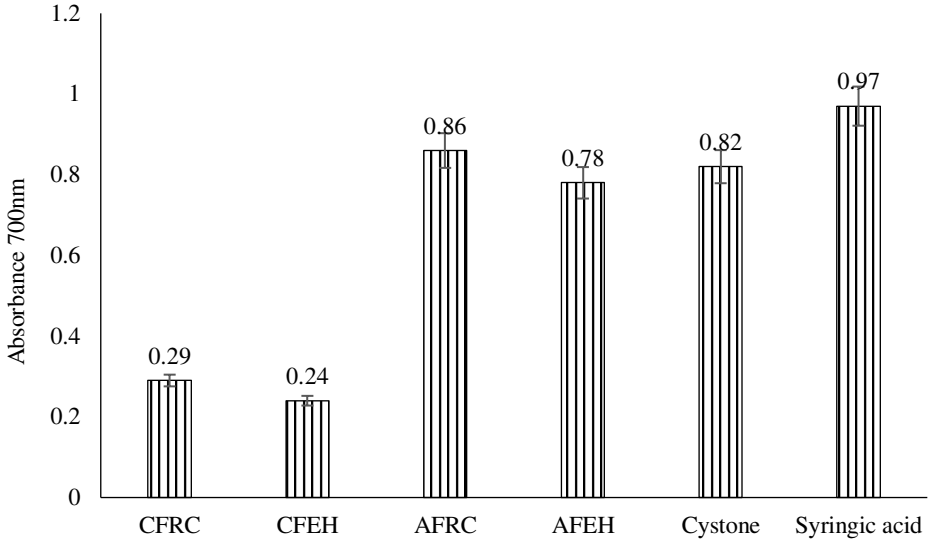

Figure 3. The reductive ability chloroform and aqueous fractions of *Ricinus communis* and *Euphorbiahirta* CFRC & AFRC; CFEH & AFEH, aqueous extract of cystone, and Syringic acid. The absorbance (A700) was plotted against the tested sample. Each value represents mean ± S.D. (n = 3).

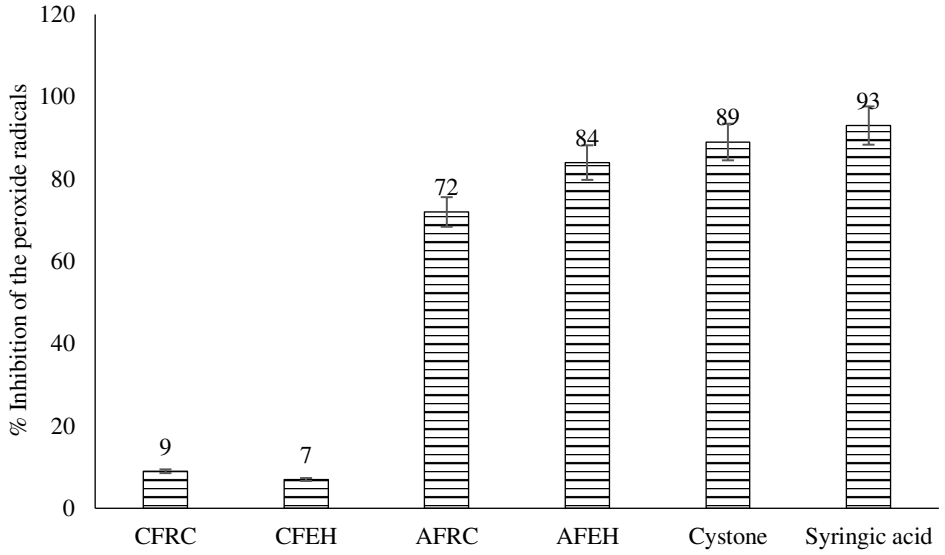

Figure 4. % Inhibition of lipid peroxidation by the chloroform and aqueous fractions of *Ricinus communis* and *Euphorbiahirta* CFRC & AFRC; CFEH & AFEH, aqueous extract of cystone, and Syringic acid. The data represent the percentage of inhibition of peroxide radicals' formation.

