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THE USE OF PERSONALIZED PHARMABIOTICS AS AN APPROACH TO THE REHABILITATION OF POST-COVID PATIENTS

Successful application of defined pro- and/prebiotic preparations for the prevention and treatment of viral respiratory infections is confirmed by meta-analyses and numerous clinical trials. To date, the protocols for the rehabilitation of patients with post-COVID conditions, an integral part of which is the restoration of the balance of gut microbiota along with nutritional supporty, are widely developed and accepted. ***Purpose.*** *To investigate the efficacy of individually prescribed pharmabiotics for targeted correction of the nasal and gut microbiota of post-COVID-19 patients in combination with aerosol inhalations.* ***Methods.*** *The post-COVID-19 patients were referred to recover using the rehabilitation facilities. In addition to the basic treatment complex, the patients were offered haloaerosol therapy with an additional prescription of individually selected pharmabiotics.* ***Results.*** *The use of individually prescribed pharmabiotics in combination with aerosol inhalation enabled therestoration of Lactobacillus spp. balance and reduction in the number of opportunistic microbiota in the gut. Thus, the personalized rehabilitation approach led to significantly improved local immune response in post-COVID-19 patients.* ***Conclusions.*** *The data obtained provide supportive evidence of the efficacy of aerosol inhalations and personalized pharmabiotics Lactobacillus rhamnosus S25 and L. plantarum A combined application in the directed modulation of the microbiome and targeted correction of local immunity in post-COVID patients. Restoring the balance of the patient's' oral and gut microbiota should be an integral part of the post-COVID patient's rehabilitation.*

Keywords*: COVID-19, post-COVID rehabilitation, gut-lung axis, pharmabiotics.*

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COVID-19 is a potentially severe acute respiratory infection caused by the SARS-CoV-2 coronavirus. To date, there is no reliable data on the pathogenesis of COVID-19. Scientists believe that the virus enters the cell by binding to angiotensin-converting enzyme 2 (ACE2) receptors, which the virus uses as an «entry gate» (de Oliveira et al., 2021; Troisi et al., 2021). Rather than being limited to the lower respiratory tract, severe acute respiratory syndrome infection caused by SARS-CoV-2 has been proven to spread to other organs, namely the gastrointestinal tract (multi-tissue infection). In particular, some manifestations of SARS-CoV-2 infection, such as the ability of SARS-CoV-2 to infect and replicate in small human intestinal enterocytes, detection of viral RNA in fecal samples and the changed composition of the gut microbiota under SARS-CoV-2, indicate significant damage to the gastrointestinal tract during the disease (de Oliveira et al., 2021; Troisi et al., 2021; Lamers et al., 2020). Host-microbiota interactions are bidirectional, complex, and potentially modulate the development and functioning of the innate and adaptive immune systems. Signals from the gut microbiota can tune immune-mediated cells to pro-inflammatory (T helper cells type 17; Th17) and anti-inflammatory (regulatory T cells; Tregs) responses, determining susceptibility to various diseases. There is a lot of data indicating that the composition of intestinal microbiota is directly related to disease severity and concentration of cytokines and inflammatory markers in plasma. Moreover, the composition of gut microbiota of recovered patients remains significantly altered compared to people who were not infected with SARS-CoV-2, which may influence the development of the post-COVID syndrome (Yeoh et al., 2021). For example, the studies conducted by a group of scientists from China demonstrate that intestinal microbiota in patients with COVID-19 is characterized by an increase in the number of *Streptococcus*, *Clostridium*, *Lactobacillus*, and *Bifidobacterium* and a decrease in the number of *Bacteroidetes*, *Roseburia*, *Faecalibacterium*, *Coprococcus,* and *Parabacteroides* compared to patients with seasonal flu and healthy people (Ferreira et al., 2020). Thus, it is most likely that a healthy gut microbiota, which protects the lungs and vital organs from an exaggerated immune response, can counteract the coronavirus infection.

In 2001, a joint consultation of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) experts agreed on a specific definition of probiotics as «live microorganisms that when administered in adequate amounts confer a health benefit on the host.»

Over the past few decades, greater research of the gut-brain-, gut-lung- and gut-liver-axes has expanded our understanding of the microbiome and fostered to the advancement of pharmabiotics. Pharmabiotics refer to live microbes administered to patients to treat a disease. Pharmabiotics differ from prebiotic and probiotic products as they are validated through clinical trials with safety and efficacy endpoints for a given indication and follow the same regulatory pathway to approval as other novel drugs (LeBegue et al., 2020).

