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Globally used antiurolithiatic plants of family Asteraceae: Historical background, mechanism of action, therapeutic spectrum, formulations with doses

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Abstract
Medicinal plants are the gift of nature and play an important role as a part of our diet to maintain health. They also serve as a versatile weapon to combat against a number of diseases. Every civilization has its own experience and knowledge of therapeutic uses of plants. The belief and observations regarding traditionally used medicinal plants, increasing the interest of people to use them against urolithiasis. Urolithiasis is a common problem afflicted for many centuries with high recurrence. World population of about 12% suffers with urolithiasis. All over the world in different countries and cultures people use plants for the prevention and cure of kidney stone according to their ethnopharmacological information. These formulations are very effective that's why these are used for hundreds of years. This review covers the eighty (80) medicinal plants of most cited family Asteraceae against urolithiasis along with their historical antiurolithiatc background shared in well-known books of Dioscorides, Pliny the Elder, Al Razi and Ibn Sina. This information was extracted to compose antiurolithiatic plants with their parts and formulations used in 21 countries such as Algeria, America, Australia, China, India, Iran, Italy, Jordan, Jordan, Kyrgyzstan, Lebanon, Libya, Mexico, Morocco, Pakistan, Palestine, Philippine, Spain, Tunisia, Turkey and Uzbekistan. Scientifically proved pharmacological activities of the same part of plant have direct (litholytic) and in direct pharmacological effects like analgesic, anti-inflammatory, antioxidant, astringent, demulcent, diuretic, litholytic, lithotriptic, antiurolithiatic, antispasmodic, ACE inhibition and Phospholipase A2 inhibition also shared as a plausible mechanism of action. The route of administration is oral in all cases. Hopefully, this book will not only be useful for the general public but also attract the scientific world for antiurolithiatic drug discovery. This valuable ethnopharmacological information will provide the opportunities for the future research and development of new natural antiurolithiatic compounds.

Keywords: urolithiasis, antiurolithiatic, natural products, drug development

Introduction
Urolithiasis is the combination of two Greek words *ouron* (urine) and *lithos* (stone). It is commonly referred as stone formation in any part of the urinary tract such as kidneys, ureters, urinary bladder and urethra. It is one of oldest, most frequent and highly recurrent disease and was initially found in the tombs of Egyptian mummies dating back to 4000 BC [1]. Epidemiological studies revealed that urolithiasis is more common in men than in women and is more prevalent between the ages of 20 to 40 in both sexes [2]. About 12% of world population is affected by different forms of urolithiasis in which the recurrence rate in female is 47-60% and in male is 70-80% [3]. It is a common clinical problem with high recurrence. After urolithiasis treatment, there is a 50% chance of stone recurrence within 7 years if left untreated. So, prophylactic management is of great importance, especially in stone formers [4]. Urinary stones are composed of insoluble crystalline compounds in which calcium as calcium oxalate monohydrate and calcium hydrogen phosphate dihydrate (75–90%), magnesium as ammonium magnesium phosphate hexahydrate (10 - 15%), uric acid and urates (3 – 10%); and 0.5–1% is composed of cystine, hippuric acid, L-tyrosine and xanthine. Calcium containing uroliths are known as brushite, whewellite, weddellite, whitlockite and carbonate apatite. Struvite and newberyite are magnesium containing whereas ammonium acid urate, mono sodium urate monohydrate, uric acid anhydrous, uric acid mono and dihydrate are commonly existing urate stones [1, 5]. Urinary stone formation is a complex physicochemical process comprises of supersaturation, nucleation, growth, aggregation and retention of stone within the urinary tract. At the initial level the stones are as small as a grain of sand and gradually increase in size as large as a pearl or even a golf ball by the process of crystal growth and aggregation.

Smaller stones may go down to the urinary tract and excreted without bringing any manifestation. Whereas, bigger stones may get stuck in the urinary tract and cause urinary tract obstruction with dysuria, hematuria, nausea and vomiting. Individuals are at the risk for stone recurrence if they have stone before or any family history of urolithiasis. Other risk factors are not drinking enough water, protein, sodium and sugar rich diet, being obese or experiencing gastric bypass surgery [6, 7].

Whewellite (calcium oxalate monohydrate) is the most common in 85% oxalate and phosphate containing calcium stones. The pathogenesis of whewellite formation includes crystal nucleation, growth, aggregation and retention. Cell debris, epithelial cells, red blood cells, urinary casts are the favorite sites for nucleation. The crystal growth starts with several atoms or molecules which form clusters in a supersaturated solution while in aggregation, crystals stick together to form a large particle. The crystal growth is a slow process and urolithiasis requires aggregation and retention followed by accumulation to obstruct the renal passage. The epithelial cell lining of the renal tubules, loop of Henle, Vasa recta, ducts of Bellini and papillary tip provide sites for initial deposition [8]. Glycosaminoglycan is an antiadherent, protective layer covering the inner renal wall and prevents crystal nucleation. The damaged layer favors the attachment of calcium phosphates, glycoprotein aggregates and cellular debris to the walls of renal papilla during early stages of stone formation and induces heterogenous nucleation of crystals. Therefore, small crystals adhered to the urothelial surface and then increase into comparatively larger particle [9]. Whewellite crystals are toxic to renal proximal tubular cells and causes inflammation-mediated cell death. These crystals are participating in both apoptosis and necrosis type of cell death mechanism. These crystals increase free radical generation and lipid peroxidation, which induces cellular injury, collapse mitochondrial functions leading to apoptosis. When these crystals are larger in size induces necrotic cell death by cell membrane rupture. Post apoptotic-necrosis promote crystallization, aggregation, crystal retention, growth, development of stone ultimately loss of renal function [10].

