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REVIEW

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Pharmacotherapy of Endometriosis: Balancing of Safety, Efficacy, and Adherence to Treatment

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The aim. To conduct a comprehensive analysis of the clinical and pharmacological efficacy of progestins (dydrogesterone, dienogest, and norethisterone acetate) for the treatment of endometriosis by systematizing data on their pharmacodynamic, pharmacokinetic characteristics, and safety profile to optimize the selection of a personalized therapeutic strategy.

Materials and methods. The search of the literature was conducted regarding randomized controlled trials (RCTs), cohort studies, and meta-analyses for the period from 1958 to 2025 from the PubMed, Cochrane Library, and eLibrary.ru databases.

Results. It was found that dienogest, dydrogesterone, and norethisterone acetate demonsrates comparable efficacy in reducing the intensity of endometriosis-associated pelvic pain. Dienogest showed efficacy comparable to gonadotropin-releasing hormone agonists with a better tolerability profile. Dydrogesterone exhibited the best safety profile with minimal impact on metabolic parameters. Norethisterone acetate showed efficacy comparable to dienogest, but with more pronounced androgenic effects. Key pharmacological features affecting the safety profile of drugs were identified, and the need for a personalized approach to the choice of therapy was justified. The main limitation is the insufficient number of direct comparative studies of various progestins.

Conclusion. All the progestins considered are effective treatments for endometriosis, but have different safety profiles, which determines the need for individual drug selection, taking into account the patient's characteristics and concomitant pathology. Promising areas for future research include conducting large multi-center RCTs, developing algorithms for personalized therapy selection, and studying the long-term effects of treatment.

Keywords: endometriosis; progestins; dienogest; dydrogesterone; norethisterone acetate; gonadotropin-releasing hormone agonists; combined oral contraceptives; chronic pelvic pain; clinical efficacy; safety

Abbreviations: GnRH agonists — gonadotropin-releasing hormone agonists; AUB — abnormal uterine bleeding; VAS — visual analog scale; CGRP — calcitonin gene-related peptide; CYP3A4) — cytochrome P450 enzyme system; ESHRE — European Society of Human Reproduction and Embryology; TNF-α — tumor necrosis factor alpha; FSH — follicle-stimulating hormone; FSFI — Female Sexual Function Index; IL-8 — interleukin-8; IL-1β — interleukin-1 beta; COCs — combined oral contraceptives; LH — luteinizing hormone; MRI — magnetic resonance imaging; NSAIDs — nonsteroidal anti-inflammatory drugs; RCTs — randomized controlled trials; RANTES (Regulated on Activation, Normal T Expressed and Secreted, or CCL5) — chemokine; SF-36 (Short Form-36) — quality of life assessment questionnaire; CPPS — chronic pelvic pain syndrome.

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Фармакотерапия эндометриоза: баланс безопасности, эффективности и приверженности к лечению

В.И. Петров[1], И.С. Кулакова[1,2], В.С. Горбатенко[1], О.В. Шаталова[1], И.Д. Безуглов[1], А.С. Игнатова[1]

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Цель. Проведение комплексного анализа клинико-фармакологической эффективности прогестинов (дидрогестерона, диеногеста и норэтистерона ацетата) для терапии эндометриоза путем систематизации данных об их фармакодинамических, фармакокинетических характеристиках и профиле безопасности для оптимизации выбора персонализированной терапевтической стратегии.

Материалы и методы. Поиск литературы проводили среди рандомизированных контролируемых исследований (РКИ), когортных исследований и метаанализов за период с 1958 по 2025 гг. в базах данных PubMed, Cochrane Library и eLibrary.ru.

Результаты. Установлено, что диеногест, дидрогестерон и норэтистерона ацетат демонстрируют сопоставимую эффективность в снижении интенсивности эндометриоз-ассоциированной тазовой боли. Диеногест показал эффективность, сравнимую с агонистами гонадотропин-рилизинг-гормона, но с лучшим профилем переносимости. Дидрогестерон проявлял наилучший профиль безопасности с минимальным влиянием на метаболические параметры. Норэтистерон ацетат показал сопоставимую с диеногестом эффективность, но с более выраженными андрогенными эффектами. Определены ключевые фармакологические особенности, влияющие на профиль безопасности препаратов, а также обоснована необходимость персонализированного подхода к выбору терапии. Основным ограничением является недостаточное количество прямых сравнительных исследований различных прогестинов.

Заключение. Все рассмотренные прогестины являются эффективными средствами терапии эндометриоза, однако имеют различные профили безопасности, что предопределяет необходимость индивидуального выбора препарата с учетом особенностей пациентки и сопутствующей патологии. Перспективными направлениями будущих исследований являются проведение крупных многоцентровых РКИ, разработка алгоритмов персонализированного выбора терапии и изучение долгосрочных эффектов лечения.

Ключевые слова: эндометриоз; прогестины; диеногест; дидрогестерон; норэтистерона ацетат; агонисты гонадотропин-рилизинг-гормона; комбинированные оральные контрацептивы; хроническая тазовая боль; клиническая эффективность; безопасность

Список сокращений: аГнРГ — агонисты гонадотропин-рилизинг-гормона; АМК — аномальные маточные кровотечения; ВАШ — визуальная аналоговая шкала; CGRP — кальцитонин-ген-связанный пептид; CYP3A4 — фермент системы цитохрома P450; ESHRE — Европейское общество репродукции человека и эмбриологии; ФНО-α — фактор некроза опухоли альфа; ФСГ — фолликулостимулирующий гормон; FSFI — индекс женской сексуальной функции; ИЛ-8 — интерлейкин-8; ИЛ-1β — интерлейкин-1 бета; КОК — комбинированные оральные контрацептивы; ЛГ — лютеинизирующий гормон; МРТ — магнитно-резонансная томография; НПВП — нестероидные противовоспалительные препараты; РКИ — рандомизированные контролируемые исследования; RANTES (Regulated on Activation, Normal T Expressed and Secreted, или CCL5) — хемокин; SF-36 (Short Form-36) — опросник для оценки качества жизни; УЗИ — ультразвуковое исследование, СХТБ — синдром хронической тазовой боли.

INTRODUCTION

Chronic pelvic pain syndrome (CPPS) is one of the most significant problems in gynecological practice. According to global estimates, its prevalence among women of reproductive age reaches 25 %, with 40 % to 87 % of cases associated with endometriosis [1]. According to the World Health Organization (WHO), endometriosis is diagnosed in one in ten women, which corresponds to approximately 190 million (10–15%) individuals aged 15 to 49 years. It is important to note that patients with endometriosis account for 40–50 % of all the cases of female infertility [2].

In 2020, M. Ghiasi et al. conducted a review of the global prevalence of endometriosis from January 1989 to June 2019. Out of 28 scientific works, 17 provided an assessment of endometriosis prevalence among women with infertility, which was 27 % in a sample of 8 172 individuals. Eleven studies examined the prevalence of endometriosis among women with CPPS, which was 29 % in a sample of 5 104 individuals. In the overall cohort, which included over 14 million women, there is a significant variation in endometriosis prevalence estimates across geographical regions: in Africa — from 0.2 % to 48 %, in Australia — from 3.4 % to 3.7 %, in the Americas — from 0.7 % to 70 %, in Asia — from 1 % to 72 %, in Europe — from 0.8 % to 70 %. A significant limitation of this review is the complexity of diagnosing endometriosis, which complicates the determination of the true prevalence of the disease in the population [3].

The increase in registered cases of endometriosis is due to a complex of factors, among which the improvement of diagnostic methods and the increased awareness of medical professionals about the clinical manifestations of the disease play a key role. The significant increase in the number of cases, combined with growing patient awareness of the impact of endometriosis on reproductive function, contributes to the expansion of the global market for the therapy of this pathology. The global market volume for endometriosis treatment is estimated at 1.6 billion US dollars in 2024, and by 2034, it is expected to grow to 5.4 billion US dollars with a compound annual growth rate of 13.3 %[1].

Endometriosis represents a colossal medical problem in the Russian Federation, causing significant demographic and socio-economic damage. One of the most significant complications of this pathology is infertility, leading to an annual decrease in reproductive potential, estimated at approximately 14,365 unborn children. Modern hormonal therapy methods can reduce potential demographic losses by about 2212 cases per year. However, at present, only 536 children are born using this treatment method, indicating partial realization of therapeutic potential. The socio-economic aspect of the disease is characterized by significant losses in the working population, reaching 33.0 million days of temporary disability per year. The use of hormonal therapy could provide a reduction in this indicator by 5.4 million days; however, the actual reduction does not exceed 1.1 million days. Considering the data provided, the economic damage from the pathology reaches 553 billion rubles per year. Potential hormonal therapy can reduce losses by 93.2 billion rubles; however, the actual reduction is only 19.1 billion rubles. Data analysis also shows that the administration of drugs to all patients in need can further reduce economic damage by 15.9 billion rubles [4].

The problem of diagnosing endometriosis is due to the frequent asymptomatic course of the disease, which complicates the assessment of its real prevalence. Given the diversity of clinical manifestations, the pathology remains one of the most socially and demographically significant diseases, which necessitates the application of a multidisciplinary approach to its treatment and diagnosis[2].

Endometriosis is predetermined by the presence of estrogen-dependent, progesterone-resistant endometriotic foci outside the uterine cavity. Despite numerous hypotheses regarding etiology and pathogenesis, key links include systemic and local hyperestrogenemia, progesterone resistance, neoangiogenesis, neurogenesis, and reduced apoptosis. These changes cause a chronic inflammatory reaction, often leading to endometriosis-associated pelvic pain. The nature of the pain varies significantly: menstruating patients experience cyclical and non-cyclical pain, accompanied by dyschesia, dysuria, dysmenorrhea, and dyspareunia [5]. Endometriotic foci have their own vascular structure and are innervated by sensory and autonomic fibers, providing afferent access to peripheral and central pain pathways. However, foci are not the sole cause of pain, as its intensity and duration do not correlate with their number, localization, or disease severity.

It should be noted that endometriosis is a chronic estrogen-dependent inflammatory disease that leads to the chronification of pelvic pain and requires lifelong continuous treatment [6]. Despite many years of research, the diagnosis and

[1] Endometriosis Treatment Market Size, By Disease Type, By Treatment Type, By Drug Class, By Administration Method, By Distribution Channel, 2025–2034; Global Market Insights Inc. – 2024. Available from: https://www. gminsights.com/industry-analysis/endometriosis-treatment-market 2

[2] Clinical Guidelines. Endometriosis. Russian Society of Obstetricians and Gynecologists; Rubricator of clinical recommendations; 2024. 62 p. Available from: https://cr.minzdrav.gov.ru/view-cr/259_2. Russian

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treatment of endometriosis remain complex and relevant for both physicians and patients. Not fully understood pathophysiological mechanisms and the diversity of clinical phenotypes complicate the assessment of published data and the selection of adequate patient management strategies [7]. To date, there is no single treatment method — neither surgical nor medical — that has demonstrated unequivocal superiority in efficacy. Modern therapy for endometriosis-associated pelvic pain is aimed at systemic or local suppression of estrogen production and inflammation, as well as inhibition of proliferation. Treatment should be personalized and consider the severity of the disease, symptoms, and the patient's reproductive plans [8].

THE AIM. To analyze the clinical and pharmacological efficacy of progestins (dydrogesterone, dienogest, and norethisterone acetate) for the therapy of endometriosis based on data on their pharmacodynamic, pharmacokinetic characteristics, and safety profile to optimize the selection of a personalized therapeutic strategy.

MATERIALS AND METHODS

A search for clinical studies was conducted in the PubMed, Cochrane Library, and eLibrary.ru databases. Key search terms used included: dydrogesterone, dienogest, norethisterone, norethindrone, progestins, gestagens, endometriosis, chronic pelvic pain, chronic pelvic pain syndrome, and their combinations, as well as their English equivalents: didrogesterone, dienogest, norethisterone, norethindrone, progestins, gestagens, and endometriosis, chronic pelvic pain. The search conducted across multiple scientific databases identified a total of 726 relevant studies, including original articles and reviews. The search was conducted for the period 1958–2025.

RESULTS AND DISCUSSION

Progestins in the Therapy of Endometriosis-Associated Pain Syndrome

In accordance with current International and Russian Clinical Guidelines, progestins are first-line therapy drugs for endometriosis with mild to moderate pain syndrome[3]. It is reported that they reduce or eliminate painful symptoms in approximately 90 % of patients [9]. Various forms of progestins (oral, injectable, intrauterine, subcutaneous implants) are widely used for the treatment of endometriosis. Progestins therapy is a more preferred option compared to commonly used nonsteroidal anti-inflammatory drugs (NSAIDs), which do not alter the course of the disease and are not ideal for long-term use due to gastrointestinal side effects.

Current Clinical Guidelines "Endometriosis" 2024, among hormonal therapy agents, consider gonadotropin-releasing hormone agonists (GnRH agonists) and combined oral contraceptives (COCs). GnRH agonists play an important role in managing patients with advanced and infiltrative forms of the disease, both after surgical intervention and with a confirmed diagnosis. However, their long-term use is limited by several side effects, including neurovegetative and psychoemotional disorders, as well as negative effects on bone mineral density. Therefore, GnRH agonist therapy lasting longer than six months requires mandatory "add-back therapy"[4].

Regarding COCs [10, 11], their application aims include contraception, empirical treatment, and prevention of recurrence after surgical interventions. Despite an extensive evidence base confirming the therapeutic and prophylactic properties of COCs and their many years of global use in genital endometriosis, the issue of prescribing estrogen-gestagenic agents remains a subject of active discussion. With the development of minimally invasive surgery techniques, allowing for earlier and more accurate diagnosis of the pathology, information has emerged about the potentially negative impact of COC use on the course of deep infiltrative and extragenital endometriosis. Adverse effects are linked to several factors: the presence of an estrogen component in COCs, the development of "progesterone resistance" in endometriotic foci, and the traditional cyclic regimen of their administration. It has been noted that pain relief during COC use can lead to delayed diagnosis and reduce the effectiveness of subsequent surgical treatment due to "masking" typical symptoms of the disease [12].

It is proven that progestins suppress estrogen action, slowing the growth of endometriotic tissue, and

[3] ESHRE Endometriosis Guideline Development Group. Endometriosis Guideline; European Society of Human Reproduction and Embryology; 2022. 192 p. Available from: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Endometriosis-guideline

[4] Clinical Guidelines. Endometriosis. Russian Society of Obstetricians and Gynecologists; Rubricator of clinical recommendations; 2024. 62 p. Russian

also possess anti-inflammatory, antiproliferative, and antiangiogenic effects. Based on available data, it can be concluded that progestins are highly effective and affordable drugs with long-term safety and absence of estrogen-deficiency side effects [8, 13].

A systematic review by M.N. D'Alterio et al. established that progestins effectively relieve pain and improve quality of life; however, treatment should be personalized and consider the patient's condition, the need for surgery, and pregnancy planning [14]. For severe pain or lack of effect from previous methods, second-line therapy — GnRH agonists — may be prescribed, but their use is limited due to potential serious side effects. In clinical practice, the efficacy and side effect profile of all hormonal drugs are individual, and finding suitable therapy is often empirical[5]. Among gestagens registered in Russia for the treatment of endometriosis, dydrogesterone, norethisterone, and dienogest are the most studied, possessing different safety profiles and the possibility of therapy personalization.

These drugs promote regression of endometriotic foci with prolonged use. The high affinity of dienogest, and to a lesser extent norethisterone, not only for progesterone but also for steroid receptors, provokes the risk of adverse reactions. Consequently, due to low patient adherence to the drug regimen because of side effects, treatment becomes clinically ineffective and unsafe, which contributes to disease recurrence. The absence of dydrogesterone's connection to steroid receptors, compared to other progestins, as well as its high selectivity for progesterone receptors, reduces the risk of adverse reactions, increases safety, and improves treatment adherence. This allows for pain relief, improved quality of life, reduced risk of self-discontinuation of medication and subsequent endometriosis recurrence, and improved subjective assessment of clinical effect, which is necessary considering long-term therapy [15].

First-line drug therapy, especially in patients with mild to moderate pain syndrome, is considered to be progestins with a level of evidence 1a. These drugs induce a range of pharmacological effects that influence the pathogenetic links of endometriosis development, and also have systemic and local effects on the endometrium[6]. The interaction between progestins and target tissues occurs through specific gestagen receptors located both on the plasma membrane and within the cell. Binding sites realize rapid, millisecond-lasting, and slow, up to 1-hour-lasting, specific biological effects of gestagens, making this group of drugs the choice for first-line therapy in endometriosis. The main objectives are to induce anovulation and hypoestrogenemia, which promotes decidualization and acyclicity of both normal and ectopic endometrium. These effects are realized through various molecular mechanisms. The mechanism of action of gestagens in endometriosis is complex and occurs at multiple levels (Fig. 1). At the systemic level, they suppress the activity of the hypothalamic-pituitary-ovarian axis, leading to suppression of cyclic hormonal fluctuations and reduced estradiol production. Directly in endometriotic foci, gestagens induce decidualization of the stromal component, followed by atrophy of pathological tissue. Additionally, they cause secretory transformation of the glandular epithelium, which collectively leads to the regression of endometriotic heterotopias. Another mechanism is competitive binding with the estrogen receptor and anti-estrogenic action. Suppression of prostaglandin E2 synthesis leads to apoptosis activation and inhibition of cell proliferation and neovascularization. By activating 17β-hydroxysteroid dehydrogenase type 2, gestagens reduce estradiol activity levels by converting it to the less active estrone [16].

When considering various progestins from the perspective of efficacy and safety in treating endometriosis-associated pelvic pain, differences in molecular structure, receptor affinity, and pharmacokinetic characteristics must be taken into account. The ideal progestin should be a progesterone receptor agonist and not possess activity towards androgen, mineralocorticoid, estrogen, or glucocorticoid receptors. The assessment of progestin activity is usually conducted at the preclinical stage of research using animal models. Next, we will consider the main progestins available for endometriosis treatment in the Russian Federation.

Dydrogesterone has been used since the 1960s for the treatment of menstrual cycle disorders,

[5] ESHRE Endometriosis Guideline Development Group. Endometriosis Guideline; European Society of Human Reproduction and Embryology; 2022. 192 p.

[6] Ibid.

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endometriosis, and threatened miscarriage. It is a retroprogesterone, close in structure and properties to natural progesterone [17]. Its structural features ensure high selectivity for progesterone receptors with practically no agonistic influence on other steroid receptors. The key advantage is a pronounced progestogenic effect without the side effects characteristic of other progestins [18].

On the one hand, dydrogesterone has low bioavailability; on the other hand, the key advantage of this drug is its metabolism without the involvement of the cytochrome P450 system. Dydrogesterone has a short half-life and no active metabolites, which collectively may require dosing twice daily.

Dienogest (or 17α-cyanomethyl-17β-hydroxy-estra-4,9-diene-3,1) is a derivative of 19-nortestosterone, a selective 4-generation progestin [19]. A distinctive feature of the molecule is an additional double bond between carbon atoms 9 and 10, as well as the absence of an ethinyl radical at the 17th atom, replaced by a cyanomethyl radical. Thanks to these structural modifications, dienogest combines the pharmacological properties of 19-norprogestins and progesterone derivatives. It affects key transcription factors such as AEBP1, HOXB6, KLF2, and RORB. The drug's mechanism of action is based on suppressing cytokines in the stroma of endometrial cells, providing a strong progestogenic and moderate estrogen-suppressing effect, as well as anti-inflammatory, antiproliferative, and antiangiogenic properties without significant androgenic, mineralocorticoid, or glucocorticoid effects [20–22].

Other advantages of the drug include high bioavailability when taken orally, a short half-life, selectivity for progesterone receptors, and no interaction with sex hormone-binding globulin. It is noted that dienogest is particularly suitable for patients with delayed reproductive plans, as it does not negatively affect ovarian reserve and protects ovarian tissue [23]. Dienogest is a weak inhibitor of CYP2C19 and CYP3A4 and can slow down the metabolism of other drugs, increasing their concentration and the risk of side effects. Active metabolites of dienogest circulate in plasma for a long time, ensuring high efficacy with a single dose, and are primarily excreted in feces, making it a drug of choice for patients with impaired renal function [19].

Norethisterone acetate is a 2-generation derivative of 19-nortestosterone, a representative of the numerous group of synthetic progestins — testosterone derivatives [24]. Modification of the testosterone molecule reduced androgenic activity, but nevertheless, this drug has a pronounced affinity for androgen receptors [25]. Positive effects of this drug include: reduction of CPPS, dysmenorrhea, and dyspareunia. Among the negative effects are dyslipidemia, weight gain due to metabolic disorders, and hyperinsulinemia with prolonged use of low doses [26]. Androgenic properties cause a number of adverse clinical manifestations: acne, hirsutism, and fluid retention. With the use of high doses of this progestin, an increase in the atherogenic index and an increased risk of cardiovascular complications occur [27]. Norethisterone acetate is a prodrug; upon absorption, it undergoes primary metabolism in the liver, and the metabolite has high bioavailability. The drug circulates in plasma primarily bound to proteins. The enzyme CYP3A4 is involved in the metabolism of norethisterone acetate, so drug interactions with inducers and inhibitors of this enzyme are possible. The elimination half-life of 8 to 12 hours allows for once-daily administration. It is mainly excreted in urine as conjugates. A comparative pharmacological profile of progestins is presented in Table 1.

Clinical Efficacy of Progestins

Long-term therapy is necessary to prevent endometriosis recurrence in women not planning pregnancy. Progestins vary significantly in cost, and inexpensive options should also be used as first-line therapy [28, 29].

Dydrogesterone is widely used in endometriosis therapy due to its safety profile and its unique ability not to suppress ovulation. However, its use is accompanied by several issues in the evidence base that limit definitive conclusions about its efficacy. These issues include an insufficient number of large randomized trials, a limited number of studies comparing the efficacy of different progestins, and their inconsistency, which adds uncertainty to the conclusions. To date, there are no reliable predictors of individual patient response and the effectiveness of a particular progestin, leading to misinterpretation of the drug's overall ineffectiveness.

One of the latest meta-analyses included 14 studies comparing dydrogesterone with placebo, letrozole, gestrinone, GnRH-α leuprolide, danazol, norethisterone acetate, and depot medroxyprogesterone acetate, as well as coagulation of endometriotic foci; and with no treatment after surgery. It was found that comparative analysis was not performed for dydrogesterone in 5 studies. There is minimal evidence of the efficacy and safety of dydrogesterone in endometriosis treatment due to a limited number of randomized controlled trials. Based on the available data, it is concluded that dydrogesterone may have some advantages over gestrinone, GnRH agonists, and other therapeutic interventions in endometriosis treatment. However, this conclusion should be approached with caution [30].

The efficacy of dydrogesterone in endometriosis-associated pelvic pain has been evaluated in several studies. Results from a prospective Russian study conducted in 2018–2021 at the gynecological department of the clinic of obstetrics and gynecology of Pavlov First Saint Petersburg State Medical University indicate the efficacy of dydrogesterone in CPPS therapy. Within the study, the effectiveness of various conservative treatment methods for endometriosis-associated pain syndrome was assessed before laparoscopic verification of the diagnosis. In the study group of 115 patients, a high rate of disease recurrence was recorded — 52 % (61 cases), which was associated with irrational drug use and low treatment adherence. Analysis of previous therapy also showed that 24 % of patients (28 individuals) received COCs without appropriate indications, 35 % (40 individuals) received nonsteroidal anti-inflammatory drugs, and 25 % (29 individuals) received other drugs prescribed by specialists from related fields. 20 patients (17 %) had no therapy, which led to disease progression and required surgical intervention. The study itself was conducted in three stages. In the first stage, after obtaining informed voluntary consent, preoperative examination was performed, including assessment of pain intensity using the Visual Analog Scale (VAS), clinical and instrumental diagnostics, and laparoscopic intervention. In the second stage, morphological and immunohistochemical examination of the surgical material was carried out to confirm the diagnosis. The third stage included dynamic observation in the postoperative period with assessment of long-term results at 6 and 12 months. The monitoring program included analysis of pain syndrome dynamics, quality of life indicators (SF-36, Short Form-36 quality of life assessment questionnaire), sexual function (FSFI, Female Sexual Function Index), registration of complications, disease recurrences, and cases of pregnancy in patients with infertility. The use of a combined approach, including surgical treatment followed by long-term anti-relapse therapy with dydrogesterone, demonstrated a statistically significant reduction in endometriosis symptoms ($p < 0.0001$) and improvement in quality of life indicators ($p < 0.05$) after 12 months [31].

A similar study conducted in India, involving 98 patients, also demonstrates the high clinical efficacy of the drug. Patients were prescribed dydrogesterone 10 mg or 20 mg per day in severe cases orally from day 5 to day 25 of the menstrual cycle for 3–6 months, with assessments every 3 months. CPPS significantly decreased ($p = 0.05$) from a mean baseline score of 1.24 ± 1.01 to 0.87 ± 0.86 (a 29 % reduction) after the first month of treatment. By the end of the sixth treatment cycle, the reduction in CPPS compared to baseline was 95 %, 87 %, and 85 %, respectively; improvement in endometriosis-associated pelvic pain symptoms was observed in 71% of patients [32].

Thanks to the widespread and prolonged use of dydrogesterone in global practice, as well as its market availability, extensive clinical experience has been accumulated. The question of comparative efficacy between continuous therapy at doses from 10 to 30 mg/day and prolonged cyclic therapy (from day 5 to day 25 of the menstrual cycle) in relieving endometriosis-associated pelvic pain and improving patients' quality of life remained open for a long time. Within the prospective observational multicenter study "ORCHIDEYA," involving 350 women and conducted in real clinical practice settings in Russian medical centers, the clinical effects of dydrogesterone therapy in patients with endometriosis were studied depending on the administration regimen. Participants received the drug according to one of two standard regimens: 10 mg — 2–3 times daily continuously or in a prolonged cyclic regimen from day 5 to day 25 of the menstrual cycle. The study included three visits: baseline, 3 months, and 6 months of therapy. It was found that both administration regimens — prolonged cyclic and continuous — led to a significant reduction

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in CPPS intensity, improvement in quality of life, and enhancement of sexual well-being. The mean change in pain indicators was -3.3 (standard deviation [SD] = ±2.2; $p < 0.0001$ compared to baseline) for patients receiving the prolonged cyclic therapy regimen, and -3.0 (SD = ±2.2; $p < 0.0001$ compared to baseline) for patients receiving the continuous therapy regimen, with no statistically significant differences between the groups [33]. The study results demonstrate the effectiveness of therapy in treating endometriosis.

Dienogest is of particular interest with a well-studied evidence base. The drug is an effective agent for the long-term treatment of all endometriosis phenotypes, as well as for postoperative therapy. Dienogest's advantages include minimal impact on metabolic parameters. This progestin has minimal effects on protein, lipid, and carbohydrate metabolism. L.V. Adamyan's demonstrated that dienogest administration allows for the discontinuation of NSAIDы use for endometriosis-associated pelvic pain. In a group of 24 patients aged 18 to 45 years with histologically confirmed endometriosis between 2021 and 2022, they were divided into subgroups of 12 people each. The first group received the progestin at a dosage of 2 mg per day; the second group received NSAIDs — ibuprofen. All women underwent minimally invasive surgery, the choice of which depended on the location of endometriotic foci. Further patient follow-up revealed a significant reduction in pelvic pain intensity on the VAS scale in the 1 group: mild — in 2 (16.67 %), moderate — in 7 (58.33 %), severe — in 3 (25 %), as well as improvement in sexual quality of life. In the 2 group, women taking NSAIDs for pain syndrome did not report positive changes during treatment; the intensity of pain syndrome on the VAS scale was: mild — in 3 (25 %), moderate — in 5 (41.67 %), severe — in 4 (33.3 %) [34].

In a systematic review by A. Samy et al., 36 RCTs were analyzed. The authors concluded that dienogest (0.94), COCs (0.782), and elagolix (0.38) showed the best results in reducing CPPS after 3 months. For reducing CPPS after 6 months of therapy, GnRH agonists (0.75), the levonorgestrel-releasing intrauterine system (0.73), and dienogest (0.65) were the most suitable medications. However, when ranking drugs by p-score, GnRH agonists (0.63) and elagolix (0.54) showed the best results in reducing CPPS after 3 months, and desogestrel (0.94) and COCs (0.91) after 6 months [35].

In a randomized study of COCs containing 2 mg of dienogest or 1.5 mg of 17b-estradiol and 2.5 mg of nomegestrol acetate, women receiving COCs with dienogest showed a more pronounced improvement in quality of life and sexual function on the SF-36 ($p < 0.01$) and FSFI ($p < 0.006$) scales [36]. In a study comparing norethisterone acetate and dienogest, the latter showed higher efficacy and a lower risk of side effects [37]. Studies evaluating the efficacy between progestins and GnRH agonists have demonstrated comparable efficacy in CPPS therapy [22, 38].

Comparing side effects between dienogest and GnRH agonists, treatment with the former significantly increases the frequency of spotting ($p = 0.0007$) and weight gain ($p = 0.03$); however, a lower frequency of estrogen-deficiency states in the form of hot flashes and vaginal dryness ($p = 0.0006$) was noted [39]. It is worth noting that with approximately comparable levels of CPPS relief, progestins provide significantly less hypoestrogenemia and demineralization.

While dienogest demonstrates high efficacy and a favorable safety profile, another synthetic progestin, norethisterone acetate, also holds an important place in endometriosis therapy. Analysis of studies dedicated to the use of this drug allows for a comparative assessment of its therapeutic value.

P. Vercellini et al. study involved 190 patients, standard doses of norethisterone acetate 2.5 mg once daily and dienogest 2 mg once daily were compared. Progestins were administered from day 1 of the menstrual cycle continuously, and results were analyzed after 6 months of use. Efficacy was assessed using a developed scale for non-menstrual pelvic pain. The drugs showed comparable efficacy in reducing pain intensity. The proportion of satisfied and very satisfied women was 71 % in the norethisterone acetate group and 72 % in the dienogest group. The use of the latter was not associated with a statistically significant improvement in overall pain relief, psychological state, sexual function, or health-related quality of life. Treatment was well tolerated by 58% of women in the norethisterone acetate group compared to 80 % of participants in the dienogest group. The study authors suggest that certain advantages of dienogest over norethisterone acetate in their study were due to the low dosage of the latter [26].

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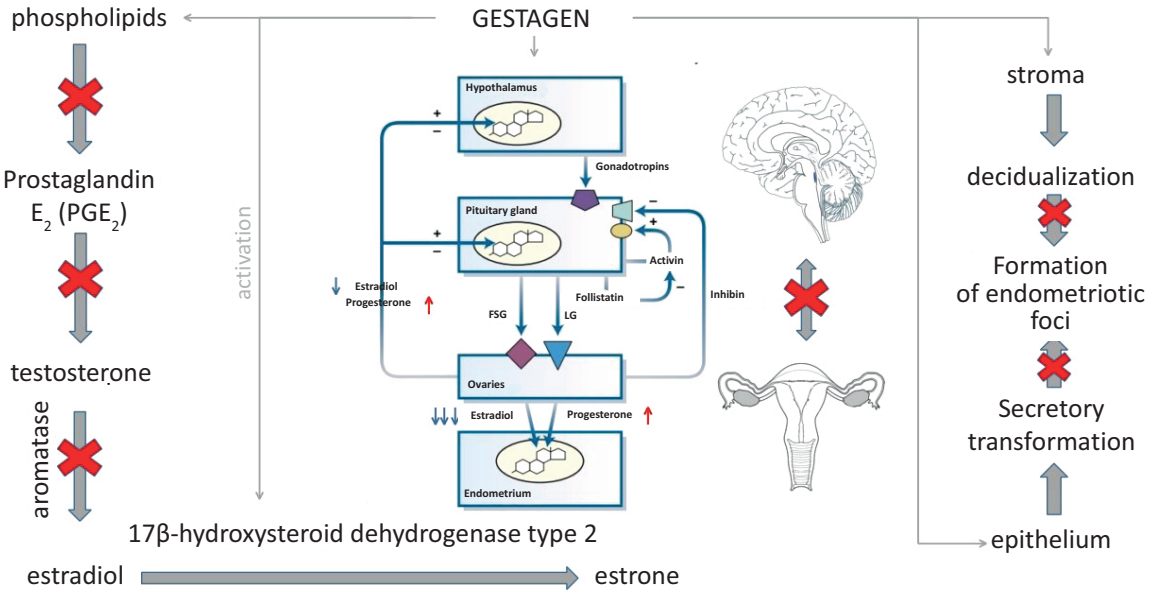

Figure 1 – Mechanism of Action of Progestins.

Table 1 – Pharmacokinetics and pharmacological effects of progestins

Parameter	Dydrogesterone	Dienogest	Norethisterone acetate
Pharmacokinetics*			
Chemical classification	Synthetic progesterone analog	Nortestosterone derivative	19-nortestosterone derivative
Prodrug	No	No	Yes
Bioavailability	Low 28 %	High 91 %	High 60 %
Metabolism involving P450 *(CYP450)*	No	Yes	Yes
Active metabolites	No	Yes	Yes
Half-life, h	5–7	9–10	8–12
Excretion	Urine 70 %	Primarily feces	Urine — 60 %, feces — 40 %
Pharmacological effects [24]			
Anti-estrogenic activity	Effective	Moderately effective	Effective
Anti-androgenic activity	Moderately effective	Effective	Ineffective
Anti-mineralocorticoid activity	Moderately effective	Ineffective	Ineffective
Estrogenic activity	Ineffective	Moderately effective	Effective
Androgenic activity	Ineffective	Ineffective	Effective
Glucocorticoid activity	Ineffective	Ineffective	Ineffective

Note: * — data on pharmacokinetic parameters are taken from official drug instructions available on the grls.minzdrav.gov.ru website.

