



## FEATURES OF THE PHYTOPHARMACOLOGICAL PREPARATIONS IN THE METAPHYLAXIS OF UROLITHIASIS

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### ABSTRACT

This research describes the pharmacological features of medicinal plants, biologically active components which have a polyvalent effect on the pathogenesis of urolithiasis. The clinical and pharmacological aspects of the therapeutic effect of phytopreparations were studied. A comparative analysis of the pharmacodynamic properties of combined phytopreparations used for the treatment and prevention of urolithiasis is presented.

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### Introduction

Improving the diagnosis of nephrolithiasis, the emergence of modern methods of its treatment has changed the structure of forms of this disease and the direction of therapy in recent years. However, neither modern early diagnosis, nor modern minimally invasive methods of treatment, do not save the patient from a possible re-stone formation in the urinary tract. Against this background, therapy aimed at the independent separation of small nodules and preventing re-stone formation after the urinary tract is freed from the concretion or its fragments – metaphylaxis of urolithiasis (MU) [1-3].

Numerous metabolic disorders in metaphylaxis of urolithiasis require the use of various medications. At the same time, despite the constant expansion of the assortment of synthetic medicines, a significant place in the treatment and prevention of this pathology is occupied by preparations of plant origin.

Throughout the history of mankind, the plant world has been a source of valuable medicinal products [4-6]. By the mid-20s of the twentieth century, 70-80% of all medicines were made from plants. Even today, a third of the drugs are extracted from

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vegetable raw materials. Phytotherapy has developed significantly in recent decades. All specialties use a wide variety of plants and herbal remedies made from them [7, 8].

## Material and Methods

Clinical and pharmacological aspects of medicinal action of phytopreparations [9, 10]:

1. Biologically active components that are part of herbal preparations belong to the most diverse chemical classes of the organic and inorganic world. Plants synthesize various nitrogen-free substances (starch, sugars, glycosides, alcohols, flavonoids, aldehydes, ketones, fats, esters, essential oils, cellulose, organic acids, etc.) and nitrogen-containing substances (alkaloids, proteins, nucleic acids, enzymes, vitamins, hormones, etc.). The components are similar or even identical in chemical structure to the physiologically active substances of the human body. Therefore, preparations of plant origin are more physiologically involved in the biochemical processes of the human body than chemical, which is sensitive to the body synthetic drugs.
2. Physiologically active substances of phytopreparations show versatile pharmacological activity, contributing to the effective treatment of many diseases without side effects on the body.
3. Phytopreparations are combined with other drugs to enhance the therapeutic effect.
4. Phytopreparations can be used with synthetic drugs to reduce the side effects of the latter.
5. Phytopreparations are less likely to cause complications especially allergic reactions in contrast to synthetic drugs. Therefore, they can be prescribed for long-term use.
6. Having established the chemical structure of physiologically active substances from plants and studied their pharmacological properties, scientists have the opportunity to synthesize a drug. This allows them to obtain such compounds in large quantities.

The need for drugs with nephroprotective activity is especially urgent today. In most cases, a combination of several synthetic drugs is used to treat diseases of the urinary system. The effectiveness of such therapy is undeniable, but with an increase in the number of drugs taken simultaneously, their side effects can also be added. Among synthetic drugs, there is not a single drug that restores urodynamics without creating a metabolic load on parenchymal organs particularly the liver.

The article analyzes the composition and pharmacological action of common in Russia and Ukraine phytopreparations recommended for the treatment of urolithiasis. The following brands of drugs were studied: Fitolit, Phytolysin, Flavia, Canephron, Trinitron – Health, Uroholum, Urolesan, Marelin, Cystone

## Results

An analysis of the literature allowed us to establish that herbal medicines have a diverse complex effect on the course of the pathological process in the kidneys which are undoubted advantages. It has a direct effect on the process of stone formation, stabilization of the ionic strength of urine and inhibitors of stone formation, acceleration of the departure of stones, their fragments and sand after successful destruction by remote lithotripsy, the possibility of long-term use without pronounced side effects [11]. Their effectiveness is confirmed both by time and by using scientifically based methods. Replenishment of the range of medicines that would contain high - quality biological compounds of plant origin is an urgent problem because the demand for them is rapidly growing. For the treatment and metaphylaxis of MU on the pharmaceutical market of Russian Federation, there are combined herbal medicinal products with biologically active substances in their composition. They have antispasmodic, antiseptic, anti-inflammatory, diuretic effects, and promote the elimination of stones and their dissolution (Table 1) [12-14].

