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INVITED REVIEW

Antiurolithic effects of medicinal plants: results of in vivo studies in rat models of calcium oxalate nephrolithiasis—a systematic review

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Abstract

Urolithiasis is one of the oldest diseases affecting humans, while plants are one of our oldest companions providing food, shelter, and medicine. In spite of substantial progress in understanding the pathophysiological mechanisms, treatment options are still limited, often expensive for common people in most parts of the world. As a result, there is a great interest in herbal remedies for the treatment of urinary stone disease as an alternative or adjunct therapy. Numerous in vivo and in vitro studies have been carried out to understand the efficacy of herbs in reducing stone formation. We adopted PRISMA guidelines and systematically reviewed PubMed/Medline for the literature, reporting results of various herbal products on in vivo models of nephrolithiasis/urolithiasis. The Medical Subject Heading Terms (Mesh term) "Urolithiasis" was used with Boolean operator "AND" and other related Mesh Unique terms to search all the available records (July 2019). A total of 163 original articles on in vivo experiments were retrieved from PubMed indexed with the (MeshTerm) "Urolithiasis" AND "Complementary Therapies/Alternative Medicine, "Urolithiasis" AND "Plant Extracts" and "Urolithiasis" AND "Traditional Medicine". Most of the studies used ethylene glycol (EG) to induce hyperoxaluria and nephrolithiasis in rats. A variety of extraction methods including aqueous, alcoholic, hydro-alcoholic of various plant parts ranging from root bark to fruits and seeds, or a combination thereof, were utilized. All the investigations did not study all aspects of nephrolithiasis making it difficult to compare the efficacy of various treatments. Changes in the lithogenic factors and a reduction in calcium oxalate (CaOx) crystal deposition in the kidneys were, however, considered favorable outcomes of the various treatments. Less than 10% of the studies examined antioxidant and diuretic activities of the herbal treatments and concluded that their antiurolithic activities were a result of antioxidant, anti-inflammatory, and/or diuretic effects of the treatments.

Keywords Kidney stones · Calcium oxalate · Urolithiasis · Nephrolithiasis · Medicinal plants · Herbal medicine · Traditional medicine

Introduction

Urolithiasis, the development of stones/crystals in the urinary tract, has been affecting humans since the dawn of history, as evident from the discovery of kidney and bladder stone in Egyptian mummies [1]. Estimated lifetime risk of urolithiasis around 2–5% in Asia, 8–15% in America and Europe, and about 20% in the Middle East [2]. It is estimated that in the United States, the population living in high-risk zones for nephrolithiasis will grow from 40% in 2000 to 56% by 2050, and to 70% by 2095 [3]. These projections highlight the need for finding ways to reduce the occurrence of this disease and less costly tests and treatments. In addition, the age of onset is decreasing and the annual incidence of urolithiasis is increasing, which can be linked to changes in climate, lifestyles, and diets [4]. The rate of recurrence is

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also increasing. After one year of the first episode the rate of urolithiasis recurrence is around 10–23%, within 5–10 years it is around 50% and 75% in 20 years. After every episode the recurrence interval decreases and the subsequent relapse rate increases [2, 5].

Kidney stones are composed of crystals and an organic matrix and are named for their main crystalline constituents. Calcium oxalate (CaOx) alone or in association with calcium phosphate (CaP) is the major component of 75–80% of the kidneys stones. Other types of stones include struvite, cystine, uric acid, and ammonium acid urate. [6, 7].

Herbal medicines are a part of the so-called traditional medicine (TM), often termed as "complementary", "alternative" or "non-conventional" medicine [8]. It refers to local knowledge, belief systems and therapeutic practices that are used in developing countries of Africa, South-East Asia and/or the Western Pacific. Complementary and alternative medicine (CAM) is used when referring to developed countries of Europe, North America and/or Australia [9]. The evolution of different systems of traditional medicine emerged as a result of the traditional knowledge of using herbs for various disorders. The use of herbal medicine in the Indo-Pakistani sub-continent has persisted for centuries and, medicinal plants and their extracts are widely used in the traditional (Unani/Ayurvedic) system of medicine. Complementary and alternative medicine (CAM) is a multibillion-dollars industry globally [10] and has achieved an exponential growth in the last two decades in industrialized countries. Recent research is now showing a remarkable increase in support for, and usage of, therapeutic practices outside mainstream medicine [11]. Many plants have been traditionally used to treat kidney stones and have been shown to be effective [12]. According to the World Health Organization, plants provide an economical and affordable source of drugs for three-quarter of the world population [13] and their therapeutic use is increasing [12]. Within the European Community, annual sales of the herbal medicine are around 7 billion USD, while in the USA, the sale of herbal products has increased from $200 million in 1988 to > $3.3 billion in 1997 [14]. In spite of such a high dependency, little scientific research has been carried. This gap between the use of herbal remedies and their scientific basis exists mainly due to the lack of active interactions between the modern health professionals and traditional healers, a lack of modern testing technology, and a shortage of qualified scientists in the field of natural products pharmacology. However, pharmaceutical research centers, universities and even pharmaceutical companies are beginning to fill this gap by bringing teams together and focusing research on phytomedicine [15, 16]. A number of reviews have been published in the past few years on the herbal and traditional medicines for urolithiasis ([8, 17–20], summarizing the results of research articles and commenting on both the potential and challenges. We reviewed the literature related to the rat models of CaOx nephrolithiasis emphasizing the variety of approaches utilized to prepare and deliver the medicine, methods used to induce the disease, anti-urolithic activities of various treatments and their proposed mechanisms of action. There is a great variation in methods of drug preparation and delivery. Every part of the plant has been ranging from seeds, flowers, fruits, leaves, bark, even whole plants and mixture of various plants have been utilized.

Methodology

Literature search

Systematic review of literature was performed according to PRISMA guidelines [21] (Supplementary Figure; PRISMA flow diagram). All publications were retrieved from PubMed in July 2019, with Medical Subject Heading (Mesh) terms; a new and thoroughly revised version of lists of subject headings compiled by National Library of Medicine (NLM) for its bibliographies and cataloguing. The Mesh term "Urolithiasis" (MeshUnique ID: D014545) was used with Boolean operator "AND" and other related Mesh terms "Complementary Therapies/Alternative Medicine; Mesh Unique ID: D000529", "Plant Extracts; Mesh Unique ID: D010936, "Traditional Medicine; Mesh Unique ID: D008519 were used to search all the records available up to date, i.e. "Urolithiasis" AND "Complementary Therapies/Complementary Therapies", "Urolithiasis" AND "Plant Extracts", "Urolithiasis" AND "Traditional Medicine".