Table 2 – Side effects of progestins*

Parameter	Dydrogesterone	Dienogest	Norethisterone acetate
Reproductive system			
Ovulation suppression	Yes	Yes	Yes
Abnormal uterine bleeding	No	Yes	Yes
Amenorrhea	No	Moderate frequency	No
Functional ovarian cysts	Yes	Yes	Yes
Mastalgia	Low frequency	Low frequency	Moderate frequency
Metabolism			
Effect on lipid profile	Minimal/neutral	Moderate	Significant
Effect on carbohydrate metabolism	Minimal	Minimal	Moderate
Risk of weight gain, fluid retention	Minimal	Moderate	Moderate/High
Nervous system			
Headaches	Minimal	Yes	Yes
Mood swings	Minimal	Yes	Yes
Decreased libido	Minimal	Minimal	Moderate
Skin reactions			
Acne	No	Minimal	Moderate
Hirsutism	No	Minimal	Minimal

Note: * — table compiled using sources [20, 26, 33, 35–37, 45].

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In the study by T.B. Gurbuz et al., the efficacy and safety of dienogest and norethisterone acetate were evaluated in patients with endometriosis-associated pelvic pain. The dienogest group (2 mg per day) included 40 patients, and the norethisterone acetate group (5 mg per day) included 30 patients. Pain severity was assessed on the VAS scale before treatment initiation, then at 6 and 12 months. Safety was assessed by the prevalence of side effects and the willingness to continue taking the drug throughout the treatment period. The drugs showed comparable efficacy in reducing pain on the VAS scale. Patients in the dienogest group discontinued treatment significantly more often and earlier than patients in the norethisterone acetate group. At six months, there were 23 patients in the norethisterone acetate group and 21 in the dienogest group; however, 16 patients in the norethisterone acetate group and 18 patients in the dienogest group completed treatment. Side effect profiles were comparable, but the dropout rate from the study after six months was higher in the dienogest group (47.5 % vs. 23.3 %; $p = 0.026$). The study authors concluded that norethisterone acetate may be an effective alternative to dienogest therapy [40].

In a retrospective cohort study by T.B. Gurbuz et al., conducted in Italy, long-term effects of treating rectovaginal endometriosis were studied. 103 women completed norethisterone acetate treatment, with a follow-up period of 5 years; the primary endpoint was treatment satisfaction after 5 years of use. Over 68 % of women who completed the study were satisfied or very satisfied with the drug. Side effects were the reason for discontinuation of treatment in 38.1% (16 women). According to the study authors, norethisterone acetate is an optimal drug for long-term treatment of rectovaginal endometriosis, considering its low cost and favorable pharmacological profile [41].

The study by S. Ferrero et al. included 40 patients with confirmed colorectal endometriosis. A twelve-month course of norethisterone therapy led to a significant reduction in pain syndrome, dyskinesia, and deep dyspareunia. After using the progestin for 12 months, a reduction in pain syndrome severity was noted — 3.5 ± 1.6 points ($p < 0.001$), dyskinesia, and deep dyspareunia. Furthermore, a trend towards a decrease in the frequency of dysmenorrhea and cyclical rectal bleeding was observed [42].

Safety and Side Effects of Progestins

The renaissance of scientific and clinical interest in dydrogesterone occurred after the first expected side effects from progestins with androgenic, glucocorticosteroid, and mineralocorticoid activity were identified. It is precisely such common adverse reactions as weight gain, emotional lability, decreased libido, rash, and hirsutism that cause low patient compliance with treatment and become frequent reasons for non-adherence to the treatment regimen and, consequently, treatment ineffectiveness, as well as endometriosis recurrence. Progestin side effects are presented in Table 2.

It has been established that the high efficacy of dydrogesterone at a relatively low dosage minimizes the adverse reactions characteristic of most progestins. It is also important to remember that to ensure an effect in the context of possible progesterone resistance, the gestagen's binding to receptors must be higher than that of endogenous progesterone [15]. Undoubtedly, dydrogesterone is a metabolically neutral drug that carries minimal side effects. Norethisterone acetate has weak androgenic activity and can cause hirsutism, acne, and negatively affect the lipid profile. The drug reliably suppresses luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion.

In the studies we examined, both with short-term and long-term use of dienogest, patients also experienced adverse reactions. According to the results of a pooled analysis of four studies conducted within the European research program, the most common adverse events with dienogest were headache, breast discomfort, acne, depressed mood, nausea, and weight gain [44].

In the study by B. Cho et al., the most frequent side effects were abnormal uterine bleeding (AUB) in 129 (4.14 %) patients, weight gain in 80 (2.57 %) patients, and headaches in 38 (1.22 %) patients. Analyzing the causes of adverse drug reactions, the authors concluded that patients with a history of allergies had a significantly higher risk of their occurrence with combination therapy or concomitant treatment compared to those without [20].

In the work by F. LaTorre et al., a study of long-term dienogest treatment for 36 months was conducted. At the first follow-up after starting dienogest, after 12 months, 23 % of 114 patients experienced breakthrough bleeding, of which 52 % had spotting, 38 % had light bleeding, and 10 % had moderate bleeding; 22 patients (19 %) discontinued the drug. Among the known reasons for treatment discontinuation were: side effects (36 %), ineffectiveness (27 %), a combination of ineffectiveness and side effects (23 %), desire to become pregnant (9 %), and seeking contraception (5 %). After 36 months of follow-up, among the adverse reactions that led to discontinuation of dienogest treatment, the most frequent were: unsatisfactory contraception, decreased

libido, vaginal dryness, and mood swings. On average, treatment was discontinued after 7.2 months. The most frequently registered side effects were fluid retention (29.3 %), weight gain (26 % with a mean of 2.0 kg), AUB (22.9 %), breast tenderness (20.7 %), abdominal bloating (18.7 %), mood swings (17.4 %), headache (16.3 %), decreased libido (15.2 %), vaginal dryness (15.2 %), hot flashes (10.9 %), acne (10.8 %), hair loss (9.8 %), insomnia (8.7 %), seborrhea (6.6 %), and hirsutism (6.6 %) [45].

R. Vercellini et al. conducted a comparison of standard doses of norethisterone acetate 2.5 mg once daily and dienogest 2 mg once daily in 180 study participants. In terms of adverse drug reactions, both groups had a comparable frequency of occurrence. However, on average, women gained weight twice as often when taking norethisterone acetate—28 patients (n = 89) — than in the dienogest group — 14 women (n = 85) %. Spotting was reported by 22 % of patients in the norethisterone acetate group and 16 % in the dienogest group. After 6 months of treatment, 24 out of 90 women in the norethisterone group were very satisfied with their treatment, 40 were satisfied, 1 was neither satisfied nor dissatisfied, 15 were dissatisfied, and 10 were very dissatisfied. In the dienogest group, the figures were: 45 out of 90 patients — very satisfied, 20 — satisfied, 1 (1 %) — neither satisfied nor dissatisfied, 14 — dissatisfied, and 10 — very dissatisfied [26].

At the present stage, the choice of treatment strategy is complex and should be based on a thorough assessment not only of the clinical status but also of drug tolerability, progesterone sensitization, and safety profile analysis [46, 47]. Clinicians are also advised to consider reversible and irreversible side effects when determining which therapy may be most suitable for specific patient groups [48, 49]. Thus, given the multifactorial nature of endometriosis-associated pelvic pain, a systematic monitoring and management of the progestin therapy safety profile is a critical component of a long-term therapeutic strategy, enabling sustained disease control while maintaining a high quality of life for patients [50].

Review Limitations

The conducted study has several important limitations that may affect the interpretation and generalization of the obtained results.

1. Limitation of design and methodology. The authors conducted a non-systematic review, which is the main limitation of this study. A systematic review's distinguishing advantage is the reproducibility of results and transparency of methodology. In our case, the choice was made in favor of a narrative review, as the studies included in this work were extremely heterogeneous. Different criteria were used in various articles to establish the diagnosis of endometriosis and evaluate the results of its treatment.

2. Small studies and retrospective design. A significant number of studies were retrospective and had small sample sizes. Large pharmacoepidemiological studies evaluating the efficacy of a particular drug in the long term are lacking.

3. Contradictory results. Significant contradictions were found in the results of different studies regarding safety and adherence.

CONCLUSION

Currently, dydrogesterone is one of the strategic options for treating endometriosis-associated pelvic pain, especially in certain population groups with dyslipidemia, diabetes mellitus, and obesity. The drug does not negatively affect the lipid profile as it does not lower high-density lipoprotein levels, which is crucial for patients with an existing risk of cardiovascular diseases; it does not worsen tissue sensitivity to insulin and has minimal impact on carbohydrate metabolism, making it a safe treatment option for women with diabetes mellitus or a high risk of its development. For patients with obesity or those at increased risk of thromboembolic complications, dydrogesterone is a more preferred alternative to progestins with high thrombogenic activity. Thus, dydrogesterone represents a first-line therapy drug for high-risk patients, without worsening metabolic disorders.

As mentioned earlier, its main difference from other progestins lies in its molecular structure, which ensures safety, metabolic neutrality, and minimal side effects necessary for long-term therapy. Dydrogesterone's high safety profile is a key advantage in the long-term treatment of endometriosis. Despite this, all available progestins today hold their rightful place in the symptomatic and pathogenetic treatment of CPPS and other symptoms caused by endometriosis. Large multicenter RCTs are needed to clarify dydrogesterone's administration regimens, dosages, treatment duration, comparisons with other progestins, and the possibility of combination with other drugs effective in endometriosis treatment. It is important to develop an algorithm for more personalized therapy, considering potential side effects.

According to the recommendations of the European Society of Human Reproduction and Embryology (ESHRE), the choice of a specific progestin for endometriosis therapy should be determined precisely by the individual side effect profile of each

drug. This approach represents a key direction for optimizing long-term disease management. The implementation of personalized progestin selection principles in clinical practice can significantly improve patient adherence to treatment and enhance their quality of life. The therapy optimization strategy should include: thorough assessment of individual risk factors for adverse reactions and comorbidities in women, regular monitoring of treatment tolerability throughout the course of therapy, timely correction of the treatment regimen if side effects occur, and consideration of reproductive plans. The implementation of this approach, recommended by ESHRE, contributes to achieving an optimal balance between treatment efficacy and tolerability, which is the key to successful long-term disease control.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Petrov V.I. — conceptualization, writing — review & editing; Kulakova I.S., Gorbatenko V.S. — data collection, writing — original draft, writing — review & editing; Bezuglov I.D. — data collection, visualization, writing — original draft, writing — review & editing; Ignatova A.S — data collection, writing — original draft; Shatalova O.V. — supervision, writing — review & editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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REVIEW

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Landscape of biotechnological innovations: Analysis of the patent portfolio operating in the Russian Federation for the period from 2005 to 2024

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The aim. To conduct a comparative analysis of long-term trends and structural features of patenting in the field of biotechnology at the national and regional levels.

Materials and methods. The study is based on data from two patent offices: the Federal Service for Intellectual Property (Rospatent) and the Eurasian Patent Office (EAPO) for the period from 2005 to 2024. The methodology includes a quantitative analysis of patent applications with classification by applicant countries and industry areas of biotechnology.

Results. It was found that the share of biotechnological patents is 4.68% in Rospatent and 8.33% in EAPO. The phenomenon of strategic duality was revealed: in the Russian Federation, Russian applicants dominate (61% of patents), while in the EAPO their share is only 9%, while non-residents form extensive patent portfolios there. The dynamics of patent activity demonstrates a clear correlation with external factors: an increase in the activity of non-residents in the EAPO after 2014 and a shift in industry priorities in the Russian Federation from medical to industrial biotechnology after 2019. At the same time, domestic patent activity in Rospatent has decreased by 16.5% the last five years.

Conclusion. The results indicate a systemic imbalance: Russia pursues a predominantly internally oriented patent strategy, focusing on the domestic market, and is significantly inferior in the formation of legal positions in the Eurasian space. The predominance of foreign patents in the EAPO creates long-term risks for the competitiveness of Russian developments in the region. The data obtained can be useful in the development of state programs to improve Russia's competitiveness in the framework of biotechnological areas in the global market.

Keywords: patent; patent portfolio; biotechnology; innovation; competitiveness; economic trend

Abbreviations: CNIPA — China National Intellectual Property Administration; EPO — European Patent Office; JPO — Japan Patent Office; IP5 — USPTO, EPO, JPO, KIPO and CNIPA; KIPO — Korean Intellectual Property Office; USPTO — United States Patent and Trademark Office; WIPO — World Intellectual Property Organization; DNA — deoxyribonucleic acid; EAPATIS — Eurasian Patent Information System; EAPO — Eurasian Patent Office; IPC — International Patent Classification; RNA — ribonucleic acid; Rospatent — Federal Service for Intellectual Property; FIPS — Federal Institute of Industrial Property.

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Ландшафт биотехнологических инноваций: анализ патентного портфеля, действующего на территории Российской Федерации, за период с 2005 по 2024 гг.

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Цель. Провести сравнительный анализ долгосрочных тенденций и структурных особенностей патентования в сфере биотехнологий на национальном и региональном уровнях.

Материалы и методы. Исследование основано на данных двух патентных ведомств: Федеральной службы по интеллектуальной собственности (Роспатент) и Евразийского патентного ведомства (ЕАПВ) за период с 2005 по 2024 гг. Методология включает количественный анализ патентов с учетом стран-правообладателей и отраслевых направлений биотехнологии.

Результаты. Установлено, что доля биотехнологических патентов составляет 4,68% в Роспатенте и 8,33% в ЕАПВ. Выявлен феномен стратегической двойственности: в РФ российские заявители доминируют (61% патентов), тогда как в ЕАПВ их доля составляет лишь 9%, при этом нерезиденты формируют обширные патентные портфели. Динамика патентной активности демонстрирует четкую корреляцию с внешними факторами: рост активности не российских заявителей в ЕАПВ после 2014 г. и сдвиг отраслевых приоритетов в РФ от медицинских к промышленным биотехнологиям после 2019 г. При этом отечественная патентная активность по данным баз данных Роспатента в последние 5 лет снизилась на 16,5%.

Заключение. Результаты свидетельствуют о системном дисбалансе: Россия реализует преимущественно внутренне-ориентированную патентную стратегию, фокусируясь на внутреннем рынке, и значительно уступает в формировании правовых позиций на евразийском пространстве. Преобладание иностранных патентов, зарегистрированных в ЕАПВ, создает долгосрочные риски для конкурентоспособности российских разработок в регионе. Полученные данные могут быть полезны при разработке государственных программ по повышению конкурентоспособности России в рамках биотехнологических направлений на мировом рынке.

Ключевые слова: патент; патентный портфель; биотехнология; инновации; конкурентоспособность; экономический тренд

Список сокращений: CNIPA — Национальное управление интеллектуальной собственности Китая; EPO — Европейское патентное ведомство; JPO — Патентное ведомство Японии; IP5 — USPTO, EPO, JPO, KIPO и CNIPA; KIPO — Корейское ведомство интеллектуальной собственности; USPTO — Ведомство по патентам и товарным знакам США; ВОИС — Всемирная организация интеллектуальной собственности; ДНК — дезоксирибонуклеиновая кислота; ЕАПАТИС — Евразийская патентная информационная система; ЕАПВ — Евразийское патентное ведомство; МПК — Международная патентная классификация; РНК — рибонуклеиновая кислота; Роспатент — Федеральная служба по интеллектуальной собственности; ФИПС — Федеральный институт промышленной собственности.

INTRODUCTION

Biotechnology permeates many areas of the economy, from healthcare and agriculture to industry and ecology [1–3]. It is one of the key factors in addressing global challenges such as ensuring food security, improving the quality of medical care, and transitioning to an environmentally sustainable economy [4–6].

Recently, investor interest in the field of biotechnology has been growing worldwide [7–9]. For example, if in 2013 there were about 40 biotechnology companies in the US market [10–12], then in 2020 investor interest was at peak [13–15]. Thus, in the first half of 2020, US biotechnology companies attracted $9.4 billion in investments, exceeding the 2018 figure (over $6.5 billion). The market volume for these

technologies is projected to be $30.7 billion in 2025, and up to $121.9 billion[1] by 2034 (average annual growth rate is 14.8 %) [16–18].

In Russia, the volume of the biotechnology market reached 440 billion[2] rubles in 2024. In 2025, the large-scale National Project "Bioeconomy" was launched to create the necessary infrastructure for processing biomass in the country, and stimulate the development of innovations for agriculture, environmental protection, and drug manufacturing. Its goal is to achieve technological superiority in the field of bioeconomy and reduce import dependence by half. According to the forecast of the Center for Industry Expertise (CIE) of the Russian Agricultural Bank[3], the biotechnology market could grow to 700 billion rubles by 2028, and by 2036, Russia intends to become one of the leading countries in this sector[4] [19]. For this purpose, the technological platform "Bioindustry and Bioresources," known as "BioTech2030"[5], has been established. An urgent task for these programs is to identify prospects, the pace of innovative development in the industry, and to improve the effectiveness of state policy aimed at supporting innovations and implementing their development programs [22–24].

The effectiveness of such state programs is aimed to stimulate the creation and implementation of innovations through their monitoring using patent activity analysis, appears to be effective, helping to determine which sectors demonstrate the greatest progress and which are slowing down [25–27]. For instance, the World Intellectual Property Organization (WIPO) recognizes patent information as a unique source of information playing an important role in strategic business plans for both countries and companies[6].

In 2024, the Joint Research Centre (JRC) of the European Commission conducted an analysis of patent activity in the field of emerging biotechnologies [28]. The overall research scheme in Figure 1.

The study examined patents granted in at least two patent offices of the IP5 consortium: USPTO (USA), EPO (EU), JPO (Japan), KIPO (Korea), and CNIPA (China)[7]. All documents were grouped according to the International Patent Classification (IPC) categories into four directions of biotechnology: agricultural, industrial, medical, and horizontal (application in various fields). The conducted analysis showed that biotechnology patents constitute about 5 % of the total number of patents granted in the IP5 countries for the period from 2001 to 2020. Moreover, over 96 % of patents in this sector relate to developments in industry and medicine. The leader in the number of patents in the field of biotechnology is the USA (39 %); the European Union is in second place (18 %, regional patents granted by the EPO); and China is in third place (10 %). The results of the conducted research allow for the formation of a picture of global trends in biotechnology patenting.

At the same time, the specifics of the Russian national patent landscape in the field of biotechnology are insufficiently known. Our study analyzed the distribution of patents for inventions related to biotechnological directions, operating in Russia, granted by Rospatent and the Eurasian Patent Office (EAPO) in 2005–2024. The inclusion of EAPO patents in the analysis is due to the fact that patents granted by EAPO are valid in Russia. The analysis focuses on four key areas identified by European Commission specialists. The relevance of patent documentation for assessing the innovative potential of a country and individual companies in this field, and for identifying risks of excessive penetration of foreign inventors into the market, is due to its unique properties: such documentation is structured, unified for most countries, and includes information about the invention, its claims, description, and drawings, which facilitates its study by researchers worldwide, accelerating data search, trend analysis, and competitor research directions. Patents are published at early stages of development, long before their market appearance, which allows for a quick assessment of innovation implementation potential, promising market segments, and risks of rights infringement.

The IPC is a useful tool for searching for the necessary information in patent documents. Developed by WIPO in 1971, the IPC has become firmly established as the most durable patent classification[8]. It serves as the basis for systematizing patent documents in over

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100 countries, covering more than 75,000 categories, grouped into 8 main sections. Each IPC level reflects a specific technical area, simplifying the search and study of patent information [29, 30].

THE AIM. To conduct a comparative analysis of long-term trends and structural features of patenting in the field of biotechnology at the national and regional levels from 2005 to 2024.

MATERIALS AND METHODS

An analysis of invention patents registered from January 1, 2005, to December 31, 2024, in Rospatent and EAPO was conducted using the databases of the Federal Institute of Industrial Property (FIPS)[9] and the Eurasian Patent Information System (EAPATIS)[10]. The choice of this time period is related to the analysis of long-term trends under significant geopolitical changes. The lower boundary (2005) was chosen because by this time the Eurasian Patent System had already completed its 10-year establishment phase. The comparison of patent activity allowed for a comparable analysis of two systems: the National (Rospatent) and the Regional (EAPO). The upper boundary (2024) is determined by the relevance of the data for forming a modern picture, including assessing the impact of key events of the last decade, such as the sanctions regime since 2014 and the COVID-19 pandemic. The chosen period is statistically significant, allowing for the leveling of short-term fluctuations and the identification of long-term trends. Furthermore, it is precisely 20 years that is the maximum term of validity for an invention patent.

Within the chosen period, the number of inventions related to biotechnology as a whole identified in the FIPS database was 26,805 units, and 3,601 units in the EAPO database (in all selected EAPO patents, Russia is indicated as the country for which legal protection is sought). Their grouping and analysis were carried out using the color classification proposed by the Joint Research Centre (JRC) of the European Commission's Science and Information Service. According to this classification, biotechnology is divided into four color categories of application: red (medicine, healthcare), white (industry), green (agriculture), and horizontal (various fields of application). Each color is associated with a set of IPC categories[11] [31–34].

Thus, agriculture (green category) includes IPC indices such as: A01H1/0 (methods of modifying genotypes), A01H4/00 (breeding of plants from tissue cultures), A01K67/00 (breeding of animals, feeding of animals, or breeding of new animal breeds; new or modified animal breeds). Medicine and healthcare (red category) includes the most numerous group of IPC categories (categories are given in abbreviated form): A61K35/12-768 (materials from mammals; compositions containing undifferentiated tissues or cells; compositions containing non-embryonic stem cells; genetically modified cells — vaccines, drugs containing antigens or antibodies, microorganisms, materials derived from them); categories related to drugs containing peptides (A61K38/00), antigens or antibodies (A61K39/00), genetic material (A61K48/00), areas of organic chemistry — compounds of unknown structure: antibiotics (C07G11/00), vitamins (C07G13/00), hormones (C07G15/00), various peptides (C07K4/00, C07K14/00, C07K17/00, C07K19/00), immunoglobulins and antibodies (C07K16/00), various types of analyses: chemical analysis of biomaterials (blood, urine) and immunological tests (G01N33/50), immunological analysis, biospecific binding (G01N33/53, G01N33/54), investigation of materials by special methods — with an inorganic carrier, a carrier — a biological cell or its fragment (G01N33/55), using microorganisms causing venereal diseases; enzymes or isoenzymes; cancer; hepatitis; monoclonal antibodies; limulus lysate (G01N33/57), immunological tests — using proteins, peptides, or amino acids (G01N33/68), hormones (G01N33/74), human chorionic gonadotropin (G01N33/76), thyroid hormones (G01N33/78), prostaglandins (G01N33/88), using fats, e.g., cholesterol (G01N33/92). The white category (industry) includes categories: biological treatment of water, characterized by the microorganisms used (C02F3/34), devices for enzymology or microbiology (C12M), microorganisms or enzymes; their compositions; reproduction, preservation, or maintenance of microorganisms; mutations or genetic engineering; culture media (C12N), fermentation or enzymatic synthesis of chemical compounds or compositions, or separation of racemic mixtures into optical isomers (C12P), methods of measurement or testing using enzymes, nucleic acids, or microorganisms; compositions or indicator papers therefor; methods of obtaining such compositions; control of conditions in microbiological or enzymatic processes (C12Q). The horizontal category includes categories: combinatorial chemistry;

[9] Rospatent's search platform. Available from: https://searchplatform.rospatent.gov.ru/. Russian

[10] EAPATIS. Available from: https://www.eapatis.com/index.htm

[11] Friedrichs S.B. van Beuzekom. Revised proposal for the revision of the statistical definitions of biotechnology and nanotechnology. OECD Science, Technology and Industry Working Papers. Available from: https://www.oecd.org/en/publications/ revised-proposal-for-the-revision-of-the-statistical-definitions-of-biotechnology-and-nanotechnology_085e0151-en.html

libraries, e.g., chemical — directed molecular evolution of macromolecules, e.g., RNA, DNA, or proteins (C40B10/00); libraries contained in microorganisms or discovered by microorganisms, e.g., bacteria or animal cells; contained in vectors or discovered by vectors, e.g., plasmids; containing only microorganisms or vectors (C40B40/02), containing nucleotides or polynucleotides or their derivatives (C40B40/06), containing RNA or DNA that encode proteins, e.g., gene libraries (C40B40/08); methods of preparing libraries — biochemical, e.g., using enzymes or whole living microorganisms (C40B50/06), investigation or analysis of materials by electrical, electrochemical, or magnetic means — biochemical electrodes (G01N27/327); information and communication technologies specifically adapted for particular application fields: bioinformatics (information and communication technologies specifically adapted for processing genetic data or protein-related data in computational molecular biology; computer chemistry; chemoinformatics; computational materials science) (before 2018: G06F19/10-24; after 2018: G16C, G16B, G16Z).

Statistical analysis

The article uses data on patent activity in the field of biotechnology in the Russian Federation. Patent selection was carried out according to IPC categories. For this purpose, available statistical data based on data from Rospatent and the Eurasian Patent Office (EAPO) were used.

RESULTS

From 2005 to 2024, patents in the field of biotechnology accounted for 4.5 % (26,805 units) of the total number of patents registered in Rospatent (593,866 Russian Federation patents were registered across all technologies), and 8.33 % (3,601 units) in EAPO (43,229 Eurasian patents across all technologies). Over the study period, the annual ratio of patents obtained by residents (inventors from Russia) in Rospatent exceeded the number of patents obtained by non-residents (inventors from other countries). Over 20 years, non-residents received 39 % of the total number of patents related to biotechnology, while Russians received 61 %. This data demonstrates either a lack of interest from non-residents in promoting biotechnological developments in the Russian market, or, in the opinion of foreigners, a lack of competition in this field in Russia.

In Eurasia, the patent activity of Russians shows the opposite — their activity is extremely low: over the study period, they received only 9 % of all patents obtained in this period in the field of biotechnology, while inventors from other countries received many times more. The leaders in the number of patents in the field of biotechnology in the Russian Federation over the last 20 years are Russia and the USA (Table 1). However, while in Rospatent more than 58 % of patents in this field belong to Russian inventors, and only 12 % to American inventors, in EAPO the share of patents from Russians is only 8.66 %, while the share of inventors from the USA is 38.27 %. Inventors from other countries predominantly chose to register their biotechnological inventions in Rospatent rather than EAPO. This may be due to the strategy of promoting patented developments in the Eurasian markets. As a rule, they are registered in other countries during export, localization of production, or in joint projects. The decision on foreign patenting requires the presence of industrial capacities in the country for product manufacturing. If these are insufficient or absent, the risk of infringement of exclusive rights is reduced, and financial investments in such patenting are not advisable.

The number of countries that most actively obtained exclusive rights in the field of biotechnology in the Russian Federation from 2005 to 2024 were identified (see Table 1).

They demonstrated a steady growth in their patent portfolios in the field of biotechnology in the Russian Federation throughout the study period (USA, UK, Korea, China). Others reduced their patent activity only in 2020–2024 (Switzerland, France).

The USA has shown a stable growth trend in the number of biotechnology patents obtained in Russia over the past 20 years (from 2005 to 2024), it increased by more than 3.7 times. The UK also shows steady growth from 2005 to 2024, with an increase in the number of patents obtained in Russia by 2.5 times, Korea — by 10.4 times, China — by 12.9 times.

To understand patent activity trends, it is important that an invention patent is valid for 20 years (Article 1363, Paragraph 1 of the Civil Code of the Russian Federation, Part Four). A valid patent grants the right holder the ability to dispose of the exclusive right to what is patented, including prohibiting others from using it (Article 1229, Paragraph 1 of the Civil Code of the Russian Federation). Obtaining patents by non-residents in other countries indicates their desire for long-term promotion of their developments in that market.

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It is worth noting that although after the growth in patent activity from 2005 to 2019, a number of countries showed a decrease in 2020–2024, the number of patents still remained at a level comparable to 2005–2009 (Switzerland, France) (Table 2).

From 2020 to 2024, Russia registered 16.48 % fewer patents compared to the period 2005–2009. This may indicate a lack of tangible results related to current state support.

In EAPO, an increase in patent activity of the aforementioned TOP-10 countries in the field of biotechnology from 2005 to 2024 was also noted (Table 3). The highest activity over the analyzed 20 years in EAPO was shown by the USA (growth of more than 27.7 times), Russia (growth of 34 times), and Germany (growth of 12 times).

Since 2015, a stable growth trend in patent activity has been observed according to the EAPO patent register, with a peak intensity in 2020–2024. From 2005 to 2014, 356 patents in the field of biotechnology were granted within EAPO, and over the next 10 years, this number increased ninefold. A possible reason is the sanction pressure from, in particular, EU countries (including Germany, Netherlands) since 2014 for Russia, but not for Eurasia[12]. An increase in patenting activity in EAPO in the field of biotechnology is noticeable in the example of Germany. Thus, since 2015, an increase in patents obtained by inventors from Germany has been observed in EAPO: from 2005 to 2014, 34 patents were registered, and from 2015 to 2024, this figure increased 7.3 times.

Obtaining a Eurasian patent is attractive to inventors because it provides protection in 8 member states of the Eurasian Patent Organization (EAPO) simultaneously: Azerbaijan, Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russia, Tajikistan, Turkmenistan, based on a single application, which makes the process of obtaining it simpler and more cost-effective than filing applications in each country separately.

In the context of global economic transformation, countries in the Eurasian region attract the attention of foreign investors due to their rich natural resources, human and industrial potential, infrastructure, and favorable geopolitical location [35–37].

Analysis of invention patents related to biotechnology showed that over the 20-year period, the attention of inventors registering their developments in Rospatent and EAPO was primarily focused on industrial and medical biotechnologies. According to Russian Federation patents, inventions in the industrial biotechnology sector accounted for 13,309 units, healthcare — 12,561, agriculture — 858, and horizontal (multisectoral) biotechnologies — 73. Moreover, while medical biotechnology dominated from 2005 to 2019, industrial biotechnology has dominated since 2020 (Table 4). In Eurasia, on the contrary, patent activity in healthcare has increased from 2015 to 2024 (Table 5). This difference in trends between national and regional offices is likely related to the beginning of growth in industrial production in Russia in preparation for and ensuring the conduct of the Special Military Operation (SMO). The growth in EAPO patent activity in healthcare may reflect the global trend of 2019–2020 in creating and patenting new drugs and vaccines based on biotechnology, in connection with the pandemic and risks of future epidemics.

Analysis of the four directions of biotechnology, considered through the lens of patents granted by Rospatent (Table 6), showed that Russia and the USA are leaders in patenting in three biotechnological directions — medicine, industry, and agriculture. According to identified Russian Federation patents, inventors from Russia received 8,246 patents in the medical field, and inventors from the USA — 1,540 patents. In the industrial sector, inventors from Russia obtained 8,178 patents, and from the USA — 1,791 patents. For agricultural developments, inventors from Russia obtained 727 patents, and from the USA — 115 patents. Patenting of developments in the horizontal biotechnology sector in Russia was only attractive to inventors from the UK (21 Russian Federation patents), the USA (17 Russian Federation patents), and Switzerland (13 Russian Federation patents).

The study of EAPO patents showed similar trends (Table 7). The medical category is most attractive to inventors from the USA (901 EAPO patents), Russia (176), and Germany (174). These countries are also attracted to the industrial sector with the highest number of patents from inventors from the USA, Russia, and Germany. The agricultural and horizontal sectors are not particularly popular in the Eurasian region. This may be explained by the fact that Russia has large agricultural lands where farming is conducted more traditionally, making patenting irrelevant. Furthermore, the USA may have different methods of conducting agriculture and, consequently, uses

[12] The history of EU sanctions against Russia // TASS. – Available from: https://tass.ru/info/2322 9017?ysclid=mbhodqhgi0779152711

biotechnological developments that are not relevant to Russia and the Eurasian region. The scarcity of the horizontal biotechnology sector is unlikely to be reliably assessed due to its very limited scope. This includes isolated, almost random, cases of patenting on specific topical subjects that do not represent a trend for Russia or the Eurasian region during the period under review.

Being among the leaders in the number of patents does not always indicate technological sovereignty in a particular field, as it is necessary to consider what exactly the patents were granted for [38–40]. Patenting of specific cases of application or obtaining known products and technologies does not lead to technological sovereignty; it only complements the reliability of legal protection and defense of a key development, which in the field of biotechnology can be a compound, a gene construct, a nucleotide sequence, an amino acid sequence, a protein, etc. [41–42].

As part of a comparative study of the patent strategy of Russian and foreign inventors in biotechnology, the direction of peptides was analyzed. Peptides are classified under IPC categories: C07K — peptides, A61K38 — medicinal preparations containing peptides. From 2005 to 2024, Rospatent registered 7,518 patents for inventions related to peptides: 2,592 from Russian inventors and 4,926 from other countries. During the same period, EAPO issued 1,938 patents dedicated to peptides. Of these, 114 were obtained by inventors from the Russian Federation, and 1,824 from other countries. Moreover, inventors from other countries showed stable inventive activity and demand in patenting inventions related to peptides, in contrast to inventors from Russia, who, despite increased government attention to biotechnology, halved their inventive activity in this field (Table 8) and only slightly increased the number of EAPO patents obtained by Russians (Table 9). Non-Russian inventors showed record growth, increasing the number of EAPO patents by 2.9 times from 2020 to 2024 compared to 2015–2019.

Although the period 2020–2024 is marked by a decrease in the activity of Russian inventors in the field of peptides, there is a positive trend: residents have begun to focus more on patenting products (key commercially attractive developments). This trend is observed in both Russian patents and EAPO patents (Tables 10 and 11).

