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Medicinal plant raw materials and phytopreparations in the therapy of chronic infectious and inflammatory diseases of the kidneys and urinary tract

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The aim. To analyze and summarize modern scientific data on the use of medicinal plant raw materials as a source of biologically active substances and herbal medicines (phytopreparations) in the therapy of chronic infectious and inflammatory diseases of the kidneys and urinary tract.

Materials and methods. The search for scientific data was carried out in international scientific electronic databases Google Scholar, Science Direct, PubMed, elibrary.ru and cyberleninka.ru. Publications for the period from 2010 to 2025 were studied. This review includes 446 sources of scientific information.

Results. Chronic infectious and inflammatory diseases of the kidneys and urinary tract (CIDKUT) are becoming an increasingly important problem and require special attention. Modern medicine and pharmacy have a variety of official medicinal plant raw materials (MPRMs) at their disposal, which are a source of biologically active substances (BASs) and phytopreparations for the treatment and prevention of kidney diseases. In addition, new promising plant objects are being actively studied. The presented results of preclinical phytochemical and pharmacological, as well as clinical studies, reliably indicate the presence of a significant influence of the identified BASs, in particular, components of essential oils and phenolic compounds, on the main links of pathogenesis and on the development of diuretic, anti-inflammatory, uroseptic, litholytic and antilithogenic effects. All of the above stimulates the development of new combined phytopreparations, for which various approaches have been noted in their standardization, the choice of methods for analyzing leading and related BAS.

Conclusion. The review examines and analyzes the current state of research in the field of using MPRM as a source of BASs of phytopreparations in the treatment of CIDKUT. It is shown that key classes of BAS of terpenoid and phenolic nature have anti-inflammatory, antibacterial, diuretic, litholytic and antilithogenic effects. A number of promising non-pharmacopoeial types of MPRMs have been identified: true bedstraw herb, annual sunflower roots, rosehip roots, angelica rhizomes and roots, cranberry fruits, which have extensive empirical experience in folk medicine, as well as the results of laboratory chemical and preclinical studies.

Keywords: chronic infectious and inflammatory diseases of the kidneys and urinary tract; biologically active substances; components of essential oils; phenolic compounds; single-component phytopreparations; combined phytopreparations; phytotherapy; diuretic activity; antibacterial activity; anti-inflammatory activity; litholytic activity; antilithogenic activity; promising sources of phytopreparations

Abbreviations: CIDKUT — chronic infectious and inflammatory diseases of the kidneys and urinary tract; PMs — pathogenic microorganisms; MPRMs — medicinal plant raw materials; BASs — biologically active substances; MP — medicinal product.

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REVIEW

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Лекарственное растительное сырье и фитопрепараты в терапии хронических инфекционно-воспалительных заболеваний почек и мочевыводящих путей

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Цель. Проанализировать и обобщить современные научные данные о применении лекарственного растительного сырья как источника биологически активных веществ и лекарственных средств растительного происхождения (фитопрепаратов) в терапии хронических инфекционно-воспалительных заболеваний почек и мочевыводящих путей.

Материалы и методы. Поиск научных данных осуществляли в международных электронных базах Google Scholar, Science Direct, PubMed, elibrary.ru и cyberleninka.ru. Основной массив научных публикаций охватывал оригинальные статьи за период с 2010 по 2025 гг. В настоящий обзор включено 446 источников научной информации.

Результаты. Хронические инфекционно-воспалительные заболевания почек и мочевыводящих путей (ХИВЗПМП) становятся все более актуальной проблемой и требуют особого внимания. В арсенале современной медицины и фармации имеется разнообразное официнальное лекарственное растительное сырье (ЛРС), являющееся источником биологически активных веществ (БАВ) и фитопрепаратов для терапии и профилактики заболеваний почек. Кроме того, активно изучаются новые перспективные растительные объекты. Представленные результаты доклинических фитохимических и фармакологических, а также клинических исследований достоверно указывают на наличие существенного влияния выявленных БАВ, в частности, компонентов эфирных масел и фенольных соединений на основные звенья патогенеза и на развитие диуретического, противовоспалительного, уросептического, литолитического и антилитогенного эффектов. Все указанное стимулирует разработку новых комбинированных фитопрепаратов, для которых отмечены различные подходы в их стандартизации, выборе методов анализа ведущих и сопутствующих БАВ.

Заключение. В обзоре рассмотрено и проанализировано современное состояние исследований в области применения ЛРС как источника БАВ фитопрепаратов в терапии ХИВЗПМП. Показано, что ключевые классы БАВ терпеноидной и фенольной природы обладают противовоспалительным, антибактериальным, диуретическим, литолитическим и антилитогенным эффектами. Выделен ряд перспективных нефармакопейных видов ЛРС: подмаренника настоящего трава, подсолнечника однолетнего корни, шиповника корни, дудника лекарственного корневища и корни, клюквы плоды, имеющие обширный эмпирический опыт применения в народной медицине, а также результаты лабораторных химических и доклинических исследований.

Ключевые слова: хронические инфекционно-воспалительные заболевания почек и мочевыводящих путей, биологически активные вещества, компоненты эфирных масел, фенольные соединения, однокомпонентные фитопрепараты, комбинированные фитопрепараты, фитотерапия, диуретическая активность, антибактериальная активность, противовоспалительная активность, литолитическая активность, антилитогенная активность, перспективные источники фитопрепаратов

Список сокращений: ХИВЗПМП — хронические инфекционно-воспалительные заболевания почек и мочевыводящих путей; ПМ — патогенные микроорганизмы; ЛРС — лекарственное растительное сырье; БАВ — биологически активные вещества; ЛП — лекарственный препарат.

INTRODUCTION

The widespread prevalence of chronic infectious and inflammatory diseases of the kidneys and urinary tract (CIDKUT) with a tendency towards exacerbation presents a significant medical and social problem [1, 2]. The growing resistance of pathogenic microflora to actively and sometimes incorrectly used antibacterial drugs, the disability of the population, and the associated annual state expenditures on healthcare significantly contribute to the urgency of this issue [3–5].

ОБЗОР
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Globally, the number of cases of chronic kidney diseases associated with infectious and inflammatory processes has exceeded 850 million [6], and urinary tract diseases — 404 million [7]. In the Russian Federation, 16,403,234 cases of CIDKUT were registered in 2023, which is 778,487 more than in 2022 [8]. However, the majority of CIDKUT cases remain "in the shadows" and are unaccounted for, due to patients not seeking medical attention; only 1/3 of the total number of people with CIDKUT are registered. This is mainly due to the age of patients, financial situation, use of self-treatment methods, and ignoring symptoms. The progression of pathological conditions and the lack of competent treatment can lead to severe consequences, such as renal failure (acute or chronic) with irreversible structural and functional changes in organs, leading to subsequent disability and significant financial costs for rehabilitation [9]. It has been established that a number of pathogenic microorganisms (PMs), including *Escherichia coli*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*, can migrate into the seminal tubules of men, causing a decrease in reproductive function. The course of the infectious process can lead to prostatitis and the development of erectile dysfunction. A similar mechanism operates in women — bacterial infection, penetrating the ovaries, disrupts the process of egg formation [10]. The problem under consideration negatively affects the demographic situation in the country [11].

The issue of CIDKUT causes concern within the medical community. The diseases are of particular significance due to the tendency of pathologies to recur and become chronic, and their treatment is associated with difficulties caused by the formation of resistant pathogenic microflora [12, 13]. Women more frequent in this group of diseases, experiencing at least one episode of CIDKUT in their lifetime [14, 15]. Furthermore, the prevalence of chronic pyelonephritis among women of various age categories has been recorded: 17 to 20 years — 12 %, 21 to 30 years — 34 %, 31 to 40 years — 12 %, 41 to 50 years — 24.0 %, and over 50 years — 18.0 % [16].

In patients with comorbidities, such as diabetes mellitus, due to the development of general and localized immune dysfunction, the ability of microorganisms to adhere to the urothelium surface increases. The use of selective sodium-glucose cotransporter inhibitors for the treatment of type 2 diabetes mellitus stimulates glucose excretion in the urine, making it a substrate for the proliferation of pathogenic flora [17, 18]. Conditions that contribute to the development of these diseases also include active sexual life, poor hygiene or lack thereof, hospital-acquired infections, as well as past or persistent infections, dehydration, unbalanced nutrition, and other lifestyle aspects [19, 20].

The main approaches in the treatment of CIDKUT include antibiotic therapy, particularly with drugs from the fluoroquinolone (ciprofloxacin), glycopeptide (vancomycin), penicillin (ampicillin), phosphonic acid derivative (fosfomycin), and nitrofurane (furagin, furadonin) groups. Phytotherapy also holds a special place in the comprehensive treatment of urological diseases [21, 22]. The therapeutic potential of phytotherapy lies in its ability to simultaneously achieve antibacterial, anti-inflammatory, diuretic, and antispasmodic effects to varying degrees, as well as to minimize side effects observed with classical antibacterial therapy, such as disruption of intestinal microflora, fungal infections, and toxic organ damage [23]. The use of medicinal plant raw materials (MPRMs) as a source of biologically active substances (BASs), as well as single-component and combined phytopreparations, significantly expands treatment possibilities, especially in cases requiring long-term treatment of chronic diseases where the use of chemotherapeutic agents has limitations [24]. Issues concerning the use of plant-based preparations are widely discussed by various research teams [25–28], whose conclusions allow phytotherapy to be positioned as a valuable addition in the acute phase of infectious and inflammatory processes or even as a sole alternative to synthetic drugs for primary and secondary prevention, and sometimes for the treatment of chronic urological diseases [29].

This review examines research results reflected in scientific literature concerning the application of MPRMs as a source of BASs and botanicals used in CIDKUT. In analyzing the materials, we have touched upon the experience of using medicinal plants in folk and official drugs, the phytochemical composition of MPRMs and botanicals, and considered preclinical and clinical studies of preparations, among other aspects.

THE AIM. To analyze and summarize current scientific data on the use of medicinal plant raw materials as a source of biologically active substances and plant-derived medicinal products (phytopreparations) in the therapy of chronic infectious and inflammatory diseases of the kidneys and urinary tract.

MATERIALS AND METHODS

For the analysis of research status in the field of CIDKUT therapy, scientific information was searched

in international electronic databases: Google Scholar, Science Direct, PubMed, elibrary.ru, and cyberleninka.ru. The main body of scientific publications pertained to the period from 2010 to 2025 and primarily included original articles. Where appropriate, scientific materials from earlier periods were used.

Search queries were formulated using keywords and phrases in Russian and English and included: “acute and chronic infectious diseases of the kidneys and urinary tract infections”; “official plant sources of medicinal products”; “phytochemical studies of plant sources”; “phytotherapy of infectious diseases of the kidneys and urinary tract”; “diuretic activity of biologically active substances”; “antibacterial activity of biologically active substances”; “pharmacological studies of biologically active substances”; “essential oils”; “phenolic compounds”; “single-component and combined phytopreparations”; “promising sources of phytopreparations for the treatment of infectious diseases of the kidney and urinary system”.

As a result of the initial search, over 2000 publications were identified. During the screening stage, irrelevant publications (based on titles and abstracts), works duplicating the main content of publications, and those not corresponding to the investigated nosology were excluded. Consequently, a body of sources comprising 446 scientific information sources was formed.

RESULTS AND DISCUSSION

In the scientific literature dedicated to CIDKUT, a significant place is occupied by issues of etiology, pathogenesis, and mechanisms of pharmacotherapy, particularly phytotherapy using plant BASs.

Chronic infectious and inflammatory diseases of the kidneys and urinary tract

CIDKUT are often associated with an ascending route of pathogen entry, usually due to the proliferation of pathogenic and opportunistic microorganisms [30] in the lower urinary tract (urethra, bladder) with subsequent spread of infection to the upper tract (ureters, kidneys) [31].According to the progression of CIDKUT, several types of disease course are distinguished:

1. Uncomplicated infection — occurs in patients without concomitant urinary tract diseases, which responds to therapy with the main group of antibiotics;
2. Complicated infection — occurs in patients with concomitant urinary tract pathologies (urolithiasis, bladder reflux);
3. Unresolved infection — a state opposite to uncomplicated infection, which does not respond to antibiotic treatment;
4. Recurrent infection (relapse) — a stage of urinary tract infection characterized by persistent bacterial or fungal infection. At this stage, the person is reinfected with the same uropathogen after a certain period, for example, two weeks after treatment of an unresolved CIDKUT [32].

Among patient visits to a urologist, 60 % of all cases are due to cystitis, about 20% are related to pyelonephritis [33–35], and 20% are due to urolithiasis [35–37]. These pathologies develop due to bacterial and/or fungal contamination of the urinary system by the following pathogens: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis*, *Staphylococcus saprophyticus*, *Staphylococcus aureus* [19, 38, 39], *Pseudomonas aeruginosa* [40, 41], *Candida albicans* [42], *Citrobacter* spp., *Serratia* spp. [43]. In most cases, *Escherichia coli* (33.8 %), *Klebsiella pneumoniae* (11.8 %), *Enterococcus faecalis* (10.3 %), and *Pseudomonas aeruginosa* (12.7 %) are identified in urine cultures [44–46]. The bacterial uropathogens causing diseases are mainly Gram-negative, which, during adhesion and further colonization of the urinary tract, penetrate the bladder and kidneys, leading to acute manifestations of diseases with subsequent relapses and chronification of infectious and inflammatory processes.

Many PMs become resistant to most known antibiotic classes [47]. Pathogens, in the process of their life activity, produce specific enzymes — β-lactamases or carbapenemases, which cause resistance to certain groups of antibacterial drugs — penicillins, cephalosporins, and broad-spectrum carbapenems. Resistance to aminoglycosides and sulfonamides is also growing [48–50]. Currently, fluoroquinolones are the only class of antibiotics with a relatively high sensitivity index towards bacteria of the *Enterobacteriaceae* family. In particular, *Escherichia coli* shows resistance to amoxicillin at 38%, trimethoprim and sulfamethoxazole at 18.1 %; resistance to ciprofloxacin, cefotaxime, nitrofurantoin, and fosfomycin at 1.8 %. *Enterococcus faecalis* demonstrates the highest level of resistance to most antibacterial drugs used in urology [51, 52].

A brief characteristic of some CIDKUT is presented in Table 1; urolithiasis is included due to its association with infectious and inflammatory processes.

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Table 1 — Brief characteristic of kidney and urinary tract diseases

Disease characteristic	Diseases		
	Cystitis	Pyelonephritis	Urolithiasis
Definition	Infectious and inflammatory disease of the bladder mucosa [53, 54].	Infectious and inflammatory disease of the kidney parenchyma and pyelocaliceal system [67, 68].	Disease associated with the formation of calculi in the organs of the urinary system [79–80].
Etiology	PMs: *Proteus* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus* spp., *Enterobacter* spp., *Enterococcus faecalis*, *Pseudomonas aeruginosa* [55–57].		1. Metabolic disorders; 2. Increased concentration of lithogenic substances; 3. Fluctuations in urine pH; 4. CIDKUT; 5. Anatomical changes in the urinary system [37, 81, 82].
Pathogenesis	1. Colonization by uropathogens: distal urethra, periurethral and vaginal areas; 2. Adhesion of PMs to the urothelium: penetration into the bladder, proliferation, biofilm formation; 3. Development of acute inflammatory process: with the formation of persistent infection [58, 59].	1. Colonization by uropathogens: distal urethra, periurethral and vaginal areas [69]; 2. Adhesion of PMs to the urothelium: penetration into the bladder, migration to the upper urinary tract; 3. Penetration of PMs into the muscular layer: impaired urination → development of pyelovenous reflux; 4. Penetration of PMs into the kidney parenchyma and pyelocaliceal system: development of acute inflammatory process.	**No single pathological pattern for the development of urolithiasis. Leading hypothesis: Randall's plaque formation [83, 84, 85]:** 1. Process initiation: formation of primary urolith; 2. Urolith formation: deposition of calcium salts in the lumen of collecting ducts; 3. Ulcer formation: destruction of the urothelial lining; 4. Plaque formation: calcification of the ulcer surface; 5. Crystalloid adsorption: detachment of the urolith → migration to the pyelocaliceal system [86, 87].
Disease course	Acute and chronic (recurrent form) [53, 60].	Acute and chronic (recurrent form) [67, 71]	Chronic with recurrent episodes (renal colic) [88, 89].
Clinical presentation	**Acute cystitis:** 1. Frequent and painful urination (worsening over time); 2. Pyuria; 3. Hematuria; 4. Lower abdominal pain. **Chronic cystitis:** 1. Recurrences; 2. Alkaline urine reaction; 3. Leukocyturia; 4. Hematuria; 5. Bacteriuria [53, 58, 61]; 6. Morphological "triad of chronic cystitis" [62].	**Acute pyelonephritis:** 1. Elevated body temperature (38.0 °C); 2. Lumbar pain; 3. Symptoms of intoxication ("triad of pyelonephritis") [79]. **Chronic pyelonephritis**: 1. Asymptomatic course / general weakness; 2. Frequent urge to urinate; 3. Mild lumbar pain [67, 73–75].	**Main symptoms:** 1. Nausea and vomiting; 2. Pain in the costovertebral angle; 3. Elevated serum levels: nitrogen, urea, creatinine, and C-reactive protein; 4. Urine: pyuria, hematuria, and crystalluria, pH 5.0–6.5 [90, 91].
Risk groups and factors	**Women:** 1. Age: reproductive age — 5 %; menopausal period — 10–15 %; elderly age — 15–20 % [60]; 2. Anatomical feature: proximity of genitourinary organs to the lower gastrointestinal tract; 3. Social factors: poor hygiene, active sexual life [63, 64]; 4. Provoking factors: hypothermia, spicy food, stress [62, 65, 66].	**Women:** 1. Cystitis; 2. Pregnancy; 3. Anatomical feature: proximity of genitourinary organs to the lower gastrointestinal tract [76, 77]. **Men**: 1. Age (from 50 years); 2. Urodynamic disorders: associated with tumorous or hypertrophic processes in the prostate gland [78]. **General:** 1. Obstructive uropathies; 2. Vesicoureteral reflux; 3. Sexual activity [76].	**General:** 1. Age: 20 to 50 years (13 % and 7 %); 2. Unbalanced diet: overly salty food, insufficient water intake, excess animal protein and citrates; diseases associated with stone formation; 3. Metabolic disorders: hyperparathyroidism, nephrocalcinosis; vitamin A and D deficiency; 4. Anatomical features: presence of a single kidney, heredity; 5. Urinary system pathologies: ureteral obstruction, pelvic diverticula and cysts, vesicoureteral reflux [81, 92, 93]

Note: PMs — pathogenic microorganisms; CIDKUT — chronic infectious and inflammatory diseases of the kidneys and urinary tract.

