



## Review

# Plant Extracts in Hyperoxaluria Treatment: A Review of Experimental and Clinical Research

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### Abstract

This article is a review of the scientific literature. The purpose of this research was the systematization of the updated information on potential herbal medicine in hyperoxaluria treatment. We analysed the English language scientific literature Medline published from January 2008 to December 2018. Data *in vitro*, experimental and clinical studies demonstrated antiurolithiatic properties of many plant extracts. Reducing hyperoxaluria is mainly caused by the ability of plants to inhibit nucleation and agglomeration of crystals by changing the ionic composition of urine and due to diuretic, nephroprotective, antioxidant and antibacterial effects.

**Keywords:** Experimental and clinical studies, hyperoxaluria, plant extracts, urolithiasis

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**H**yperoxaluria (excessive urinary oxalate excretion) is a major risk factor for kidney stone diseases (KSD).<sup>[1–3]</sup> The upper limit of normal level for urinary oxalate excretion is considered to be 40 mg (0.40  $\mu\text{mol}$ ) in 24 hour urine; this index is slightly higher in men - 43 mg/d vs 32 mg/d in women.<sup>[3]</sup> This difference is associated with a larger body habitus and increased food intake in men. Taking into consideration the demonstration of these norms, the regular definition of hyperoxaluria is urinary oxalate excretion that exceeds 44 mg/d or 0.44  $\mu\text{mol}/\text{d}$ .<sup>[1, 3–5]</sup> The alternative indicator of hyperoxaluria, which eliminates the differences in body mass and food volume, is the ratio of excretion  $>32$  mg/day of oxalate per gram of isolated creatinine (or  $>40$   $\mu\text{mol}/\text{mol}$ ).<sup>[1]</sup>

There are 3 main types of hyperoxaluria:

- 1. Primary hyperoxaluria:** ( $\geq 1$   $\mu\text{mol}/\text{d}$ ). It is characterized by inherited (genetic) overproduction of oxalate and associated with genetic defects (type I is the AGXT gene mutation, type II is the GRHPR gene and type III is the DHDPSL gene).<sup>[6, 7]</sup>
- 2. Secondary hyperoxuria:** ( $\geq 0.5$   $\mu\text{mol}/\text{d}$ , usually  $\leq 1$   $\mu\text{mol}/\text{d}$ ). It

occurs due to intestinal hyperabsorption of oxalate (enteral) or dietary abuse (dietary). Enteral hyperoxaluria is most commonly associated with a bowel resection, bariatric surgery, Crohn's disease and pancreatic insufficiency.<sup>[1]</sup>

### 3. Idiopathic or mild hyperoxuria:

 ( $\geq 0.45$ – $0.85$   $\mu\text{mol}/\text{d}$ ).<sup>[1, 2]</sup>

As all forms of KSD, clinical implications of hyperoxaluria are associated with the formation of stones and subsequent damage of the urinary system: renal obstruction, urosepsis, chronic kidney disease and even death. In particular, primary hyperoxaluria is associated with the most serious life expectancy and prognostic factors.<sup>[6]</sup> After all, 50% of patients younger than age 15 years and 80% of those under age 30 require renal replacement therapy; mortality (infant mortality in particular) exceeds 50%.<sup>[7, 8]</sup> Moreover, in terms of the effectiveness of therapeutic and prophylactic measures, secondary and idiopathic types of hyperoxaluria are prognostically favorable.<sup>[6, 8]</sup> However, existing therapeutic strategies are very limited. First of all, they are based on dietary measures, such as reducing the consumption of high-oxalate and

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fat foods and increasing fluid intake to 2.5-3 liters per day.<sup>[1, 7, 9]</sup> The use of pyridoxine hydrochloride at a dose of 5-20 mg/kg/day is effective in the patients with proven primary hyperoxaluria of type I. In case of enteric hyperoxaluria, increasing calcium intake in a food diet (>500 mg/day) is added to the dietary recommendations, and, the patients are prescribed potassium citrate.<sup>[1, 9, 10]</sup> However, the use of potassium citrate causes a number of the gastrointestinal side effects (belching, bloating, diarrhea), and, accordingly, these factors make impossible to use it in most cases.<sup>[11]</sup>