***Pasanabheda* (*Bergenia ligulata* (Wall.) Engl.)**

Bergenia ligulata is commonly known as Pashanbheda, ashmabhid, ashmabhedi, nagabhid, upalbhedak, pashana, zakhmehayat, asmaribheda, parwatbhed, and shilabhed (stone breaker) as it dissolves slabs [38]. Chemically, the plant contains phenolic compound trihydroxy benzoic acid glycoside (Berginin), tannic acids, *β*-sitosterol, and a new 4(4′-*β*-d-glucopyranosyloxy-1′-benzyloxy)-6-methyltetrahydropyran-2-one also termed as Paashaanolactone [39]. Pasanabheda is also the key ingredient of cystone tablets that possesses diuretic effect, demulcent and antimicrobial activities [Figure 4]. As it has a rich content of mucilage renders demulcent property to this herb. It also soothens and protects the inflamed tissues [40].

***Manjishtha* (*Rubia cordifolia* L.)**

Rubia cordifolia is a species of flowering plants belonging to a coffee family, i.e., Rubiaceae [41]. This plant is of economic importance as a red pigment source in many parts of Asia, Europe, and Africa. The plant's root contains an organic compound called Alizarin (1, 2-dihydroxy-anthraquinone), a red colour dye used in textiles. This dye is also known as rose madder. Manjishtha is used for its diuretic effect and maintaining a healthy urinary tract, which helps to dissolve kidney stones [42].

***Nagarmotha* (*Cyperus scariosus* R.Br.)**

Cyperus scariosus is found widely all over the India mainly in damp location and collected invariably to extract its essential oil. Phytochemical studies reveal presence of polyphenol, flavonol, alkaloid, saponins, sesquiterpenoids, and essential oil, namely cyperene, pinene, camphene, pinocarveol, myrtenol [43]. The rhizomes of the plant possess pleasant aromatic odour *used as* a spasmolytic, diuretic, anti-inflammatory, antimicrobial and anti-fungal agent, and it is the ingredients several Ayurvedic formulations [44-45].

***Apamarga* (*Achyranthes aspera* L.)**

Achyranthes aspera, generally known as apamarga, is a plant belonging to the family Amaranthaceae family. This plant is widely used in Ayurveda as an herbal medicine for ages [46]. Its roots and leaves are the active component and typical ingredients of various drug formulations, including Csytone (Himalaya), used to treat kidney stones. The plant has been scientifically proven for its anti-nephrolithiasis potency and ability to preserve the renal functioning and protect it from the renal injury. *A. aspera* contains triterpenoid saponins possessing oleanolic acid and alkaloids like achyranthine and betaine (Figure 5) [47].

***Gaozaban* (*Onosma bracteatum* Wall.)**

Onosma bracteatum, known as Gaozaban, is found in the mediterranean regions, including Europe and Asia. *Onosma bracteatum* is also referred to as Gojihva, which belongs to the family of Boraginaceae. In India, it is found in Kashmir and Kumaon region and sold in the local market as a medicinal herb. Small hair-like structures cover the leaves with small nodules giving it a rough appearance like a cow tongue [48]. The leaves contain potassium, calcium with mineral acids, lycopsamine, and supindineviridiflorate as the predominant pyrrolizidine alkaloids [Figure. 5]. *Onosma bracteatum* is listed in the German Commission E as an herb used to alleviate pulmonary infections and kidney disease as a diuretic and spasmolytic [49].