Inclusion criteria

In vivo original research articles, PubMed Indexed journals, indexed with Mesh Terms as stated above, studies on rats model of CaOx renal stones.

Exclusion criteria

In vitro studies, mechanistic in vivo studies without antiurolithic effect, studies on bladder stone disease, review articles, and studies in languages than English.

Results

A total of 234 articles were extracted using Mesh terms "Urolithiasis" AND "Complementary Therapies" Or "Alternative Medicine" in advance search of PubMed (Supplement Prisma Flow Chart) Based on inclusion and exclusion criteria, a total of 90 articles of animal origin were retrieved. A total of 249 articles were extracted using Mesh

terms "Urolithiasis" AND "Plant Extract" in advance search of PubMed. After selecting animal studies, a total of 142 were retrieved. A total of 52 articles were extracted using Mesh terms "Urolithiasis" AND "Medicine, Traditional" in advance search of PubMed. After selecting animal studies, a total of 20 were retrieved.

After combining all the articles and removing the duplicates, a total of 163 articles were left. After thoroughly screening and reading, another 27 articles were excluded due to unavailability of full text, while another 48 articles were excluded which were either review articles, written in languages other than English, studies involving stone induced by foreign body implantation, or studies focused on mechanisms of urolithiasis risk factors without any investigation of antiurolithic effect. A total of 88 publications were included in this systematic review. Data from all the eligible articles were independently extracted by two researchers and compiled in the form of tables and figures.

Tables 1, 2, 3, 4 show a systematic/chronological compilation of pharmacological studies conducted on aqueous (Table 1), hydroalcoholic (Table 2), alcoholic (Table 3), and other types of extract/formulation (Table 4) of medicinal plants. Each table provides information about the referenced study, year of study, common and scientific name of the plant, part of the plant used, type of extract, crystal inducing agent/model, and antiurolithic activity/mechanism. Reduced crystals deposition, improved renal morphology, reduced oxidative stress, change in urinary pH, decrease in lithogenic factors in urine such as calcium, oxalate, phosphate, increased urinary citrate, improved renal function, altered protein expression, and signs of diuresis were considered as signs of antiurolithic actions of the herbal extracts.

The majority of studies used 0.75–1% ethylene glycol (EG) in drinking alone [22–37] or in combination of ammonium chloride [38–55] (Fig. 1). A small number of studies used other methods to induce CaOx nephrolithiasis. Several used EG along with zinc disk placed in the bladder of the rats for the development of a foreign body stone [56–59]. Others used a combination of gentamicin and calculi producing diet of 5% ammonium oxalate [60, 61], or intraperitoneal injection of sodium oxalate to the Wistar rats [62]. Introduction of CaOx pellet into the bladders of adult male Wistar rats [63], or 3% glycolate diet for 4 weeks [27], or daily intra-abdominal injection of glyoxylate (80 mg/kg) for 12 days [64], or insertion of a series of 15 knots of 5–0 chromic catgut into the urinary bladder [65] were some of the other methods employed. One study employed subcutaneous injection of gentamicin in addition to 5% ammonium oxalate in the rat diet [66]. Other studies involved a single dose of 200 mg glycolic acid given orally [67], implantation of a CaOx seed into the bladder of male Wistar rats [68], 3% glycolic acid mixed with food for 45 days [69], EG and 1 alpha(OH)D3 and 1 alpha-D3-induced calcium oxalate nephrolithiasis [70], high protein diet [71], and administration of glycollic acid [72].

As illustrated in Figs. 2 and 3 most of the studies utilized aqueous extracts [22–32, 35–40, 64, 67, 73–79], and leaves [29, 30, 33, 35, 38, 40, 44, 49, 66, 80, 81] were the most commonly utilized herbal preparation. Other parts used were fruits [25, 28, 35, 41, 82–86], roots [23, 26, 29, 37, 64, 87–89], seeds [32, 50, 90–95], rhizome [31, 53, 96–98], stem [22, 24, 41], flowers [39, 46], aerial part [23, 42, 45, 47, 76, 99, 100], in addition to other parts such as essential oil of seed [73] or root [73]. Some studies used whole plants [77–79, 101, 102], fronds [43], root bark [52, 103], bark [72], herbal tea [27], rose calyx [75], capitulum [104], pulp [105], herbal medication (Tutukon) [106], spores [107], polyphenolic compounds [108], diosmin: a flavanone glycoside [109], or poly-herbal formulations such as Cystone [110], polyherbal ayurvedic Gokshuradi [55], Mallorcan: a folk herbal extract [111], Wulingsan: a traditional Chinese herbal antilithic formula [112], Choreito [113], Kampou medicines like Takusha [114] and Takusva [70, 115], Zhulingtang (a traditional Chinese herbal formula) [116], Choreito (a herbal preparation), and urajirogashi (a herb) [113].

Other methods of extraction included hydroalcoholic [22–25, 27–32, 35, 36, 38–40, 64, 67, 73, 74, 76–79, 93], or alcoholic [29, 33, 47, 49, 60, 80, 83, 88, 90, 95, 99, 102, 105–107, 117], while some studies utilized formulations/constituents like infusions [104], decoctions [61, 69, 85, 118, 119], ultrahigh diluted homeopathic preparation [103], coconut water [120], polysaccharides [100], saponin-rich fraction [84], herbal powder [72, 81, 89, 92, 119], isolated constituents [28], pasteurized juice [91], juice [66, 86] or triterpenoids extracted from plant [121] (Fig. 2).

Calcium oxalate nephrolithiasis in rat models is associated with changes in urinary oxalate, citrate, pH, markers of oxidative stress, production of crystallization modulators and inflammatory molecules, crystalluria and CaOx crystal deposition in the kidneys [54]. All studies did not investigate all the above-mentioned changes associated with nephrolithiasis. But all of them examined crystal deposition in the kidneys and a reduction in crystal deposition was considered a successful outcome of the treatment (Fig. 4). Signs of improved renal structure and functions were reported by most of the studies. Changes in urinary excretion of calcium, oxalate, magnesium, and phosphate were also reported by most studies. Less than 20% of the studies reported changes in urinary pH, citrate, oxidative stress, altered protein expression, and diuresis.