Calcium phosphate urinary stones which are about 15% of urinary stones are found in the form of brushite, dahllite, hydroxyapatite, whitlockite and octacalcium phosphate. Brushite crystals form urinary stone, promote whewellite (calcium oxalate) stone formation and act as a precursor to form apatite and octacalcium phosphate type urinary crystals [11, 12]. Among all urinary phosphate crystals, brushite has the greater hardness and difficult to remove surgically by the shock wave and ultrasonic lithotripsy. Brushite crystals grow rapidly with high recurrence rate and cause a significant degree of renal tissue injury as compare to other forms of stone[13, 14]. Brushite crystals induce apoptosis of renal proximal tubular epithelial cells and collecting ducts which create sites for crystal attachment followed by growth and maturing into brushite and whewellite stones[12].

Urate crystals are found in different forms as uric acid anhydrous, monohydrate and dihydrate, mono sodium urate mono hydrate and ammonium acid urate. Mono sodium urate monohydrates (MSUM) are deposited in peripheral joints and periarticular soft tissues causing gout whereas in collecting ducts and medullary interstitium as a urinary calculi. In addition to hyperurecemia some localized factors such as temperature, pH and mechanical stress also play an important role in crystal formation [15-17]. The pathogenesis of mono sodium urate monohydrate urolithiasis involves urine pH persistently less than 5.5, plasma urate supersaturation beyond 6.8 mg/dl or 405 μmol/L, hyperuricosuria, low urinary volume, dietary intake of high purine and also genetic factors. Epidemiological studies revealed that males are three times more affected than females. Elderly people of more than 60 years have two times more tendency than younger. Symptoms of disease include dysuria, nausea and hematuria [17, 18]. The MSUM renal calculi also promote calcium oxalate mono hydrate crystallization [19].

Dissolution and prevention of the stone recurrence are the main focus of urolithiasis treatment. Generally, physicians do not treat kidney stone they just medicate the pain until the stones pass out their own. Standard pharmaceutical drugs (allopurinol, citrate, cystone and thiazide diuretics) are used to prevent and treat urolithiasis but these are not effective in all cases due to common kidney stone recurrence and potential side effects. Surgical treatment causes long term renal damage, hypertension and stone recurrence [20, 21]. Now, the Extracorporeal Shock Wave Lithotripsy and percutaneous nephrolithotomy, have almost become the standard procedure for eliminating kidney stones but the traumatic effect of shock waves, persistent residual stone fragments as potential nidus for new stone formation, acute renal injury, decrease in renal function and an increase in stone recurrence ESWL induced hypertension, sever haematuria, steinstrasse (multiple small stone blocking the ureter), pancreatitis and infection are reported as after effects [21]. These complications can lead to large perfusion of the collecting system, extravasations of irrigating fluid, urosepsis, and ureteral injury. ESWL is less effective in calcium oxalate monohydrate (COM) and cystine stones [20]. Due to the adverse effects of available antiurolithiatic drugs alternative treatment modalities composed of herbal remedies have been the mainstay of medical therapy for thousands of years, especially in Eastern civilizations. Although it is believed that the resurgence of interest in phytotherapy became popular in the second half of the 19th century in Western countries, this complementary medical therapy was widely used in Europe much before that date [22]. Traditionally used herbal medicine is the synthesis of the therapeutic experience of generations of practicing physicians of indigenous system of medicine [23]. Antiurolithiatic plants are used since ancient periods before inventing modern treatments for treating (dissolution or elimination) kidney stones and to avoid their recurrence [24].

Ancient Mesopotamia were using opium (*Papaver somniferum* L.) and cannabis (*Cannabis sativa* L.) in case of pain and bleeding caused by kidney or bladder stones. In Ancient Greek periods, Hippocrates (460 BC to 370 BC) in his famous book *Oath of Medical Ethics for Physicians* quoted

"I will not cut for calculus, even for the patients in whom the disease is manifest; I will leave this operation to be performed by practitioners."

This statement, suggested surgery as one of the way of urolithiasis management

Hippocrates in his book *Internal affections* wrote,

"From the kidneys these four diseases arise. In the first one, the patient suffers the following: a sharp pain attacks his kidneys, loin, flank, and his testicle on the same side as the kidney; he urinates frequently, and drips urine a little at a time; together with the urine, sand, too, is passed, and when the sand discharges through the urethra, it provides violent pain in it. When the patient has finished urinating, the pain stops; later, though, he labors under the same distress again. When he is passing urine, he rubs his penis because of pain.