In addition, with the development of predictive, preventive, and personalized medicine (P3 medicine), personalized pharmabiotics began to be used. The term «personalized pharmabiotics» means that pharmabiotics are personally (individually) selected for a given patient based on the state of his/her microbiota.

The number of studies assessing the impact of pro- and prebiotics use on–frequency, duration, and severity of viral respiratory infections in humans is significantly increasing. The potential of probiotics use is supported by experimental studies, meta-analyses, and clinical trials on other coronaviruses and such viruses as influenza viruses, rhinoviruses, and respiratory syncytial virus (Waki et al., 2014; Luoto et al., 2014; Turner et al., 2017; Kumar et al., 2010; Liu et al., 2020; Wang et al., 2019). Probiotics such as *Lactobacillus* and *Bifidobacterium* have been proven to restore human health by eliminating patho-

genic microorganisms and regulating immune responses in intestinal epithelial cells (Kurian et al., 2021). Finally, although the mechanisms involved in SARS-CoV-2 infection are not yet fully understood, there is research evidence that directly links gut microbiota to COVID-19, confirming the likely role of probiotics in both the prevention and treatment of COVID-19 (Zuo et al., 2020; Liu et al., 2021; Yeoh et al., 2021; Gou et al., 2020; Mańkowska-Wierzbicka et al., 2023).

According to medical statistics, contracting COVID-19 often results in a number of specific problems in various body systems. Hence, complex rehabilitation following coronavirus infection should include a whole set of measures.

Recently, in addition to the terms «post-COVID syndrome» and «chronic COVID-19,» a new definition has appeared in the foreign medical literature — «long COVID». People unable to get rid of the coronavirus infection consequences for a long time are called «long haulers» in medical slang.

Since the virus causes systemic disorders in the body, it is absolutely necessary to not only treat patients correctly but also manage the imbalance that occurs after the illness. Restorative therapy is needed to alleviate the post-COVID syndrome and eventual recovery, as dysbiotic gut microbiome may in turn contribute to immune and health-related problems after COVID-19. Everyone needs recovery after a coronavirus infection, regardless of the severity of the disease. However, the scope of restorative and rehabilitation programs should rely on an individual approach to each patient. Now, most countries across the world offer protocols for the rehabilitation of patients with post-COVID conditions including restoration gastrointestinal tract (GIT) microbiota' balance and patient nutritional support (Ferreira et al., 2020; Zuo et al., 2020). However, in Ukraine, this issue remains open and therefore extremely relevant.

The **purpose** of our work was to investigate the possibility of using personalized pharmabiotics for targeted correction of the microbiota of postcovid-19 patients in combination with aerosol inhalations.

Materials and Methods. A total of 100 people who had contracted COVID-19 and treated at the State Institution «Rehabilitation Scientific and Practical Medical Center of the Ministry of Health of Ukraine» took part in the study. All patients signed the «Informed Consent of the Study Participant». During the performance of the scientific research submitted for examination, compliance with safety rules was ensured by the principles of the Declaration of Helsinki, adopted by the General Assembly of the World Medical Association (1964—2016), the Council of Europe Convention on Human Rights and Biomedicine (1997), the European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes (1986), the relevant provisions of the WHO, the International Council of Medical Scientific Societies, the International Code of Medical Ethics (1983) and the relevant laws of Ukraine (The Ethics Committee of the State Higher Educational Establishment «Uzhhorod National University») approved the study protocol No. 9/7 on 07/06/20223).

Taking into account the peculiarities of the convalescence period, apart from the basic treatment complex, patients were also offered haloaerosol therapy (HAT) with additional prescription of individually selected pharmabiotics.

All clinical bacterial strains used in this study are preserved in the collection of microorganisms at the Research Development and the Educational Center of Molecular Microbiology and Mucosal Immunology at the Uzhhorod National University.

The basic treatment complex included methods of equipment-based physiotherapy and the necessary medical treatment:

- singlet oxygen therapy;
- electrophoresis with a solution of heparin or lidase on the rib cage;

- individual inhalations according to indications (broncholytics, dekasan, phytoncides);
- aeroionotherapy;
- other physiotherapeutic procedures as indicated;
- chest massage as indicated;
- exercise therapy.