Unfortunately, at present, the effectiveness of pharmacotherapy for the treatment of the most common "idiopathic" hyperoxaluria forms (up to 40%) has not been proven.<sup>[9, 12, 13]</sup> A probiotic approach with the use of *O. formigenes*, *Eubacterium lentum*, *Lactobacillus acidophilus* and all other microorganisms is considered promising today.<sup>[14, 15]</sup> A substantial body of research has been conducted on the ability of probiotics to reduce oxalate excretion. These studies have led to promising, but, all in all, ambiguous results requiring confirmation with the help of larger, well-designed randomized clinical trials.<sup>[16]</sup>

Consequently, none of the existing treatment methods is devoid of any disadvantages, such as a large number of side effects and/or lack of the evidence base. On the other hand, due to the limited choice of pharmacotherapy, the interest of the public in the use of herbal medicines in KSD treatment in general and hyperoxaluria in particular is increasing.<sup>[12, 17-19]</sup> Unlike allopathic drugs, which tend to effect only one aspect of lithogenesis, most plants have multifactorial effects acting through antispasmodic, antibacterial, diuretic, analgesic, antioxidant and other effects.<sup>[12, 20]</sup> That is exactly why the use of herbal preparations, which have been used since ancient times in many countries of the world, is further developing. Nevertheless, as an alternative to hyperoxaluria treatment, the effectiveness and the mechanism of phyto-preparations' action have not been cleared up yet.<sup>[21-23]</sup>

The purpose of this work was to systematize the current data obtained *in vitro*, to conduct the experiment on animals, to get the results of clinical studies, to determine the potential of phytotherapy in hyperoxaluria treatment.

A total of 98 original scientific works published in the Medline system between the periods of January 2008 and December 2018 were analyzed. We found out that most of the researches, namely 54% (n=53), were conducted in the experiment on animals and 41% (n=40) *in vitro* studies. And, only 5 works (5%) were the randomized clinical trials.

## In Vitro Studies

Experimental studies *in vitro* are widely used to study the processes of crystals' nucleation, their growth and agglomeration.<sup>[12, 24]</sup> It is necessary to remind that according to the crystallization theory, which appeared in the middle of the last century, the formal crystallization process involves several stages:

- Crystal nucleus formation in a supersaturated solution (nucleation);

- Crystal growth;
- Crystal aggregation;
- Delay of aggregates in the urinary system with formation of uralite (agglomeration).<sup>[1, 12]</sup>

It is a general idea that intervention in the processes of nucleation and aggregation of oxalates is one of the potential therapeutic strategies for the prevention and KSD treatment. Consequently, many of the tested plants in an *in vitro* system contain glycosaminoglycans. They are inhibitors of crystallization and prevent formation and agglomeration of oxalates. Thus, Surendra K. Pareta and his co-authors demonstrated the antilithogenic properties of *Achyranthes indica* and *Ammi visnaga* due to the inhibitory effect on crystallization.<sup>[25]</sup> The authors showed that the extracts of these plants changed a urine pH level that interfered with citrate reabsorption in kidneys and aggregation of oxalates in the urinary system.<sup>[25]</sup> A similar "*in vitro*" effect was also shown with the use of *Hyptis suaveolens* and *Tinospora cordifolia*.<sup>[26]</sup> A. Barzgarnejad argued that urinary concretions could be dissolved *in vitro* with the help of *Juniperus fruit*.<sup>[27]</sup> Moreover, the efficiency of a fruit of juniper had a dose-dependent effect: the higher the concentration of the extract was (the authors used solutions of 200, 500 and 1000 µg/ml), the smaller the weight of the dry powder of the concrement was (1310, 1240 and 1120 mg, respectively).<sup>[27]</sup>