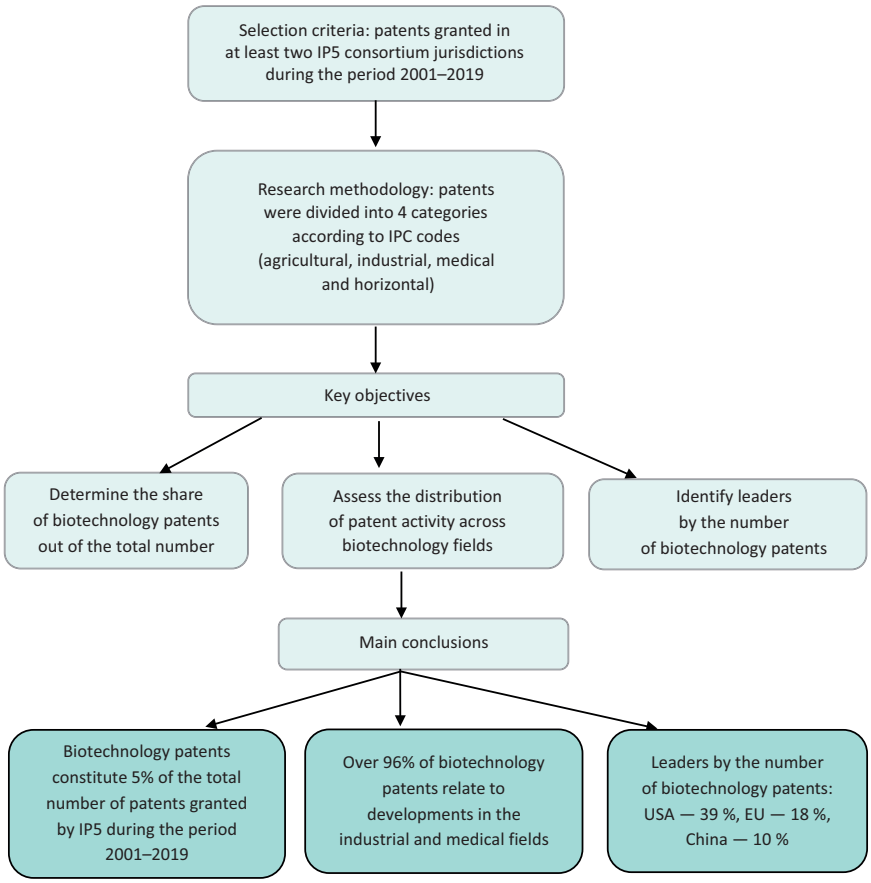

Figure 1 — Scheme of patent activity analysis in emerging biotechnologies conducted by JRC.

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Table 1 — TOP-10 countries that most actively obtained exclusive rights for their developments in biotechnology in the Russian Federation from 2005 to 2024

Country	Number of patents obtained in Rospatent, units	Country	Number of patents obtained in EAPO, units.
Russian Federation	16 376	USA	1 378
USA	3 401	Russian Federation	312
Switzerland	875	Germany	282
Germany	874	Netherlands	216
Japan	844	Switzerland	209
Korea	608	France	134
France	538	United Kingdom	134
United Kingdom	381	Japan	127
China	379	Denmark	116
Denmark	265	Belgium	102

Table 2 — Dynamics of patent acquisition in Rospatent by inventors from TOP-10 countries over 20 years

Applicant country	Number of RF patents obtained			
	2005–2009	2010–2014	2015–2019	2020–2024
Russian Federation	3 992	4 442	4 608	3 334
USA	325	704	1 164	1 208
Germany	174	197	271	232
Switzerland	116	200	336	223
Japan	109	224	267	244
France	63	128	205	142
United Kingdom	55	68	120	138
Denmark	43	79	68	75
Republic of Korea	31	60	193	324
Netherlands	23	99	138	94
Belgium	20	33	45	49
China	18	37	91	233

Table 3 — Dynamics of patent acquisition in EAPO by inventors from countries included in the TOP-10 over 20 years

Applicant country	Number of EAPO patents obtained			
	2005–2009	2010–2014	2015–2019	2020–2024
USA	34	41	364	941
Russian Federation	5	31	116	170
Germany	14	20	79	168
Switzerland	7	19	66	117
Netherlands	0	0	61	104
United Kingdom	2	8	30	96
Japan	7	5	32	83
Belgium	1	3	29	69
China	0	1	19	62
Denmark	10	14	34	58

Table 4 — Data on the distribution of registered patents in Rospatent by year and according to color classification

Biotechnology directions	Number of RF patents obtained			
	2005–2009	2010–2014	2015–2019	2020–2024
Healthcare	3 042	3 552	4 123	1 844
Industry	4 993	3 634	2 982	2 000
Agriculture	323	211	281	134
Horizontal biotechnologies	0	32	50	18

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Table 5 — Data on the distribution of registered patents in EAPO by year and according to color classification

Biotechnology directions	Number of EAPO patents obtained			
	2005–2009	2010–2014	2015–2019	2020–2024
Healthcare	0	13	610	1 556
Industry	137	206	399	633
Agriculture	0	0	12	134
Horizontal biotechnologies	0	0	0	6

Table 6 — Statistical data on the distribution of registered patents in Rospatent by country and according to classification by direction

Applicant country	Healthcare	Industry	Agriculture	Horizontal direction
Russian Federation	8 246	8 178	727	7
USA	1 540	1 791	115	17
Germany	444	464	3	2
Switzerland	488	389	2	13
France	269	271	8	0
United Kingdom	167	199	3	21
Japan	380	474	8	4
China	126	254	2	0
Korea	209	408	1	1
Denmark	138	133	0	0

Table 7 — Data on the distribution of registered patents in EAPO by country and according to color classification

Applicant country	Healthcare	Industry	Agriculture	Horizontal direction
USA	901	467	6	4
Russian Federation	176	130	1	5
Germany	174	105	0	3
Netherlands	73	0	0	8
Switzerland	135	73	0	2
France	81	48	0	5
United Kingdom	93	79	0	2
Japan	69	60	0	0
Denmark	55	59	0	2
Belgium	77	24	0	1

Table 8 — Dynamics of RF patent acquisition for developments related to peptides

Applicant	Patent acquisition period, years			
	2005–2009	2010–2014	2015–2019	2020–2024
Resident	680	800	791	321
Non-resident	633	1 124	1 582	1 587

Table 9 — Dynamics of EAPO patent acquisition for developments related to peptides

Applicant	Patent acquisition period, years			
	2005–2009	2010–2014	2015–2019	2020–2024
Resident	1	6	47	60
Non-resident	32	44	443	1 305

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Table 10 — Patenting objects in RF patents for developments related to peptides

Applicant \ Patenting object	Patent acquisition period, years							
	2005–2009		2010–2014		2015–2019		2020–2024	
	product	"method" only	product	"method" only	product	"method" only	product	"method" only
Resident	236	444	375	425	316	475	233	88
Non-resident	511	122	944	180	1 443	139	1 489	98

Table 11 — Patenting objects in EAPO patents for developments related to peptides

Applicant \ Patenting object	Patent acquisition period, years							
	2005–2009		2010–2014		2015–2019		2020–2024	
	product	"method" only	product	"method" only	product	"method" only	product	"method" only
Resident	0	1	6	0	40	7	54	6
Non-resident	29	3	41	3	375	68	1 188	117

DISCUSSION

The conducted analysis of patent activity in the field of biotechnology for the period 2005–2024 reveals a complex and ambiguous picture of the Russian Federation's positioning in both national and regional markets. The obtained data indicate structural imbalances and a dependence of patenting dynamics on geopolitical and macroeconomic factors.

In the domestic market, there is a stable dominance of Russian applicants, who account for 61 % of the total number of invention patents related to biotechnology. This may be an indicator of significant scientific and technical potential and active inventive activity in the country. However, simultaneously, this situation allows for the hypothesis of insufficient competition or limited commercial attractiveness of the Russian biotechnology market for leading foreign players, with the exception of strategically oriented companies from the USA, China, and a number of other countries, which demonstrate a steady growth in their patent portfolios.

In the context of the Eurasian Patent Office (EAPO), the picture changes radically. The share of Russian patents here is only 9 %, which indicates a critically low level of external patent activity by domestic developers. The Eurasian space has become a zone of strategic dominance for non-residents, primarily from the USA (38.27 %) and European Union countries. This creates a paradoxical situation: inventions created in Russia are actively protected within national borders, but their legal protection and potential market opportunities across the entire Eurasian region are extremely limited. In the future, this could lead to legal and commercial barriers for Russian developments in the Eurasian market.

The dynamics of patent activity show a clear correlation with the foreign policy context. The sharp increase in patenting through EAPO by Germany, the Netherlands, and other countries since 2014–2015 can be seen as an element of economic strategy under sanctions, allowing them to maintain legal positions and control over technologies in the Eurasian market. The corresponding growth in Russia's indicators in EAPO (34-fold over 20 years) reflects the course towards Eurasian economic integration. However, a negative signal is the decrease in the absolute number of domestic patent applications in Rospatent in the last five-year period (by 16.48 % compared to the baseline period 2005–2009). This trend suggests the need for additional state support measures in the context of declared goals for achieving technological sovereignty.

Significant differences are also observed in the sector structure of patent flows. In Russia, since 2019, a shift in priorities from medical to industrial biotechnology has been noted, which is a direct consequence of import substitution policies and preparation for changes in foreign economic conditions. This trend reflects the adaptation of the national innovation system to the geopolitical situation. In EAPO, on the contrary, the global trend associated with the COVID-19 pandemic — growth in activity in the field of medical biotechnology — persists and is strengthening. This emphasizes that for international companies, the Eurasian region remains a promising market for high-tech medical products.

Thus, the study conducted showed that Russia demonstrates a patent strategy focused on the domestic market and sectors related to increased industrial production. At the same time, there is a noticeable lag in establishing legal positions in the integrated Eurasian market, where foreign companies hold dominant positions. To change this trend, a

comprehensive set of measures is required, going beyond general support for inventiveness. Targeted programs to stimulate foreign patenting, in-depth analysis of foreign patent portfolios to identify niches and minimize legal risks, as well as the development of a balanced sector policy that combines the development of critically important industrial biotechnologies with support for competitive medical research oriented towards global and regional markets are necessary.

Study Limitations

This study, despite the representativeness of the data and the identified significant trends, has several methodological limitations that are important to consider when interpreting the results and planning future work:

- The study operates with data on granted patents; however, several years can pass between the moment of application filing, the decision on commercialization, and the granting of a patent. Thus, the obtained data may not fully reflect the current decline or growth in inventive activity due to administrative delays.
- The study focuses on the number of patents and their affiliation with sector but does not assess their qualitative aspects — technological significance, commercial potential, and so on. Consequently, leadership in the number of patents does not necessarily mean leadership in breakthrough developments.
- The analysis of dynamics focuses on leading countries, which provides a general picture but may overlook important specific changes in the activity of smaller players or the emergence of new ones.
- The study analyzes the supply of technologies (patents) but does not consider the demand for them from industry and the market. Low patent activity in any area may be a consequence of the absence of visible demand or production capacities for implementation, which is partly noted in the text but is not the subject of in-depth analysis.

The indicated limitations do not negate the main conclusions of the study regarding the structural imbalance of patent strategies and the dominance of non-residents in EAPO, but they set the framework for their correct interpretation.

CONCLUSION

The field of biotechnology demonstrates continuous growth due to technological progress and increased investment driven by the global need for innovations across various industries. Growth determines the development of the industry, which companies will have to pay attention to in order to maintain competitiveness. A legal framework is needed that creates conditions for effective management of patent-protected innovations, as a key factor of competitiveness in the global biotechnology market and for achieving technological sovereignty. In leading biotechnology countries like the USA and China, the state pays special attention to this aspect. This indicates the importance of active state participation in regulating and stimulating the development of this industry to ensure its sustainable growth and maintain competitiveness. The level of biotechnology development is clearly reflected in the quantity and quality of invention patents in this field. To adequately assess the potential of created innovations in their various aspects, it is advisable to classify them by categories, which serves as an important tool for understanding their economic impact. Patent activity objectively reflects the economic trends of the industry, contributing to its monitoring and forecasting the effectiveness of state support programs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Tatiana N. Erivantseva — conceptualization, data collection, analysis of literary sources, writing — original draft; Alexey V. Alekhin — writing — review & editing. All authors made an equivalent and equal contribution to the preparation of the publication. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept and preparation of the article, read and approved the final version before publication).

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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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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].

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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

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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

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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].

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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*)

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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

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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

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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.

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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

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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

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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].

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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

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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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Interim results of the first stage of a multicenter open multi-cohort study of the safety, pharmacokinetics, pharmacodynamics and efficacy of veranafusp alfa in adult patients with mucopolysaccharidosis type II

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This article presents the interim results of the first stage (administration of the drug to patients aged ≥18 years with mucopolysaccharidosis type II) of a multicenter open multi-cohort phase II-III study (IDB-MPS-II-III), **the aim** of which was to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of veranafusp alfa in patients with MPS II.

Material and methods. The interim analysis included data from 3 patients aged 18 years and older who had previously received idursulfase (2/3) and idursulfase beta (1/3). An individual dose increase (1–2–3 mg/kg) was performed after 2 weeks, followed by administration at a dose of 3 mg/kg for up to 52 weeks (a total of 52 weekly infusions). Standard PK parameters were evaluated. The PD criterion was the level of glycosaminoglycans (GAGs) in urine, blood and cerebrospinal fluid (CSF). Efficacy parameters included assessment of the dynamics of GAGs concentration in urine, blood and CSF, range of motion in joints, liver and spleen volume, change in the 6-minute walk test (6MWT, 6-minute test), left ventricular myocardial mass, forced vital capacity of the lungs (FVC). Safety parameters included assessment of the frequency of adverse events (AEs) and adverse reactions (ARs), including allergic and infusion reactions, as well as assessment of the frequency of formation of anti-drug antibodies (ADAs) and their neutralizing activity.

Results. The studied drug demonstrated non-linear PK in the blood and a dose-dependent increase in concentration in the CSF. Patients showed a decrease or stability in the level of GAG in the urine, a decrease in the level of heparan sulfate (HS) in the CSF in 2 (66.6%) of 3 patients, as well as a decrease in the level of dermatan sulfate (DS) in the CSF in the range of 17.19–80.96%. There was an average decrease in liver volume by 42.500 ± 218.496 cm^3, spleen volume by 24.350 ± 9.405 cm^3 and left ventricular myocardial mass by 15.333 ± 43.016 g relative to the baseline level. The average increase in walking distance according to the results of the 6MWT, after 1 year of therapy, was 76.067 ± 83.561 m. The average values of FVC and FEV1 did not change statistically significantly. 9 AEs were registered in 3 patients (100.0%) of mild severity, mainly from the liver and biliary tract, and 3 ARs, which were infusion reactions and were registered mainly in the first 4 months of therapy. During the analyzed period, the frequency of formation of ADAs at screening was in 2 patients, and at week 52 — in 3 patients, which indicates the development of *de novo* ADAs during treatment with veranafusp alfa in 1 patient.

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Conclusion. Weekly intravenous administration of the drug under study to adult patients at a dose of 3 mg/kg for 1 year provided control of the level of GAG in the urine and stabilization and/or improvement of somatic symptoms according to spirometry, echocardiography, 6MWT, range of motion in large joints, liver and spleen size, comparable to the results of the effectiveness of treatment with idursulfase in patients previously receiving enzyme replacement therapy. There was a tendency to decrease the level of HS in the cerebrospinal fluid, which may indicate the ability of veranafusp alfa to penetrate the BBB and deliver idursulfase to brain tissue, preventing the accumulation of pathological substrate in the CNS to prevent neurodegenerative changes.

Keywords: mucopolysaccharidosis type II; Hunter syndrome; glycosaminoglycans; veranafusp alfa; Clotilia; HIR-Fab-IDS; efficacy; safety

Abbreviations: MPS II — type II mucopolysaccharidosis; FK — pharmacokinetics; PD — pharmacodynamics; GAG — glycosaminoglycans; CSF — cerebrospinal fluid; 6MT — 6-minute test; FVC — functional vital capacity of the lungs; AE — adverse events; AR — adverse reactions; SAR — serious adverse reactions; ADA — anti-drug antibodies; HS — heparan sulfate; DS — dermatan sulfate; VFE1 — volume of forced exhalation in the 1st second; BBB — blood-brain barrier; CNS — central nervous system; ERT — enzyme replacement therapy; IEC — independent ethics committee; IDMC — independent data monitoring committee; MRI — magnetic resonance imaging; Echo-CG — echocardiography; SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate; RR — respiratory rate; CT — clinical trials.

Промежуточные результаты первого этапа многоцентрового открытого мультикогортного исследования безопасности, фармакокинетики, фармакодинамики и эффективности веренафуспа альфа у взрослых пациентов с мукополисахаридозом II типа

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В данной статье представлены промежуточные результаты первого этапа (введение препарата пациентам в возрасте ≥18 лет с мукополисахаридозом II типа) многоцентрового открытого мультикогортного исследования фазы II-III (IDB-MPS-II-III), **целью** которого являлась оценка безопасности, фармакокинетики (ФК), фармакодинамики (ФД) и эффективности веренафуспа альфа у пациентов с МПС II.

Материал и методы. В промежуточный анализ вошли данные 3 пациентов в возрасте от 18 лет, ранее получавших идурсульфазу (2/3) и идурсульфазу бета (1/3). Индивидуальное повышение дозы (1–2–3 мг/кг) выполняли через 2 недели с последующим введением в дозе 3 мг/кг длительностью до 52 недель (всего 52 еженедельные инфузии). Оценивались стандартные параметры ФК. Критерием ФД был уровень гликозаминогликанов (ГАГ) в моче, крови и спинномозговой жидкости (СМЖ). Параметры эффективности включали оценку динамики концентрации ГАГ

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в моче, крови и СМЖ, объема движений в суставах, объема печени и селезенки, изменение теста 6-минутной ходьбы (6МТ), массы миокарда левого желудочка, функциональной жизненной емкости легких (ФЖЕЛ). Параметры безопасности включали оценку частоты нежелательных явлений (НЯ) и нежелательных реакций (НР), включая аллергические и инфузионные реакции, а также оценку частоты образования антилекарственных антител (АЛА) и их нейтрализующей активности.

Результаты. Исследуемый препарат продемонстрировал нелинейную ФК в крови и дозозависимое увеличение концентрации в СМЖ. У пациентов отмечалось снижение или стабильность уровня ГАГ в моче, снижение уровня гепарансульфата (ГС) в СМЖ у 2 (66,6%) из 3 пациентов, а также снижение уровня дерматансульфата (ДС) в СМЖ в диапазоне 17,19–80,96%. Отмечено среднее снижение объема печени на 42,500±218,496 см^3, объема селезенки на 24,350±9,405 см^3 и массы миокарда левого желудочка на 15,333±43,016 г относительно исходного уровня. Средний показатель увеличения дистанции ходьбы по результатам 6МТ после 1 года терапии составил 76,067±83,561 м. Средние показатели ФЖЕЛ и ОФВ1 статистически значимо не изменялись. Были зарегистрированы 9 НЯ у 3 пациентов (100,0%) легкой степени тяжести преимущественно со стороны печени и желчевыводящих путей и 3 НР, которые являлись инфузионными реакциями и регистрировались преимущественно в первые 4 месяца терапии. В анализируемый период образование антилекарственных антител (АЛА) на скрининге отмечалось у 2 пациентов, а на неделе 52 — у 3 пациентов, что свидетельствует о развитии *de novo* АЛА при лечении веренафуспом альфа у 1 пациента.

Заключение. Еженедельное внутривенное введение исследуемого препарата взрослым пациентам в дозе 3 мг/кг в течение 1 года обеспечило контроль уровня ГАГ в моче и стабилизацию и/или улучшение соматических симптомов по показателям спирометрии, эхокардиографии, 6МТ, диапазона движений в крупных суставах, размеров печени и селезенки, сравнимые с результатами эффективности лечения идурсульфазой у пациентов, ранее получавших ферментную заместительную терапию. Наблюдалась тенденция к снижению уровня ГС в спинномозговой жидкости, что может свидетельствовать о способности веренафуспа альфа проникать через ГЭБ и доставлять идурсульфазу в ткани мозга, препятствуя накоплению патологического субстрата в ЦНС для предупреждения нейродегенеративных изменений.

Ключевые слова: мукополисахаридоз II типа; синдром Хантера; гликозаминогликаны; веренафусп альфа; клотилия; HIR-Fab-IDS; эффективность; безопасность

Список сокращений: МПС II — мукополисахаридоз II типа; ФК — фармакокинетика; ФД — фармакодинамика; ГАГ — гликозаминогликаны; СМЖ — спинномозговая жидкость; 6МТ — тест 6-минутной ходьбы; ФЖЕЛ — функциональная жизненная емкость легких; НЯ — нежелательные явления; НР — нежелательные реакции; СНР — серьезные нежелательные реакции; АЛА — антилекарственные антитела; ГС — гепарансульфат; ДС — дерматансульфат; ОФВ1 — объем форсированного выдоха за первую секунду; ГЭБ — гематоэнцефалический барьер; ЦНС — центральная нервная система; ФЗТ — ферментная заместительная терапия; НЭК — независимый этический комитет; НКМД — независимый комитет по мониторингу данных; МРТ — магнитно-резонансная томография; Эхо-КГ — эхокардиография; САД — систолическое артериальное давление; ДАД — диастолическое артериальное давление; ЧСС — частота сердечных сокращений; ЧДД — частота дыхательных движений; КИ — клинические исследования.

INTRODUCTION

Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is a lysosomal storage disease with an X-linked recessive inheritance pattern. In MPS II, mutations in the *IDS* gene reduce the activity of the lysosomal enzyme iduronate-2-sulfatase (I2S, iduronate 2-sulfatase), leading to the accumulation of glycosaminoglycans (GAGs), primarily heparan sulfate (HS) and dermatan sulfate (DS) fractions, in the lysosomes of cells in various tissues. This causes damage to parenchymal organs (hepatosplenomegaly), the musculoskeletal system, and the respiratory and cardiovascular systems. Progressive damage to the central nervous system (CNS) leads to intellectual decline, behavioral abnormalities, seizures, and motor and speech impairments [1]. MPS II is the most common form among all types of mucopolysaccharidoses. The incidence of the disease in the population is estimated at 1:140,000–156,000 newborns [2]. The International Register of Patients with Hunter Syndrome (Hunter Outcome Survey, HOS) includes over 1000 patients [3].

Patients with MPS II require lifelong enzyme replacement therapy (ERT) with recombinant idursulfase (IDS) preparations, which mimic the effect of the endogenous enzyme [4, 5]. In the Russian Federation, the registered drugs Elaprase® and Hunterase® are used [6].

Available ERT IDS drugs do not penetrate the blood-brain barrier (BBB), which limits their ability to influence the course of the neurodegenerative process. Therefore, there is a clinical need for drugs capable to cross the BBB for the treatment of the neuropathic form of MPS II [7–9]. JSC “GENERIUM” is developing the drug veranafusp alfa (Clotilia®, internal code GNR-055), whose active substance is IDS covalently linked to the C-terminal part of the Fab-fragment (Fragment Antigen Binding) of a monoclonal antibody to the human insulin receptor (HIR, Human Insulin Receptor) (Fig. 1). The molecule is created using “Trojan horse” technology, where the Fab fragment acts as a “carrier,” binding with high specificity to its target, the insulin receptor (the half-maximal concentration for interaction with the insulin receptor was EC_{50}=109.7 ± 13.4 pM) [10], on

BBB cells. This initiates the natural process of receptor-mediated transcytosis, which "transports" the entire therapeutic molecule HIR-Fab-IDS across the BBB, allowing the enzyme to reach the brain.

Veranafusp alfa is predicted to have a high degree of distribution and to exert the effect of IDS in the CNS and peripheral organs. Specific binding to mannose-6-phosphate residues on the oligosaccharide chains of membrane mannose-6-phosphate receptors and to the insulin receptor itself, which are present in somatic tissues, is associated with expected improved enzyme internalization and subsequent catabolism of GAGs accumulated in the organs of the main body systems, compared to registered drugs with a similar mechanism of action [8, 9].

The insulin receptor is expressed in virtually all human tissues. For peripheral tissues, it acts as an additional pathway to the mannose-6-phosphate-dependent internalization pathway, increasing the bioavailability of the recombinant enzyme to insulin-sensitive tissues. In the brain, the construct provides the only possible pathway for transcytosis across the capillary endothelium cells of the CNS that form the BBB. The binding site on the receptor is located away from the insulin binding site, thus the antibody does not interfere with insulin transport and binding. Therefore, the hybrid protein fragment of the antibody (Fab portion) with the enzyme should specifically interact with the human insulin receptor while retaining the activity of the unmodified I2S enzyme.

Preclinical studies have shown that IDS, as part of the modified veranafusp alfa molecule, retains the main functional properties of the free recombinant enzyme; its specific enzymatic activity (2.16×10^9 U/mol) was determined to be within the range established for Elaprase® (2.73×10^9 U/mol) and, apparently, slightly exceeded it on an equimolar basis [10], suggesting that the drug can be expected to have at least comparable efficacy in ERT.

Results from Phase I clinical trials (IDB-MPS-I and IDB-MPS-I02) showed good tolerability and a favorable safety profile of veranafusp alfa following single intravenous (IV) administration at doses ranging from 0.3–12 mg/kg in healthy volunteers [11].

THE AIM of the Phase II–III study (IDB-MPS-II-III) is to investigate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of veranafusp alfa in patients of different age groups with MPS II.

MATERIALS AND METHODS

Drug

The active substance of veranafusp alfa (manufactured at a concentration of 5 mg/mL for infusion) is a modified recombinant IDS enzyme within the hybrid protein HIR-FAB-IDS, produced on a Chinese Hamster Ovary (CHO) cell line, which provides IDS with a glycosylation profile similar to the natural profile of the endogenous enzyme (see Fig. 1). The obtained protein is purified using affinity and ion-exchange chromatography, with specific viral and recombinant DNA inactivation and removal processes.

Study Design

A multicenter open multi-cohort study of the safety, PK, PD, and efficacy of veranafusp alfa (JSC "GENERIUM", Russia) in patients with MPS II was conducted at 9 clinical centers in the Russian Federation and 2 centers in the Republic of Kazakhstan (RK). Adult patients were enrolled into cohort 1 at 2 centers: National Medical Research Center of Hematology, and Vernadsky Crimean Federal University.

The Phase II-III study (IDB-MPS-II-III) was initiated after approval by the Ethics Council of the Ministry of Health of Russia (Extract from Minutes No. 273 dated April 20, 2021), the Central Commission for Bioethics of the Ministry of Health of the Republic of Kazakhstan, and obtaining permits from the Ministry of Health of Russia (No. 499 dated September 3, 2021) and the Ministry of Health of the Republic of Kazakhstan. Ethical review was conducted by the Independent Ethics Committees (IECs) of the research centers. An Independent Data Monitoring Committee (IDMC) and a Safety Monitoring Committee were established to assess safety in the study. The study design and protocol complied with the ethical principles of the Declaration of Helsinki of the World Medical Association (1964), as amended (2024), the decision of the Eurasian Economic Commission Council dated November 3, 2016, No. 79 "On Approval of the Good Clinical Practice Rules of the Eurasian Economic Union," the standards of Good Clinical Practice of the International Council for Harmonisation ICH GCP (E6), and the current regulatory requirements of the Russian Federation and the Republic of Kazakhstan.

The study was conducted in three stages with sequential enrollment of patients into age cohorts, considering the assigned dosage. The first stage (cohort 1) included 3 patients aged ≥18 years (Fig. 2).

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After analyzing the data from the first stage and obtaining approval from the IDMC, the second stage (cohorts 2–7) involved the enrollment of 15 patients (at the time of the interim report) aged <18 years (results are being prepared for publication). The presented interim analysis included safety, PK, PD, and efficacy assessment results from the first stage in adult patients with individual dose escalation of 1–2–3 mg/kg, including the screening period (4 weeks) and the treatment period (52 weeks).

Patients

Inclusion Criteria. In the first stage, according to the inclusion criteria, male patients aged ≥18 years who agreed to suspend standard ERT (at a weekly dose of 0.5 mg/kg according to the instructions) 7 days before the first administration of veranafusp alfa were enrolled in the study. Participation in the study was voluntary and included signing an information sheet with an informed consent form.

*Non-inclusion Criteria***.** According to the exclusion criteria, individuals with hypersensitivity to IDS / another component of the drug, with neutralizing antibodies to the standard ERT drug, or with conditions that potentiate the risk of therapeutic intervention were not allowed to participate in the study. Restrictions to participation included contraindications for lumbar puncture and magnetic resonance imaging (MRI), a history of hematopoietic stem cell/bone marrow transplantation, blood/blood component transfusion, or vaccination within 30 days prior to screening. Individuals with positive human immunodeficiency virus test results, active viral hepatitis B and/or C, and a history of poorly controlled seizure disorder were not included in the study.

Exclusion Criteria. In accordance with the exclusion criteria, a patient could discontinue participation in the study if they refused further participation, if there was a condition preventing the execution of protocol procedures or endangering their safety, low adherence to therapy or non-compliance with protocol requirements, development of an adverse reaction (AR) or neutralizing anti-drug antibodies (ADAs) affecting the safety and efficacy of therapy and preventing further participation in the study, loss of contact with the patient, or by the investigator's decision.

Treatment

Dosage and Administration Regimen. Weekly intravenous infusions of the drug were administered at doses of 1–3 mg/kg. Individual dose escalation (1–2–3 mg/kg) was performed every 2 weeks to the next dose level of 2 mg/kg and 3 mg/kg, followed by administration at a dose of 3 mg/kg for up to 52 weeks (a total of 52 weekly infusions). The starting dose of veranafusp alfa in the IDB-MPS-II-III study was selected based on the analysis of dosing regimens in the Phase I study IDB-MPS-I using NOAEL (No Observed Adverse Effect Level) and MABEL (Minimal Anticipated Biological Effect Level) approaches; the dose that produces the minimal expected biological effect, considering information on the efficacy and safety in patients of drugs in this class with similar mechanisms of action [10, 11]. The tenfold maximum administered dose (3 mg/kg) constitutes the NOAEL, while the dose ranges for multiple administration calculated based on preclinical safety data were a maximum of 30 mg/kg for adults (therapeutic index 100)[1,2] [11].

The duration and rate of administration were chosen considering the results of a study of valanafusp alfa, which is similar in formulation and active substance type (IDS with an IgG domain to the insulin receptor) [7]. Veranafusp alfa was administered weekly IV over 3 hours (±10 minutes). The infusion rate was selected based on recommendations for the infusion duration of Elaprase® [6, 12] and the general properties of veranafusp alfa. The course of therapy included 52 infusions.

Study Endpoints

An interim analysis was conducted upon completion of 52 weeks of therapy. The duration of observation and the timing of biological material collection (urine, blood, and CSF) for PK / PD parameter assessment were chosen based on the results of previous studies of veranafusp alfa, published data on Elaprase® [6, 12], and available development data for similar drugs capable of crossing the BBB: valanafusp alfa, a complex molecule of antibody to the insulin receptor and IDS (AGT-181), and pabinaufusp alfa, a complex molecule of antibody to the transferrin receptor and IDS (JR-141, IZCARGO®) [7–9].

[1] European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in human and early clinical trials with investigational medicinal products", 2018. Available from: https:// www.ema.europa.eu/en/documents/ scientific-guideline/guideline-strategies-identify-and-mitigate-risks-first-human-and-early-clinical-trials-investigational-medicinal-products-revision-1_en.pdf

[2] FDA Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 2005. Available from: https:// www.fda.gov/ media/72309/download

PK parameters included C_{max} and C_{min} (maximum and minimum concentrations), AUC_{0-t} and $AUC_{0-\infty}$ (area under the concentration-time curve from time zero to the last measurement time or infinity), $T_{1/2}$ (half-life), and CL (total clearance). Blood samples were collected before infusion, at 3 hours/end of infusion, and at 30 min, 60 min, 90 min, 2 h, 4 h, 6 h, and 24 h after its completion. CSF samples for drug concentration measurement in cerebrospinal fluid were collected before the first drug administration (Day 1) and 2 hours after the end of infusion (Weeks 10 and 52). Concentrations of the investigational drug in serum and CSF were determined by a validated enzyme-linked immunosorbent assay (ELISA) method in accordance with GLP requirements.

PD parameters included analysis of GAG excretion dynamics in urine, as well as their concentration in serum and CSF after multiple administrations of veranafusp alfa compared to baseline. Measurements were performed using ELISA kits "Human HS (Heparan Sulfate) ELISA Kit," cat. No. E-EL-H2364, and "Human DS (Dermatan Sulfate) ELISA Kit," cat. No. E-EL-H1725 (Elabscience®, USA). Samples were collected at screening before the last infusion of IDS as part of standard ERT and during the treatment period on Day 1 (W1), W4, W8, W10, W14, W26, W30, W34, W40, W45, and W52. A general urine analysis was performed at screening and during treatment on Day 1 (W1), W10, W17, W34, W42, and W52. Urinary GAG levels were calculated considering creatinine levels. Determination of GAG (HS and DS) levels in blood was performed at screening before the last infusion of IDS as part of standard ERT and during treatment on Day 1 (W1), W4, W8, W10, W14, W26, W30, W34, W40, W45, and W52. Determination of GAG (HS and DS) levels in CSF was performed during treatment before the first administration of GNR-055 on Day 1 (W1) and 2 hours after the end of infusion at weeks W10 and W52.

Efficacy parameters included the dynamics of changes in the range of motion in large joints, liver and spleen volume by MRI, results of the 6MWT, changes in left ventricular myocardial mass by echocardiography (Echo-CG), forced expiratory volume in the first second (FEV1), and forced vital capacity (FVC) by spirometry. The dynamics of GAG (HS and DS) excretion in urine and their levels in serum (Week 4, Week 8, Week 10, Week 26, and Week 52) and in CSF (Week 10 and Week 52 (W52)) were assessed compared to baseline. The dynamics of changes in the range of motion in large joints, liver and spleen volume by MRI, 6MWT results, left ventricular myocardial mass by Echo-CG, and changes in FVC by spirometry were assessed at 10, 26, and 52 weeks of the study compared to baseline.

