



## REVIEW ARTICLE

## KIDNEY STONES FORMATION AND USE OF MEDICINAL PLANTS AS ANTIUROLITHIATIC AGENTS

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### Article Info:



#### Article History:

Received: 21 May 2017  
 Reviewed: 6 July 2017  
 Accepted: 26 August 2017  
 Published: 15 September 2017

#### Cite this article:

Arya P, Pandey S, Verma V. Kidney stone formation and use of medicinal plants as antiurolithiatic agents. Universal Journal of Pharmaceutical Research 2017; 2(4): 36-41. <http://doi.org/10.22270/ujpr.v2i4.RW1>

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### Abstract

There is an old and famous fact “the garden is the poor man's apothecary” and treatment of each and every disease is hidden in nature. Medicinal plants are highly esteemed all over the world as a rich source of therapeutic agents for the prevention and treatment of various diseases. Since ages, herbs are being used for treating different ailments in different parts of world by different communities. A kidney stone, also known as a renal calculus is a solid concretion or crystal aggregation formed in the kidneys from dietary minerals in the urine. The problem of urinary stones or calculi is a very ancient one these stones are found in all parts of the urinary tract, the kidney, and the urinary bladder and may vary considerably in size. Urolithiasis is a complex process that occurs from series of several physicochemical event including super-saturation, nucleation, growth, aggregation and retention within the kidneys. Present article deals with reason, types of kidney stones, risk factors associated, diagnosis and treatment methods including many medicinal plants as herbal option for treatment of urinary stones.

**Keywords:** Kidney stone, medicinal plants, urolithiasis.

### INTRODUCTION

Natural plant products have been used throughout human history for various purposes since more than 5000 Yrs and for much of history, herbal medicine was the only medicine. Herbal medicines are naturally occurring, plant-derived substances that are used to treat or prevent different diseases<sup>1</sup>. Medicinal plants contain complex mixtures of organic chemicals that may come from any raw or processed part of a plant. On an average 25% of the drugs prescribed worldwide are derived from plants<sup>2</sup>. Of the 252 drugs in the World Health Organization's essential medicine list, 11% are exclusively of plant origin<sup>3</sup>. Herbal medicine, also called botanical medicine, uses the plant's seeds, berries, roots, leaves, bark or flowers for medicinal purposes. At present scenario, many researchers are working on different medicinal plants to create the pharmaceutical products<sup>4</sup>. Urolithiasis (nephrolithiasis) or kidney stones are the condition characterized by formation of urinary calculi in the urinary tract. It is a common disorder affecting approximately 12% of the population, with a recurrence rate of 70-81% in males, and 47-60% in females. Urine contains chemicals that prevent the crystals from forming<sup>5</sup>. However these

inhibitors do not seem to work for everyone, thus stones are developed in some people form. If the crystals remain tiny enough, they will travel through the urinary tract and pass out of the body in the urine without being noticed. Urinary stones of up to 5 mm. of diameter are generally passes through the urinary tract, whereas those exceeding 7 mm of diameter almost always require surgical intervention<sup>6</sup>. It causes serious health problems such as severe pain at the end of urination, urinary-tract obstruction and infection that adversely affect well-being of individuals<sup>7</sup>. In general, urolithiasis affects all age groups from less than 1 year old to more than 70 yrs. The risk of stones formation is generally high in men 2-4 times, which could be due to the larger muscle mass of men as compared to women, enhancing capacity of testosterone and inhibiting capacity of oestrogen in stones formation. Moreover male urinary tract being more complicated than the female urinary tract. Estrogen may also help to prevent the formation of calcium stones by keeping urine alkaline and raising protective citrate levels<sup>8</sup>. Calculi can occur in various sites in the urinary tract in the following order of frequency i.e. vesical<renal<ureteral<urethral. In general, the occurrence of calculus is higher in the lower part of the urinary tract in all age

groups<sup>9</sup>. Many synthetic drugs like diuretics and narcotic analgesics are used in treatment of kidney stones. However overuse of these drugs, results in higher incidence of adverse drug reactions. Shock wave lithotripsy, ureteroscopy, percutaneous nephrostolithotomy, and open or laproscopic stones removal are the treatment approaches for kidney stones<sup>10</sup>. However these treatment methods are costly and painful are non-convenient for patients. There are many medicinal plants that have shown to be effective in treatment of kidney stones disease. In the present article, an attempt has been made to emphasize on potent medicinal plants that are used in treatment of urolithiasis<sup>11</sup>.

