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Prospects for the use of an original medicine based on hexapeptide succinate for organ protection in various diseases

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The aim. To analyze and summarize the available results of experimental and clinical scientific studies of synthetic analogs of leu-enkephalin; to evaluate the expansion of the spectrum of application of the original medicine based on hexapeptide succinate in patients with various diseases of different etiologies.

Materials and methods. An analysis of scientific literature data in the PubMed, eLibrary.ru and CyberLeninka databases was carried out. The search depth was 50 years (from 1976 to 2024), the list of references includes 60 scientific papers.

Results. It was revealed that receptors for endogenous opioid peptides are widespread in living organisms. Modern neuropharmacology recognizes 4 main types of opioid receptors: μ (MOR) — mu, δ (DOR) — delta, κ (KOR) — kappa and NOP — nociceptive receptor, which bind to endogenous opioids such as enkephalins, endorphins, endomorphins, dynorphins and nociceptin. Due to their antioxidant, immunomodulatory, and anti-inflammatory properties, analogs of opioid peptides are widely used in Russian medicine. A number of experimental and clinical studies are presented, to prove that agonists of delta-opioid receptors can "soften" organ damage in a variety of diseases accompanied by oxidative stress and endothelial dysfunction. The dose-dependent regulatory effect is realized with intravenous, intramuscular and intranasal administration. The therapeutic efficacy of leu-enkephalin analogs based on tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine is analyzed, and the prospects for using the new original Russian medicine Ambervin® Pulmo with the inclusion of succinic acid salts are also discussed.

Conclusion. The information on the functional properties of leucine-enkephalin analogs presented in the article indicates broad prospects for the use of medicines based on tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine with the inclusion of succinic acid salt in the complex therapy of many diseases for the purpose of organ protection.

Keywords: delta opioid receptor; leucine-enkephalin analogs and derivatives; tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate (dalargin); succinate; acute respiratory distress syndrome; cytokine storm; COVID-19; organ protection; ischemia-reperfusion

Abbreviations: WHO — World Health Organization; ARVI — acute respiratory viral infection; ACE 2 — angiotensin-converting enzyme 2; ARDS — acute respiratory distress syndrome; OP — opioid peptides; IL — interleukin; TNF — tumor necrosis factor; CHD — coronary heart disease; LPO — lipid peroxidation.

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Перспективы применения оригинального препарата на основе сукцината гексапептида с целью органопротекции при различных заболеваниях

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Цель. Проанализировать и обобщить имеющиеся результаты экспериментальных и клинических научных исследований синтетических аналогов лей-энкефалина и оценить возможности расширения спектра применения оригинального препарата на основе сукцината гексапептида в перспективе у пациентов с заболеваниями различной этиологии.

Материалы и методы. Проведён анализ данных научной литературы в базах PubMed, eLibrary.ru и CyberLeninka. Глубина поиска составила 50 лет (с 1976 по 2024 гг.), список литературы включает 60 научных работ.

Результаты. Установлено, что благодаря антиоксидантным, иммуномодулирующим, противовоспалительным свойствам, аналоги опиоидных пептидов широко применяются в России и за рубежом. Приведён ряд экспериментальных и клинических исследований, который доказывает, что агонисты δ-опиоидных рецепторов могут «смягчать» повреждения органов при самых разных заболеваниях, сопровождающихся оксидативным стрессом и эндотелиальной дисфункцией. Установлено, что их дозозависимый регуляторный эффект реализуется при внутривенном, внутримышечном и интраназальном введении. Проанализирована терапевтическая эффективность аналогов лей-энкефалина на основе тирозил-D-аланил-глицил-фенилаланил-лейцил-аргинина и отражены перспективы использования в клинической практике нового оригинального отечественного лекарственного препарата Амбервин® Пульмо с включением солей янтарной кислоты.

Заключение. Информация о функциональных свойствах аналогов лейцин-энкефалина, представленная в обзоре научных публикаций, свидетельствует о широких перспективах применения лекарственных препаратов на основе тирозил-D-аланил-глицил-фенилаланил-лейцил-аргинина с включением соли янтарной кислоты в комплексной терапии различных заболеваний с целью органопротекции.

Ключевые слова: дельта-опиоидный рецептор; аналоги лейцин-энкефалина и производные; тирозил-D-аланил-глицил-фенилаланил-лейцил-аргинина диацетат (даларгин); сукцинат; острый респираторный дистресс-синдром; цитокиновый шторм; COVID-19; органопротекция; синдром ишемии-реперфузии

Список сокращений: ВОЗ — Всемирная организация здравоохранения; ОРВИ — острая респираторная вирусная инфекция; АПФ 2 — ангиотензинпревращающий фермент 2; ОРДС — острый респираторный дистресс-синдром; ОП — опиоидные пептиды; ИЛ — интерлейкин; ФНО — фактор некроза опухоли; ИБС — ишемическая болезнь сердца; ПОЛ — перекисное окисление липидов.

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INTRODUCTION

The COVID-19 pandemic was officially declared over by the World Health Organization (WHO) in May 2023, but periodic, including seasonal, increases in the incidence of this infection continue to pose a threat to the health of all mankind[1]. Cases of the disease that require hospitalization and lead to death are still registered. A key problem is the rapid evolution of the virus: emerging variants of SARS-CoV-2 strains are increasingly resistant to immune protection formed after previous infections or vaccination.

The virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface and penetrates inside, using cellular mechanisms to replicate its genome and synthesize viral particles. This process initiates an inflammatory response with activation of immune cells and release of pro-inflammatory cytokines, which leads to the development of inflammation in the affected tissues [1, 2].

The variety of clinical manifestations in the acute period of the disease is due to the fact that ACE2 is the main entry receptor for SARS-CoV-2, which is expressed on the membranes of cells of various organs and tissues. Cells of the mucous membrane of the oral and nasal cavities, lungs, heart, digestive tract, liver, kidneys, spleen, brain, as well as the walls of blood vessels can be affected, which explains the significant spectrum of potential organ damage during SARS-CoV-2 infection [1, 2].