***Sahadevi* (*Vernonia cinerea* Lin.)**

*Vernonia cinerea*is a medicinal herb of Asteraceae family. This plant is an erect and rarely branching annual herb [50]. It is considered a diuretic, antispasmodic, and antimicrobial. This plant helps treat urinary disorders that include dysuria and spasms of the urinary bladder. The plant contains 26-Methyl-hepatocosanoic acid; 3-*β*-acetoxyurs-19-ene; 4-sulfo-benzocyclobutene; α-amyrin; apigenin-4'-O-beta-D-glucoside; α-spinasterol; *β*-amyrinaceate; *β*-sitosterol; luteolin; luteolin-7-O-galactoglucoside; and quercetin [51].

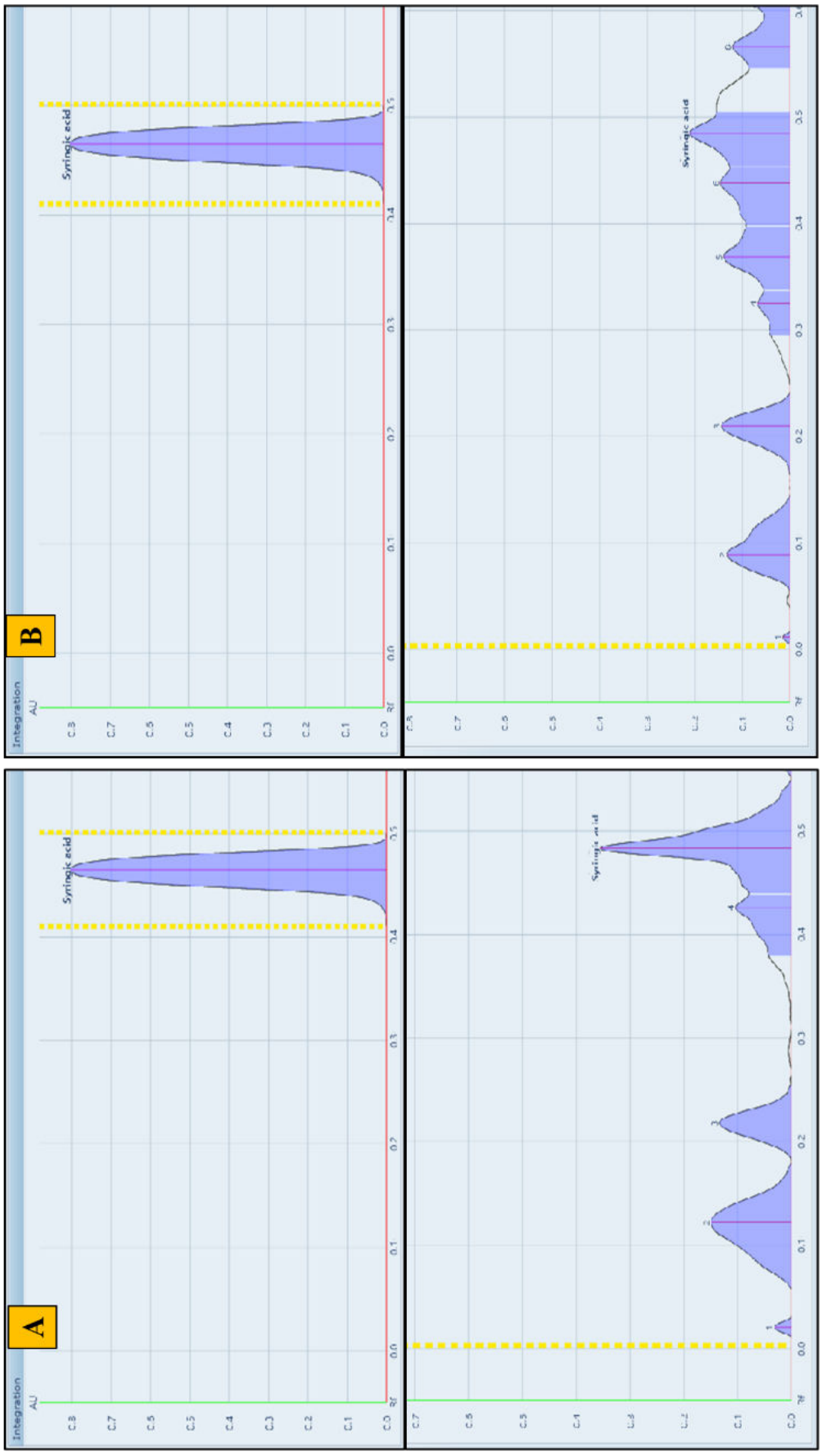

Figure 5. Densitogram of methanolic extract of *Ricinus communis*(A) and*Euphorbiahirta*(B)with thestandard of syringic acid (R_F0.50).

***Punnarnava (Boerhavia diffusa* L. nom. cons.)**

Boerhavia diffusa is commonly known as punnarnava, which means that it rejuvenates or renews the body. Various part of *Boerhaavia diffusa* plant has reported a broad spectrum of antioxidant, diuretic, litholytic, anticancer, etc. [53]. It contains flavonoids (rotenone) and quinolone alkaloid lunamarine (Punarnavin) (Figure 5) [54].

***Common chicory* (*Cichorium intybus* L.)**

Cichorium intybus is a moderately woody, herbaceous plant of the family Asteraceae. This perennial plant has blue flowers that are rarely white or pink. *Cichorium intybus* is cultivated for a salad while the roots baked and grounded to use as coffee due to its diuretic property. It is used as a sweetener in food manufacturing and as a source of dietary fiber [55]. The phyto-constituents present in *C. intybus* plant is the lactones, aesculetin, umbelliferone, sesquiterpene, aesculin, cichoriin, scopoletin, 6,7-dihydrocoumarin, lactucin and lactucopicrin [56].

