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Review

The mechanistic insight of polyphenols in calcium oxalate urolithiasis mitigation

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ABSTRACT

About 12% of world population is affected by different forms of urolithiasis of which the recurrence rate in female is 47–60% and in male is 70–80%. Standard therapeutic agents (allopurinol, citrate, cystone and thiazide diuretics) are used to prevent and treat urolithiasis but these are not universally-effective due to common kidney stone relapse and other side effects. Surgical treatment causes long-term renal damage, hypertension and stone recurrence. Polyphenols, the plant-derived bioactive molecules, have showed protection against cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases, among a number of other ailments. The role of these phytochemicals in urolithiasis management is emerging. Hence, the present review discusses peer-reviewed published literature till date on this aspect and highlights that polyphenols could effectively inhibit the formation of calcium oxalate urinary stones (most common renal stone), correlating with their antioxidant, anti-inflammatory, diuretic and angiotensin-converting enzyme (ACE) inhibition. Further, we have proposed the prospects and challenges in developing the plant polyphenols into drugs against kidney stone prevention. This review might be a stepping stone for further investigation into the clinical implications of the polyphenols in urolithiasis remediation.

1. Introduction

Urolithiasis, characterized by uroliths or mineral deposition in urinary system, is a common health problem, with worldwide occurrence and high recurrence. This pathology is estimated to affect 12% of the world population with 70–80% and 47–60% recurrence in males and females, respectively [1]. Due to disturbed urine flow rate, uric acid excretion rate, and urine pH, the stones are formed. Increased bone resorption, hypercalciuria and hyperphosphaturia are risk factors of calcium oxalate kidney stones. Urease-producing bacteria such as *Proteus* cause struvite (magnesium—ammonium—phosphate) stones, which can cause severe aching and sepsis. Stones with ammonium hydrogen urate in the core result due to poor nutrition and dehydration.

The dissolution and prevention of the stone relapse are the main focus of urolithiasis treatment. Medications are prescribed to resolve the pain and stones pass out their own. Standard pharmaceutical drugs such as allopurinol, citrate, cystone and thiazide diuretics are used to prevent and treat urolithiasis [2], but these are not effective in all patients, due to common kidney stone recurrence and potential side effects. Surgical treatment causes long-term renal damage, hypertension and reformation of stones. Now, the Extracorporeal Shock Wave Lithotripsy (ESWL) and percutaneous nephrolithotomy, have almost become the standard procedure for eliminating the kidney stones but the traumatic effect of shock waves, persistent residual stone fragments as potential nidus for new stone formation, acute renal injury, decrement in the renal function and an increment in stone recurrence, ESWL induced hypertension, severe hematuria, steinstrasse (multiple small stone blocking the ureter), pancreatitis and infection are reported as repercussions [1]. These complications can lead to large perfusion of the collecting system, extravasations of irrigating fluid, urosepsis, ureteral injury. Further, ESWL is less effective in calcium oxalate monohydrate (COM) and cystine stones. In this regard, benign but effective therapy is being sought-after.

Antiurolithiatic plants are used since ancient times, in the form of

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decoction, infusion, or juice, to eliminate kidney stones and to prevent their recurrence. Although medicinal plants have milder efficacy and longer therapy duration, these are affordable and less expensive, with fewer side effects. On the basis of available ethnopharmacological information, more scientific studies are needed to explore natural and safe antiurolithiatic compounds [3]. Phytochemicals have complex molecular structures which act through multiple biochemical pathways to produce desired therapeutic effects. Some of these secondary metabolites are bioactive, having great selectivity of cellular targets. In contrast, some of the metabolites have multiple cellular targets, which may combine together to produce specific biological activity. Some of the phytochemicals exert biological effect by synergistic mechanism. Some inactive adjuvant substances enhance the potency of bioactive compounds. Plants also contain byproducts which may increase the absorption rate or solubility of active phytochemicals or may induce metabolic enzymes [4].

Over the years, plant-based products have demonstrated broad-range of therapeutic potentials [5–10]. Polyphenols encompass anthocyanins, chalcones, flavones, isoflavones, flavonols, phenolic acids and stilbenoids. Cyanidin, delphinidin, malvidin are anthocyanins [11]; curcumin is grouped under chalcones [12–14]; apigenin, diosmin and luteolin are classified under flavones [15]; genistein and daidzein are reported as isoflavones [16] ; catechin, kaempferol, quercetin, rutin are the examples of flavonols. Phenolic acid consists of hydroxycinnamic and hydroxybenzoic acids [17]. Hydroxycinnamic acids comprise caffeic, chlorogenic, coumaric, ferulic and sinapic acid; whereas hydroxybenzoic acid includes gallic, protocatechuic, syringic and vanillic acid. Resveratrol is a stilbenoid [11]. Each of the polyphenol members boast thousands of scientific validation reports regarding their health benefits.

2. Pathophysiology of calcium oxalate urolithiasis

Oxalate is widely distributed in plant-based foods as potassium, sodium and ammonium oxalates (water-soluble form) and as insoluble calcium oxalates. It is being recommended to limit the intake of oxalate-rich foods, specifically for individuals at risk for kidney stone formation [18]. Oxalate is poorly absorbed under non-fasting conditions. It has been demonstrated that only 2–12% of oxalate (soluble form) is absorbed from foods but that once absorbed, free oxalate binds to calcium ions to form insoluble calcium oxalate [19]. Oxalate has been shown to be toxic to renal epithelial cells of cortical origin. It has been observed that the exposure of renal epithelial cells to oxalate leads to the disruption of the normal activities of the renal epithelium, caused changes in gene expression, impairment of mitochondrial function, forming reactive oxygen species and thus, decreased cell viability [20]. Membrane injury is considered to be the prime reason for the binding of calcium oxalate crystal and subsequent growth into kidney stones. Oxalate-induced membrane injury is mediated by lipid and protein peroxidation through the generation of ROS with altered biochemical reactions, including the depletion of the antioxidant defensive system and failure of the calcium pump. Calcium and oxalate accumulate and then precipitate in the presence of membrane fragments to form stones [21]. Renal epithelial cell injuries in renal papilla invites calcium oxalate to form attached renal calculi and the development of calcium oxalate papillary calculi. Antioxidants play an important role in the avoidance of calculi formation [22], and by protecting membrane injury. These stones attached to tips renal papilla and prevent calcium oxalate retention [21]. Calcium oxalate crystals are generally grown from microns to several centimeters. These stones attach to the tips of renal papilla and when detached, hinder urine flow due to their large size. These crystals have a stronger affinity for the membranes of renal epithelial cells and therefore they make strong adhesion contacts with these cells, and form stable aggregates instead of excretion and lead to the retention of mineral in renal collecting ducts for urolithiasis development [23]. Fig. 1 illustrates the mechanism of stone formation (Table 1).

3. The mechanistic insight of polyphenols in oxalate urolithiasis

Pumpkin (*Cucurbita* sp.) seeds ingestion has been observed to avoid kidney stones. *Hibiscus sabdariffa* aqueous extract significantly lowered the stone formation risk in the kidneys and serum of rat models. Although in earlier studies caffeic acid [24], catechin [25], curcumin, rutin [26], diosmin [27], quercetin [28,29] and resveratrol [30] have prevented the ethylene glycol-induced calcium oxalate crystallization in rats, the mechanistic insights underlying these effects have been barely-explained. The antioxidant, anti-inflammatory, ACE-inhibitory, and diuretic activities of polyphenols are contributive to the calcium oxalate calculi prevention [31].