The treatment course lasted 21 days.

After completing the treatment course, patients were additionally prescribed individually selected pharmabiotics. The course of pharmabiotics lasted seven days. All the patients gave informed consent.

The intensity of the local immunity of mucous membranes (oral and intestinal), including specific antibodies to COVID-19, secretory immunoglobulin A, and inflammatory and anti-inflammatory cytokines, was studied in patients. Personalized pharmabiotics were selected after gut and upper respiratory tract microbiota studies in order to modulate microbiota and directly correct local immunity.

Quantitative analysis of microbiota was conducted using the routine cultural method.

Saliva samples diluted in 0.9% sodium chloride and faecal samples in MRS broth after serial dilutions were plated at the amount of 10 μL of each dilution (10^1, 10^2, 10^4, 10^6, 10^8, 10^{10}) on appropriate nutrient media, in particular MRS agar, Bifidobacterium agar, meat-peptone agar (MPA), 5% blood agar (BA), Sabouraud medium, Endo medium, Bile medium, Strepto medium, Clostridial agar, and selective staphylococcal medium with mannitol. All dishes were incubated for 24—48 hours at 37±1 °C under appropriate cultivation conditions (aerobic and anaerobic).

Morphological and tinctorial properties of microorganisms were determined using the Gram method by digitizing the swab.

The state of the upper respiratory tract (URT) and gastro-intestinal tract (GIT) mucous membranes microbiocenosis of the patients was evaluated using the persistence index (C%) and the frequency index (Pi):

$$C\% = p/P \times 100,$$

where *C%* is the persistence index; *p* is the number of samples containing the tested strain of bacteria; *P* is the total number of samples that contain all isolated strains of bacteria.

$$Pi = A/B,$$

where *A* is the number of species strains; *B* is the total number of strains.

Immune parameters including IgA, IL-6, and TNF-ά were measured using an immunosorbent system Labor Diagnostika Nord (Germany) according to the manufacturer's instructions.

For microbiome modulation of local immunity in post-COVID patients, a personalized selection of pharmabiotics was conducted. Deposited, authorial strains of lactobacilli, namely *Lactobacillus bulgaricus* S6, *L. delbrueckii* subsp. *bulgaricus* S19, *L. rhamnosus* S25, *L. plantarum* A, *L. bulgaricus* A6, and *L. bulgaricus* A 22 were selected as pharmabiotics based on their biological properties. These strains were isolated from traditional dairy products and endemic plants in high mountain, ecologically clean areas of the Rhodope Mountains in Bulgaria (Ilyazova et al., 2022).

Personalized selection of pharmabiotics was carried out by co-cultivation of isolated from post-COVID patient's microorganisms and strains of probiotic lactic acid bacteria. Co-cultivation was conducted in 96 well polystyrene microplates. 100 μL of isolated microorganisms' suspension was plated into the wells and 100 μL of probiotic cultures suspension was added. Suspensions were prepared in meat-peptone broth (MPB) (isolated microorganisms) and MRS broth (probiotic cultures) with a McFarland turbidity of 0.5 using an electronic device Densi-La-Meter (PLIVA-Lachema Diagnostika, Czech Republic), which corresponds to the concentration of $1.5 \cdot 10^8$ CFU/mL. Microplates with suspensions were incubated at 37 ± 1°C for 24 hours. After that, aliquots of 10 μL were plated