In the context of phytotherapy possibilities, asymptomatic bacteriuria requires more detailed consideration. This is a condition (not considered a disease) in which bacteria are detected in the bladder or kidneys at a concentration of $\geq 10^5$ CFU/mL of urine, with the absence of clinical symptoms [94–96]. Asymptomatic bacteriuria occurs in 2.7 % of women aged 15 to 24 years and increases to 20–50 % in women over 80 years. In men, its prevalence is significantly lower but increases with age from 6 % to 20 %. Asymptomatic bacteriuria is also widespread in long-term care facilities, where its incidence ranges from 25 % to 50 % among patients [97]. Specifically, it is detected in patients with prolonged bladder catheterization (for 4 weeks) [19, 98].

It was previously reported that asymptomatic bacteriuria is a clinically dangerous condition requiring diagnosis and treatment. In the 1950s, it was first diagnosed using urine culture. With the advent of new diagnostic methods, it was found that pregnant women with a high incidence of pyelonephritis often had asymptomatic bacteriuria that was not treated. Further development and refinement of screening methods, as well as long-term patient follow-up, allowed asymptomatic bacteriuria to be reclassified as a condition not requiring treatment. Treatment of asymptomatic bacteriuria with antimicrobial drugs did not reduce the incidence of symptomatic infections. It was also reported that therapy increased the risk of developing pyelonephritis [94, 99].

There is still debate regarding the use of antibiotics for treating asymptomatic bacteriuria. Some studies suggest that antibiotic use and lack of treatment do not affect the development of CIDKUT. Antibiotic therapy only led to the appearance of a significant number of side effects [100]. A study by U. Lindberg et al. found that children with asymptomatic bacteriuria who did not receive antibiotic treatment had significant advantages over children who were treated with antibacterial agents [101]. In a study by L.A. Petty et al. among 2733 hospitalized adult patients diagnosed with asymptomatic bacteriuria, 82.7 % were prescribed antimicrobial drugs. In most cases, therapy did not yield positive results, and in some cases, it could even be harmful, causing side effects. As a result, the duration of hospitalization increased by 37 % without noticeable improvement in clinical indicators [96, 102]. It was also found that 15 % of patients treated for asymptomatic bacteriuria experienced symptomatic CIDKUT recurrences accompanied by the development of acute pyelonephritis [103].

Other studies indicate that pregnant women should be screened for asymptomatic bacteriuria in the first trimester of pregnancy and undergo treatment if positive [97]. Antimicrobial therapy for asymptomatic bacteriuria during pregnancy reduces the risk of pyelonephritis, low birth weight, and premature birth. Some data suggest that the presence of asymptomatic bacteriuria in a person protects the body from developing PM infections [104]. The authors investigated the possibility of preventing CIDKUT recurrences using a vaccine (administered into the urinary tract) with an avirulent strain of *Escherichia coli* 83972. A placebo-controlled study proved that the strain reduces the frequency of CIDKUT recurrences.

Subsequently, programs for the rational use of antibacterial agents were developed, which revealed that antibiotic therapy for asymptomatic bacteriuria is one of the important factors in the development of PMs resistance to antimicrobial drugs [98, 102]. In this regard, the use of antibacterial BASs from medicinal plants can be a promising strategy in the development of medicinal products and their clinical application.

The presented information serves as a fundamental basis for the development of new plant-derived medicinal products (MPs) for the treatment of CIDKUT. The shortcomings of traditional antibiotic therapy have been identified, and the potential for using phytopreparations for preventing disease recurrence and treating specific patient categories is emphasized. Thus, the outlined provisions allow for the integration of scientific knowledge with practical clinical tasks.

Plant sources of medicinal products for the treatment of chronic infectious and inflammatory diseases of the kidneys and urinary tract

Among the wide variety of medicinal plants used in medicine as sources of BASs for treating kidney and urinary tract diseases, MPRMs containing primarily essential oil and phenolic compounds are leading. These BASs possess diuretic, antiseptic, anti-inflammatory [25, 105, 106], litholytic, and antilithogenic effects [107–109], which fully align

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with the etiology and pathogenesis of the diseases presented in Table 1.

Studies have shown that flavonoids and anthocyanins effectively eliminate the key causes of CIDKUT, as they possess anti-inflammatory, antioxidant, and angioprotective properties [110].

Diuretic activity is formed by phenolic compounds and essential oil components. Essential oils have a vasodilatory effect on renal vessels, improving their blood circulation and increasing hydrostatic pressure in the glomerular capillaries. As a result, glomerular filtration increases, which, in turn, increases diuresis [111, 112]. The diuretic effect of phenolic carboxylic acids is due to the "osmotic effect": upon entering the renal tubules, phenolic acid glucuronides create high osmotic pressure, significantly reducing the reabsorption of water and sodium ions. Water excretion occurs without disrupting the ionic balance (potassium-sparing effect) [113, 114]. A diuretic effect can also be observed during the accelerated elimination of xenobiotics, as well as toxins formed in the body during diseases.

The antibacterial properties of essential oil components are due to their ability to perforate and thus damage the lipid envelope of the bacterial cell wall. Terpenes act on the outer membrane, making it permeable, disrupting osmotic pressure, and leading to lysis of the microorganism's cell [115, 116].

The antibacterial activity of phenolic compounds, using catechin as an example, was studied by A. Fathima and J.R. Rao using models to assess activity against *Escherichia coli* and *Bacillus subtilis*. The study showed that catechin increases bacterial membrane permeability and causes oxidative damage to bacterial liposomes [117].

One of the most important properties of natural BASs is anti-adhesive activity, which manifests as disruption of microbial adhesion (attachment to the urothelium surface), preventing biofilm formation, thereby hindering PMs proliferation [118]. For example, A-type proanthocyanidins, due to the presence of an ester bond between C2→O→C7′ atoms in their molecular structure, connecting two flavan-3-ol structural units, are inhibitors of microbial type I and P fimbriae [119].

To enhance anti-adhesive activity, an additional component, D-mannose, is included in phytopreparations. It is a monosaccharide, an epimer of glucose, and participates in biochemical processes (e.g., protein N-glycosylation). Excess D-mannose is excreted unchanged by the kidneys. The anti-adhesive effect of D-mannose is due to its competitive interaction with mannose-sensitive fimbriae of pathogenic microorganisms, which prevents the adhesion of bacteria with mannosylated proteins on the surface of the human urinary tract [120, 121]. Clinical studies confirm the effectiveness of this approach. A group of women (n = 103) with acute recurrent CIDKUT took 2 g of D-mannose for 6 months. Relapses occurred in only 14.6% of women ($p < 0.0001$) [122].

The antilithogenic effect of phenolic compounds has been demonstrated in several studies. In an *in vivo* experiment, catechin contributed to a reduction in the number of crystals formed by a mixture of melamine and cyanuric acid in the kidneys and prevented nephrotoxicity [123]. Rutin and curcumin in the "ethylene glycol model" of urolithiasis normalize calcium and oxalate levels [124]. In a group of rats treated with quercetin and hyperoside (quercetin-3-O-galactoside), the amount of calcium oxalate crystalline deposits significantly decreased [125]. When hydroxycinnamic acids, caffeic and rosmarinic acids, were used in experiments, it was found that caffeic acid regulates biochemical parameters and reduces calcium oxalate deposition in the kidneys [126]. Rosmarinic and caffeic acids at concentrations from 0.03 to 0.3 mg/mL reduced the amount of monohydrate and dihydrate forms of calcium oxalate crystals formed in urine [127].

In many countries, medicinal products (MPs) whose efficacy in treating kidney and urinary system diseases has been confirmed by numerous scientific studies are widely used. Sources of MPRMs used for creating such phytopreparations include common bearberry (*Vaccinium vitis-idaea* L.) of the *Ericaceae* family, common uva-ursi (*Arctostaphylos uva-ursi* L.) of the *Ericaceae* family, silver birch (*Betula pendula* Roth.) of the *Betulaceae* family, downy birch (*Betula pubescens* Ehrh.) of the *Betulaceae* family, knotgrass (*Polygonum aviculare* L.) of the *Polygonaceae* family, Siberian oregano (*Orthosiphon stamineus* Benth.) of the *Lamiaceae* family, common horsetail (*Equisetum arvense* L.) of the *Equisetaceae* family, tropical wormwood (*Aerva lanata* (L.) Juss.)

of the *Amaranthaceae* family [27, 128, 129], Canada goldenrod (*Solidago canadensis* L.) of the *Asteraceae* family [130], garden lovage (*Levisticum officinale* Koch.) of the *Apiaceae* family [131], rosemary (*Rosmarinus officinalis* L.) of the *Lamiaceae* family [132, 133], common juniper (*Juniperus communis* L.) of the *Cupressaceae* family [134–136], blue cornflower (*Centaurea cyanus* L.), Georgian madder (*Rubia iberica* (Fish. ex DC). C. Koch) of the *Asteraceae* family, wild strawberry (*Fragaria vesca* L.) of the *Rosaceae* family, dyers' madder (*Rubia tinctorum* L.) of the *Rubiaceae* family, bicolor lespedeza (*Lespedeza bicolor* Turcz.) of the *Fabaceae*[1] family, and others. Let's consider some of them from the perspective of their contained BASs and corresponding spectrum of activity.

Common bearberry (*Vaccinium vitis-idaea* L.)

Common bearberry (*Vaccinium vitis-idaea* L.) is a perennial evergreen shrub of the genus *Vaccinium* L. of the *Ericaceae* Juss. family [137].

Vaccinium vitis-idaea is a rich source of phenolic compounds: phenol glycosides, flavonoids, proanthocyanidins, and phenylpropanoids [138]. The leading compounds in the leaves of common bearberry *(Vaccinii vitis-idaeae folia)* are simple phenols (phenol glycosides): hydroquinone in the form of arbutin [129, 139]. The authors analyzed the phenolic compounds of 10 different cultivated varieties of *V. vitis-idaea*. Arbutin was the leading compound in all varieties of *V. vitis-idaea*, with a content ranging from 36.059±1472.12 μg/g to 56.968 ± 2325.73 μg/g dry raw material (41–78 % of the total phenolic compounds) [140].

Ethanol extract of bearberry leaves exhibits anti-adhesive and antibacterial activity, established by agar diffusion and serial dilution methods on *Staphylococcus aureus* strains. Destruction of the formed microbial biofilm was noted; the leaf extract solution at a concentration of 0.01% inhibited biofilm formation in 69.9% of cases and promoted biofilm destruction in 62.5 % of cases [141]. A study of the antibacterial activity of a 60% aqueous-alcoholic extract showed significant efficacy against *Escherichia coli* but minimal antimicrobial activity against *Pseudomonas aeruginosa* [142]. When investigating the antibacterial and antifungal activity of an aqueous solution of dry extract on cultures of PMs *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus*, and *Candida albicans*, inhibition of bacterial growth zones of 12 mm, 10 mm, and 24 mm, respectively, was recorded. *Candida albicans* was resistant to the aqueous extract solution [143].

Common bearberry leaves are part of preparations such as "Leaves of Common Bearberry", filter bag No. 20, and "Brusniver®" collection, filter bag No. 20 (JSC "Krasnogorsklekredstva", Russia), which are used as diuretic, anti-inflammatory, and antiseptic agents for infectious diseases of the urinary system — cystitis and pyelonephritis [129].

Common uva-ursi (*Arctostaphylos uva-ursi* L.)

Common uva-ursi (*Arctostaphylos uva-ursi* L.), or bearberry, is a perennial evergreen shrub of the genus Arctostaphylos L. of the *Ericaceae Juss*. family. The leading compounds in the leaves of common uva-ursi (*Arctostaphylos uvae-ursi folia*), like bearberry, are simple phenols (phenol glycosides): hydroquinone in the form of arbutin [144, 145]. The arbutin content in A. uva-ursi leaves (summed with methylarbutin and free hydroquinone) ranged from 8 % to 25 %. In a single-component phytopreparation produced by Fito-Bot LLC, the arbutin content was determined spectrophotometrically as 9.1 ± 1.04 %, and by high-performance liquid chromatography — 8.7 ± 0.91 % [146].

BASs of common uva-ursi leaves possess anti-adhesive action [147]. The combined use of dry extract with low doses of ciprofloxacin reduced the adhesiveness index and adhesion coefficient. In the absence of treatment with dry *A. uva-ursi* extract, adhesion indicators increased [148]. It is known that BASs of common uva-ursi inhibit the growth of Gram-negative PMs: *Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*; Gram-positive: *Staphylococcus aureus* and *Staphylococcus saprophyticus*, as well as pathogenic yeast *Candida albicans* [149].

In a study by V.A. Kurkin et al. on the effect of individual substances isolated from *A. uva-ursi* leaves on the excretory function of mongrel rats, it was found that 1,3,6-tri-O-galloylglucose at a dose of 10 mg/kg,

[1] Biologically active compounds of medicinal plants as a source of diuretics: a monograph; Kurkin VA, Pravdivtseva OE, Kurkina AV, Zaitseva EN, Tsibina AS. SamSMU; Samara: JSC "Polygraphic association "Standard"; 2024. 86 p. Russian

ОБЗОР
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after intragastric administration for 4 hours, stimulated diuresis by 34 %, with a daily diuresis of 75 %. Arbutin at a dose of 20 mg/kg stimulated daily diuresis by only 31 %. A decoction of leaves (at a dose of 100 mg/kg) stimulated daily diuresis by 74 % [150].

Upon single intragastric administration of a decoction of *A. uva-ursi* leaves to male and female white mongrel rats, a dose-dependent diuretic effect was observed, manifesting 24 hours after administration. At a dose of 50 mg/kg, no significant excretion of water and electrolytes was recorded over 4 and 24 hours of the experiment; at a dose of 100 mg/kg, a slight decrease in diuresis was observed in the experimental group compared to the control after 4 hours; at a dose of 100 mg/kg over 24 hours, a significant increase in indicators was found — water excretion by 74% compared to the control, sodium and potassium excretion by 68 %, and creatinine by 75 % ($p < 0.05$) [151].

Leaves of common uva-ursi are part of phytopreparations such as “Leaves of Common Uva-ursi” pack 50 g, collection “Fito-nefrol®” 50 g, “Urological Collection” filter bag No. 20, collection “Brusniver-T®” filter bag No. 20 (JSC “Krasnogorsklekredstva”, Russia) [129]. All uva-ursi drugs are used as diuretic, anti-inflammatory, and antiseptic agents for infectious diseases of the urinary system [150].

Silver birch (*Betula pendula* Roth.) and downy birch (*Betula pubescens* Ehrh.)

Silver birch (*Betula pendula* Roth.) and downy birch (*Betula pubescens* Ehrh.) are trees of the genus *Betula* L. of the *Betulaceae* Gray. family [152].

The main pharmacologically active substances in birch leaves (*Betulae folia*) are flavonoids, and in birch buds (*Betulae gemmae*) — essential oil components. The leading compounds are the flavonol hyperoside (quercetin-3-O-galactoside) and the tricyclic sesquiterpene α-copaene, respectively. Quercetin and myricetin glycosides constitute 1–3% of all flavonols present in *Betula* leaves, calculated as hyperoside. Among them are the aglycone quercetin, quercetin-3-O-glucuronide, and isoquercitrin (quercetin-3-O-glucoside) [153], quercetin-3-O-glucuronide, quercetin-3-O-rhamnoside, and myricetin-3-O-galactoside. B. *pendula* and B. *pubescens* buds are a rich source of essential oil, with quantities ranging from 0.5 % to 3.8 %. The main components of the buds are sesquiterpenes — α-copaene (11.8%), germacrene D (11.4 %), δ-cadinene (10.8 %), aromadendrene (6.25 %), and β-caryophyllene (3.4 %). The component composition of the leaf essential oil is represented by monoterpenes, among which α-pinene (2.22 %) and bornyl acetate (2.74 %) are leading [154–156].

BASs of *B. pendula* and *B. pubescens* leaves and buds possess antibacterial and diuretic actions. The antimicrobial activity of dry aqueous and methanolic extracts of *B. pendula* leaves and buds was investigated by scientists from Bosnia and Herzegovina on test cultures of *Bacillus subtilis*, *Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa.* Ciprofloxacin and penicillin were used as standard drugs. The results showed that the aqueous leaf extract inhibited *Staphylococcus aureus* growth by 13.4 mm; the methanolic leaf extract — by 12.0 mm; the aqueous bud extract — by 10.2 mm; the methanolic bud extract — by 11.2 mm; ciprofloxacin — by 19.5 mm. Extracts against Bacillus subtilis showed the following activity: methanolic bud extract — 11.0 mm; aqueous bud extract — 8.0 mm; penicillin — 32.0 mm. When tested against *Pseudomonas aeruginosa*, the following zones of growth inhibition were established: methanolic bud and leaf extracts — 11.6 mm and 11.0 mm, respectively; ciprofloxacin — 28.0 mm. *Escherichia coli* showed resistance to all tested samples [157].

An aqueous extract of *B. pendula* leaves at concentrations of 0.20 mg/mL and 0.25 mg/mL was investigated for anti-inflammatory activity. The extract inhibited prostaglandin activity by 23 ± 2 % and reduced platelet-activating factor activity in exocytosis by 76 ± 4 % [158]. A decrease in the secretion of interleukins IL-6 and IL-8 was also confirmed [159].