***Giloy* (*Tinospora cordifolia*)**

Tinospora cordifolia is commonly known as Giloy or Guduchi indigenous to the tropical region of Asian countries. It is a woody creeping plant of family Asclepiadaceae**.** This plant extract has been shown to have anti-lipoxygenase, lithotriptic, diuretic, and anti-inflammatory activity. The plant contains tinosporaside; palmatine; columbin; berberine; tinocordifolioside; choline; tembeterine; tinosporal; tinosporon and tinosporic acid (Figure 5) [57].

***Talmakhana* (*Asteracantha longifolia* L.)**

Asteracantha longifolia L. (F. Acanthaceae) is a component of ayurvedic and Unani medicine, 'Kokilaaksha' and 'Talmakhana.' It is a prickly, corpulent annual herb widespread in sodden areas. Plant's seeds are prickly, bitter, aphrodisiac, booster, and sedative, utilize for treatment of blood and kidney problems. *A. longifolia* contains lupeol; stigmasterol; butelin; and luteolin [58] (Figures 5, 6).

***Cucurbit* (*Cucumis sativus* L.)**

C. sativus is a semi-woody, herbaceous creeping plant of the family of Cucurbitaceae. This plant is indigenous to the tropical and sub-tropical regions in India, including Myanmar and Sri Lanka**.** Its extract has shown to have refrigerant, tonic, anti-urolithiasis, antioxidant and anti-inflammatory activities. The plant contains cucumegastigmane, cucurbitacins, vitexin, orientin, cucumerin, apigenin and isoscoparin [59].

***Horsegram or Kulthi* (*Dolichos biflorus* Linn.)**

Dolichos biflorus Linn. is commonly known as Horsegram or Kulthi. It is a popular crop mostly known for its drought resistance. These are woody herbaceous stems, native in southern India, produced as a minor food crop or fodder for horses [60]. The seed of *D. biflorus* is acclaimed to have litholytic property in ayurvedic. The literature suggests that these plants effectively prevent the deposition of stone-forming material in the urinary bladder [61]. The seed contains polysaccharides; their purification and characterization demonstrate three pentose and three hexose sugar [62].