Many physicians that do not understand the diseases, when they see the sand, think the patient is suffering from stones of the bladder, which he is not, but rather from the stones of the kidneys…….. When the case is such, clean the patient downwards with scammony juice (obtained by incision of the living root of Convolvulus scammonia L.*) or the root itself, first applying vapor-baths to the whole body. On the following day, clean downwards with juice from white chick-peas (Cicer arietinum* L.*) to the amount of two choes (6.55Liters); add salt and give this drink".*

Greek Dioscorides in his book *De Materia Medica* (50-70 AD) and Pliny the Elder (an ancient Roman naturalist) in *Naturalis Historis* (70-79 AD) have shared number of medicinal plants used against urolithiasis along their mode of action. "Greco-Arabic" or "Greco-Islamic" medicine extended from Spain to Central Asia and India. Arab-Islamic physicians and scholars developed a large and complex medical literature exploring and synthesizing the theory and practice of medicine. They introduced many new ideas and upgraded the knowledge about herbs and their therapeutic effects and safety. The Arabs and Muslims appreciated Greco-Roman culture and learning, and translated tens of thousands of scientific and medical texts into Arabic for further study. The following Greco-Arabic Muslim scientist has shared urolithiasis management.

Abu Bakr Mohammad Ibn Zakariya Al-Razi (Rhazes, 864–930 AD) --- *Al-Hawi fi al-Tibb* (Comprehensive Book on Medicine) (Part 7, book I) precisely explained the urolithiasis management. He wrote,

The differentiation between kidney calculi and renal obstruction or pyelonephritis is that; with inflammation, (there are) mixed fevers, rigors, and polyuria with frequency; with obstruction, (there is) oliguria and the urine is clear and with stones, the urine is either clear or not and with sandy sedimentation……..Do not lie long on your back. Avoid cheese, milk derivatives, especially fresh cheese, hard-boiled eggs, unleavened bread. Use diuretics— cucumbers (Cucumis sativus L.*), melons (Cucumis melo* L.*), figs (Ficus carica* L.*), grapes (Vitis vinifera* L.*), and crystal — clear water from natural sources. …… Sedatives for renal colic attacks are useful and after the pain had subsided, a number of herbal remedies including wormwood (Artemisia absinthium* L.*), birthwort (Aristolochia clementis* Alain.*), and pepper (Piper nigrum* L.*) to help calculi's expulsion. Juice of radish leaves (Raphanus sativus* L.*), caper (Capparis spinosa* L.*), Prunus mahaleb* L.*, water of soaked chick peas (Cicer arietinum* L.*) and bitter almonds (Prunus amygdalus var. amara* (DC.) Focke.*) are effective for breaking the calculi. This recommendation of "diet, hydration, and diuresis" is what is currently advised for patients with urinary calculi……During such times (having kidney calculus), the frequency of bathing and the number of times that one enters Khazineh (A big bathtub full of hot water) should be increased, prescriptions should be followed and medications should be used. If such orders be followed consistently, the patients will not feel the pain and before its complete formation, calculus will be broken into small pieces and pain will not be intensified……After getting out of bath or Khazineh, the patient should be ordered to move and jump around incessantly and for a long duration of time. Having done this, the patient should enter Khazineh again and stay there till the time he feels that the pain has been displaced and it is running down the* inguinal"**.**

Abubakr Al-Akawayni Al-Bokhari (?–983 AD) --- *Hidayat al-Mutallimin fi-al-Tibb* (Learner's Guide to Medicine) about urolithiasis and its management stated,