**Table 1. Comparative characteristics of combined herbal remedies for treatment and prevention of urolithiasis**

Medicinal product	The drug	Effect on urine pH	Pharmacodynamic features
Fitolit	knot grass ( <i>Polygonum aviculare</i> ) amber ( <i>Hypericum perforatum</i> ) bottlebrush ( <i>Equisetum arvense</i> L)	alkalization	antispasmodic diuretic anti-inflammatory analgesic antiseptic antimicrobial
Phytolysin	parsley ( <i>Petroselinum crispum</i> ) Agropyron repens bottlebrush ( <i>Equisetum arvense</i> L) drooping birch ( <i>Betula pendula</i> ) knot grass ( <i>Polygonum aviculare</i> ) lovage ( <i>Levisticum officinale</i> L.) bulb onion ( <i>Allium cepa</i> ) trigonella ( <i>Trigonella</i> ) European goldenrod ( <i>Solidago virgaurea</i> ) essential oils	has no effect	antispasmodic, diuretic , anti-inflammatory analgesic litholytic bacteriostatic

Flavia	toothpick ammi ( <i>Ammi visnaga</i> ) nettle ( <i>Urtica L.</i> ) wild camomile ( <i>Matricaria chamomilla</i> )	optimization	antispasmodic anti-inflammatory diuretic antimicrobial choleric detoxifying sedative
Canephron	bloodwort ( <i>Centaurium erythraea</i> ) lovage ( <i>Levisticum officinale L.</i> ) rosemary ( <i>Rosmarinus</i> )	leaching	antispasmodic vasodilating diuretic anti-inflammatory antimicrobial litolytic nephroprotective antioxidant
Trinitron - Health	bloodwort ( <i>Centaurium erythraea</i> ) lovage ( <i>Levisticum officinale L.</i> ) rosemary ( <i>Rosmarinus</i> )	alkalization	antispasmodic vasodilatation diuretic anti-inflammatory anti-microbial litholytic nephroprotective antioxidant
Uroholium	wild carrot ( <i>Daucus carota</i> ) knot grass ( <i>Polygonum aviculare</i> ) Indian kidney tea ( <i>Orthosiphon aristatus</i> ) corn silk black elder ( <i>Sambucus nigra</i> ) wild hop ( <i>Humulus lupulus</i> ) amber ( <i>Hypericum perforatum</i> ) knot grass ( <i>Polygonum aviculare</i> ) peppermint ( <i>Mentha piperita</i> ) amber ( <i>Hypericum perforatum</i> )	has no effect	spasmolytic diuretic anti-inflammatory antiseptic antimicrobial hypoazotemic choleric
Urolesan	wild carrots ( <i>Daucus carota</i> ) common hops ( <i>Humulus lupulus</i> ) origanum ( <i>Origanum vulgare</i> )	acidification	antispasmodic diuretic anti-inflammatory antibacterial choleric
Marelin	European madder ( <i>Rubia tinctorum</i> ) bottlebrush ( <i>Equisetum arvense L</i> ) European goldenrod ( <i>Solidago virgaurea</i> )	acidification	antispasmodic diuretic anti-inflammatory analgesic litolytic
Cystone	didymocarpus stem saxifraga ligulata Indian madder ( <i>Rubia cordifolia</i> ) chaff-flower ( <i>Achyranthes</i> ) filmy rash goldendrop ( <i>Onosma</i> ) ironweed ( <i>Vernonia</i> )	has no effect	diuretic antispasmodic antiseptic antimicrobial anti-inflammatory litolytic

## Discussion

In General, combined herbal preparations for the treatment and metaphylaxis of MU have a positive effect on certain links in the pathogenesis of stone formation which contributes to the departure of concretions and reduce of the inflammatory process in the kidneys [15-18].

Among them, special attention should be paid to preparations containing polyphenols (flavonoids, anthocyanins, phenolcarboxylic acids, coffee acid metabolites - rosemary and lito-spermic acids, tannins, coumarins, etc.). These compounds are widely distributed in the plant world, well-studied in chemical and pharmacological terms, but despite this, intensive research continues to create new generations of medicines based on them. Along with previously known and widely used drugs for the treatment of urolithiasis-avisan, madder dye, cystone, phytolysin, urolesan, cystenal in recent years, new ones have appeared, the effectiveness in the treatment and prevention of repeated stone formation has been confirmed by the results of clinical studies [19, 20].