With the help of *in vitro* studies and using renal epithelial cells, the cytotoxic effect of oxalates was proven due to the unbalance of oxidant/antioxidant systems, membrane integrity damage and apoptosis.<sup>[1, 12, 17]</sup> After all, it is a well-known fact that oxidative stress leads to inflammation due to the excessive formation of lipid peroxidation products. In turn, the loss of cell membranes integrity further contributes to the preservation of oxalate crystals and the growth of stones in the renal tubules.<sup>[17]</sup> For example, recent studies have shown that malondialdehyde excretion may be considered as a marker of renal cell damage.<sup>[17]</sup> Thus, the treatment with natural antioxidants is considered as a second therapeutic strategy that reduces hyperoxaluria-induced oxidative stress. The vegetable extracts such as *Holarrhena antidysenterica*, *Origanum vulgare* and *Terminalia chebula* can inhibit cell damage, preferably by inhibiting free radicals.<sup>[28-31]</sup> Protective action of *Paronychia argentea*, *B. ligulata*, *Quercus salieina*, *Achyranthus Aspera* and *Ammi visnaga* also occurs due to stimulation of antioxidant activity.<sup>[23, 31, 32]</sup> The effects of the main plant extracts are given in Table 1.

## In Vivo Study

The bulk of kidney physiology data was obtained from the experimental animal studies, and, most of the animals were rats. A calcium oxalate KSD model was the most detailed study. Acute or chronic hyperoxaluria was induced in rats by induction of sodium oxalate, ammonium oxalate, oxy-L-proline, ethylene glycol and glycolic acid. Lithogenic agents were administered to rats by means of food or water, oral route using gastric probe, intravenous or intraperitoneal injections.<sup>[17]</sup>