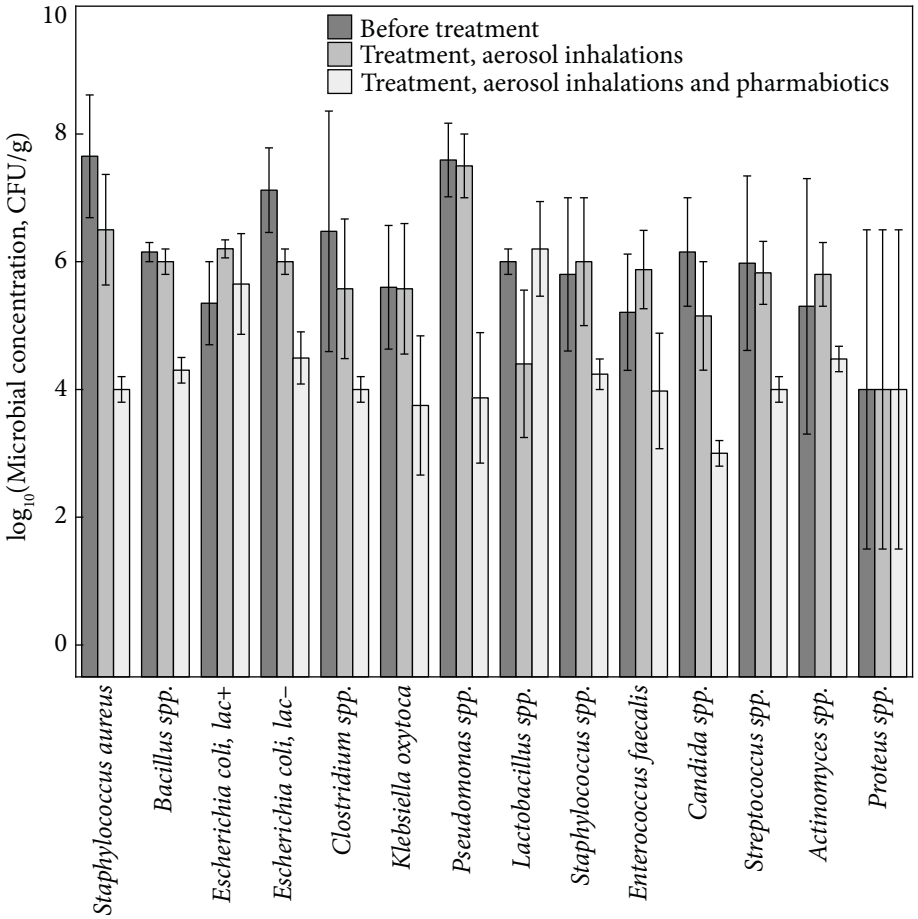

Fig. 1. The composition of the intestinal microbiota of post-COVID patients before and after the treatment

on appropriate agarized nutrient media using the streak culture method and incubated for 24 hours at 37 ± 1°C. Evaluation of the antagonistic properties of the above-mentioned lactobacilli strains in relation to isolated opportunistic microorganisms was carried out.

The study of microbiota state and intensity of mucous membranes (URT, GIT) local immunity was conducted in three stages:

1 — during rehabilitation;

2 — after the treatment complex before taking pharmabiotics;

3 — after taking pharmabiotics.

The basic statistical analysis of the data was conducted applying the well-known methods of descriptive statistics and statistical inference, using the Anaconda — Python environment and the OriginPro software package of OriginLab for numerical data analysis. Data correlation analysis and methods of comparison of two or more dependent or independent groups of data using the Mann-Whitney, Wilcoxon, and Kruskel-Wallis criteria were applied. The results were considered statistically significant at $p<0.05$ level.

Results. ***Personalized selection of pharmabiotics***. The results of individual selection of pharmabiotics indicated that of six lactobacilli only two strains, namely *L. rhamnosus* S25 and *L. plantarum* A, were the most effective for target microbiome modulation. Therefore, taking into account individual (personal) state of microbiota, the course of pharmabiotics for post-COVID patients included taking *L. rhamnosus* S25 or/and *L. plantarum* A strains.

Study of intestinal microbiota. In patients who had contracted COVID-19, the key intestinal microbiome representatives, namely *Staphylococcus* spp. (including *S. aureus*), *Streptococcus* spp., *Candida* spp., *Enterococcus faecalis*, and *Actinomyces* spp. were revealed in increased quantities compared to the reference levels (Fig. 1). The strains of *Escherichia coli* were identified in significantly lower amount (5.3 ± 0.8 $\log_{10}$ CFU/mL) compared to the normal level (10^7—10^8 CFU/mL). A decrease in the number of typical *Escherichia coli* down to 10^5—10^6 CFU/mL or an increase to 10^9—10^{10} CFU/mL is considered the first stage of microbiological disorders. At the same time, there was a significant decrease in the number of *Lactobacillus* spp. (5.9 ± 2.9 $\log_{10}$ CFU/g) compared to the reference levels (10^6—10^8 CFU/mL). The number of *Bifidobacterium* spp. was even lower than the detection limit.