## TYPES OF STONES

There are several types of renal stones having composition and pathogenesis. The stones types are named after its mineral composition. These chemicals are part of a person's normal diet and make up important parts of the body, such as bones and muscles.

**Table 1: Different types of stones.**

Stone types	Constituents	% Incidence of all stones
Calcium oxalate	Calcium, oxalate	70 %
Calcium phosphate	Calcium, phosphate	10 %
Uric acid	Uric acid	5-10 %
Struvite	Calcium, ammonia, phosphate	10 %
Cystine	Cystine	Less than 1%
Medication-induced stones	indinavir, ephedrine, guaifenesin, silica)	Less than 1%

### 1. Calcium stones

Most kidney stones are calcium stones, combined with oxalate, phosphate, or occasionally uric acid. Calcium oxalate crystal formation is also one of the toxic effects of ethylene glycol poisoning. Oxalate is a naturally occurring substance found in food. Some fruits, vegetables, nuts and chocolate, have high oxalate levels. Liver also produces oxalate. Dietary factors, high doses of vitamin D, intestinal bypass surgery and several metabolic disorders can increase the concentration of calcium or oxalate in urine. All calcium stones are radio-opaque, and calcium oxalate and calcium phosphate stones are black, grey, or white and small (1 cm in diameter) dense and sharply circumscribed on radiographs. Calcium oxalate stones appear as 'envelopes' microscopically. The formation of calcium phosphate stones is associated with conditions such as hyperparathyroidism and renal tubular acidosis<sup>12</sup>.

### 2. Uric acid stones

Uric acid stones are smooth, round, yellow-orange and nearly radiographically transparent. About 5–10% of all stones are formed from uric acid. Uric acid stones can form in people who don't drink enough fluids or who lose too much fluid, those who eat a high-protein diet, diets high in purines, especially those containing meats and fish and those who have gout certain

metabolic abnormalities; including obesity or certain genetic factors also may increase your risk of uric acid stones<sup>18</sup>. These patients also have a tendency to form urate stones. Urate stones are especially common after colon resection. Uric acid stones appear as pleomorphic crystals, usually diamond-shaped, squares or rods which are polarizable<sup>13</sup>.

### 3. Struvite or infection or triple phosphate stones

Struvite is a crystalline substance composed of magnesium ammonium phosphate. About 10–15% of urinary calculi are composed of struvite. Struvite stones form most often in the presence of infection by urea-splitting bacteria. Using the enzyme urease, these organisms metabolize urea into ammonia and carbon dioxide. This alkalinizes the urine, resulting in favorable conditions for the formation of struvite stones. They are also commonly seen in people with underlying metabolic disorders, such as idiopathic hypercalciuria, hyperparathyroidism, and gout. Struvite stones are large, gnarled, and laminated. These stones can grow quickly and become quite large, sometimes with few symptoms or little warning. Signs of struvite stones include urinary pH greater than 7, staghorn calculi, and urease that grow bacteria on culture (proteus, klebsiella, pseudomonas)<sup>14</sup>.

### 4. Protease-related stones

This is the newest type of stones. The increasing incidence of HIV-positive patients has led to widespread use of the protease inhibitor indinavir sulphate. In 4-12% of patients this drug, may leads to formation of stones<sup>15</sup>.

### 5. Cystine stones.

These stones are rare and form in people with a hereditary disorder that causes the kidneys to excrete too much of certain amino acids (cystinuria). People who are homozygous for cystinuria excrete more than 600 mg per day of insoluble cystine. The stones are greenish- yellow, flecked with shiny crystallites, and are moderately radio-opaque with a rounded appearance<sup>16</sup>.

### 6. Silicate stones or drug induced stones

These are stones are found very rarely. These stones can form as a result of taking certain medications or herbal products like loop diuretics, acetazolamide, topiramate, zonisamide, laxatives (when abused), ciprofloxacin, sulfa medications, triamterene, indinavir, ephedrine, guaifenesin, and products containing silica<sup>17</sup>.