Discussion

It is important for any drug development to understand the pathogenesis of a disease, in this case, kidney stones. Nephrolithiasis, formation of stones in the kidneys, is a complex,

Table 1 In vivo studies on the therapeutic effects of aqueous Extracts of Medicinal Plants against CaOx nephrolithiasis

Reference year plant name	Common name Name	Part used	Type of extract	Hyperoxaluria inducing Agent	Antiurolithic activities								
					Reduced crystals deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	**↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)**	**Improved renal functions**	**Altered Protein expression**	**Diuresis**
[38] 2018 *Polygonum Aviculare* L	Wire weed, knotweed, knotgrass,	Leaves	Aqueous extract	EG + AC	+	+							
[35] 2018 *Aliciella heterostyla*	Cactus	Fruit	Aqueous and ethanolic extracts	EG	+		+						
[36] 2017 *Tragia involucrate*	Stinging nettle	Leaves	Aqueous extract and its silver nanoparticles	EG	+	+							
[37] 2017 *Radix Paeoniae Alba*	White poeny root	Dried root without bark	Aqueous extract	EG	+	+						+	
[39] 2017 *Phlogacanthus thyrsiformis Hardow* (Mabb)	Ram basak	Flowers	Aqueous extract & silver nanoparticles	EG + AC	+								
[22] 2017 *Cerasus Avium*	Cherry	Stem	Aqueous extracts	EG	+								
[73] 2016 *Nigella Sativa* L	Black Cumin	Essential oil from seed	Hydro distillation	EG + AC	+	+				+	+		+

Table 1 (continued)

Reference year plant name	Common name Name	Part used	Type of extract	Hyperoxaluria inducing Agent	Antiurolithic activities								
					Reduced crystals deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	**↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)**	**Improved renal functions**	**Altered Protein expression**	**Diuresis**
[40] 2015 *Malva Neglecta* Wallr	Common mallow	Leaves	Aqueous extract	EG + AC	+	+							
[74] 2013 *Gardeniae Fructus*	Sanshishi		Hot water extract		+								
[23] 2012 *Petroselinum sativum*	Parsley	Aerial part and roots	Aqueous extracts	EG	+	+							
[24] 2012 *Costus igneus*	Fiery costus or spiral flag	Stem	Aqueous and ethanolic extract and isolated compounds lupeol and stigmasterol	EG	+					+	+		
[75] 2012 *Hibiscus sabdariffa* L	Roselle	Calyx	Aqueous extract	EG + AC	+	+					+		
[25] 2012 *Bombax ceiba* L	Red silk-cotton	Fruit	Aqueous and ethanol extracts	EG	+					+			
[26] 2012 *Achyranthes aspera* Linn	Chaff-Flower	Root	Aqueous extract	EG	+	+					+		

Table 1 (continued)

Reference year plant name	Common name Name	Part used	Type of extract	Hyperoxaluria inducing Agent	Antiurolithic activities								
					Reduced crystals deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	**↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)**	**Improved renal functions**	**Altered Protein expression**	**Diuresis**
[27] 2011 *Hibiscus sabdariffa*	Roselle	Herbal tea	Aqueous extract	EG	+						+		
[27] 2011 *Phyllanthus amarus*	Carry Me Seed	Herbal tea	Aqueous extract	3% glycolic acid in diet	+				+		+		
[28] 2011 *Ammi visnaga* L. And its constituents khellin and visnagin	Bishop's weed	Fruit	Aqueous extract	EG	+				+	+			
[64] 2011 *Rubus idaeus*	Raspberry	Young roots	Aqueous extract	Glyoxylate (i.p. injections)	+		+			+	+		
[29] 2010 *Salvadora persica*	Wild Guava (Miswak; Toothbrush Tree)	Leaves	Aqueous and alcoholic extracts	EG	+	+				+	+		
[30] 2009 Urocalun: compound herbal formulation		Twig leaves	Aqueous extracts of *Quercus salicina* Blume/*Quercus stenophylla* Makino	EG	+		+		+				

Table 1 (continued)

Reference year plant name	Common name Name	Part used	Type of extract	Hyperoxaluria inducing Agent	Antiurolithic activities								
					Reduced crystals deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	**↓ lithogenic factors in urine (Ca++, Ox, Phosphate)**	**Improved renal functions**	**Altered Protein expression**	**Diuresis**
[31] 2009 *Cynodon dactylon*	Bermuda Grass	Rhizome	Aqueous extract	EG	+								
[32] 2007 *Trigonella foenum-graecum* L	Common Fenugreek, Greek-clover,	Seeds	Aqueous extract	EG	+								
[67], 2007, (122), 1997 *Cymbopogon schoenanthus* (Al-Ethkher)	Lemongrass		Extract	Glycolic acid	+	+		+		+	+		+
[76] 2006 *Aerva lanata*	Mountain knotgrass	Aerial parts	Aqueous suspension of dried powdered of aerial parts	EG	+	+			+	+			
[77–79] 2004, 2003 *Herniaria hirsute*	Rupture wort	Whole herb	Aqueous extract	EG	+					+			
[93] 2001 *Ammi visnaga* (AI-Khillah)	Bishop's Weed	Seed	Aqueous extract	Glycolic acid	+					+			+

Urinary lithogenic factors: increased Ca++, Ox and Phosphate and reduced Mg++in urine

+indicate the presence of activity/mechanisms, EG ethylene glycol, AC ammonium chloride

Table 2 In vivo studies on therapeutic effect of hydro-alcoholic extracts of medicinal plants against CaOx nephrolithiasis in rats

Reference year plant name	Common name	Part used	Type of extract	Hyperoxaluria inducing agents	Antiurolithic Activities								
					Reduced crystaldeposition	Improved renal architecture	Reduced oxidative stress/ antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca++, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[33] 2017 *Chenopodium album* Linn	Fat hen	Leaves	Methanolic and aqueous extracts	EG	+			+		+	+		
[96] 2017 *Bergenia ligulata*	Velvet leaf	Dried rhizome	Aqueous methanolic extract and dichloromethane (DCM) fraction	EG	+	+							
[34] 2017 *Musa paradisiaca*	French plantain	Pseudostem	Aqueous-ethanol extract	EG	+		+	+		+	+		
[41] 2016 *Peucedanum grande C. B.* Clark	Doqu, Hill Carrot	Fruit	50% aqueous-ethanolic (hydroalcoholic) extract	EG + AC	+	+				+	+		
[101] 2016 *Vernonia cinerea* Less	Tagulinai	Whole plant	Hydro-alcoholic extract	EG	+	+				+	+		+
[42] 2015 *Desmodium styracifolium*	Coin-leaf	Arial part	70% aqueous ethanol	EG + AC	+	+	+	+	+	+	+		
[94] 2015 *Dolichos biflorus*	Kulattha	Seeds	70% hydro-alcoholic extract	EG	+	+	+			+			

Table 2 (continued)