A complete physical examination was performed at screening and during treatment on Day 1 (W1), Day 2 (W1), W2, W4, W7, W10, W16, W21, W26, W30, W35, W39, W43, W47, and W52.

Assessment of vital signs included body temperature measurement (axillary temperature), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and respiratory rate (RR), and was performed at screening and during treatment before/after each veranafusp alfa infusion, as well as in case of an infusion reaction at the investigator's discretion and at each new dose level (2 mg/kg and 3 mg/kg) during infusion and 1, 4, 6, and 24 hours after its completion — W4 and W7.

Electrocardiography (ECG) was performed in 12 standard leads at screening and during treatment: W10, W16, W26, W40, and W52. Echo-CG, spirometry, goniometry, 6MWT, and abdominal MRI to monitor liver and spleen sizes were performed at screening and during treatment: W10, W26, and W52.

Complete blood count and biochemical blood tests were performed on Day 1 (W1), W10, W17, W34, W42, and W52.

Safety and immunogenicity parameters included assessment of the frequency and severity of adverse events (AEs), including serious adverse events (SAEs), related to the use of the investigational drug. Qualitative and quantitative analysis of adverse reactions (ARs), serious adverse reactions (SARs), the incidence of allergic and infusion reactions, and the frequency of anti-drug antibody (ADA) formation and their neutralizing activity were assessed. Infusion AEs were recorded and analyzed separately. Determination of ADAs and their neutralizing activity against veranafusp alfa was performed on Day 1 (W1), W4, W10, W26, W40, and W52 using a validated enzyme-linked immunosorbent assay.

Statistical Analysis

The populations for PK and PD parameter assessment consisted of patients for whom sufficient data were obtained to assess at least one parameter. The Safety Analysis Set (SAF) included patients who received at least one dose of the drug. The primary group for describing baseline characteristics and analyzing efficacy parameters was the Full Analysis Set

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(FAS) population. Patients who completed the study without significant protocol deviations were included in the Per-Protocol (PP) Analysis Set.

Given the orphan nature of the disease, it was planned to enroll up to 4 patients in cohort 1 of the first stage of the study. The size of cohort 1 was determined considering the studied dose levels of the investigational drug, the possibility of IDMC review for a decision on proceeding to the second stage of the study, and the availability of patients with MPS II for participation in the study, the total number of whom in the Russian Federation is 140 [13]. Hypothesis testing was not planned. Therefore, the analysis was descriptive. For quantitative indicators, the following were calculated: number of observations (N), minimum and maximum values (Min, Max), arithmetic mean (M), standard deviation (SD), 95% confidence interval for the mean, median (Me), and interquartile range (IQR). For pharmacokinetic parameters, the geometric mean (gMean) and coefficient of variation (CV%) were additionally calculated. For qualitative indicators, absolute values and proportions (%) were determined. To assess the dynamics of quantitative indicators between visits, the t-test (Student's t-test) for dependent samples or the Wilcoxon test was used. The dynamics of qualitative indicators between visits were analyzed using McNemar's test or Cochran's test.

Stata 14 and PkSolver or R version 4.4.2 programs were used for data analysis.

RESULTS

Patients Characteristics

As part of the interim analysis, data from 3 adult male patients of Caucasian ethnicity with a confirmed diagnosis of MPS II (Hunter syndrome), non-neuropathic form, confirmed by molecular genetic analysis and I2S enzyme activity levels, were assessed.

The mean age of the patients was 32.67 ± 13.32 years (range 18.0 to 44 years), mean body weight was 62.93 ± 11.29 kg, and mean height was 158.33 ± 8.96 cm. No deviations from reference values were found in thyroid function parameters. All patients received standard ERT weekly prior to study enrollment in the form of intravenous infusion of IDS — 1 patient, and IDS beta—2 patients.

Analysis of Veranafusp Alfa Pharmacokinetic Parameters

Representative curves of mean veranafusp alfa concentrations in serum after administration of escalating doses of 1 mg/kg, 2 mg/kg, and 3 mg/kg at different weeks of the study are shown in Figure 3.

After multiple IV administrations over 52 weeks, the mean C_{max} was reached at the end of drug administration at the 3-hour mark ± 10 minutes / end of infusion ± 5 minutes, followed by a decrease to the 24-hour mark ± 20 minutes after the end of administration (Table 1, Fig. 3). After multiple administrations of the drug at a dose of 3 mg/kg, the mean veranafusp alfa concentrations at Weeks 26 and 52 increased, reaching 15085.63 ± 4432.99 ng/mL (W52).

During Stage 1, the concentration of veranafusp alfa in CSF increased with increasing dose, and in one of the three patients, after administration at a dose of 3 mg/kg at Week 10, it reached 272.57 pg/mL.

Analysis of Veranafusp Alfa Pharmacodynamic Parameters

Changes in Urinary GAG Levels. Analysis of GAG levels indicates stabilization/reduction of this parameter during veranafusp alfa treatment (without achieving statistically significant differences in mean values). The primary analysis of urinary GAG was based on HS concentration per creatinine in urine (Table 2).

After 1 year of therapy with the investigational drug, the mean urinary HS level showed a tendency to decrease, while the mean DS level remained stable. At Week 52, a decrease in urinary HS level was observed in 2 (66.6 %) out of 3 patients, amounting to 47.59 % in one patient and 61.77 % in the second patient relative to baseline; a decrease in DS level was noted in 2 (66.6%) out of 3 patients, amounting to 15.11 % in one patient and 30.11 % in the second patient relative to baseline.

Changes in Serum GAG Levels. The primary analysis of serum GAG was based on HS and DS concentrations. Changes in HS and DS levels did not reach the threshold of statistical significance. A decrease in serum HS level at Week 52 relative to baseline was observed in 1 (33.3 %) out of 3 patients, amounting to 37.04 % relative to baseline; a decrease in DS level was noted in 2 (66.6 %) out of 3 patients, amounting to 50.5 % in one patient and 69.6 % in the second patient relative to baseline.

Changes in Cerebrospinal Fluid Glycosaminoglycan Levels. The primary analysis of CSF GAG was based on DS and HS concentrations (Figs. 4 and 5).

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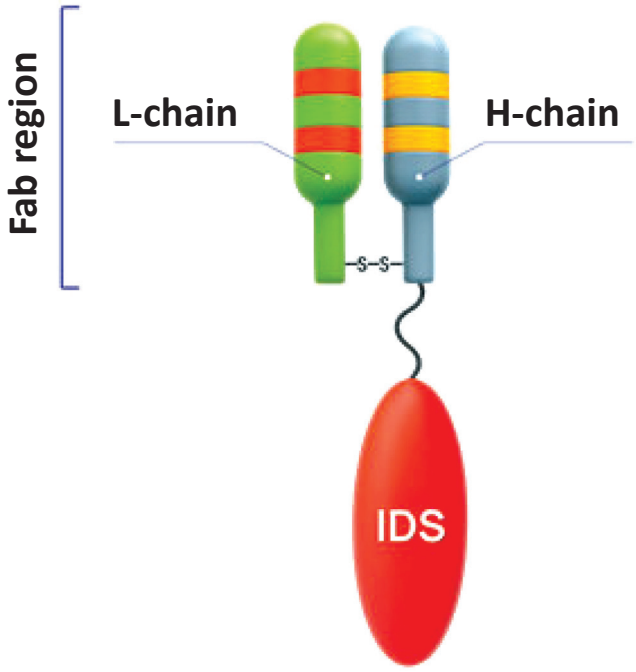

Figure 1 — Structure of the hybrid protein HIR-Fab-IDS (verenafusp alfa).

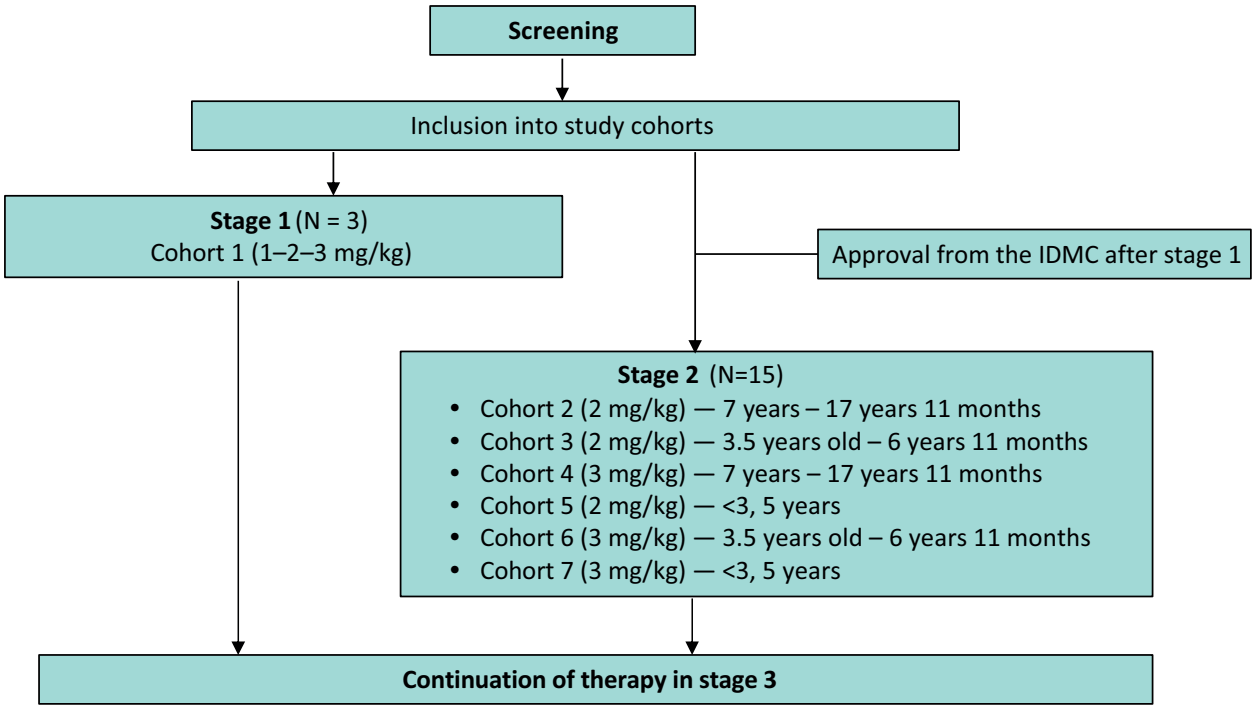

Figure 2 — Study design.
Note: IDMC, An Independent Data Monitoring Committee.

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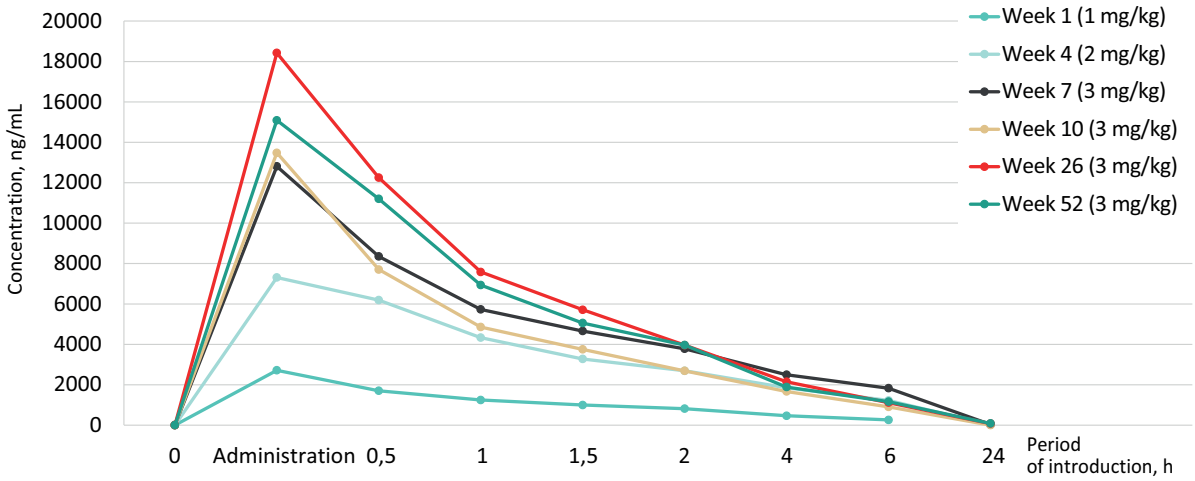

Figure 3 — Veranafusp alfa concentration in serum of adult patients with MPS II 0-24 hours after infusion at escalating doses of 1, 2, or 3 mg/kg.

Note: Week 1 — 1 mg/kg; Week 4 — 2 mg/kg; Weeks 7, 10, 26, and 52 — 3 mg/kg.

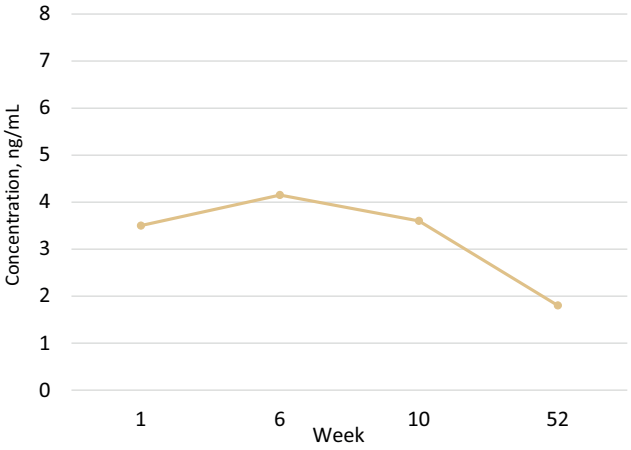

Figure 4 — Dynamics of changes in dermatan sulfate level in cerebrospinal fluid (median) of adult patients with MPS II receiving 3 mg/kg veranafusp alfa.

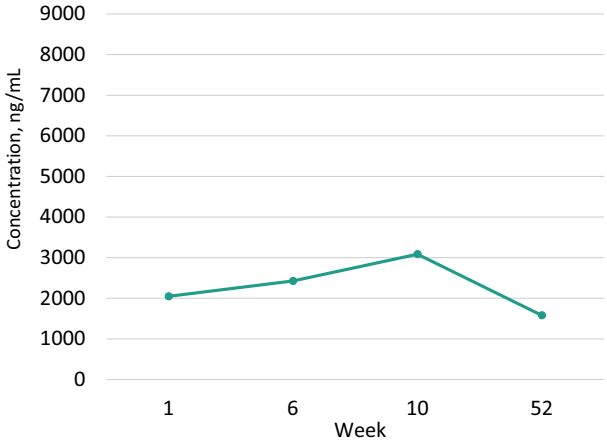

Figure 5 — Dynamics of changes in heparan sulfate level in cerebrospinal fluid (median) of adult patients with MPS II receiving 3 mg/kg veranafusp alfa.

Table 1 — Pharmacokinetic Parameters in Serum of Adult Patients with Mucopolysaccharidosis Type II Receiving 3 mg/kg Veranafusp Alfa

Weeks	Pharmacokinetic Parameters (Me [Q1; Q3])				
	AUC_{0-t}, h×ng/mL	C_{max}, ng/mL	$AUC_{0-\infty}$, h×ng/mL	$T_{1/2}$, h	CL, mL/h
W 10	19 333.97 [15 196.57; 22 558.86]	11 762.17 [10 529.78; 15 568.50]	24 163.24 [18 251.11; 26 818.71]	2.22 [2.20; 2.56]	124.16 [112.97; 183.64]
W 26	24 189.42 [22 632.87; 36 005.87]	19 563.13 [17 489.35; 19 925.37]	24 940.8 [23 343.37; 36 575.70]	1.31 [1.29; 2.44]	120.29 [91.26; 129.12]
W 52	39 131.58 [24 921.26; 41 636.72]	15990.94 [13130.40; 17493.51]	39293.12 [25006.57; 42202.66]	3.25 [1.92; 3.97]	76.35 [71.43; 178.10]

Note: C_{max} — maximum concentration; C_{min} — minimum concentration; AUC_{0-t} — area under the concentration-time curve from time zero to the last measurement time; $AUC_{0-\infty}$ — area under the concentration-time curve from time zero to infinity; $T_{1/2}$ — half-life; CL — total clearance.

Table 2 — Dynamics of Changes in Glycosaminoglycan Levels Relative to Baseline in Adult Patients with Mucopolysaccharidosis Type II Receiving 3 mg/kg Veranafusp Alfa

GAG	Visit	Urinary GAG Level, mg/mmol creatinine		Serum GAG Level, ng/mL		CSF GAG Level, ng/mL	
		Mean±SD	Δ*	Mean±SD	Δ*	Me	Q1; Q3
HS	Screening	0.00815 ± 0.00782	-0.00300 ± 0.00466	695.554 ± 100.089	2.669 ± 256.752	2090.41	1588.5; 2570.8
	Week 52	0.00515 ± 0.00395		698.223 ± 180.357		1579.53	1574.88; 3012.88
DS	Screening	0.00677 ± 0.00659	0.00101 ± 0.00306	4.866 ± 1.800	-0.360 ± 4.504	3.5	3.1; 4.95
	Week 52	0.00778 ± 0.00957		4.506 ± 5.004		1.8	1.15; 4.39

Note: * Δ — change from baseline; GAG — glycosaminoglycans; HS — heparan sulfate; DS — dermatan sulfate; CSF — cerebrospinal fluid.

Table 3 — Change in Range of Motion in Large Joints at Week 52 Compared to Baseline Values in Adult Patients with Mucopolysaccharidosis Type II Receiving 3 mg/kg Veranafusp Alfa

Joint Function	Left Joint (Mean ± SD)	Right Joint (Mean ± SD)
Shoulder Joints		
Flexion	0.000 ± 0.000°	1.000 ± 3.606°
Extension	10.000 ± 17.321°	11.667 ± 12.583°
Abduction	6.667 ± 11.547°	(-)1.667 ± 7.63°
Hip Joints		
Flexion	1.667 ± 2.887°	(-)1.667 ± 7.638°
Extension	1.667 ± 2.887°	0.000 ± 5.000°
Abduction	(-)1.667 ± 2.887°	(-)1.000 ± 3.606°
Elbow Joints		
Flexion	3.333 ± 5.774°	3.333 ± 5.774°
Extension	(-)8.333 ± 7.638°	(-)5.000 ± 5.000°
Knee Joints		
Flexion	3.333 ± 5.774°	3.333 ± 5.774°
Extension	0.000 ± 0.000°	0.000 ± 0.000°

Analysis of GAG levels showed a tendency towards a decrease in HS and DS levels in CSF after dose escalation to 3 mg/kg at week 6, after 1 year of therapy with the investigational drug. At Week 52, a decrease in DS level was noted in 2 (66.6 %) out of 3 patients in the range of 17.19–80.9 6% (Fig. 4).

A decrease in CSF HS level was observed in 2 (66.6 %) out of 3 patients, amounting to 23.30 % in one patient and 48.95% in the second patient relative to baseline (Week 1), starting from week 10 after reaching the 3 mg/kg dose. The HS concentration in these patients by the end of the treatment period (Week 52) was comparable to data from subjects without MPS II, in whom the median HS concentration was 1290.9 ng/mL (Fig. 5).

The dynamics of range of motion in large joints were characterized by stabilization and/or improvement of motor function. Maintenance of a stable state or a tendency towards increased range of motion in large joints after 52 weeks of therapy with the investigational drug was observed in goniometry measurements for the shoulder, hip, elbow, and knee

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joints. A non-significant tendency for a decrease in range of motion after 52 weeks of therapy was recorded for abduction of the right shoulder, flexion of the right hip, and abduction of the left and right hips, and extension of the left elbow (Table 3).

The dynamics of somatic manifestations of MPS II were characterized by a tendency towards an increase in walking distance based on 6MWT results of 76.067 ± 83.561 m (p = 0.25) in the studied cohort of patients at week 52.

After 52 weeks of therapy with the investigational drug, tendencies towards a decrease in liver volume by 42.500 ± 218.496 cm^3, spleen volume by 24.350 ± 9.405 cm^3, and left ventricular myocardial mass by 15.333 ± 43.016 g (~9%; p = 1.0) relative to baseline were noted. Mean FVC and FEV1 values did not change significantly and were 2.63 L and 1.5 L at week 52, respectively.

Analysis of Veranafusp Alfa Safety Parameters

General Characteristics of Safety Parameters. A total of 9 AE episodes were recorded in 100% of patients. AEs were recorded in the system organ classes of infections and infestations (100 %), hepatic and biliary disorders (66.7 %), cardiac disorders (33.3 %), and gastrointestinal disorders (33.3 %); all AEs in all patients were of grade 1 (mild) severity.

No hypoglycemic events were observed during the 52-week treatment period with weekly intravenous administration of the investigational drug GNR-055. 77.8 % of recorded AEs resolved with recovery, and for most of them (66.7 %), no drug therapy was required.

Adverse Reactions. AR episodes occurred in 1 (33.3 %) patient. All three recorded ARs were infusion reactions and were characterized by the occurrence of 1 (33.3 %) episode of paroxysmal tachycardia and 2 (66.7 %) episodes of nausea. All infusion reactions recorded during the analyzed period (100.0 %) resolved completely without the use of drug therapy. These infusion reactions were observed within the first 2 months of therapy with the investigational drug and did not require changes in its administration regimen.

Immunogenicity Analysis. ADAs to IDS were detected in 2 patients at screening before the administration of the investigational drug, and in 3 patients at week 52, indicating the de novo development of ADAs during veranafusp alfa therapy in 1 patient.

The safety profile of veranafusp alfa was consistent with that described for hybrid proteins based on IDS, primarily including manageable AEs of mild to moderate severity, among which only three ARs were observed in the form of transient infusion reactions.

DISCUSSION

The assimilation of scientific knowledge in the field of cellular and molecular mechanisms of MPS II formation and modern biotechnological advancements has led to the development of recombinant analogs of the I2S enzyme. The introduction of IDS into clinical practice has significantly improved the prognosis for patients with MPS II [12]; however, a significant limitation of current ERT is its inability to cross the BBB and influence the course of the neurodegenerative process that develops in most patients. Currently, drugs for the treatment of the neuropathic form of MPS II are being developed that operate on the “Trojan horse” principle, using endogenous receptors on BBB cells to deliver the enzyme to the brain (in Japan, IZCARGO®, based on idursulfase and the transferrin receptor, was registered in 2021) [14]. The investigational veranafusp alfa (Clotilia®, JSC “GENERIUM”) is a medicinal product containing the enzyme IDS covalently linked to the Fab fragment of an antibody to the insulin receptor, for the delivery of ERT to CNS tissues. Similar to the active substance of Elaprase®, membrane mannose-6-phosphate receptors are used for enzyme internalization into tissues, with expected improved distribution of veranafusp alfa due to the favorable distribution profile of the endogenous insulin receptor in the tissues of major organs.

Preclinical studies have demonstrated the efficacy of veranafusp alfa in an animal model of MPS II. The drug successfully crossed the BBB of primates (0.56–1.09 ng equivalent ng substance/g tissue in various brain regions); radiolabeled IDS was not detected in most brain regions [10].

According to the presented interim results of the IDB-MPS-II-III study, the pharmacokinetic profile of veranafusp alfa after multiple administrations in adult patients with MPS II corresponds to the distribution characteristics of hybrid monoclonal antibody-enzyme proteins [7–9].

The results obtained from the analysis of the first stage of the IDB-MPS-II-III study after 1 year of veranafusp alfa therapy were comparable to data obtained from long-term use of IDS regarding GAG

levels in urine and serum in patients with MPS II who had previously received standard enzyme replacement therapy [15, 16].

When analyzing the PD of IDS biosimilars, several authoritative sources rely on the reduction of urinary GAG levels in MPS II patients after one year of therapy [17–19]. However, not all patients show a decrease in urinary GAG levels during the first year of IDS treatment. It has been shown that fluctuations in the average change of this indicator from ~40 % to 60 % are possible during the first year of ERT [20]. Moreover, exceeding the upper limit of normal for this indicator has been described in 31 (32.9 %) out of 94 patients after 3 years of IDS treatment [16, 21], with urinary GAG levels decreasing from 362.0 µg/mg creatinine at baseline to 81.7 µg/mg. A decrease in ERT efficacy in terms of urinary GAG may be associated with the development of antibodies to the drug, while the impact of ADAs on clinical efficacy and safety indicators remains unproven [17, 22–24]. The effect of previously administered ERT in some study participants may also have influenced the magnitude of GAG dynamics. The demonstrated stabilization of urinary GAG excretion during veranafusp alfa use in the IDB-MPS-II-III study is consistent with literature data. Differences in results across cited studies are most likely due to the wide variability of population characteristics in statistically small patient samples.

In our study, one patient showed a decrease in serum HS level at Week 52, amounting to 37.04 % from baseline; a decrease in DS level in two patients was 50.5 % and 69.6 % relative to baseline.

Analysis of CSF GAG levels showed that after 1 year of therapy with the investigational drug, a decrease in HS and DS levels was observed in 2 (66.6 %) patients. At Week 52, the decrease in CSF HS level was 23.30 % in one patient and 48.95% in the second patient relative to baseline (Week 1); a decrease in DS level was noted in 2 (66.6 %) out of 3 patients in the range of 17.19–80.96 %.

It is hypothesized that the accumulation of GAGs, primarily the HS fraction, in the brain parenchyma leads to the development of neurocognitive impairments in MPS II [25]. It has been established that CSF of patients with MPS II contains a higher concentration of HS [16, 25, 26]. In the study by C.J. Hendriksz et al., it was shown that in healthy volunteers, depending on age, the average GAG level in CSF is below ~200 ng/mL and ranges from 50–70 ng/mL. In contrast, in patients with MPS II, the concentration of GAG in CSF is elevated, averaging ≥ 350.0 ng/mL in the absence of cognitive impairment, and ≥850.0 ng/mL in children with the neuropathic form of the disease and cognitive disorders [25]. In another study, the concentration of HS in CSF ranged from 0.8 to 1.7 µmol/L in patients with MPS II without cognitive impairment and from 2.3 to 4.3 µmol/L in patients with MPS II and cognitive impairment [26]. Therefore, monitoring HS levels in CSF provides information about the degree of nervous system involvement in patients with MPS II and can serve as an objective parameter for assessing treatment efficacy [27].

Analysis of CSF GAG levels demonstrated a decrease in HS at Week 52 in most patients from the first stage of the IDB-MPS-II-III study. While the dynamics of mean HS values in CSF were not statistically significant, likely due to the small sample size and the presence of the non-neuropathic form of the disease, the median HS level at Week 52 was comparable to data from patients of similar age without MPS II.

Analysis of the results of the IDB-MPS-II-III study confirms the ability of veranafusp alfa to cross the BBB. The observed tendency towards a decrease in CSF GAGs indicates the drug's ability to deliver IDS to brain tissues and suppress the accumulation of pathological substrate in the CNS. Thus, the decrease in CSF GAGs observed in our study may reflect the catabolic activity of veranafusp alfa.

Another registered ERT drug capable of delivering IDS as part of a hybrid protein to the CNS (IZCARGO®, JCR Pharmaceuticals) uses the transferrin receptor as a target on the surface of BBB cells. The minimal presence of the receptor in muscle tissue cells of peripheral organs may have been the reason for the observed limited therapeutic effect of this drug on the musculoskeletal system and cardiac function in MPS II patients [8]. The presented interim results of the veranafusp alfa study, which uses the insulin receptor, widely distributed in the CNS and peripheral tissues, as a target, may indicate the high efficacy of the drug, including when compared to published results of clinical studies of standard ERT drugs [28–30]. For example, according to the HOS analysis (n = 94), a year-long course of IDS therapy provides stabilization of most somatic manifestations of MPS II [16, 30]. It has been shown that the distance covered in the 6MWT increases by 10.9 % with IDS at a dose of 0.5 mg/kg

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and by 27.9% with IDS at a dose of 1.5 mg/kg over a year [20]. In our study, weekly IV administration of veranafusp alfa to adult patients was associated with a tendency to increase the distance covered in the 6MWT by ~15% (p = 0.250). The increase in patient mobility is consistent with the registered expansion (and/or stabilization) of the range of motion in large joints after a year of veranafusp alfa therapy.

According to spirometry and Echo-CG parameters, the veranafusp alfa therapy course provided control over respiratory and cardiovascular system functions. Literature data indicate that after one year of treatment with recombinant idursulfase-based drugs, respiratory and cardiovascular system functional parameters stabilize or show a tendency towards improvement [18, 20, 21].

The effect of IDS on liver and spleen size described in the literature involves a reduction in these parameters in adult patients by an average of one-third or stabilization of organ volume in the absence of hepatomegaly at the start of therapy [16, 18, 30]. In the IDB-MPS-II-III study, a tendency towards a decrease in organ size was recorded in the adult population, which, however, did not reach statistical significance, most likely due to the small sample size. It should be noted that there was no organomegaly at the initial stage of the IDB-MPS-II-III study, as previously treated patients were included.

Thus, with weekly IV administration of veranafusp alfa for one year in adult patients, control of GAG levels in urine and blood was maintained, and a tendency towards a decrease in HS and DS concentration in CSF was observed, which may indicate veranafusp alfa's ability to penetrate the CNS and exert a therapeutic effect on the symptoms of neurological manifestations of the disease.

The safety profile of veranafusp alfa in the IDB-MPS-II-III study was consistent with that described for recombinant idursulfase-based drugs [16, 31, 32]. The AEs/ARs recorded in the study were of mild or moderate severity, had a predictable spectrum, and were easily managed. In the IDB-MPS-II-III study, the incidence of infusion reactions in adult patients was 33.3 %, comparable to HOS estimates (31.7 %) [32].

Veranafusp alfa treatment for one year was associated with the *de novo* appearance of ADAs to idursulfase in 1 (33.3 %) patient, which is comparable to data from other researchers. Furthermore, ADAs were detected in 2 (66.7 %) other patients at screening, likely against previous ERT drugs. For instance, in the pivotal Phase II/III clinical trial evaluating IDS over 53 weeks of therapy, ADAs to the drug developed in ~50 % of patients [21]. Analysis of data from 15 clinical trials within a systematic review established the incidence of neutralizing ADAs in the range of 15.9–53.6 % [22]. Researchers believe that ADA production is not age- or duration-dependent but is likely a marker of genotype. The presence of antibodies is not considered a factor determining clinical outcomes [22]. The identified ADAs did not affect the efficacy of the ongoing therapy.

Thus, during the analyzed period of the study, veranafusp alfa demonstrated a favorable safety profile.

Study Limitations

The heterogeneity of baseline participant characteristics and the small sample size due to the orphan nature of the disease significantly increase the probability of underestimating the real clinical effect during statistical interpretation of the results. The results of the IDB-MPS-II-III study are limited to a 52-week timeframe. Continuation of this clinical study, as well as conducting additional clinical and observational studies with a larger number of patients and extended observation periods, will enhance the representativeness of the results of veranafusp alfa use in patients with MPS II.

CONCLUSION

The presented interim analysis results of veranafusp alfa (Clotilia®, JSC "GENERIUM", Russia) in adults with MPS II during the first stage of the Phase II–III clinical study demonstrated characteristic PK parameters and the ability to provide pharmacodynamic control of GAG metabolism, including in the CNS. The study confirmed veranafusp alfa's ability to cross the BBB and reduce GAG accumulation in the CNS, which is important for preventing neurodegeneration. During the analyzed period, veranafusp alfa demonstrated stabilization and/or improvement of somatic symptoms based on spirometry, echocardiography, 6MWT, range of motion in large joints, and liver and spleen sizes, with efficacy comparable to the results of treatment in patients previously receiving idursulfase ERT. A favorable safety profile of veranafusp alfa was established.

Continuation of this study and new studies including a larger number of patients will provide additional information on the efficacy and safety of veranafusp alfa in different age groups of patients with MPS II.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Elena A. Lukina, Rodion V. Ponomarev, Svetlana V. Trishina, Elena S. Gabitova — investigation, data processing and interpretation of results; Nato D. Vashakmadze, George A. Karkashadze, L.S. Namazova-Baranova — investigation, data analysis, selection of literary sources, writing the text of the article. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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Therapeutic potential of HSP70 in correcting cognitive deficits and its effect on beta-amyloid formation in Alzheimer's Disease

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Alzheimer's disease (AD) is characterized by the progressive accumulation of beta-amyloid and impaired cognitive function. Existing treatments are not effective enough, it's necessary to search for new therapeutic strategies targeting key pathogenetic mechanisms.

The aim. To investigate the therapeutic potential of intracellular and extracellular forms of heat shock protein HSP70 for correcting cognitive deficits and reducing amyloid load in AD.

Materials and methods. The study was performed on APPswe/PS1dE9/Blg transgenic mice, modeling AD, and lines created on their basis expressing intracellular (Tg_h) or extracellular (Tg_h_mod) forms of human HSP70. Behavioral tests were used to assess cognitive functions: Open Field, Novel Object Recognition, Y-maze, Barnes Maze. Amyloid load was assessed by histological method.

Results. The extracellular form of HSP70 (Tg_h_mod) significantly reduced amyloid load by 37% (p = 0.0033) and demonstrated marked cognitive improvement — by 40–45% in the Y-maze and Barnes Maze tests, whereas the intracellular form (Tg_h) reduced amyloidosis by 23.6% (p = 0.0273) but did not show significant memory recovery. The results indicate that the neuroprotective effect of extracellular HSP70 is likely mediated not only by chaperone activity but also by additional mechanisms critical for synaptic function.