Recent studies have shown that some symptoms can persist for a long time after an infection. This condition, which can develop both in patients with a mild course of COVID-19 and in those who have had the disease in a severe form, affecting various organs and systems, including the respiratory, cardiovascular, nervous, gastrointestinal and musculoskeletal systems, was called “Long COVID” and was recognized by the scientific community. The most common symptoms of Long COVID are fatigue, shortness of breath, heart disorders, cognitive disorders, including problems with memory and concentration, sleep disturbance, symptoms of post-traumatic stress disorder, myalgia and headaches [1].

[1] After the end of the international public health emergency, WHO/Europe launches a plan to move to a new stage of action in connection with COVID-19. Available from: https://www.who.int/europe/ru/news/item/12-06- 2023-with-the-international-public-health-emergency-ending--who-europe-launches-its-transition-plan-for-covid-19. Russian

It is known that the deterioration of patients against the background of a new coronavirus infection SARS-CoV-2 with an increase in the content of cytokines, which can lead to complications such as pneumonia and acute respiratory distress syndrome (ARDS) [2, 3]. In turn, the outcome of these conditions can be multiple organ failure and death.

Oxidative stress and endothelial dysfunction underlie many severe diseases of various etiologies and lead to damage to organs and tissues at the cellular level. In this regard, the search for effective anti-inflammatory drugs with organoprotective properties has become an especially urgent task during the COVID-19 pandemic and continues to be one of the most sought-after requests of the medical community. Safety of a wide range of doses, high efficiency and a minimum number of adverse reactions are the main requirements for medicines. It is known that analogues of opioid peptides (OPs), which meet these parameters, are used in clinical practice in Russia [4].

Currently, sufficient evidence has already been accumulated that agonists of delta-opioid receptors can mitigate damage to various organs. Synthetic analogues of leu-enkephalin have found application in schemes of pathogenetic therapy for many diseases: gastric and duodenal ulcers, pancreatitis, pneumonia of various origins, COVID-19, ARDS, metabolic and toxic and chemical liver damage, multiple organ failure syndrome, septic shock, ischemic stroke, myocardial infarction. Despite the heterogeneity of the etiology of diseases in which synthetic analogues of leu-enkephalins were used and the unclear mechanism of their action, they demonstrated pronounced organoprotective properties, which was shown in numerous experimental and clinical studies. The development of drugs based on regulatory peptides today is one of the promising areas and allows expanding the range of their use in various diseases.

THE AIM. To analyze and summarize the available results of experimental and clinical studies of synthetic analogues of leu-enkephalin and to evaluate the expansion of the spectrum of application of the original drug based on hexapeptide succinate in the future in patients with various diseases, regardless of etiology.

MATERIALS AND METHODS

PubMed, CyberLeninka, eLibrary.ru search databases were used. The following keywords were used for the search: opioid receptor; leu-enkephalin,

ОБЗОР
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leucine / analogs and derivatives; tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine / dalargin; succinate; acute respiratory distress syndrome; cytokine storm; COVID-19; organ protection; ischemia-reperfusion injury.

A simple search for “leu-enkephalin” in PubMed (as of July 11, 2024) showed about 30,000 results. The peak of publication activity on the keywords “opioid receptor” or “opioid peptide” is noted in the 2000s and 2010s. For example, in 1986, about 700 articles were found for these requests, while in 2016 — 2500, and in 2021 — 2800. The number of articles on “opioid peptide” is stable at hundreds per year. In 2024 (data until July 11, 2024), > 300 articles have already been published on this request.

The search depth was 50 years (from 1976 to 2024). Most studies were conducted on experimental models *in vitro* or models *in vivo.*

RESULTS AND DISCUSSION

Preclinical studies

In vitro studies

Opioids are natural, synthetic or semi-synthetic chemical compounds that interact with opioid receptors, causing analgesia and other physiological effects [5]. Their clinical use began after the isolation of morphine from opium poppy (*Papaver somniferum* L.) in 1806. Among the alkaloids of opium, morphine (10–15 %), codeine (1–3 %), noscapine (4–8 %), papaverine (1–3 %) and thebaine (1–2 %) are of pharmacological significance [6]. These exogenous ligands bind to the same receptors as endogenous OPs, including enkephalins, endorphins, endomorphins, dynorphins and nociception / orphanin.

The hypothesis about the existence of opioid receptors was first proposed in the 1950s, but experimental evidence of their diversity was obtained only in the 1970s when studying the mechanisms of action of analgesics. Thus, the first two types of opioid receptors were discovered, which were named after the drugs used in these studies to distinguish them: mu (μ) for morphine and kappa (κ) for ketocyclazocine [7]. The third type of opioid receptors was found in the vas deferens of mice: its pharmacological profile differed significantly from previously identified (μ and κ) and was named delta (δ) to indicate this difference [8]. Together μ, κ and δ, opioid receptors (MOR, KOR, DOR, respectively) are considered classical opioid peptide receptors based on their structural homology and sensitivity to the non-selective opioid receptor antagonist — naloxone [9].

Later, a fourth type of receptor was identified, structurally homologous to classical opioid receptors, but not sensitive to traditional opioid ligands [10]. After the discovery of its endogenous ligands (nociceptin [11] and orphanin [12]) the receptor known as NOR (nociceptin receptor). Despite structural similarity, NOR is often excluded from the classical group due to its insensitivity to naloxone.

The four main families of endogenous OPs demonstrate preferential activity against the corresponding receptor systems: β-endorphins (MOR), dynorphins (KOR), enkephalins (DOR) and nociception / orphanin (NOR) [13]. However, both endogenous and exogenous opioids rarely exhibit absolute selectivity and more often activate different types of receptors [14].