## CAUSES OF UROLITHIASIS

Kidney stones often have no definite, single cause, although several factors may be responsible for it. Kidney stones form when urine contains more crystal-forming substances such as calcium, oxalate and uric acid than the fluid in urine gets diluted. At the same time, urine may lack substances that prevent crystals from sticking together, creating an ideal environment for kidney stones to form. Dietary factors that increase the risk of stones formation include low fluid intake and high dietary intake of animal protein, sodium, refined sugars, calcium oxalate, grapefruit juice, apple juice, fructose and high fructose corn syrup, and cola

drinks<sup>18</sup>. Other reason for stones formation includes inadequate urinary drainage, foreign bodies in urinary tract, microbial infections, vitamin abnormalities like vitamin A deficiencies, excess vitamin D, and metabolic diseases like hyperthyroidism, cystinuria, gout, intestinal dysfunction etc<sup>19</sup>.

In order to form stones within the urinary tract, urine must be supersaturated for precipitating crystalline component. The agents who can modify nucleation, crystallization, and aggregation, pH of the urine also play important role in stones formation. Some reports have described that vegetarians are at lower risk for stones formation in contrast to non-vegetarians<sup>20</sup>.

A family history of kidney stones (increases risk by three times), insulin resistant states, a history of hypertension, primary hyperparathyroidism, a history of gout, chronic metabolic acidosis, and surgical menopause are all associated with increased risk of kidney stones. Various drug that increase the risk of stones disease i.e. decongestants (ephedrine, guaifenesine), diuretics (triamterene), protease inhibitors (indinavir), anticonvulsants (felbamate, topiramate).

Pathogenesis of kidney stones based on two basic aspects<sup>21</sup>-

1. Increased urinary excretion of stones forming constituents like calcium, phosphorus, uric acid, oxalate and cysteine.

2. Physicochemical changes that influence stones formation like pH of urine, stones matrix and protective substances in urine.

Symptoms of kidney stones include colicky pain, nausea/ vomiting, hematuria, pyuria, dysuria, oliguria.

**Table 2: Stone promoters and inhibitors.**

<b>Stone promoters</b>	Low urine volume, calcium, low urine pH, sodium oxalate, urate
<b>Stone Inhibitors</b>	Inorganic inhibitors, citrate, magnesium, osteopontin glycosaminoglycans, organic inhibitors, prothombin fragment

### Mechanism of calcium oxalate stone formation

Exact mechanism of stone formation is not clearly understood. The proposed mechanism includes following steps

#### 1. Urinary supersaturation-

Urine is a highly saturated solution containing various crystalloids and colloids. Urine does not precipitate under normal condition due to presence of stone forming inhibitors present in urine.

When the urine becomes supersaturated (when the urine solvent contains more solutes than it can hold in solution) with one or more calculogenic (crystal-forming) substances, a seed crystal may form through the process of nucleation<sup>22</sup>.

#### 2. Formation of nidus (crystal nucleation)

The first step in the transformation from a liquid to a solid phase in a supersaturated solution is termed as nucleation. This process starts with the combination of stone salts in solution into loose clusters that may increase in size by addition of new components or clusters. Nuclei form the first crystals that do not dissolve and have a characteristic lattice pattern. In

urine, nuclei usually form on existing surfaces, a process called heterogeneous nucleation.

### 3. Crystal growth

Whenever a crystal nucleus achieved a critical size and relative super saturation remains above one, the overall free energy is decreased by adding new crystal components to the nucleus. This process is called crystal growth. Crystal growth is one of the prerequisites for particle formation and thus for stone formation. In each step of stone formation, crystal growth and aggregation have important functions<sup>23</sup>.

### 4. Crystal aggregation

In this process crystals in solution stick together to form large particles. It is the most important step in stone formation. Although crystal growth is definitely a step in renal stone formation, the process of growth is so slow that crystals cannot become large enough to obstruct the renal tubules and be retained there by this mechanism alone, as several minutes are required for the tubular fluid to pass through the kidney. Crystal aggregation is promoted by viscous binding, implying that crystal-foreign compounds with multiple binding sites, such as abnormally self-aggregating Tamm-Horsfall glycoprotein or other macromolecules, attach to crystal surfaces and act as a kind of glue<sup>24</sup>.

### 5. Crystal-Cell Interaction

Crystal-cell interaction mechanism is very complex, and many of them remain unexplored. Crystallization is caused by the condition of urinary supersaturation. Then, the crystals that have formed attach to renal tubular epithelial cells and are taken into them.