Reference year plant name	Common name	Part used	Type of extract	Hyperoxaluria inducing agents	Antiurolithic Activities								
					Reduced crystaldeposition	Improved renal architecture	Reduced oxidative stress/ antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca++, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[97] 2014 *Bergenia ciliata*	Hairy Bergenia	Rhizome	Hydro-methanol (30:70) extract	EG	+					+			
[43] 2013 *Adiantum capillus veneris* Linn	Maidenhair fern	Fronds	Hydro alcoholic extract (aqueous ethanol)	EG +AC		+				+	+		
[82] 2012 *Rosa canina* L	Rose Hips / Dogrose	Fruit	Hydroalcoholic extract	EG	+				+	+			
[24] 2012 *Costus igneus*	Fiery costus or spiral flag	Stem	Aqueous and ethanolic extract and isolated compounds lupeol and stigmasterol	EG	+					+	+		
[50] 2012 *Holarrhena antidysenterica*	Conessi / Kurchi	Seeds	Hydro-alcoholic extract	EG +AC	+	+				+	+		
[44] 2012 *Hypericum perforatum* L	St. John's-wort	Leaves	Hydroalcoholic extract	EG +AC	+					+			

Table 2 (continued)

Reference year plant name	Common name	Part used	Type of extract	Hyperoxaluria inducing agents	Antiurolithic Activities								
					Reduced crystaldeposition	Improved renal architecture	Reduced oxidative stress/ antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca++, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[45] 2012 *Hygrophila spinose*	In ayurvedic literature as Ikshura, Ikshugandha, and Kokilasha	Arial part	Aqueous-methanolic (80%) extract	EG +AC	+					+			
[25] 2012 *Bombax ceiba* L	Red silk-cotton	Fruit	Aqueous and ethanol extracts	EG	+					+			
[98] 2011 *Bergenia ciliata*	Paashaanbhed	Rhizome	Hydro-alcoholic extract	EG	+	+							
[46] 2011 *Helichrysum plicatum* DC. Subsp. Plicatum extract	Everlastin, Immortal flower or fadeless flower	Flower	Hydroalcoholic extract (50%)	EG + AC	+	+				+	+		
[29] 2010 *Salvadora persica*	Wild Guava (Miswak; Toothbrush Tree)	Leaves	Aqueous and alcoholic extracts	EG	+	+				+	+		
[87] 2010 *Rubia cordifolia*	Indian Madder	Root	Hydro-alcoholic extract	EG	+	+			+	+	+		
[52] 2010 (105) *Berberis vulgaris*	Barberry	Root bark	Crude aqueous-methanol extract	EG	+	+	+				+		

Table 2 (continued)

Reference year plant name	Common name	Part used	Type of extract	Hyperoxaluria inducing agents	Antiurolithic Activities								
					Reduced crystaldeposition	Improved renal architecture	Reduced oxidative stress/antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[53] 2009 *Bergenia ligulata*	Bergenia, Winter Begonia	Rhizome	Aqueous-methanolic extract	EG	+	+	+			+			

Urinary lithogenic factors: increased Ca + +, Ox and phosphate and reduced Mg + + in urine
+ indicate the presence of activity/mechanisms, EG Ethylene Glycol, AC Ammonium Chloride

multifactorial, and multistep process resulting from physicochemical changes in the urinary environment, leading to crystal nucleation, growth aggregation, and retention at specific sites within the kidneys [2, 122, 123]. Interacting urinary ions and a variety of crystallization modulatory macromolecules are involved [124–127]. Most of the idiopathic CaOx stones develop over a foundation of biological apatite, called Randall's plaque (RP). The plaque starts in the renal papillary interstitium, which grows outward to the papillary surface and becomes exposed to the pelvic urine once surface epithelium/urothelium disintegrates [128]. Some stones, however also form attached to tubular crystal deposits seen plugging the terminal collecting ducts [128, 129]. Thus kidney stones are crystal deposits in the kidneys, but all renal crystalline deposits are not kidney stones.

Several in vitro and in vivo models have been established to explore the pathogenesis of CaOx nephrolithiasis and to develop therapeutic agents and protocols for testing their efficacies [122, 130, 131]. In the in vitro crystallization experiments, calcium oxalate crystal nucleation, growth, and aggregation are investigated in the absence and presence of the crystallization modulators [132, 133]. These in vitro methods give an easy and quick estimate of crystallization modifying activity, preliminary screening for anti-urolithic activity and possible mode(s) of action. However, the biological system and the pathogenesis of urolithiasis is too complex and these in vitro results cannot be safely extrapolated for the therapeutic effect [131]. Therefore, in vivo animal models of CaOx nephrolithiasis to better understand the pathogenesis of nephrolithiasis and investigate the anti-urolithic actions and potential of various drugs have been developed [134].

Experimental nephrolithiasis is produced by the administration of hyperoxaluria inducing agents through diet, drinking water or injection [79, 122, 135]. These in vivo models have a great contribution in understanding of several human pathologies and will remain as a main tool for providing methods and designs to the researcher for the countless biochemical events, physiological processes, and testing of novel pharmaco-therapeutic agents [136]. Investigators have been utilizing these models of hyperoxaluric rats for decades despite obvious differences between rats and human kidneys. The rat kidneys are smaller weighing around 0.75–1.2 g, measuring $1.6 \times 1 \times 0.9$ cm, and are unipapillate, while human kidneys weigh approx.. 170 g, measure $11 \times 6 \times 2$ cm and are multi-papillary, however, despite the gross differences, the cortex–medulla ratio (2:1) of rat's kidney is similar to human's [137]. The majority of the studies of herbal use discussed here have utilized the rat model of nephrolithiasis by giving EG in their drinking water alone [33, 34] or with an addition of ammonium chloride [79, 138, 139]. EG, a precursor of oxalic acid, quickly absorbed from the GIT and metabolized to oxalic acid by hepatic enzymes.

Table 3 In vivo studies on therapeutic effect of alcoholic extracts of medicinal plants against CaOx nephrolithiasis in rats

Reference year plant name	Common name	Part used	Type of extract	Hyperoxaluria inducing agents	Antiurolithic activities								
					Reduced crystals deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[105] 2018 *Citrullus lanatus*	Water melon	Pulp	Ethanolic extract	EG	+	+		+	+	+	+		+
[33] 2017 *Chenopodium album* Linn	Fat hen	Leaves	Methanolic and aqueous extracts	EG	+			+		+	+		
[49] 2016 *Ipomoea eriocarpa*	Tiny Morning Glory	Leaves	Ethanolic extract	EG	+	+				+	+		
[60] 2015 *Sarghassum Wightii*	Brown algae		Phlorotannin rich extract	5% ammonium oxalate in diet + gentamycin	+	+				+			
[106] 2015 Herbal medication (Tutukon)	A compound preparation of herbal ingredients: essential oils, flavonoids quercetin, polysaccharides, rosmarinic acid, boldin, flavone glycosides			EG	+							+	
[47] 2014 *Urtica dioica*	Stinging Nettle	Aerial part	Methanol extract	EG + AC	+					+	+		
[107] 2014 *Lygodiumja ponicum*	Lygodii Spora	Spores	Ethanol extract	EG	+	+	+		+	+			