Beware that when the stone enlarges in the kidney it hinders the urine, causes intolerable pain, and may lead to mental confusion from pain. Each occasion of the pain is called an episode (the pain is intermittent). During the episode of pain, the patient should sit in a tub of warm water in which the leaves of cabbage (*Brassica oleracea* L.), *leaves of marsh-mallow* (*Althaea officinalis* L.), *chamomile* (*Anthemis nobilis* L.), *dwarf yellow* (*Astragalus hamosus* L.), *fenugreek* (*Trigonella foenum-graecum* L.), *flaxseed* (*Linum usitatissimum* L.), *seed of mingwort* (*Artemisia absinthium* L.), *and starthistle* (*Centaurea calcitrapa* L.) *have been brewed. And after getting out of the water tub, the back (of the patient) should be massaged gently with the oil of wallflower* (*Cheiranthus × cheiri* L.), *and then he should jump (up and down) on one foot, or ride a horse trotting in place, or climb fast down a ladder until the stone comes out of there……..If the stone lodges in the penis, its sign is that of penile pain. If so, (the penis) must be sucked with the mouth to expel (the stone), or (the patient must) put the penis in the warm water and massage it to expel (the stone) and even have marsh-mallow (Althaea officinalis* L.*) decoction and violet oil (essential oil extracted from the flowers of Viola odorata* L.*) instilled in the urethra and milked outward to expel the stone. If the stone is large or lodged transversely and cannot be expelled then an incision (of the urethra) has to be made to extract the stone. And again those single medicines (used) for the extraction of stone are that I mention: Jews' Stone (Lapis Judaicus) grinded in clean water and three Deram-Sang (37.5 gram) of it consumed, root of cumin (Cuminum cyminum* L.*),* Scholopendriun (*Asplenium scolopendrium* L.*), seeds of Caper* (*Capparis spinosa* L.*), Capillaire* (*Adimantum capillus-veneris* L.*), round cypress (Cyperus rotundus), root of star-thistle (Centaurea calcitrapa* L.*), caraway (Cuminum carvi* L.*), seeds of melon (Cucumis melo* L.*), seeds of cucumber (Cucumis sativus* L.*), seeds of pentaphyllum (Gynostemma pentaphyllum* (Thunb.) Makino.*), and beetroot (Beta vulgaris* L.*) concentrate; these drugs are the first line (medications). And ground pine (Teucrium chamaepitys* L.*), dittany (Marrubium pseudodictamnus* L.*), herb ivy (Ajuga iva* (L.) Schreb.*), decoction of black pea (Lathyrus niger* (L.) Bernh.*), asparagus root (Asparagus officinalis* L.*), Indian Djatrah (?), crown of the root of agrimony (Agrimonia eupatoria* L.*), seeds of radish (Raphanus sativus* L.*), and …… these drugs are stronger, and the strongest of them is beetle (Cantharidae), but care should be taken as it could lead to bladder ulceration. Now that I gave the guidelines (for treatment), I proceed to pay attention to stone prevention. As it is known that the etiologies of stone are concentrated materials, natural heat, and obstruction in the ducts, I have to mention, briefly highly concentrated foods like... fresh fruit, and cow and camel meats,…… and everything that is concentrated should be avoided, particularly fresh cheese.. ……..And also the use of those drugs that dilate the urinary duct like the seed of melon (Cucumis melo* L.*), cucumber (Cucumis sativus* L.*), white cucumber (Cucumis anguria* L.*), seeds of marsh-mallow (Althaea officinalis* L.*), seeds of sweet squash (Cucurbita maxima* Duchesne.*), and……. is recommended".*

Sheikh Bu Ali Sina / Ibn Sina (Avicenna, 980–1037 AD) --- *Al Qanoon Fit Tibb* (Canon of Medicine) He shared that pharmacotherapeutic regimen natural medicines for the management and treatment of urolithiasis must contain 6 actions to obtain optimal results for urolithiasis management.

1. Calculus dissolving and destructing drugs: These are

categorized into four groups. First: drugs acting on small and soft gravel; Second: affect kidney calculi, but do not have suitable effects on bladder calculi for example Hajrul Yahud (Jew's stone). Third: drugs mainly affect kidney calculi and have some benefits on bladder calculi. Fourth: drugs with dissolving effect on both kidney and bladder calculi, like *scorpion ash.*

2. Drug targeting agents for kidney calculi for example, black pepper fruit (*Piper nigrum* L.), pennyroyal leaves (*Mentha pulegium* L.), and cinnamon bark (*Cinnamomum verum* J.Presl.).
3. Drugs needed to maintain antiurolithiatic medicines at the site of action and concentrate in the kidney. These drugs usually are highly viscose and sticky. Examples are the gums of polypody of the Oak *(Polypodium vulgare* L.) and Persian walnut (*Juglans regia* L.).
4. Strong diuretics are needed to pass gravel, which remain from calculus destruction.
5. Drugs behave as kidney tonics are needed as calculi usually cause some harm to the kidneys. Spikenard (*Nardostachys jatamansi* (D.Don) DC.), ginger (*Zingiber officinale* Roscoe), iris (*Iris* × *germanica* L.), centaurea (*Centaurea cyanus* L.), fruit of vitex (*Vitex agnus-castus* L.), burra gokhru (*Calotropis gigantea* (L.) Dryand.), pomegranate (*Punica granatum* L.), camel grass (*Cymbopogon schoenanthus* (L.) Spreng.), damask rose (*Rosa* × *damascena* Herrm.), sandalwood (*Santalum album* L.), and cassia (*Cinnamomum cassia* (L.) J.Presl.), used in formulations.
6. Drugs to control pain or sedatives during colic attacks, helped to move the calculi once the pain had subsided. These drugs included *opium* (*Papaver somniferum* L.), flax (*Linum usitatissimum* L.), turkish pine (*Pinus brutia* Ten.), hazel (*Corylus avellana* L.), and marshmallow (*Althaea officinalis* L.) [25].