4. Antioxidant

ROS are free radicals comprising of singlet oxygen superoxide anion ($O2^{*-}$), hydroxyl (OH^{*-}) and peroxy (ROO^{*}) radicals, as well as non-radical molecules, such as hydrogen peroxide and hypochlorous acid [32]. Free radicals quickly react with lipids and proteins, render them unstable, and initiate a cascade of chain reactions. Under normal physiologic conditions, these reactions are important for immune response, gene expression, signal transduction and growth regulation. But the overproduction of ROS, injure and damage renal epithelial cells [32–34]. Free-radical scavenging enzymes such as catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, heme oxygenase-I, superoxide dismutase and endogenous antioxidants as vitamin C, vitamin E, reduced glutathione, not only maintain the normal physiologic concentration of free radicals, but also provide protection against endothelial oxidative damage. Renal exposure to oxalates causes lipid peroxidation and produce ROS followed by renal cell injury and inflammation. The resultant loss of membrane integrity promotes fibrosis and collagen formation, facilitates calcium oxalate adhesion, retention and subsequent stone formation. The ROS triggers phospholipase A2 activation through nuclear transcription factor NF-κB. The activation of phospholipase A2 generates arachidonic acid, which increases ROS production which in turn causes inflammation, cellular damage and crystal formation [35–37]. Thus, the vicious cycle continues. Antioxidants are compounds that can delay, inhibit or prevent the oxidative degeneration by decreasing localized oxygen concentrations, scavenging ROS or RNS species and their intermediates, binding or chelating with metal ions and decompose lipid peroxides [38]. *In vitro* and *in vivo* studies suggest that the antioxidant activity of natural polyphenols play an important in the prevention of calcium oxalate monohydrate type urolithiasis, particularly by inhibiting renal endothelial tissue injury caused by cytotoxic substances with oxidative capacity [22,39–41]. By scavenging free radicals, increasing endogenous antioxidant enzymes level and chelation of transition metals, and lowering membrane lipid peroxidation, the polyphenols protect the cells against oxidative stress.

Catechin [42,43], curcumin [44], daidzein, genistein [45], kaempferol [46], luteolin [47,48], quercetin [46] and syringic acid [32] are reported to scavenge peroxide free radicals. Superoxide dismutase is useful in protecting tissue injury, and glutathione participates in membrane stabilizing during oxidative stress [49]. Catechin [50], cyanidin, malvidin [51], caffeic acid [52,53], diosmin [54], *p*-coumaric acid [55], gallic acid [56], protocatechuic acid [57,58], apigenin [59], resveratrol [30] and vanillic acid [60] are reported to inhibit lipid peroxidation by increasing the activity of endogenous antioxidants such as CAT, SOD, and GSH.

Transition metals such as copper and iron play an important role in generation of free radicals leading to lipid peroxidation [33]. Cyanidin, delphinidin, malvidin [38], caffeic, chlorogenic, ferulic [33], gallic [56], protocatechuic [57,58], syringic acid [32], rutin [61] and curcumin [44] reduced lipid peroxidation by forming chelate with iron and

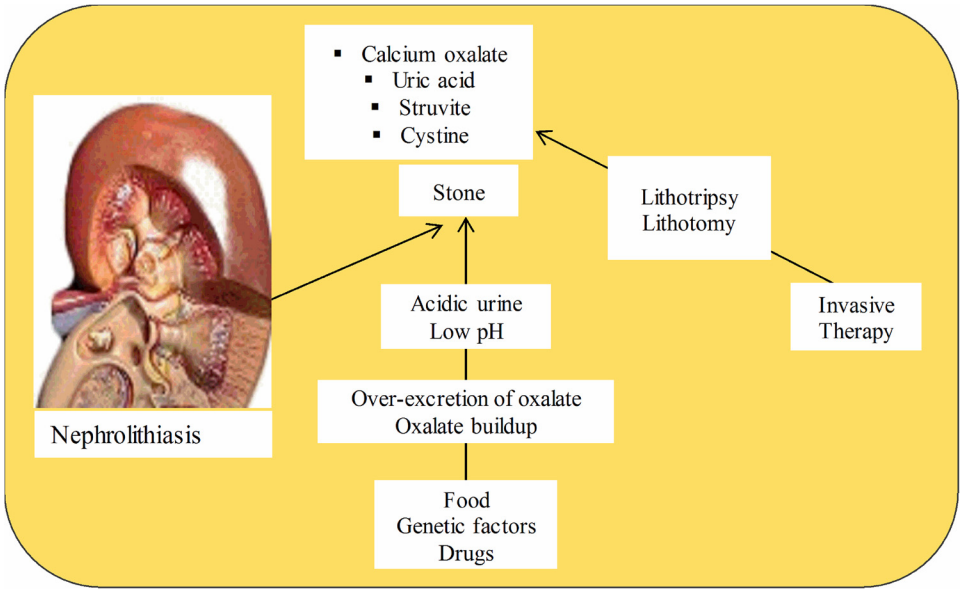

Fig. 1. Showing the mechanism of kidney stone formation. The type of stones (calcium oxalate, uric acid, struvite and cystine), causing factors include food rich in oxalate, genetic factors and drugs and the different types of treatment.

copper ions.

5. Anti-inflammatory

Arachidonic acid, nitric oxide (NO), prostaglandin-E2, COX-2 and cytokines (IL-1β, IL-6 and TNF-α) are closely associated with pain and inflammation [62,63]. The release of reactive species is responsible for the oxidative stress-induced inflammation [64]. Antispasmodic, analgesic and anti-inflammatory activities play an important role in symptomatic relief [35]. Apigenin [65], catechin [50], curcumin [66], cyanidin [67], ellagic acid [53], ferulic acid [68], gallic acid [69,70], luteolin [71], malvidin [72], *p*-coumaric acid [55], sinapic acid [73] and syringic acid [74] have shown anti-inflammatory activity by reducing PG-E_2, cytokines IL-1β, IL-6 and TNF-α production. Chlorogenic acid [75], curcumin [66], daidzein, genistein [76], delphinidin [77], diosmin [54], gallic acid [69], syringic acid [74] and vanillic acid [78] prevent inflammation by the inhibition of nitric oxide production and NF-κB activation. Kaempferol [79], quercetin [46] and resveratrol [80] inhibit COX-1 and COX-2 by suppressing NF-κB activation and similarly rutin has shown anti-inflammatory activity by the inhibition of PLA_2 activity [81].

6. ACE inhibition

Renin-angiotensin aldosterone system (RAAS) activates the NADPH oxidase in renal cells, which produces ROS. Angiotensin converting enzyme inhibition (ACE-I) by decreasing ROS production, significantly reduces calcium oxalate crystal deposition and renal inflammation [82]. Free hydroxyl groups of phenolic compounds form chelate with the Zinc atom present within the active center of ACE, thus inhibiting ACE *in vitro* [70]. *In vitro* ACE inhibition by apigenin, kaempferol, luteolin [83], caffeic acid, chlorogenic acid, quercetin [84], catechin [85], cyanidin, delphinidin [86], daidzein [87], genistein [88], malvidin [51] and sinapic acid [89] also play important role against oxidative tissue damage and inflammation.

7. Diuretic

Polyphenols possessing diuretic property has been often reported. Extracts of *Opuntia ficus indica* fruit, *Camellia sinensis* (green tea), and *Hibiscus sabdariffa* have been traditionally used as diuretic. The diuretic action increases the quantity of fluid passing through the kidneys as a result of flushing out the salt deposits. Therefore, the increment in urine volume decreases the saturation of the salts and thus prevents the precipitation of the crystals at physiological pH [35]. Chlorogenic acid, cyanidin, delphinidin, quercitin [90], gallic acid [91], genistein [92], luteolin [93], protocatechuic acid [58] and rutin [94] are reported to possess diuretic activity.

Fig. 2. shows the renal stone prevention mechanisms of polyphenols.