Table 3 (continued)

Reference year plant name	Common name	Part used	Type of extract	Hyperoxaluria inducing agents	Antiurolithic activities								
					Reduced crystals deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[83] 2013 *Pedalium murex* Linn	Bada Gokhru	Fruit	Ethanolic extract	EG	+	+				+	+		
[95] 2012 *Hordeum vulgare*	Barley	Seeds	Ethanolic extract	EG	+	+	+		+	+			+
[102] 2012 *Leea macrophylla*	Hastikarnapalsa	Whole plant	Ethanolic extract	EG	+	+				+	+		
[117] 2012 *Asparagus racemosus*	Shatavari / shatamuli		Ethanolic extract	EG + AC	+	+				+	+		
[88] 2011 *Urtica dentata* hand; a traditional Chinese herbal medicine,		Root	N-butanol extract (NBE)	EG + AC	+	+				+	+		+
[29] 2010 *Salvadora persica*	Wild Guava (Miswak; Toothbrush Tree)	Leaves	Aqueous and alcoholic extracts	EG	+	+				+	+		

Table 3 (continued)

Reference year plant name	Common name	Part used	Type of extract	Hyperoxaluria inducing agents	Antiurolithic activities								
					Reduced crystals deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca++, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[99] 2010 *Paronychia argentea*	Algerian tea	Aerial part	Butanolic extract	EG	+	+				+	+		
[90] 2007 *Nigella sativa* L	Black cumin	Seeds	Ethanolic extract	EG	+					+			
[80] 2005 *Asparagus racemosus Willd*	Shatavari / Shatamuli	Leaves	Ethanolic extract	EG	+	+				+	+		

Urinary lithogenic factors: increased Ca++, Ox and phosphate and reduced Mg++in urine

+indicate the presence of activity/mechanisms, EG ethylene glycol, AC ammonium chloride

Table 4 In vivo studies on therapeutic effect of medicinal plant formulations against CaOx nephrolithiasis

Reference year plant name	Common name	Part used	Type of extract/ formulation	Hyperoxaluria inducing agents	Antiurolithic activities							
					Reduced crystal deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[108] 2017 *Quercus gilva Blume*	The red-bark oak	Polyphenolic compounds: (−)-epicatechin, procyanidin, and procyanidin		EG	+		+					+	
[109] 2016 *Teucrium gnaphalodes L'Her*	Iberian Germander	Diosmin: a flavanone glycoside		EG + AC	+	+				+	+		
[104] 2016 *Helichrysum stoechas* (L.) and *Helichrysum graveolens*	Immortal flower	Capitulum	Infusions	Sodium oxalate	+				+	+	+		+
[118] 2016 *Glechoma longituba*	No-Kanzo	NA	Decoction	EG	+	+	+		+	+		+	
[106] 2015 Herbal medication (Tutukon)	A compound preparation of herbal ingredients: Essential oils, flavonoids quercetin, polysaccharides, rosmarinic acid, boldin, flavone glycosides			EG	+							+	
[103] 2013 *Berberis Vulgaris*	Barberry	Root bark	Ultrahigh diluted homeopathic preparation	EG	+					+	+		
[120] 2013 *Cocos nucifera* L	Coconut		Coconut water	EG	+	+	+				+		

Table 4 (continued)

Reference year plant name	Common name	Part used	Type of extract/ formulation	Hyperoxaluria inducing agents	Antiurolithic activities								
					Reduced crystal deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[110] 2013 Cystone; an approved Ayurvedic poly herbal proprietary medicine	Syrup preparation of extracts of Tribulus terrestris L., Boerhavia diffusa L., Saxifraga ligulata Murray, Cyperus rotundus L., Asparagus racemosus Willd., Dolichos biflorus L., Vetiveria zizanioides L., Curcuma zedoaria Roxb., Saindhava Suvarchika, Yavakshara, Narasara			EG	+	+	+	+	+	+	+		+
[55] 2013 *Gokshuradi Yog (GY)* i	Polyherbal ayurvedic formulation			EG + AC	+		+						+
[100] 2012 *Orthosiphon stamineus* Benth	*Kumis kucing*,	Aerial part	Polysaccharides and ethyl acetate fraction	EG + AC		+				+	+	+	
[84] 2012 *Solanum xanthocarpum* Schrad & Wendl	Yellow Berried Nightshade	Fruit	Saponin-rich fraction	EG	+	+				+	+	+	
[61] 2012 *Desmodium styracifolium*	Coin-leaf desmodium	Not given	Decoction	5% ammonium oxalate (AmOX)	+	+	+		+	+		+	
[61] 2012 *Pyrrosia petiolosa*	Shearer's pyrrosia leaf	Not given	Decoction	EG	+	+	+			+		+	
[119] 2012 *Flos carthami*	Safflower		Herbal powder	EG	+								

Table 4 (continued)

Reference year plant name	Common name	Part used	Type of extract/ formulation	Hyperoxaluria inducing agents	Antiurolithic activities								
					Reduced crystal deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[28] 2011 *Ammi visnaga* L. isolated constituents khellin and visnagin	Bishop's weed		Isolated constituents	EG	+								
[85] 2010 *Pinus eldarica* medw:	Tehran pine	Fruit	Decoction	EG	+					+			+
[81] 2010 *Orthosiphon grandiflorum*	Java tea	Fresh leaves	Finely powdered		+		+	+					
[116] 2009 Zhulingtang (a traditional Chinese herbal formula)	Composed of 5 dried herbs: Polyporus umbellatus (Pers.) Fries, Poria cocos (Schw.) Wolf, alismatis rhizoma, talcum and colla corii asini			EG + vit. D_3	+	+							
[91] 2009 *Punica granatum*	Pomegranate	Seeds	Pasteurized juice	EG	+	+	+					+	
[111] 2009 Folk herbal extract; Mallorcan	Contains fluid extracts of *Arctotaphylos uva-ursi* L., *Zea mays* L. and *Ricinus zanzibariensis* L. tincture of *Sabal serrulata* L., mother tincture of *Agathosma betulina* L., glycerin, and anis essence			EG	+								

Table 4 (continued)