Yavakshara

Yavakshara is an ayurvedic product known as Yabshool, Jwachhar, and carbonate of potash, and prepared from the mature fruit plant of *Hordeum vulgare.* At the maturation stage, the plant is uprooted and roasted, then soaked in distilled water. The aqueous extract is filtered and dried, called salt of tartar, fictitious carbonate of potash, and Yavakshara. In Ayurveda, Yavakshara treats anorexia, micturation, kidney stones, urinary diseases, abdominal pain, bloating, ascites, cardiac disease, jaundice, and enlargement of glands [63].

Anti-Nephrolithiasis Herbs: Unani Systems

Several single and multiple Unani drug combination formulations have used for the management of Nephrolithiasis. It provides curative treatment using different drugs in the irrigation, massage, poultice,

sitz bath, and orally taken Unani drug formulations [64]. Many of abovementioned drugs are also used in Unani formulations also. The different Unani drug formulations with pharmacological established herbal drug ingredients used to expel kidney stones are summarized here**.**One of the potent drug used in clinical management of Nephrolithiasis, is Jews stones.

***Hajrul Yahud* (Jews stone)**

Jews stone is the larger spines of normal echinoids, particularly cidaroids identified as *Lapis judaicus* (English: Jews' stones; Arabic: Hajarul Yahud; Persian: Sang-e-Jahudan) and usually festooned by a series of longitudinal, delicately tuberculated striae [65]. Hajrul yahud was grown in the late Jurassic period in North Africa, Europe, and the Middle East, and its spines have a short neck and a bulbous head festooned with beaded ribs. *Lapis judaicus* has an extensive history of use in both eastern and western traditional medicines for urinary diseases. DioscoridesPedanius (first century AD) suggested the use of *Lapis judaicus* for dissolving kidney stones. Its fine powder has been used in different Ayurvedic and Unani formulations [66]. Kushta and Majoon are two essential Unani formulations containing Hajrulyahood, a mineral origin drug used in the calcinated form [67].

Anti-Nephrolithiasis Herbs: Homeopathy

In the homeopathic medicine system, there are more than a hundred homeopathic remedies useful in treating kidney stones (Mechanisms of plants and natural products in the prevention of kidney stones shown in (Figure 3). The effectiveness of the above remedies has been established on healthy subjects and clinical trials on renal calculi patients. While many medicines can remove kidney stones or renal calculi, the homeopathy system also prove significant results in the treatments of urinary calculi. Homeopathic medicine in urinary calculi is valuable in all age groups, which will result in severe complications. The different homeopathic drug formulations with the pharmacological established activity of herbal drug ingredients used to expel kidney stones are summarized here**.**

***Berberry* (*Berberis vulgaris* Linn.)**

B. vulgaris (F. Berberidaceae), generally recognized like 'berberry', occurs Southern Europe and the Northeast area of the U.S. and in South Asia including the North part of Asia [68-69]. The homeopathic medicine *Berberis vulgaris* is a more preferred remedy to remove the renal calculus of the left kidney or left ureter. In the homeopathic medicine system, *B. vulgaris* has been mostly used kidney stones and urinary tract infections. Berberine is an isoquinoline alkaloid present in this part as the main constituent with medicinal use in kidney stone disease [70-71].

***Hydrangea root bark* (*Hydrangea arborescens* L.)**

Hydrangea arborescens is known as wild hydrangea or seven barks belonging to the family Hydrangeaceae. *H. arborescens* plants are small to medium-sized, deciduous shrubs [72]. Its roots contain multiple chemicals and minerals such as resins, soda, lime potassium, magnesia, sulphuric acid, phosphoric acids, and a proto-salt of iron. The root of *H. arborescens* plant used medicinally by Americans and afterward by the early colonist for the treatment of nephrolithiasis [73-74].