A standardized leaf extract containing hyperoside (0.53 %), quercetin-3-O-glucuronide (0.36 %), myricetin-3-O-glucoside (0.32 %), and chlorogenic acid (0.28 %) exhibits diuretic activity. The extract was administered orally at doses of 25 mg/kg and 50 mg/kg to male and female Sprague Dawley albino rats, and diuresis was measured over 24 hours for 3 days. The control group received placebo. At a dose of 50 mg/kg, the urine volume increased by 15.4 % compared to the control. Analysis of Na^+ and

K^+ excretion over 24 hours was performed only in the group receiving the extract at a dose of 50 mg/kg. No statistically significant differences were found between the group receiving the extract at 25 mg/kg and the control group over 24 hours ($p > 0.05$). Excretion for Na^+ was 0.13±0.04 mmol/L and 0.16 ± 0.05 mmol/L, respectively, and for K^+ was 0.18 ± 0.03 mmol/L and 0.20 ± 0.05 mmol/L, respectively. Under experimental conditions, *B. pendula* leaf extract has a weak diuretic effect [160].

Birch buds are part of the phytopreparation "Birch Buds" pack 50 g; birch leaves are part of several phytopreparations — "Birch Leaves" filter bag No. 20, "Phytolysin®", capsules No. 40, and "Phytolysin®", paste for preparing oral suspension (Herbapol, Poland). Preparations from birch MPRMs are used for the treatment of kidney and bladder diseases as diuretic, antibacterial, anti-inflammatory, antispasmodic, and antilithogenic agents [129].

Knotgrass (*Polygonum aviculare* L.)

Knotgrass (*Polygonum aviculare* L.), or *Polygonum*, is an annual herbaceous plant of the genus *Polygonum* L. of the *Polygonaceae* Juss. family [161].

The main pharmacologically active substances in knotgrass herb (*Polygoni avicularis herba*) are flavonoids. The leading compound is the flavonol avicularin (quercetin-3-O-α-arabinofuranoside). Studies of 70% ethanol extracts from raw materials from various growing regions found that avicularin dominates in the Republic of Khakassia — 4.9 mg/g, in the Irkutsk region — 2.0 mg/g, and in the Altai Republic — 2.2 mg/g of air-dry raw material. In the Republic of Buryatia, quercetrin is dominant — 2.4 mg/g, hyperoside and juglanin — 2.1 mg/g in the Transbaikal Territory [162]. In *P. aviculare herba* from the Volgograd, Rostov, and Voronezh regions, the sum of flavonoids calculated as avicularin is 2.5 %, 1.33 ± 0.03 %, and 1.61 ± 0.03 %, respectively [163, 164]. In South Korea, it was found that the maximum concentration of the sum of flavonoids is contained in the ethyl acetate fraction — 208.9 mg/g. The dominant compounds are avicularin, myricetin, quercetin, kaempferol, and their glycosides — myricitrin, isoquercitrin, and juglanin [165]. From an aqueous extract in Poland, the following were isolated: myricetin-3-O-β-D-glucuronide, quercetin-3-O-β-D-glucuronide, isorhamnetin-3-O-β-D-glucuronide [166].

The chronic toxicity of dry extract was studied in male and female rats with daily administration for one month at doses of 0.15 mL/kg and 1.5 mL/kg. Control animals received 35 % ethanol at a dose of 1.5 mL/kg. The extract did not exert toxic effects on the rats' bodies with prolonged administration and did not cause pathomorphological changes in organ systems. A slight tendency towards accelerated blood clotting time was noted [167].

The antimicrobial and antifungal activity of aqueous and organic extracts of the plant was tested on clinical isolates of *Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, Salmonella paratyphi, Shigella flexneri, Staphylococcus aureus, Bacillus subtilis, Streptococcus pyogenes, Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, and Candida albicans.* The chloroform extract showed the greatest effect (*Proteus mirabilis* — 28 mm and *Escherichia coli* — 27 mm), and the aqueous extract (*Bacillus subtilis* — 25 mm and *Proteus mirabilis* — 24 mm) [168].

C.H. Jang et al. investigated the anti-inflammatory effect of a dry ethanol extract (extractant — 70 % ethanol). The BASs of the extract at doses of 33.3 μg/mL, 100 μg/mL, and 200 μg/mL affected the transcription factor NRF2, regulating HO-1 (heme oxygenase-1) levels, and reducing cyclooxygenase-2 levels. A dose of 200 μg/mL reduced IL-1β levels to approximately 1 pg/mL and demonstrated almost 40% inhibition of IL-6 levels. Myricitrin, avicularin, myricetin, quercetin, and kaempferol inhibit NF-κB activity [169]. BASs of ethanol extract from *P. aviculare* leaves at doses of 500 mg/kg have an inhibitory effect on the acute phase of inflammatory paw edema in rats induced by carrageenan [170].

An aqueous extract was studied for its ability to mitigate the consequences of oxalate nephrolithiasis induced by ethylene glycol and ammonium chloride in male Wistar albino rats. Animals received the extract at doses of 100 mg/kg and 400 mg/kg for 28 days (starting from the 14th day of ethylene glycol administration); the prophylactic group received the extract at the same dosage (from the beginning of ethylene glycol administration). According to the study results, in the prophylactic ($p < 0.001$) and therapeutic ($p < 0.001$) groups, the number of calcium oxalate concretions decreased compared to the control group [171].

ОБЗОР
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V.V. Mantatov et al. established the prostatoprotective activity of a dry extract (extractant — 40 % ethanol) in sexually mature male Wistar rats. A decoction of the "Brusniver®" collection was used as a comparison drug. Experimental animals were administered the extract intragastrically at a dose of 200 mg/kg once daily throughout the experiment; the decoction of the "Brusniver®" collection was administered in a volume of 10 mL/kg body weight; the control group received purified water. In a model of chronic prostatitis, it was found that *P. aviculare* extract exerts a pronounced prostatoprotective effect, characterized by normalization of the morphofunctional state of the rat prostate gland, by suppressing the inflammatory process and regulating lipid peroxidation induction. A decrease in malondialdehyde concentration and an increase in catalase activity in rat serum indicate a pronounced antioxidant effect in the experimental group (40 % less compared to the control). On the 14th day, a decrease in blood erythrocyte sedimentation rate by 45 %, the number of leukocytes in blood and prostate secretion by 23 % and 27 %, respectively, and malondialdehyde concentration in serum by 21 % were observed compared to the control data. On the 21st day of the experiment, no signs of inflammatory reaction in the prostate were detected, and all blood parameters normalized [172].

Knotgrass herb is part of botanicals such as "Knotgrass (Sporish) Herb" pack 50 g, "Knotgrass (Sporish) Herb" filter bag No. 20, "Phytolysin®", capsules No. 40, and "Phytolysin®", paste for preparing oral suspension (Herbapol, Poland). Knotgrass preparations are used for the treatment of kidney and bladder diseases as diuretic, antibacterial, anti-inflammatory, antispasmodic, and antilithogenic agents [173, 174].

Siberian oregano (*Orthosiphon stamineus* Benth.)

Siberian oregano (*Orthosiphon stamineus* Benth.), or kidney tea, is a perennial herbaceous plant of the genus *Orthosiphon* Benth. of the *Lamiaceae* Lindl. family [161].

The main pharmacologically active substances in Siberian oregano leaves (*Orthosiphonis staminei folia*) are phenylpropanoids. The leading compound is the phenylpropanoid rosmarinic acid — an ester of caffeic acid and 3,4-dihydroxyphenyl lactic acid. In an infusion of *O. stamineus* leaves grown in Germany, the amount of rosmarinic acid was 243 ± 22 μg/mL [175]. The rosmarinic acid content varies from 17.43 mg/kg to 931.44 mg/kg in raw materials. Polymethoxylated flavone derivatives are also found among the components [176, 177], such as sinensetin, isosinetin, eupatorin, salvigenin, 6,7,4'-tetramethoxyflavone, 5-hydroxy-6,7,3,4'-tetramethoxyflavone, 6-hydroxy-5,3'-trimethoxyflavone, and 5,6,7,3'-tetramethoxy-4'-hydroxy-8-C-prenylflavone [178, 179]. The content of polymethoxylated flavones in raw materials ranges from 0.5 % to 0.7 %. Sinensetin and its isomer isosinetin are leading among this group of flavonoids, with contents ranging from 122.98 mg/kg to 469.54 mg/kg and from 50.60 mg/kg to 419.07 mg/kg of dry raw material, respectively [180]. The concentration of sinensetin in an extract obtained by maceration was 0.42 ± 0.006 %, and in an extract obtained by Soxhlet apparatus — 0.30 ± 0.006 % [181]. In 12 samples from different regions of Indonesia, the sinensetin content ranged from 0.0238 mg/g to 0.1533 mg/g [182].

An aqueous extract of Siberian oregano herb, containing rosmarinic, chicoric, and caffeic acids, was tested for antiproliferative activity in mice. It was found that administration of the extract at a dose of 750 mg/kg for 4–7 days reduced the bacterial load in the urinary tract of mice. The extract exhibits dose-dependent anti-adhesive activity, reducing *fimH* gene expression but activating *fliC* gene expression in *Escherichia coli* strains NU14 and UTI89 [183].

An aqueous extract of Siberian oregano was tested for anti-adhesive activity. Twenty healthy volunteers participated in the experiment, taking an infusion of *O. stamineus* leaves 4 times a day for 7 days. Urine samples were collected on days 1 (pre-infusion control), 3, 6, and 8. The study results showed that the samples had an anti-adhesive effect with strong *fliC* gene expression [175].

The toxicity of Siberian oregano extracts was also studied. N.R. Abdullah et al. determined the acute toxicity of a standardized extract containing 0.15 %, 0.21 %, and 0.05 % sinensetin, eupatorin, and 3'-hydroxy-5,6,7,4'-tetramethoxyflavone, respectively, at a dose of 5000 mg/kg in Sprague Dawley albino rats for 14 days. No cases of toxicity or death were

recorded. The extract did not affect general behavior, food/water intake, relative organ weight, hematology, or clinical biochemistry. The LD^{50} was >5000 mg/kg body weight of the rat [184]. Under similar experimental conditions, M.F. Yam et al. investigated a dry methanolic extract (extractant 50% methanol) for 14-day acute and 28-day subchronic toxicity (at doses of 1250 mg/kg, 2500 mg/kg, and 5000 mg/kg), and R. Pariyani et al. investigated aqueous, aqueous-alcoholic (extractant 50 % ethanol), and alcoholic extracts at a dose of 5000 mg/kg. As a result, none of the investigated extracts showed toxic effects [185, 186]. H. Muhammad et al. investigated the chronic toxicity of a dry aqueous extract at doses of 250, 500, 1000 and 2000 mg/kg in male and female Sprague Dawley albino rats for 60 days. No cases of toxicity or death were recorded. It was found that erythrocyte, hematocrit, hemoglobin, and platelet levels were significantly higher in the group receiving the extract at a dose of 2000 mg/kg. According to the authors, this may be related to erythropoiesis stimulation, which requires further study [187].

Scientists from Malaysia investigated the diuretic activity of *O. stamineus* leaf BASs by administering a methanolic extract to Sprague Dawley albino rats at a dose of 2000 mg/kg for 7 days. Hydrochlorothiazide (at a dose of 10 mg/kg) was used as a standard drug. In the first 8 hours after extract administration, Na^+ and K^+ excretion ($p < 0.05$ and < 0.01, respectively) comparable to hydrochlorothiazide was observed. Additional administration of the extract at a dose of 500 mg/kg enhanced diuresis from day 3 to day 7 ($p < 0.01$) and Na^+ and K^+ excretion ($p < 0.05$ and < 0.01, respectively) on days 2 and 7. The authors proposed a recommended dose for rats of 420 mg/kg. The extract at doses of 500 mg/kg, 1000 mg/kg, and 2000 mg/kg exhibited hypouricemic activity, reducing uric acid levels for 6 hours and demonstrating efficacy comparable to allopurinol [188]. The antihyperuricemic effect is due to the regulation of xanthine oxidase, adenosine deaminase activity, and urate transporters [189]. Y. Adam et al. administered an aqueous extract orally at doses of 5 and 10 mg/kg to Sprague Dawley albino rats, while control groups received furosemide (at a dose of 10 mg/kg). The extract demonstrated dose-dependent diuretic activity, selective K^+ ion excretion in urine while maintaining normal Na^+ and Cl^- excretion levels. Extracts slightly increased serum urea and creatinine levels and blood glucose levels, but these indicators remained within normal limits [190].

R.M. Oktaviani et al. established the influence of a 70 % ethanol extract on the pharmacokinetic parameters of furosemide. Male Sprague-Dawley albino rats were administered a suspension of the test extract for 4 and 7 days, followed by administration of a furosemide suspension at a dose of 7.2 mg/200 g. After 4 days, the average urine volume in rats was 18.5 ± 1.0 mL (furosemide 15.7 ± 1.6 mL), and by day 7, it decreased to 16.2 ± 0.8 mL (furosemide 15.7 ± 1.6 mL). The authors concluded that the decrease in urine volume by day 7 was related to the distribution process and increased elimination rate of BASs. Thus, the 70% ethanol extract of Siberian oregano improves the pharmacokinetic parameters of furosemide ($p < 0.05$) [191].

The antilithogenic activity of an aqueous extract was compared with the drug "Cystone®" *in vitro*. The sum of BASs in the Siberian oregano extract inhibited the crystallization of calcium oxalate by 73.48% compared to the control, while the MP "Cystone®" inhibited it by 80.68 % [192]. M.B. Ambursa et al. studied the litholytic activity of a standardized aqueous extract containing 8.99 % of rosmarinic acid, 0.35 % of sinensetin, 0.45 % of eupatorin, and 0.3 % of 3-hydroxy-5,6,7,4-tetramethoxyflavone at concentrations of (1 mg/mL, 2 mg/mL and 4 mg/mL) on calculi obtained from patients who underwent stone removal procedures. The extract at a dose of 4 mg/mL showed a better effect in terms of lytic impact on calcium oxalate stones than a potassium citrate solution (70 % vs. 41 %) [193].

Leaves of Siberian oregano (kidney tea) are part of botanicals such as "Leaves of Siberian Oregano (Kidney Tea)" pack 50 g and "Leaves of Siberian Oregano (Kidney Tea)" filter bags 1.5 g ×20. Siberian oregano preparations are used for the treatment of kidney and bladder diseases as diuretic agents [194].

Common horsetail (*Equisetum arvense* L.)

Common horsetail (*Equisetum arvense* L.) is a perennial herbaceous plant of the genus *Equisetum* L. of the *Equisetaceae* Michx. ex DC. family.

The main pharmacologically active substances in common horsetail herb (*Equiseti arvensis herba*)

ОБЗОР
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are flavonoids, among which the leading one is the flavonol quercetin. In a 50 % aqueous-alcoholic extract obtained from *E. arvense herba*, the flavonoid content was 1.67 ± 0.07 % calculated as quercetin [195]. A dry ethanol extract (extractant — 70 % ethanol) from raw material harvested in Uzbekistan contained 2.283 mg of quercetin, 0.508 mg of rutin, and 0.375 mg of gallic acid [196]. A methanolic extract from horsetail herb harvested in Iraq contained 179.5 μg/mL of total flavonoids, including luteolin — 100.6 μg/mL; kaempferol-3-O-glucoside — 42.4 μg/mL; kaempferol — 26.6 μg/mL; quercetin — 9.9 μg/mL [197]. The component composition of aqueous and ethanol extracts from raw material harvested in Turkey was as follows (calculated as dry raw material): rutin (14.383 μg/kg), chicoric (21.313 μg/kg), salicylic (9.639 μg/kg), 4-hydroxybenzoic (1.535 μg/kg), and vanillic acids (2.32 μg/kg); quercetin (32.995 μg/kg), epicatechin (24.97 μg/kg), rutin (6.236 μg/kg), gallic (0.95 μg/kg), p-coumaric (5.974 μg/kg), chicoric (39.984 μg/kg), and cinnamic acids (1.769 μg/kg), respectively [198].

From raw material harvested in the Khanty-Mansiysk Autonomous Okrug, luteolin, luteolin-7-O-β-D-glucopyranoside, and luteolin-4-O-β-D-glucopyranoside were isolated from the ethyl acetate fraction of the alcoholic extract [199]. In raw material from Pakistan, the methanolic extract identified quercetin, apigenin, luteolin, kaempferol-3-O-glucoside, isoquercitrin, apigenin-4′-O-glucoside, kaempferol-6′′-O-acetylgenistin, daidzein-4′,7-diglucoside (puerarin), tricin-6′′-O-acetylglycitin, 4′,5-dihydroxy-7-methoxyflavone (genkwanin), myricetin-7-O-methylchrysin, trans-ferulic acid, dihydroactinidiol, 2′,4′-dihydroxy-4-prenyloxichalcone, pinolenic acid, 4-(sec-butoxy)benzoic acid, and 8-acetylharpagide [200]. From raw material harvested in South Korea, the dichloromethane:methanol fraction of the alcoholic extract yielded: luteolin-5-O-β-D-glucopyranoside (12.0 mg), kaempferol-3,7-di-O-β-D-glucopyranoside (3.4 mg), (Z)-3-hexenyl-β-D-glucopyranoside (2.5 mg), 4-*O*-β-D-glucopyranosyl caffeic acid (2.2 mg), (7S,8S)-threo-7,9,9′-trihydroxy-3,3′-dimethoxy-8-O-4′-neolignan-4-O-β-β-D-glucopyranoside (1.2 mg), 4-O-caffeoylshikimic acid (1.0 mg), clemastanin B (0.6 mg), and icariiside B2 (0.5 mg) [201].

The acute toxicity of methanolic and aqueous extracts was studied in albino mice. As a result, none of the investigated extracts showed toxic effects. LD_{50} of extracts from *E. arvense herba* was > 5000 mg/kg [202].