8. Future directions and conclusions

Here, the naturally-occurring polyphenols which possess potential to prevent the urinary calculi are summarized. The antiurolithiatic activity of plant polyphenols are supposed to be due to their diuretic, antioxidant, anti-inflammatory and ACE inhibition. Other possible mechanisms related to antilithiatic effect of flavonoids are still elusive. The structures of polyphenols like resveratrol, quercetin, and catechin resemble that of estrogen hormone. Like estrogen is elaborated in higher amount in stress conditions, the polyphenols are produced in higher amounts in stress situations (such as cold, drought, pathogen attack). So, it is likely that these phytochemicals act as antagonist of the estrogen and resolve inflammation.

Polyphenols encompass a large biochemical variety, but only a few of them have been characterized so far. In this regard, polyphenols other than caffeic acid, catechin, curcumin, rutin, diosmin, quercetin and resveratrol need to be purified and administered to animal models of urinary stone disease. Emerging technologies such as green nanotechnology can be recruited to develop efficient drugs for modern urinary stone therapy [95]. The models studied by present research paradigms are almost always calcium oxalate, while calcium hydrogen phosphate dihydrate (brushite) and mono sodium urate mono hydrate (urate) urinary crystals are also component of urinary stones. So, the potential roles of plant polyphenols in the prevention of brushite and urate urinary stone should be studied in further investigations.

While reporting the positive effects, and the potential of plant polyphenols, the negative aspects ought not be dismissed. In this regard, the polyphenols endowed with antiurolithiatic activity may cause certain side effects which must be taken seriously. For example, the polyphenols rich extracts from *Carthamus tinctorius* L., (safflower) can induce bleeding in animals [96]. So, the drugs containing those

Table 1
List of plants containing polyphenols with antiurolithiatic activity.

Family	Polyphenol containing plants with their parts	Mechanistic insight behind antiurolithiatic effects		Use of same plant parts in different countries against urolithiasis
		Reported antiurolithiatic activity against calcium oxalate	Supporting antiurolithiatic effects	
Amaryllidaceae	*Allium cepa* L. (onion, bulb)	Antiurolithiatic against calcium oxalate [31]	Anti-inflammatory, demulcent, diuretic [99]	Bulb infusion — India [31]
Annonaceae	*Annona reticulata* L. (custard apple, fruit)	Antiurolithiatic against calcium oxalate [100]	———	Fruit—India [100]
Apiaceae	*Apium graveolens* L. (celery, leaves)	Leaves antiurolithiatic against calcium oxalate [31]	Anti-inflammatory, antioxidant, demulcent, diuretic [101]	Leaves decoction — Bosnia, Herzegovina, Iran, Morocco [102]
	Carum carvi L. (caraway, fruit)	———	Analgesic, anti-inflammatory, antioxidant, diuretic [101]	Fruit decoction — Iran, Turkey [101]
	Cuminum cyminum L. (cumin, fruit)	Fruits antiurolithiatic *against* calcium oxalate [101]	———	Fruits — Iran [101]
	Daucus carota subsp. *sativus* (Hoffm.) Arcang. (carrot, roots)	Seeds Antiurolithiatic against calcium oxalate [101]	———	Roots — Lebanon, India, Turkey [101]
	Petroselinum crispum (Mill.) Fuss. (parsley, leaves)	Leaves antiurolithiatic against calcium oxalate [101]	Antioxidant, diuretic [101]	Leaves infusion / decoction — Italy, Tunisia Bosnia, Herzegovina, Iran, Turkey, Spain [101]
Arecaceae	*Phoenix dactylifera* L. (dates, fruit)	Fruits antiurolithiatic against calcium oxalate [103]	———	Fruits—India [103]
Asteraceae	*Cichorium intybus* L. (chicory, leaves)	Roots antiurolithiatic against calcium oxalate [31]	———	Leaves raw eaten — Algeria, America, Pakistan, Palestine, Iran ; Leaves / roots decoction / maceration — Lebanon [104]
	Cynara scolymus L. (globe artichoke, head)	———	Diuretic [104]	Leaves infusion — Italy and Tunisia [104]
Brassicaceae or Cruciferae	*Brassica oleracea* L. (cauliflower, fruit)	Aerial parts antiurolithiatic against calcium oxalate [105]	Analgesic, anti-inflammatory, antioxidant [105]	Fruit ash — Iran [105]
Capparaceae	*Capparis spinosa* L. (capers, leaves)	———	Antioxidant, anti-inflammatory, diuretic [99]	Leaves — Algeria, Saudi Arabia [99]
Cucurbitaceae	*Cucumis melo* L. (melon, fruit)	Seeds, fruits, fruit skin antiurolithiatic against calcium oxalate [99]	Analgesic, anti-inflammatory, antioxidant, diuretic [99]	Seeds / fruit juice — India, Iran, Pakistan [99]
Ericaceae	*Vaccinium macrocarpon* Aiton. (American cranberry, fruit)	Fruit antiurolithiatic against calcium oxalate [106]	———	———
	Vaccinium oxycoccos L. (cranberry, fruit)	Fruit antiurolithiatic against calcium oxalate [107]		
	Vaccinium vitis-idaea L. (lingonberry, fruit)	———	Antioxidant [99]	Fruits — Serbia [99]
Fabaceae	*Glycine max* (L.) Merr. (soybean)		———	Seeds decoction — India [108]
	Macrotyloma uniflorum (Lam.) Verdc. (horse gram)	Seeds antiurolithiatic against calcium oxalate [108]	diuretic [108]	Seeds decoction / infusion — Jordan, India, Iran, Nepal, Pakistan [108]
	Phaseolus vulgaris L. (kidney bean)	Seeds antiurolithiatic against calcium oxalate [108]	Analgesic, anti-inflammatory [109] Diuretic [108]	Seeds decoction / infusion — India [108]
Lamiaceae	*Mentha spicata* L. (spearmint)	———	Antioxidant, anti-inflammatory [110]	Leaves decoction / infusion — Iran, India [110]
	Ocimum basilicum L. (sweet basil)		Antioxidant [110]	Leaves and seeds — India; Palestine [110]
	Origanum majorana L. (majoram)		Anti-inflammatory, antioxidant, diuretic [110]	Plant decoction — Palestine [110]
	Origanum vulgare L. (oregano wild majoram)		Antioxidant [110]	Aerial parts decoction — Iran [110]
	Rosmarinus officinalis L. (rosemary)		Anti-inflammatory, diuretic [110]	Leaves / stem decoction — Jordan [110]
Lauraceae	*Cinnamomum verum* J.Presl. (Ceylan cinnamon)		Anti-inflammatory, antioxidant [111]	Leaves decoction — India ; stem bark — Iran, Jordan [111]
Moraceae	*Ficus carica* L. (Figs, fruit);	Fruits antiurolithiatic against calcium oxalate [112]	Anti-inflammatory, antioxidant, demulcent, diuretic [113]	Fruits raw eaten — Jordan, Pakistan, Palestine [113]
	Morus alba L. (white mulberry)	———	———	Fruit juice — Palestine [113]
Myrtaceae	*Syzygium aromaticum* (L.) Merr. & L.M.Perry. (clove, flower bud)		Analgesic, anti-inflammatory, antioxidant [113]	Inflorescence powder —India [113]

(*continued on next page*)

Table 1 (*continued*)