***Lycopodium (Lycopodium clavatum* L.)**

Lycopodium belongs to a genus of club mosses, referred to as ground pines or creeping cedar moss-like plants of Lycopodiaceae's family. These are flowerless, branched, erect, prostrate stems with needle-like leaves that cover the stem. *L. clavatum* is one of the pivotal medicines of the homeopathic material medica that belongs to an ancient family with a geological history of over 380 million years [75]. Lycopodium is a profound acting homeopathic medicine frequently used as a legitimate medicine. *L. clavatum* affects entire fat metabolism, a disturbing one in proving, regulates protein metabolism, and cures gout and kidney stones. In materia medica, symptoms given are reddish-yellow sand in the urine with a strong smell [76]. *L. clavatum* contain alkaloids like lycodoline, lucidioline, alpha-obscurine, lycopodine, lycodine, lycoposerramine-L, lycoposerramine-M, 11alpha-O-acetyl-lycopodine, des-N-methyl-a-obscurine, and clavolonine [77].

Sarsaparilla (Smilax sp)

Sarsaparilla is a member of Liliaceae family that has alternate leaves, umbels of flowers widely seen in temperate, swampy, and warm areas. In homeopaths, sarsaparilla is an important medicine; to expel a left-sided stone and be evenly effective based on symptoms and used to treat rheumatism, leprosy, psoriasis, tumors, and cancer as traditional medicine. Sarsaparilla has anti-inflammatory, aphrodisiac, Testosterogenic, and Progesterogenic effects and a male rejuvenator [78-79]. The main chemicals constituents of sarsaparilla are flavonoids such as acetyl-parigenin, smitilbin, taxifolin, astilbin, isoastilbin, kaempferol, dihydroquercetin, engeletin, isoengetitin[Figure. 4], phenolic compounds like ferulic acid and resveratrol, and steroids like beta-sitosterol, diosgenin, parigenin, sarasaponin, sarsaparilloside, sarsasapogenin, sitosterol-d-glucoside, smilagenin, smilasaponin, and stigmasterol [80]. The use of sarsaparilla is much more appropriate for the patients having a white deposit in the urine. There is forceful pain at the cease of urination. There is also smoldering and acerbic in the urethra after the urination. Urine exceeds in a stream that is thin and shabby. Sarsaparilla roots have saponins known to help the body absorb other drugs more effectively [81].

***Cantharis* (*Cantharis sp.*)**

The poisonous Spanish fly (*Cantharis sp.*) is superficially similar, sometimes called cantharis. Homeopathic medicine cantharis contains a terpene known as cantharidin. It shows the most desirable results in kidney stone cases where marked influential burning in the urethra during urination is a prominent symptom. Patients with kidney stones who suffer from burning in the urethra can benefit from cantharis and a marvelous homeopathic medicine used for kidney stones. However, it works exceptionally well in cases where burning maturation is the characteristic symptom [82].

***Hairy rupture wort* (*Herniaria glabra* L.)**

Herniaria glabra, most commonly known as hairy rupture wort, is a flowering plant from Caryophyllaceae's family. Its species are native to Eurasia, also known in other continents, including North America [83]. *Herniaria labra* contained phenolics, flavonoids, flavonols, and saponins. *H. glabra* evaluated in rats models of Nephrolithiasis as a protective therapy [84].

***Visnaga* (*Ammi visnaga* Lam.)**

Ammi visnaga is a member of Umbelliferae family commonly known as toothpick-plant, toothpick weed, visnaga, and khella. The plant is indigenous to Europe, Asia and North Africa [85]. The active chemical constituents are coumarin derivatives like khellin, visnagin, and visnadine obtained from *A. visnaga* seeds widely used for the treatment of several diseases, including kidney stones [86].

***Apium (Apium graveolens* L.)**

Apium is the genus of nearly 20 species belonging to Apiaceae's flowering plant, distributed throughout Europe, Asia, South America, Australia, and Africa. These species grow up to 1 m height in the wet soil of marshes. The plant has pinnate to bi-pinnate leaves and small white flowers in compound umbels [87]. The active chemical constituents are volatile oil apiol, phenolic, apigenin, lunularin, and apiin used to obstinate urine [88].