Opioid receptors are widely represented in the CNS and peripheral nervous system [15]. In the periphery, they are expressed in the lungs, heart, kidneys, small intestine and pancreas, modulating organ functions, inflammatory processes and homeostasis [16]. Additional localization includes neuroendocrine cells (adrenal glands, pituitary gland), immune cells (leukocytes) and ectodermal cells, where opioid receptors are involved in the regulation of nociception and inflammation [5]. Signal transduction is carried out through interaction with endogenous ligands (β-endorphins, dynorphins, enkephalins, nociceptins), ensuring the maintenance of homeostasis under physiological conditions.

The importance of OPs in the regulation of physiological systems was consistently revealed in the second half of the XX to early XXI century. Initially, their action was associated exclusively with the CNS through μ-, δ- and κ-receptors [14, 17], but later their peripheral effects were revealed, including modulation of the immune response (for example, met-enkephalin in rheumatoid arthritis) [18, 19]. OPs are formed from three main precursors (proopiomelanocortin, proenkephalin, prodynorphin) by proteolytic processing with subsequent modifications (acetylation, phosphorylation), which determine their activity [20].

Peripheral effects (decreased peristalsis, modulation of inflammation) are mediated by all receptors: MOR — respiratory depression, constipation; DOR — cardioprotection, antidepressant effect; KOR — sedation, mood modulation, diuresis; NOR — mediates

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bipolar pain effects: hyperalgesia (low doses) and analgesia (high doses) [21]. In addition, two subtypes of δ-receptors are known that bind to enkephalins (the precursor of which is proenkephalin). They play an important role in analgesia and reducing gastric motility [20, 22].

The opioid system is considered one of the most complex neurotransmitter systems of the body, playing the most important role in main biological processes. The use of exogenous opioids for analgesia has limitations due to their undesirable side effects, including sedation, respiratory depression and constipation. However, experiments have shown that drugs that bind to δ-opioid receptors (DOR) do not have side effects on the respiratory system and gastrointestinal tract. Activation of DOR enhances signals that promote survival and reduces oxidative damage to neurons [23], and activation of DOR reduces ion imbalance caused by hypoxia [24]. It has been shown that the degree of respiratory depression depends on the stimulated receptor: MOR causes a more significant decrease in respiratory rate than DOR and KOR [25]. Thus, the development of drugs specific to DOR may be clinically useful.

Recent studies show that enkephalins act as modulators of cardiac function and play a vital role in aging, ischemic preconditioning, heart failure and hypertension [26]. The biological activity of peptides is largely determined by their post-translational modifications, such as acetylation, phosphorylation, methylation and glycosylation [27, 28]. Of particular interest are OPs — endorphins and enkephalins are actively involved in the regulation of immune processes. Their synthesis is carried out by various cells of the immune system, including macrophages, lymphocytes, monocytes and mast cells [29].

The production of these peptides is under cytokine control: in particular, the level of enkephalin increases under the influence of interleukin-4 (IL-4), IL-10 and transforming growth factor beta (TGF-β) [30, 31].

Different classes of peptides demonstrate multidirectional effects on antibody formation in inflammation models, while α-endorphin and leu-enkephalin suppress this process, β-endorphin enhances it by 2–3 times [32].

The effect of OPs on immune reactions is characterized by dose dependence: physiological concentrations stimulate immunity; high concentrations suppress for it [33]. The study by S.V. Gein et al. (2020) demonstrated their modulating effect not only on the humoral, but also on the cellular component of immunity, including the functional activity of NK cells, proliferation of T-effectors and chemotaxis of leukocytes: β-endorphin increases the activity of NK cells through MOR receptors, and enkephalins inhibit the proliferation of T-lymphocytes [34].

An important aspect is the participation of OPs in regenerative processes. It has been established that leukocytes enhance the synthesis of endorphins in the focus of inflammation, which in turn stimulate the phagocytic activity of neutrophils [35]. In addition, increased secretion of enkephalins by immunocompetent cells also enhances the bactericidal activity of blood serum [36].

In vivo studies

According to the study by C.W. Tang et al., experimental administration of leu-enkephalin at a dose of 5 mg/kg increased the survival rate of laboratory animals. It has been shown that this effect is associated with a decrease in serum levels of not only "early" pro-inflammatory cytokines (TNFα, IL-1), but also the "late" mediator of inflammation is HMGB1. It is important to note that the effectiveness of OPs persisted both at the initial stage of development of the septic shock model and in the later phase [37].

The anti-inflammatory properties of the synthetic analogue of leu-enkephalin were confirmed in the works of Russian scientists (2020): on a model of acute respiratory distress syndrome in mice, its use significantly reduced mortality [38, 39].

In a series of experiments on rats, it was found that tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine (dalargin) improves collagen metabolism in liver and kidney tissues under conditions of repeated stress, and also enhances metabolic activity of the kidneys in experimental diabetes mellitus [40].

The stress-protective activity of the drug was demonstrated in several experimental and clinical studies. For example, a 28-day course of intranasal administration of hexapeptide (0.2 mg/kg) against the background of ulcerogenic stress led to normalization of the distribution index of medium-mass molecules in the blood serum of rats [41]. Normalization of the area of hepatocyte nucleoli and a decrease in the intensity of lipid peroxidation (LPO) were noted in the liver and blood serum of rats that underwent antenatal hypoxia and received intraperitoneal administration

ОБЗОР
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of an analogue of leu-enkephalin (100 μg/kg), which indicates pronounced antioxidant protection [42, 43]. In addition, in the work of N.A. Bebyakova et al. it was shown that against the background of acute stress, the administration of the peptide to rats caused a significant increase in the level of NO compared to the control (p < 0.001), which confirms its stress-limiting properties and interaction with endothelial factors [44].

Experimental data also indicate the participation of OPs in the neuroendocrine regulation of processes related to food intake and digestion. It turned out that enkephalins play an important role in the control of cognitive functions, such as learning and memory, as well as in the regulation of appetite, thirst and sexual behavior. According to the results of a comparative study by T.A. Czyzyk et al. (2012), conducted on mice receiving a high-calorie diet, it was found that the introduction of endogenous opioids contributes to an increase in energy metabolism and reduces the intensity of weight gain. In this regard, agonists of δ-opioid receptors can be characterized not only as agents capable of correcting eating behavior, but also eliminating metabolic disorders [45]. Of course, the data obtained during tests on animal models still need to be studied for use in clinical practice.