Family	Polyphenol containing plants with their parts	Mechanistic insight behind antiurolithiatic effects		Use of same plant parts in different countries against urolithiasis
		Reported antiurolithiatic activity against calcium oxalate	Supporting antiurolithiatic effects	
Oleaceae	*Olea europaea* L. (olive, fruit)	Fruit oil antiurolithiatic against calcium oxalate [113]	ACE inhibitor, analgesic, anti-inflammatory, antioxidant, demulcent [113]	Fruit decoction — Italy, Jordan, Palestine [113]
Poaceae	*Hordeum vulgare* L. (barley)	Whole plant antiurolithiatic against calcium oxalate [105]	Anti-inflammatory, antioxidant, diuretic, demulcent [105]	Seeds decoction / infusion — Jordan, Pakistan, Turkey [105]
	Triticum aestivum L. (wheat)	Wheat bran antiurolithiatic against calcium oxalate [105]	———	Wheat bran — India [105]
	Zea mays L. (maize)	*Zea mays* hair antiurolithiatic against calcium oxalate [105]	Anti-inflammatory, antioxidant, demulcent, diuretic [105]	Leaves / fruit — Bangladesh; seeds decoction — Iran, Israel, Palestine; flowers decoction — India, Jordan, Pakistan, Yemen, Uzbekistan; corn silk decoction — Spain, Turkey, Italy, Tunisia; corn silk infusion — Algeria [105]
Punicaceae	*Punica granatum* L. (pomegranate fruit)	Fruits antiurolithiatic against calcium oxalate [105]	Anti-inflammatory, antioxidant [113]	Fruit or fruit rind decoction — India [105]
Rosaceae	*Crataegus monogyna* Jacq. (hawthorn)	———	———	Aerial parts infusion — Bosnia, Herzegovina, Turkey [114]
	Cydonia oblonga Mill. (quince)			Leaves decoction — Turkey [114]
	Malus pumila Mill. (apple, fruit)	Fruits antiurolithiatic against calcium oxalate [115]		———
	Prunus avium (L.) L. (sweet cherry, fruit)	———	Antioxidant, diuretic [114]	Fruit raw eaten — Iran ; stem decoction — Turkey; fruit juice — Palestine [114]
	Prunus virginiana L. (Black chokeberry, fruit)		———	Fruits — Iran [114]
	Pyrus communis auct. iber. (pear)		Diuretic [114]	Ripe fruits eaten — India [114]
Rubiaceae	*Coffea arabica* L. (coffee beans)		Analgesic, antioxidant, diuretic [113]	Seed husk beverage — Yemen [113]
Rutaceae	*Citrus limon* (L.) Osbeck. (lemon, fruit)	Fruits antiurolithiatic against calcium oxalate [113]	Analgesic, antioxidant, demulcent, diuretic [113]	Fruit juice — India, Pakistan [113]
	Citrus paradisi Macfad. (grapefruit)	Fruits antiurolithiatic against calcium oxalate [115]	———	———
	Citrus sinensis (L.) Osbeck (orange)	———	Anti-inflammatory, antioxidant [113]	Fruit juice — India, Pakistan [113]
Solanaceae	*Lycopersicon esculentum* Mill. (tomato fruit)		———	Fruits — Iran [116]
Theaceae	*Camellia sinensis* (L.) Kuntze. (green tea, leaves)	Leaves antiurolithiatic against calcium oxalate [117]		———
Vitaceae	*Vitis vinifera* L. (grapes)	———	Anti-inflammatory, antioxidant [116]	Fruit juice — Iran [116]
Zingiberaceae	*Curcuma longa* L. (turmeric)		———	Roots — Iran [116]
	Elettaria cardamomum (L.) Maton. (cardamom)		Antioxidant, diuretic [116]	Fruit — India [116]

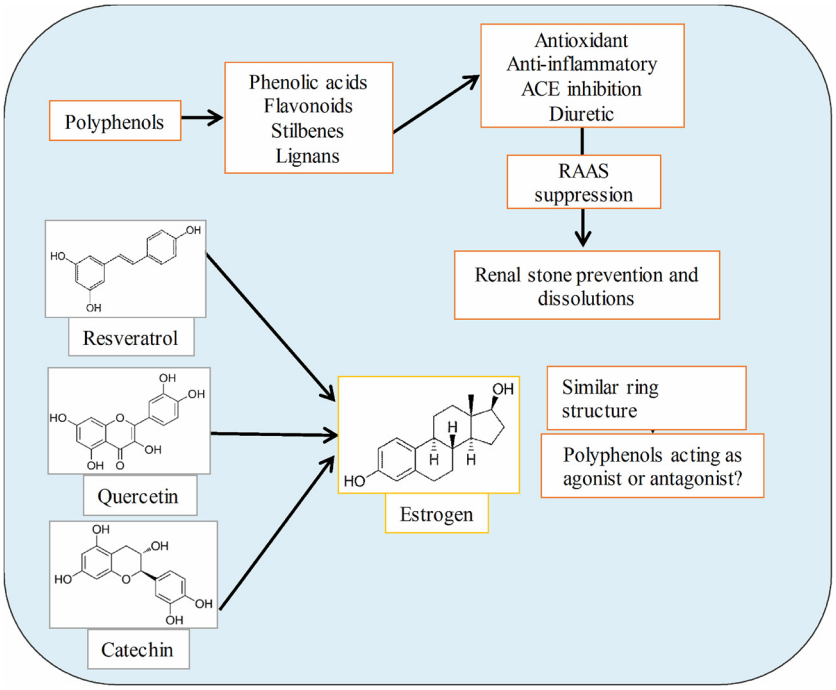

Fig. 2. Showing the underlying mechanisms of different polyphenols for the prevention of renal stone formation: The antioxidant, antiinflammatory, (ACE) angiotensin-converting-enzyme regulation and diuretic.

polyphenols must be recommended to only specific patient groups after a series of clinical trials. Chenopodiaceae family members contain high oxalate content, and excess intake of the dietary oxalic acid can cause renal stones. Some polyphenols are controversial in their biological effect. Lignans, the diphenolic compounds, abundant in flaxseed, sesame, and cruciferous vegetables are metabolized into phytoestrogens. The flavonoid isoflavone genistein in soy is a phytoestrogen as well. Phytoestrogens have structural and functional similarity to 17β-estadiol, and disputable reputation pertaining to human health.

Currently, more than 95% of studies regarding the antilithiatic effects of plant polyphenol have been conducted in experimental animals. On account of the metabolic and enzymatic differences between experimental animals and human beings, *in vivo* study-elicited results are inadequate, and clinical trials are urgently needed to ascertain which polyphenols can indeed play protective roles against the urinary calculi and have promise to be applied in stone prevention [97]. Clinical studies on the concentration, bioavailability, efficacy, safety, and exact mechanism of action are required. The absorption, distribution, metabolism, excretion, and biological activity of the polyphenols in the human body must be further examined through multi-pronged research. The effects of plant polyphenols on the recurrence of urinary stone disease in patients after shock wave lithotripsy, which is known to generate ROS and cause renal damage, ought to be determined [98].

In conclusion, it is important to understand that renal stone are the resultant of acidic urine, and the crystallization of the minerals. As long as acidosis is not resolved, the stone formation will continue. Medications might impart temporary relief, but the cause of the disease will remain active. Cause of renal acidification can be genetic, or life stage-related (*e.g.* pregnancy, aging, infections) but in modern times, its mostly due to lifestyle mistakes. Environmental exposures and dietary factors impact urine pH, and promote stone formation. Disciplined lifestyle can prevent inflammation and calculi formation. If expecting polyphenols to mitigate renal stones is too naive, at least they can be used to maintain physiological pH, as they act as buffers.