One of the combined phytopreparations of complex action for the treatment of MU and inflammatory diseases of the urinary tract is Canephron N. The composition of the drug is Golden millet, lovage, and rosemary, the active substances of which

(bitterness, phenolcarboxylic acids, essential oils, phthaleines, rosemary acid, flavonoids) cause anti-inflammatory, diuretic, antispasmodic, antimicrobial, vasodilating, nephroprotective, and antioxidant effects. The excretion of organic phenol carboxylic acids, their glucuronide, and sulfated metabolites in the urine leads to a change in the reaction of urine and as a consequence, to an increase in the excretion of uric acid salts. In this case, the effect of the drug is partly due to its diuretic activity. The pH value of urine in slightly alkaline intervals (pH 6.2-6.8) provides a colloidal state of urine which prevents the accumulation of uric acid crystals in the urinary tract, formation and concretions growth. Scientists of the Sechenovs' urological clinic of MMA and the Moscow Academy of fine chemical technology also noted the positive effect of Canephron N on phosphate (stone mass decreases by 63%) and oxalate concretions in the conducted experiment. At the same time, the solubility of oxalate stone increases with an increase in its composition of vedelite (calcium-oxalate-dihydrate) and decreases with an increase in its composition of vevelite (calcium-oxalate-monohydrate) [21, 22].

In the treatment of urolithiasis, phytotherapy with essential oils has long been used. One of the drugs, which is based on a combination composed of terpenes from softwood, is rowatinex. In 2010 in Hungary, based on the Department of Urology, Semmelweis University (Budapest) scientists in a randomized placebo-controlled study of the use of a drug based on a composition of terpenes in MU found that 67.9% of patients had stones removed. In 2009-2010, in an study in the Institute of urology (Moscow) results of the drug rowatinex in patients with MU were examined following their clinical properties of the drug such as lithokinetic effect, spasmolytic effect, and reduced pain from renal colic due to stones of the kidneys and ureters, as well as anti-inflammatory and antimicrobial action. These properties of the drug allow it to be used for the complex treatment of patients with urolithiasis, complicated by chronic pyelonephritis, in patients with renal colic, as well as in patients who have undergone remote lithotripsy of the kidneys and ureters. Rowatinex is registered in Russia as enteric-soluble gelatin capsules as a litholytic, antispasmodic, and diuretic agent [23].

Currently, the search and development of new medicines is one of the most complex scientific research and is practically inseparable from chemistry, biology, physics, and many other related branches of science. Special importance for the creation of a new drug in the joint work of a chemist and pharmacologist after the initial screening of many biologically active substances is given to the selection of the most promising sample from the spectrum of studied compounds. In research on the development of a new drug, adequate further assessment of the chemical stability, safety and pharmacological activity of the selected compound is of particular importance. One of the alternative ways to improve the pharmacological properties of the selected compound is to create a combined preparation, a newly synthesized product with already known biologically active compounds, which requires detailed research on the chemical and pharmacological compatibility of these components. Scientific knowledge obtained as a result of research of new biologically active compounds and complex medicines expand the understanding of the influence of chemical structure on the living organism and stimulates the scientific research for the new and more effective biologically active substances.

Researchers of PJSC SPC "Borschagovskiy KhFZ" (Kiev, Ukraine) have developed a new original combined drug flarosuccin in the form of syrup for the treatment and metaphylaxis of MU, which contains the total plant extract of birch leaves, linden flowers, astragalus herb and a buffer succinate complex [24, 25].