Clinical studies

The world's first peptide drug based on an analogue of leu-enkephalin — tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine (Tyr-D-Ala-Gly-Phe-Leu-Arg) — was developed in the USSR in 1983 in the laboratory of Professor M.I. Titov (All-Union Cardiology Research Center of the USSR Academy of Medical Sciences) [46]. Since its creation, it has found successful application in gastroenterology to stimulate tissue regeneration in gastric and duodenal ulcers, acute and chronic pancreatitis, as well as pancreonecrosis [46, 47]. In addition, the drug has been shown to correct disorders of lipoperoxide homeostasis in patients with erosive and ulcerative gastropathy [35].

In a study of Crohn's disease, the addition of tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine to standard 5-ASA therapy led to a significant improvement in histological and proliferative activity, as well as a decrease in the intensity of free radical oxidation compared to monotherapy [48].

The ability of the leu-enkephalin analogue to protect the body from the effects of stress factors has been shown in many studies. Its organoprotective properties are manifested by a decrease in the release of cortisol and catecholamines, the intensity of the LPO process, and a decrease in the formation of free radicals. All these processes reduce the harmful effects of free radicals on the lipids of cell membranes, contributing to effective protection of cells from damage caused by oxidative stress [46].

The effect of hexapeptide on carbohydrate metabolism was evaluated in a clinical study involving 123 patients (mean age 56.7 ± 5.1 years) with stable coronary heart disease (CHD) and metabolic syndrome. Of the 123 patients, 63 received standard CHD therapy (control group), and 60 patients in the main group were additionally prescribed tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine intranasally at a dose of 2 mg/day in courses of 10 days for 3 months.

As a result, patients receiving peptide therapy showed a significant decrease in initially elevated indicators: insulin level by 21.7 % (p < 0.001), C-peptide by 8.9% (p=0.017) and HOMA-IR index by 38.2 % (p < 0.001). No significant changes in carbohydrate metabolism were noted in the control group, while in the main group the positive effect persisted throughout the entire observation period.

Thus, intermittent intranasal administration of tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine in combination with standard therapy contributed to a decrease in hyperinsulinemia and insulin resistance in patients with CHD and metabolic syndrome, which confirmed its ability to correct carbohydrate metabolism disorders [49].

The ability of the synthetic analogue of leu-enkephalin to stabilize metabolic homeostasis by reducing oxidative stress and inhibiting pathological processes has also been demonstrated in liver diseases associated with toxic effects and metabolic disorders [50].

In cases accompanied by endothelial dysfunction (multiple organ failure syndrome, septic shock, ischemic stroke, myocardial infarction, ARDS), the peptide at a dose of 50–200 μg/kg (with intravenous administration) has been shown to inhibit the degradation of intercellular contacts of endothelial cells and prevent their apoptosis [51].

At the same time, the breakdown products of the drug can circulate in the blood for a long time, despite the fact that the half-life is on average 15 min. At the same time, endonasal administration of

peptide solutions entails direct penetration into the cerebrospinal fluid, bypassing the blood-brain barrier. Therefore, intranasal administration of tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate has been proven and is used to enhance the effect [52].

Therapy with hexapeptide diacetate has demonstrated significant efficacy in patients with COVID-19 complicated by moderate to severe ARDS. Against the background of treatment, a significant reduction in the frequency and duration of non-invasive ventilation (NIV) was noted. On the 6th day of therapy, the need for NIV was recorded 4.9 times less often (p = 0.020), and on the 7th day — 6.7 times less often (p = 0.013) compared with the control group.

In the main group receiving the leu-enkephalin analogue, positive dynamics according to CT studies were observed 3.2 times more often (p = 0.040) than in the control group. The data obtained indicate that the use of the drug affects the key pathogenetic mechanisms of ARDS development: it helps to reduce the area of lung tissue damage and increases the oxygenation index. These effects, most pronounced on the 4–7th day of therapy, probably caused positive clinical dynamics in patients [53].

Thus, the results of the pilot study demonstrated the high clinical efficacy of tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine diacetate for pathogenetic therapy of COVID-19.

As a result of the studies, pulmono-, cardio-, hepato-, gastro-, pancreato-, cerebroprotective, as well as antinociceptive effects have been proven. Further study of the role of neuropeptides and the opioid system proved to be promising for the development of new drugs based on synthetic OPs.

Studies of the leu-enkephalin analogue Ambervin® Pulmo during the COVID-19 pandemic

The long-term experience of successful use of tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine in various fields of medicine, supported by positive results of preclinical and clinical studies, became the basis for studying its organoprotective properties in the context of the COVID-19 pandemic. In this context, main attention was paid to the pulmonoprotective effect of this synthetic analogue of leu-enkephalin [54].

In 2021, the pharmaceutical company PROMOMED RUS developed the original medicine Ambervin® Pulmo, which for the first time implemented a rational combination of two biologically active compounds with proven efficacy — succinic acid salt and synthetic hexapeptide (tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine). The use of succinic acid (SA) in clinical practice dates back to 1972, when the Pharmcommittee of the Ministry of Health of the USSR issued a permit for its medical use. The ability of succinate to modulate energy metabolism due to participation in tissue respiration and oxidative phosphorylation processes, as well as to maintain ATP synthesis under hypoxia, underlies the wide therapeutic use of SA [55–58].

In the course of studies to assess the specific pharmacological activity of the Ambervin® Pulmo on the ARDS model with intravenous and combined intramuscular and inhalation administration to C57Bl mice, the pulmonoprotective effect was confirmed [59]. The results of determining the level of cytokines in the lung tissue showed a significant increase in the level of IL in the control group compared with other control groups, which indicates the development of a “cytokine storm” in animals of this group. The use of the Ambervin® Pulmo contributed to a significant (more than 2 times) decrease in the level of pro-inflammatory cytokines IL-1 and IL-6 in the lung tissue.