References

[1] A. Tiwari, V. Soni, V. Londhe, A. Bhandarkar, D. Bandawane, S. Nipate, An overview on potent indigenous herbs for urinary tract infirmity: urolithiasis, Asian J. Pharm. Clin. Res. 5 (1) (2012) 7–12.
[2] A. Khan, S. Bashir, S.R. Khan, A.H. Gilani, Antiurolithic activity of *Origanum vulgare* is mediated through multiple pathways, BMC Complement. Altern. Med. 11 (1) (2011) 96.
[3] S. Ahmed, M.M. Hasan, Z. Alam Mahmood, Antiurolithiatic plants: formulations used in different countries and cultures, Pak. J. Pharm. Sci. 29 (6) (2016) 2129–2139.
[4] T. Efferth, E. Koch, Complex interactions between phytochemicals. The multitarget therapeutic concept of phytotherapy, Curr. Drug Targets 12 (1) (2011) 122–132.
[5] M. Jawad, H. Khan, S. Pervez, S.S. Bawazeer, T. Abu-Izneid, M. Saeed, M.A. Kamal, Pharmacological validation of the anxiolytic, muscle relaxant and sedative like activities of *Capsicum annuum* in animal model, Bangl. J. Pharmacol. 12 (4) (2017) 437–447.
[6] H. Khan, S. Amin, ACE inhibition of plant alkaloids. Targeted approach for selective inhibition, Mini-Rev. Org. Chem. 14 (2017) 85–89.
[7] H. Khan, S. Amin, S. Patel, Targeting BDNF modulation by plant glycosides as a novel therapeutic strategy in the treatment of depression, Life Sci. 196 (2018) 18–27.
[8] H. Khan, Z. Khan, S. Amin, Y.N. Mabkhot, M.S. Mubarak, T.B. Hadda, F. Maione, Plant bioactive molecules bearing glycosides as lead compounds for the treatment of fungal infection: a review, Biomed. Pharmacother. 93 (2017) 498–509.
[9] H. Khan, S.M. Nabavi, A. Sureda, N. Mehterov, D. Gulei, I. Berindan-Neagoe, H. Taniguchi, A.G. Atanasov, Therapeutic potential of songorine, a diterpenoid alkaloid of the genus Aconitum, Eur. J. Med. Chem. 153 (2018) 29–33.
[10] H. Marya, S.M. Khan, S. Nabvi, Habtemariam, Anti-diabetic potential of peptides: future prospects as therapeutic agents, Life Sci. 193 (2018) 153–158.
[11] C. Manach, A. Scalbert, C. Morand, C. Rémésy, L. Jiménez, Polyphenols: food sources and bioavailability, Am. J. Clin. Nutr. 79 (5) (2004) 727–747.
[12] S.F. Nabavi, H. Khan, G. D'Onofrio, D. Šamec, S. Shirooie, A.R. Dehpour, S. Argüelles, S. Habtemariam, E. Sobarzo-Sanchez, Apigenin as neuroprotective agent: of mice and men, Pharmacol. Res. 128 (2018) 359–365.
[13] N. Karim, I. Khan, H. Khan, B. Ayub, H. Abdel-Halim, N. Gavande, Anxiolytic potential of natural flavonoids, SM J. Steroids Horm. 1 (2018) 1001–1010.
[14] A. Rauf, R. Khan, M. Raza, H. Khan, S. Pervez, V. De Feo, F. Maione, N. Mascolo, Suppression of inflammatory response by chrysin, a flavone isolated from Potentilla evestita Th. Wolf. In silico predictive study on its mechanistic effect, Fitoterapia 103 (0) (2015) 129–135.
[15] E.P. Gutiérrez-Grijalva, M.A. Picos-Salas, N. Leyva-López, M.S. Criollo-Mendoza, G. Vazquez-Olivo, J.B. Heredia, Flavonoids and phenolic acids from Oregano: occurrence, biological activity and health benefits, Plants 7 (1) (2018) 2.
[16] S. Poschner, A. Maier-Salamon, M. Zehl, J. Wackerlig, D. Dobusch, B. Pachmann, K.L. Sterlini, W. Jäger, The impacts of genistein and daidzein on estrogen conjugations in human breast cancer cells: a targeted metabolomics approach, Front.