Reference year plant name	Common name	Part used	Type of extract/ formulation	Hyperoxaluria inducing agents	Antiurolithic activities								
					Reduced crystal deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[112] 2008 Wulingsan; a traditional Chinese herbal antilithic formula	Composed of five dried herbs: Alisma ori-entalis (Sam.) Juzep., Polyporus umbellatus(Pers) Fries, Atractylodes macrocephala Koidez, Poria cocos (Schw.) Wolf, and Cin-namomon cassia Presl			EG	+	+							
[66] 2008 *Sesbania grandiflora*	Corkwood tree; Hum-mingbird tree;	Leaves	Juice	5% ammonium oxalate in diet + genta-mycin	+		+			+			
[86] 2007 *Citrus limon*	Lemon	Fruit	Juice	EG	+						+		
[69] 2002 *Rotula aquatic* lour	Carmona viminea, /Ehretia viminea, /Rhabdia viminea		Decoction	3% glycolic acid in diet						+			
[89] 2002 *Cyclea peltata* Lam	Ink berry	Root	Powdered	EG						+			
[114] 1999 Takusha,; a kampo medicine			A kampo medicine	EG + vit. D_3	+							+	

Table 4 (continued)

Reference year plant name	Common name	Part used	Type of extract/ formulation	Hyperoxaluria inducing agents	Antiurolithic activities								
					Reduced crystal deposition	Improved renal architecture	Reduced oxidative stress/ mediated antioxidant effect	↑ urine pH	↑ urine Citrate	↓ lithogenic factors in urine (Ca + +, Ox, Phosphate)	Improved renal functions	Altered Protein expression	Diuresis
[115, 70] 1995, 2016 Takusya (Kampou medicine)			Mixture of 16 plant extracts	EG + 1α(OH)D_3	+	+							+
[121] 1993 *Desmodium styracifolium*- (Osbeck) Merr,	Coin-leaf desmodium		Triterpenoid extracted from the plant	EG + 1α(OH)D_3	+					+			+
[72] 1990 *Crataeva nurvala*	Three leaved caper	Bark	Decoction	Glycolic acid	+					+			
[92] 1989 *Trigonella foenumgraecum*	Fenugreek	Seed	Powdered seeds	3% glycolic acid diet	+								
[113] 1986 Choreito (a herbal preparation), and urajirogashi (a herb)				3% glycolic acid diet	+					+			+

Urinary lithogenic factors: increased Ca + +, Ox and phosphate and reduced Mg + + in urine

+ indicate the presence of activity/mechanisms, EG = ethylene glycol, AC = ammonium chloride