Poly-Herbal Clinical Formulations

Different herb-based drug formulations are clinically used to expel-out kidney stones**.**

Cystone

Cystone is an Ayurvedic medicine in tablet form made by Himalaya Herbal Healthcare used for treatment Nephrolithiasis. In the clinical management of chronic UTI and prevention, Cystone has prescribed for the recurrence of kidney stones. The medicine has some ingredients with potential as a potent Anti-lithiatic and lithotropic agent [89]. The elements present in these formulations mostly work to dissolve on every step of stones formation. This formulation contains *didymocarpus pedicellate, achyranthes Aspera, onosmabracteatum, bergenialigulata, Rubiacordifolia, cyperusscariosus,*

vernoniacinerea, and a purified form of shilajit. The individual plant components of gokshuradi are well known to possess several pharmacological effects, including removing the kidney stones [90-91].

Neeri KFT

Neeri KFT is a natural kidney function toner, poly-herbal ayurvedic proprietary Syrup. The phytoconstituents in the formulation work as a powerful antioxidant, nephroprotective, immune-modulator, thereby multi-mechanism having a propensity to ensure further degenerative alterations. It also endorses restoring nephrons functional capability and normalizes kidneys digressed operational parameters like serum creatinine, serum proteins, serum urea, etc. [92-93].

Crashcal

"Crashcal" is a polyherbal tablet dosage form manufactured by Sampurna-Jeevan Pharmachem. Pvt. Ltd., India. It effectively controls urinary disorders, and it has the best anticalcifyinglithotriptic effect. Crashcal tablets consist of *Bergenia ligulata*, *Dolichosbiflorus*, B*oerhavia diffusa*, *Tribulus terrestris*, M*imosa pudica*, *crataevanurvala*, Asphaltum, *Commiphora mukul*, *Tribulus terrestris* including hajrulyahood bhasma [94].

Renomet

"Renomet" is a polyherbal formulation manufactured by Matxin Labs Pvt. Ltd. It contains *Bergenia lingulata*, *Tribulus terrestris*, *Dolichosbiflorus*, and *crataevanurvala*. Renomet formulation has proven to be safe and effective in reducing stones' size and virtually eliminates it from the kidney [95].

Ural Syrup

"Ural Syrup" is another proprietary Ayurvedic drug produced by Vasu Healthcare, India. It has excellent lithotriptic properties, and it possesses like alkalizing agents. Its lithotriptic action breaks down the stone into gravel, promotes dieresis, and treats burning micturition safely, even in pregnancy [96].

Unex Plus

"Unex Plus" recommends diuretic action, reduces painful micturition, and is sometimes used as an adjuvant to anti-hypertensive therapy. It helps the ailment of genitourinary area and effective in reducing stones' size and virtually eliminates it from the kidney [97].

Stonill plus

"Stonill plus" syrup is a natural lithotriptic polyherbal formulation manufactured by Satyam Health Care, India, using high-grade, which requires the essential herbal ingredients that are beneficial to eliminating renal calculi. This syrup is useful for treating renal colic, cystitis, recurrent calculi, dysuria and excellent lithotriptic properties [98].

Lithocare

Lithocare is a research-based ayurvedic formulation containing anti-inflammatory, anti-infective and diuretic herbal constituents. It promotes urine flow and tackles infection. It also clears urinary dumps and urinary pain in cystitis and inflammation. Lithocare is very helpful in preventing stone development and avoids the situation of surgery. Lithocare is also employed for other urinary symptoms with urinary incontinence, hypotonic, enuresis, and neurogenic bladder [99].

Kaltropsin syrup

"Kaltropsin syrup" is a safe, pleasant-tasting the drug manufactured by United Pharmaceuticals. It has diuretic effects in various types of urinary disorders. Kaltropsin has Lithotryptic, antimicrobial and nephroprotective actions [100].