Medicinal plants are considered as a rich source of therapeutic agents due to the belief and observations regarding traditionally used medicinal plants for the prevention of various ailments. According to WHO 75% people rely on traditional medicines for the prevention and cure of different ailments. A number of plants are employed to cure and prevent urolithiasis. Although medicinal plants produce slow recovery, these are affordable and less expensive, evidence based traditionally proven dissolution or elimination of kidney stones, less relapse of urolithiasis, their successful prophylactic use, less side effects, not only revealing their therapeutic potential but encourages patient's belief and increasing their interest in traditional practices to find an herbal cure for kidney stones[26]. The belief and observations regarding traditionally used medicinal plants, increasing the interest of people to use natural medicine for their primary health care needs. A wide range of medicinal plants have been used in different countries and cultures as a prophylactic and curative agent for urolithiasis. The use of antiurolithiatic plants in the form of decoction, infusion, juice, powder taken along with water, raw eaten are cheaper than modern medicine / techniques [27]. Most of the remedies are very useful, but their mechanism of action remains unclear. Various research findings and data from different part of the globe are contributing and helping the scientific community in evaluating and establishing the pharmacological activities of these plants. Few scientific studies reveal the mechanism of actions of these antiurolithiatic plants and the results show very interesting and multidimensional action, responsible for their effectiveness at different stages of urolithiasis, such as, the diuretic action increases the quantity of fluid going pass through the kidneys as a result flush out the deposits. Therefore, the increase in urine volume decreases the saturation of the salts and prevents the precipitation of the crystals at physiological pH. Breaking, disintegration and dissolution of preformed stones (litholytic activity) and binding inhibition among particles to form stones (lithotriptic activity) play an important role in this pathological condition. Crystal inhibitors decrease crystal nucleation, aggregation and growth. Furthermore, they inhibit crystallization by their adsorption to the crystal surface which makes them unable for renal tubular attachment (crystallization inhibition activity). In urine different crystalloids like oxalate, uric acid, calcium and cystine are present with mucin and sulphuric acid colloids in dissolved form. The disturbance in crystalloid-colloid balance (increase in crystalloid and decrease in colloid) causes renal stone formation. Renal exposure to oxalate and calcium oxalate causes lipid peroxidation, produces Reactive Oxygen Species followed by renal cell injury and inflammation. This loss of membrane integrity, promotes fibrosis and collagen formation, facilitates calcium oxalate retention and subsequent stone formation [28, 29]. Renin-Angiotensin System activates the NADPH oxidase in renal cells, which produces Reactive Oxygen Species. Angiotensin converting enzyme inhibition significantly reduces calcium oxalate crystal deposition and renal inflammation. The Reactive Oxygen Species end up phospholipase A2 activation through nuclear transcription factor NF-κB. Activation of cytosolic phospholipase A2 generates arachidonic acid and lysophosphatidylcholine, which increase reactive oxygen species production that in turn increase in cell death and crystal formation [28, 30]. The obstructing stone causes renal colic and in this condition an antispasmodic activity of the smooth muscles along with analgesic and anti-inflammatory activities play an important role in symptomatic relief from renal colic and dysuria. Antispasmodics help in stone passage. The obstruction of urine outflow by stones decreases the glomerular filtration rate (GFR) resulting nitrogenous waste (urea, creatinine and uric acid) accumulation in blood [28].The anti-adherent layer of Glycosaminoglycans in renal tubule plays an important role in urolithiasis as a defender. Its damage potentiate bacterial attack, resulting stone nucleus (nidus) formation, leading to urinary stone formation. In urinary tract infection the urea splitting organisms (*Proteus mirabilis*), splits urea into ammonia and carbon dioxide. These byproducts damage the glycosaminoglycan leading to the bacterial adherence, followed by biofilm formation and mineral encrustation. They also make the urine alkaline which provides a favorable environment for precipitation of calcium and magnesium phosphate and calcium carbonate crystals which are already present in that medium in large amount [31, 32]. *Proteus mirabilis* and *Escherichia coli* alter urokinase activity leading to matrix (non crystalline portion of kidney stone) formation. This matrix formation increases crystal adherence to renal epithelium to form stone [28]. Astringent action tightens and tones the weak, atonic, swollen or injured tissues and makes it harder for bacteria to adhere them. Demulcents causing urinary tissues moistening or lubrication, soothe inflammation, irritation and injury thus facilitate stone expulsion [33].

Increasing demand for medicinal plants in both developing and developed countries make them to become as one of the leading areas of research. The understandings of the pathophysiology of stone formation and the mode of action of

these plant based medicines are of great importance for the development of safe and effective antiurolithiatic medicines. Currently known herbal drugs exert their antiurolithiatic effect with multidimensional pharmacological actions as angiotensin converting enzyme inhibition, analgesic, antiinflammatory, antioxidant, antispasmodic, astringent, crystallization inhibition, diuretic, demulcent; litholytic, lithotriptic, phospholipase A2 inhibition and by changing the ions concentrations in urine such as increase magnesium and citrate excretion e.g., decreasing the calcium and oxalates. Closer attention is required for bioactivity-safety evaluation, phytochemical analysis and plant conservation. Extraction and isolation along with clinical trials may develop proactive antiurolithiatic compounds. This could be helpful in creating mass awareness about conservation of such plants to promote ethno- medico-botany knowledge within the region, besides contributing to the preservation of such medicinally important species before they are extinct [34].