Biologically active substances of medicinal plants included in the preparation of flarosuccin are known and the spectrum of their pharmacological activity is comprehensively studied by scientists. Thus, the chemical composition of birch wart leaves (*Betula verrucosa*) contains flavonoids and polyphenols up to 3%, including quercetin and myricitin glycosides up to 1.2%, up to 4% proanthocyanidins, sterols, up to 0.5% essential oil, carotene [26]. Special attention was paid to the pharmacological properties of birch, which is associated with the presence of a significant amount of damarane triterpenoids in its composition. Such compounds, which are also obtained from the roots and leaves of ginseng (*Panax ginseng*), are characterized by adaptogenic activity [27]. Various preparations and extracts from birch leaves exhibit anti-inflammatory properties in the caragenin and formalin models of inflammation, and tularoan activity in the destruction of the gastric mucosa caused by acute stress and it has choleric and anti-lambliotic effects [28]. With the adrenaline model of experimental hyperglycemia and the aloxan model of diabetes mellitus, the hypoglycemic, antidiabetic activity of decoction of birch leaves was studied, which is due to the ability of the phytopreparation to reduce the insulin resistance of peripheral tissues [29]. The nephroprotective effect of a thick extract from birch leaves has been studied by scientists at the National University of Pharmacy. Studies have proven the positive effect of the extract on kidney function in experimental nephropathy [14]. In the flowers of Linden (*Tilia cordata*), a significant amount of flavonoid compounds, in particular flavones, flavonols and flavonones, tannins, carotene, saponins, ascorbic acid, essential oil, were found. Linden flowers have an enveloping, anti-inflammatory, anti-tonic, diuretic, and hemostatic effect [9, 10].

In nature, there are several species of Astragalus (Danish, Daur, solidarity, cherstantively, serpoplodnogo). In the grass of Astragalus in addition to organic compounds, there are flavonoids (quercetin, kaempferol), polysaccharides (the rifle, basarin), triterpene saponins, alkaloids, vitamins, organic acids, mucilage, starch, salt, organic compounds biome for metal (selenium, iron, phosphorus, calcium, magnesium, sodium, silicon, strontium, manganese, molybdenum, vanadium). Such a unique composition of physiologically active substances of Astragalus exhibits anti-oxidant, antihypertensive, sedative, anti-inflammatory effects and has a regulating effect on the immune system and blood clotting processes [29-31].

Unlike other types of Astragalus, the sickle-shaped Astragalus (*Astragalus falcatus*) contains the main flavonoid component of robinson to 85%, 3-O- $\beta$ -D- has galactopyranosyl-(6 $\rightarrow$ 1)-O- $\alpha$ -L-rhamnopyranoside kaempferol, which has shown the diuretic and hypo-azotemic effect and is intended for the treatment of chronic renal failure accuracy [32, 33].

The ability of plant flavonoids to influence the biochemical processes underlying the regulation of vascular permeability and resistance of the vascular wall allows them to be used for the treatment and prevention of various inflammatory, allergic and hemorrhagic lesions. The positive effect of polyphenols on the vascular wall is also due to their ability to eliminate lymphovenous stasis and improve the functional state of the lymph nodes. At the same time, plastic and reparative processes are improved, as evidenced by the data on the increase in the number of free and attached ribosomes in the cells of the lymph nodes, as well as the restoration of mitochondria. Stimulation of lymphatic drainage occurs due to an increase in the level of norepinephrine. In addition to stabilizing norepinephrine in tissues, flavonoids increase the sensitivity of norepinephrine receptors, which improves the hemodynamics of venous and lymphatic vessels. The properties of these adrenal and dopamine receptors explain the cardiogenic effect of plants, as well as the ability to improve blood circulation in the kidneys and abdominal organs [34].

The anti-inflammatory effect of plant phenolic compounds is associated with inhibition of exudative inflammatory processes, which is explained by the ability of flavonoids to limit the tissue effects of cytokinins and proinflammatory prostaglandins.

The anti-inflammatory effect is inherent in the various groups of phenols that stimulate the synthesis and release adrenal cortex hormones, increase resistance, and decrease the permeability of histohematic barriers [27, 28].

The natural components of medicinal plants are easily digested when they enter the body in the form of biologically available compounds, they allow to restore impaired organ functions, improve the state of the immune system by normalizing the functions of the lymph nodes and intestines, as well as the functional state of the liver and kidneys, and eliminate pathological disorders due to the action of biologically active substances. Natural compounds are more active than synthetically obtained preparations since they contain a naturally created healing biological complex in which one component corrects and complements the effect of the other [34-36].

## Conclusion

Thus, the new original domestic drug flarosuccin urolitholytic action, due to the original composition of the dosage form and the complex effect on the pathogenesis of urolithiasis, is a promising tool in terms of its conservative treatment, which necessitates its comprehensive toxicological and pharmacological research for use for this purpose.

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