When investigating the antibacterial activity of 96 % ethanol and methanolic extracts from the raw material, the following minimum inhibitory concentration (mg/mL) values were established: *Staphylococcus aureus* — 15.5 ± 0.56, 20.58 ± 0.8; *Escherichia coli* — 12.58 ± 0.8, 15.41 ± 0.52; Enterococcus faecalis — 5.42 ± 0.38, 5.25 ± 0.43; *Streptococcus pyogenes* — 16.00 ± 1.30, 17.5 ± 0.76, respectively. At a concentration of 0.1 %, the ethanol extract reduced the biofilm formation process of *Staphylococcus aureus* by 95.90 %, and the methanolic extract — by 69.86 %. At a concentration of 0.05 %, the effect decreased to 77.8 % for the ethanol extract and to 69.38 % for the methanolic extract. At a concentration of 0.01 %, the ethanol extract reduced biofilm formation by 63.0 %, and the methanolic extract — by 48.72 % [203]; the 96 % ethanol extract showed antifungal activity against *Candida glabrata* (28.0 ± 0.57 mm), comparable to nystatin (22.6 ± 0.33 mm) [204].

In Brazil, the diuretic effect of a standardized dry extract (0.026 % flavonoids) was studied in a double-blind, randomized clinical trial involving 36 healthy male volunteers aged 20 to 55 years, with heights from 150 to 185 cm and weights from 50 kg to 90 kg. Participants were divided into three groups (n = 12) and alternately received the standardized dry extract (900 mg), placebo (corn starch, 900 mg), and hydrochlorothiazide (25 mg) for four consecutive days. The diuretic effect of the extract was assessed by monitoring the water balance of volunteers over 24 hours. The E. arvense extract exerted a diuretic effect (522.62 ± 463.03 mL) (p < 0.05) and was equivalent to hydrochlorothiazide (542.01 ± 935.37) (p < 0.067). The extract caused a significant decrease in creatinine (p = 0.003), uric acid (p = 0.010), Cl^- (p = 0.042), Mg^{+2} (p = 0.044), and phosphate (p = 0.032) levels. Rare minor side effects were reported; one volunteer complained of a severe headache [205].

Extract of common horsetail herb is part of complex herbal MPs: “Marelin®”, film-coated tablets (ZAO “VIFITEKH”, RF), “Phytolysin®”, capsules No. 40, and “Phytolysin®”, paste for preparing oral suspension (Herbapol, Poland), “Tonsilgon® N”, film-coated tablets,

"Tonsilgon® N", oral drops (Bionorica, Germany), "Polyhemastat®", powder for local and external use (OOO "Tekhnopark-Tsentr", RF), "Depuraflox®", dry extract (Sanofi-Aventis, Germany), collection-powder "Arfazetin-E®" (JSC "Krasnogorsklekredstva", RF), "Common Horsetail Herb" pack 50 g, "Common Horsetail Herb" filter bags 1.5 g ×20. Preparations of common horsetail are used for the treatment of kidney and bladder diseases, urolithiasis, and upper respiratory tract diseases as diuretic, antibacterial, hemostatic, and immunomodulatory agents [206, 207].

Aerva lanata (L.) Juss.

Aerva lanata (L.) Juss., or pol-pala, is a biennial herbaceous plant of the genus *Aerva* L. of the *Amaranthaceae* Juss. family.

The main BASs of *Aervae lanatae herba* are flavonoids, among which the dominant one is the flavonol rutin (quercetin-3-O-rutinoside). When obtaining a dry extract of *A. lanata* in Uzbekistan using various alcohol concentrations, the flavonoid content (calculated as rutin) was as follows: 96 % alcohol — 0.87 ± 0.01 %; 70 % alcohol — 0.98 ± 0.01 %; 50 % alcohol — 1.23 ± 0.02 %; 30 % alcohol — 1.32 ± 0.02 %; water — 1.36 ± 0.03 % [208]. An aqueous-alcoholic extract obtained from plants growing in India contained 4.34 ± 0.63 mg/g of total tannins calculated as tannin; total phenol content was 127.84 ± 1.50 mg/g calculated as gallic acid; total flavonoid content was 77.61 ± 3.78 mg/g calculated as rutin [209]. Additionally, kaempferol, quercetin, apigenin, betulin, cantin-6-one (indole alkaloid), vanillic, syringic, and ferulic acids were detected. From the ethyl acetate extract, cantin-6-one (3.275 g), rutin (0.697 g) were isolated, and from the methanolic extract, kaempferol (0.437 g) was isolated [210]. Uzbek scientists isolated vanillic, syringic, and ferulic acids from the butanol fraction of Aerva herb [211].

Indian scientists studied the possibility of using botanicals from *A. lanata herba* as a treatment for urolithiasis. I. Arthi et al. found that an aqueous extract at a dose of 500 mg/kg body weight of Wistar albino rats reduced ($p < 0.001$) the levels of major stone-forming components — calcium, oxalates, and phosphates in urine — to 2.09 ± 0.08 mg/dL, 3.03 ± 0.12 mg/dL, and 5.17 ± 0.04 mg/dL, respectively ("Cystone®" — 0.52 ± 0.03 mg/dL, 1.49 ± 0.05 mg/dL, and 3.80 ± 0.08 mg/dL, respectively) and in the kidneys — to 2.61 ± 0.03 mg/dL, 4.27 ± 0.04 mg/dL, and 3.36 ± 0.07 mg/dL, respectively ("Cystone®" — 1.60 ± 0.07 mg/dL, 3.41 ± 0.06 mg/dL, and up to 2.51 ± 0.06 mg/dL). At a dosage of 1000 mg/kg, the results were lower [212]. B.M. Dinnimath et al. isolated quercetin and betulin from *A. lanata herba*, which showed diuretic and antilithogenic effects in an oxalate nephrolithiasis model induced by ethylene glycol administration in male Wistar rats. Urine volumes on days 14 and 28 in the control group were 9.47 ± 0.08 mL and 9.38 ± 0.09 mL, while in the other groups (before treatment) they were 12.65 ± 0.11 mL and 12.76 ± 0.10 mL. After administering quercetin to rats, urine volume increased from 12.76 ± 0.10 mL to 21.35 ± 0.20 mL and 21.50 ± 0.21 mL in rats receiving betulin. Microscopic urine analysis showed a significant decrease in calculus size ($p < 0.001$) with increased excretion of calcium, magnesium, oxalate, and phosphate ($p < 0.001$). A decrease in urea and creatinine levels was observed [213]. B. Mandal et al. studied the activity of ethyl acetate and methanolic extracts at doses of 32 and 200 mg/kg, respectively, and the "Cystone®" as a reference at a dose of 750 mg/kg from day 15 to 30. The experiment results showed: an increase in diuresis upon administration of methanolic extract — 7.85 ± 0.83 mL and ethyl acetate extract — 6.22 ± 0.59 mL compared to the control group — 5.07 ± 0.61 mL and the "Cystone®" group — 8.80 ± 0.78 mL ($p < 0.0001$); a decrease in oxalate, calcium, and uric acid levels (g/100 mg kidney weight) upon administration of methanolic extract — 5.42 ± 0.41, 1.29 ± 0.21, and 5.42 ± 0.72, and ethyl acetate extract — 7.16 ± 0.55, 1.36 ± 0.33, and 5.22 ± 0.62, respectively, compared to the control group — 10.51 ± 0.60, 2.58 ± 0.30, and 7.64 ± 0.80, and the "Cystone®" — 3.68 ± 0.63, 1.25 ± 0.16, and 4.72 ± 0.66, respectively ($p < 0.0001$) [214]. In an *in vitro* study, S.K. Sarma et al. found that the highest percentage of calcium oxalate calculus dissolution was observed with the "Cystone®" (98 %); ethyl acetate and methanolic extracts from *Aerva lanata herba* also showed significant activity (87 % and 78 %, respectively) [215].

When an ethanol extract from *Aerva lanata herba* was administered to Wistar albino rats, a direct dose-diuretic activity relationship was established: as the

ОБЗОР
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dose increased from 200 mg/kg to 1600 mg/kg, urine volume increased from 0.46 ± 0.008 mL to 1.01 ± 0.03 mL (p < 0.05); control group — 0.40 ± 0.005 mL; furosemide (at a dose of 25 mg/kg) — 1.10 ± 0.01 mL (p < 0.05). Acute toxicity was not detected in the experiment [216]. Upon single intragastric administration of an infusion from the raw material to male and female white mongrel rats, a pronounced dose-dependent and temporary effect on kidney excretory function was observed; high doses had a predominantly inhibitory effect on renal excretion. Thus, the infusion at a dose of 50 mg/kg increased diuresis by 151 %, natriuresis by 56 %, kaliuresis by 39 %, and creatininuria by 81 % over 4 hours of the experiment compared to the control; at the same dose after 24 hours, a significant inhibition of diuresis by 65 %, natriuresis by 70 %, and kaliuresis by 71 % occurred; creatininuria changed insignificantly; a dosage of 100 mg/kg reduced sodium excretion by 53 %, potassium by 58 %, and creatinine by 49 % over 4 hours; the same dose after 24 hours led to a decrease in water excretion by 41 %, sodium by 58 %, and potassium by 47 % [151]. Considering the results, it was proposed to use a phytopreparation based on *A. lanata* as a standard preparation with a diuresis volume of 8.8 ± 1.1 mL for studying the diuretic activity of other plants, particularly dried juice from horseradish roots [217].

The antidiuretic effect was discussed in the study by N.S. Sundar et al. Wistar albino rats receiving 2-decyl-1-tetradecanol from *A. lanata* had a total urine volume of 1.30 ± 0.27 mL/kg compared to the control group's 1.32 ± 0.22 mL/kg per day, a decrease of 2 %. Upon administration of furosemide (at a dose of 10 mg/kg), urine excretion was 7.38 ± 0.53 mL, and upon combined administration of 2-decyl-1-tetradecanol (at a dose of 0.5 g/kg) with furosemide — 7.49 ± 0.48 mL. Biochemical analysis revealed: in animals receiving furosemide, urea (33.76 ± 2.9 mg/dL) and creatinine (1.22 ± 0.06 mg/dL) levels were reduced, while ALT and AST levels were elevated — 89.84 ± 7.5 and 127.75 ± 22.0 U/L, respectively; in animals receiving 2-decyl-1-tetradecanol (combined with furosemide), urea (35.26 ± 2.2 mg/dL), creatinine (0.98 ± 0.03 mg/dL), ALT — 66.18 ± 3.3 U/L, and AST — 139.70 ± 18.1 U/L; in the control group, urea (35.62 ± 2.4 mg/dL), creatinine (0.97 ± 0.14 mg/dL), ALT (64.36 ± 4.2 U/L), and AST (139.10 ± 19.1 U/L). Upon administration of antidiuretic hormone (10 mg/kg), similar results were obtained. The authors also determined the LD100 of *A. lanata herba* extract, which was 20.4 g/kg body weight of the rat [218].

An ethyl acetate extract showed efficacy against *Staphylococcus aureus* (20 mm), *Streptomyces griseus*, and *Bacillus subtilis* (18 mm); the ethanol extract showed better results against *Salmonella typhi* (25 mm), *Staphylococcus aureus* (23 mm), *Bacillus subtilis* (22 mm), *Escherichia coli* (22 mm), and *Streptomyces gresius* (21 mm) [219, 220].

Aerva lanata herba is part of phytopreparations such as "Aerva lanata Herb" pack 50 g, "Aerva lanata Herb" filter bags 1.5 g ×20. Drugs of *Aerva lanata* are used for kidney and bladder diseases as diuretic and anti-inflammatory agents [194].

Rosemary (*Rosmarinus officinalis* L.)

Rosemary (*Rosmarinus officinalis* L.) is a perennial evergreen shrub of the genus *Rosmarinus* L. of the *Lamiaceae* Lindl. family.

The main classes of BASs in rosemary leaves (*Rosmarini officinalis folia*) are essential oil components, including the main ones — the monocyclic monoterpene 1,8-cineole and bicyclic monoterpenes α-pinene and camphor, as well as phenylpropanoids, particularly rosmarinic acid. In 70 % alcoholic extracts of *R. officinalis* leaves harvested in the botanical garden of Pyatigorsk Medical Pharmaceutical Institute, catechin, epicatechin, quercetin, apigenin, rosmarinic acid (0.181–0.184 % calculated as dry raw material), caffeic, gallic, chlorogenic, and ferulic acids were found; in rosemary raw material from the Nikitsky Botanical Garden (Republic of Crimea), the sum of phenolic acids was 3.69 ± 0.12 % calculated as rosmarinic acid, and cinnamic acid was also identified [221, 222]. In rosemary leaf samples harvested in the USA, the content of rosmarinic acid was 14311.0 ± 636.4 μg/g, luteolin-3'-acetyl-O-glucuronide — 1488.50 ± 47.58 μg/g, luteolin-7-O-glucuronide — 1053.68 ± 68.83 μg/g, sage acid — 819.93 ± 46.07 μg/g, 12-methoxycarnosic acid — 982.78 ± 32.77 μg/g, carnosic acid — 797.75 ± 32.70 μg/g, carnosol — 698.78 ± 21.07 μg/g, rosmadial — 588.64 ± 24.14 μg/g, and rosmanol —

218.48 ± 11.70 μg/g [223]. In a methanolic extract from raw material grown in Egypt, the predominant compounds were naringenin — 2038 μg/g, ferulic acid — 2017.27 μg/g, catechin — 1094.63 μg/g, caffeic acid — 868.92 μg/g, gallic acid — 564.98 μg/g, syringic acid — 310.83 μg/g, rutin — 226.78 μg/g, and chlorogenic acid — 144.27 μg/g [224].

Rosemary leaf essential oil is a mobile liquid from colorless to light yellow with a strong specific camphor odor. The average yield of essential oil obtained from R. officinalis leaves varies from 1.0 % to 2.5 % depending on the plant's growing region: in the Krasnodar Territory (Russia) — 2.58 % [225]; in the Republic of Dagestan (Russia) — 2.36 % [226]; in Iraq — 1.5 % [227]. The main components of essential oil from rosemary leaves grown in the Republic of Crimea (Russia) are camphor 18.9–32.6 %, 1,8-cineole 14.2–22.9 %, α-pinene 8.3–12.0 %, linalool 8.2 % [228]; in Saudi Arabia — bornyl acetate 26.59 %, 1,8-cineole 17.38 %, camphor 10.42 %, borneol 9.78 %, β-caryophyllene 7.80 %, α-pinene 3.85 % [229]; in Algeria — camphor 41.2 %, camphene 18.1 %, α-pinene 17.4 % [230]; in the Republic of Dagestan (Russia) — α-pinene 40.93–47.51 %, verbenone 15.92 %, 1,8-cineole 9.06 %, camphor 4.39 %, limonene 4.33 % [226]; in Iraq — 1,8-cineole 53.63 %, camphor 37.32 %, borneol 3.66 %, β-linalool 0.84 % [227].

A 90 % methanolic extract of rosemary showed antibacterial activity against *Acinetobacter baumannii* and *Enterococcus faecalis* with inhibition zones at 100 mg/mL — 33 mm and 25 mm, at 50.0 mg/mL — 31 mm and 20 mm, at 20 mg/mL — 30 mm and 18 mm, at 12.5 mg/mL — 27 mm and 23 mm, respectively [227]. An infusion of rosemary leaves grown in India inhibited the growth zone of *Streptococcus pyogenes* by 4 mm and *Escherichia coli* by 5 mm; a methanolic extract inhibited the growth zone of *Escherichia coli* by 8 mm, *Staphylococcus aureus* by 10 mm, and *Streptococcus pyogenes* by 11 mm; an acetone extract showed activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Escherichia coli*, slowing pathogen growth by 7 and 8 mm, respectively [231]. The antibacterial activity of a dry extract (extractant 96 % ethanol) of raw material from Jordan was tested against PMs isolated from the urine of 500 patients with CIDKUT. The extract demonstrated inhibition zones: 10 mm for *Enterococcus faecalis* and 16 mm for *Escherichia coli*. Minimum inhibitory concentration and minimum bactericidal concentration values of *R. officinalis* extract ranged as follows: *Escherichia coli* (4 and 8 mg/mL); *Klebsiella pneumoniae* (8 and 16 mg/mL); *Pseudomonas aeruginosa* (16 and 32 mg/mL); *Enterococcus faecalis (*32 mg/mL and 64 mg/mL). Also, a concentration of 100 mg/mL reduced *Escherichia coli* biofilm formation by 70 % [232].

In a model of oxalate nephrolithiasis in Sprague-Dawley albino rats, the antilithogenic activity of an ethanol extract from rosemary leaves at a dosage of 200 mg/kg was established, which on the 35th day of the experiment reduced serum creatinine levels — 4.80 ± 1.360 mg/dL, urea — 24.51 ± 1.097 mg/dL, uric acid — 4.46 ± 1.003 mg/dL, calcium — 3.92 ± 0.026 mg/dL, and protein in urine — 1.30 ± 2.001 mg/dL ($p < 0.01$) compared to the control of 6.97 ± 1.370 mg/dL, 28.18 ± 1.096, 6.28 ± 0.072, 4.03 ± 1.009, and 7.83 ± 0.930 mg/dL, and the standard drug "Cystone®" — 4.82 ± 0.098 mg/dL, 24.47 ± 1.027 mg/dL, 4.38 ± 0.860 mg/dL, 3.73 ± 0.039 mg/dL, and 1.27 ± 1.021 mg/dL ($p < 0.01$), respectively. Administration of the extract contributed to a reduction in the amount of substances responsible for stone formation [233]. The extract at a dose of 200 mg/kg demonstrated a diuretic effect, and at a dose of 400 mg/kg — an antipyretic effect in Wistar rats [234]. A dry methanolic extract at a dose of 100 mg/kg exerted a nephroprotective effect in Wistar albino rats, binding to nickel chloride and protecting kidney tissue from oxidative damage [235].

When investigating the antispasmodic activity of a dry aqueous extract at doses of 150 μg/mL, 300 μg/mL, 600 μg/mL, and 1200 μg/mL on isolated smooth muscle fragments of the urinary bladder of male Sprague Dawley albino rats, it was found that the extract does not possess myogenic activity towards spasms of rat bladder smooth muscle induced by acetylcholine and potassium chloride [236]. Studies of the essential oil show that its anti-inflammatory activity arises from the inhibition of NF-κB transcription and suppression of the arachidonic acid cascade [237].

Rosemary leaf extract is part of botanicals such as "Kanefron® N", film-coated tablets, and "Kanefron® N", oral drops (Bionorica, Germany) [238] and their

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analogues. Rosemary drugs are used in the therapy of kidney and urinary tract diseases as diuretic, antispasmodic, antibacterial, and anti-inflammatory agents [239].