Conclusion. A comparative study of the effectiveness of intracellular and extracellular forms of HSP70 in correcting both molecular and behavioral disorders in an AD model was conducted for the first time. It was found that the modified form of HSP70 has therapeutic potential. HSP70, especially its extracellular form, is a promising target for the development of AD therapy, providing a comprehensive effect on amyloid pathology and cognitive functions.

Keywords: Alzheimer's disease; HSP70; amyloid plaques; cognitive functions; neuroprotection

Abbreviations: AD — Alzheimer's disease; Aβ — beta-amyloid; APP/PS1 — APPswe/PS1dE9/Blg; Tg_h_mod — C57Bl/6-Tg_h(HSPA1A)-/+mod; Tg_h — C57Bl/6-Tg_h(HSPA1A)-/+; HSPA1A — human protein HSP70; WT — wild-type mice; IP — preference index; ID — discrimination index.

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Терапевтический потенциал HSP70 в коррекции когнитивного дефицита и его влияние на образование бета-амилоида при болезни Альцгеймера

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Болезнь Альцгеймера (БА) характеризуется прогрессирующим накоплением бета-амилоида и нарушением когнитивных функций. Существующие методы лечения недостаточно эффективны, что требует поиска новых терапевтических стратегий, направленных на ключевые патогенетические механизмы.

Цель. Исследовать терапевтический потенциал внутриклеточной и внеклеточной форм белка теплового шока HSP70 для коррекции когнитивного дефицита и снижения амилоидной нагрузки при БА.

Материалы и методы. Исследование выполняли на трансгенных мышах линии APPswe/PS1dE9/Blg, моделирующих БА, и созданных на их основе линиях, экспрессирующих внутриклеточную (Tg_h) или внеклеточную (Tg_h_mod) формы человеческого HSP70. Для оценки когнитивных функций применяли поведенческие тесты: Открытое поле, Распознавание нового объекта, У-лабиринт, Лабиринт Барнса. Амилоидную нагрузку оценивали гистологическим методом.

Результаты. Внеклеточная форма HSP70 (Tg_h_mod) значимо снижала амилоидную нагрузку на 37% (p=0.0033) и демонстрировала выраженное когнитивное улучшение — на 40–45% в тестах У-лабиринт и Лабиринт Барнса, тогда как внутриклеточная форма (Tg_h) уменьшала амилоидоз на 23,6% (p=0,0273), но не показывала значимого восстановления памяти. Полученные результаты указывают на то, что нейропротекторный эффект внеклеточного HSP70, вероятно, опосредован не только шаперонной активностью, но и дополнительными механизмами, критически важными для синаптической функции.

Заключение. Впервые проведено сравнительное исследование эффективности внутриклеточной и внеклеточной форм HSP70 в коррекции как молекулярных, так и поведенческих нарушений в модели БА. Установлено, что модифицированная форма HSP70 обладает терапевтическим потенциалом. HSP70, особенно его внеклеточная форма, является перспективной мишенью для разработки терапии БА, оказывая комплексное воздействие на патологию амилоида и когнитивные функции.

Ключевые слова: болезнь Альцгеймера; HSP70; амилоидные бляшки; когнитивные функции; нейропротекция

Список сокращений: БА — Болезнь Альцгеймера; Аβ — бета-амилоида; APP/PS1 — APPswe/PS1dE9/Blg; Tg_h_mod — C57Bl/6-Tg_h(HSPA1A)-/+mod; Tg_h — C57Bl/6-Tg_h(HSPA1A)-/+; HSPA1A — человеческий белок HSP70; WT — беспородные мыши; ИП — индекс предпочтения; ИД — индекс дискриминации.

INTRODUCTION

Alzheimer's disease (AD) remains the most common cause of dementia worldwide, posing a serious medical and social problem. Its pathogenesis is based on the accumulation of extracellular senile plaques in the brain, consisting of beta-amyloid (Aβ), and intraneuronal neurofibrillary tangles of hyperphosphorylated tau protein. These processes trigger a cascade of neurodegenerative changes, including synaptic dysfunction, chronic neuroinflammation, and neuronal death, ultimately leading to progressive cognitive deficits [1].

Despite progress in understanding the molecular basis of AD (amyloid and tau pathology, neuroinflammation), most approved drugs are only symptomatic. There is currently no therapy capable to slow or stop the progression of the disease, making the investigation of approaches targeting key pathogenetic links, such as proteostasis disruption and the accumulation of toxic protein aggregates, highly relevant [2, 3].

In this regard, considerable attention is paid to the search for endogenous neuroprotective factors capable of modulating key disease links. One such promising agent is the 70 kDa heat shock protein — HSP70 [4, 5].

Heat shock proteins (HSPs) are involved in a wide

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range of cellular housekeeping processes, including the folding of newly synthesized polypeptides, refolding of metastable proteins, assembly of protein complexes, degradation of misfolded proteins, and dissociation of protein aggregates. Under normal conditions, HSPs constitute 5–10 % of the total cellular protein content and function as an integrated network to maintain proteostasis [6]. Under extreme conditions, heat shock transcription factors are activated in response to stress to mitigate damage, leading to the transcription of a large number of HSPs. Based on their primary function as molecular chaperones (they are also involved in numerous processes in eukaryotic cells), impaired HSP function is linked to many diseases [7, 8].

HSP90 / HSP70 acts an important role in maintaining the normal physiological state of tau protein, as well as blocking its abnormal phosphorylation and accumulation, and participates in the pathological process associated with tau protein and Aβ [9, 10].

In neurodegenerative pathologies such as AD, Parkinson's disease, and Huntington's disease, HSP70 acts as a primary protective mechanism, correcting protein folding (including α-synuclein) and suppressing apoptosis. However, excessive expression can exacerbate neuroinflammation through TLR4 activation [11, 12]. It is important to note that HSP70 functions not only as an intracellular chaperone but also as an extracellular signaling mediator, interacting with receptors (TLR2/4) and modulating the inflammatory response, which is particularly significant for long-lived neurons, ensuring their resistance to stress and premature death [13].

HSP70 is often released from cells under stress conditions and/or in transformed cells. According to studies, endogenous HSPs exhibit neuroprotective activity in rodent models of Huntington's disease [14].

THE AIM. To determine the effect of intracellular and extracellular HSP70 on amyloid plaque accumulation in the brain and to evaluate its impact on cognitive functions in mice using a battery of behavioral tests.

MATERIALS AND METHODS

Study Design

The study design and animal housing conditions were selected in accordance with the recommendations of the Eurasian Economic Commission Board dated November 14, 2023 No. 33. Sexually mature mice were used in the study. Starting from week 17, behavioral screening was conducted to identify short-term and long-term memory impairments using the following tests: Open Field, Novel Object Recognition, Y-maze, and Barnes Maze. After the tests were completed, histological analysis of amyloid plaque accumulation in the brain was performed.

Study Conditions and Duration

Experimental and control animals were housed in the pathogen-free vivarium of the Belgorod National Research University under artificially regulated light-dark cycles (12 / 12 hours) at a temperature of +22–26 °C; they had free access to food and water. The study was conducted from January to September 2025.

Animals

The following lines were used in the study: APPswe/PS1dE9/Blg is overexpressing human mutant *APP* and *PSEN1* genes cDNA; C57Bl/6-Tg_h(HSPA1A)-/+mod — expressing a modified human HSP70 protein (HSPA1A) in milk; C57Bl/6-Tg_h(HSPA1A)-/+ is expressing a modified human HSP70 protein (HSPA1A) in cells. Crosses between the APPswe/PS1dE9/Blg line and the C57Bl/6-Tg_h(HSPA1A)-/+mod (Tg_h_mod) and C57Bl/6-Tg_h(HSPA1A)-/+ (Tg_h) lines were used in the experiment (n=11). Outbred mice derived from these crosses (WT, *n* = 11) were as controls.

Ethics Approval

Animal experiments were conducted in accordance with the "Rules of Laboratory Practice in the Russian Federation" dated April 01, 2016 No. 199n. The study was approved by the Commission for the Control of Laboratory Animal Husbandry and Use of Belgorod National Research University (Expert Opinion No. 01-01i/24 dated 09.01.2024).

Open Field Test

The animal was placed in an "Open Field" apparatus (NPK Otkrytaya Nauka, Russia), and its movements were recorded. The apparatus is a square chamber with a base of 50×50 cm, made of opaque acrylic glass. Animal behavior was assessed based on one parameter characterizing mouse behavior — locomotor activity. The EthoVision software (Noldus Information Technology, Netherlands) allows for

automatic acquisition of selected parameters: distance traveled, activity, and average speed of all movements in cm/sec. Each animal was tested for 5 minutes under 40 lux (dim lighting) [15].

Novel Object Recognition Test

A simple behavioral test based on the innate exploratory behavior of rodents. The test is divided into three phases: habituation, training / adaptation, and testing. On the first day of the test, the animal was placed in an empty 50×50 cm arena to explore it for 5 minutes under 40 lux. The second day of the test (adaptation) involves placing the animal in the same arena with two identical objects. On the third day (testing) the animal was placed in the arena with one of the familiar objects from the previous phase and one new object [16]. The following parameters were recorded: number of approaches to the new and old object and time spent near them; preference index (IP), calculated by formula 1; and discrimination index (ID), calculated by formula 2.

$$PI = \left(\frac{T_n}{T_n} + T_o\right) \times 100, \quad (1)$$

$$DI = \frac{T_n - T_o}{T_n + T_o}, \quad (2)$$

where PI — preference index; DI — discrimination index; T_n — time spent exploring the new object; T_o — time spent exploring the old object.

Barnes Maze Test

This test is used to investigate spatial learning and memory in animals. The apparatus (NPK Otkrytaya Nauka, Russia) consists of a circular platform 122 cm in diameter, containing 40 holes 5 cm in diameter, one of which is an exit (shelter). Distal visual cues are represented by 4 black and white images with different figures and patterns, located in different cardinal arms — North, South, West, East. Video recording is performed for 5 minutes. Measurements include total distance traveled by the animal, speed of movement, and time to find the exit within the allotted period.

Training days (Days 1–4): The animal gets acquainted with its surroundings for 3 minutes to locate the "shelter". Each mouse has 4 trials per day with a 15-minute interval.

Test day (day 5): The "shelter" area is covered by a flap. The animal remains on the platform for 5 minutes, during which time spent in the exit, number of approaches, and time spent in this zone are recorded [17].

Y-Maze

Working memory was assessed using the Y-Maze Test (NPK Otkrytaya Nauka, Russia) with arm dimensions of 32.5×8.5×15 cm (L×W×H). The test was conducted under dim lighting (40 lux). Mice were allowed to explore two arms of the maze for 5 minutes, while the third arm was blocked. After a 30-minute break between trials, a second trial was conducted, during which animals were allowed to explore all three arms for 5 minutes. Entry into the arm was recorded when more than half of the mouse's body crossed the boundary between two others. The number of entries and time spent in each one were recorded. Analysis was performed in two scenarios: the entire 5-minute test duration, or the first 2 minutes of "active exploration" [18].

Histology

Animals were subjected to terminal anesthesia; their brains were dissected, and fixed in Carnoy's solution (6 parts 96% ethanol, 3 parts chloroform, 1 part glacial acetic acid) for 12 hours. The tissue was dehydrated by sequential passage through ethanol solutions of increasing concentration: 75 % — 1 hour, 96 % (I) — 5 minutes, 96 % (II) — 45 minutes, 100 % (I) — 5 minutes, 100 % (II) — 45 minutes. Then, it was incubated for 30 minutes in a mixture of 100% ethanol–chloroform (1:1), 1 hour in chloroform (I), left overnight in chloroform (II), after which the tissues were infiltrated with paraffin (3 changes of 1 hour each) at 60°C. Paraffin sections 8 µm thick were mounted on polylysine-coated slides.

Sections were deparaffinized for 20 minutes in xylene and rehydrated by sequential incubation in ethanol: 10 minutes in 100 %, 5 minutes in 95 %, 5 minutes in 50 %, then washed three times in deionized water for 5 minutes each. Sections were stained with Congo red solution (0.5 % Congo red in 50 % ethanol) for 5 minutes and differentiated in a 0.2 % potassium hydroxide solution in 80 % ethanol for 1 minute, washed three times in deionized water for 5 minutes, and mounted using Glasseal mounting medium (Labiko LLC, Russia) [19].

Microscopy of samples was performed using a Nikon Eclipse Ti microscope equipped with a motorized stage. Panoramic visualization of mouse brain sections in TRITC fluorescence mode was performed using a 10x objective with NIS Elements AR software (version 4.6), with frame stitching, 10 % overlap, and automatic

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post-processing. The resulting images were loaded into QuPath software (version 0.5.1) for detection and analysis of aggregates. Object detection was based on the threshold brightness of amyloid fluorescence spots relative to the background brightness of intact brain tissue. Morphometric data were expressed as %area of plaques/mm² of cerebral cortex. After automatic object detection, manual verification was performed to exclude false identifications. To confirm reproducibility, two independent researchers also performed manual counts [20].

Statistical Analysis

Statistical analysis was performed using GraphPad Prism Software 8.0 ("GraphPad Software Inc.", USA). Data are presented as M ± SD. Depending on the type of distribution and equality of variances, the significance of the results was assessed using parametric (ANOVA, Tukey's test) or non-parametric (Mann-Whitney U test) criteria. An unpaired Student's t-test was used to identify differences in intergroup comparisons. Differences were considered significant at $p \leq 0.05$.

RESULTS

Effect of HSP70 on Locomotor Activity

The Open Field test was used to assess general locomotor activity. As shown in Figure 1, no statistically significant differences were observed between the control group and the experimental groups, indicating no impairment of locomotor function in the animals, which allows us to compare the results of further tests without any adjustments [21].

Using Open Field test, we can also analyze the anxiety states of animals by looking at the time spent in the center versus the periphery, as these two indicators are mutually interchangeable. We assessment the time spent in the periphery and the number of transitions to this zone. There were no statistically significant differences in the number of transitions between the two sectors, but there were differences between the control group and the APP/PS1 group ($F(3, 35) = 3.860$; $p = 0.0391$).

Effect of HSP70 on Short-Term Memory Formation

The Novel Object Recognition test was performed to assess long-term memory. The perirhinal cortex is responsible for object recognition and spatial memory; impairments in its structure or function manifest as a lack of interest in new objects [22]. Thus, we observe that the number of approaches to the "new" toy increases when it is replaced 24 hours after the initial familiarization with the toys, in almost all mouse lines except for the positive control and the double transgenic Tg_h animals. The percentage of interest in the new object was statistically significantly lower between the WT group and the APP/PS1 and Tg_h groups ($F(7, 70) = 1.782$; $p = 0.0108$ and $p = 0.0319$). A significant difference can be observed in the IP, which indicates the degree of preference for the unfamiliar object. In the negative control and Tg_h_mod groups, it is above 50%; in the APP/PS1 and Tg_h groups, it differs significantly by 23% and 22% respectively ($F(3, 34) = 4.526$; $p = 0.0204$ and $p = 0.0209$) from the control group. A similar pattern is observed for the ID ($F(3, 42) = 3.874$; $p = 0.0368$ and $p = 0.0435$), indicating a decline in long-term memory functions and physiological changes in the perirhinal cortex.

To further confirm hippocampal impairments, the Y-Maze Test was conducted to analyze pathologies in short-term memory formation.

Figure 3 presents data on the preference for the new arm for exploration. Exploratory activity is driven by the innate curiosity of rodents, who strive to explore unvisited places. A mouse with intact working memory and, consequently, intact prefrontal cortex functions will remember previously visited arms and will tend to enter the less visited arm. Spatial memory, determined by the hippocampus, is also involved in this test by opening a new arm half an hour after exploring two others. As seen from the percentage of time spent by animals exploring the new arm, the negative control shows a typical pattern for healthy mice, with more time spent exploring the new arm (35 %) compared to the old one (29 %). The positive control also shows a typical pattern for AD mice, where the total time exploring the new arm does not exceed 20%. The experimental Tg_h_mod line shows a similar pattern to the negative control, while the Tg_h line, although showing a pronounced difference in visiting the new and old arms, exhibits a more blurred pattern of exploration of both the "old" and "new" arms, differing only in the time spent in the "landing" arm versus the "new" arm. The percentage of entries into the new arm decreases by 14 % ($p = 0.0398$) in the positive control group compared to the negative control, and by 28 % ($p = 0.0099$) in the Tg_h group. The Tg_h_mod group's

indicators increased statistically significantly by 40 % (p = 0.0156) compared to the Tg_h group.

Effect of HSP70 on Long-Term Memory Formation

The Barnes Maze test measures spatial learning and memory. The test is based on rodents' aversion to open spaces, which motivates the subject to seek shelter. The first 4 days are training days: to establish a correct trajectory for mice in finding the "shelter" and reduce the percentage of errors in hiding in false shelters, mice use visual cues to develop this trajectory. The latency to find the platform indicates the learning speed of the mice. As shown in Figure 4, progress in learning is observed in the positive control only on the third day; thereafter, almost identical parameters are observed, indicating a lack of progress in remembering the platform's location. The same pattern was observed in the Tg_h group — as seen from the graph, the learning process in both groups occurs almost identically. The negative control shows a typical pattern for healthy mice, with a tendency to learn each subsequent day. The tendency for a decrease in latency to find the platform in the Tg_h_mod group is similar to the negative control, but there are no statistically significant differences on the third and fourth days. The speed of the negative control increases daily, and the distance decreases, which fully correlates with the tendency for reduced time to find the platform. The positive control shows the opposite trend with increased speed and distance in the test and increased time to find the platform, indicating a lack of learning in this mouse line. In the Tg_h group, a decrease in total distance and speed in the test should be noted, resulting in almost no change in latency to find the shelter, but based on the overall data, it can be concluded that the learning process in this animal line is weakly expressed. The Tg_h_mod line shows a jump-like change in speed and total distance on the second day and almost unchanged values of these parameters on days 3 and 4 of training, while we see a decrease in latency to find the platform. Considering all the data, high learning ability in the test can be stated.

On the fifth day of the test, we also investigated learning and spatial memory. The latency in both experimental groups shows an intermediate result and does not statistically differ from the control. The number of entries into the shelter zone shows a statistical difference between the positive and negative controls (p=0.0409). The total time spent in the "shelter" zone in the positive control group was statistically significantly different from the Tg_h_mod group (p = 0.0184) and the negative control group (p = 0.0020). Compared to the WT group, this parameter is practically unchanged in the Tg_h group and increases by 45% in the Tg_h_mod group.

Effect of HSP70 on Amyloid Plaque Formation

To confirm the theory of slowing AD development, in addition to studying short-term and long-term memory, a histological analysis of amyloid plaques in the cortex and hippocampus of mouse brains was performed at 5 months of age. Amyloid aggregates are one of the most prominent markers of the disease, and their quantity and area indicate the degree of disease progression. Both investigated forms of HSP70 protein significantly reduced amyloid load compared to the control APP/PS1 group in the cerebral cortex (Fig. 5A). The extracellular form of HSP70 showed a more pronounced effect: the difference in mean ranks with the control was 10.00 (p = 0.0033), whereas for the intracellular form, this value was 8.00 (p = 0.0273). Critically, a direct comparison between the two experimental groups revealed no statistically significant differences (mean rank difference -2.00, p > 0.9999). This indicates that although both forms are effective in reducing plaque numbers, their anti-amyloidogenesis action likely relies on similar or overlapping molecular mechanisms.

Analysis of amyloid deposit distribution by size revealed a selective and region-specific action of HSP70. In the cerebral cortex, a significant reduction under the influence of both protein forms was observed exclusively in the pool of small plaques with a diameter less than 100 µm (p = 0.0104 for the extracellular and p = 0.0015 for the intracellular form). The difference between the experimental groups was not significant (p = 0.7061). The number of medium (100–500 µm) and large (>500 µm) plaques in the cortex did not statistically differ from the control or from each other. In the hippocampus, the picture was different: extracellular HSP70 (Tg_h_mod) demonstrated the most pronounced effect, significantly reducing the number of both small plaques (<100 µm, p = 0.0013) and large conglomerates (>500 µm, p = 0.028). The intracellular form (Tg_h) in the hippocampus showed a tendency towards a reduction in small deposits (p = 0.0884). These data suggest that the neuroprotective mechanism,

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especially for extracellular HSP70, may be related not only to a general reduction in amyloid load but also to the selective inhibition of early aggregation stages (small plaques) in the hippocampus, a structure crucial for memory, which aligns with the better cognitive performance observed in this experimental group.

Both variants of HSP70 (extracellular and intracellular) significantly reduce amyloid load compared to the APP/Ps1 control group.

DISCUSSION

The conducted study demonstrates the comprehensive neuroprotective effect of heat shock protein HSP70 in a transgenic AD model. The obtained data not only confirm the key role of HSP70 in maintaining proteostasis but also reveal a fundamentally important difference in the functional consequences of expressing its intracellular and extracellular forms. This difference places HSP70 among promising agents with a multimodal mechanism of action, which is critically important for the development of therapies for complex neurodegenerative diseases.

The most intriguing result of the study is the dissociation between the effect on the neuropathological marker (amyloid plaques) and the cognitive phenotype. Both investigated forms of HSP70 showed a statistically significant and comparable reduction in total amyloid load in the cerebral cortex. This result is in full agreement with the canonical chaperone function of HSP70, which involves preventing Aβ peptide aggregation and stimulating its clearance, as also described in the literature [23]. However, a detailed analysis of plaque distribution by size revealed important nuances: effective reduction was observed predominantly in the pool of small plaques (<100 μm), which may indicate that HSP70 inhibits early stages of Aβ aggregation or enhances the clearance of small, potentially more toxic oligomers.

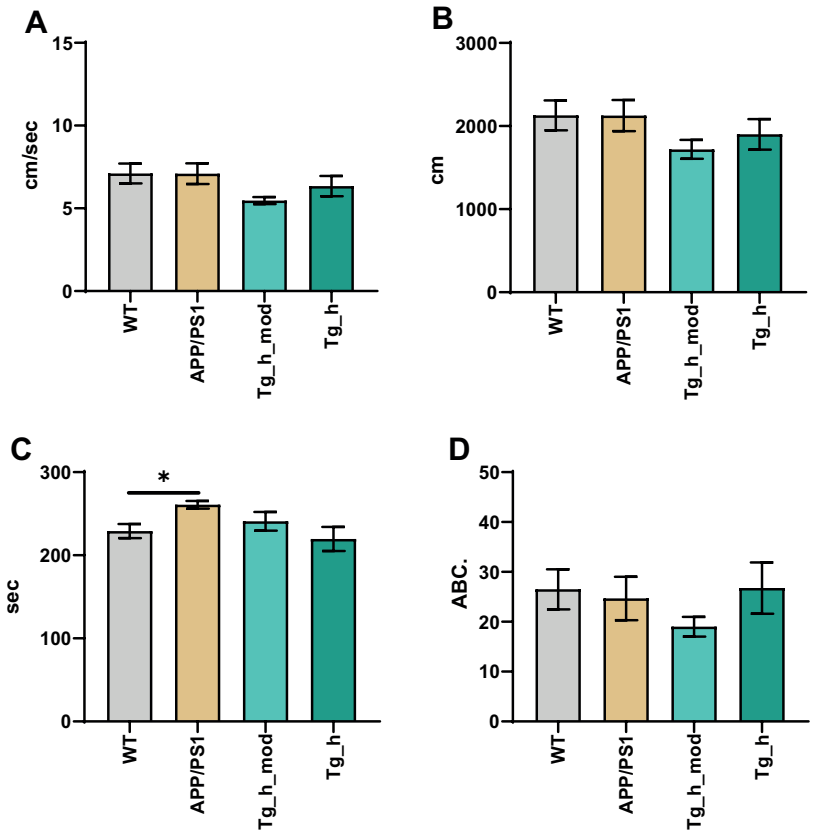

Figure 1 — Open Field Test results.
Note: A, speed of movement; B, distance traveled in 5 minutes; C, time spent in the periphery; D, number of transitions between sectors.
* — $p < 0.05$ (Tukey's test).

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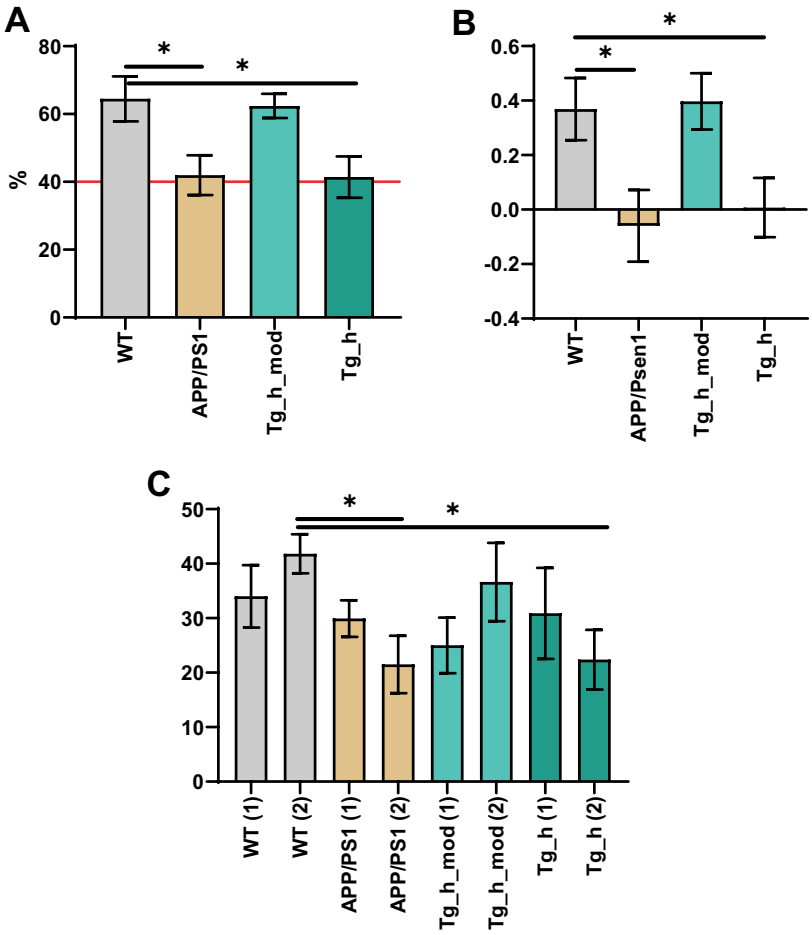

Figure 2 — Novel Object Recognition Test Activity results.
Note: A, preference index; B, discrimination index; C, number of approaches to the new toy (1-training day, 2-test day).
* — $p < 0.05$ (Tukey's test).

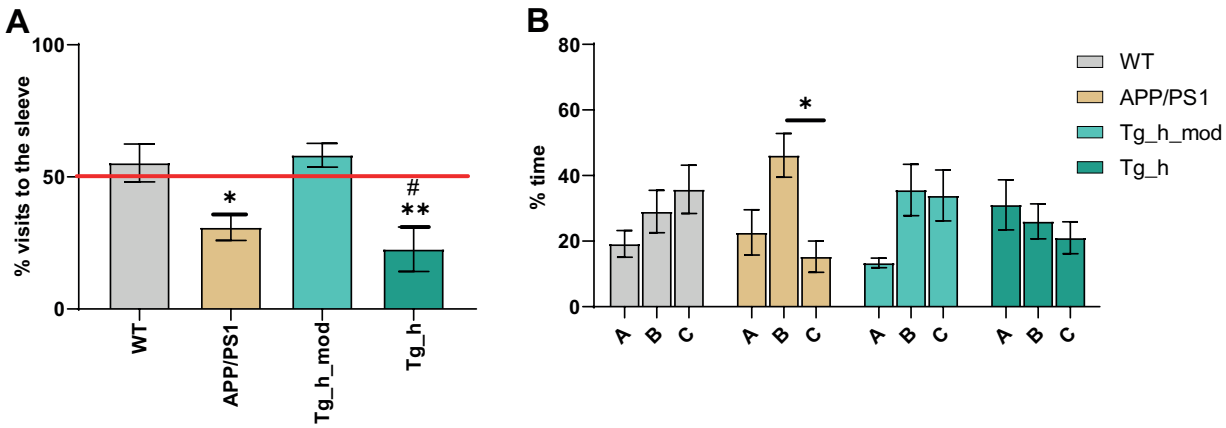

Figure 4 — Barnes Maze Test results.
Note: A, number of entries into the shelter zone on day 5; B, time spent in the shelter zone on day 5; C, latency to find the shelter zone from days 1 to 4 of training. * — $p < 0.05$; ** — $p < 0.01$ (Kruskal-Wallis test).

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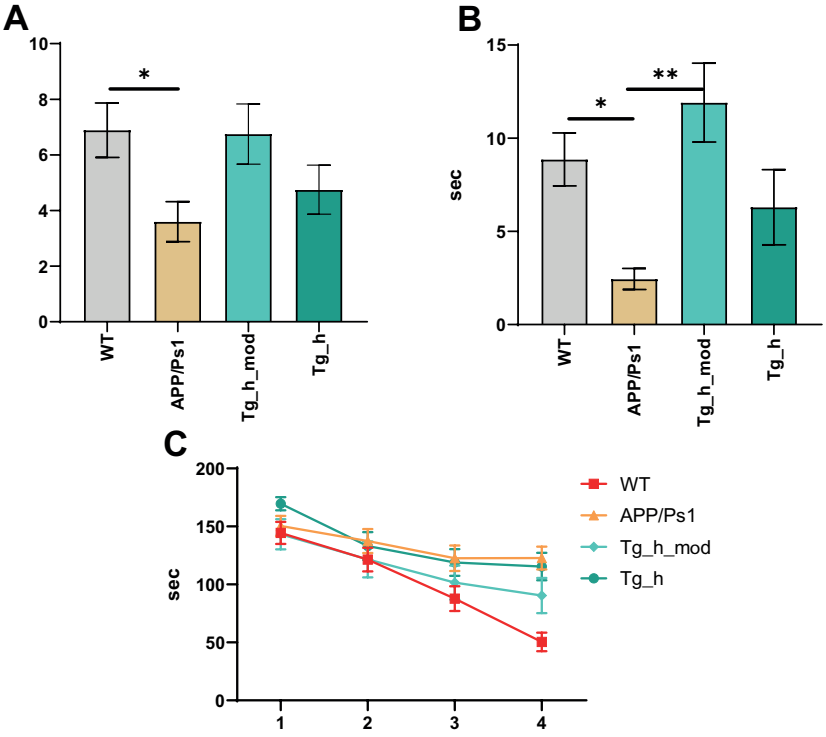

Figure 3 — Y-Maze Test "New" Arm Preference results.
Note: A, number of entries into the "new" arm; B, distribution of time spent in arms (C-new arm). * — $p < 0.05$; ** — $p < 0.01$ (Kruskal-Wallis test, comparison with WT); # — $p < 0.05$ (Kruskal-Wallis test, comparison with Tg_h_mod).

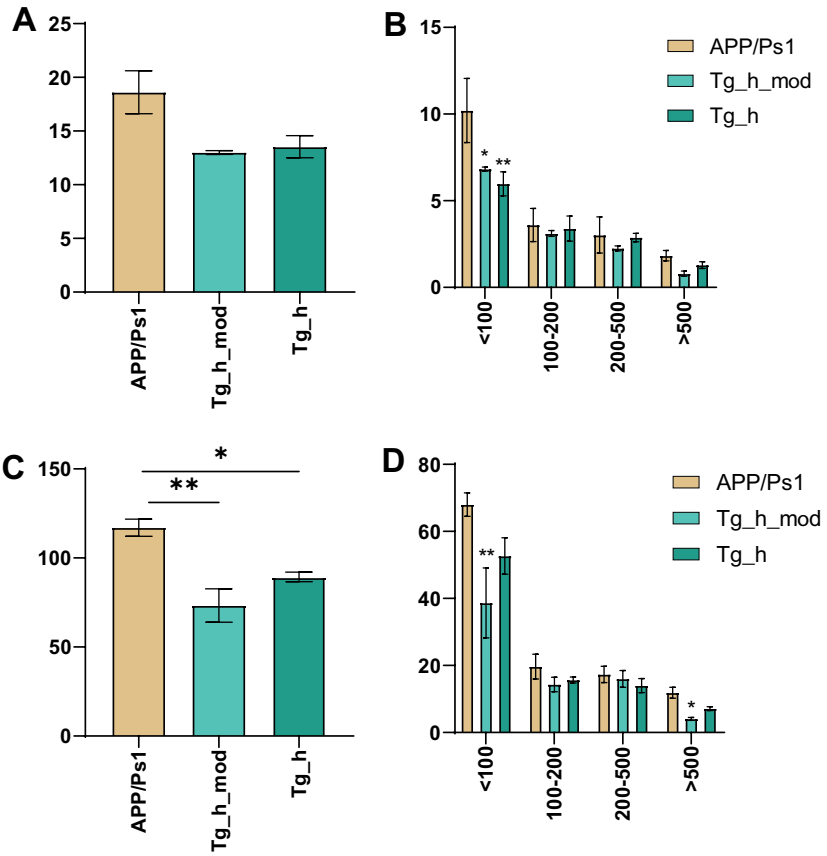

Figure 5 – Histology results.
Note: The figure shows the total number of amyloid plaques in the hippocampus (A) and cerebral cortex (C); distribution of amyloid deposits by size in the hippocampus (B) and cerebral cortex (D). * — $p < 0.05$; ** — $p < 0.01$ (Kruskal-Wallis test).