This review covers eighty (80) mono herbal formulations of family Asteraceae against urolithiasis along with their historical antiurolithiatc background shared in well-known books of Dioscorides, Pliny the Elder, Al Razi and Ibn Sina. This information was extracted to compose antiurolithiatic plants with their parts and formulations used in 21 countries such as Algeria, America, Australia, China, India, Iran, Italy, Jordan, Jordan, Kyrgyzstan, Lebanon, Libya, Mexico, Morocco, Pakistan, Palestine, Philippine, Spain, Tunisia, Turkey and Uzbekistan

Scientifically proved pharmacological activities of the same part of plant have direct (litholytic) and in direct pharmacological effects like analgesic, anti-inflammatory, antioxidant, astringent, demulcent, diuretic, litholytic, lithotriptic, antiurolithiatic, antispasmodic, ACE inhibition and Phospholipase A2 inhibition also shared as a plausible mechanism of action. The route of administration is oral in all cases (table-1). Hopefully, this review will not only be useful for the general public but also attract the scientific world for antiurolithiatic drug discovery. This valuable ethnopharmacological information will provide the opportunities for the future research and development of new natural antiurolithiatic compounds.

Abbreviations Used

BD= twice a day
before breakfast= every morning in empty stomach.
CHPD: Calcium hydrogen phosphate dihydrate / brushite
COD: Calcium oxalate dihydrate / weddellite
COM: Calcium oxalate monohydrate / whewellite
days= days required to dissolve / expel kidney stones.
MSUM: Mono sodium urate monohydrate
OD= once daily.
tbsp.= table spoon.
TID= three times a day.
tsp.= tea spoon.

Table 1: Antiurolithiatic plants of family Asteraceae

Antiurolithiatic plants	Explaination
Aaronsohnia pubescens K. Bremer & Humph.	Leaves infusion --- Libya [35].
Achillea ageratum L.	Dioscorides (*De Materia Medica*): Whole plant is diuretic [25].
Achillea falcata L.	Aerial parts infusion --- Lebanon [36].
	Pharmacological activities: Antispasmodic, litholytic [36].
Achillea fragrantissima (Forssk.) Sch.Bip.	Shoots --- Jordan [37].
Achillea santolina	Flowers --- Iran [38].
Acmella oleracea (L.) R. K. Jansen.	Plant decoction --- Australia [35].
	Pharmacological activities: Analgesic, anti-inflammatory, antioxidant, diuretic [36].
Ageratum conyzoides L.	Leaves / root decoction BD. --- India [35, 39].
	Pharmacological activities: Analgesic, anti-inflammatory, antioxidant, antispasmodic, litholytic [36].
	Antiurolithiatic spectrum: Whole plant against Whewellite [40].
Anthemis chia L.	Dioscorides (*De Materia Medica*): Roots are diuretic and litholytic [25].
Anthemis nobilis Boiss.	Flowers decoction / infusion --- Iran [35].
	Pharmacological activities: Anti-inflammatory, antispasmodic [36].
Arctium lappa L.	Aerial parts decoction --- Iran [41] ; Roots decoction --- India [35].
	Pharmacological activities: anti-inflammatory, antioxidant [36].
Arnica montana L.	Aerial part decoction --- India [35].
	Pharmacological activities: Antioxidant, astringent, diuretic [36], lithotriptic [42].
	Antiurolithiatic spectrum: Whole plant against Whewellite [42].
Artemisia arborescens (Vaill.) L.	Dioscorides (*De Materia Medica*): Aerial parts are litholytic [25].
Artemisia abrotanum L.	Ibn Sina (*Al Qanoon Fit Tibb*): Fruits are litholytic [25].
	Fruit infusion --- Iran [35].
Artemisia absinthium L.	Dioscorides (*De Materia Medica*): Leaves are diuretic [25]. Al Razi / Rhazes (*Al-Hawi fi al-Tibb*): Leaves expel stones [25]. Ibn Sina (*Al Qanoon Fit Tibb*): Whole plant is litholytic and expels stones [25].
	Plant infusion --- Iran [35]; Leaves decoction --- Italy, Tunisia [43].
	Pharmacological activities: Analgesic, anti-inflammatory, antispasmodic [36].
Artemisia campestris L.	Dioscorides (*De Materia Medica*): Leaves are litholytic [25].
Artemisia herba-alba Asso.	Dioscorides (*De Materia Medica*): Wood is diuretic [25]. Pliny the Elder (*Naturalis Historis*): Wood is diuretic [25].
	Shoots --- Jordan [37].
Artemisia scoparia Waldst. & Kit.	Plant infusion --- Uzbekistan, Kyrgyzstan [35].
	Pharmacological activities: Analgesic, anti-inflammatory, diuretic [36].
Artemisia vulgaris L.	Ibn Sina (Al Qanoon Fit Tibb): Whole plant is litholytic [25].
	Plant infusion --- Iran [35].
	Pharmacological activities: Analgesic, anti-inflammatory, astringent, diuretic [36].