**Table 1.** Plant extracts with urologic properties and their effects

Plant extract	Type of research	Identified effects	Source of information
<i>Achyranthes indica</i>	<i>In vitro</i>	Inhibition of oxalate crystallization	Surendra K. Pareta (2011) <sup>[33]</sup>
<i>Alcea rosea</i> root	<i>In vivo</i> animals	Reducing oxalate deposits in kidneys of rabbits; diuretic, anti-inflammatory	M. Ahmadi (2012) <sup>[34]</sup>
<i>Ammi visnaga</i>	<i>In vivo</i> animals	antioxidant, nephroprotective	A. Vanachayangkul (2015) <sup>[35]</sup>
	<i>In vitro</i>	Inhibition of oxalate crystallization	R. Kachkoul (2018) <sup>[32]</sup>
<i>Achyranthes aspera</i>	<i>In vivo</i> animals	Inhibition of oxalate crystallization, reducing crystals' size; nephroprotective	S. Aggarwal (2012) <sup>[36]</sup>
<i>Angelica sinensis</i>	<i>In vitro</i>	Inhibition of the calcium oxalate's crystallization	S. Wang (2018) <sup>[37]</sup>
<i>Arbutus unedo</i> L.	<i>In vitro</i>	Inhibition of the calcium oxalate's crystallization	R. Kachkoul (2018) <sup>[38]</sup>
<i>Berberine</i>	<i>In vitro, In vivo</i> animals	Anti-oxidant, diuretic, hypocalciuric	S. Bashir (2011) <sup>[39]</sup>
<i>Boerhaavia diffusa</i>	<i>In vivo</i> animals	Inhibition of oxalates, reducing their size; diuretic, cytoprotective	F. Yasir (2011) <sup>[40]</sup>
<i>Camellia sinensis</i>	Clinical	Decrease of urinary oxalate excretion, calcium oxalate deposit formation	A. Rodgers (2016) <sup>[41]</sup>
<i>Costus arabicus</i> L.	<i>In vitro</i>	Inhibition of calcium oxalate crystal growth and adhesion to renal epithelial cells.	M.R. De Cógáin (2015) <sup>[42]</sup>
<i>Crataeva nurvala</i>	Clinical, <i>In vivo</i> animals	Dissolving kidney stones and facilitating their passage; anesthetic	Patankar S. (2008) <sup>[43]</sup>
<i>Cymbopogon citratus</i>	<i>In vivo</i> animals	Inhibition of calcium oxalate renal stone formation in rats due decreasing free radical mediated lipid peroxidation	Sanjay Agarwal (2010) <sup>[44]</sup> Faten Y. Ibrahim (2013) <sup>[45]</sup>
<i>Dolichous biflorus</i>	Clinical	Reducing oxalates' size	R. Singh (2010) <sup>[46]</sup>
	<i>In vitro</i>	Decrease of nucleation and aggregation of calcium oxalate monohydrate crystals	S. Saha (2015) <sup>[47]</sup>
<i>Helichrysum graveolens</i> (M.Bieb.) Sweet and <i>Helichrysum stoechas</i> ssp. <i>barellieri</i> (Ten.) Nyman	<i>In vivo</i> animals	Decrease formation and growth of crystals, urine oxalate level	N. Orhan (2015) <sup>[48]</sup>
<i>Hibiscus sabdariffa</i>	<i>In vivo</i> animals	Reducing oxalate concentration in rats' blood and increasing their excretion	S. Woottisin (2011) <sup>[49]</sup>
<i>Holarrhena antidysenterica</i>	<i>In vitro, In vivo</i> animals	Dosage-dependent inhibition effects of oxalate aggregation; antioxidant, epithelial cell defense	A. Khan (2012) <sup>[30]</sup>
<i>Hyptis suaveolens</i>	<i>In vitro</i>	Inhibition of oxalate aggregation	Agarwal Kumkum (2012) <sup>[50]</sup>
<i>Juniperus fruit</i>	<i>In vitro</i>	Dose-dependent inhibition of oxalate aggregation	A. Barzgarnejad (2010) <sup>[51]</sup>
<i>Launaea procumbens</i> L.	<i>In vivo</i>	Decrease urinary calcium, oxalate and phosphate excretion	Makasana A (2014) <sup>[52]</sup>
<i>Moringa oleifera</i>	<i>In vivo</i> animals	Inhibition of oxalates, reducing their size	Jameel Fahad (2010) <sup>[53]</sup>
<i>Origanum vulgare</i>	<i>In vitro, In vivo</i> animals	Inhibition of oxalate aggregation; diuretic, antioxidant, antispasmodic, epithelial cell defense, hypocalciuric and hyperciturial	Aslam Khan (2011) <sup>[28]</sup>
<i>Orthosiphon stamineus</i>	Clinical	Lithogenic effects in comparison with placebo have not been defined	Premgamone (2009) <sup>[54]</sup>
<i>Paronychia argentea</i>	<i>In vivo</i> animals	Reducing oxalate concentration in rats' blood; nephroprotective	S. Bouanani (2010) <sup>[31]</sup>
<i>Pomegranate juice</i>	Clinical	Decrease of serum paraoxonase activity and supersaturation of calcium oxalate	C.R. Tracy (2014) <sup>[55]</sup>
<i>Punica granatum</i>	<i>in vitro</i>	Inhibition of oxalate crystallization	R. Kachkoul (2018) <sup>[32]</sup>
<i>Radix Paeoniae Alba</i>	<i>In vitro</i>	Reduce urinary and renal oxalate levels and increased urinary calcium and citrate levels	X. Li (2017) <sup>[56]</sup>
<i>Rubia cordifolia</i>	<i>In vivo</i> animals	Inhibition of oxalate aggregation; nephroprotective	Divakar K (2010) <sup>[57]</sup>
<i>Rosa canina</i>	<i>In vivo</i> animals	Reducing the size and stones' amount ; diuretic	Tayefi-Nasrabadi H. (2012) <sup>[58]</sup>
<i>Terminalia chebula</i>	<i>In vitro</i>	Inhibition of oxalates; cytoprotective	Tayal S. (2012) <sup>[29]</sup>
<i>Tinospora cordifolia</i>	<i>In vitro</i>	Inhibition of oxalate aggregation	Goyal Parveen Kumar (2011) <sup>[26]</sup>