The results of histological analysis showed positive changes in the lung tissue with the introduction of the Ambervin® Pulmo, expressed in a moderate degree of interstitial edema, the absence of edematous fluid in the alveoli, bronchi and bronchioles.

Preclinical studies of tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine succinate demonstrated that intramuscular administration against the background of ARDS development reduced the area of spread of inflammatory infiltrate. Moreover, hexapeptide succinate almost 2 times more often increased the survival rate of animals compared with hexapeptide diacetate: the survival rate increased by 70 %, and in the comparison group — by 35 %.

Thus, as a result of experimental studies, it was shown that a pronounced anti-inflammatory effect with the introduction of tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine succinate is formed due to the suppression of the synthesis of one of the main pro-inflammatory mediators of the cytokine storm in the lungs — IL-6 and other pro-inflammatory cytokines (in particular IL-1β), and a simultaneous increase in the formation of the anti-inflammatory cytokine IL-10 [59]. It is possible that the effectiveness of tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine succinate

ОБЗОР
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is explained by the inclusion in the structure of the medicine, on the one hand, of a fragment of SA, which enhances its antioxidant properties, and on the other hand, of a δ-opioid receptor agonist hexapeptide, which suppresses the synthesis of pro-inflammatory cytokines in the lungs and inhibits the entry into the systemic circulation of one of the main mediators of the cytokine storm — IL-6.

A clinical study to assess the efficacy, safety and tolerability of intramuscular and inhalation use of hexapeptide succinate in complex therapy compared with standard therapy in patients with moderate COVID-19 was conducted on the basis of 10 research centers in Russia in 2022 and confirmed the results obtained at the preclinical stage [59].

Patients (*n* = 312) older than 18 years, hospitalized with moderate COVID-19, were randomized into 3 groups: the first received standard therapy in accordance with the current version of the Interim Guidelines of the Ministry of Health of Russia "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)" (hereinafter is Interim Guidelines) for 10 days; the second — hexapeptide succinate intramuscularly at 1 mg/day; the third — the same medicine by inhalation at 10 mg/day for 10 days. Therapy with hexapeptide succinate, both with intramuscular and inhalation administration, contributed to a reduction in the duration of the disease and the complete disappearance of symptoms of the disease in more than 80% of patients. The effectiveness of the medicine was also confirmed in comorbid patients. The use of the Ambervin® Pulmo was associated with the restoration of lung function, normalization of oxygenation, disappearance of shortness of breath, a decrease in the level of C-reactive protein below 10 mg/L and a reduction in the duration of symptoms compared with standard therapy.

There was also a decrease in indicators of inflammation (ESR, IL-6, d-dimer) and metabolic parameters (lactate, triglycerides). At the same time, there were no statistically significant differences in the frequency and nature of adverse events between the therapy groups [59].

Thus, the data obtained indicate that the use of tyrosyl-D-alanyl-glycyl-phenylalanyl-leucyl-arginine succinate in the complex therapy of COVID-19 in inhalation or intramuscular form in patients leads to a reduction in the duration and a decrease in the severity of symptoms of COVID-19. In addition to efficacy, the safety of hexapeptide succinate was shown, which confirms the feasibility of using the drug in schemes of pathogenetic therapy of COVID-19. In results the medicine was included in the Interim Guidelines [59].

Later, in a clinical study conducted by O.A. Radaeva et al. also studied the cytokine-mediated effects of Ambervin® Pulmo in the acute period of COVID-19 and in the convalescence period. Three groups of patients with COVID-19 were formed. In group 1 (*n* = 14), in addition to standard COVID-19 therapy, patients were injected intramuscularly with the medicine according to the scheme of 1 mg 1 per day for 10 days; group 2 (*n* = 13), in addition to standard COVID-19 therapy, received the Ambervin® Pulmo by inhalation at 10 mg 1 per day for 10 days; group 3 (*n* = 17) received standard therapy in accordance with the Interim Guidelines [60].

The reduction in the number of days of hospitalization in the groups receiving hexapeptide succinate and the increase in the level of IFN-β against the background of suppression of HMGB1 growth (a cytokine mediator associated with an unfavorable course of COVID-19) in the blood serum of patients with COVID-19 reflect positive dynamics, more pronounced with intramuscular administration of this analogue of leu-enkephalin [60].

It is known that a decrease in HMGB1 minimizes the risk of developing cardiovascular post-covid complications, while against the background of an increase in HMGB1, the synthesis of endothelial adhesion molecules increases and the barrier function of endothelial cells is impaired [39, 60]. A decrease in the level of HMGB1 is one of the most significant advantages of the drug based on hexapeptide succinate, which allows expanding the possibility of using this drug in the therapy of other diseases.

CONCLUSION

According to WHO experts, SARS-CoV-2 will continue to evolve, which will lead to the emergence of new variants of the virus with unpredictable properties. Despite previous immune experience (previous illness or vaccination), the risk of re-infection remains, including co-infection with various strains. In this regard, the search for new effective and safe pharmacological agents with anti-inflammatory and organoprotective activity remains relevant.

The organoprotective effect of hexapeptide

succinate established in preclinical and clinical studies, as well as its ability to correct disorders of antiviral immunity, allow us to consider OPs as promising compounds for the treatment of respiratory infections of the upper and lower respiratory tract of various etiologies (ARVI, pneumonia), post-infectious conditions (including post-covid syndrome) and other diseases of various etiologies. The prospects for their study are additionally confirmed by the involvement of OPs in the pathogenesis of a wide range of conditions — from mental (schizophrenia, addiction) and metabolic (obesity) disorders to somatic pathology, which opens up opportunities for the development of new therapeutic strategies in various fields of medicine. Thus, the creation of drugs based on regulatory peptides with a wide range of pharmacological activity is one of the most promising areas of pharmacology.