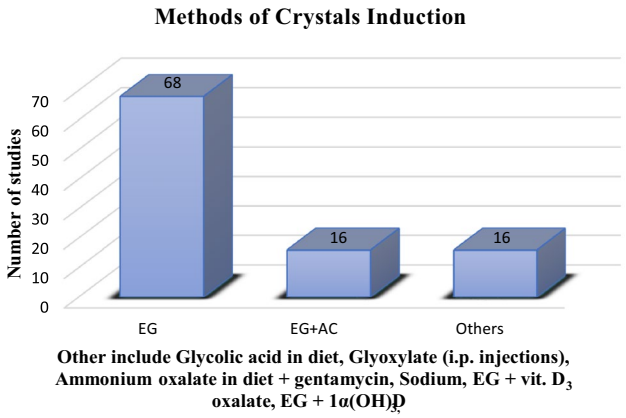

Fig. 1 Number of studies based on the methods used for crystals induction

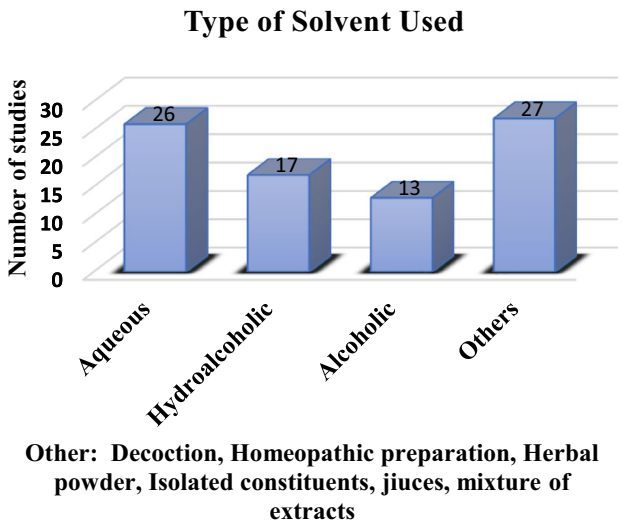

Fig. 2 Number of studies based on the type of solvent used

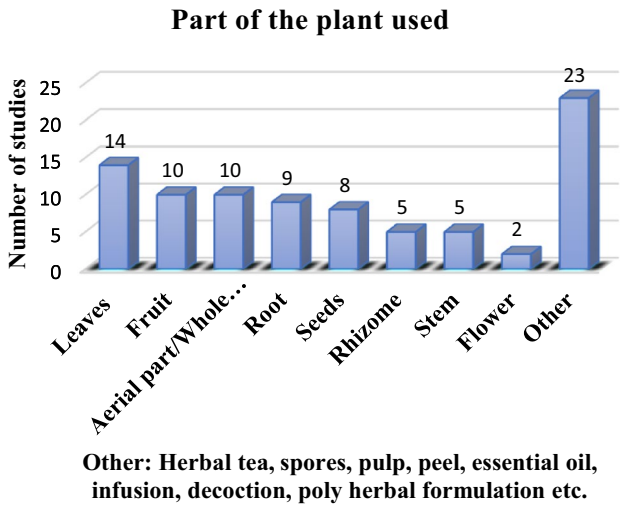

Fig. 3 Number of studies based on the part of the plant used

EG mostly affects the kidneys with considerable variability in sensitivity across the strains, species, and sexes. Rats are more sensitive than mice and male rats are more sensitive than females. EG (0.75–1%) alone gives variable results of CaOx deposition [140]. To achieve a uniformly high rate of renal crystal deposition and reducing the time required for crystal deposition, a pH reducing, hypercalciuric or nephrotoxic protocol such as ammonium chloride (AC) [140, 141], vitamin D3 [121], gentamicin [142] or a magnesium-deficient diet has been used in combination with EG. However, treatment with AC 1% or more cannot be extended beyond 4–5 days as rats become sick, lose body weight and drink less water [140]. Hydroxy-L-proline (HLP), a physiologic precursor of oxalate is also used for induction of hyperoxaluria in the rats by oral administration or by intraperitoneal injection [54, 143]. Other hyperoxaluric rat models are produced by inbreeding of hyperoxaluric progeny [144, 145], the administration of sodium oxalate [146], or glycolic acid [147]. In addition, several other models of nephrolithiasis have been developed such as transgenic mouse with selective knockout (KO) of osteopontin (OPN) [148] and Tamm–Horsefall protein (THP) [149], oxalate, sodium phosphate [150], and cysteine transporter [151]. KO mouse model and fly model of CaOx crystals have also been developed. Despite the genomic advantages of the mice model, its overall accuracy and consistency in relation to human kidney stone disease remains controversial among researchers [152]. However, the hyperoxaluric rat model of nephrolithiasis represents a well- established and relatively economic model for the study of urolithiasis [134]. When EG is given at a concentration of 0.75% or above in drinking water, rats developed hyperoxaluria, leading to crystalluria and CaOx crystal deposition in kidney's tubules [122]. Frequency of crystal deposition in kidney range from 80 to 100% of the kidney's area, depending upon the co-administered drug [121, 153] and it takes about 1–3 weeks to develop nephrolithiasis. The prominent features of hyperoxaluria-induced nephrolithiasis include development of oxidative stress in the kidneys, high water intake and polyuria, decreased urinary Ca^{++}, Mg^{++}, and citrate contents, lower urinary pH, increased phosphate excretion, renal hypertrophy, CaOx crystalluria, and loss of body weight [54, 79, 121]. Other signs of renal damage are increased urinary protein loss, lower creatinine clearance, and raised serum creatinine and blood urea nitrogen (BUN) [54, 154]. All rats, as well as other animal models of hyperoxaluria such as Drosophila [155, 156] and pig [157, 158], do not produce kidney stones similar to idiopathic CaOx stones of human. They produce intratubular deposits of CaOx crystals.

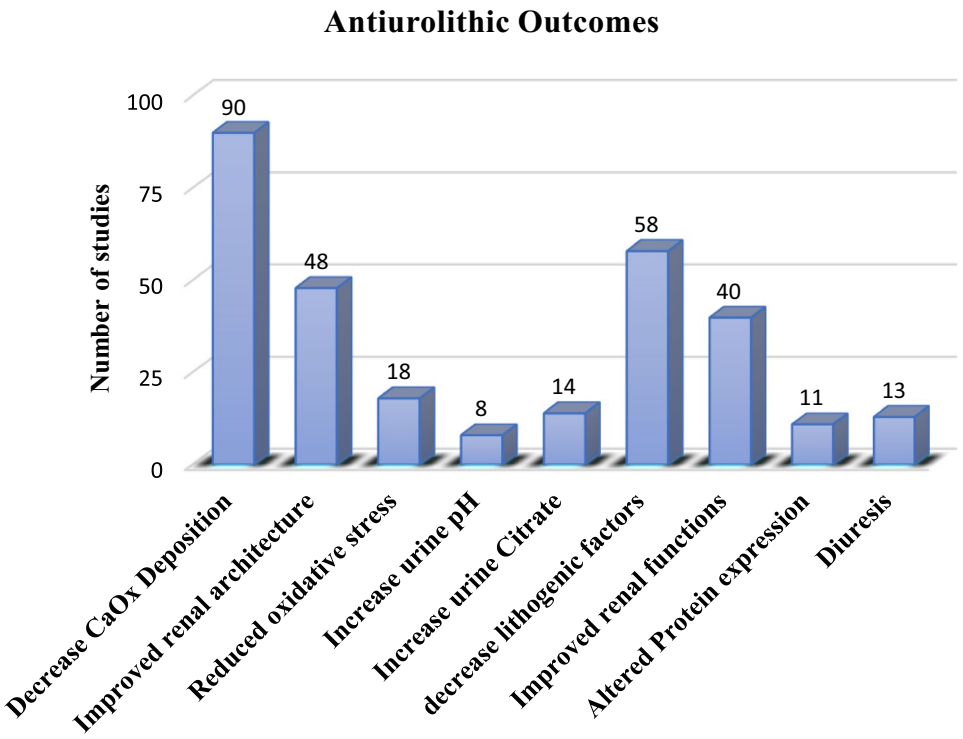

Fig. 4 Number of studies based on the mechanism of antiurolithic activity

Both animal model and tissue culture studies have shown that high oxalate and CaOx as well as CaP crystals cause overproduction of reactive oxygen species (ROS) by the renal epithelial cells leading to renal injury [159, 160]. Signs of oxidative stress have also been reported from clinical studies [159, 161]. Reactive oxygen species also regulate the production of various crystallization modulators which are known to inhibit crystal nucleation, growth, and aggregation [162]. These crystallization modulators also participate in the cellular inflammatory cascade. In addition, the ROS may stimulate osteogenic changes in the renal epithelial [163], and/or vascular endothelial cells. Antioxidants are shown to reduce hyperoxaluria and crystal-associated injury [164]. Herbal treatments of hyperoxaluric rats appear to reduce the oxidative stress, thereby reducing renal epithelial injury, membrane-associated crystal nucleation, and crystal deposition within the renal tubules and kidneys.

A significant majority of studies reviewed here utilized the most well-recognized model of experimental CaOx nephrolithiasis, administration of ethylene glycol through diet. Eight different parts of the plants, including flowers, seeds, fruits, leaves, stems, roots, rhizomes, were used to prepare the herbal treatments. Leaves were the most common ingredient. Aqueous, alcoholic, and hydro-alcoholic solvents were employed to prepare the treatments. Common indicators of nephrolithiasis, such as renal CaOx crystal deposits, markers of oxidative stress, urinary calcium, citrate, oxalate, phosphate, and pH, in addition to improved renal structure and functions were assessed to determine the efficacy of herbal administration. Unfortunately, all studies did not investigate all of these aspects of nephrolithiasis. However, all the treatments resulted in reduction of CaOx crystal deposition in the kidneys. Majority of studies showed an improvement in both the structure and function of the kidneys following herbal treatments. Studies that determined oxidative stress found that the herbal treatments had antioxidant properties.

Based upon the available data, we can visualize the following sequence of events when hyperoxaluric rats are treated with the diverse herbal preparations. Under normal circumstances, renal epithelial cells produce sufficient ROS to regulate various metabolic processes including inhibition of crystallization by the production of needed macromolecular inhibitors. Crystals, if formed due to the increased intake of calcium and oxalate and the decreased water in the urine, stay small and un-aggregated. Cell membranes are intact and do not promote crystal adherence thereby reducing chances of their retention within the tubules. Crystals, if any, move freely with the urine and discharged during urination (Fig. 5a). The administration of hyperoxaluric agents such as EG alone or in combination with other agents, as discussed above, leads to the production of abnormal urine with high oxalate, low citrate and in the case with vitamin D, increased calcium. Epithelial cells respond by producing access ROS. Cells are injured and respond aberrantly, producing inactive molecular inhibitors or macromolecules that promote crystal nucleation instead of reducing it. Cell membranes promote crystal nucleation and aggregation even