Aster tripolium L.	Ibn Sina (*Al Qanoon Fit Tibb*): Fruits are litholytic [25].
	Fruit extract --- Iran [35].
Blumea balsamifera (L.) DC.	Leaves infusion --- Philippine [35].
	Pharmacological activities: Antioxidant, diuretic, litholytic [36].
Calendula officinalis L.	Plant decoction --- Pakistan [35].
	Pharmacological activities: Antioxidant, astringent, demulcent, diuretic [36].
Centaurea calcitrapa L.	Flower decoction --- Spain [44].
Centaurea iberica Trev. ex Spreng.	Aerial parts --- Turkey [45].
Centipeda minima (L.) A.Braun & Asch.	Plant juice --- India [3].
	India: Juice of whole plant in 250 ml of water. 250 ml OD till stone expulsion [3].
Centratherum anthelminticum (L.) Kuntze.	Seeds --- India [46]
	Pharmacological activities: Diuretic [46], lithotriptic [47].
	Antiurolithiatic spectrum (reported): Seeds against Whewellite [48].
Cichorium intybus L.	Leaves raw eaten --- Algeria [49], America, Pakistan, Palestine [35], Iran [38] ; Leaves / roots decoction / maceration --- Lebanon [50].
Cnicus benedictus L.	Dioscorides (*De Materia Medica*): Whole plant is diuretic and used against dysuria [25].
Cousinia alexeenkoana Bornm.	Flowers / leaves --- Iran [38].
Cynara cardunculus L.	Capitula (heads) decoction --- Italy, Tunisia [43].
Cynara scolymus L.	Ibn Sina (*Al Qanoon Fit Tibb*): Roots are litholytic and expel stones [25].
	Roots decoction --- Iran [35] ; Leaves infusion --- Italy and Tunisia [43].
	Pharmacological activities: Roots: diuretic, lithotriptic [36].
Echinops echinatus Roxb.	Plant extract --- Pakistan [51].
Echinops spinosus L.	Roots / flower decoction --- Morocco [35].
	Pharmacological activities: Diuretic [36].
Enhydra fluctuans Lour.	Plant decoction --- India [35].
	Pharmacological activities: Antioxidant [36].
Erigeron karvinskianus DC.	Whole plant --- Mexico [52].
	Pharmacological activities: Lithotriptic [36].
Eupatorium birmanicum DC.	Leaves decoction --- India [35].
	India: Boil 250 g of leaves in one L of water. 250 ml BD with a pinch of salt till stone expulsion [3].
	Pharmacological activities: Analgesic, diuretic [36], lithotriptic [53].
Eupatorium purpureum L.	Roots tincture --- America [35].
	Canada: 1 tsp. dried root in 8 oz. water, boil for 15 mins, keep cover for 45 mins then filter. 250 ml BD till stone expulsion [3].
	Pharmacological activities: Diuretic, lithotriptic [36].
Gundelia tournefortii L.	Leaves --- Iran [38].
Helianthus annuus L.	Roots --- India [3].
	India: Pound 20 g of roots with 100 ml of butter milk. 100 ml OD for 15 days [3].
	Pharmacological activities: Lithotriptic [53].
	Antiurolithiatic spectrum (reported): Leaves against Whewellite [54].
Helichrysum arenarium Moench.	Flower decoction / infusion --- Turkey [35].
	Pharmacological activities: Antioxidant [36], diuretic [55].
Helichrysum graveolens (M.Bieb.) Sweet.	Flowers --- Turkey [56].
	Pharmacological activities: Diuretic, lithotriptic [56].
	Antiurolithiatic spectrum (reported): Flowers against Whewellite [56].
Helichrysum maracandicum Popov.	Inflorescence decoction --- Uzbekistan, Kyrgyzstan [35].
	Pharmacological activities: Anti-inflammatory, antioxidant, diuretic [36].
Helichrysum pallasii (Sprengel) Ledeb.	Whole plant infusion --- Turkey [35].
	Pharmacological activities: Antioxidant [36], diuretic [55].
Helichrysum plicatum DC.	Aerial parts decoction / infusion --- Turkey [35].
	Pharmacological activities: anti-inflammatory, antispasmodic, diuretic [36], lithotriptic [57].
	Antiurolithiatic spectrum (reported): Flowers against Whewellite [57].
Helichrysum stoechas (L.) Moench.	Flower infusion--- Turkey [58].
	Pharmacological activities: Diuretic [58].
	Antiurolithiatic spectrum (reported): Flowers against Whewellite [59].
Inula helenium L.	Dioscorides (*De Materia Medica*): Whole plant is diuretic [25].
Inula oculus-christi L.	Flowers decoction --- Turkey [35].
	Pharmacological activities: Antioxidant [36].
Inula viscosa (L.) Aiton	Aerial parts decoction --- Turkey [58].
Kalimeris indica (L.) Sch.-Bip.	Plant decoction --- China [35].
Lactuca sativa L.	Fresh leaves raw eaten --- Iran [41].
Matricaria aurea (Loefl.) Sch.Bip.	Flowers and shoot --- Jordan [37].
Matricaria chamomilla L.	Ibn Sina (*Al Qanoon Fit Tibb*): Flowers are diuretic [25].
	Aerial parts maceration --- Algeria [49]; Flowers decoction --- Iran, Palestine [35], Spain [44].
	Pharmacological activities: Analgesic, anti-inflammatory, antioxidant, antispasmodic [36].