As for the state of GIT mucous membranes microbiocenosis of the patients, the highest values of detection frequency indicators and persistence index were demonstrated by *Staphylococcus* spp. (C% — 100%; Pi — 0.18) (Table 1). The lowest rates of persistence and detection frequency were characteristic of *Proteus* spp. representatives (C% — 20%; Pi — 0.05). *Lactobacillus* spp. had a high detection frequency, but their persistence index was low (C% — 100%; Pi — 0.09). For *E. coli lac+,* the detection frequency was 80% and persistence index was 0.07.

After aerosol inhalations and the use of personalized pharmabiotics, the species composition of gut microbiota remained practically unchanged. However, the use of personalized pharmabiotics made it possible to restore the balance of *Lactobacillus* spp. (6.2 ± 2.9 $\log_{10}$ CFU/g) and reduce the number of key opportunistic microbiota representatives to normal values (Fig. 1).

Detection frequency indicators of *Lactobacillus* spp. and *E. coli lac+* increased to 0.13 and 0.09 compared to the data obtained before the therapy (Table 1).

Study of oral microbiota. The oral microbiota of the post-COVID patients was represented by the excessive number of key microorganisms such as *Staphylococcus* spp. (including *S. aureus*), *Clostridium* spp., *Actinomyces* spp., *Streptococcus* spp., and *Candida* spp. (Fig. 2). After the use of aerosol inhalations, the number of these condi-

Table 1. **Persistence index and frequency index of intestinal microbiota representatives**

Microorganisms	Persistence index (C%)			Frequency index (Pi)		
	Before treatment	Treatment, HAT	Treatment, HAT & pharm.	Before treatment	Treatment, HAT	Treatment, HAT & pharm.
Staphylococcus spp.	100	100	100	0.18	0.17	0.11
Lactobacillus spp.	100	100	100	0.09	0.09	0.13
Streptococcus spp.	80	80	70	0.14	0.12	0.10
Enterococcus faecalis	80	80	80	0.09	0.09	0.10
Escherichia coli, lac+	80	80	85	0.07	0.07	0.09
Escherichia coli, lac-	60	60	60	0.08	0.08	0.06
Clostridium spp.	80	80	80	0.07	0.06	0.01
Candida spp.	40	40	25	0.03	0.03	0.02
Actinomyces spp.	40	40	20	0.03	0.03	0.01
Klebsiella oxytoca	80	80	60	0.06	0.06	0.05
Bacillus spp.	40	40	40	0.06	0.05	0.02
Pseudomonas spp.	60	60	40	0.06	0.06	0.03
Proteus spp.	20	20	10	0.05	0.05	0.02