Despite similar anti-amyloid efficacy, the extracellular form of HSP70 (Tg_h_mod) demonstrated incomparably more pronounced positive effects on cognitive functions in all behavioral tests, reaching levels close to the wild-type (WT) group. In contrast, Tg_h mice expressing intracellular HSP70, although having a lower amyloid load, showed only minor or partial improvements in memory and learning. This observation is of key importance — merely reducing the number of amyloid plaques is insufficient to restore synaptic transmission and neuronal network functions. Extracellular HSP70 likely mediates additional protective mechanisms critically important for cognitive function. Intracellular HSP70 may directly impede the formation of Aβ oligomers, while the secreted form, as shown in other studies, can modulate neuroinflammation by interacting with microglia, stimulating phagocytosis and amyloid clearance [24].

The data from the Barnes Maze test are of particular interest. The fact that the Tg_h_mod line showed a learning dynamic comparable to the wild-type (WT) group suggests that HSP70 supports the functional reserves of neuronal networks responsible for navigation and spatial memory formation. It is known that HSP70 induction can alleviate synaptic defects and improve NMDA receptor-dependent signaling in the hippocampus, which is a key mechanism for spatial learning [25].

Within the scope of the conducted study, the obtained statistical data convincingly confirm the main conclusions. In behavioral tests, the extracellular form of HSP70 (Tg_h_mod) showed a statistically significant advantage in restoring cognitive functions. In the Novel Object Recognition test, the IP in this group was significantly higher than in the APP/PS1 and Tg_h groups — ($F(3, 34) = 4.526$; $p = 0.0204$ compared to APP/PS1). In the Y-maze, the Tg_h_mod group not only differed significantly from the positive control ($p = 0.0398$) but also demonstrated a 40 % better result in the percentage of entries into the new arm compared to the Tg_h group ($p = 0.0156$, Kruskal-Wallis test). In the Barnes Maze test, the time spent in the shelter zone in Tg_h_mod was 45% longer than in WT and statistically significantly differed from APP/PS1 ($p = 0.0184$). Meanwhile, the intracellular form (Tg_h) showed no significant improvements in most tests compared to APP/PS1, except for a tendency towards improvement. Histological data revealed a different picture: both forms of HSP70 significantly and approximately equally reduced the total amyloid load in the cortex compared to the APP/PS1 control ($p = 0.0033$ for extracellular and $p = 0.0273$ for intracellular form), with no significant difference in their efficacy when compared directly ($p > 0.9999$). However, analysis by plaque size showed that in the hippocampus, only extracellular HSP70 significantly reduced the number of both small (<100 µm, $p = 0.0013$) and large (>500 µm, $p = 0.028$) plaques.

Notably, in all cognitive tests, the Tg_h_mod line demonstrated a more pronounced positive effect compared to the Tg_h line [26]. This may be related to specific expression patterns or post-translational modifications of the protein in this model, which enhance its stability, chaperone activity, or secretion capacity. This observation has important practical implications, suggesting that the therapeutic efficacy of HSP70 can be optimized through targeted modification, which is a promising arm for drug development [27, 28].

Study Limitations

The conclusions are drawn based on a specific transgenic mouse line that primarily models the amyloid pathway of pathogenesis. Extrapolating the results to sporadic forms of human AD requires further verification. Additionally, the study involved a transgenic animal line expressing a modified human HSP70 protein in milk, which is a limiting factor for projecting this effect onto an exogenous protein.

CONCLUSION

As evidenced by the behavioral tests, crossing a mouse line with a neurodegenerative disease with mice producing heat shock protein does not lead to changes in locomotor function or the psychological state of the animals. However, tests such as Novel Object Recognition, Y-maze, and Barnes Maze show positive changes in learning processes, short-term, and long-term memory. The expression of extracellular HSP70 protein shows a greater effect on the restoration of both short-term and long-term memory, as well as an improvement in spatial memory functions. The expression of intracellular HSP70 protein influences these processes to a lesser extent. Although histological data indicate that both proteins affect the slowing of amyloid plaque formation to approximately the same degree.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Elena V. Kuzubova, Alexandra I. Radchenko — supervision, investigation; Yulia V. Stepenko, Amina O. Rumyantseva, Nikita S. Zhunusov — data analysis, writing — original draft; Marina A. Rzhevskaya, Alina A. Apostol — investigation; Elena B. Artyushkov, Anastasia Yu. Adonina — data analysis, writing — review & editing; Oleg S. Gudyrev — visualization; Liliya V. Korokina — conceptualization, supervision. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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Научно-практический журнал
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ОРИГИНАЛЬНАЯ СТАТЬЯ
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Comparative study of the efficacy and safety of tirzepatide drugs in metabolic syndrome

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In the last decade, developed countries have seen a steady increase in the prevalence of metabolic disorders. The most significant among them are obesity and type 2 diabetes mellitus. Tirzepatide is an innovative drug, representing the first-in-class dual agonist of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. Tirzepatide combines the action of two key incretin hormones, providing more comprehensive and effective regulation of glycemia and metabolism compared to traditional GLP-1 monoagonists. Tirzepatide was unavailable in Russia for a long time. However, in 2025, the first domestically produced tirzepatide drug, Tirzetta® (LLC "PROMMOMED RUS"), appeared.

The aim. To conduct a comparative evaluation of the efficacy and safety of the reproduced drug Tirzetta® (INN: Tirzepatide, manufacturer LLC "PROMMOMED RUS") and the reference drug Mounjaro® (INN: Tirzepatide, manufacturer "Eli Lilly") in a mouse model with induced metabolic syndrome (MS).

Materials and methods. The study was conducted on male mice of the C57BL/6 line. To metabolic syndrome (MS) was induced in animals with a diet high in fat and carbohydrates. Three batches of Tirzetta® and one series of Munjaro® were investigated. The drugs were administered at a dosage of 150 μg/kg subcutaneously once every three days for 15 days. During the experiment, glucose tolerance and insulin sensitivity tests were performed. The type of metabolism was determined by indirect calorimetry data. Mice were euthanized on 25th day for humane reasons upon reaching any of the following criteria: body weight loss of more than 15% in a week; serious injuries (fractures, amputations, etc.), appearance of non-healing wounds; seizures; unconscious state. A complete blood count was performed, and the following parameters were determined: glucose, triglycerides, cholesterol, AST, ALT. Necropsy was performed after euthanasia. During necropsy, the thoracic and abdominal organs of the animals were examined, and organs were dissected and weighed.

Results. In the MS group animals, body weight increased to 39.5 ± 0.6 g compared to the control group (31.9 ± 0.6 g), representing a 24% increase. Significant hyperglycemia was recorded with a glucose concentration of 14.9 ± 2.7 mmol/L versus 6.1 ± 0.4 mmol/L in the control, as well as a pronounced decrease in glucose tolerance in the loading test. The investigated tirzepatide drugs demonstrated a pronounced hypophagic effect with a 26–28% reduction in body weight, normalization of glycemia with a 48–53% decrease in glucose concentration, and improvement in glucose tolerance and

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insulin sensitivity. Indirect calorimetry data indicated a decrease in the respiratory exchange ratio, suggesting lipolysis activation. A significant reduction in triglyceride content in blood serum and liver was revealed. The bioequivalence of the investigated drugs Tirzetta® and Mounjaro® was established in the experimental MS model in mice based on a set of therapeutic efficacy and safety indicators.

Conclusion. Studies on an experimental model of induced MS in mice showed equivalent efficacy of Tirzetta® (INN: Tirzepatide, manufacturer LLC "PROMMOMED RUS", Russia) and Mounjaro® (INN: Tirzepatide, manufacturer "Eli Lilly", USA).

Keywords: tirzepatide; bioequivalence; metabolic syndrome; mice; indirect calorimetry; glucose tolerance test; hypophagic effect; lipolysis; glycemia; insulin sensitivity; preclinical study

Abbreviations: GLP-1 — glucagon-like peptide-1; GIP — glucose-dependent insulinotropic polypeptide; GTT — glucose tolerance test; T2DM — type 2 diabetes mellitus; MS — metabolic syndrome; BMI — body mass index; EMA — European Medicines Agency; INN — international nonproprietary name; EAEU — Eurasian Economic Union; IS — insulin sensitivity; MS — metabolic syndrome; BW — body weight; SOP — standard operating procedure; TG — triglycerides; FS — physiological saline; VCO_2 — carbon dioxide production rate; VO_2 — oxygen consumption rate; CS — comparator product; SPF — specific pathogen free.

Сравнительное исследование эффективности и безопасности лекарственных препаратов тирзепатида при метаболическом синдроме

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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В последнее десятилетие в развитых странах отмечается устойчивое увеличение распространённости метаболических нарушений. Среди них наиболее значимыми являются ожирение и сахарный диабет 2 типа. Тирзепатид — это инновационный лекарственный препарат (ЛП), представляющий собой первый в своем классе двойной агонист рецепторов глюкагоноподобного пептида-1 (ГПП-1) и глюкозозависимого инсулинотропного полипептида (ГИП). Тирзепатид объединяет действие двух ключевых инкретиновых гормонов, что обеспечивает более комплексное и эффективное регулирование гликемии и метаболизма по сравнению с традиционными моноагонистами ГПП-1. Долгое время тирзепатид был недоступен в России, однако в 2025 году появился первый препарат тирзепатида отечественного производства — Тирзетта® (ООО «ПРОМОМЕД РУС»).

Цель. Провести сравнительную оценку эффективности и безопасности воспроизведённого препарат Тирзетта® (МНН: Тирзепатид, производитель ООО «ПРОМОМЕД РУС») и референтного препарата Мунджаро® (МНН: Тирзепатид, производитель «Эли Лилли») на модели мышей с индуцированным метаболическим синдромом (МС).

Материалы и методы. В исследовании использовали самцов мышей линии C57BL/6. Для проведения исследования у животных был индуцирован метаболический синдром (МС) при помощи диеты с высоким содержанием жира и углеводов. Далее исследовали эффективность ЛП тирзепатида, используя три серии препарата Тирзетта® и одну серию Мунджаро®. Исследовали три серии препарата Тирзетта® и одну серию Мунджаро®. Препараты вводили в дозировке 150 мкг/кг подкожно один раз в три дня в течение 15 дней. В ходе эксперимента проводили тесты на переносимость глюкозы и чувствительность к инсулину. Тип метаболизма определяли по данным непрямой калориметрии. Мышей подвергали эвтаназии на 25 день по соображениям гуманности при достижении любого из перечисленных ниже критериев: снижение массы тела более, чем на 15% за неделю; серьёзные травмы (переломы, ампутации и т.п.); появление незаживающих ран; судороги; бессознательное состояние. Проводили общий анализ крови и определяли следующие показатели: глюкоза, триглицериды, холестерин, АСТ, АЛТ. Некропсию проводили после эвтаназии. В ходе некропсии осматривали органы грудной и брюшной полости животных, иссекали и взвешивали их.

Результаты. У животных группы МС масса тела увеличилась до 39,5±0,6 г по сравнению с контрольной группой (31,9±0,6 г), что составляет прирост в 24%. В группе МС до лечения была зарегистрирована значительная гипергликемия с концентрацией глюкозы 14,9±2,7 ммоль/л против 6,1±0,4 ммоль/л в контроле, а также выраженное снижение переносимости глюкозы в нагрузочном тесте. Исследуемые препараты тирзепатида продемонстрировали выраженное гипофагическое действие со снижением массы тела на 26–28%, нормализацию гликемии с уменьшением концентрации глюкозы на 48–53%, улучшение толерантности к глюкозе и инсулиновой чувствительности. По данным непрямой калориметрии на фоне приёма ЛП тирзепатида отмечено снижение дыхательного коэффициента, свидетельствующих об активации липолиза. Выявлено значительное снижение содержания триглицеридов в сыворотке крови и печени. Установлена биоэквивалентность исследуемых препаратов Тирзетта® и Мунджаро® в экспериментальной модели МС у мышей по комплексу показателей терапевтической эффективности и безопасности.

Заключение. Исследования на экспериментальной модели мышей с индуцированным МС показали эквивалентную эффективность ЛП Тирзетта® (МНН: Тирзепатид, производитель ООО «ПРОМОМЕД РУС», Россия) и Мунджаро® (МНН: Тирзепатид, производитель «Эли Лилли», США).

Ключевые слова: тирзепатид; биоэквивалентность; метаболический синдром; мыши; непрямая калориметрия; глюкозотолерантный тест; гипофагическое действие; липолиз; гликемия; инсулиновая чувствительность; доклиническое исследование

Список сокращений: ГПП-1 — глюкагоноподобный пептид-1; ГИП — глюкозозависимый инсулинотропный полипептид; ГТТ — глюкозотолерантный тест; СД2 — сахарный диабет 2 типа; МС — метаболический синдром; ИМТ — индекс массы тела; ЕМА — Европейское агентство по лекарственным средствам; ЛП — лекарственный препарат; МНН — международное непатентованное наименование; ЕАЭС — Евразийский экономический союз; ИЧ — чувствительность к инсулину; МС — метаболический синдром; МТ — масса тела; СОП — стандартная операционная процедура; ТГ — триглицериды; ФР — физиологический раствор; VCO_2 — скорость продукции углекислого газа; VO_2 — скорость потребления кислорода; ПС — препарат сравнения; СПФ — свободные от патогенной флоры.

INTRODUCTION

According to World Health Organization (WHO)[1] data, in 2022, there were over 2.5 billion individuals over 18 years of age with overweight (BMI = 25–29 kg/m^2) and over 890 million people suffering from obesity (BMI > 30 kg/m^2) worldwide. As of 2021, the prevalence of obesity in the USA is 56%, in the UK — 52 %, in Israel — about 50 % of women and 60% of men have overweight or obesity. Russia does not significantly differ from the aforementioned countries in this indicator: over 60% of the adult population of Russia is overweight, and about 26 % is obese[2].

It is important to note that individuals with overweight and obesity are diagnosed significantly more often with diabetes mellitus (5–20 %), hypertension (34–64 %), gallbladder diseases (35–45 %), and osteoarthritis (5–17 %). It has been established that the epidemiological links between BMI and type 2 diabetes mellitus (T2DM) are very strong: over 75 % of cases of the disease are associated with overweight and obesity. More than 2/3 of patients with T2DM have a BMI > 27 kg/m^2, and more than 50 % have a BMI > 30 kg/m^2 [1, 2].

Tirzepatide is a polypeptide with affinity for two receptors of the incretin axis — glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor. Native GIP and GLP-1 are

[1] WHO. Obesity and overweight. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

[2] Fatness. A modern view on pathogenesis and therapy. Vol. I; A.S. Ametov [et al.]. Moscow: GEOTAR-Media; 2021. 384 p. Russian

key incretin hormones secreted by intestinal cells in response to food intake. They enhance glucose-dependent insulin secretion from pancreatic β-cells, suppress postprandial glucose and glucagon surges from α-cells. In addition, GIP and GLP-1 regulate gastric and intestinal motility, appetite, and, primarily, lipolysis. However, GIP and GLP-1 have a short half-life, which makes the development of exogenous incretin receptor agonists highly promising for the treatment of obesity, overweight, and associated diseases [3–5].

Tirzepatide is a linear peptide of 39 amino acids conjugated with a C20 fatty acid at the N-terminus. This conjugation increases the stability of the compound by effectively binding to plasma albumin, which significantly prolongs the drug's half-life and allows for a once-weekly dosing regimen. The amino acid sequence of tirzepatide is based on the sequence of endogenous GIP but with key substitutions that increase affinity for GLP-1 receptors and mediate pharmacological action comparable to endogenous GLP-1 [6].

As a drug, tirzepatide was approved by the FDA on May 13, 2022, under the brand name Mounjaro® (Eli Lilly, USA)[3] for the treatment of adults with T2DM, making it the first and only GIP and GLP-1 receptor agonist for this indication. Later, on November 8, 2023, tirzepatide was approved as a drug for weight management in adults with obesity or overweight with comorbidities under the brand name Zepbound® (Eli Lilly, USA)[4]. Previously, on September 15, 2022, tirzepatide was also approved by the European Commission[5].

In the Russian Federation, tirzepatide was first registered on January 23, 2025, under the brand name Tirzetta® (PROMED RUS LLC, Russia)[6]. This drug is effective for several indications: obesity, overweight, prediabetes, and T2DM.

MATERIALS AND METHODS

Test system

The study used 80 male C57BL/6 mice aged 8–10 weeks. The animals were obtained from the FRC IC&G SB RAS (Novosibirsk, Russia) nursery. According to the health certificate provided by the manufacturer, the mice were specific pathogen-free (SPF) according to the FELASA–2014 list. The adaptation period after receiving the animals was 10 days.

The animals were housed in groups (n = 10) in individually ventilated cages GM500 (Tecniplast, Italy) with a floor area of 500 cm2. Wood shavings (fraction 3, IP Filonich, Russia) were used as bedding. Throughout the study, except for periods before glucose tolerance testing and necropsy, the animals had unlimited access to food and purified water. A complete feed P22 (BioPro, Russia) was used for feeding the control group mice.

For environmental enrichment, mice were provided with nesting material (paper tissues) and shelters (red plastic houses). Materials supplied to the animals were sterilized by autoclaving. Routine animal care was carried out in accordance with current GLP regulations.

The temperature in the animal housing rooms ranged from 20 to 26 °C, relative humidity from 30 % to 70 %, the light cycle was 12 hours, and illumination was approximately 400 Lux at 1 m above the floor. The animals were under regular observation by a veterinarian.

Design of Experiment

A population of 54 mice (males) with MS was developed in the first stage. The animals were divided into 6 experimental groups of 10–12 individuals each. The control group of mice (K) consisted of individuals without MS, and the remaining groups consisted of mice with induced MS. Mice in the control group K and one of the MS groups received placebo. The other four groups of mice with MS received tirzepatide: as part of the reference drug Mounjaro® (RD), or as part of the drug Tirzetta® from one of three batches (T1, T2, T3) (Fig. 1, Table 1).

Animals were assigned to experimental groups by randomization using GraphPad software. All mice were individually marked with ear tags (model 1005, National Band and Tag Company, USA; weight 0.25 g).

Induction of metabolic syndrome

MS was induced in all mice, except for animals in group K, using a modified diet consisting of high-fat and high-carbohydrate feed and fructose syrup for drinking [1, 2].

The high-fat feed was prepared in the laboratory with the following composition (by mass): complete feed — 35 %; rendered beef fat — 30 %; whole condensed milk with sugar 8.5–35 %.

To prepare the feed, melted beef fat was added to the non-pelleted (powdered) complete feed in a mixer bowl at a rate of 300 g per 350 g of complete feed and

[3] FDA. Drug Trials Snapshots: MOUNJARO. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-mounjaro

[4] FDA. FDA Approves New Medication for Chronic Weight Management. Available from: https://www.fda.gov/ news-events/press-announcements/fda-approves-new-medication-chronic-weight-management

[5] EMA. Mounjaro. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/mounjaro

[6] Tirzetta®. The State Register of Medicines of the Russian Federation. Available from: https://grls.minzdrav.gov.ru/Grls_View_v2.aspx?routingGuid=f72153a0-29eb-4756-9a93-0b5455cf8423. Russian

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mixed for 2–3 minutes until the fat was absorbed into the feed. Then, 350 g of condensed milk was added to the mixture and mixed for another 3–5 minutes until homogeneous. The prepared mixture was distributed into silicone molds, frozen, and stored at a temperature not exceeding –18 C until use, but no longer than 1 month.

The actual nutritional value of the feed was (by mass): crude protein — 10.9 ± 0.5 %; fats — 33.7 ± 0.8 %; carbohydrates — 45.5 %; moisture — 7.4 ± 0.4 %; total ash — 2.5 ± 0.3 %; energy value — 5315 kcal/kg.

A 30 % fructose syrup was prepared in the laboratory by placing a known weight of fructose in a graduated cylinder, bringing the volume to 2 L with purified water, and mixing until dissolved. The prepared syrup was poured into sterile bottles and stored at a temperature not exceeding 8 C until use, but no longer than 2 weeks.

The “high-fat” feed was provided in the feeder grid without restriction, similar to the standard complete feed, and was replaced with fresh feed at least once a week. Animals were provided with fructose syrup as drinking water. Water bottles were replaced at least once every 3 days. During the testing period in PhenoMaster, feed and syrup were provided in the PhenoMaster feeders /waterers.

The metabolic status of all mice was assessed monthly, starting from the 2nd month from the beginning of MS induction, but not exceeding 6 months. Animals were used in experiments upon reaching the following criteria: average body weight (for all mice receiving the modified diet) of at least 40 g, reduced glucose tolerance compared to control group mice, or after 6 months of feeding the modified diet.

Mouse body weight was measured weekly. Weighing was performed with an accuracy of ±0. g using Vibra CJ-2200CE scales (Vibra, Japan).

Samples

To form a representative quality profile and obtain reliable comparability data, three batches of the reproduced drug Tirzetta® were used in the studies. Information on the investigated batches is presented in Table 2.

A “placebo” was used as a vehicle for the investigated drugs, which was a solution containing (per 0.5 mL): sodium chloride (4.1 mg), disodium hydrogen phosphate heptahydrate (0.7 mg); 1 M sodium hydroxide solution or 1 M hydrochloric acid solution (to pH 6.5–7.5), water for injection (up to 0.5 mL). All samples were stored at a temperature of 2 to 8 C for the duration of the shelf life indicated by the manufacturer.

Working solutions of tirzepatide for administration to animals were prepared by mixing the investigated drugs at a concentration of 5 mg/mL and placebo to obtain a solution with a concentration of 0.15 mg/mL. Working solutions were prepared immediately before use and used within 2 hours of preparation.

Dosing regimen

To accustom mice to subcutaneous administration procedures and minimize the impact of associated stress on study results, mice were injected with physiological saline from day 1 to day 7 (d1…d7, =7 injections). Investigated substances were administered from day 8 to day 23 of the experiment.

T1, T2, T3, RD, and placebo were administered subcutaneously once every three days (see Table 1). Administration was carried out in the scruff area using 0.5 mL syringes with G 29 needles (5 mL/kg). Administration was performed in the afternoon (from 18:00 to 21:00), before the evening peak of food consumption. Investigated drugs were administered at a dose of 150 µg/kg subcutaneously, every third day — from day 8 to day 23 of the experiment. The tirzepatide dose was selected based on the literature data [7].

Observation

During the study, food and water intake, feeding behavior, and physiological parameters were determined using the PhenoMaster system, and blood glucose concentration was measured. Food and water intake were assessed individually. In the specified system, feeder weight registration is carried out with high temporal resolution, allowing for the analysis of animal feeding behavior: amount eaten / drunk per feeding / drinking episode, number of feeding and drinking bouts, and duration of intervals between them.

Non-fasting blood glucose concentration was measured on days 6, 9, 12, 15, and 18 of the experiment using a portable glucose meter OneTouch Verio Reflect (LifeScan, Switzerland) and test strips according to the manufacturer’s instructions. Blood for measurement (3–5 µL) was obtained by tail tip puncture. Measurements were taken in the evening, before the peak food consumption, prior to drug administration.

Monitoring of physiological parameters in the PhenoMaster system was conducted from day 6 to day 15 of the experiment inclusive (2 days before and 8 days after the start of substance administration).

During monitoring, the following parameters from Table 1 were recorded. System setup, calibration, startup, and control were performed according to the manufacturer’s instructions.

Challenge tests

During the experiment, glucose tolerance and insulin sensitivity tests were performed. The tests were conducted after a 9-hour fast and 15–18 hours after the last drug administration. The glucose tolerance test was performed once on day 21 of the experiment. Insulin sensitivity was tested once on day 24 of the experiment.

In the evening before the testing (21:30 ± 30 min), food was removed from the animals; mice consuming fructose syrup were given water instead of syrup. Testing was conducted the next day in the morning (11:30 ± 40 min).

The glucose tolerance test consisted of measuring mouse blood glucose concentration 15 minutes and immediately before (0 minutes) intragastric administration of 2 g/kg glucose (administration volume 5 mL/kg), and at 15, 30, 45, 60, 90, and 120 minutes after glucose administration. Data analysis involved comparing blood glucose concentration curves and areas under the curves.

The insulin sensitivity test consisted of measuring mouse blood glucose concentration immediately before (0 min) intravenous administration of 4 U/kg insulin (administration volume 5 mL/kg), and at 15, 30, 60 minutes, 2, 3, 4, and 6 hours after insulin administration. Data analysis involved comparing the blood glucose concentration curves themselves and the time to recovery of concentration.

Metabolic assessment

Metabolic type was determined by indirect calorimetry data. For this purpose, oxygen consumption and carbon dioxide production by animals were measured in the PhenoMaster system for 2 days before the start of substance administration and 8 days after the start of dosing. Based on these data, the respiratory exchange ratio (RER) was calculated, which determined the spectrum of utilized substrates. RER was calculated as the ratio of carbon dioxide volume produced to oxygen volume consumed.

Heat production (energy expenditure) was determined using the oxygen equivalent EE, the value of which depends on the RER value:

$$M = V_{O2} \times EE(RER),$$

where M is heat production (energy expenditure, kcal/kg/h); V_{O2} is oxygen consumption (mL/kg/h); EE(RER) is the energy equivalent of oxygen, kcal/L O_2.

Euthanasia and blood sample collection

Mice were euthanized on day 25 for humane reasons upon reaching any of the following criteria:

- body weight loss of more than 15 % in a week;
- serious injuries (fractures, amputations, etc.), appearance of non-healing wounds;
- seizures;
- unconsciousness.

Euthanasia, combined with blood sample collection, was performed by inhalation of 2 % isoflurane in an induction chamber. In the evening before euthanasia, food was removed from the animals, and mice consuming fructose syrup were given water instead.

Blood tests

Collected blood was divided into 2 samples: for complete blood count (CBC) and for serum preparation. Blood for CBC was stabilized with EDTA and stored at room temperature until analysis, but no longer than 2 hours.

To obtain serum, blood was placed in tubes with a clotting activator and separation gel. After clotting, but no later than 1 hour after collection, serum was separated by centrifugation (Centrifuge Neuation iFuge UC02R, Neuation, China) at 2500 g and room temperature for 15 minutes. Serum was transferred to labeled microcentrifuge tubes, frozen, and stored at a temperature not exceeding –18 °C until biochemical analysis, but no longer than 3 months.

CBC was performed on the Balio-560 instrument (Balio Diagnostics, France) using reagents Diluent, Lyc 1, Lyc 2 (Dymind, China) and control materials “Veterinary Gemkontrol 5D” (MBS Technology, Russia).

Biochemical analysis of serum was performed on the A25 analyzer (Biosystems, Spain) using reagent kits and control materials from Hospitex Diagnostics (Italy) according to the instructions of the reagent and equipment manufacturers. The following parameters were determined: glucose, triglycerides, cholesterol, AST, ALT.

Necropsy

Necropsy was performed after euthanasia. During necropsy, organs of the thoracic and abdominal cavities of the animals were examined, and the following organs were dissected and weighed: brain, heart, lungs, kidneys, salivary glands, pancreas, liver, thymus, spleen, testes, epididymides, accessory glands, gastrocnemius muscle, soleus muscle, visceral fat, adrenal glands.

During the study, a visual assessment of the following fat depots was performed:

1. Subcutaneous:
   - interscapular;
   - anterior subcutaneous (right and left);
   - shoulder (right and left);

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– inguinal (right and left);
– popliteal (right and left).

2. Visceral:
– pericardial;
– perirenal (right and left);
– mesenteric;
– gonadal (right and left).

Assessment was performed using the following scoring scale: not expressed (adipose tissue practically absent); weakly expressed (little adipose tissue); moderately expressed (adipose tissue present); strongly expressed (a lot of adipose tissue).

The total score for an animal was calculated as the sum of scores for all fat depots.

Measurement of triglyceride and cholesterol content in the liver

To determine triglyceride content, a fragment of the right lateral lobe of the liver weighing approximately 100 mg was dissected and weighed (± 1 mg, Vibra ALE323R). The sample was homogenized in 20 volumes of a chloroform-methanol mixture (in a volume ratio of 2:1), after which the sample was mixed for 20 minutes on an automatic shaker. Then, the precipitate was separated by centrifugation at 20,000 g for 10 minutes. The supernatant was collected and mixed with 400 µL of physiological saline and thoroughly mixed on a vortex mixer. To separate the phases, the sample was centrifuged at 20,000 g for 10 minutes. The lower phase, containing lipids, was collected and stored at a temperature not exceeding –18 °C until lipid and cholesterol concentration analysis, but no longer than 3 months.

Quantitative determination of triglycerides and cholesterol in liver extracts was performed using reagent kits and control materials from Hospitex Diagnostics (Italy) according to the manufacturer's instructions. The optical density of the samples was measured on a Plate Screen microplate spectrophotometer (Hospitex Diagnostics, Italy).

Ethical review

The study was approved by the Ethics Committee of the Federal State Budgetary Institution of Science "State Research Center of the Russian Federation — Institute of Biomedical Problems of the Russian Academy of Sciences" for Biomedical Ethics (No. 681 dated March 17, 2025).

Data analysis

The difference in efficacy between the comparator product (Mounjaro®) and the three batches of the investigated product (Tirzetta®) was analyzed.

For primary analysis, data were tabulated and descriptive statistics were calculated: mean (M), standard deviation (SD), standard error (SEM).

For group comparisons, analysis of variance (ANOVA) methods were used, followed by pairwise group comparisons using Sidak or Tukey, as well as multiple linear regression. The statistical significance threshold was $p \leq 0.05$.

The overall comparison of drug effects was carried out by determining Cohen's d for all 53 investigated parameters. Based on Cohen's d, metrics RE (relative efficacy), SS (safety assessment), Sel (selectivity), and CS (composite score) were determined:

$$RE = \frac{|\, d \text{ Drug } vs\ MC \,|}{|\, d \text{ CS } vs\ MC \,|} + 0.01,$$

RE=1.0 means equivalence to CS; RE > 1.0 indicates superiority over CS (stronger recovery); RE < 1.0 means a weaker effect.

$$SS = \frac{1}{1 + e^{(-6 \times ln\,(SS))}},$$

The coefficient 6 was chosen empirically for optimal differentiation. The result is in the range from 0 to 1, where 0.5 ≈ equivalence to CS, > 0.5 indicates better safety, <0.5 indicates worse safety.

$$Sel = \frac{|\, d \text{ Drug } vs\ MS \,|}{|\, d \text{ Drug } vs\ Con \,|} + 0.01,$$

With subsequent normalization:

$$Sel = \min\left(1.0 \times \frac{\ln(1 + Selectivity)}{2.5}\right),$$

High selectivity (close to 1) means that the drug's action against MS is more pronounced than against Con.

The composite score combines all three metrics into a single indicator for drug ranking:

$$CS = 0.70 \times RE + 0.20 \times SS + 0.1 \times Sel,$$

Bootstrap analysis (10,000 iterations) was used to determine the statistical significance of differences in composite scores between drugs. Normality of residuals was checked using the Shapiro-Wilk test. Homogeneity of variances was confirmed by Levene's test. Intergroup analysis was performed using analysis of variance (ANOVA).

If ANOVA showed significance ($p < 0.05$), Tukey HSD post-hoc tests were performed for all pairwise comparisons. Particular attention was paid to contrasts of each drug with CS. If the contrast with CS was not significant, the drug was considered statistically equivalent to CS for that parameter.

Multivariate analysis of variance (MANOVA) was used to check if drugs differed simultaneously on two

dependent variables: efficacy (d_vs_MS) and safety (d_vs_Con). Pillai's Trace test statistic, based on the eigenvalues of the matrix, was used. If the MANOVA result was significant, ANOVA was performed for each variable separately to determine which indicator caused the difference. Holm's correction for multiplicity was applied for all pairwise comparisons.

To quantitatively compare the structure of biological effects between drugs, three complementary metrics were used:

- Adjusted Rand Index (ARI) — measures the proportion of pairs of parameters that are in the same cluster for both the comparator drug and the investigated drug (or in different clusters in both cases).
- Normalized Mutual Information (NMI) — based on mutual information between two clusterings.
- Jaccard Index — the proportion of agreement in the classification of parameter pairs.

Statistical significance of similarity was assessed by a permutation test: clusters of the drug were randomly permuted, metrics were recalculated, and a distribution under the null hypothesis was collected. P-value was calculated as the proportion of permutations where ARI/NMI/Jaccard ≥ observed value. If $p < 0.05$, the similarity was statistically significant.

In addition to clustering, a direct comparison of the profiles of all 53 parameters was performed: an integrated similarity index was calculated as a weighted sum of three indices: Euclidean distance, Cosine similarity, Pearson correlation. Based on these indices, an integrated similarity index was calculated as a weighted sum of these three indices. Weights: 40% Euclidean (absolute differences in values), 40 % Cosine (pattern and direction of effects), 20% Pearson (synchronicity). The result was converted to a percentage of similarity (multiplied by 100).

Comparative analysis of effect magnitudes was implemented in R. Main packages:

- tidyverse — data manipulation (filter, mutate, summarize)
- stats — ANOVA, MANOVA, k-means
- car — Levene, Type III ANOVA tests
- mclust — Adjusted Rand Index
- custom functions for NMI, Jaccard Index, and permutation test.

RESULTS

Induction of metabolic syndrome

In mice receiving the "high-fat" diet, body weight gradually increased and significantly exceeded the weight of control mice from week 8 of feeding (Fig. 2). After three months of feeding, the BW of mice on the "high-fat" diet was 39.5 ± 0.6 g, which is 24 % higher than in mice on standard feed (31.9 ± 0.6 g).

Intragastric administration of 2 g/kg glucose led to a more pronounced increase in blood glucose concentration in mice on the "high-fat" diet and fructose syrup than in individuals consuming standard feed (Fig. 3A). Thus, in mice on the modified diet, the maximum blood glucose concentration was 20.3 ± 3.7 mmol/L, and on the control feed — 14.9 ± 2.7 mmol/L (Fig. 3B); the increase in the area under the blood glucose concentration curve was 19.8±3.2 and 28.0 ± 6.2 mmol/L×h in mice on standard and modified diets, respectively (Fig. 3C). The half-time for blood glucose recovery in mice on standard feed and water was 30 minutes, and in mice on "high-fat" feed and fructose syrup — 56 minutes ($F(1, 470) = 6.01$, $p = 0.0146$).