## DIAGNOSIS OF UROLITHIASIS

Diagnosis of urolithiasis is done on the basis of clinical symptoms of the location and severity of the pain. Imaging like x-ray, computed tomography, ultrasound is used to confirm the presence of stones<sup>22</sup>. Furthermore, a number of other tests can be undertaken to help establish both the possible cause and consequences of the stones. Microscopic study of urine, to detect presence of proteins, red blood cells, bacteria, cellular casts and crystals. Blood tests for the presence of a raised white cell count (neutrophilia) suggestive of infection, a check of renal function and to look for abnormally high blood calcium blood levels (hypercalcaemia).

## TREATMENT AND PREVENTION

Prevention and treatment of recurrent urolithiasis aims to increase the daily fluid intake to at least 2.5 L to 3 L per day along with pain controlling drugs and medications to monitor salts that may increase or reduce formation of stones. In general physicians usually do not treat kidney stones, they just medicate the pain until the stones pass out their own<sup>23</sup>. Vegetarian diet, to drink plenty of water, heavy on herbs, can be helpful in the prevention and treatment of kidney stones. The severe nature of renal colic has promoted a lower threshold at which narcotic analgesic, thiazide like diuretic and potassium citrate is prescribed.

Table 3: List of medicinal plants used in urolithiasis and urinary tract trouble.

Plant	Family	Part used	Plant	Family	Part used
<i>Abutilon indicum</i> (L.) <sup>25</sup>	Malvaceae	Seed and Leaf extract	<i>Centella asiatica</i> (Linn.) Urban. <sup>40</sup>	Apiaceae	Whole plant
<i>Amaranthus spinosus</i> (L.) <sup>26</sup>	Amaranthaceae	Root or plant	<i>Cinnamomum bejolghota</i> (Buch.-Ham.) Sweet <sup>25</sup>	Lauraceae	Bark
<i>Argemone maxicana</i> (L.) <sup>18</sup>	Papaveraceae	Root	<i>Daucus carota</i> (L.) <sup>46</sup>	Apiaceae	-
<i>Amaranthus viridis</i> (L.) <sup>11</sup>	Amaranthaceae	All parts	<i>Digera Muricata</i> (L.) <sup>28</sup>	Amaranthaceae	Leaves
<i>Abrus precatorius</i> Linn. <sup>17</sup>	Malvaceae	Leaves	<i>Diospyros melaoxylon</i> (Rox) <sup>47</sup>	Ebenaceae	Fruit and bark
<i>Abutilon indicum</i> Linn. <sup>27</sup>	Malvaceae	Whole plant	<i>Equisetum debile</i> (Roxb.) <sup>48</sup>	Equisetaceae	All parts
<i>Actinodaphne angustifolia</i> (Blume) Nees <sup>28</sup>	Lauraceae	Leaves	<i>Gomphrena celosioides</i> 20(Mart.) <sup>49</sup>	Amaranthaceae	Whole plant
<i>Aeschynomene indica</i> Linn <sup>29</sup>	Papilionaceae	Young tender leaves	<i>Grewia flavescens</i> (A. Juss) <sup>50</sup>	Tiliaceae	Root
<i>Aerava lanta</i> (L.) <sup>30</sup>	Amaranthaceae	Leaves	<i>Pedaliium murea</i> (L.) <sup>51</sup>	Pedaliaceae	Fruits
<i>Ageratum conyzoides</i> (L.) <sup>22</sup>	Asteraceae	Leaves	<i>Phyllanthus emblica</i> (L.) <sup>35</sup>	Euphorbiaceae	Seed Powder
<i>Amaranthus caudatus</i> (L.) <sup>24</sup>	Amaranthaceae	Leaves	<i>Capsella bursa pastoris</i> (Linn.) Medik <sup>42</sup>	Brassicaceae	Whole plant
<i>Bambusa nutans</i> Wall. <sup>28</sup>	Poaceae	Shoots	<i>Cardamine hirsuta</i> Linn <sup>43</sup>	Brassicaceae	Whole plant except root
<i>Bauhinia acuminata</i> Linn. <sup>25</sup>	Caesalpiniaceae	Bark or leaves	<i>Cassia fistula</i> (L.) <sup>26</sup>	Caesalpinioideae	Fruit
<i>Bonnaya brachiata</i> Link <sup>31</sup> and Otto.	Scrophulariaceae	Whole plant	<i>Celosia arigentia</i> <sup>29</sup>	Amaranthaceae	Seed
<i>Bonnaya reptans</i> (Roxb.) <sup>32</sup> Spreng.	Scrophulariaceae	Whole plant	<i>Ceropegia bulbos</i> (L.) <sup>44</sup>	Asclepidaceae	Tubers
<i>Benincasa hispida</i> (Thund.) Cogn <sup>33</sup>	Cucurbitaceae	Fruit	<i>Carica papaya</i> Linn <sup>33</sup>	Caricaceae	Young Fruit
<i>Berberis aristata</i> DC <sup>34</sup>	Berberidaceae	Leaves	<i>Celosia argentea</i> Linn <sup>37</sup>	Amaranthaceae	Roots
<i>Beta vulgaris</i> (L.) <sup>35</sup>	Amaranthaceae	Rhizomes	<i>Celtis timorensis</i> Span <sup>45</sup>	Ulmaceae	Aerial parts
<i>Bombex ceiba</i> (L.) <sup>36</sup>	Bombacaceae	Stem and bark	<i>Phyllanthus fraternus</i> (Webster.) <sup>52</sup>	Euphorbiaceae	Whole plant
<i>Borhaavia diffusa</i> (L.) <sup>37</sup>	Nyctagenaceae	Root	<i>Pedaliium murea</i> (L.) <sup>48</sup>	Pedaliaceae	Fruits
<i>Cordia grandis</i> Roxb.	Boragineae	Fruits	<i>Solanum nigrum</i> Linn <sup>53</sup>	Solanaceae	Seeds
<i>Costus speciosus</i> (Koenig) Smith <sup>38</sup> .	Zingiberaceae	Roots	<i>Stephania hermandifolia</i> Walf. <sup>28</sup>	Menispermaceae	Leaves
<i>Curcuma angustifolia</i> Roxb <sup>40</sup>	Cucurbitaceae	Whole plant	<i>Solanum surattence</i>	Solanaceae	Root powder
<i>Tubiflora Acaulis</i> (L.F.) <sup>56</sup>	Acanthaceae	Leaves	<i>Tagetes erecta</i> Linn.	Asteraceae	Leaves
<i>Wedelia chinensis</i> (Osborne) Merril <sup>40</sup>	Asteraceae	Whole plant	<i>Xanthium strumarium</i> Linn.	Asteraceae	Roots