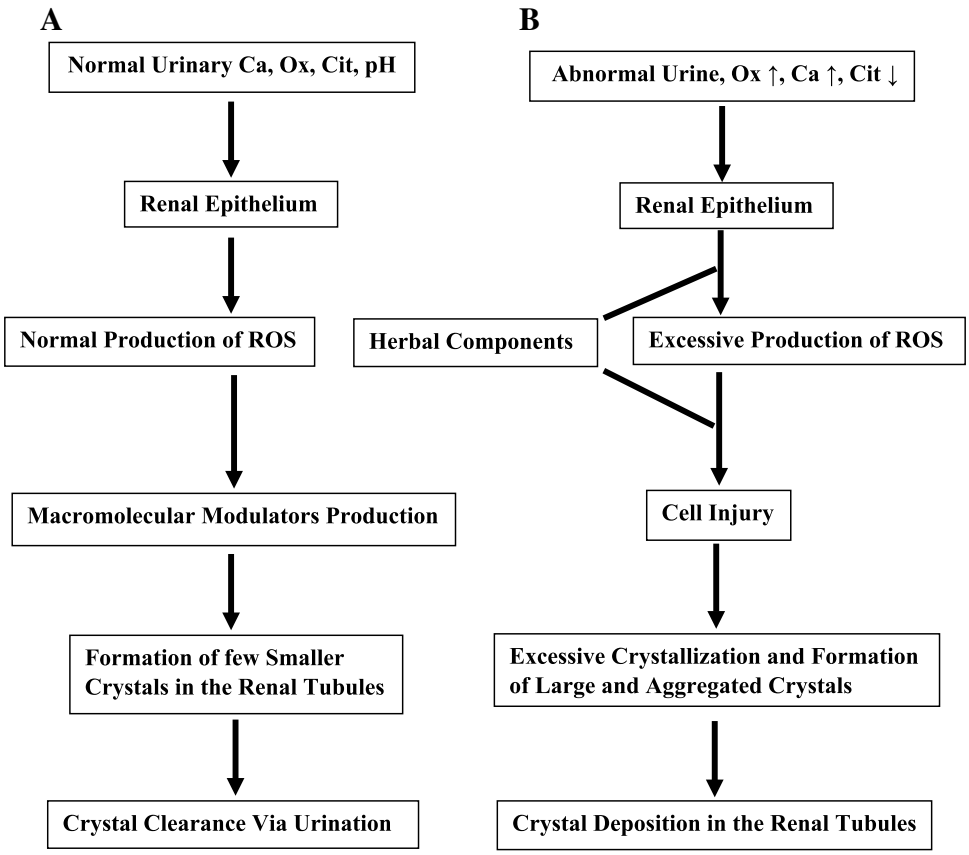

Fig. 5 Diagrammatic representation of crystallization within the kidneys. The (A) side represents normal urinary conditions. Occasional changes in the urinary calcium (Ca), oxalate (Ox), citrate (Cit), conducive to crystallization lead to the production of reactive oxygen species (ROS) sufficient to generate crystallization inhibitors. Small crystals are formed which are urinated out. The (B) side denotes abnormal and lithogenic urinary conditions. Persistently high Ca and/or Ox, and low Cit causes overproduction of ROS, injuring the renal tubular epithelium. Cells die, release membrane vesicles promoting crystal nucleation and aggregation. Production of active inhibitors is affected thereby crystals grow unimpeded. Herbal therapies appear to act either on the production of ROS or as their neutralizers. These actions will reduce cell injury and influence the production of active/normal macromolecular inhibitors resulting in reduced crystallization, the formation of small un-aggregated crystals which should easily pass during urination

under lower supersaturation promoting crystal deposition within the tubules. Herbal preparations contain compounds which diminish the production of ROS or/and have antioxidants that neutralize the ROS, leading to a reduction in cell injury and direction towards normalization. As a result, there is a reduction in crystal deposition in the kidneys as has been reported by all the studies undertaken to date (Fig. 5b).

Conclusions and future direction

Idiopathic CaOx stones form by the deposition and growth of CaOx crystals on Randall's plaques or the Randall's plugs. Plaques are subepithelial deposits of CaP on renal papillae, originating deep inside the medullary/papillary interstitium. We do not yet fully understand the pathogenesis of plaques, which may involve both tubular and vascular inflammation. Plugs are crystal deposits within the terminal collecting ducts and form as the result of urinary supersaturation and crystal attachment to injured renal tubular epithelium. Most of the plugs are also made of CaP. Reactive oxygen species are likely involved in both the plaque and plug formation because they play a significant role in the production of crystallization modulators, tubular epithelial injury as well as inflammation. Tubular injury produces cellular debris that can promote heterogeneous nucleation of CaP and also provides sites for their adherence and retention within the tubules. Crystallization modulators affect crystal formation by promoting or inhibiting their formation and growth. Animal model studies show that herbal treatments lead to the production of antioxidants, which may be responsible for their positive role in stopping crystal formation/deposition in the animal kidneys and may reduce stone recurrence when given to stone patients.

Where do the recurrent stones form? Do the new stones form on the remnant of the plaque or plug left after stone has passed? Or do they form on the new plaques and new plugs?

Whatever the case, herbal treatment with antioxidant properties can decrease stone recurrence by reducing the crystallization, which shall reduce crystal deposition on the plaques and plugs. In addition, the treatments may reduce crystal formation and deposition in the terminal collecting ducts and the formation of new plugs by reducing epithelial injury. It is unclear whether herbal treatments would have any effect on the formation and deposition of CaP in the renal interstitium and the initiation of the Randall's plaque. It is however possible that herbal treatment stops disintegration of the urothelium and exposure of the sub-urothelial CaP deposits on the papillary surface to the pelvic urine, thereby lessening the possibility of a new stone development.

Great progress has been made in developing and understanding of the mode of action of herbal extracts/preparations as a therapy for stone recurrence. But the range of methodologies used for inducing nephrolithiasis, and in preparing and delivering the extracts does not allow for the comparison between various treatments. In addition, many studies do not consider all aspects of nephrolithiasis. There is also a dearth of knowledge about the bioactive components of various herbal preparations, and their safety profile. What is the effect of extraction method on the bioactive compounds, their quality and quantity? Many of the herbal/alternative medicines are shown to be injurious to the kidneys [19, 20]. Future studies are needed to determine the active compounds present in the herbal preparations and whether those compounds reach the kidneys and urine, and are nontoxic to the kidneys. Researchers should agree upon a panel of features to be investigated to determine the efficacy of a treatment. The herbal treatment should induce changes in the urinary environment that reduce supersaturation, inhibit crystallization, and eventual crystal deposition in the kidneys. It should have antioxidant properties and be able to reduce the production of reactive oxygen species. It should be nontoxic and improve renal structure and functions.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval The article does not contain any studies with human or animal subjects.

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