Pharmacol. 8 (699) (2017).
[17] O. Taofiq, A.M. González-Paramás, M.F. Barreiro, I.C. Ferreira, Hydroxycinnamic acids and their derivatives: cosmeceutical significance, challenges and future perspectives, a review, Molecules 22 (2) (2017) 281–287.
[18] K. Judprasong, S. Charoenkiatkul, P. Sungpuag, K. Vasanachitt, Y. Nakjamanong, Total and soluble oxalate contents in Thai vegetables, cereal grains and legume seeds and their changes after cooking, J. Food Comp. Anal. 19 (4) (2006) 340–347.
[19] S. Noonan, Oxalate content of foods and its effect on humans, Asia Pac. J. Clin. Nutr. 8 (1) (1999) 64–74.
[20] A. Aggarwal, S. Tandon, S. Singla, C. Tandon, Diminution of oxalate induced renal tubular epithelial cell injury and inhibition of calcium oxalate crystallization in vitro by aqueous extract of Tribulus terrestris, Int. Braz. J. Urol. 36 (4) (2010) 480–489.
[21] R. Selvam, Calcium oxalate stone disease: role of lipid peroxidation and antioxidants, Urolo. Res. 30 (1) (2002) 35–47.
[22] F. Grases, R.M. Prieto, I. Gomila, P. Sanchis, A. Costa-Bauzá, Phytotherapy and renal stones: the role of antioxidants. A pilot study in Wistar rats, Urol. Res. 37 (1) (2009) 35–40.
[23] J.A. Wesson, M.D. Ward, Pathological biomineralization of kidney stones, Elements 3 (6) (2007) 415–421.
[24] F. Yasir, M.I. Attia-tull-Wahab, Choudhary, Protective effect of dietary polyphenol caffeic acid on ethylene glycol-induced kidney stones in rats, Urolithiasis 45 (2017) 1–10.
[25] W. Zhai, J. Zheng, X. Yao, B. Peng, M. Liu, J. Huang, G. Wang, Y. Xu, Catechin prevents the calcium oxalate monohydrate induced renal calcium crystallization in NRK-52E cells and the ethylene glycol induced renal stone formation in rat, BMC Complement. Altern. Med. 13 (1) (2013) 228.
[26] J. Ghodasara, A. Pawar, C. Deshmukh, B. Kuchekar, Inhibitory effect of rutin and curcumin on experimentally-induced calcium oxalate urolithiasis in rats, Pharmacogn. Res. 2 (6) (2010) 388–392.
[27] A. Noorafshan, S. Karbalay-Doust, F. Karimi, Diosmin reduces calcium oxalate deposition and tissue degeneration in nephrolithiasis in rats: a stereological study, Korean J. Urol. 54 (4) (2013) 252–257.
[28] W. Zhu, Y.-f. Xu, Y. Feng, B. Peng, J.-p. Che, M. Liu, J.-h. Zheng, Prophylactic effects of quercetin and hyperoside in a calcium oxalate stone forming rat model, Urolithiasis 42 (6) (2014) 519–526.
[29] B.M. Dinnimath, S.S. Jalalpure, U.K. Patil, Antiurolithiatic activity of natural constituents isolated from *Aerva lanata*, J. Ayurveda Integr. Med. (2017) 226–232.
[30] S.H. Hong, H.-J. Lee, E.J. Sohn, H.-S. Ko, B.S. Shim, K.S. Ahn, S.-H. Kim, Anti-nephrolithic potential of resveratrol via inhibition of ROS, MCP-1, hyaluronan and osteopontin *in vitro* and *in vivo*, Pharmacol. Rep. 65 (2013) 970–979.
[31] S. Ahmed, M.M. Hasan, Z.A. Mahmood, Antiurolithiatic plants: multidimensional pharmacology, J. Pharmacogn. Phytochem. 5 (2) (2016) 4–24.
[32] O. Cikman, O. Soylemez, O.F. Ozkan, H.A. Kiraz, I. Sayar, S. Ademoglu, S. Taysi, M. Karaayvaz, Antioxidant activity of syringic acid prevents oxidative stress in l-arginine–induced acute pancreatitis: an experimental study on rats, Int. Surg. 100 (5) (2015) 891–896.
[33] N. Razzaghi-Asl, J. Garrido, H. Khazraei, F. Borges, O. Firuzi, Antioxidant properties of hydroxycinnamic acids: a review of structure-activity relationships, Curr. Med. Chem. 20 (36) (2013) 4436–4450.
[34] J. Zuo, A. Khan, P.A. Glenton, S.R. Khan, Effect of NADPH oxidase inhibition on the expression of kidney injury molecule and calcium oxalate crystal deposition in hydroxy-L-proline-induced hyperoxaluria in the male Sprague–Dawley rats, Nephrol. Dial. Transplant. 26 (6) (2011) 1785–1796.
[35] S. Ahmed, M. Hasan, Z. Mahmood, Antiurolithiatic plants: multidimensional pharmacology, J. Pharmacogn. Phytochem. 5 (2) (2016) 04–24.
[36] J.A. Jonassen, L.C. Cao, T. Honeyman, C.R. Scheid, Intracellular events in the initiation of calcium oxalate stones, Nephron Exp. Nephrol. 98 (2) (2004) e61–e64.
[37] F. Abbas, R. Khan, J.J. Talati, M. Afzal, I. Rizvi, The prevalence of silent kidney stones-an ultrasonographic screening study, J. Pak. Med. Assoc. 53 (1) (2003) 24–25.
[38] M.G. Miguel, Anthocyanins: antioxidant and/or anti-inflammatory activities, J. Appl. Pharm. Sci. 1 (6) (2011) 7–15.
[39] F. Grases, R.M. Prieto, R.A. Fernandez-Cabot, A. Costa-Bauz, F. Tur, J.J. Torres, Effects of polyphenols from grape seeds on renal lithiasis, Oxid. Med. Cell. Longev. 2015 (2015) 6.
[40] A. Golshan, P. Hayatdavoudi, M.A.L.R. Hadjzadeh, A. Khajavi Rad, N. Mohamadian Roshan, A. Abbasnezhad, S.M. Mousavi, R. Pakdel, B. Zarei, A. Aghaee, Kidney stone formation and antioxidant effects of *Cynodon dactylon* decoction in male Wistar rats, Avicenna J. Phytomed. 7 (2) (2017) 180–190.
[41] P. Holoch, C. Tracy, Antioxidants and self-reported history of kidney stones: the national health and nutrition examination survey, J. Endourol. 25 (12) (2011) 1903–1908.
[42] M. Suzuki, M. Mori, F. Nanjo, Y. Hara, Radical scavenging mechanisms of catechins on 2,2-diphenyl-1-picrylhydrazyl radical, caffeinated beverages, Am. Chem. Soc. (2000) 146–153.
[43] S.B. Lotito, C.G. Fraga, (+)-Catechin as antioxidant: mechanisms preventing human plasma oxidation and activity in red wines, BioFactors (Oxf. Engl.) 10 (2–3) (1999) 125–130.
[44] T. Ak, İ. Gülçin, Antioxidant and radical scavenging properties of curcumin, Chem-Biol. Interact. 174 (1) (2008) 27–37.
[45] P. Foti, D. Erba, P. Riso, A. Spadafranca, F. Criscuoli, G. Testolin, Comparison between daidzein and genistein antioxidant activity in primary and cancer lymphocytes, Arch. Biochem. Biophys. 433 (2) (2005) 421–427.
[46] L. Wang, Y.-C. Tu, T.-W. Lian, J.-T. Hung, J.-H. Yen, M.-J. Wu, Distinctive antioxidant and antiinflammatory effects of flavonols, J. Agric. Food Chem. 54 (26) (2006) 9798–9804.