The pharmacological profile of hexapeptide succinate, including its clinical efficacy and safety, is confirmed by experimental and clinical studies. The combination of succinate with OP modulates the immune response, affecting the activity of macrophages and suppressing the production of pro-inflammatory cytokines. This manifestation enhances the anti-inflammatory activity of the compound and opens up prospects for its use in diseases such as rheumatoid arthritis and inflammatory bowel diseases.

In addition, succinate in the composition of the drug improves energy metabolism in neurons and provides protection against oxidative stress, which underlies the observed neuroprotective effects, including reducing anxiety and improving emotional state. Further controlled clinical trials are needed to confirm efficacy in neurodegenerative diseases, depression, chronic neuropathic pain, and cognitive impairment.

The synthetic analogue of leu-enkephalin-leucyl-arginine succinate also demonstrates a vasoprotective effect, which is realized through a decrease in the permeability of the vascular wall, normalization of microcirculation and stimulation of reparative processes in damaged tissues. The cardio- and pulmonoprotective properties of the compound allow us to consider it as a promising component of complex therapy of cardiovascular diseases and pneumonia of various etiologies, especially community-acquired.

The analysis revealed a number of limitations associated with the insufficient study of the molecular mechanisms of action of leu-enkephalin analogues, in particular, their selectivity for subtypes of δ-opioid receptors. In addition, there are no data on long-term follow-up of patients, which requires further research with a well-designed design and long-term monitoring of efficacy and safety.

Despite these limitations, the presented data demonstrate a favorable safety profile, proven efficacy and a wider therapeutic potential of hexapeptide succinate compared to the precursor drug. Promising directions for further research include a detailed study of its pharmacodynamics, expansion of indications for use and optimization of dosing regimens for the treatment of various diseases, primarily respiratory, especially community-acquired pneumonia.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. BMJ. 2021;374:n1648. DOI: 10.1136/bmj.n1648. Erratum in: BMJ. 2021;374:n1944. DOI: 10.1136/bmj.n1944
2. Chen R, Lan Z, Ye J, Pang L, Liu Y, Wu W, Qin X., Guo Y, Zhang P. Cytokine storm: the primary determinant for the pathophysiological evolution of COVID-19 deterioration. Front Immunol. 2021;12:589095. DOI: 10.3389/fimmu.2021.589095
3. Osuchowski MF, Winkler MS, Skirecki T, Cajander S, Shankar-Hari M, Lachmann G, Monneret G, Venet F, Bauer M, Brunkhorst FM, Weis S, Garcia-Salido A, Kox M, Cavaillon JM, Uhle F, Weigand MA, Flohé SB, Wiersinga WJ, Almansa R, de la Fuente A, Martin-Loeches I, Meisel C, Spinetti T, Schefold JC, Cilloniz C, Torres A, Giamarellos-Bourboulis EJ, Ferrer R, Girardis M, Cossarizza A, Netea MG, van der Poll T, Bermejo-Martín JF, Rubio I. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med. 2021;9(6):622–642. DOI: 10.1016/S2213-2600(21)00218-6
4. Carr R, Frings S. Neuropeptides in sensory signal processing. Cell and Tissue Research. 2019;375(1):217–25. DOI: 10.1007/s00441-018-2946-3
5. Zöllner C, Stein C. Opioids. Handb Exp Pharmacol. 2007;(177):31–63. DOI: 10.1007/978-3-540-33823-9_2
6. Toubia T, Khalife T. The Endogenous Opioid System: Role and Dysfunction Caused by Opioid Therapy. Clin Obstet Gynecol. 2019;62(1):3–10. DOI: 10.1097/GRF.0000000000000409
7. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther. 1976;197(3):517–32.
8. Lord JA, Waterfield AA, Hughes J, Kosterlitz HW. Endogenous opioid peptides: multiple agonists and receptors. Nature. 1977;267(5611):495–9. DOI: 10.1038/267495a0
9. Dietis N, Rowbotham DJ, Lambert DG. Opioid receptor subtypes: fact or artifact? Br J Anaesth. 2011;107(1):8–18. DOI: 10.1093/bja/aer115
10. Bunzow JR, Saez C, Mortrud M, Bouvier C, Williams JT, Low M, Grandy DK. Molecular cloning and tissue distribution of a putative member of the rat opioid receptor gene family that is not a mu, delta or kappa opioid receptor type. FEBS Lett. 1994;347(2–3):284–8. DOI: 10.1016/0014-5793(94)00561-3
11. Meunier JC, Mollereau C, Toll L, Suaudeau C, Moisand C, Alvinerie P, Butour JL, Guillemot JC, Ferrara P, Monsarrat B, et al. Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. Nature. 1995;377(6549):532–5. DOI: 10.1038/377532a0
12. Reinscheid RK, Nothacker HP, Bourson A, Ardati A, Henningsen RA, Bunzow JR, Grandy DK, Langen H, Monsma FJ Jr, Civelli O. Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor. Science. 1995;270(5237):792–4. DOI: 10.1126/science.270.5237.792
13. Shenoy SS, Lui F. Biochemistry, Endogenous Opioids. 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
14. Stein C. Opioid Receptors. Annu Rev Med. 2016;67:433–51. DOI: 10.1146/annurev-med-062613-093100
15. Corder G, Castro DC, Bruchas MR, Scherrer G. Endogenous and Exogenous Opioids in Pain. Annu Rev Neurosci. 2018;41:453–473. DOI: 10.1146/annurev-neuro-080317-061522
16. Peng J, Sarkar S, Chang SL. Opioid receptor expression in human brain and peripheral tissues using absolute quantitative real-time RT-PCR. Drug Alcohol Depend. 2012;124(3):223–8. DOI: 10.1016/j.drugalcdep.2012.01.013
17. Sergalieva MU, Tsibizova AA, Krintsova TA, Samotrueva MA. Opioid peptides: physiological role, molecular mechanisms and pharmacological activity. Russian Journal of Pain. 2023;21(3):43–49. DOI: 10.17116/pain20232103143
18. Shang Y, Filizola M. Opioid receptors: Structural and mechanistic insights into pharmacology and signaling. Eur J Pharmacol. 2015;763(Pt B):206–13. DOI: 10.1016/j.ejphar.2015.05.012
19. Kaserer T, Lantero A, Schmidhammer H, Spetea M, Schuster D. μ Opioid receptor: novel antagonists and structural modeling. Sci Rep. 2016;6:21548. DOI: 10.1038/srep21548
20. Bodnar RJ. Endogenous opiates and behavior: 2014. Peptides. 2016;75:18–70. DOI: 10.1016/j.peptides.2015.10.009
21. Pinaeva OG, Sazonova EN, Lebedko OA. Correction of the negative effect of antenatal hypoxia on liver tissue homeostasis in newborn albino rats with opioid peptides. Bull Exp Biol Med. 2016;162:203–206. DOI: 10.1007/s10517-016-3576-y
22. Dhaliwal A, Gupta M. Physiology, Opioid Receptor. 2023 Jul 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
23. Husain S. Delta Opioids: Neuroprotective Roles in Preclinical Studies. J Ocul Pharmacol Ther. 2018;34(1-2):119–128. DOI: 10.1089/jop.2017.0039
24. Chao D, Xia Y. Ionic storm in hypoxic/ischemic stress: can opioid receptors subside it? Prog Neurobiol. 2010;90(4):439–70. DOI: 10.1016/j.pneurobio.2009.12.007
25. Pattinson KT. Opioids and the control of respiration. Br J Anaesth. 2008;100(6):747–58. DOI: 10.1093/bja/aen094
26. van den Brink OW, Delbridge LM, Rosenfeldt FL, Penny D, Esmore DS, Quick D, Kaye DM, Pepe S. Endogenous cardiac opioids: enkephalins in adaptation and protection of the heart. Heart Lung Circ. 2003;12(3):178–87. DOI: 10.1046/j.1444-2892.2003.00240.x
27. Tyagi A, Daliri EBM, Kwami Ofosu F, Yeon SJ, Oh DH. Opioid peptides of food origin in human health: A review. Int J Mol Sci. 2020;21(22):8825. DOI: 10.3390/ijms21228825
28. Garg S, Nurgali K, Mishra VK. Food Proteins as Source of Opioid Peptides-A Review. Curr Med Chem. 2016;23(9):893–910. DOI: 10.2174/0929867323666160219115226
29. Plein LM, Rittner HL. Opioids and the immune system - friend or foe. Br J Pharmacol. 2018;175(14):2717–2725. DOI: 10.1111/bph.13750
30. Tian J, Jiao X, Wang X, Geng J, Wang R, Liu N, Gao X, Griffin N, Shan F. Novel effect of methionine enkephalin against influenza A virus infection through inhibiting TLR7-MyD88-TRAF6-NF-κB p65 signaling pathway. Int Immunopharmacol. 2018;55:38–48. DOI: 10.1016/j.intimp.2017.12.001

