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## Characteristics of the New Comprehensive Herbal Medicine for the Treatment and Prevention of Urolithiasis

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### Abstract

Urolithiasis is the disease characterized by the formation and accumulation of stones in the urinary tract. Despite significant advances in the treatment of urolithiasis, the problem of the prevention and treatment of this disease remains relevant even now. One solution of this problem is to use a multiplant remedies providing comprehensive pharmacotherapeutic effect on various links in the pathogenesis of the disease. We have proposed a multiplant collection for the treatment and prevention of urolithiasis based on leaves of *Vaccinium vitis-idaea* (L.), herb of *Equisetum arvense* (L.), roots of *Arctium lappa* (L.), fruits of *Anethum graveolens* (L.), and herb of *Artemisia vulgaris* (L.). This article provides an overview of the pharmacological properties of the components of the proposed remedy, due to different groups of biologically active substances.

### Keywords

Urolithiasis; Medicinal plants; Medicinal plant species

### Introduction

Urolithiasis is the disease, the most constant and essential feature of which is the formation and the presence of single or multiple stones in the urinary tract – renal calices, renal pelvis, ureter, bladder, and urethra [1].

According to the foreign literature, the incidence of urolithiasis in the world population is about 12%. The age structure of the incidence of urolithiasis is characterized by high rates among people of the working age, particularly in the age group of 25-50 yrs. Most often, the disease occurs among men from 70% to 81% of cases, in women: 47-60% [2].

By the number of patients, urolithiasis takes one of the first places in the world as compared with other urological diseases (34.2% in Russia). The incidence varies greatly in different countries and averages 1-5% in Asia, 5-9% in Europe, 13% in North America, and up to 20% in Saudi Arabia. In the developed countries of the world, 400 thousand people out of every 10 million suffer from urolithiasis. Its incidence in adults in Russia is 460 per 100,000 population [1,3].

Urolithiasis is a comprehensive syndrome comprising exogenous and/or endogenous etiologial factors, and multivariate pathogenesis.

Exogenous factors of urolithiasis include the following ones: hot climate, dehydration, hardness of drinking water, characteristics of nutrition, lack or an overdose of some vitamins (A, D, etc.), hypodynamia, urinary tract infection, and overdose and uncontrolled use of certain drug substances.

Endogenous factors include disturbance of calcium and phosphorus metabolism, metabolism of oxalic acid (oxalates), uric acid, cystine metabolism, some endocrinopathies (hyperparathyroidism, hyperthyroidism, Cushing's disease, etc.), osteoporosis, a number of diseases of the gastrointestinal tract, and disturbance of lithogenic substances transport [1,4,5].

Urolithiasis leads to a long-term disability, and incapacity in the population. It is characterized by recurrences (their rate can reach 80%) and complications. Due to its wide prevalence, characteristics

of the development and course, urolithiasis remains to be one of the most urgent problems in the modern medicine. Particularly over the past decade, there was a trend toward a higher incidence of the disease associated with the growing influence of adverse environmental factors on the human body [1,6].

The world practice has shown that drugs based on medicinal plants are widely used as an effective component of conservative treatment of urolithiasis after removal of the urinary stones, and as the monotherapy for the prevention of the primary urolithiasis in the presence of the risk factors and recurrent stone formation.

Medicinal vegetable raw material has the following mechanism of action: it selectively affects blood circulation of the kidneys and urinary tract, and causes spasmolytic, analgesic, diuretic effect, as well as affects pH of the urine. Often its impact is synchronously interconnected with the effect on the liver, pancreas, and intestines by metabolism and transport (removal) of lithogenic substances [4].

Thus, the study of multicomponent herbal medicines having a wide spectrum of pharmacological activity for the treatment and prophylaxis of urolithiasis seems to be a promising research area. High pharmacotherapeutic efficacy of these agents is caused by harmonious combination of biologically active substances contained in plants, and providing not only an adequate impact on the main elements of the pathological process but also contributing to the pharmacological regulation of many functional systems and increasing the adaptive capacities of the organism as a whole system.

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## Methods

In order to determine the acute toxicity and pharmacological activity of the studied object, we used some well-known methods of analysis [7]:

- Acute toxicity was determined on white mice and rats according to the guidelines of the Pharmacological Committee [8]. Determination of acute toxicity was conducted according to the Kerber's method with the determination of LD50 [7].
- Diuretic activity was determined in white mice by the method of Berkhin [9].
- Anti-inflammatory activity was determined in albino rats. Determination of anti-inflammatory activity of multicomponent herbal medicine and the control drug was limited to the assessment of their impact on the exudative phase of inflammation by Strel'nikov [10], on the proliferation phase – by Trinus [11] and the process of alteration – by Oyvin [12].
- Antibacterial activity *in vitro* was determined by serial dilutions on meat-peptone broth. Gram-positive and Gram-negative strains of bacteria were used as test organisms [7,13].
- Antioxidant activity was determined in albino rats. Serum MDA concentration was determined by the method of Temirbulatov and Seleznev [14].
- Spasmolytic activity was determined on isolated segment of small intestine of white rats [15].

## Results and Discussion

During screening studies intended to select individual components of the herbal medicines, the main emphasis was made on comprehensive study of their pharmacological effects and assessing the contribution of each type of herbal raw materials in the formation of a stable comprehensive pharmacotherapeutic action of the herbal medicine in general.