[47] A. Popov, A. Osipov, E. Korepanova, O. Krivoshapko, A. Artyukov, A. Klimovich, A study of the antioxidant and membranotropic activities of luteolin using different model systems, Biophysics 61 (6) (2016) 843–850.
[48] M. Majewska, M. Skrzycki, M. Podsiad, H. Czeczot, Evaluation of antioxidant potential of flavonoids: an in vitro study, Acta Pol. Pharm. 68 (4) (2011) 611–615.
[49] A.B. Lende, A.D. Kshirsagar, A.D. Deshpande, M.M. Muley, R.R. Patil, P.A. Bafna, S.R. Naik, Anti-inflammatory and analgesic activity of protocatechuic acid in rats and mice, Inflammopharmacology 19 (5) (2011) 255–263.
[50] T.A. Abd El-Aziz, R.H. Mohamed, H.F. Pasha, H.R. Abdel-Aziz, Catechin protects against oxidative stress and inflammatory-mediated cardiotoxicity in adriamycin-treated rats, Clin. Exp. Med. 12 (4) (2012) 233–240.
[51] W. Huang, Y. Zhu, C. Li, Z. Sui, W. Min, Effect of blueberry anthocyanins malvidin and glycosides on the antioxidant properties in endothelial cells, Oxid. Med. Cell. Longev. 2016 (2016) 10.
[52] İ. Gülçin, Antioxidant activity of caffeic acid (3,4-dihydroxycinnamic acid), Toxicology 217 (2) (2006) 213–220.
[53] P. Chao, C. Hsu, M. Yin, Anti-inflammatory and anti-coagulatory activities of caffeic acid and ellagic acid in cardiac tissue of diabetic mice, Nutr. Metab. (Lond.) 6 (2009) 33.
[54] M. Crespo, J. Galvez, T. Cruz, M. Ocete, A. Zarzuelo, Anti-inflammatory activity of diosmin and hesperidin in rat colitis induced by TNBS, Planta Med. 65 (07) (1999) 651–653.
[55] S.J. Pragasam, V. Venkatesan, M. Rasool, Immunomodulatory and anti-inflammatory effect of p-coumaric acid, a common dietary polyphenol on experimental inflammation in rats, Inflammation 36 (1) (2013) 169–176.
[56] B. Badhani, N. Sharma, R. Kakkar, Gallic acid: a versatile antioxidant with promising therapeutic and industrial applications, RSC Adv. 5 (35) (2015) 27540–27557.
[57] X. Li, X. Wang, D. Chen, S. Chen, Antioxidant activity and mechanism of protocatechuic acid in vitro, Funct. Foods Health Dis. 1 (7) (2011) 232–244.
[58] S. Kakkar, S. Bais, A review on protocatechuic acid and its pharmacological potential, ISRN Pharmacol. 2014 (2014) 9.
[59] A. Rašković, S. Gigov, I. Čapo, M. Paut, B.K. Milijašević, S. Kojić-Damjanov, N. Martić, Antioxidative and protective actions of apigenin in a paracetamol-induced hepatotoxicity rat model, Eur. J. Drug Metab. Pharmacokinet. 42 (5) (2017) 849–856.
[60] S. Kumar, P. Prahalathan, B. Raja, Antihypertensive and antioxidant potential of vanillic acid, a phenolic compound in L-NAME-induced hypertensive rats: a dose-dependence study, Redox Rep. 16 (5) (2011) 208–215.
[61] R.A. Khan, M.R. Khan, A. Khan, Comparative antioxidant scavenging and lipid peroxidation activity of rutin and gallic acid, Bangl. J. Pharmacol. 10 (3) (2015) 637–638.
[62] V. Mollace, C. Muscoli, E. Masini, S. Cuzzocrea, D. Salvemini, Modulation of prostaglandin biosynthesis by nitric oxide and nitric oxide donors, Pharmacol. Rev. 57 (2) (2005) 217–252.
[63] G.S. Supinski, L.A. Callahan, Free radical-mediated skeletal muscle dysfunction in inflammatory conditions, J. Appl. Physiol. 102 (5) (2007) 2056–2063.
[64] P. Arulselvan, M.T. Fard, W.S. Tan, S. Gothai, S. Fakurazi, M.E. Norhaizan, S.S. Kumar, Role of antioxidants and natural products in inflammation, Oxid. Med. Cell. Longev. 2016 (2016) 5276130.
[65] J.-H. Lee, H.Y. Zhou, S.Y. Cho, Y.S. Kim, Y.S. Lee, C.S. Jeong, Anti-inflammatory mechanisms of apigenin: inhibition of cyclooxygenase-2 expression, adhesion of monocytes to human umbilical vein endothelial cells, and expression of cellular adhesion molecules, Arch. Pharm. Res. 30 (10) (2007) 1318–1327.
[66] J.S. Jurenka, Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research, Altern. Med. Rev. 14 (2) (2009) 141–153.
[67] Y.H. He, C. Xiao, Y.S. Wang, L.H. Zhao, H.Y. Zhao, Y. Tong, J. Zhou, H.W. Jia, C. Lu, X.M. Li, A.P. Lu, Antioxidant and anti-inflammatory effects of cyanidin from cherries on rat adjuvant-induced arthritis, Zhongguo Zhong yao za zhi (Chin. J. Chin. Mater. Med.) 30 (20) (2005) 1602–1605.
[68] H. Zhu, Q.-H. Liang, X.-G. Xiong, J. Chen, D. Wu, Y. Wang, B. Yang, Y. Zhang, Y. Zhang, X. Huang, Anti-inflammatory effects of the bioactive compound ferulic acid contained in *Oldenlandia diffusa* on collagen-induced arthritis in rats, Evid. Based Compl. Altern. Med. 2014 (2014) 10.
[69] L.A. BenSaad, K.H. Kim, C.C. Quah, W.R. Kim, M. Shahimi, Anti-inflammatory potential of ellagic acid, gallic acid and Punicalagin A&B isolated from Punica granatum, BMC Complement. Altern. Med. 17 (1) (2017) 47.
[70] M. Hidalgo, S. Martin-Santamaria, I. Recio, C. Sanchez-Moreno, B. de Pascual-Teresa, G. Rimbach, S. de Pascual-Teresa, Potential anti-inflammatory, anti-adhesive, anti/estrogenic, and angiotensin-converting enzyme inhibitory activities of anthocyanins and their gut metabolites, Genes Nutr. 7 (2) (2012) 295–306.
[71] I.H. Jeon, H.S. Kim, H.J. Kang, H.-S. Lee, S.I. Jeong, S.J. Kim, S.I. Jang, Anti-inflammatory and antipruritic effects of luteolin from Perilla (*P. frutescens* L.) leaves, Molecules 19 (6) (2014) 6941–6951.
[72] W.-Y. Huang, J. Wang, Y.-M. Liu, Q.-S. Zheng, C.-Y. Li, Inhibitory effect of Malvidin on TNF-α-induced inflammatory response in endothelial cells, Eur. J. Pharmacol. 723 (2014) 67–72.
[73] K.-J. Yun, D.-J. Koh, S.-H. Kim, S.J. Park, J.H. Ryu, D.-G. Kim, J.-Y. Lee, K.-T. Lee, Anti-inflammatory effects of sinapic acid through the suppression of inducible nitric oxide synthase, cyclooxygase-2, and proinflammatory cytokines expressions via nuclear factor-κB inactivation, J. Agric. Food Chem. 56 (21) (2008) 10265–10272.
[74] J.R. Ham, H.-I. Lee, R.-Y. Choi, M.-O. Sim, K.-I. Seo, M.-K. Lee, Anti-steatotic and