Garden lovage (*Levisticum officinale* Koch.)

Garden lovage (*Levisticum officinale* Koch.) is a perennial herbaceous plant of the genus *Levisticum* Hill. of the *Apiaceae* Lindl. family.

The main classes of BASs in garden lovage rhizomes and roots (*Levistici officinalis rhizomata et radices*) are essential oil, containing phthalide (Z)-ligustilide, and furanocoumarins, among which pimpinellin dominates. The component composition of coumarins was studied in methanolic extracts of dried and fresh roots of 3-year-old L. officinale cultivated in the Republic of Bashkortostan (Russia). Psoralen, bergapten, imperatorin, osthol, umbelliferone, aesculin, isopimpinellin, isobergapten, angelicin, xanthotoxin, isoimperatorin, peucedanin, and vaginol-8-O-glucoside (apterin) were identified in the lovage raw material. The total coumarin content in fresh and dried roots varied from 1739 to 2902 μg/g (variety Gerakl) and from 15.12 to 24.46 mg/g (variety Lider), respectively. The leading furanocoumarins were apterin, xanthotoxin, isopimpinellin, and pimpinellin, with contents ranging from 197 μg/g to 357 μg/g, from 152 μg/g to 352 μg/g, from 486 μg/g to 863 μg/g, from 904 μg/g to 1296 μg/g, and from 1.53 μg/g to 4.11 mg/g, from 1.40 μg/g to 3.75 mg/g, from 4.83 μg/g to 7.80 mg/g, and from 7.36 μg/g to 11.26 mg/g, respectively.

Significant differences in coumarin content in fresh and dried lovage roots were found during raw material storage at different temperature regimes (in a cool place and at room temperature) in an experiment [240].

In Iran, from the ethyl acetate extract of lovage rhizomes and roots, furanocoumarins bergapten, isogosferol, oxypeucedanin, oxypeucedanin hydrate, and imperatorin; the phenylpropanoid ferulic acid; and the polyacetylene (polyine) falcarindiol were isolated individually [241]. In studies by Russian scientists, a 96 % ethanol extract showed a total coumarin content of 6.67 % calculated as angelicin and dry raw material [242], and in the initial raw material — 0.213 ± 0.009 % calculated as psoralen and dry raw material [243].

The yield of essential oil obtained from dried *L. officinale* rhizomes and roots varies from 0.11 % to 1.80 % [244]. The main components in the essential oil from raw material grown in the Republic of Moldova are α-terpinyl acetate — 30.99 %, β-phellandrene — 22.39 %, (Z)-ligustilide — 11.18 %, β-myrcene — 8.65 %, sabinene — 3.39 %, with the first identification of 6-butylcyclohepta-1,4-diene — 0.56 % and 7-formyl-4-methylcoumarin — 0.15 % [245]; in the essential oil from raw material grown in Iran, terpinyl acetate — 21.1–42.1 %, Z-β-ocimene — 13–28.1 %, neocnidilide — 4.8–11.6 %, Z-ligustilide — 0.8–5.8 %, and pentylcyclohexadiene 2.2–2.4 % [246]; in the essential oil from raw material grown in France and Belgium — phthalide isomers (Z)-3-butylidenephtalide and (Z)-ligustilide — 73.2–82.6 %; in the essential oil from raw material grown in Scotland — β-phellandrene — 48.9 %, phenylacetaldehyde — 17.2 %; in the essential oil from raw material grown in the Netherlands, α-terpinyl acetate — 38.2 %; in the essential oil from raw material grown in Estonia, (E)-ligustilide — 52.4–70.9 %, pentylcyclohexadiene — 12.3 %, β-phellandrene — 11.3 % [244].

Phthalides 7-methoxy-3-propylidenephtalide, 5-hydroxybutylidenephtalide, and 7-hydroxybutylidenephtalide, isolated from *L. officinale*, exhibit antibacterial activity. Minimum inhibitory concentration studies showed varying sensitivity of PMs to 7-hydroxybutylidenephtalide, which ranges as follows: *Escherichia coli* (16 μg/mL), *Staphylococcus aureus* (64 μg/mL), and *Enterococcus faecium* (128 μg/mL). 5-Hydroxybutylidenephtalide demonstrated moderate activity against *Staphylococcus aureus* (128 μg/mL) and *Escherichia coli* (256 μg/mL). The lowest activity was observed with 7-methoxy-3-propylidenephtalide with a minimum inhibitory concentration of > 256 μg/mL against all strains [248]. The essential oil of Iranian origin, containing terpinyl acetate 21.1–42.1 %, Z-β-ocimene 13–28.1 %, neocnidilide 4.8–11.6 %, Z-ligustilide 0.8–5.8 %, and pentylcyclohexadiene 2.2–2.4 %, exhibits antibacterial activity against strains of *Staphylococcus aureus, Enterococcus faecium, Escherichia coli*, and *Pseudomonas aeruginosa* with minimum inhibitory concentration values of 32 mg/mL [246].

In *in vivo* studies, a dry ethanol extract (extractant

70 % ethanol) showed that diuresis induced by the extract (at a dosage of 975 mg/kg) was 6.37 ± 1.16 mL ($p < 0.01$) compared to the hydrochlorothiazide group (at a dosage of 4.6 mg/kg) of 9.4 ± 1.36 mL ($p < 0.01$) and the control group of 2.12 ± 0.55 mL [252].

Extracts of garden lovage rhizomes and roots are part of botanicals such as "Phytolysin®", capsules No. 40, and "Phytolysin®", paste for preparing oral suspension (Herbapol, Poland), "Kanefron® N", film-coated tablets, and "Kanefron® N", oral drops (Bionorica, Germany), and their analogues [253]. Lovage preparations are used for the treatment of kidney and bladder diseases as diuretic, antibacterial, anti-inflammatory, antispasmodic, and antilithogenic agents [105, 254].

Canada goldenrod (*Solidago canadensis* L.)

Canada goldenrod (*Solidago canadensis* L.) is a perennial herbaceous plant of the genus *Solidago* L. of the *Asteraceae* L. family.

The main BASs of Canada goldenrod herb (*Solidago canadensis herba*) are flavonoids. The most significant compound is the flavonol rutin (quercetin-3-O-β-rutinoside) [255]. In a dry alcohol-ether extract from *S. canadensis* inflorescences, aglycones — quercetin, kaempferol, and isorhamnetin, and their glycosides quercetin-3-O-β-D-rutoside (rutin), quercetin-3-O-β-D-glucoside (isoquercitrin), quercetin-3-O-6"-acetylglucoside, quercetin-3-O-β-D-rhamnoside; kaempferol-3-6"-acetyl-β-glucoside, kaempferol-3-O-α-L-rutoside (nicotiflorin), kaempferol-3-6"-O-acetyl-β-glucoside; isorhamnetin-3-O-α-L-rhamnopyranoside were found [256]. From the butanol fraction of an 80 % ethanol extract of *S. canadensis herba* (Russian raw material samples), 4 individual compounds were isolated: quercetin-3-O-β-D-6"-acetyl-glucopyranoside (8.2 mg); quercetin-3-O-rutinoside (rutin) (6.93 mg); quercetin (3.34 mg); and isorhamnetin-3-O-β-D-rutinoside (narcissin) (3.02 mg) [257]. In a 70 % ethanol extract of raw material from the Tver region, chicoric, caffeic, chlorogenic, quinic, and ferulic acids were identified. The total content of hydroxycinnamic acid derivatives was (1.16 g ± 10.7 mg)/100 g, with caffeic acid being dominant (0.6 g ± 12.3 mg)/100 g, calculated as dry raw material [258].

The component composition of essential oil from *Canada goldenrod herba* was also studied; its basis consists of monoterpene (49.02 %) and sesquiterpene (24.26 %) hydrocarbons, monoterpene (7.13 %) and sesquiterpene (6.03 %) alcohols, esters, and monoterpene carbonyl compounds (3.88 %). In the essential oil obtained from Egyptian raw material, the main components were germacrene D (9.86–29.47 %), α-pinene (3.38–29.17 %), γ-cadinene (0.39–20.36 %), myrcene (2.98–13.74 %), and limonene (4.81–11.47 %) [259]; in the essential oil of goldenrod herb from Slovakia, the main components are germacrene D (34.9 %), limonene (12.5 %), α-pinene (11.6 %), β-elemene (7.1 %), and bornyl acetate (6.3 %) [260].

The minimum inhibitory concentration against PMs was studied for the essential oil obtained from a Romanian raw material sample containing α-pinene (27.89 %), germacrene D (13.17 %), limonene (12.28 %), and bornyl acetate (5.76 %). It ranged from 1.41 mg/mL to 2.81 mg/mL for Gram-positive PMs and from 2.81 mg/mL to 22.5 mg/mL for Gram-negative PMs. Adhesion to the substrate was prevented only in Gram-positive bacterial strains and some yeasts (*Candida albicans* and *Candida famata*) at concentrations from 0.70 mg/mL to 2.81 mg/mL. The microbial adhesion index of the essential oil ranged from 0.19 % to 82.48 %. When testing antimicrobial and antifungal activities, the following values were obtained: *Candida utilis* — resistant; *Candida albicans* — 7.67 ± 0.47 mm; *Acinetobacter baumannii* — 7.67 ± 0.47 mm; *Pseudomonas aeruginosa* — 8 ± 0.82 mm; *Klebsiella pneumoniae* — 8 ± 0.82 mm; *Escherichia coli* — 8.33 ± 0.47 mm; *Candida famata* — 8.33 ± 0.47 mm; *Enterococcus faecalis* — 10.67 ± 0.47 mm; *Bacillus subtilis* — 21.5 ± 0.41 mm; *Staphylococcus aureus* — 22.67 ± 0.47 mm [261].

Upon analysis of scientific literature on the diuretic activity of *S. canadensis herba* botanicals, a deficit of scientific data was found. In studies by P.M. Abdel Baki et al., the diuretic activity of essential oil and standardized dry extract from *S. canadensis* inflorescences was studied (total phenolic compounds in the ethanol fraction — 9.38 ± 0.004 g calculated as gallic acid, and flavonoids in the aqueous extract — 39.75 ± 0.005 g calculated as rutin per 100 g of dry extract, respectively). Diuretic activity was calculated relative to furosemide (at a dose of 20 mg/kg, it showed equivalent activity). Results: 70 % ethanol

ОБЗОР
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extract (at a dose of 400 mg/kg) exhibited the highest diuretic activity (91 % of furosemide activity) and was higher than spironolactone and "Cystinol®" (59 % and 74 % of furosemide activity, respectively); the ethyl acetate fraction of the ethanol extract (400 mg/kg) showed moderate effect values (58 % of furosemide activity); the aqueous extract (400 mg/kg) showed lower diuretic activity (46 % of furosemide activity); the essential oil (400 mg/kg) showed the lowest efficacy (31 % of furosemide activity) [262].

Extract of Canada goldenrod herb is part of complex herbal MPs — "Marelin®", film-coated tablets (ZAO "VIFITEKH", Russia), "Phytolysin®", capsules No. 40, "Phytolysin®", paste for preparing oral suspension (Herbapol, Poland), "ProstaNorm®", film-coated tablets (JSC "PharmVILAR", Russia). Goldenrod preparations are used for the treatment and prevention of kidney, bladder, and prostate diseases as diuretic, antispasmodic, anti-inflammatory, and lithokinetic agents [263].

Common juniper (*Juniperus communis* L.)

Common juniper (*Juniperus communis* L.) is a perennial shrub of the genus *Juniperus* L. of the *Cupressaceae* Gray. family.

The main group of BASs in common juniper fruits (*Juniperi communis fructus)* is essential oil. The dominant component is the bicyclic monoterpene α-pinene (from 31.0 % to 49.0 %) [264]. Monoterpene hydrocarbons constitute the main group of essential oil components (73.5–93.7 %) [265]. In the essential oil from juniper fruits collected in India, the component composition is represented by monoterpene hydrocarbons, including α-pinene (14.31–27.37 %), D-limonene (15.80–29.70 %), β-myrcene (4.12–14.23 %); sesquiterpene alcohols, including β-elemene (0.77–3.65 %) and germacrene D (0.20–6.15 %); sesquiterpenoid hydrocarbons, including α-cadinol (5.63 %) and α-bisabolol (0.95–6.71 %) [266]. In an essential oil sample from fruits collected in Portugal, 97 compounds were identified, constituting (99.2–99.9 %) of the total oil, with high content of α-pinene (41.6 %), β-pinene (27.6 %), and limonene (6.4 %). A commercial essential oil sample contained a lower amount of α-pinene (31.1 %) [267]. Essential oil from juniper fruits growing in northern Iran included sabinene (36.8 %), α-pinene (20 %), limonene (10.6 %), germacrene D (8.2 %), and myrcene (4.8 %) as main components [268]. Analysis of the volatile organic compound composition of essential oil from different regions of Russia (Saratov, Moscow, Leningrad, Novosibirsk regions) showed that elevated concentrations of main components were found in the Novosibirsk region: α-pinene (59.81 %), β-pinene (14.84 %), α-limonene (2.50 %), β-caryophyllene (2.20 %), terpinene-4-ol (2.0 %), α-terpineol (1.73 %), o-cymene (1.72 %), camphene (1.70 %), and longifolene (1.14 %) [269].

The diuretic effect of *J. communis* botanicals is due to the ability of essential oil components (terpinene-4-ol, etc.) to irritate the urothelium of the renal glomeruli, promoting increased diuresis [270], which explains the contraindications for individuals with acute inflammatory kidney diseases [271].

In studies, a 10 % infusion of dried juniper fruits, juniper essential oil (0.1 % aqueous solution), and terpinene-4-ol (0.01 % aqueous solution) effectively stimulated diuresis in rats from the 2nd day without electrolyte loss, with the infusion showing the greatest diuretic activity on the second (+43 %) and third days (+44 %) [272]. An aqueous extract from juniper fruits at doses of 500 mg/mL, 1000 mg/mL, and 2000 mg/mL *in vitro* reduced the weight of calculi consisting of calcium oxalate (50 %), calcium phosphate (20 %), ammonium magnesium orthophosphate (10 %), and ammonium (20 %) from 1458 mg to 1162 mg, 1124 mg, 1136 mg, 1144 mg, 1096 mg, 1126 mg, and 1130 mg, respectively [273].

Dry hexane, chloroform, ethyl acetate, methanolic, and aqueous extracts (aqueous solutions in 1 % dimethyl sulfoxide) at a dose of 10 μL were tested for antibacterial activity against PMs *Acinetobacter baylyi, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa*, and *Staphylococcus aureus*. All tested extracts were moderate inhibitors of bacterial growth. The most susceptible bacterial species to all extracts was *Klebsiella pneumoniae*. *Proteus* spp. were very sensitive to all extracts except the hexane extract. Methanolic, aqueous, and ethyl acetate extracts inhibited the growth of *Acinetobacter baylyi and Staphylococcus aureus*, while *Escherichia coli* and *Pseudomonas aeruginosa* were inhibited only by methanolic and aqueous extracts. The ethyl acetate extract

demonstrated the highest activity against the growth of *Proteus mirabilis, Proteus vulgaris*, and *Staphylococcus aureus*. The ethyl acetate extract was an effective inhibitor of bacterial growth with minimum inhibitory concentration values < 1000 μg/mL against several bacterial species [274]. Essential oil from Romanian juniper fruits exhibits strong antifungal activity against *Aspergillus niger* (20.33 mm) and antibacterial activity against *Micrococcus luteus* (22.66 mm) and Staphylococcus aureus (17.33 mm), with lower efficacy against Gram-negative bacteria such as *Escherichia coli* (7 mm), which showed resistance to ampicillin. *Candida albicans* demonstrated resistance to the essential oil [271].

Dyers' madder and Georgian madder (*Rubia tinctorum* L.)

Dyers' madder (*Rubia tinctorum* L.) and Georgian madder (*Rubia iberica* (Fish. ex DC). C. Koch) are perennial herbaceous plants of the genus *Rubia* L. of the *Rubiaceae* Juss. family.

The main group of BASs in madder rhizomes and roots (*Rubiae rhizomata* et radices) are anthraquinones, among which the dominant and most active component is ruberythric acid (alizarin-2-xylosylglucoside). Madder rhizomes and roots are a source for obtaining "Madder Extract", tablets (JSC "Pharmcenter VILAR", ZAO "VIFITEKH", Russia), "Urocistenal", oral drops (OOO "Pharmamed", Russia), and others.

Madder rhizome and root extract possesses diuretic, antispasmodic, and stone-dissolving effects on phosphate calculi, promoting their excretion from the kidneys and urinary tract. The litholytic (stone-dissolving) effect of anthraquinones from madder is explained by complex formation with calcium and magnesium cations, which are components of loose-structure renal stones, primarily of phosphate nature. Extractive substances from madder rhizomes and roots help reduce the tone and increase the peristalsis of the renal pelvis and ureters, promoting the movement and excretion of calculi from the body.

Experimental studies have established that a renal stone weighing 20 mg decreased by 5 mg after 15-day exposure to a 5 % madder extract solution. The stone turned red and acquired a loose structure. During the study, the effect of dry madder extract on diuresis under water load in rats was evaluated. Single administration of the extract (at a dose of 100 mg/kg) caused a 114 % increase in diuresis. With 12-fold administration of the extract (at a dose of 100 mg/kg) over 14 days, the following dynamics were observed: on the first day, diuresis increased by 40 %, and by the eighth day — by 55 %.

Clinical studies have demonstrated the efficacy of the extract in nephrolithiasis. In patients with calculi of various localization (kidneys, ureters, and bladder), taking the extract at 2 tablets 3 times a day for 15–25 days contributed to: a decrease in pain intensity and an increase in the excretion of sand and small calculi. After completing the course of treatment and surgical removal of large stones from the renal pelvis, no recurrences were observed within 6 months. Administration of the extract for one month contributed to an improvement in urine composition, a decrease in pyuria, and the disappearance of erythrocytes[2].