As we have already mentioned above, in an *in vitro* system, *Ammi visnaga* inhibits the crystallization process by inhibiting the growth of crystals and their aggregation. P. Vanachayangkul and his co-authors conducted their research on rats and demonstrated that oral administration of 125, 250 or 500 mg/kg of *Ammi visnaga* extract for a period of 14 days significantly reduced the amount of kidney oxalate deposits.<sup>[35]</sup> In other works, P. Vanachayangkul and K. Haug tried to find out the pharmacokinetic characteristics of *Ammi visnaga*, but, they did not reach any definite conclusions.<sup>[59]</sup>

The experimental study on a model of ethylene glycol-induced hyperoxaluria on rats demonstrated the effectiveness of *Alcea rosea* root for a period of 28 days.<sup>[34]</sup> The authors described diuretic, anti-inflammatory, nephroprotective effects of the extract and reducing concentration of lithogenic agents in urine.<sup>[34]</sup> The use of *Berberine*, *Boerhaavia diffusa*, *Hibiscus sabdariffa*, *Moringa oleifera*, *Rubia cordifolia*, *Rosa canina*, *Pyracantha crenulata* and *Pinus oil* demonstrated similar effects.<sup>[25, 31, 32, 39, 40, 49, 53, 57, 58]</sup>

## Clinical Studies

All modern randomized clinical studies are devoted to the use of specific herbal medicines or some types of juice: lemon, orange or apple.<sup>[60]</sup> And, only 5 works are focused on plant extracts of *Orthosiphon stamineus*, *Dolichous biflorus* and *Crataeva nurvala*. A. Premgamone with his co-authors demonstrated the absence of any anti-lithogenic effects of *Orthosiphon stamineus* (*kidney tea*).<sup>[54]</sup> The authors believed that the flavonoids, which were contained in *Orthosiphon stamineus*, acted as adenosine A1 receptor antagonists increasing diuresis and inhibiting sodium reabsorption.<sup>[54]</sup>

In another study (47 patients took part in this trial), Rana Gopal Singh and his co-authors identified a significant reduction in the size of the concrements in comparison with potassium citrate in 6 months after the patients used *Dolichous biflorus*.<sup>[46]</sup>

S. Patankar and his colleagues conducted a prospective, randomized, double-blind, placebo-controlled study involving 77 patients. The authors came to the conclusion that *Crataeva nurvala* had prospects for UHC treatment because it could dissolve oxalate concrements and anesthetize their passage.<sup>[43]</sup>

## Summary

*In vitro* data, the experimental and clinical studies have demonstrated the urolithic properties of many plant extracts. Reducing hyperoxaluria is mainly due to the ability of plants to inhibit nucleation and agglomeration of crystals by changing ionic composition of urine through diuret-

ic, nephroprotective, antioxidant and antibacterial effects. Nevertheless, the general disadvantage of all these studies is lack of phytochemical characteristics of the plants. Since many extracts contain oxalates (and/or citrate), this important factor must take into account in order to eliminate possible negative side effects. In addition, some of the plants contain saponins, and, in fact, they are promoters of crystallization. It is clear that the use of phytotherapy cannot be an alternative to shock-wave lithotripsy or, if it is necessary, surgical interventions; but, undoubtedly, it can be used to treat hyperoxaluria. Further preclinical and clinical studies on the efficacy and safety of plant products will allow the creation of new phytotherapeutic agents.

## Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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