anti-inflammatory roles of syringic acid in high-fat diet-induced obese mice, Food Funct. 7 (2) (2016) 689–697.
[75] S.J. Hwang, Y.-W. Kim, Y. Park, H.-J. Lee, K.-W. Kim, Anti-inflammatory effects of chlorogenic acid in lipopolysaccharide-stimulated RAW 264.7 cells, Inflamm. Res. 63 (2014) 81–90.
[76] M. Hämäläinen, R. Nieminen, P. Vuorela, M. Heinonen, E. Moilanen, Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-κB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-κB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages, Mediators Inflamm. 2007 (2007) 10.
[77] R. Watson, F. Schönlau, Nutraceutical and antioxidant effects of a delphinidin-rich maqui berry extract Delphinol®: a review, Minerva Cardioangiol. 63 (2 Suppl) (2015) 1–12.
[78] Cs. Calixto-Campos, T.T. Carvalho, M.S. Hohmann, F.A. Pinho-Ribeiro, V. Fattori, M.F. Manchope, A.C. Zarpelon, M.M. Baracat, S.R. Georgetti, R. Casagrande, Vanillic acid inhibits inflammatory pain by inhibiting neutrophil recruitment, oxidative stress, cytokine production, and NFκB activation in mice, J. Nat. Prod. 78 (8) (2015) 1799–1808.
[79] M.J. Park, E.K. Lee, H.S. Heo, M.S. Kim, B. Sung, M.K. Kim, J. Lee, N.D. Kim, S. Anton, J.S. Choi, B.P. Yu, H.Y. Chung, The anti-inflammatory effect of kaempferol in aged kidney tissues: the involvement of nuclear factor-kappaB via nuclear factor-inducing kinase/IkappaB kinase and mitogen-activated protein kinase pathways, J. Med. Food 12 (2) (2009) 351–358.
[80] S. Das, D.K. Das, Anti-inflammatory responses of resveratrol, Inflamm. Allergy-Drug Targets (Formerly Curr. Drug Targets-Inflamm. Allergy) 6 (3) (2007) 168–173.
[81] L. Selloum, H. Bouriche, C. Tigrine, C. Boudoukha, Anti-inflammatory effect of rutin on rat paw oedema, and on neutrophils chemotaxis and degranulation, Exp. Toxicol. Pathol. 54 (4) (2003) 313–318.
[82] S. Joshi, A.B. Peck, S.R. Khan, NADPH oxidase as a therapeutic target for oxalate induced injury in kidneys, Oxid. Med. Cell. Longev. 2013 (2013) 18.
[83] M.R. Loizzo, A. Said, R. Tundis, K. Rashed, G.A. Statti, A. Hufner, F. Menichini, Inhibition of angiotensin converting enzyme (ACE) by flavonoids isolated from Ailanthus excelsa (Roxb) (Simaroubaceae), Phytother. Res. 21 (1) (2007) 32–36.
[84] K.S. Bhullar, G. Lassalle-Claux, M. Touaibia, H.V. Rupasinghe, Antihypertensive effect of caffeic acid and its analogs through dual renin–angiotensin–aldosterone system inhibition, Eur. J. Pharmacol. 730 (2014) 125–132.
[85] J. He, Bioactivity-guided fractionation of Pine needle reveals catechin as an antihypertension agent via inhibiting angiotensin-converting enzyme, Sci. Rep. 7 (1) (2017) 8867.
[86] D. Ojeda, E. Jiménez-Ferrer, A. Zamilpa, A. Herrera-Arellano, J. Tortoriello, L. Alvarez, Inhibition of angiotensin convertin enzyme (ACE) activity by the anthocyanins delphinidin-and cyanidin-3-O-sambubiosides from Hibiscus sabdariffa, J. Ethnopharmacol. 127 (1) (2010) 7–10.
[87] A. Choudhury, K.V. Pai, Angiotensin converting enzyme inhibition activity of daidzein, J. Drug Deliv. Ther. 4 (6) (2014) 92–98.
[88] M.F. Montenegro, L.R. Pessa, J.E. Tanus-Santos, Isoflavone genistein inhibits the angiotensin-converting enzyme and alters the vascular responses to angiotensin I and bradykinin, Eur. J. Pharmacol. 607 (1) (2009) 173–177.
[89] L. Quinn, S.G. Gray, S. Meaney, S. Finn, P. McLoughlin, M. Hayes, Extraction and quantification of sinapinic acid from Irish rapeseed meal and assessment of angiotensin-I converting enzyme (ACE-I) inhibitory activity, J. Agric. Food Chem. 65 (32) (2017) 6886–6892.
[90] E. Jiménez-Ferrer, J. Alarcón-Alonso, A. Aguilar-Rojas, A. Zamilpa, J. Tortoriello, M. Herrera-Ruiz, Diuretic effect of compounds from *Hibiscus sabdariffa* by modulation of the aldosterone activity, Planta Med. 78 (18) (2012) 1893–1898.
[91] R. Kateel, M.S. Rai, A. Kumar, Evaluation of diuretic activity of gallic acid in normal rats, J. Sci. Innov. Res. 3 (2) (2014) 217–220.
[92] I. Giménez, R.M. Martinez, M. Lou, J.A. Mayoral, R.P. Garay, J.O. Alda, Salidiuretic action by genistein in the isolated, perfused rat kidney, Hypertension 31 (2) (1998) 706–711.
[93] T. Boeing, L.M. da Silva, M. Mariott, S.F. de Andrade, P. de Souza, Diuretic and natriuretic effect of luteolin in normotensive and hypertensive rats: role of muscarinic acetylcholine receptors, Pharmacol. Rep. 69 (2017) 1121–1124.
[94] S. Uesugi, Comparative research on diuretic actions of some flavone compounds, Folia Pharmacol. Japonica 50 (6) (1954) 502–522.
[95] P. Das, K. Kumar, A. Nambiraj, R. Rajan, R. Awasthi, K. Dua, M. Himaja, Potential therapeutic activity of *Phlogacanthus thyrsiformis* Hardow (Mabb) flower extract and its biofabricated silver nanoparticles against chemically induced urolithiasis in male Wistar rats, Int. J. Biol. Mcromol. 103 (2017) 621–629.
[96] W.-C. Lin, M.-T. Lai, H.-Y. Chen, C.-Y. Ho, K.-M. Man, J.-L. Shen, Y.-J. Lee, F.-J. Tsai, Y.-H. Chen, W.-C. Chen, Protective effect of *Flos carthami* extract against ethylene glycol-induced urolithiasis in rats, Urol. Res. 40 (6) (2012) 655–661.
[97] C.R. Tracy, J.R. Henning, M.R. Newton, M. Aviram, M.B. Zimmerman, Oxidative stress and nephrolithiasis: a comparative pilot study evaluating the effect of pomegranate extract on stone risk factors and elevated oxidative stress levels of recurrent stone formers and controls, Urolithiasis 42 (5) (2014) 401–408.
[98] S.R. Khan, Hyperoxaluria-induced oxidative stress and antioxidants for renal protection, Urol. Res. 33 (5) (2005) 349–357.
[99] S. Ahmed, M.M. Hasan, Antiurolithiatic plants of Acanthaceae, Amaranthaceae, Amaryllidaceae, Anacardiaceae, Apocynaceae, Arecaceae, Asparagaceae, Aspleniaceae, Caesalpiniaceae, Capparidaceae, Caryophyllaceae, Chenopodiaceae, Cucurbitaceae, Cupressaceae, Ericaceae, Equisetaceae and Euphorbiaceae, World J. Pharm. Pharm. Sci. 6 (8) (2017) 156–182.
[100] S. Ramachandran, B. Rani, N. Sahu, C. Ramesh, Evaluation of antiurolithiatic activity of ethanolic extract of Annona reticulata against ethylene glycol and ammonium chloride induced urolithiasis in albino Wistar rats, Int. Res. J. Pharm. 5 (11) (2014) 834–837.
[101] S. Ahmed, M.U.A. Siddiqui, M.M. Hasan, Globally used antiurolithiatic plants of family Apiaceae, World J. Pharm. Res. 6 (7) (2017) 358–364.
[102] S. Ahmed, M. Siddiqui, M. Hasan, Globally used antiurolithiatic plants of family Apiaceae, World J. Pharm. Res. 6 (7) (2017) 358–364.
[103] C.S. Reddy, P. Vardhaman, Evaluation of *Phoenix dactylifera* fruits for anti-urolithiatic activity, Hygeia: J. Drug Med. 5 (2013) 135–140.
[104] S. Ahmed, M.M. Hasan, Z.A. Mahmood, Globally used antiurolithiatic plants of family Asteraceae: historical background, mechanism of action, therapeutic spectrum, formulations with doses, J. Pharmacogn. Phytochem. 6 (3) (2017) 394–402.
[105] S. Ahmed, M.M. Hasan, A review on globally used antiurolithiatic monoherbal formulations belonging to Boraginaceae, Brassicaceae, Malvaceae and Poaceae families, World J. Pharm. Pharm. Sci. 6 (8) (2017) 48–61.
[106] A.R. Dhole, V.R. Dhole, C.S. Magdum, S. Mohite, Herbal therapy for urolithiasis: a brief review, Res. J. Pharmacol. Pharmacodyn. 5 (1) (2013) 06–11.
[107] A. Aggarwal, S. Singla, C. Tandon, Urolithiasis: phytotherapy as an adjunct therapy, Ind. J. Exp. Biol. 53 (2014) 103–111.
[108] S. Ahmed, M.M. Hasan, Z.A. Mahmood, Antiurolithiatic plants of family Fabaceae: a memoir of mechanism of action, therapeutic spectrum, formulations with doses, J. Pharmacogn. Phytochem. 6 (3) (2017) 592–596.
[109] S.G. Salma, M.M. Baig, S. Hasan, S.A. Ahmed, Fatima, Analgesic and anti-inflammatory effects of *Phaseolus vulgaris* L. fixed oil in rodents, J. Basic Appl. Sci. 14 (2018) 174–179.
[110] S. Ahmed, M.S. Khatri, M.M. Hasan, Plants of family Lamiaceae: a promising hand for new antiurolithiatic drug development, World J. Pharm. Pharm. Sci. 6 (7) (2017) 90–96.
[111] S. Ahmed, M.M. Hasan, A comprehensive glimpse on globally used antiurolithiatic plants of Convolvulaceae, Costaceae, Ebenaceae, Fagaceae, Hypericaceae, Lauraceae, Liliaceae and Lythraceae, World J. Pharm. Res. 6 (8) (2017) 224–233.
[112] S. Alok, S.K. Jain, A. Verma, M. Kumar, M. Sabharwal, Pathophysiology of kidney, gallbladder and urinary stones treatment with herbal and allopathic medicine: a review, Asian Pac. J. Trop. Dis. 3 (6) (2013) 496–504.
[113] S. Ahmed, M.M. Hasan, Exploring globally used antiurolithiatic plants of M to R families: including Myrtaceae, Phyllanthaceae, Piperaceae, Polygonaceae, Rubiaceae and Rutaceae, J. Pharmacogn. Phytochem. 6 (5) (2017) 325–335.
[114] S. Ahmed, S. Gilani, M.M. Hasan, Antiurolithiatic potential of globally used medicinal plants belonging to the family Rosaceae, J. Pharmacogn. Phytochem. 6 (4) (2017) 1028–1031.
[115] V. Butterweck, S.R. Khan, Herbal medicines in the management of urolithiasis: alternative or complementary? Planta Med. 75 (10) (2009) 1095–1103.
[116] S. Ahmed, M.M. Hasan, Exploring globally used antiurolithiatic plants of S to Z families: including Saxifragaceae, Scrophulariaceae, Solanaceae, Urticaceae, Vitaceae, Zingiberaceae and Zygophyllaceae, J. Pharmacogn. Phytochem. 6 (4) (2017) 1430–1436.
[117] B.C. Jeong, B.S. Kim, J.I. Kim, H.H. Kim, Effects of green tea on urinary stone formation: an in vivo and in vitro study, J. Endourol. 20 (5) (2006) 356–361.