Official medicinal products for the treatment and prevention of chronic infectious and inflammatory diseases of the kidneys and urinary tract

In most recommendations in global medical practice, antibiotic therapy is considered the primary and standard method for preventing CIDKUT recurrences [275]. For example, the recommended first-line empirical antibiotic therapy for acute uncomplicated bacterial cystitis in healthy non-pregnant women includes a 5-day course of nitrofurantoin, a single dose of fosfomycin, or a 5-day course of pivmecillinam [29, 276].

Plant-derived drugs are widely used as auxiliary, and less commonly, as primary agents in the comprehensive treatment and prevention of CIDKUT [277]. Combined MPs registered under the trade names "Kanefron® N", "Cystone®", "Phytolysin®", "Urolesan®", "Urohol®", "Rovatinex®", "Fito-nefrol®", and "Brusniver®" have gained the widest distribution [278, 279]. The active components of the listed MPs allow for the desired pharmacological effects, including improved renal blood flow, suppression of PMs, and increased diuresis, consequently leading to improved urodynamics of the urinary tract [280].

[2] Medicinal preparations from plants (VILAR's experience): a scientific publication; Vechkanova SA, Kolkhir VK, Sokolskaya TA, Voskoboinikova IV, Bykov VA. Moscow: MADRID; 2009. 432 p. Russian

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Medicinal products of the "Kanefron® N" series

The therapeutic effect of the "Kanefron® N" series of MPs (Bionorica SE, Germany) is achieved through the combination of BASs from a mixture of MPRMs — herb of centaury *(Centaurii herba),* roots of garden lovage (*Levistici officinalis radices*), and leaves of rosemary (*Rosmarinus officinalis folia*). "Kanefron® N" series MPs are used in three dosage forms — as film-coated tablets containing either a mixture of powdered MPRMs or a total extract from the MPRM mixture in one formulation, and as a solution (drops) containing an extract from the MPRM mixture in another. "Kanefron® N" series MPs possess diuretic, antispasmodic, antibacterial, and anti-inflammatory activity and are used in the treatment of acute and chronic kidney and bladder infections (pyelonephritis and cystitis), as well as urolithiasis [281].

In studies on rats with cystitis, it was found that "Kanefron® N" series MPs reduce the intensity of the inflammatory process and hyperalgesia. Researchers attribute these effects to the inhibition of prostaglandin E2 and leukotriene B4 biosynthesis [282]. "Kanefron® N" series MPs selectively inhibited NF-κB cytokines, responsible for the immune response in inflammatory reactions, positioning them as immunomodulators. The study authors also found that "Kanefron® N" series MPs exhibit RIPK1 inhibitor properties — a protein involved in cell apoptosis, which is of particular significance in inflammatory processes caused by uropathogens [283].

In primary healthcare, treatment with "Kanefron® N" allows avoiding additional antibiotic load in most patients with acute recurrent cystitis and chronic pyelonephritis [284].

Several studies on the use of "Kanefron® N" series MPs in combination with traditional MPs have proven that "Kanefron® N" effectively reduces inflammation, improves renal microcirculation, and lowers pro-inflammatory cytokine levels [285, 286]. The combination of "Kanefron® N" + "Furamag®" (furazidin) significantly reduces the number of relapses in the long term [287, 288]. The combination of "Kanefron® N" + "Flamax Forte®" (ketoprofen) achieves efficacy without the use of antibacterial agents [289].

Studies confirm the safety of "Kanefron® N" series MPs regarding the fetus. During the first trimester of pregnancy, "Kanefron® N" did not exert a teratogenic effect on the fetus or affect the general condition of newborns [290]. Therapy in women of reproductive age suffering from acute recurrent cystitis shows a decrease in the frequency of relapses, as well as cases of bacteriuria and pyuria. The use of MP "Kanefron® N" reduces the risk of bacterial resistance to antibiotics [291]. In the treatment of asymptomatic bacteriuria in pregnant women, in the group treated with the classical antibiotic therapy regimen (fosfomycin 3 g single dose or cefixime 400 mg once daily for 7 days or amoxicillin-clavulanate (500 + 125 mg) three times daily for 7 days), cystitis occurred in one patient, and pyelonephritis in three; in the group receiving therapy with the plant-based preparation, the outcome was more favorable — one case of cystitis and no cases of pyelonephritis [292].

In the treatment of chronic pyelonephritis, 6 months after completing treatment with "Kanefron® N", patients showed no bacteriuria, leukocyturia, lumbar pain, or elevated temperature. In the second group, the situation was as follows: patients retained leukocyturia and bacteriuria. Thus, the second group of patients showed slower recovery and retained some symptoms even six months after the start of treatment [293]. A comparison of the efficacy of monotherapy with "Kanefron® N" and ciprofloxacin revealed that with phytotherapy for 30 days, the probability of recurrence within a year was 5 %, while with antibiotic use, this indicator reached 12.5 %. Side effects were not identified with phytotherapy, whereas they were observed in 18.8% of cases in classical therapy [294].

The efficacy of "Kanefron® N" series MPs was also studied in Phase III clinical trials. In the group of patients using "Kanefron® N", it was found that 238 patients (83.5 %) did not require additional antibiotic therapy ($p < 0.0014$). During the study, 13 patients (4.0 %) experienced side effects in the form of gastrointestinal dyspeptic disorders, while in the group receiving fosfomycin antibiotic therapy, there were 22 such cases (6.6 %). In the group using fosfomycin, one patient experienced an exacerbation of chronic pancreatitis, and one case (0.3 %) of mild pyelonephritis was recorded. In 5 patients (1.5 %) in the group using "Kanefron® N", pyelonephritis was detected — in 4 patients in a mild form and in 1 in a moderate form. The authors attribute this to the

fact that 3 episodes of pyelonephritis occurred on the same day and 1 episode the next day, which may indicate that the disease could have developed without diagnostic signs [295, 296].

During the study of the efficacy of monotherapy with "Kanefron® N" series preparations, it was found that they demonstrated high efficacy in treating acute cystitis. Fifty-one women participated in the study, with "Kanefron® N" ensuring complete recovery in 22 patients from the main group (88.5 %), and the risk of recurrence was recorded in two (7.7 %) [297].

The State Pharmacopoeia of the Russian Federation, 15th ed. (pharmacopoeial articles: GPhM.3.4.0028.22 "Centaury Herb + Garden Lovage Rhizomes and Roots + Common Rosemary Leaves Liquid Extract, Oral Solution" and GPhM.4.0027.22 "Centaury Herb + Garden Lovage Rhizomes and Roots + Common Rosemary Leaves, Tablets") regulates the quality of MPs comprising the "Kanefron® N" series, as well as its analogues —"Nephrosten®" (ZAO "Evalar", Russia), "Kanefit®" (ZAO "VIFITEKH", Russia), Phytofron®" (JSC "PharmVILAR", Russia), etc.

Medicinal products of the "Phytolysin®" series

"Phytolysin®" series MPs (Herbapol, Poland) are produced in two dosage forms — capsules for oral administration and paste for preparing oral suspension. "Phytolysin®" is a combined MPs containing a mixture of extractive substances or thick extracts of curly parsley roots, fenugreek seeds, knotgrass herb, creeping wheatgrass rhizomes, birch leaves, common horsetail herb, garden lovage rhizomes and roots, common goldenrod herb, and dry outer scales of onion bulbs. The composition has diuretic, anti-inflammatory, and antispasmodic effects and promotes reduced crystallization [105, 254]. "Phytolysin®" series preparations help reduce clinical symptoms of infectious diseases, normalize diuresis, and increase urine pH, which directly affects the level of stone-forming substances. With prolonged use, they reduce the number of urolithiasis recurrences [298] by enhancing uric acid excretion [299]. Comprehensive therapy of acute and recurrent chronic cystitis with "Phytolysin®" series preparations allowed for the relief of major infection manifestations within 3–4 days. Patients reported no recurrences for six months after therapy [300]. Combined antibacterial therapy using "Phytolysin®" in conjunction with fosfomycin achieved sterile urine cultures in patients after three months of treatment [301].

Medicinal products of the "Urolesan®" series

"Urolesan®" series MPs (OOO "ART-PHARM", Russia) are available in three dosage forms — capsules for oral administration, solution (drops) for oral administration, and syrup. An analogue of "Urolesan®" is "Urohol®", oral drops (ZAO "VIFITEKH", Russia). The active components of the MPs are Siberian fir needle essential oil, peppermint leaf essential oil, wild carrot seed liquid extract, common hop cone liquid extract, common oregano herb liquid extract, and castor bean seed fixed oil. The drop form of the preparation contains ethanol (60 % to 80 % vol.).

In clinical studies (n = 195), it was found that when "Urolesan®" series MPs were prescribed, positive dynamics in relieving acute cystitis symptoms were achieved in 82.6 % of cases in capsule form and 80.9% in drop form [302].

The litholytic activity of "Urolesan®" series MPs was established. Ninety-five patients diagnosed with urolithiasis participated in the study. The size and average density of concretions in patients were (7.4 ± 0.5) mm and (767 ± 25) Hounsfield units, respectively. Patients were divided into a control group (n = 40) and a group receiving treatment with "Urolesan®" for 1 month. As a result, in the "Urolesan®" group, a reduction in concretion size and density to (6.2 ± 0.3) mm and (623 ± 20) units, respectively, was observed. Results in the control group were as follows: stone size and density 7.2 ± 0.3 mm and 754 ± 22 units, respectively [303].

The possibility of using "Urolesan®" series MPs was also studied in pediatric practice. Sixty-three children aged 5 to 15 years diagnosed with "chronic complicated pyelonephritis and secondary hyperoxaluria" participated in the study. Patients were divided into two groups: Group 1 received "Urolesan®" syrup according to the instructions for use in combination with antibiotic therapy and furazidin in prophylactic dose; Group 2 received antibiotic therapy in combination with furazidin in prophylactic dose and did not receive "Urolesan®". As a result, general urine analysis parameters normalized in both groups, with Group 1 showing improvements 2–3 days earlier.

ОБЗОР
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Normalization of oxalate excretion and urine pH after one month of therapy was recorded in 25 (78.1 %) patients (in the control group, 19–61.3 %), and serum uric acid levels were 1.2–1.5 μmol/L compared to baseline. Asymptomatic bacteriuria was observed in only one patient in Group 1 and four in Group 2. Relapses were absent in 30 patients (93.7 % of cases) in Group 1 and 25 (80.6 %) patients in Group 2. During therapy, botanicals were well tolerated. Two patients experienced a mild allergic rash while taking "Urolesan®" [304, 305].

"Brusniver®" herbal collection

The herbal collection "Brusniver®" (JSC "Krasnogorsklekredstva", Russia) consists of the following components: common bearberry leaves — *Vaccinii vitis-idaeae folia* (50 %), St. John's wort herb — *Hyperici herba* (20 %), rosehip fruits — *Rosae fructus* (20 %), three-part beggar-ticks herb — *Bidenti tripartitae herba* (10 %). The collection in the form of infusion and decoction exhibits antimicrobial, pronounced anti-inflammatory, and mild diuretic activity.

The bacteriostatic effect of an aqueous extract from the "Brusniver®" collection was studied using the double serial dilution method. *In vitro* experiments showed that the extract from the collection had antimicrobial and antifungal activity against a range of pathogenic microorganisms, including Gram-positive *Staphylococcus aureus* 209-P; Gram-negative *bacteria Escherichia coli M-17, Proteus vulgaris H-3137, Pseudomonas aeruginosa 44;* yeast-like and mold fungi *Microsporum lanosum, Candida albicans* 1755. During the study, the effect of the infusion from the collection on diuresis in rats was evaluated. The infusion was administered at a dose of 1000 mg/kg and exerted a diuretic effect in experiments with 5-hour diuresis, increasing urine output by 11.9 %.

The efficacy of combined therapy in patients (n = 31) with various nosological forms of CIDKUT (pyelonephritis, urolithiasis, urethritis, prostatitis, and cystitis) was studied in clinical trials using an infusion from the "Brusniver®" collection in combination with broad-spectrum antibacterial drugs (cephalosporins, aminoglycosides, semi-synthetic penicillins). The therapy demonstrated a positive effect in 26 patients (83.8 %)[3].

[3] Ibid.

Official medicinal products for the treatment and prevention of urolithiasis

Medicinal products "Rovatinex®", enteric-coated capsules

Currently, terpenes derived from plant raw materials are successfully used in medicine [306]. Terpene-based preparations possess antispasmodic, diuretic, anti-inflammatory, and lithokinetic actions [307]. An example of such a preparation is "Rovatinex®" [308]. The active substances of "Rovatinex®" (Rova Pharmaceuticals Ltd, Ireland) are anethole, borneol, camphene, and cineole, which exert diuretic, anti-inflammatory, and antibacterial effects; pinene enhances renal blood flow; fenchone initiates antispasmodic effect [309]. "Rovatinex®" is a drug of choice for lithokinetic therapy of calculi of various chemical etiologies, as well as in the complex therapy of chronic pyelonephritis [21, 310].

In *in vivo* studies, it was demonstrated that upon administration of "Rovatinex®", patients experienced a decrease in leukocyturia, and daily diuresis increased, which facilitated the effective passage of calculi. Stone migration after extracorporeal shock wave lithotripsy and administration of "Rovatinex®" in the control group was observed on days 1–5 [309]. Urine pH was also normalized, which directly affects the reduction of urolithiasis recurrences. Course administration of "Rovatinex®" was not accompanied by complications or side effects [311–313].

In a study by W.N. Jaffal, the lithokinetic activity of "Rovatinex®" and tamsulosin after extracorporeal shock wave lithotripsy was investigated. Patients were divided into groups: Group A, consisting of 28 patients, served as the control group; Group B, consisting of 28 patients, received tamsulosin capsules 0.4 mg once daily; Group C, consisting of 28 patients, received "Rovatinex®" one capsule three times a day before meals. Clinical success was defined as the presence of residual calculi with a diameter of 4 mm or less. Clinical success was achieved in: 23 % of patients in Group A; 48 % in Group B; 44 % in Group C. After 8 weeks, the following dynamics were observed: Group A — 46 %; Group B — 80 %; Group C — 76 %. No complications were observed during treatment, except for hematuria, which was noted in 26 % of patients in Group A, 8 % in Group B, and 12 % in Group C [314].

Later, in a study by H.R. Mohammed et al., the efficacy of "Rovatinex®" was confirmed. Four weeks

after taking "Rovatinex®" (n = 30), 8 (13.3 %) patients had complete disappearance of calculi, compared to the control group (1 patient — 6.7 % in the control group). After eight weeks — in 53.3 % of patients (33.3 % in the control group) ($p > 0.05$). After twelve weeks, in 93.3 % of cases in the group receiving medicine "Rovatinex®", complete stone clearance was observed compared to the control group (80 %) ($p > 0.05$) [315].

Medicinal product "Cystone®", tablets

"Cystone®" (Himalaya Drug Co., India) includes the following active components: extract of two-lobed stem flowers, extract of saxifrage tongue stem, extract of heart-leaved madder stem, extract of couch grass rhizomes, extract of rough-fruited cinquefoil seeds, extract of bracteate onosma herb, extract of ash-colored vernonia, powder of silicate of lime, and powder of purified mumijo [316]. 192 patients participated in clinical studies. The study showed that in 107 (64.84 %) patients, "Cystone®" promoted stone dissolution (lysis); in 10 (6.06 %) patients, stone size decreased; in 17 (10.3 %) patients, size did not change; in 31 (18.78 %) patients, stone size increased [317, 318]. The use of "Cystone®" in combination with hydrochlorothiazide did not enhance the efficacy of monotherapy with the plant-based drug in treating and eliminating urinary tract stones [319].

Medicinal products containing madder extract

Extracts from madder rhizomes and roots (see subsection "Dyers' madder and Georgian madder") are part of many herbal collections and combined MPs with urolithic activity. The most well-known among them are "Cystenal", oral drops, "Madder Extract", 250 mg tablets, and "Marelin®", film-coated tablets.

"Marelin®" is a combined MPs (ZAO "VIFITEKH", Russia), which includes extracts of dyers' madder rhizomes and roots, Canada goldenrod herb, common horsetail herb, lily of the valley cardiac glycoside sum, kellin furanocoumarin, and salicylamide. The preparation has diuretic properties, enhances the peristalsis of the renal pelvis and ureter musculature. It is used as a remedy for treating kidney stone disease [25, 320].

In studies conducted by V.V. Ivanov, the clinical efficacy of "Marelin®" was investigated. It was found that over six years of therapy, 30 patients in the main group (100 people) receiving therapy with "Marelin®" experienced recurrent relapses. In the control group (also 100 people), which did not receive treatment with the botanicals, relapses occurred in 70 people [321].

Promising sources of plant-based medicinal products for the treatment of chronic infectious and inflammatory diseases of the kidneys and urinary tract

The current state of the Russian pharmaceutical market is characterized by the prevalence of domestic monopreparations. In the segment of multicomponent plant-based MPs, approximately 70 % are represented by foreign products [322, 323]. Under these conditions, the search for new sources of BASs among non-official domestic plant raw materials, and the expansion of the range of medicinal products with a full technological production cycle within the country, leading to a reduction in imports of drugs and raw materials from other countries, become particularly significant. This is especially important for ensuring national security and supply stability. Competitive Russian drugs can be in demand on the international market, contributing to increased exports and strengthening the position of the Russian Federation in the international pharmaceutical market.

True bedstraw (*Galium verum* L.)

True bedstraw (*Galium verum* L.) is a perennial herbaceous plant of the genus *Galium* L. of the *Rubiaceae* Juss. family [324].

Currently, true bedstraw is not an official MPRMs source. Data on the plant's use in folk medicine should be considered. The above-ground part of *G. verum* is used for epilepsy seizures and psychoses. In Serbia, *G. verum* is used as a tonic, antiscorbutic, and sedative agent. Several other properties have been noted: diaphoretic, diuretic, and antispasmodic; it is also used for treating skin diseases [325].