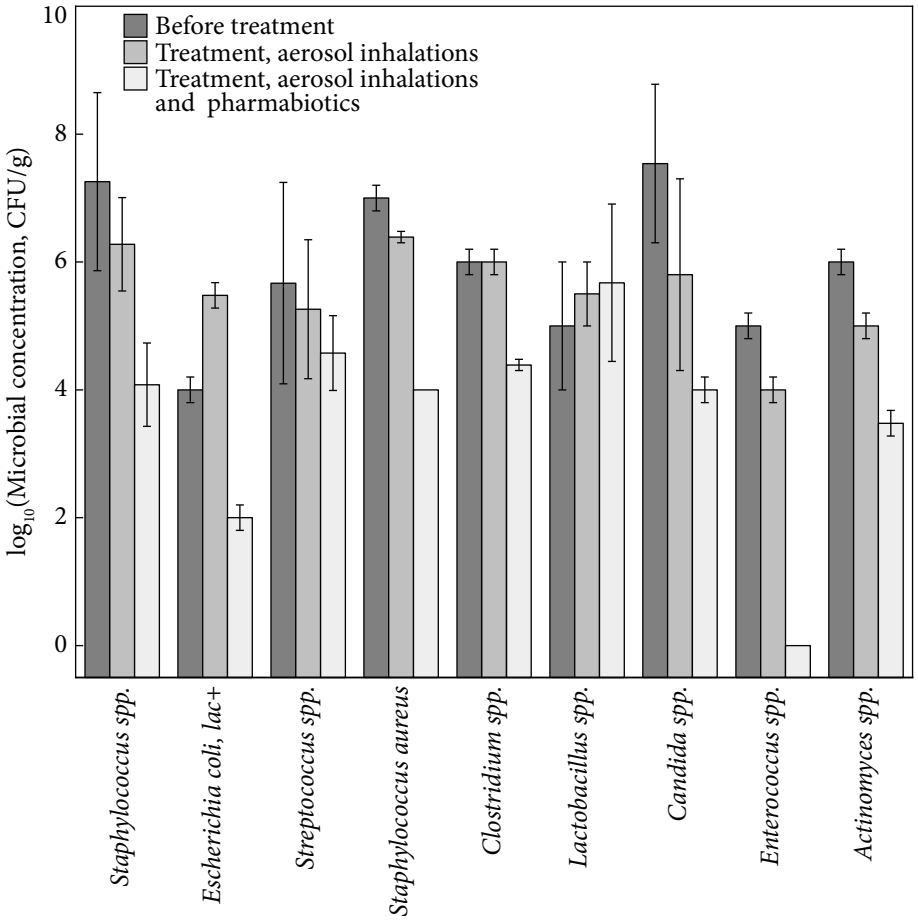

Fig. 2. The oral microbiota composition of the post-covid patients before and after the treatment

tionally pathogenic microorganisms was significantly decreased but was still higher than normal values. A decrease in the number of *Staphylococcus* spp. from 7.4 ± 1.1 $\log_{10}$ CFU/mL to 6.5 ± ± 1.0 $\log_{10}$ CFU/mL was revealed, as well as a decrease in the number of *Candida* spp. from 7.6 ± ± 0.9 $\log_{10}$ CFU/mL to 5.9 ± 0.8 $\log_{10}$ CFU/mL, and *Actinomyces* spp. from 6.0 ± 0.6 $\log_{10}$ CFU/mL to 5.2 ± 0.6 $\log_{10}$ CFU/mL. However, no significant differences were found in the amount of *Clostridium* spp., as the number of this anaerobic bacterium remained at the level of 6.0 ± 0.2 $\log_{10}$ CFU/mL. After the personalized pharmabiotics treatment course, the number of *Staphylococcus* spp. (including *S. aureus*), *Actinomyces* spp., *Streptococcus* spp., and *Candida* spp.) decreased to the normal values. The number of *Enterococcus spp*. decreased to the detection limit. At the same time, there was a tendency to increase the number of *Lactobacillus* spp. (5.7 ± 1.2 $\log_{10}$ CFU/mL) compared to that during treatment (5.0± 1.0 $\log_{10}$ CFU/mL).

Analysis of the obtained data showed that *Staphylococcus* spp. and *Streptococcus* spp. were the dominant representatives of the oral microbiota. They demonstrated the highest values of the detection frequency index (Pi — 0.12) and persistence index (C — 100%) at the time of treatment (Table 2).

After the use of aerosol inhalations together with personalized pharmabiotics, several changes in oral microbiota were detected. The detection frequency of such bacteria as *Staphylococcus* spp. (C% — 85%; Ri — 0.08), *Clostridium* spp. (C% — 20%; Ri — 0.01), *Candida* spp. (C% — 35%; Ri — 0.02), and *Actinomyces* spp. (C% —

10%; Ri — 0.01) was reduced. At the same time, the persistence index and detection frequency index of *Lactobacillus* spp. and *E. coli, lac+* were increased (C% — 55%, Ri — 0.09; C% — 25%, Ri — 0.05, respectively).

Study of immunological parameters. Immunomodulation includes natural and therapeutic processes aimed at modifying the immune response. In all patients who had contracted COVID-19 the level of IgA was within the lower range of the norm — 0.7—0.83 pg/mL on average versus a norm of 0.7—4 mg/mL (Table 3). However, an increase in the IgA level (2.14—2.56 mg/mL) was observed after the use of aerosol inhalations and personalized pharmabiotics.

The rate of IL-6 in post-COVID patients ranged from 7.5 to 9.41 pg/mL, which was significantly higher than the normal rate of 1.5 to 7.0 pg/mL. This indicates an increase in IL-6 production due to the stress factor, SARS-CoV-2 in this case. As known, IL-6 stimulates macrophages, which trigger active inflammatory processes. Their excessive amount can damage healthy cells. Some studies of early cases of COVID-19 in China indicate that the immune response to the coronavirus may be very active: in patients with severe symptoms, elevated levels of cytokines, particularly IL-6, were found (Troisi et al., 2021). The so-called cytokine storm occurs. Therefore, it is extremely important to achieve normalization of the serum levels of the acute phase proteins as soon as possible in order to avoid damage to lung tissues due to an autoimmune reaction.