Thus, at the time of use in experiments, mice receiving the modified diet had 25 % greater BW than individuals on the standard diet, and glucose tolerance was significantly lower.

Therefore, it can be concluded that the experimental model of MS was successfully reproduced.

Effect of tirzepatide drugs on body weight

The BW of mice receiving tirzepatide (RD, T1, T2, and T3) was significantly lower than in mice with untreated MS and control individuals. Significant differences in BW persisted throughout the experiment (Fig. 4A). To assess the integral changes in mouse BW over the experimental period, areas under the BW change curve relative to baseline (before substance administration) values were calculated for the interval from day 1 to day 18 of the experiment (Fig. 4B).

By day 18 of the experiment, the BW of the control group mice receiving standard feed had practically not changed (-0.5 ± 1.0 %). Mice with untreated MS lost 8.5 ± 1.5 %, presumably due to numerous experimental stress manipulations (PhenoMaster monitoring, blood glucose measurement, etc.). In mice receiving tirzepatide, BW reduction was 25.9 ± 1.1 % for RD, and 28.2 ± 1.1 %, 27.4 ± 1.2 %, and 26.8 ± 1.6 % for the investigated tirzepatide drugs T1, T2, and T3, respectively.

Thus, it can be concluded that the administration of 150 µg/kg tirzepatide led to a pronounced reduction in BW of mice with MS, with mouse BW being lower than control group values, without signs of MS. The reduction in BW upon administration of the investigated tirzepatide drugs and the comparator product was equally pronounced and occurred with indistinguishable dynamics. The T1, T2, and T3 drugs did not differ from the comparator product or from each other in any of the analyzed BW characteristics.

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Table 1 — Experimental scheme for assessing the effect of tirzepatide on mice with induced metabolic syndrome

Group	Number of animals, *n*	Administered substance, administration regimen	Recorded parameters (registration graph)
Con	12	Placebo, 5 ml/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	1. BW (daily — d_1…d_{25}); 2. Food and water/syrup intake in housing cages (daily — d_1…d_{25}); 3. Physiological parameter monitoring in PhenoMaster (d_6…d_{15}): • food intake, min^{-1}; • water intake, min^{-1}; • motor activity, min^{-1}; • O_2 consumption, h^{-1}; • CO_2 production, h^{-1}. 4. Non-fasting blood glucose, glucometer (weekly — d_5, d_9, d_{12}, d_{15}, d_{18}); 5. Glucose challenge test (once — d_{20}); 6. Insulin challenge test (once — d_{24}); 7. Organ weight (terminal — d_{25})*; 8. Visual assessment of fat depots (terminal — d_{25}); 9. CBC (terminal — d_{25}); 10. Blood biochemistry (terminal — d_{25})**; 11. Liver triglycerides (terminal — d_{25}).
MS	12	Placebo, 5 ml/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	
RD	10	Mounjaro, 150 µg/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	
T1	10	Tirzepatide (batch 1), 150 µg/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	
T2	10	Tirzepatide (batch 2), 150 µg/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	
T3	10	Tirzepatide (batch 3), 150 µg/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	

Notes: * — brain, heart, lungs, kidney, salivary glands, pancreas, liver, thymus, spleen, adrenal glands, testes, epididymides, accessory glands, gastrocnemius muscle, visceral fat; ** — glucose, triglycerides, cholesterol, AST, ALT. Con — control group; MS — metabolic syndrome; CS — reference drug; T1, T2, T3 — Tirzetta® drug batch; BW — body weight; CBC — complete blood count.

Table 2 — Characteristics of investigated batches of the reproduced drug and comparator product

Drug Name	Manufacturer	Batch
Tirzetta®, solution for subcutaneous injection, 5 mg/mL (T1)	JSC “Biokhimik”, Russia	OP030524
Tirzetta®, solution for subcutaneous injection, 5 mg/mL (T2)	JSC “Biokhimik”, Russia	OP050524
Tirzetta®, solution for subcutaneous injection, 5 mg/mL (T3)	JSC “Biokhimik”, Russia	OP060524
Mounjaro®, solution for injection, 5 mg/mL (RD)	Eli Lilly, USA	D665365A

Table 3 — Comparative analysis of effect differences in composite scores

Comparison	Difference	95% Confidence Interval		*p*
T1 vs. T2	0,113	-0,527	0,835	0,378
T1 vs. T3	-0,257	-0,883	0,174	0,811
T2 vs. T3	-0,147	-0,646	0,227	0,733

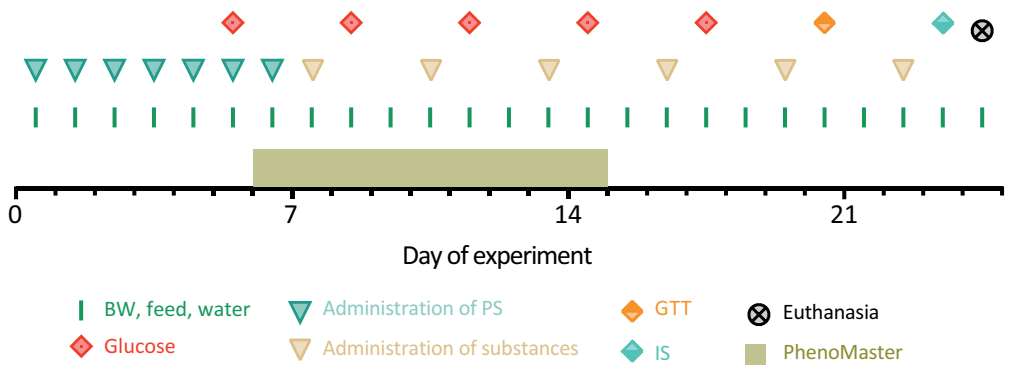

Figure 1 — Experimental schedule for assessing the effect of tirzepatide on mice with diet-induced metabolic syndrome.
Note: BW — body weight; PS — physiological solution; GTT — glucose tolerance test; IS — insulin sensitivity.

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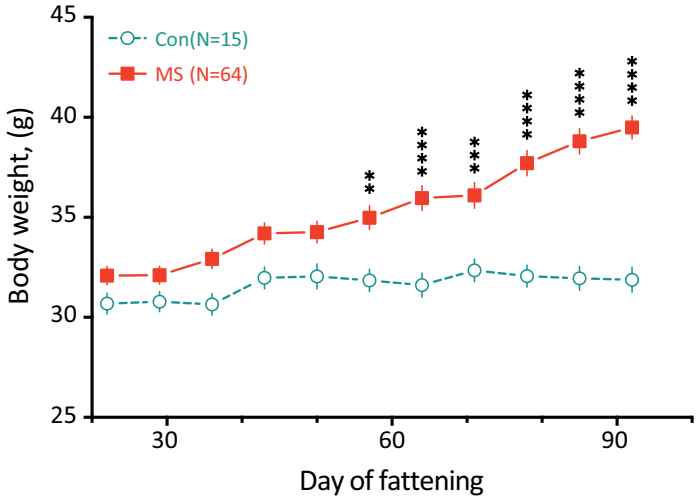

Figure 2 — Body weight of mice on a standard diet (K) and fed a "fatty" diet with 30% fructose syrup during the fattening period (MS).

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test.

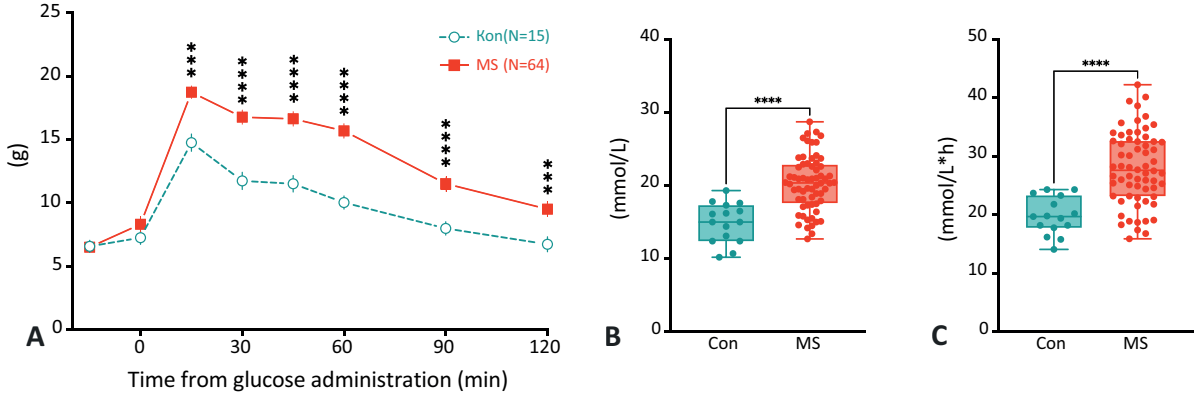

Figure 3 — Blood glucose concentration in experimental animals.

Note: A — blood glucose concentration in mice after intragastric administration of 2 g/kg glucose; B — maximum blood glucose concentration; C — increment of the area under the blood glucose concentration curve. * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test.

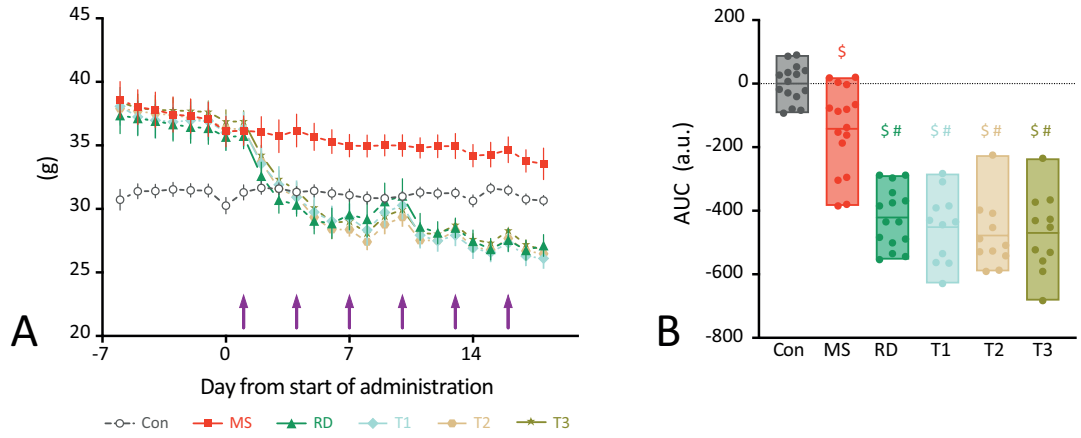

Figure 4 — Dynamics of body weight changes in mice during the experiment (A) and by day 18 (B).

Note: $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test.

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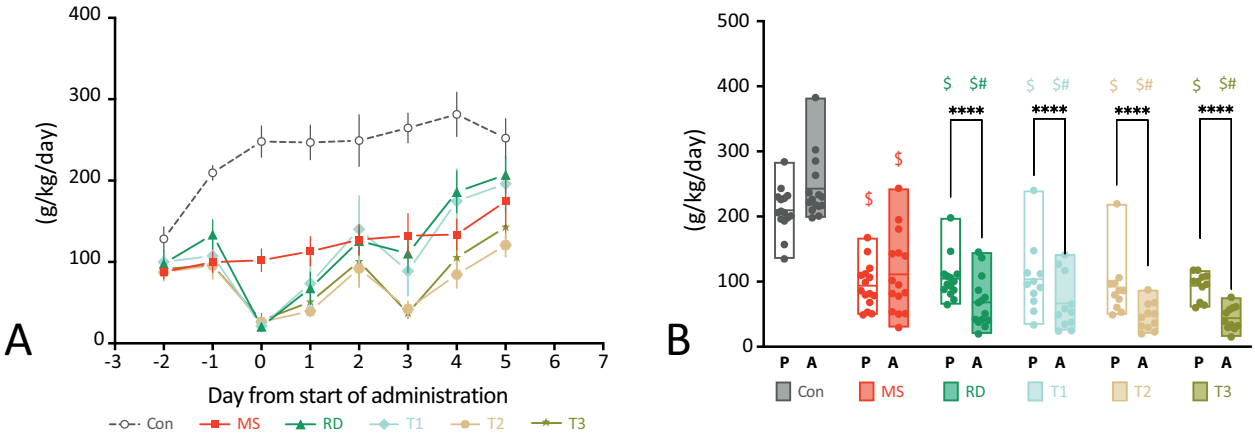

Figure 5 — Daily feed intake by mice during their stay in the PhenoMaster system.
Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

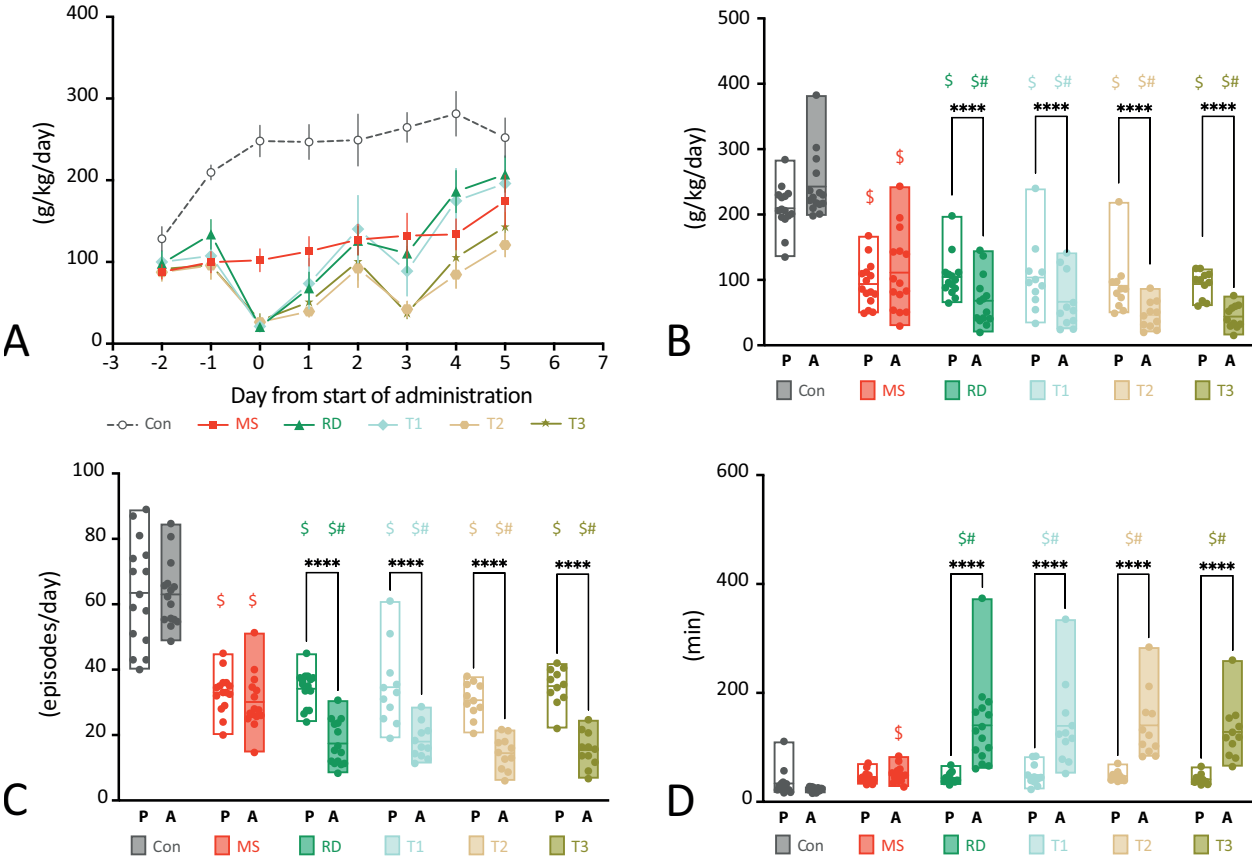

Figure 6 — Daily feed intake (A, B), average feed intake per feeding episode (C), and number of feeding episodes (D) in mice during their stay in the PhenoMaster system.
Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

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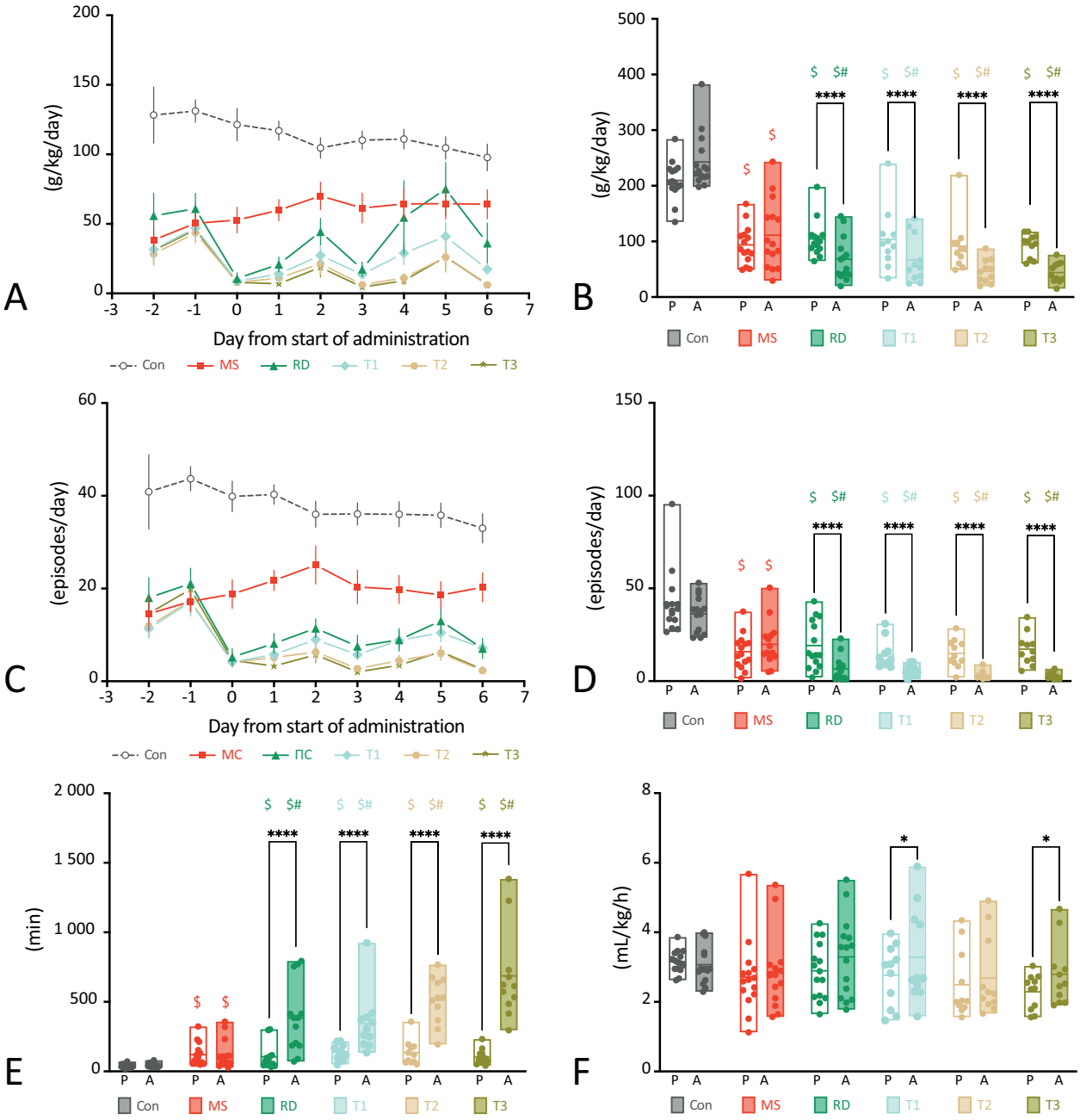

Figure 7 — Water/fructose syrup intake (A, B), number of intake episodes (C, D), duration of interval between episodes (E), and volume of water/fructose syrup intake per drinking episode during mice's stay in the PhenoMaster system.

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

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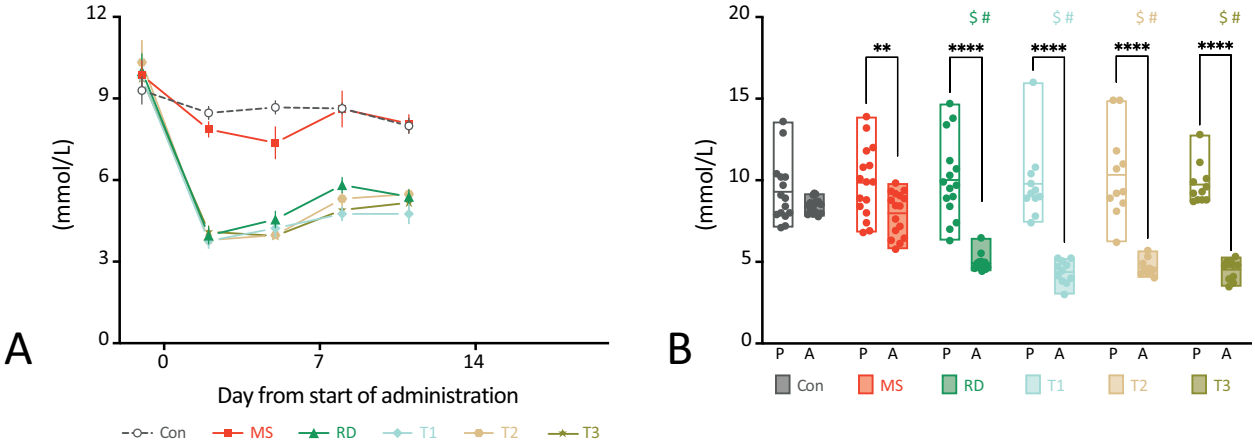

Figure 8 — Blood glucose in mice during their stay in the PhenoMaster system.
Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

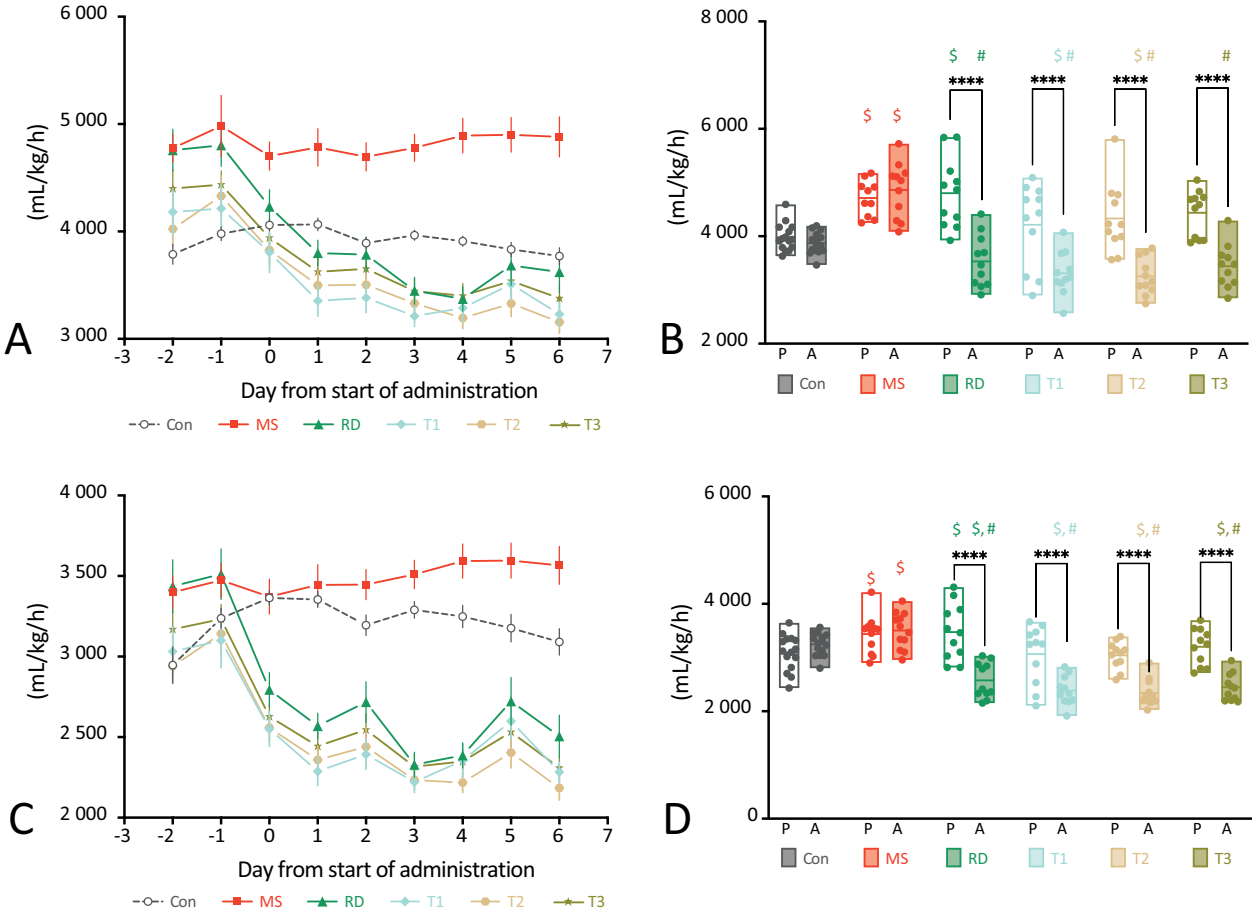

Figure 9 — Oxygen consumption (A, B) and carbon dioxide production (C, D) during mice's stay in the PhenoMaster system.
Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

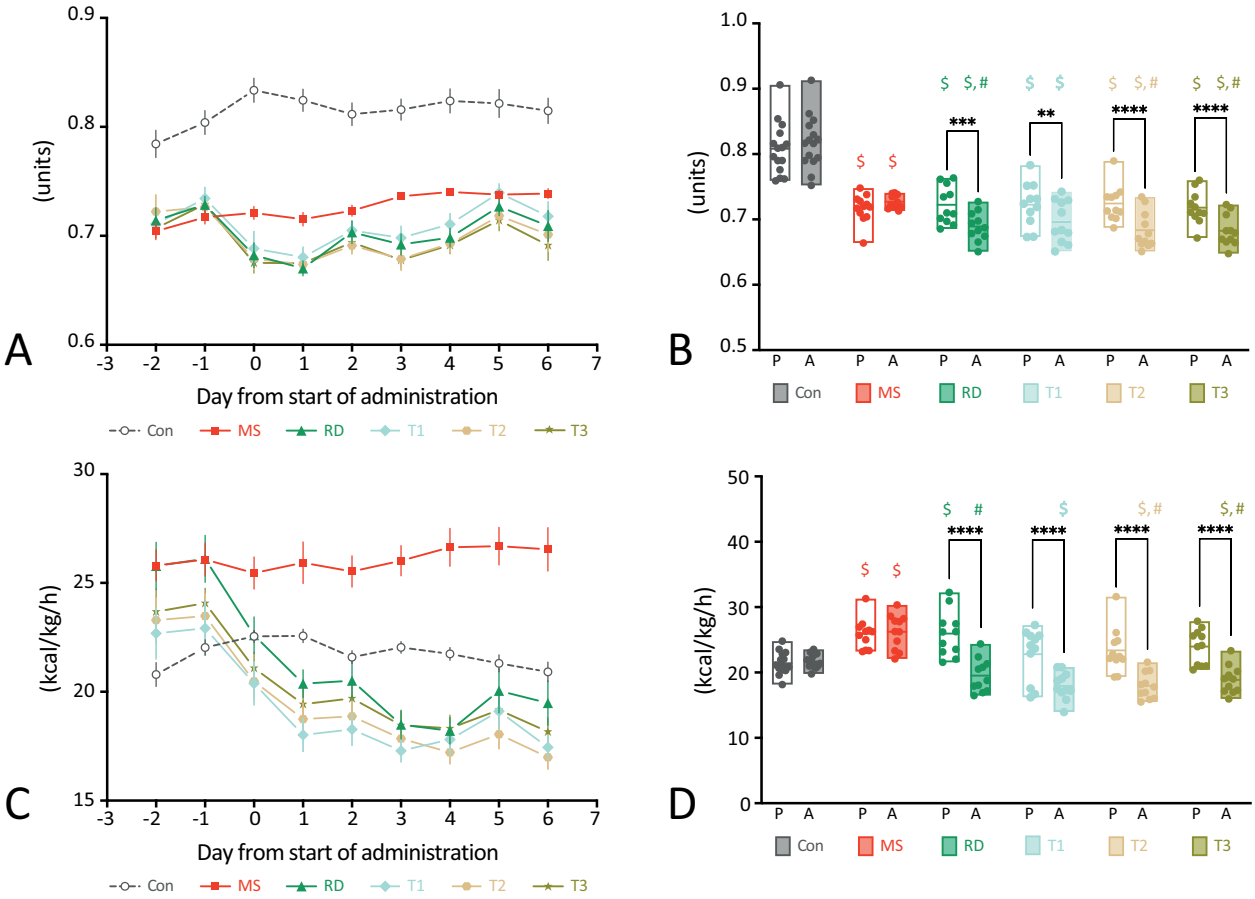

Figure 10 — Respiratory quotient (A, B) and heat production (C, D) during mice's stay in the PhenoMaster system.

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

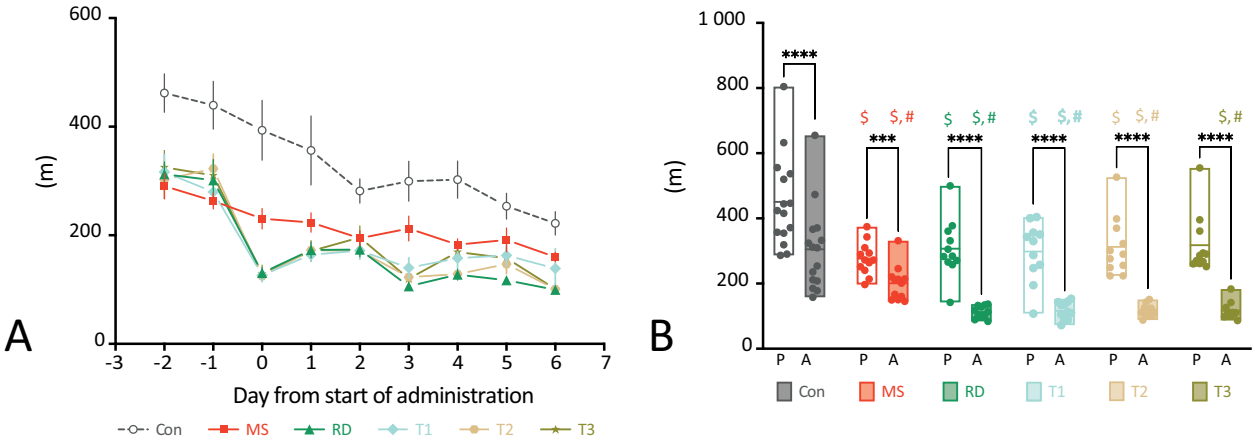

Figure 11 — Dynamics of locomotor activity (A) and its comparative analysis (B) before and during mice's stay in the PhenoMaster system.

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

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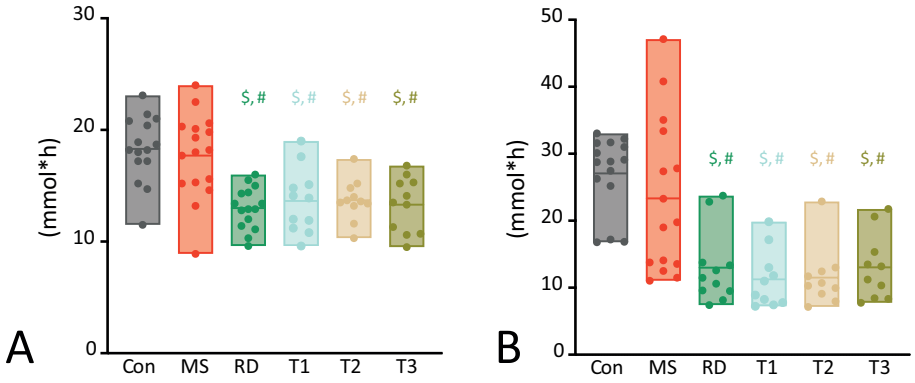

Figure 12 — Area under the curve of blood glucose concentration in mice during the glucose tolerance test (A) and insulin sensitivity test (B).
Note: $ — $p < 0.05$ vs. group K; # — $p < 0.05$ vs. group MS, Sidak's test.

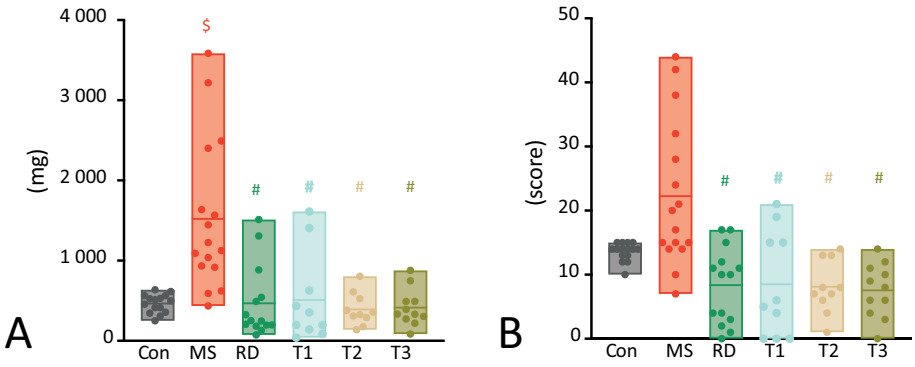

Figure 13 — Visceral fat mass (A) and fat depot severity (B) in experimental animals.
Note: $ — $p < 0.05$ vs. group K; # — $p < 0.05$ vs. group MS, Sidak's test.