31. Gein SV, Tendryakova SP. Agonists of μ- and δ-opioid receptors in the regulation of IL-2, IL-4, and IFN-γ production by peripheral blood cells in vitro. Human Physiology. 2015;41(3):323–7. DOI: 10.1134/S0362119715030056

32. Karkischenko VN, Pomytkin IA, Skvortsova VI. The Opioidergic System of Immune Cells: A New Pharmacological Target in the Therapy of "Cytokine Storm". Journal Biomed. 2020;16(4):14–23. DOI: 10.33647/2074-5982-16-4-14-23

33. Zhang Y, Wang R, Shi W, Zheng Z, Wang X, Li C, Zhang S, Zhang P. Antiviral effect of fufang yinhua jiedu (FFYH) granules against influenza A virus through regulating the inflammatory responses by TLR7/MyD88 signaling pathway // J Ethnopharmacol. 2021;275:114063. DOI: 10.1016/j.jep.2021.114063

34. Gein SV, Kadochnikova YaA. Endomorphin-1 affecting innate immune cells *in vitro*. Russian Journal of Immunology. 2020;23(2):119–124. DOI: 10.46235/1028-7221-371-EAI

35. Coccia R, Foppoli C, Blarzino C, De Marco C, Rosei MA. Interaction of enkephalin derivatives with reactive oxygen species. Biochim Biophys Acta. 2001;1525(1-2):43–9. DOI: 10.1016/s0304-4165(00)00169-0

36. Gein SV, Gen SV, Baeva TA. Endomorphins: structure, localization, immunoregulatory activity. Problems of Endocrinology. 2020;66(1):78–86. DOI: 10.14341/probl10364

37. Tang CW, Feng WM, Du HM, Bao Y, Zhu M. Delayed administration of D-Ala2-D-Leu5-enkephalin, a delta-opioid receptor agonist, improves survival in a rat model of sepsis // Tohoku J Exp Med. 2011;224(1):69–76. DOI: DOI: 10.1620/tjem.224.69

38. Karkischenko VN, Pomytkin IA, Gasanov MT, Nesterov MS, Fokin YuV, Taboyakova LA, Alimkina OV, Khvostov DV. Prophylactic and Therapeutic Administration of Leutragin Increases the Survival Rate of Animals in a Model of Fatal Acute Respiratory Distress Syndrome. Journal Biomed. 2020;16(4):44–51. DOI: 10.33647/2074-5982-16-4-44-51

39. Karkischenko VN, Pomytkin IA, Petrova NV, Nesterov MS, Ageldinov RA, Zotova LV, Koloskova EM, Slobodenyuk VV, Skvortsova VI. Leutragin Inhibits Expression of Cytokines, Including Interleukin-6, in a "Cytokine Storm" Model in C57BL/6Y Mice with Induced Acute Respiratory Distress Syndrome. Journal Biomed. 2020;16(4):34–43. DOI: 10.33647/2074-5982-16-4-34-43

40. Perevedentseva SE, Savinova NV, Trofimova SR. The effect of dalargin on the parameters of collagen metabolism in tissues of rats under the action of repeated stress. Health, demography, ecology of the Finno-Ugric peoples. 2022;2:54–8. EDN: MXAFIW

41. Usenko OYu, Petrushenko VV, Savolyuk SI, Radyoga YaV, Grebenyuk DI. Experimental estimation of the local application efficacy of biological stimulator for the soft tissues reparation in treatment of chronic gastric ulcers. Klin Khir. 2016;9:62–5.