After a course of aerosol inhalations and personalized pharmabiotics, the IL-6 indicator was 2.32—5.58 pg/mL, which is within the normal range.

In our studies, the level of TNF-α in all patients was within the range of 5.88—5.9 pg/mL (reference values 0—13 pg/mL), i.e. it had no diagnostic value.

Table 2. **Persistence index and frequency index of the oral microbiota representatives**

Microorganisms	Persistence index (C%)			Frequency index (Pi)		
	Before treatment	Treatment, HAT	Treatment, HAT & pharm.	Before treatment	Treatment, HAT	Treatment, HAT & pharm.
Staphylococcus spp.	100	90	85	0.12	0.1	0.08
Lactobacillus spp.	40	40	55	0.07	0.07	0.06
Streptococcus spp.	100	100	100	0.12	0.12	0.11
Enterococcus spp.	20	20	20	0.06	0.04	0.02
Escherichia coli, lac+	20	20	25	0.04	0.04	0.05
Clostridium spp.	40	40	20	0.03	0.03	0.01
Candida spp.	40	40	35	0.05	0.03	0.02
Actinomyces spp.	20	20	10	0.02	0.02	0.01

Table 3. **Immunological indicators of post-COVID patients before and after the treatment**

Indexes	Values			Reference values
	Before treatment	Treatment, HAT	Treatment, HAT & pharm.	
SIgA, mg/mL	0.7—0.83	1.2—1.23	2.14—2.56	0.7—4
IL-6, pg/mL	7.5—9.41	6.45—7.0	2.32—5.58	1.5—7.0
TNF-α, pg/mL	5.88—7.57	5.2—5.9	4.6—5.32	0—13

Thus, the complex use of aerosol inhalations and personalized pharmabiotics made it possible to improve the state of mucous membrane microbiota of URT and GIT of the patients who had contracted COVID-19.

Discussion. Mucosal surfaces, particularly those of the lungs and intestines, play an important role in modulating immune responses, thereby reducing the number of pathogens and preventing excessive inflammation or tissue damage. The formation of an adaptive immune response on mucous membranes involves certain peculiarities. The main antigen-presenting cells of mucosal membrane are B-lymphocytes and mast cells. Local synthesis of IL-4 is observed, which causes a Tx2-dependent humoral response, mainly accompanied by the formation of IgA antibodies. The latter can penetrate through the epithelial cells to the surface of mucous membranes, where they interact with pathogens and neutralize them, thereby contributing to their rapid elimination. However, the harmonious setting of local immunity directly depends on the balance of the so-called «local microbiota»: violation of mucosal tolerance together with a dysbiotic state can contribute to infection and progression of infections, including those caused by SARS-CoV-2. Since under COVID-19, respiratory and gastrointestinal mucosal membranes are affected and changes in microbiota composition occur, it is plausible to suggest that targeted correction based on the modulation of the gut-lung axis and restoration of eubiosis may be an important therapeutic approach to limiting COVID-19 harmful effects.

Recently, there has been increasing evidence that the use of pharmabiotics and nutraceutical support demonstrates anti-inflammatory properties and improves the body's immunomodulatory properties (Ferreira et al., 2020; Kumar et al., 2010; Wei et al., 2021).

Numerous probiotics have been shown to be beneficial under coronavirus infections, but evidence detailing their effectiveness in treating COVID-19 in particular is limited (Ferreira et al., 2020). *L. plantarum* Probio-38 and *L. salivarius* Probio-37 can inhibit transmissible gastroenteritis coronavirus (Luoto et al., 2014; Kumar et al., 2010). Probiotic *E. faecium* NCIMB 10415 has been approved in the European Union as a feed additive for young piglets for the treatment of transmissible coronavirus gastroenteritis (Kumar et al., 2010; Wei et al., 2021). Recombinant IFN-λ3-anchored *L. plantarum* can inhibit swine gastroenteritis caused by coronavirus *in vitro* (Liu et al., 2020; Averina, 2017). However, the clinical utility of probiotics in human infections caused by SARS-CoV-2 requires further evaluation (Ferreira et al., 2020; Han et al., 2021).

Registered clinical trials of probiotics under COVID-19, mostly *Lactobacillus* and *Bifidobacterium-Lactobacillus* mixtures, are ongoing; hence, the preventive or therapeutic role of probiotics in such patients may be elucidated in the near future.