Matricaria recutita L.	Flowers --- Iran [38].
Meiogyne minuta (G.Forst.) Less.	Plant infusion --- India [35].
Nanothamnus sericeus Thomson.	Aerial parts --- India [60].
Onopordum acanthium L.	Seeds powder with honey --- Turkey [35].
	Pharmacological activities: antioxidant [36].
Saussurea costus (Falc.) Lipsch.	Dioscorides (*De Materia Medica*): Roots are diuretic [25].
Scolymus maculatus L.	Leaves maceration --- Algeria [49].
Sonchus oleraceus L.	Bark infusion --- India [61].
	Pharmacological activities: Analgesic, anti-inflammatory, antioxidant, diuretic [36].
Silybum marianum (L.) Gaertner.	Shoots decoction --- Palestine [35].
	Pharmacological activities: Anti-inflammatory, diuretic [36].
Solidago virga-aurea L.	Aerial parts decoction ---- India [35].
Sphaeranthus indicus L.	Roots decoction --- India [35].
	India: Boil 10 g of powdered plant in one L of water. 500 ml BD for 7 days [3].
	Pharmacological activities: Analgesic, anti-inflammatory, antioxidant, diuretic [36], lithotriptic [62].
Tagetes erecta L.	Leaves --- India [53].
	Pharmacological activities: Lithotriptic [53].
Tanacetum chiliophyllum (Fisch. & E.Mey. ex DC.) Sch.Bip.	Flower decoction --- Turkey [35].
Tanacetum parthenium (L.) Sch.Bip.	Dioscorides (*De Materia Medica*): Roots (gum resin) are litholytic [25].
	Whole plant decoction --- Turkey [55]; Flower with oxymel --- Iran [35].
	Pharmacological activities: Anti-inflammatory [36], diuretic [55].
Taraxacum androssovii Schischk.	Leaves infusion --- Turkey [55]
	Pharmacological activities: Anti-inflammatory [55].
Taraxacum fedtschenkoi Hand.-Mazz.	Leaves infusion --- Turkey [55].
	Pharmacological activities: Anti-inflammatory [55].
Taraxacum macrolepium Schischk.	Leaves infusion --- Turkey [55].
	Pharmacological activities: Anti-inflammatory [55].
Taraxacum officinale F.H. Wigg.	Whole plant --- India [63]; Leaves / roots decoction --- India [63]. Roots decoction --- America [35].
	Appalachia: Boil 1 ounce of chopped root in 500 ml of water. Drink several times a day for at least 10 days [3]; India: ½ tsp. dry plant powder with water BD [63].
	Pharmacological activities: Diuretic [63].
	Antiurolithiatic spectrum (reported): Whole plant against Whewellite [64].
Trapogon buphtalmoides (DC.) Boiss.	Leaves raw eaten --- Turkey [35].
	Pharmacological activities: Antioxidant [36].
Tragopogon porrifolius L.	Whole plant --- Iran [38].
Taraxacum androssovii Schischkin.	Leaves infusion --- Turkey [35].
Taraxacum fedtschenkoi Hand.-Mazz.	
Taraxacum macrolepium Schischkin.	
Taraxacum syriacum Boiss.	Roots decoction --- Palestine [65].
	Palestine: Boil 300 g of roots in 500 ml of water. Take 100 ml TID before each meal [65].
Tridax procumbens L.	Leaves infusion --- India [63], Turkey [35].
	Pharmacological activities: Litholytic [36], lithotriptic [66].
	Antiurolithiatic spectrum (reported): Leaves against Whewellite [66].
Tripolium pannonicum (Jacq.) Dobrocz.	Dioscorides (*De Materia Medica*): Diuretic [25].
Vernonia cinerea (L.) Less.	Whole plant --- India [67].
	Antiurolithiatic spectrum (reported): Whole plant against Whewellite [68].
Wedelia chinensis (Osbeck) Merr.	Whole plant --- India [53].
	Pharmacological activities: Lithotriptic [53].
Xeranthemum longipapposum Fisch. & C. A. Mey.	Aerial parts --- Iran [38].
Xanthium strumarium L.	Roots decoction / infusion --- India, Uzbekistan, Kyrgyzstan [35].
	Pharmacological activities: Analgesic, antioxidant, diuretic [36], lithotriptic [53].

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