True bedstraw herb (*Galii veri herba*) has attracted the scientific community's attention as a promising source of BASs in the last decade. In a study by I.L. Shynkovenko et al., the chromatographic profile of an alcoholic extract of *G. verum* (extractant 96% ethanol) was studied. Seven saponins belonging to the ursane type (ursolic, euscaphic, tormentic acids, and uvaol), oleanane type (oleanolic acid), and lupane

ОБЗОР
DOI: 10.19163/2307-9266-2026-14-1-31-80

type (betulin and lupeol) were detected, with lupane-type saponins predominating (2.50 mg/mL), and lupeol being the dominant compound (1.60 mg/mL) [326].

In G. verum herba, iridoid glycosides — derivatives of asperuloside and loganin — were identified [327]: asperuloside, asperulosidic acid, diacetyl-asperulosidic acid, 10-diacetylasperulosidic acid, 6-O-epi-acetylscandoside, daphylloside, diacetyl-daphylloside, loganin, 10-hydroxyloganin, monotropein, scandoside, seco-galioside, geniposidic acid, 10-hydroxymoronoside [328, 329]. The sum of iridoids calculated as asperuloside in *G. verum herba* growing in Estonia was 40.8 ± 2.9 mg/g [330]. L.Ö. Demirezer et al. isolated and identified 7 iridoid glycosides individually, such as asperuloside, asperulosidic acid, diacetyl-asperulosidic acid, monotropein, 6-O-epi-acetylscandoside, daphylloside, and diacetyl-daphylloside [331].

Gas chromatography-mass spectrometry was used to establish the profile of volatile organic compounds. In a study by I. Ciotlaus et al., it was found that the volatile organic compounds of the dry herb extract were mainly aldehydes — 35.48 %, monoterpenes — 35.48 %, alcohols — 11.96 %, sesquiterpenes — 3.71 %, acetates — 3.14 %, and others — 10.11 %. The main composition of fresh herb was represented by monoterpenoids (73.57 %). Fifty compounds were identified, among which the dominant components were linalool — 30.08 % and eucalyptol — 13.87 % [332]. K. Antoniak et al. conducted a study of the essential oil of *G. verum herba* growing in Poland. The analysis yielded 2.60 mL/kg of essential oil, in which 71 components were identified, with the predominant compounds being palmitic acid — 10.87 %, anethole — 8.39 %, menthol — 5.28 %, and linoleic acid — 4.91 %. Carvone, β-ionone, phytol, menthone, estragole, linalool, and β-farnesene were present in smaller quantities [333].

One of the dominant groups of BASs in the above-ground part of *G. verum* are phenolic compounds [334–336]. In ethanol (35 %, 50 %, 60 %, 70 %, and 100 %) and methanol (70 %, 80 %, and 100 %) extracts, the following BASs were identified: gallic acid, caffeic, chlorogenic, neochlorogenic, 3,5- and 4,5-dicaffeoylquinic, vanillic, coumaric, ferulic acids, umbelliferone, and flavonoids: catechin, kaempferol, quercetin, quercitrin, isoquercitrin, rutin, hyperoside, luteolin, apigenin-7-O-rutinoside, isorhamnetin-3-O-glucoside [326, 328, 337]. When studying aqueous, alcoholic (96 %), and aqueous-alcoholic extracts of various concentrations (20 % and 60 %), it was found that all extracts contained chlorogenic acid and rutin; the alcoholic extract also contained cynaroside and quercetin; the aqueous extract and 20 % aqueous-alcoholic extract contained polysaccharides [338].

The content of phenolic compound classes in 20 %, 60 %, and 96 % extracts of *G. verum herba* was also determined. Hydroxycinnamic acid derivatives, flavonoids, and polyphenolic compounds were determined in the obtained extracts. It was found that the 20 % extract contained 3.1 % hydroxycinnamic acid derivatives, 0.24 % flavonoids, and 2.9 % polyphenolic compounds; the 60 % extract contained 4.13 % hydroxycinnamic acid derivatives, 0.16 % flavonoids, and 3.84 % polyphenolic compounds; the 96 % extract contained 2.7 % hydroxycinnamic acid derivatives, 0.18 % flavonoids, and 2.9 % polyphenolic compounds [339]. The dominant components (in μg/g dry extract) in the alcoholic extract of dry extract (1 mg/mL) were: chlorogenic acid (15.561 ± 778), cynaroside (9612 ± 288), isoquercitrin (6873 ± 206), and quercetin (179.1 ± 53.7) [340]. The quantitative composition of phenolic compounds in *G. verum herba* was determined in terms of leading compounds. According to the authors [324], the content of flavonoid substances in raw material sources is as follows: from the Russian Federation — 23.4 mg/g (hyperoside); in Ukraine and the Republic of Belarus — 4.18 mg/g and 130.7 mg/g, respectively (rutin) [336, 339, 343]; from Romania, Estonia, and Croatia — 6.88 μg/g, 7.3 mg/g, and 23.11 mg/g, respectively (quercetin) [330, 337, 342]. The content of polyphenol substances calculated as gallic acid was as follows: raw material from Romania, Moldova, Estonia, and the Republic of Belarus — 1.97 mg/g [337], 26.21 mg/g [343], 27.2 mg/g [333], and 119.5 mg/g [341], respectively. Analysis of the data indicates a lack of standardization in approaches to the quantitative assessment of phenolic compounds in *G. verum herba*. However, a trend towards using quercetin and gallic acid as standard substances for assessing flavonoid and polyphenol content is observed.

An aqueous extract of the herb, administered intragastrically to male and female white mice and rats, showed no acute or chronic toxicity. No animal

died during the experiment. Thus, the aqueous extract of *G. verum*, according to the classification of chemical substances by hazard level, belongs to hazard class IV — slightly hazardous substances (GOST 12.1.007.76) [344].

A.L. Zayko and T.A. Bryukhanova studied the effect of *G. verum* extracts on kidney excretory function. Wistar albino rats were used in the experiment. Animals received aqueous (1:1) and alcoholic extracts (20 %, 60 %, and 96 %). A decoction of common horsetail herb (1:10) served as a comparison drug. The results showed that the 60 % aqueous-alcoholic extract had the highest diuretic activity compared to the comparison drug (2.13±0.09 mL of urine excreted after 2 hours and 3.86 ± 0.11 mL after 4 hours), with 1.89 ± 0.04 mL of urine excreted after 2 hours and 3.80 ± 0.07 mL after 4 hours [345]. An infusion of *G. verum herba* (1:10) was studied for antilithogenic activity using an oxalate (ethylene glycol) nephrolithiasis model. The infusion was administered enterally at 1 mL/day to male Wistar rats. No formation of new calculi and slowed growth of existing ones were detected. Stone size decreased by 64 % [346].

Phenolic compounds of *G. verum herba* exhibit anti-inflammatory, antibacterial, and antioxidant effects [347, 348]. The herb infusion affected the exudation phase. The effect reached statistically significant results after the first hour and peaked at two hours. Inflammation reduction was recorded at 37 %, which is one and a half times higher than the activity indicators of the control group [349]. Alcoholic extracts also showed the ability to reduce pro-inflammatory IL-8 and IL-6 levels [350].

The antifungal activity of an ethyl acetate-alcoholic (8:2) fraction of *G. verum herba* against 10 *Candida* species was studied, showing a decrease in the order: *C. famata, C. intermedia ATCC 14439, C. intermedia Y-59, C. rugosa, C. tropicalis F-195, C. tropicalis 195, C. albicans, C. parapsilosis, C. utilis, and C. glabrata.* The antifungal activity of G. verum was at the level of the antifungal drug fluconazole [351]. The authors studied the antimicrobial activity of aqueous, alcoholic (96 %), and aqueous-alcoholic extracts of *G. verum herba* at various concentrations (20 % and 60 %) against PMs: *Proteus vulgaris, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Bacillus subtilis.* The extracts were active against both Gram-positive and Gram-negative microorganisms. However, Gram-negative *Proteus vulgaris and Pseudomonas aeruginosa* showed the least sensitivity to all extracts. The extracts exhibited only bacteriostatic activity against these microorganisms [338]. This is discussed in the studies by A.D. Semenescu et al. and A. Ohindovschi et al. Gram-negative bacterial strains, due to their more complex cell wall structure, are resistant to extracts from *G. verum herba* [352, 353].

The effect of an alcoholic extract of *G. verum herba* on the regenerative processes of the skin of laboratory mice was studied. The alcoholic extract of the herb activated the skin regeneration process compared to the control group, stimulating phagocytosis, promoting fibroblast proliferation, new vessel formation (neoangiogenesis), and growth of new granulation tissue [354, 355].

Annual sunflower (*Helianthus annuus* L.)

Annual sunflower (*Helianthus annuus* L.), or sunflower, is an annual herbaceous plant of the genus *Helianthus* L. of the *Asteraceae* Bercht. family. The seeds of the plant contain up to 52% fatty oil, phospholipids, and unsaturated fatty acids. Therefore, *H. annuus* is widely used as an oilseed crop in the food industry as a rich source of fatty oil [356]. In folk medicine, the roots of annual sunflower (*Helianthi annui radices*) are used, from which extracts are applied as anti-inflammatory, choleretic, and diuretic agents. A decoction of *H. annuus radices* is taken for the treatment of diabetes mellitus, cholelithiasis, and urolithiasis [357].

The use of *H. annuus radices* as a source of BASs for the production of botanicals with diuretic and litholytic activities is promising [358]. The pharmacological activities of *H. annuus* roots are attributed to the presence of water-soluble polysaccharides, namely the polyfructosan inulin [356], which reaches 5.99 ± 0.13 % [359]. Phenolic compounds were also identified in the roots of *H. annuus* growing in the Foothill regions of the Stavropol Territory, including hydroxycinnamic acid derivatives: chlorogenic, neochlorogenic, caffeic, and ferulic acids; flavonoids: rutin, hyperoside, luteolin-7-glucoside, apigenin, dihydroquercetin, naringenin; coumarin; polyphenolic compounds: tannin, gallic and ellagic acids, epicatechin, and epigallocatechin gallate [360].

ОБЗОР
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V.V. Melik-Husseinov et al. analyzed the solubility of stones *in vitro*, showing that a calculus immersed for 14 days in a 10 % aqueous suspension of dry alcoholic extract of *H. annuus radices* decreased by 12.6 %. Samples immersed in a 10 % decoction of *H. annuus radices* decreased by 11.8 %. The control stone sample immersed in purified water decreased by 7.4 %. The *in vitro* study confirmed the *in vivo* litholytic activity study in male Wistar rats with an ethylene glycol nephrolithiasis model. The decoction also increased kidney excretory function by 2.3 times, confirming the diuretic activity of *Helianthi annui radices* BASs [361].

Rosehip (*Rosa* L.)

Rosehip (*Rosa* L.) is a perennial shrub of the genus *Rosa* L. of the *Rosaceae* Juss. family. Plants of the genus *Rosa* L. have long been used in official medicine. Rosehip fruits (*Rosae fructus*) are used as raw material, containing organic acids, vitamins, carotenoids, flavonoids, fatty oil, etc. [362]. *Rosa* L. fruits are raw material for obtaining "Holosas", which has a choleretic effect. Authors of publications propose using dog rose roots (*Rosae caninae* radices) as a promising source of BASs and phytopreparations with diuretic activity [363, 364]. *Rosa canina L*. is a plant widely distributed in the North Caucasus region [365, 366]. Currently, epicatechin, 4-hydroxybenzoic, gallic, syringic, p-coumaric, and ellagic acids, as well as the flavonoid naringenin, have been identified in the roots of *R. canina* L. by high-performance liquid chromatography. Spectrophotometric methods determined that the total content of phenolic compounds in dried rosehip roots reaches 12.73 % [367].

In an experiment, the diuretic activity of dry extracts from dog rose roots was studied in Wistar rats. A 2.0 mL solution of dry 70 % alcoholic extract was administered intragastrically at doses of 50.0 mg/kg and 100.0 mg/kg. According to the study results, diuretic activity was observed within the first two hours. The maximum effect at both studied doses occurred at the end of the 1st hour of observation and was 56 % (at a dose of 50.0 mg/kg) and 76 % (at a dose of 100.0 mg/kg) of the total diuresis. The final cumulative diuresis in the experimental groups over 5 hours was almost 2.5 times higher than the control group's result [363, 364, 368].

Garden Angelica (*Angelica archangelica* L.)

Garden Angelica (*Angelica archangelica* L.), or angelica, is a perennial herbaceous plant of the genus *Angelica* L. of the *Apiaceae* Lindl. family. In Chinese medicine, it is called "female ginseng" due to the presence of phytoestrogens [369]. Benedictine monks used angelica as a universal antidote — "Theriac". In Rus', *A. archangelica* was cultivated in apothecary gardens at monasteries and peasant farms. *A. archangelica* is used as a diaphoretic, diuretic, antiseptic, and antidepressant agent. Additionally, it helps normalize digestion. It is used to treat anorexia, migraines, bronchitis, chronic fatigue, and menstrual cycle disorders [370].

Rhizomes and roots of garden angelica (*Angelicae archangelicae rhizomata et radices*) are included in the pharmacopoeias of Great Britain, Germany, Austria, and also in the European Pharmacopoeia [371]. The pharmacological action of *A. archangelica* botanicals is attributed to the components of essential oil and coumarins [372].

The essential oil obtained from *A. archangelica rhizomata et radices* is a yellow liquid with a fresh herbaceous and slightly pungent odor with earthy and woody undertones [373]. The essential oil content in the underground part of *A. archangelica* varies significantly depending on the plant's growing region. For example, in the Republic of Bashkortostan — 0.82 % [374], in the vicinity of Mount Ozren, Serbia — 0.10 % [375]. Indian scientists tracked the dynamics of essential oil increase with increasing altitude: in the high-altitude plant physiology research center in Pothivas (2200 m) — 0.28 %; Tungnath, Rudraprayag (3300 m) — 0.33 %; Dayara, Uttarkashi (3500 m) — 0.35 % [376].

The geographical factor influences not only the content but also the component composition of the essential oil of *A. archangelica rhizomata et radices*. A study by A. Forycka et al. showed that the essential oil of Romanian, Finnish, and Serbian A. archangelica contains 62 to 122 components [377]. In domestic raw material from the Kemerovo region, 75 components were detected [378], and from Serbia — 88 compounds. However, the composition of dominant components remains unchanged. Monoterpenes constitute the largest part of the essential oil composition [379, 380]. In the essential

oil of *A. archangelica* growing in the Republic of Bashkortostan, sesquiterpenoids predominate, being 2.6 times more numerous than monoterpenoids [374].

Depending on the leading component, several types of essential oil can be distinguished, with β-phellandrene, α-pinene, sabinene, and myrcene dominating, with β-phellandrene content — 24.78–28.18 %, α-pinene — 14.52–18.14 %, α-phellandrene — 9.61–14.35 %. Essential oil from northern European regions is characterized by a high level of α-pinene — 65.3 %, α-phellandrene — 5.9–15.4 %, and δ-3-carene — 15.3 %, while in southern samples, its level is the lowest: 0–0.2 %; in the east and northeast, the leading component is α-pinene — 15.7 to 20.8 %; in the northeast, high concentrations of β-phellandrene — 13.5–16.9 %, δ-3-carene — 15.4–16.9 %, limonene — 8.0–9.0 %, sabinene — 5.0–7.5 % were noted, while the concentration of the latter in the east was higher: 5.9–14.85 %; in the southeast, the data are as follows: β-phellandrene — 13.8–18.5 %, α-pinene — 11.4–15.0 %, δ-3-carene — 10.8–11.9 %, α-cymene — 6.8–10.6 %, and α-phellandrene — 5.9–8.6 % [377, 381, 382]. The dominant components of Siberian subspecies *A. archangelica* are limonene (30.47 %) and α-pinene (23.6 %) [383].

The essential oil composition changes during storage depending on the raw material preparation (whole or ground). In a study conducted over 2.5 months, it was found that by the end of the storage period, the content of monoterpenes in whole raw material was 66.7–72.5 %, with α-pinene (15.7–19.4 %), as well as 3-carene, D-limonene, and β-phellandrene being the leading components. Studying ground raw material showed a 70 % decrease in monoterpenes, and α-pinene, 3-carene, and limonene decreased by 3.5–4 times [384].

From *A. archangelica rhizomata et radices*, the following were isolated and identified: prenylated coumarins — osthol, umbelliprenin, imperatorin, isoimperatorin, fellopterin [385]; hydroxycoumarins — umbelliferone; furanocoumarins — angelicin, bergapten, xanthotoxin, oroselone, methoxsalen, xanthotoxol, archanglicin, pimpinellin, isopimpinellin [386–388]. The total coumarin content in the rhizomes and roots of *A. archangelica* collected in Bashkiria was 1.09 %, with dominant components being angelicin, methoxsalen, bergapten, osthol, and oroselone [389, 390].

Essential oil containing monoterpenes β- and α-phellandrene (268 mg/g and 208 mg/g, respectively), α-pinene (111 mg/g), sabinene (87 mg/g), p-cymene (84 mg/g), 3-carene (74 mg/g) exhibits strong antifungal activity (inhibition zone 22–28 mm) against *Aspergillus niger and Penicillium venetum*; moderate activity (inhibition zone 15–21 mm) against *Candida albicans and Cladosporium cladosporioides*; moderate antibacterial activity (inhibition zone 15–21 mm) against Staphylococcus aureus; no antibacterial effect (inhibition zone less than 7 mm) was established against Pseudomonas aeruginosa [373, 376]. Essential oil containing α-pinene (29.7 %), δ-3-carene (14.2 %), phellandrene, and limonene (13.2 % each) has the following minimum inhibitory concentration values: 14.2 μL/mL for *Staphylococcus aureus* and 28.4 μL/mL for *Escherichia coli*. The minimum bactericidal concentration is 56.8 μL/mL and 113.6 μL/mL, respectively [375, 390].