Nilstone

"Nilstone" is also great ayurvedic therapy for renal stones. It breaks up the stones entirely and is best used in urinary tract infection, burning micturition, and cystitis [101].

Calcury®

"Calcury®" is a natural lithotriptic and diuretic polyherbal formulation manufactured by Charak Pharma Pvt. Ltd., India. Calcury is used as an alternative medical therapy in selective patients with minimal Nephrolithiasis [102-103].

Challenges in Herbal Therapy

Hence, in presence of so many phytoconstituents, of Akaloids, phenolic and steroids/triterpenoids category of drugs targets and pathways are very complicated**.** So, in any of individual herb, elucidation of exact mechanism of action is quite challenging and often misleading one too [104-105]. Due to above-mentioned complicated issues with their mechanisms and pathophysiology of disease, prediction of performance of these herbs in clinical patients could not be addressed [106]. Consequently, based on an evidence-based long history of safe usage, integrating of these phytoconstituents are useful for various proposes in reliable manners . But, due to possible toxicity and lack of specific actions on different targets, combined dosage form-based approaches provide overall better pharmacological responses .

Future Scope and Discussion

Presently, the management of kidney stones by surgical means and surplus bodily shock wave intervention (lithotripsy) are frequently employed, threatening the soft tissues of the kidney and sometimes leading to cancer . Numerous researchers found that chemical molecules from the plant matrix could be used as synergist enhancers when prescribed in combination with conventional medicine to mitigate chemotherapy's side effects . Various herbal bio-actives were critically studied and compiled in the article to prevent and treat nephrolithiasis. Unfortunately, the documented info-chemical characterization of all herbal bio-actives and their single or combined preparations is inadequate. Researchers have further shown that in contrast to the conventional medicines bearing many side effects such as headache, visceral pain, fatigue, and stone recurrences, integration of bioactive components not only ameliorated such side effects but also improve performances. These herbs are not only effective in the clinical management of nephrolithiasis and kidney stones but also to reduce other types of severe complications. Subsequently, this study's findings revealed that increasing charge of lithotripsy and conventional medicine and poor monetary conditions lead people to rely on (TM) for their primary healthcare needs. Many marketed TM formulations in Ayurveda, Unani, and Homeopathic medicine system are used amongst the Asian country population due to its affordability and scarcity of lithotripsy clinics. Hence, recently emphasis is given towards exploitation of TM and the promotion of their formulations as more effective and safer options . So, current review hence stresses upon role of different types of herbs present in Ayurvedic, Unani, and Homeopathic TM formulations are a choice to treat kidney stones without causing any side effects. As scientists are becoming aware of significant outcomes and distinctions of these herbs, mainly product-specificity; some additional studies are needed to focus on the bio-actives components responsible for lithotriptic action.

CONCLUSIONS

In this review, we collected and compiled the details related to the lithotriptic effects of many herbal medicines, including their poly-herbal formulations in India and other Asian countries. These herbal medicines could help the global community venture into a field of alternative and integrative medicine systems. Standardization of medicinal plants, along with the methodical research, desires to be undertaken. Here a stab was made to investigate the TM for the treatment of Nephrolithiasis. We conclude that more interdisciplinary research should be encouraged to develop newer high-quality plant-derived herbal drugs to treat and avert Nephrolithiasis. Moreover, scientific research into the possible effect of interactions between prescribed drugs and TM inside humans requires urgent attention.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that there is no conflict of interest, financial or otherwise.

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Contribution of the Authors

Pradeep Singh	**:**	Data collecting
Muhammad Arif	:	Designing of work
Md Noushad Javed	**:**	Helping in drawing of figures
Md Sabir Alam	**:**	Helping in drawing of chemical structures

Declaration of interest

All authors report no declaration of interest.

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