So, representatives of *Staphylococcus* spp. (including *S. aureus*), *Streptococcus* spp., *Clostridium* spp., *E. faecalis, K. oxytoca, Candida* spp., and *Actinomyces* spp. prevailed in mucous membrane microbiota of URT of the patients who had contracted COVID-19; in GIT microbiota, *Staphylococcus* spp. (including *S. aureus*), *Streptococcus* spp., *Clostridium* spp., and *Candida* spp. had the largest numbers.

After the use of aerosol inhalations and personalized pharmabiotics, the qualitative composition of URT and GIT mucous membrane microbiota ~~of~~ remained practically unchanged. However, a significant decrease in the amount of opportunistic microbiota to normal levels was revealed. The frequency of detection of *Enterococcus* spp. and *Candida* spp. decreased to 0.02, whereas *Clostridium* spp. and *Actinomyces* spp. — to 0.01.

The use of aerosol inhalations in combination with personalized pharmabiotics significantly improved the local immune response state of the patients who had contracted COVID-19, as evidenced by an increase in IgA (from 0.7—0.83 to 2.14—2.56 mg/mL) and a decrease in IL-6 (from 7.5—9.41 to 2.32—5.58 pg/mL).

Thus, the obtained results prove the effectiveness of aerosol inhalations and the use of personalized pharmabiotics *L. rhamnosus* S25 and *L. plantarum* A in modulating the microbiome and targeted correction of local immunity in post-COVID patients. Restoring the balance of URT and GIT mucous membrane microbiota of the patients who have contracted COVID-19 should be an integral part of the rehabilitation of post-COVID patients.

Conclusions. The data obtained provide supportive evidence of the efficacy of the combined application of aerosol inhalations and personalized pharmabiotics *L. rhamnosus* S25 and *L. plantarum* A in the directed modulation of the microbiome and targeted correction of local immunity in post-COVID patients.

Restoring the balance of the patient's oral and gut microbiota should be an integral part of the post-COVID patient's rehabilitation.

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Conflict of Interest. The authors declare that they have no conflict of interest.

Ethical approval. The bioethics committee of State Higher Educational Institution «Uzhhorod National University», protocol No 9/7 of 07.06.2023.

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ВИКОРИСТАННЯ ПЕРСОНАЛІЗОВАНОЇ ФАРМАКОТЕРАПІЇ ЯК ПІДХОДУ ДО РЕАБІЛІТАЦІЇ ПОСТКОВІДНИХ ПАЦІЄНТІВ

Успішне застосування визначених про-/і пребіотиків для профілактики та лікування вірусних респіраторних інфекцій підтверджено мета-аналізом та численними клінічними дослідженнями. На сьогодні розроблено та прийнято протоколи реабілітації пацієнтів із постковідними станами, невід'ємною частиною яких є нутритивна підтримка та відновлення балансу мікробіоти кишківника. **Мета.** Дослідити ефективність індивідуально призначених фармакобіотиків для цілеспрямованої корекції назальної та кишкової мікробіоти хворих, які перехворіли на COVID-19, у поєднанні з аерозольними інгаляціями. **Методи.** Пацієнтам, які перенесли COVID-19, крім основного лікувального комплексу, була запропонована галоаерозольтерапія з додатковим призначенням індивідуально підібраних фармабіотиків. **Результати.** Застосування індивідуально призначених фармабіотиків у поєднанні з аерозольними інгаляціями дозволило відновити баланс *Lactobacillus* spp. і зменшити кількість умовно-патогенної мікробіоти кишківника. Персоналізований реабілітаційний підхід сприяв значному покращенню місцевої імунної відповіді в пацієнтів після COVID-19. **Висновки.** Отримані дані доводять ефективність аерозольних інгаляцій і персоналізованих фармакобіотиків *Lactobacillus rhamnosus* S25 і *L. plantarum* A у комбінованому застосуванні для спрямованої модуляції мікробіоти та корекції місцевого імунітету в пацієнтів, які перехворіли на COVID-19. Відновлення балансу мікробіоти верхніх дихальних шляхів та кишківника має бути невід'ємною частиною реабілітації постковідних пацієнтів.

Ключові слова: *COVID-19, постковідна реабілітація, вісь кишечник-легені, фармакотерапія.*