The available drugs used to prevent urolithiasis are not effective in all patients, and many of them are associated with adverse effects that compromise their long term use<sup>24</sup>. For treatment of urolithiasis medicinal

or surgical procedure is carried out. Surgical treatment like-

1. Shock wave treatment which is the only non-invasive treatment for stones disease



2. Endoscopic management, both ureteroscopic and percutaneous nephrolithotomy provides an efficient way to treat stones.

#### Medicinal plants as antiurolithiatic agents

One of the best ways to prevent and treat urolithiasis is to control the process of crystallization events. This is best achieved by the use of herbal extracts since they have been widely used in folk medicine to treat kidney stones. Herbal remedies, are regarded as quite safe with minimal or no side effects, cost effective, readily available and easily affordable.

#### CONCLUSIONS

Since ancient times, medicinal plants has wide acceptance due to a large no. of advantages such as lesser toxic effects, safe, effective, cheap, less chances of recurrence of disease, easily available in rural areas. There is no proper medicine in allopathy for the treatment of urolithiasis, and those drugs are present are having side effects. Furthermore the surgical treatment is another option but it has the more chances of recurrence. So, medicinal plants are considered suitable for the treatment of kidney stones. The present review containing information of kidney stones and plants used as antiurolithiasis agents, it will help in guiding the researcher to identify new source of drugs for this ever prevailing human ailment to overcome the various disadvantages faced by the wide range of population now-a-days and get relieve from the disease.

#### AUTHOR'S CONTRIBUTION

**Arya P:** writing, review, and editing. **Pandey S:** writing, review and editing. **Verma V:** formal analysis, writing, review, and editing. Final manuscript was read and approved by all authors.

#### ACKNOWLEDGEMENTS

The authors extend their thanks and appreciation to the Government Polytechnic, Kashipur, Uttarakhand, India to provide necessary facilities for this work.

#### DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

#### CONFLICT OF INTEREST

None to declare.

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