The possibility of using coumarins as antibacterial agents is actively being investigated. Hexane, dichloromethane, and methanol extracts, and the coumarin osthol, were tested for antimicrobial activity against Gram-positive (*Staphylococcus aureus* and *Micrococcus luteus*), Gram-negative (*Pseudomonas aeruginosa*) PMs; and antifungal activity against the *Candida albicans* strain. The results showed that osthol coumarin possessed the highest antibacterial and antifungal activity against all tested strains. Along with osthol, the hexane extract also exhibited these activities — against Pseudomonas aeruginosa, Micrococcus luteus, and Candida albicans strains with minimum inhibitory concentrations of 2.5 μg/mL and 0.625 μg/mL, respectively. The methanol extract showed only antifungal activity [391, 392]. A solution of dry methanolic extract of *A. archangelica* roots and rhizomes, containing bergapten, xanthotoxin, imperatorin, and angelicin, inhibited the growth zone of Escherichia coli strain by 210 mm compared to the reference drug cefixime (220 mm); and 200 mm for *Staphylococcus aureus* strain compared to vancomycin (260 mm). All tested strains were also resistant to the aqueous extract solution of *A. archangelica rhizomata et radices* [393].

The extract of *A. archangelica* exhibits antispasmodic activity on intestinal smooth muscle spasms induced by acetylcholine (muscle tone increased by 63.4 ± 1.44 %). Upon administration

ОБЗОР
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of *A. archangelica* extract, a decrease in tone was observed by 53.3 ± 1.29 % [394]. Methanolic extract of *A. archangelica* at doses of 100 mg/kg, 200 mg/kg, and 400 mg/kg also helps reduce pain and improve motor activity in rats with fibromyalgia induced by reserpine at a dose of 0.5 mg/kg [395].

Bergapten, one of the furanocoumarins in *A. archangelica*, exhibits antifibrotic effects in a model of renal fibrosis induced by unilateral ureteral obstruction. Bergapten demonstrated a reduction in fibronectin and α-SMA expression in the damaged kidneys of mice with unilateral ureteral obstruction, thereby reducing fibrotic changes in the tissues. Bergapten also showed a nephroprotective effect associated with ferroptosis inhibition [396]. *A. archangelica* essential oil reduces the production of the pro-inflammatory cytokine IL-6 in cultures of human umbilical vein endothelial cells [397].

It is known that furanocoumarins exhibit various toxic effects, including changes in liver metabolism — the "grapefruit effect". They inhibit enzymes of the cytochrome P450 family and its isoforms (CYP3A4, CYP2C9), leading to increased bioavailability of medicinal and toxic substances in the body [398, 399]. The amount of bergapten required for inhibition (IC_{50}) of CYP2C9 and CYP3A4 ranges from 9.92 μM to 50.00 μM and from 24.92 μM to 77.50 μM, respectively.

Human contact with furanocoumarins combined with short-wave (280–315 nm) and long-wave ultraviolet radiation (315–400 nm) causes phytophotodermatitis. In the past, substances were added to sunscreens based on the hypothesis that psoralen causes melanogenesis, thereby reducing the harmful effects of ultraviolet radiation (UV). Studies conducted in the 1980s showed that such products caused erythema on human skin and were responsible for tumors in hairless albino mice [400].

Cosmetic products contain plant-derived components (essential oils and extracts) containing furanocoumarins as fragrance ingredients. Cold-pressed bergamot essential oil contains 22079 ppm furanocoumarin, grapefruit 8879 ppm, lemon 6103 ppm, and bitter orange 2585 ppm [401]. In the European Union, limits for furanocoumarin content in cosmetic products have been established. The addition of furanocoumarins to products is prohibited unless they are part of essential oils and extracts. The total amount of furanocoumarins should not exceed 1 mg/kg per kg^{-1} of product used for body sun protection and skin tanning products. In Switzerland, the level should be less than 1 mg/kg in all products exposed to sunlight [402].

The toxic effect of furanocoumarins is due to their ability to intercalate DNA and interact with pyrimidine bases, leading to disruption of transcription and replication processes. They integrate into DNA, forming non-covalent bonds with pyrimidine bases (even before light exposure). Upon UV light exposure, photons activate furanocoumarins, leading to the formation of covalent bonds and photoadducts [403]. Linear (psoralen derivatives) and non-linear (angelicin derivatives) furanocoumarins differ in the severity of their photosensitizing effect. Non-linear ones exhibit less pronounced photocytotoxic and photogenotoxic activity. Angelicin, interacting with cell DNA, can form only mono-adducts with pyrimidine bases of one DNA strand under UV light. Psoralen, due to its linear structure, under the influence of double bonds at positions 3,4 of the coumarin ring and 4',5' of the furan cycle, cross-links double bonds at positions 5,6 of the pyrimidine bases of two DNA strands, forming di-adducts. Cells damaged by angelicin are capable of restoring their DNA structure, making it less toxic compared to psoralen [401, 404].

Studies on the toxicity of individual furanocoumarins are currently lacking, and data obtained from studies of 8-methoxypsoralen and 5-methoxypsoralen are used for their assessment. However, as a rule, furanocoumarins in plant objects occur as complex mixtures, and due to this, an overestimation of toxic effects may occur if 8-methoxypsoralen is used as a general toxic equivalent. The toxicity of the sum of furanocoumarins can be significantly higher or lower than the toxicity of each coumarin separately [405].

The highest phototoxicity is observed in the following order (decreasing): 8-methoxypsoralen, 5-methoxypsoralen, trimethylpsoralen, 4,5',8-trimethylpsoralen, bergapten, and angelicin. Not all furanocoumarins exert effects with the same degree of toxicity under identical conditions combined with UV irradiation. In studies of local phototoxicity of methanolic solutions of these furanocoumarins *in vivo* on Hanford miniature pigs irradiated with UV light, toxic effects were observed at doses of 100 and 1000 ppm and no effect at doses of 1 ppm and 10 ppm (0.02 μg/cm²) with irradiation of

10 J/cm². In experiments on Hartley albino guinea pigs, it was found that with UV irradiation of 13 J/cm², toxicity was observed at a dose of 10 ppm and no effect at a dose of 5 ppm.

There is also data from studies on volunteers: after irradiation with sunlight and an arc xenon lamp for 30 minutes, a minimal effect was detected at a dosage of 100 ppm and no effect at 50 ppm. When using water baths (3750 ppm), gels, and creams (25 ppm to 100 ppm) with irradiation doses (0.25–7.0 J/cm²) and an exposure of 15 minutes, the intensity of erythema formed was greater with the gel. The minimum sensitivity threshold was 25 ppm for the gel and 100 ppm for creams and baths. A dosage of 5 ppm is considered the threshold, while 50 ppm is the concentration for 100 % erythema formation on human skin. It is evident that the concentration of furanocoumarins is only half of the overall picture, while UV light exposure plays an equally, if not more, significant role.

In animal photocarcinogenicity studies, an inverse correlation was found between furanocoumarin dose and UV dose affecting the formation of tumors ≥ 1 mm: at a dose of 5 ppm, 500 J/cm² of UV irradiation was required; for 15 ppm, 400 J/cm²; for 50 ppm, 230 J/cm²; for 100 ppm, 140 J/cm²; and for 250 ppm, 100 J/cm² [401].

Therefore, when developing instructions for use for MPs containing furanocoumarins, it is necessary to calculate and indicate the predicted exposure to UV light that the consumer may experience, which can lead to photodermatitis. Consumer awareness will allow them to minimize excessive sun exposure and avoid toxic effects during the course of therapy.

Cranberry (*Vaccinium* L.)

Cranberry (*Vaccinium macrocarpon* Ait.) and common cranberry (*Vaccinium oxycoccus* L.) are considered promising sources of BASs for the development and production of MPs aimed at treating and preventing chronic inflammatory diseases of the kidneys and urinary tract [406].

Large cranberry (*V. macrocarpon* Ait.) and common cranberry (*V. oxycoccus* L.) are perennial evergreen dwarf shrubs of the genus *Vaccinium* L. of the *Ericaceae Juss*. family [407, 408].

Cranberry species have been used by humans for a long time: in culinary arts, medicine, and the chemical industry. Iroquois and Chippewa Indians used *V. macrocarpon* fruits as a laxative and for "blood purification". Cranberry fruits were also used to treat fever and stomach spasms. In Russia, fruits were used to treat scurvy and dissolve stones. They were used as agents with antipyretic, expectorant, diuretic, and anti-inflammatory effects [409]. In Karelian folk medicine, juices, morses, decoctions, and tinctures were made from cranberry fruits to treat skin, cold, genitourinary diseases, and scurvy [410].

In scientific medicine, large cranberry fruits (*Vaccinii macrocarponis fructus*) and common cranberry fruits (*Vaccinii oxycocci fructus)* are sources of phenolic compounds (proanthocyanidins, phenylpropanoids, flavonoids), which determine their pharmacological activity [411]. Analysis of phenolic compounds in *V. oxycoccus fruits* revealed the following order of decreasing quantitative content: flavan-3-ols (41.5–52.2 %); flavonols (18.6–30.5 %); anthocyanins (8.0–24.4 %); phenolic acids (5.0–12.1 %) [412]. In *V. oxycoccus fructus* growing in Latvia, the following BAS content was found: flavonols were 2079.44 ± 102.99 μg/g, and anthocyanins — 6993.79 ± 350.22 μg/g [413].

R. Šedbarė et al. determined the content of phenolic and triterpene compounds in *V. oxycoccus* MPRMs growing in two wetland sites (oligotrophic, eutrophic, and mesotrophic types) located 250 km apart. Comparing the BAS content of *V. oxycoccus fructus*, the concentration of anthocyanins varied 12-fold (8352 μg/kg vs. 698 μg/kg); flavonols — more than 5-fold (2811 μg/kg vs. 518 μg/kg); proanthocyanidins — 3.3-fold (3038 μg/kg vs. 919 μg/kg); chlorogenic acid — 72-fold (1224 μg/kg vs. 17 μg/kg); triterpene compounds — 1.6-fold (6542 μg/kg vs. 4060 μg/kg). The harvest time also plays a role — fruits collected in October in the oligotrophic zone contain 2.7 times lower flavonols than in cranberry samples from the same site collected in late August. For anthocyanins and proanthocyanidins, the opposite trend was observed: fruits collected in October contained twice the amount of BASs as fruits collected in August. The chlorogenic acid content remained stable and was independent of temporal factors, maintaining a high level regardless of fruit ripeness. In the same study, scientists proposed the following BASs as markers for confirming the authenticity of cranberry fruits: chlorogenic acid, anthocyanins

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(cyanidin-3-galactoside, cyanidin-3-arabinoside, peonidin-3-galactoside, peonidin-3-arabinoside, cyanidin-3-glucoside, and peonidin-3-glucoside), flavonols (myricetin-3-galactoside and quercetin-3-galactoside) [414].

Currently, in *V. oxycoccus fructus*, the following flavonoids have been identified: hyperoside, myricetin-3-O-galactoside, quercetin-3-galactoside, quercetin-3-α-L-arabinofuranoside, quercetin 3-rhamnoside; anthocyanins: cyanidin-3-O-galactazide, peonidin-3-O-galactoside, peonidin-3-O-arabinoside, cyanidin-3-O-arabinoside, peonidin-3-O-galactoside, and peonidin-3-O-arabinoside; triterpene compounds: ursolic and oleanolic acids [413, 415]; phenylpropanoids: chlorogenic, p-coumaric, rosmarinic, and p-hydroxybenzoic acids, and the content of substances was determined: quercetin (0.39 mg/100 g); myricetin (0.23 mg/100 g); chlorogenic acid (0.42 mg/100 g), p-hydroxybenzoic acid (0.41 mg/100 g); rosmarinic acid (0.12 mg/100 g); p-coumaric acid (0.27 mg/100 g) [416]. It was established that chlorogenic acid is the dominant hydroxycinnamic acid in the fruits of *V. macrocarpon* and *V. oxycoccus* [417, 418].

In the study by V.Yu. Ermakova et al., it is proposed to use peonidin-3-arabinoside as a marker compound for the identification of *V. macrocarpon* and *V. oxycoccus fructus*. The content of anthocyanidins in *V. oxycoccus fructus* from the Moscow and Tver Regions was also determined: 0.17 % and 0.21 % (1.31 % and 1.58 % of absolutely dry raw material mass), respectively. In fruits of *V. macrocarpon* of foreign origin, the content was 0.27 % (1.64 % of absolutely dry raw material mass) [419].

Promising directions for studying the pharmacological activity of *V. macrocarpon* and *V. oxycoccus fructus* BASs are anti-adhesive and antibacterial activities [420].

The pharmacological effect of *V. macrocarpon* and *V. oxycoccus fructus* BASs lies in the ability of polyphenolic compounds [421, 422], such as A-type proanthocyanidins, to inhibit microbial adhesion to the urothelium [423]. A-type proanthocyanidins inhibit type I and P fimbriae, which are used for the attachment of pathogenic Escherichia coli to the urothelium, biofilm formation, and subsequent colonization [424, 425]. It is also known that A-type proanthocyanidins can weaken the reservoir of pathogenic Escherichia coli in the gastrointestinal tract and suppress the inflammatory cascade. A similar result was obtained for Candida albicans strains [426, 427].

However, the issue of low bioavailability of A-type proanthocyanidins has been discussed recently [428, 429]. There is an opinion that their pharmacological activity is due to the formation of a large number of metabolites [430, 431], including sulfated metabolites of pyrogallol, valerolactone, benzoic, and phenolic acids; glucuronidated metabolites of flavonols and cinnamic acids. In particular, the metabolic composition included 2,3-dihydroxybenzoic, isoferulic, α-hippuric, benzoic, 4-hydroxyphenylacetic acids, as well as catechol-O-sulfate, 4-methylcatechol-O-sulfate, and 4-O-sulfates of ferulic and vanillic acids [432]. The experiment showed that over time (from 4 to 8 hours), the content of A-type proanthocyanidin metabolites increased in urine samples, and the content of *Escherichia coli* decreased [433].

A solution of a thick ethanol extract of *V. macrocarpon* in dimethyl sulfoxide solution exhibited antibacterial activity. The sensitivity of *E. coli* to *V. macrocarpon* extract BASs at a dosage of 100 mg/mL varied in the order: *Staphylococcus aureus* (90 %), *Enterococcus sp.* (85 %), *Proteus vulgaris* (75 %), *and Escherichia coli* (60 %). It was also found that the antibacterial effect of *V. macrocarpon* extract is dose-dependent. For example, *Escherichia coli* showed an increase in the inhibition zone from 12 mm (at an extract concentration of 12.5 mg/mL) to 25 mm (at an extract concentration of 100 mg/mL). Similarly, for *Proteus vulgaris*, the inhibition zone increased from 13 mm to 26 mm [434].

The use of products based on *V. macrocarpon* and *V. oxycoccus fructus* reduced the risk of CIDKUT recurrences in women, children, and patients with indwelling catheters by 32 %, 45 %, and 51 %, respectively [435–437].

In a randomized, double-blind, placebo-controlled study of cranberry extract chewing gum containing cyanidin-3-galactoside, cyanidin-3-glucoside, peonidin-3-arabinoside, peonidin-3-galactoside, peonidin-3-glucoside, myricetin, myricetin-3-O-galactoside, myricetin-3-O-rhamnoside, quercetin, quercetin-3-O-galactoside, quercetin-3-O-rhamnoside, benzoic, chlorogenic, 3,4-dihydroxybenzoic, and p-coumaric acids, and placebo gum, anti-adhesive activity of BAS metabolites against P-type fimbriae of Escherichia

coli was established. Anti-adhesive properties were attributed to metabolites of catechol, valerolactone, α-hippuric, benzoic, vanillic, phenylsulfonic, and 3,4-dihydroxyphenylsulfonic acids present in urine [438].

Additionally, the efficacy of BASs obtained from different raw material processing methods is being investigated. A.B. Howell et al. compared the efficacy of juice and powder from whole cranberry fruits and found that juice from cranberry fruits had the highest activity due to containing the soluble form of A-type proanthocyanidins [439].

Products derived from *V. macrocarpon* and *V. oxycoccus fructus* (capsules [440–442] and juice [443, 444]) are recommended for the treatment and prevention of CIDKUT recurrences. To reduce the number of CIDKUT episodes, it is recommended to take dry cranberry extract at a dosage of at least 36 mg daily, which reduces the risk of recurrence by 18 %. Analysis of the results showed a significant reduction in CIDKUT risk only when the extract was taken for a course of at least 12–24 weeks [445]. In a clinical study of the efficacy of *V. macrocarpon fructus* juice (proanthocyanidin content — 0.56 %) in preventing CIDKUT recurrences in women with two or more CIDKUT episodes per year, it was found that cranberry juice consumption did not have a statistically significant effect [446].

In conclusion, despite the ambiguous results of studies, cranberry can be used as an additional component in phytocompositions. For its use as a standalone agent, more in-depth and prolonged pharmacological research is needed.

CONCLUSION

This review analyzes the current state of research in the application of MPRMs as sources of BASs and botanicals used in the therapy of chronic infectious and inflammatory diseases of the kidneys and urinary tract. Among the plant BASs used for this purpose, phenolic compounds, including simple phenols, anthraquinones, and flavonoids, possessing anti-inflammatory, antibacterial, antioxidant, and antilithogenic properties, are of particular importance. Phenylpropanoids with diuretic, anti-inflammatory, antilithogenic, and immunomodulatory actions; coumarins with antispasmodic and antibacterial activity; proanthocyanidins with anti-adhesive action; and terpenoids and essential oils with antibacterial, antifungal, diuretic, and anti-inflammatory properties are also significant.

The herb of true bedstraw, roots of annual sunflower, roots of dog rose, rhizomes and roots of garden angelica, and fruits of large cranberry and common cranberry are promising for further research and development of new drugs. These plants have extensive empirical use in folk medicine, as well as reliable results from phytochemical and preclinical studies. The need to expand the nomenclature of domestic plant-derived drugs based on official and promising raw material sources necessitates improving approaches to drugs' standardization and substantiating the development of new drugs from the perspective of phytopharmacology and the interrelationships between the chemical composition of phytocompositions, the structure of natural compounds, and their activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Denis I. Shishkalov — conceptualization, search and analysis of scientific literature, data systematization and generalization, formation of the main sections of the draft, writing—original draft, writing—review & editing; Vera V. Artemyeva — writing — original draft, writing—review & editing, working in databases, compiling a references; Ifrat N. Zilfikarov —structures of the work, administration, conceptualization, writing—review & editing; Elena V. Avdeeva — writing—review & editing, data analysis; Vladimir A. Kurkin — writing—review & editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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