42. Pinaeva OG, Lebed'ko OA, Pinaev SK, Sazonova EN. Hepatoprotective Effect of Neonatal Administration of Non-Opioid Leu-Enkephalin Analogue in Adult Albino Rats Subjected to Antenatal Hypoxia. Bull Exp Biol Med. 2019;167(4):428–31. DOI: 10.1007/s10517-019-04542-9

43. Pinaeva OG, Lebedko OA, Pinaev SK, Sazonova EN. The effect of neonatal administration of dalargin on morphometric indexes of hepatocytes and free radicals oxidation in albino rats exposed to hypoxia. Far East Medical Journal. 2017;(3):67–71. EDN: ZIGBOF

44. Bebyakova NA, Levitsky SN, Khromova AV, Shabalina IA, Komandresova TM. Cardio-vascular effects of dalargin in conditions of acute stress. International Research Journal. 2014;(8(27)):34–6. EDN: SMYZMD

45. Czyzyk TA, Romero-Picó A, Pintar J, McKinzie JH, Tschöp MH, Statnick MA, Nogueiras R. Mice lacking δ-opioid receptors resist the development of diet-induced obesity. FASEB J. 2012;26(8):3483–92. DOI: 10.1096/fj.12-208041

46. Bulgakov SA. Hexapeptide dalargin in clinical gastroenterology: 30 years' of clinical application of the drug. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2016;26(3):103–12. DOI: 10.22416/1382-4376-2016-26-3-103-112

47. Alekseenko SA, Timoshin SS, Bolonyaeva NA, Ozhegov EV, Zhivotova EY, Fleischman MY, Zhavnenko MY. Influence of dalargin on reparative ability of the gastrointestinal mucosa in various gastroenterological diseases. Far East Medical Journal. 2010;(3):24–8. EDN: NPFWDL

48. Bolonaeva NA, Ghivotova EU, Fleishman MU, Isaenko LP, Sazonova EN, Alexeenko SA, Timoshin SS. Dalargin in nsaid-gastropathy prophylactic and treatment measures. Far East Medical Journal. 2005;(2):28–30. EDN: RXGIOV

49. Dontsov A.V. Influence of dalargin on carbohydrate metabolism in coronary heart disease patients with metabolic syndrome. People and Health. 2016;(1):21–5. EDN: VSZEFV

50. Grebenchikov OA, Ovezov AM, Skripkin YuV, Zabelina TS, Ulitkina ON, Lugovoy AV, Prikhodko AS, Ryzhkov AYu, Zinovkin RA. Synthetic Analogue of Leu-Enkephalin Prevents Endothelial Dysfunction *in vitro*. General Reanimatology. 2018;14(2):60–68. DOI: 10.15360/1813-9779-2018-2-60-68

51. Moisieieva N, Gulevskyy O, Gorina O. Effect of Leu-Enkephalin (Dalargin) on Apoptosis and Necrosis of Leukocytes After Cold Stress. Problems of Cryobiology and Cryomedicine. 2022;32(1):14–23. DOI: 10.15407/cryo29.03.246

52. Glazunova IB, Silina LV, Bobyntsev II. Influence of dalargin on efficiency of atopic dermatitis therapy. People and Health. 2008;(3):22–6. EDN: JVIGDR

53. Magomedov MA, Burda NG, Misikov ZF, Ryzhkov AYu, Antonova VV, Cherpakov RA. Synthetic Analogue of Leu-Enkephalin in COVID-19 (a Prospective Clinical Study). General Reanimatology. 2022;18(4):11–9. DOI: 10.15360/1813-9779-2022-4-11-19

54. Bebyakova NA, Levitsky SN, Shabalina IA. Influence of structural modification of dalargin molecule on peptide vasoactive effect in acute stress. Fundamental research. 2011;12(4):704–7. EDN: OULAOZ

55. Pizova NV. Succinic acid derivatives in therapy for cerebrovascular disease. Neurology, Neuropsychiatry, Psychosomatics. 2010;2(1):67–8. DOI: 10.14412/2074-2711-2010-74

56. Privalov AA, Kholmanskikh NV, Obukhov NG. Use of reamberin in treatment of patients with the disorders of cerebral circulation of ischemic type. Herald of North-Western State Medical University named after II Mechnikov. 2006;7(1):102–5. EDN: NTJNXR

57. Spichak II, Kopytova EV. Application of polyionic

reamberin solution in medicine and experience with its use in pediatric oncology. P.A. Herzen Journal of Oncology. 2018;7(5):47–55. DOI: 10.17116/onkolog2018705147

58. Alasheev AM, Lantsova EV. Efficacy of Mexidol in combination with cerebral revascularization in the treatment of ischemic stroke. S.S. Korsakov Journal of Neurology and Psychiatry. 2024;124(3-2):67–74. DOI: 10.17116/jnevro202412403267

59. Balykova LA, Radaeva OA, Zaslavskaya KYa, Bely PA, Pavelkina VF, Pyataev NA, Ivanova AYu, Rodoman GV, Kostina NE, Filimonov VB, Simakina EN, Bystritsky DA, Agafyina AS, Koryanova KN, Pushkar DYu. Efficacy and safety of original drug based on hexapeptide succinate in complex COVID-19 therapy in adults hospitalized patients. Pharmacy & Pharmacology. 2022;10(6):573–88. DOI: 10.19163/2307-9266-2022-10-6-573-588

60. Radaeva OA, Balykova LA, Pyataev NA, Zaslavskaya KYa, Kostina YuA, Eremeev VV,Taganov AV, Belyy PA. Features of cytokine status dynamics in patients with COVID-19 using Ambervin® Pulmo. Infectious Diseases: News, Opinions, Training. 2023;12(4):17–24. DOI: 10.33029/2305-3496-2023-12-4-17-24

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