Effect of tirzepatide drugs on feeding behavior

As shown in Figure 5, feed intake sharply decreased in animals receiving tirzepatide compared to the control group and the MS group, regardless of the type of administered drug: RD or T1–T3. The trend towards decreased feed intake was most pronounced immediately after drug administration and faded with repeated administrations (Fig. 5A). On average, for the first three tirzepatide administrations, the decrease in feed intake was 44 ± 10 %, 44 ± 9%, 51 ± 10%, and 60 ± 5% for the comparison drug, T1, T2, and T3, respectively (Fig. 5B). Overall, under the action of tirzepatide, feed intake was lower than in animals with untreated MS or control individuals.

We also analyzed the number of feeding episodes and the amount of food consumed per meal (Fig. 6). The amount of food consumed per feeding episode remained relatively stable during the observation period (Fig. 6A, B). A slight increase in food consumed per episode presumably reflects the adaptation of mice to using the unfamiliar feeders of the PhenoMaster system. The reduction in food intake was due to a sharp decrease in the number of feeding episodes (Fig. 6C), which was also reflected in the increase in time intervals between meals (Fig. 6D).

Water/fructose syrup intake during the observation period in PhenoMaster is shown in Figure 7. The response to the start of tirzepatide drug administration was similar to changes in food intake: fructose syrup consumption sharply decreased (Fig. 7A, B) due to a decrease in the frequency of syrup intake (Fig. 7C) and an increase in intervals between drinking (Figure 7D, E), but not a decrease in the volume of fluid consumed per drinking episode (Fig. 7F). No significant differences in drinking behavior parameters were found between animals receiving the comparison drug and the studied drugs.

Thus, it can be concluded that the studied tirzepatide drugs significantly reduced feed and fructose syrup intake in mice with MS. Mounjaro® reduced feed intake by 1.5–2.2 times. For Tirzetta® drugs, a trend towards a greater reduction in feed intake was observed — by 1.9–2.5 times. The change in daily caloric intake was expressed as a decrease in the frequency of feeding and drinking episodes.

Effect of tirzepatide drugs on blood glucose levels

Blood glucose levels were determined during the period of drug administration. Measurements were taken the day after administration. The obtained data are presented in Figure 8. Before substance administration, blood glucose concentration (non-fasting) in mice of all groups was similar (Fig. 8A). After substance administration, blood glucose in groups K and MS decreased slightly and did not differ between groups. In mice of groups RD, T1, T2, and T3, blood glucose sharply decreased after the start of tirzepatide administration. There were no differences in blood glucose concentration between animals in these groups. The glucose reduction was 48 ± 3 % in mice receiving tirzepatide as part of the comparison drug (Mounjaro®) and 53 ± 4 %, 52 ± 4 %, and 53 ± 2 % in mice receiving the studied tirzepatide drugs (Tirzetta®) T1, T2, and T3, respectively (Fig. 8B).

Effect of tirzepatide drugs on lipolysis level

Oxygen consumption in animals fed a high-fat diet and fructose syrup was predictably higher than in control animals on a standard feed and water. In MS group animals, oxygen consumption remained relatively stable throughout the observation period in PhenoMaster. In groups RD, T1, T2, and T3, after the start of tirzepatide administration, there was a gradual decrease in oxygen consumption to values lower than before administration in mice of the MS group and even the K group (Fig. 9A, B). The decrease in oxygen consumption was 26 ± 1 % in mice receiving the comparison drug, and 20 ± 1 %, 24 ± 2 %, and 22 ± 2 % in animals of groups T1, T2, and T3, respectively.

Carbon dioxide production was initially similar in animals of all groups. After the start of tirzepatide administration, CO_2 production in mice of groups RD, T1, T2, and T3 decreased by 21–26 % (Fig. 9C, D).

The respiratory quotient was 0.81, which correlates well with the indicators of animals on a standard diet consisting mainly of carbohydrates with a smaller proportion of protein and fat. In mice fed a “fatty” diet, the respiratory quotient was significantly lower, reflecting the utilization of fats primarily. After the start of tirzepatide administration as part of the studied drugs or RD, a further decrease in the respiratory quotient was observed, indicating an increase in the proportion of fats in the substrates utilized during respiration, presumably related to lipolysis (Fig. 10A, B). Similar patterns were found when analyzing animal heat production (Fig. 10C, D).

Effect of tirzepatide drugs on locomotor activity in mice

Locomotor activity of mice was recorded in the PhenoMaster system from day 6 to day 15 of the experiment, inclusive (two days before and 8 days after substance administration, d_6–d_{15}).

Over 10 days of observation, locomotor activity gradually decreased as animals became accustomed to the new conditions. Initially, all animals fed a “fatty” diet were less active than mice on a regular diet. Within 24 hours after tirzepatide administration as part of RD or the studied drugs T1, T2, and T3, there was a decrease in mouse locomotor activity (Fig. 11). This effect was equally pronounced for all tirzepatide drugs. Thus, it can be concluded that the decrease in body weight with tirzepatide intake is not mediated by increased locomotor activity.

Effect of tirzepatide drugs on glucose tolerance and insulin sensitivity

Based on the results of the loading tests, it was concluded that tirzepatide drugs improved glucose tolerance and insulin sensitivity in mice with metabolic syndrome (Fig. 12A, B).

During testing at the end of the experiment, intragastric administration of 2 g/kg glucose caused a similar rise in blood glucose concentration in control animals and mice with untreated MS, which is likely due to the loss of BW in MS mice as a result of numerous experimental manipulations. In groups RD, T1, T2, and T3, the rise in blood glucose was significantly less pronounced. For example, in mice receiving Mounjaro®, the area under the blood glucose concentration curve was 27 ± 3 % lower than in mice with untreated MS, and in mice of groups T1, T2, and T3, it was 23 ± 5 %, 23 ± 3 %, and 25 ± 4 %, respectively (Fig. 12A).

In mice receiving Mounjaro®, the area under the blood glucose concentration curve was 44 ± 7 % lower than in mice with untreated MS, and in mice of groups T1, T2, and T3, it was 52 ± 6 %, 51 ± 6 %, and 44 ± 7 %, respectively (Fig. 12B).

Thus, administration of tirzepatide drugs, both original and generic, equally improved insulin sensitivity and glucose tolerance in mice with metabolic syndrome.

Effect of tirzepatide drugs on visceral fat mass reduction

Visceral fat mass in mice with induced MS exceeded the values for control group mice on a normal diet. Administration of tirzepatide drugs led to a reduction in visceral fat mass by 69 ± 8 % in mice of group RD and by 67 ± 12 %, 74 ± 4 %, and

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73 ± 5 % in mice receiving drugs T1, T2, and T3, respectively (Fig. 13A). Similar results were obtained during visual assessment of subcutaneous and abdominal fat depot severity in mice (Fig. 13B).

Changes in mass caused by tirzepatide administration were detected for the heart, lungs, liver, salivary glands, spleen, epididymis, accessory glands, and gastrocnemius muscle (Fig. 14).

Pancreas mass was reduced in all MS mice; however, tirzepatide administration did not significantly affect this parameter.

Changes in mass were observed for several organs, but not in all experimental groups. The masses of the brain, thymus, and adrenal glands did not change depending on the induction of metabolic syndrome and tirzepatide administration.

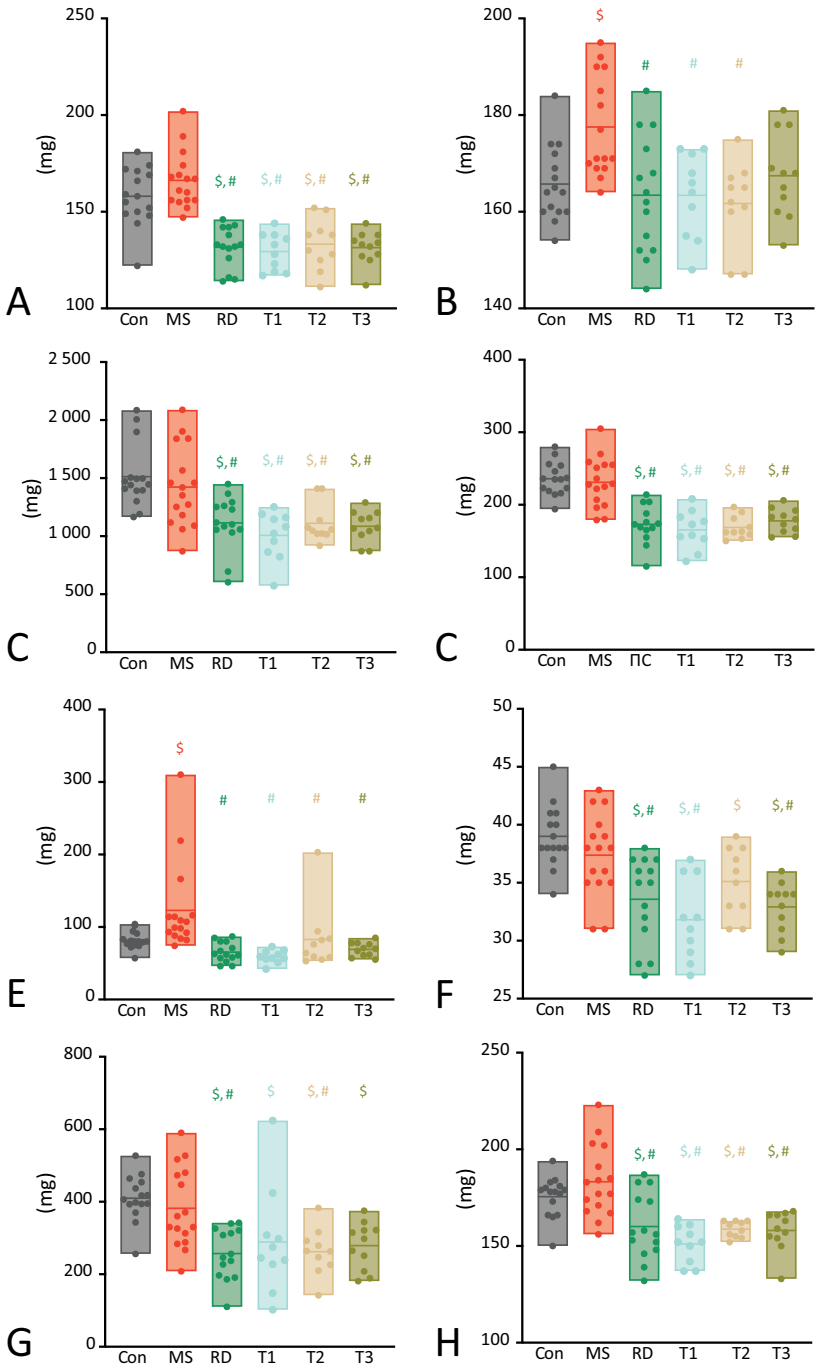

Figure 14 — Mass of the heart (A), lungs (B), liver (C), salivary glands (D), spleen (E), epididymis (F), accessory glands (G), and gastrocnemius muscle (H) in experimental animals.
Note: $ — p <0.05 vs. group K; # — p < 0.05 vs. group MS, Sidak's test.

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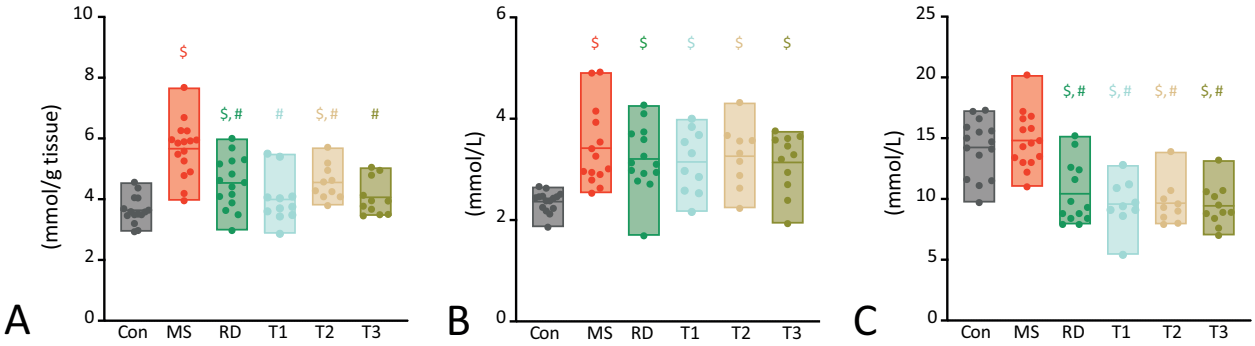

Figure 15 — Triglyceride content in the liver (A), cholesterol (B), and serum glucose (C) in experimental animals.

Note: $ — $p < 0.05$ vs. group K; # — $p < 0.05$ vs. group MS, Sidak's test.

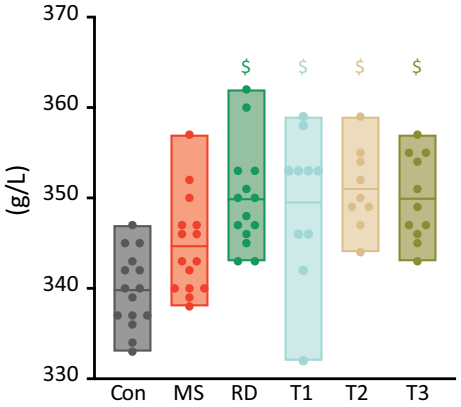

Figure 16 — Average hemoglobin content in the erythrocyte mass of experimental animals.

Note: $ — p < 0.05 vs. group K.

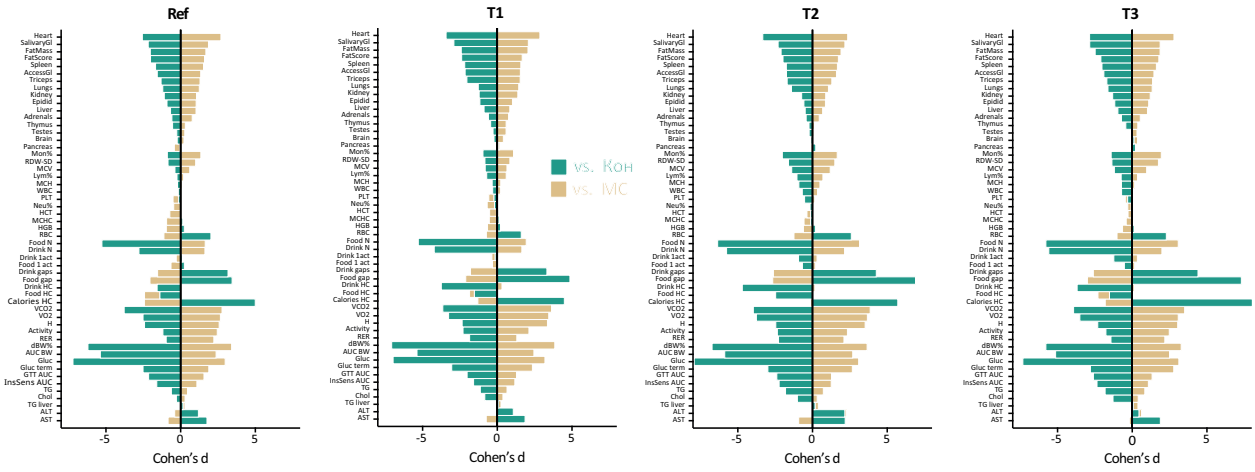

Figure 17 — Effect magnitudes of the studied drugs, T1, T2, T3, PS versus the control group and the group of mice with untreated metabolic syndrome, grouped by semantic blocks.

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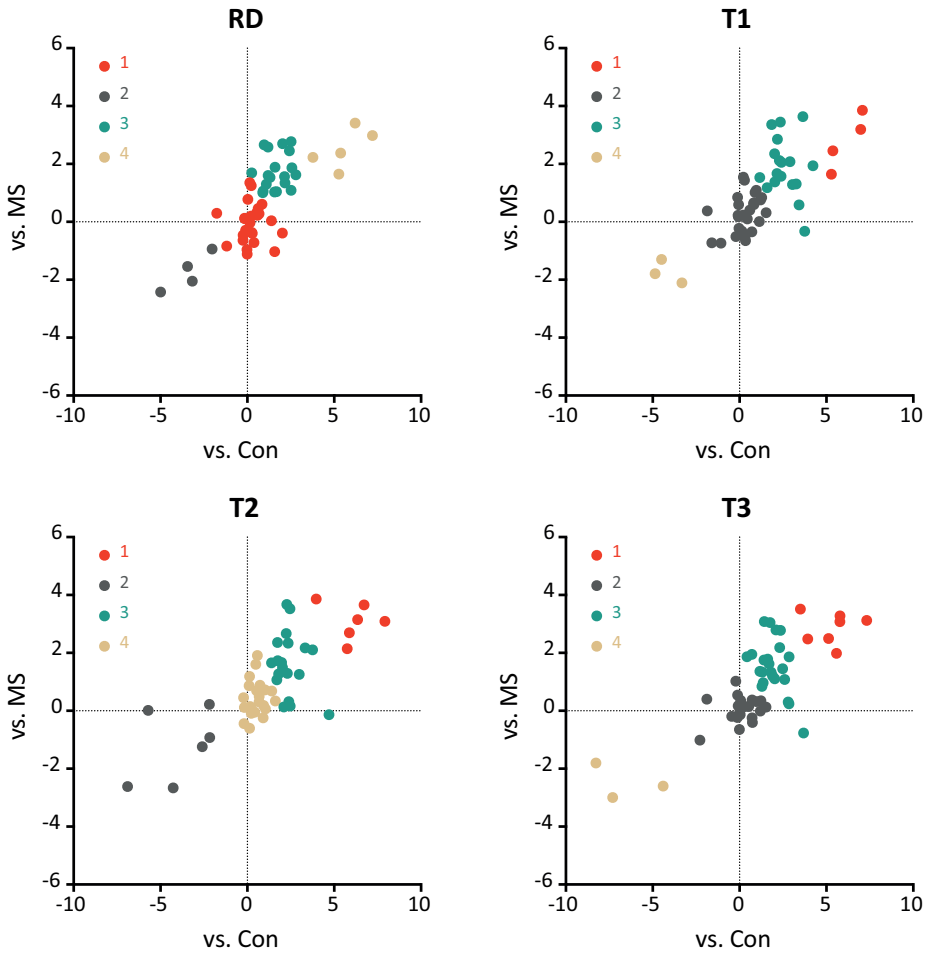

Figure 18 —Effect magnitudes (Cohen's d) of the studied drugs, T1, T2, and T3, and the comparison drug versus the control group (Con) and the group of mice with untreated metabolic syndrome (MS), grouped by clusters.

Effect of tirzepatide drugs on liver triglyceride content

Liver triglyceride content in mice with untreated MS was 56 ± 6 % higher than in control individuals receiving standard feed (Fig. 15A). In the livers of mice receiving tirzepatide, triglyceride content was lower than in mice with untreated MS by 20 ± 4 %, 30 ± 4 %, 20 ± 4 %, and 28 ± 3 % for groups RD, T1, T2, and T3, respectively. Liver triglyceride content did not differ between mice receiving different tirzepatide drugs.

Serum triglyceride concentration did not differ significantly between experimental groups of mice. Serum cholesterol was elevated in all mice with induced MS but did not differ between mice receiving tirzepatide and placebo, which serves as a marker of drug safety (Fig. 15B). Glucose concentration in mice receiving tirzepatide was lower than in individuals with MS receiving placebo and did not differ depending on the tirzepatide drug used (Fig. 17C). Thus, tirzepatide demonstrated pronounced efficacy in normalizing hepatic steatosis and hyperglycemia, along with a good safety profile regarding blood lipid content, suggesting that tirzepatide is compatible with hypocholesterolemic drugs.

Additionally, to assess the toxic effect of tirzepatide on the liver, ALT and AST concentrations were measured in mouse serum. No significant effect of MS and tirzepatide on these parameters was found.

Effect of tirzepatide drugs on hematological parameters

The study results revealed a significant difference between the control and experimental groups in hemoglobin content in the erythrocyte mass (Fig. 16).

Other hematological parameters did not differ significantly between the animal groups.

Comparative analysis of drug effect magnitudes

Figure 17 shows the effect magnitudes of the studied drugs (T1, T2, T3, RD) in comparison with the control and untreated MS groups.

For each of the 53 parameters, two types of comparisons were calculated:

1) relative to control (vs. Con) — drug effect on

healthy animals (reflects impact on a healthy organism, potential side effects);

2) relative to untreated animals with metabolic syndrome (vs. MS), reflecting efficacy. The full data matrix contained (53 parameters) × (4 groups: RD, T1, T2, T3) × (2 comparison types) = 424 Cohen's d values.

Effect coefficient values were chosen arbitrarily, prioritizing efficacy (70 %). It should be noted that modeling CS changes with different weight values for the indicators used in its calculation (in increments of 0.01) showed that the choice of drug (T1, T2, or T3) was independent of the weight values.

Differences in calculated metrics did not reach statistical significance based on one-way and multifactorial analysis of variance. Bootstrap analysis results are in good agreement with ANOVA results (Table 3).

As an alternative method for comparing data, the structure of drug effects (structure of Cohen's d values) on the studied indicators was assessed. Clustering of effects in a two-dimensional space (d vs. Con, d vs. MS) is shown in Figure 18. Each of the 53 parameters is represented as a point in a two-dimensional coordinate space (d_vs_Con, d_vs_MS). Algorithm: random selection of 4 initial centroids, iterative assignment of points to the nearest centroid, and recalculation of centroids as the mean of current clusters until convergence (parameters in R: nstart = 30, iter.max = 100, ensuring a global optimum).

When comparing the profiles of effects in this space, as well as based on the results of topological analysis of the effect matrix and the space of three statistical difference metrics between the studied drugs (T1, T2, T3) and the comparison drug (PS), no differences were found.

Thus, in terms of in vivo effects, Tirzetta® and Mounjaro® drugs are bioequivalent.

DISCUSSION

This study conducted a comprehensive comparative evaluation of the efficacy of three batches of the generic drug Tirzetta® (T1, T2, T3) and the reference drug Mounjaro® (RD) in a mouse model of MS. The study covered a wide range of indicators of energy metabolism, morphofunctional parameters, and biochemical characteristics.

The most pronounced effect of all tirzepatide drugs was a significant reduction in BW [8–10]. The dynamics of BW change showed a progressive decrease, starting from the first day of drug administration. By day 18 of the experiment, BW reduction was 25.9 ± 1.1 % for Mounjaro® and up to 28.2 ± 1.1 % for Tirzetta®. It is important to note that BW reduction was mediated by lipolysis activation and fat mass loss without signs of emaciation or deterioration of the animals' general condition, indicating the physiological nature of this process. Such a mechanism of action is a unique feature of tirzepatide compared to GLP-1 agonists, which are characterized by a pronounced decrease in muscle mass, requiring dietary adjustments and increased physical activity [8–10].

The results of feeding behavior analysis revealed that the reduction in BW was due to a substantial decrease in the intake of both standard feed and fructose syrup. These changes were observed equally for Tirzetta® and Mounjaro®.

The results of indirect calorimetry are of particular significance, providing a complete picture of the metabolic changes underlying the reduction in BW [11]. Oxygen consumption decreased in all groups receiving tirzepatide: by 26 ± 1 % for Mounjaro® and up to 24 ± 2 % in Tirzetta® groups.

Similar dynamics were observed for carbon dioxide production. The most informative indicator was the decrease in the respiratory quotient from 0.73 in the untreated group to 0.68–0.69 in all treatment groups, indicating a shift in energy metabolism towards lipolysis [12]. These data fully correlate with the decrease in fat depot mass: visual and instrumental assessments showed a significant reduction in fat accumulation in all studied locations in animals receiving tirzepatide compared to the untreated MS group. Statistically significant differences between Mounjaro® and Tirzetta® drugs were absent.

A comprehensive assessment of glycemic status using various methodological approaches demonstrated high consistency of results. In vivo measurements of blood glucose concentration over time revealed a pronounced hypoglycemic effect of all tirzepatide drugs, achieving normoglycemia by the end of the observation period. It should be noted that under Tirzetta® intake, the hypoglycemic effect was more pronounced. Glucose concentration reduction was 48 ± 3 % for Mounjaro® and 53 ± 4 % for Tirzetta®. The glucose tolerance test demonstrated a significant improvement in glucose tolerance in all groups receiving tirzepatide, with normalization of glucose utilization kinetics. The area under the glucose concentration curve was comparable for Mounjaro® and Tirzetta®. The insulin sensitivity test revealed restoration of insulin tolerance equally for Mounjaro® and Tirzetta®. Terminal glucose concentration measurements fully confirmed the in vivo monitoring data, showing a decrease in glycemia in all treatment groups without intergroup differences.

Biochemical analysis of liver tissue revealed a pronounced hypolipidemic effect of all tirzepatide drugs. Triglyceride concentration decreased from 5.66 ± 0.23 to 4.54 ± 0.22 mmol/g for Mounjaro® and to 4.55 ± 0.19 mmol/g for Tirzetta®, indicating

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correction of hepatic steatosis. The activity of liver transaminases (AST, ALT) remained within physiological limits in all treatment groups, confirming the absence of hepatotoxic effects and good tolerability of all studied drugs.

Hematological parameters showed no significant changes in any of the tirzepatide-receiving groups. The number of erythrocytes, leukocytes, platelets, hemoglobin level, and hematocrit remained within reference values, confirming the absence of systemic toxic effects and good tolerability of all studied drugs. Our data are supported by several preclinical studies of tirzepatide, which, in addition to weight loss, show a positive trend in increased glucose tolerance [13, 14].

Morphometric analysis of internal organs showed that changes in their absolute mass were primarily due to a decrease in adipose tissue [15, 16], rather than direct drug effects on the organs.

The study by J.O.A. Bittencourt et al. (2025) also investigated the therapeutic potential of tirzepatide in a mouse model combining obesity and type 2 diabetes mellitus [17]. For 4 established groups, a high-fat and sucrose diet was administered for 12 weeks. Animal therapy involved tirzepatide administration (10 nmol/kg/day) for 4 weeks. In mice of 2 experimental groups (obesity+T2DM), BW increased 1.3-fold compared to the control group. Tirzepatide normalized BW and reduced relative BW by 25 %. Histological and molecular analyses showed that tirzepatide reversed the whitening of brown adipose tissue, restored the morphology of multilocular adipocytes, and increased the expression of key thermogenic markers. Another study by T. Ma et al. (2025) on flying squirrels, comparing the effects of semaglutide, tirzepatide, and physiological saline, also confirms this. Both studied drugs showed similar effects—it was found that both semaglutide and tirzepatide increased insulin sensitivity, improved metabolism, and promoted weight loss [18].

The obtained results demonstrate the high efficacy of Tirzetta® and Mounjaro® drugs in correcting the main manifestations of MS. The mechanism of action includes reduced appetite and food intake, activation of lipolysis with a shift in energy metabolism towards fat oxidation, improved glycemic control and insulin sensitivity, and normalization of lipid profile [19, 20]. The observed effects were equally pronounced for Tirzetta® and Mounjaro® drugs, indicating their bioequivalence.

Previously, we showed the equivalence of physicochemical properties and biological activity of Tirzetta® and Mounjaro® [5]. It should be noted that according to the results of the physicochemical property study, Tirzetta® contains 4.2 times fewer impurities than Mounjaro®, which suggests greater safety for Tirzetta®. It is necessary to consider that the treatment of type 2 diabetes and obesity is long-term. Moreover, taking such drugs may become lifelong [21]. Organic impurities, such as phenol and benzyl alcohol, can accumulate in the body during long-term therapy, potentially leading to toxicity [22].

As a result of additional analysis of integral effect magnitudes (Cohen's d), performed on the entire set of parameters, an aggregated assessment was obtained based on a composite index including parameters of efficacy, safety, and selectivity, which allowed not only quantitative comparison of the structural similarity of profiles but also identification of characteristic differences at the level of effects not visible in traditional significance testing.

Comparison of drug effect magnitudes allows for quantitative assessment of therapeutic efficacy, safety, and dose-dependency in the target organism. Metrics RE (relative efficacy), SS (safety assessment), Sel (selectivity), and CS (composite score), calculated based on Cohen's d, provide a standardized multifactorial assessment of drugs in in vivo studies. They allow ranking compounds by a combination of therapeutic effects, toxicity, and specificity [23].

This approach solves the problem of subjectivity in comparing drug effects by translating differences into a universal scale of standard deviations [24]. This is particularly relevant in in vivo studies where analytes (e.g., tumor growth or biomarkers) have different units of measurement and variances. Without standardization, p-value only shows statistical significance, without considering the magnitude of the effect. Thus, a drug may be significantly better by one criterion, but in practice, this difference, although statistically significant, is still small and has no therapeutic benefit [24, 25]. When analyzing the effect magnitudes of Tirzetta® and Mounjaro® s, they were found to be equivalent—differences in effect magnitudes did not reach statistical significance (MANOVA $p = 0.977$; bootstrap analysis $p > 0.05$).

Study Limitations

Although the use of multiple methodological approaches ensures a high degree of reliability of the study results, it is necessary to note several limitations that should be considered when interpreting the results. For instance, experimental animal models have species-specific metabolic characteristics that can influence the pharmacokinetic and pharmacodynamic parameters of drugs [26]. Nevertheless, the combination of in vitro, in vivo, and physicochemical analysis methods provides a comprehensive characterization of the drugs and high reliability of conclusions about drugs bioequivalence, meeting current regulatory requirements.

CONCLUSION

Based on the results of the comprehensive study, it has been established that the drug Tirzetta® (manufacturer: LLC "PROMED RUS", Russia) does not differ from the reference drug Mounjaro® (manufacturer: Eli Lilly, USA) in all studied indicators of efficacy and safety. At the same time, the drugs demonstrated a favorable safety profile without signs of toxic effects. No statistically significant differences were found between Tirzetta® batches either. All studied drugs demonstrated comparable hypophagic effects with body weight reduction of 26–28 %, pronounced hypoglycemic properties with a decrease in blood glucose concentration of 48–53 %, a positive impact on lipid metabolism, and improved glucose tolerance and insulin sensitivity. Tirzepatide promoted lipolysis and preferential reduction of body fat mass, confirming its targeted efficacy. Such selective reduction of the lipid component is particularly important for physiological weight loss, minimizes the risk of sarcopenia, and preserves functional muscle tissue—a key factor for long-term metabolic improvement and quality of life.

Thus, Tirzetta® can be considered a therapeutic analog of Mounjaro® drug.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Victoria S. Scherbakova, Kira Ya. Zaslavskaya, Petr A. Bely — conceptualization, data curation, formal analysis, writing—review & editing; Alexander A. Andreev-Andrievskiy, Sofya V. Drugova, Mikhail A. Mashkin — conceptualization, investigation, formal analysis, visualization; Ksenia N. Koryanova, Ekaterina S. Mishchenko, Larisa I. Shcherbakova, Irina N. Dyakova, Polina A. Podlesnaya, Yuri G. Kazaishvili — conceptualization, investigation, formal analysis, visualization, writing—original draft. All the authors confirm their authorship compliance with the ICMJE international criteria (all the authors made a significant contribution to the conceptualization, conduct of the study and preparation of the article, read and approved the final version before publication).

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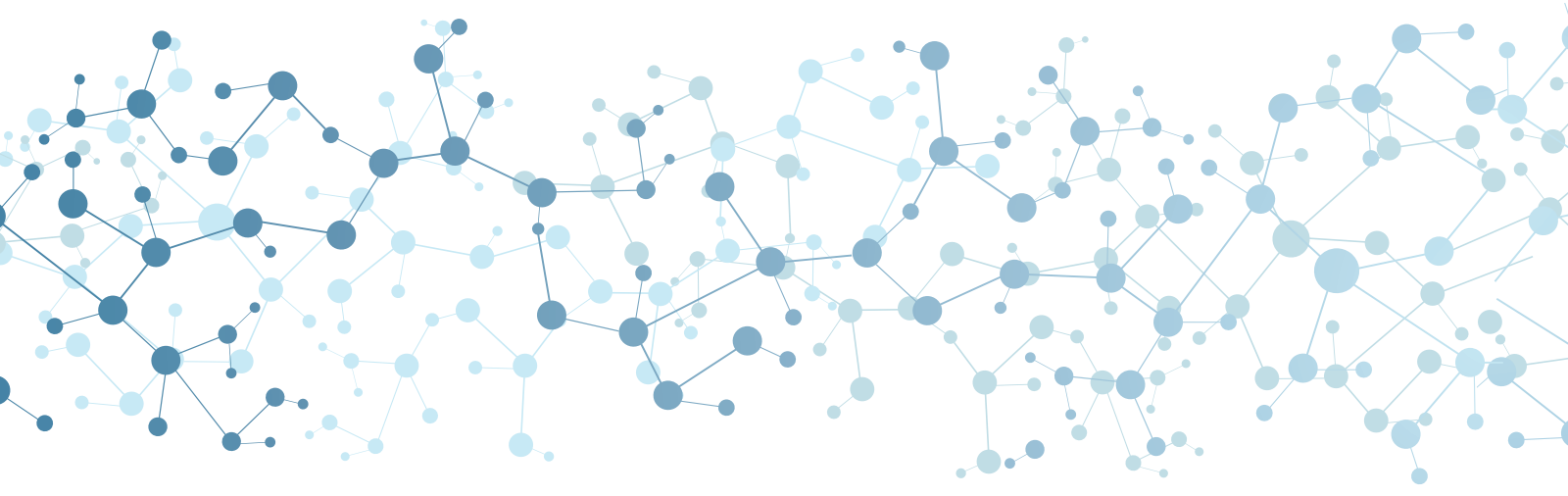

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