*Diuretic* action is aimed at the increasing of urine volume and the frequency of urination. The urine is removed with excess of salts, products of metabolism, which is important in case of violation of the colloidal state and often leads to the development of urolithiasis. Diuretic effect is indicated in case of small peripheral edema, hypertension, after endoscopic interventions, and lithokinetic therapy of small stones of pyelocaliceal system and ureters [16]. Plant diuretics are called water diuretics since they excrete only water from the organism. Herbal diuretics stimulate the glomerular filtration rate as well as the formation of primary urine due to an increase in the renal blood flow and/or acceleration of osmotic processes. Water diuretics have a number of advantages over saluretics that implement their diuretic effect through significant violations of water-salt metabolism, especially in the course administration. In this regard, water diuretics may find wide application in the treatment of chronic diseases such as urolithiasis, which requires prolonged use of diuretic drugs [17].

*Antioxidant activity* improves antioxidant status of renal tissue, cell membrane integrity, and preventing relapse. The impact of oxalate crystals and/or calcium oxalate on renal epithelial cells leads to the formation of reactive oxygen species (ROS), oxidative stress (OS), the subsequent damage, and inflammation. Damage and inflammation of renal epithelial cells plays an important role in the stone formation. Excessive ROS production and decreased cellular antioxidant capacity

due to decreased expression of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) and antioxidants lead to the OS. OS is accompanied by activation of lipid peroxidation of cell membranes and consequent damage and inflammation. Violation of the integrity of the membrane leads to the subsequent facilitation of the retention of calcium oxalate crystals and promotes the growth of urinary tract stones. It was experimentally proved that the detection of malondialdehyde (MDA) in the urine is an indicator of ROS in kidneys of patients with calcium oxalate stones. MDA excreted by the kidneys is considered as a marker of renal epithelium damage due to OS. According to the latest research data, the treatment by natural antioxidants reduced renal tissue damage caused by calcium oxalate crystals [18].

*Antimicrobial activity* is aimed at combating infection complicating the course of urolithiasis. Urinary infection accompanying urolithiasis is the most frequent "concomitant" manifestation or complication. In some cases, it precedes urinary stone formation and causes changes in the kidney and/or urinary tract in the form of circulatory disorders, lymphatic outflow obstruction affects urodynamics or makes certain "lithogenic" changes of the urine, especially in the presence of Gram-negative microorganisms. In other cases uroinfection joins secondary to the existing urolithiasis of noninfectious origin. The leading position (85%) in urolithiasis is taken by Gram-negative microorganisms, up to 10% – Gram-positive microorganisms, and up to 15% – by microbial associations. Furthermore, the inflammatory process in the urinary tract may be caused by fungi and viruses [4].

*Anti-inflammatory activity* is aimed at the direct change in tissue microcirculation, reduction of capillary permeability, and inhibition of the enzymes involved in the formation of inflammatory mediators, and prostaglandins biosynthesis and hyaluronidase, as well as slowing the synthesis of ATP, which significantly reduces energy-supply of inflammatory processes [19].

*Spasmolytic effect* is aimed at eliminating pain syndrome caused by the spastic reduction of the ureters, bladder, and urethra resulting in irritation by the calculi [16]. This effect can be used in case of lithokinetic therapy, crystalluria, after removal of drainage systems (stents, nephrostomy), and chronic urinary stones excretion. Due to spasmolytic effect on the muscles of the gallbladder and bile ducts, the bile flow is facilitated. Choleric effect complements the effectiveness of urolithic therapy due to elimination of the lithogenic substances with bile [4].

*Urolithic activity* is aimed at the dissolution of urinary stones [20].

*Immunomodulatory activity* is able to provide a stimulating effect on the main elements of cellular and humoral immunity. When giving herbal medicine to patients with urolithiasis, it is essential to improve the body's resistance [16].

The totality of the pharmacological effects of the drug determines its comprehensive urolithic activity – prevention of crystal formation and growth of crystals in the urinary tract.

## Conclusion

The initial composition of the comprehensive herbal medicine was selected and proposed taking into account the data on the pharmacological effects of each component on the body. The preliminary pharmacological test data have also shown the effectiveness and the prospects of the proposed multicomponent herbal medicine for the further study.

The list of pharmacological activities of medicinal plants being the component of herbal medicines:

Medicinal plants	Types of the research	Pharmacological activities
<i>Artemisia vulgaris</i> (L.)	<i>In vitro</i>	Antioxidant [21,22]
	<i>In vivo</i> animals	Anti-inflammatory [23,24]
	<i>In vitro</i>	
	<i>In vivo</i> animals	Analgesic [23]
	<i>In vivo</i> animals	Spasmolytic [15]
<i>Anethum graveolens</i> (L.)	<i>In vivo</i> animals	Antioxidant [25,26]
	<i>In vitro</i>	
	<i>In vivo</i> animals	Anti-inflammatory [27]
	<i>In vivo</i> animals	Spasmolytic [28]
	<i>In vitro</i>	Antimicrobial [29]
	<i>In vivo</i> animals	Diuretic [30]
<i>Equisetum arvense</i> (L.)	<i>In vivo</i> animals	Adaptogenic [26]
	<i>In vitro</i>	Antimicrobial [31,32]
	<i>In vivo</i> animals	Diuretic [33]
	<i>In vitro</i>	Anti-inflammatory [34,35]
	<i>In vivo</i> animals	
	<i>In vitro</i>	Antioxidant [32]
<i>Vaccinium vitis-idaea</i> (L.)	<i>In vitro</i>	Urolithic [20]
	<i>In vivo</i> animals	Antioxidant [36]
	<i>In vitro</i>	Anti-inflammatory [24]
	<i>In vitro</i>	Antimicrobial [31]
<i>Arctium lappa</i> (L.)	<i>In vivo</i> animals	Diuretic [33]
	<i>In vitro</i>	Antioxidant [37,38]
	<i>In vivo</i> animals	Preventing precipitation of crystals in kidneys [39]

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