https://doi.org/10.15407/microbiolj84.01.057

S. STAROVOITOVA[1], O. DEMCHENKO[2], V. BILA[2], M. SPIVAK[3]*

[1] National University of Food Technologies,
68 Volodymyrska Str., Kyiv, 01601, Ukraine
[2] Communal non-profit enterprise "Kyiv Perinatal Center",
9 Predslavynska Str., Kyiv, 03150, Ukraine
[3] D.K. Zabolotny Institute of Microbiology and Virology, NAS of Ukraine,
154 Akademika Zabolotnoho Str., Kyiv, 03143, Ukraine
* Author for correspondence; e-mail: n.spivak@ukr.net

THE ROLE OF INTESTINAL MICROBIOTA AND ITS RECOVERY IN COVID-19

Today, during the SARS-CoV-2 pandemic, when there are no clear therapeutic strategies for prevention and treatment, attention should be paid to alternative treatments, which may include the use of bacteria-therapeutic drugs based on probiotic microorganisms, i.e. representatives of the host normobiota. Experimental data show that changes in immune balance in patients with SARS-CoV-2 may be mediated by corresponding changes in the host intestinal microbiota. This statement is especially significant for the elderly, whose intestinal biota is less diverse. Especially the number of useful representatives decreases, which leads to greater sensitivity of the older generation to SARS-CoV-2. The composition and function of the intestinal microbiota may be a potential biological mechanism responsible for the diversity of susceptibility of different groups of people to SARS-CoV-2. A bidirectional connection along the intestine-lung axis due to soluble microbial metabolites transported by the bloodstream is shown. The intestinal microbiota produces many diffusing metabolites with immunomodulatory properties. Given the potential beneficial effects of bacteriotherapeutic drugs and functional foods enriched with probiotic microbiota during respiratory viral infection, their use as therapeutic agents during SARS-CoV-2 infection can be considered. Since the microbiota can be maintained using adequate, safe, and relatively inexpensive bacteriotherapeutic drugs (pro-, pre-, para-, post-, synbiotics, immunobiotics, functional foods enriched with probiotic microorganisms, etc.), their use should be considered as adjunctive therapy to limit SARS-CoV-2 progression in infected patients or as a prophylactic strategy for uninfected people at risk during the expansion of SARS-CoV-2.

Keywords: *microbiota, probiotics, SARS-CoV-2, normobiota, probiotic microorganisms.*

Citation: Starovoitova S., Demchenko O., Bila V., Spivak M. The Role of Intestinal Microbiota and its Recovery in COVID-19. *Microbiological journal.* 2022 (1). P. 63—71. https://doi.org/10.15407/microbiolj84.01.057

In today's reality, searching for and developing various approaches to the prevention, treatment, and alleviation of the disease that caused the global pandemic — SARS-CoV-2 — are issues of great importance and priority.

Current studies on the composition and functions of the human microbiome (a community of all microorganisms inhabiting the body) cause interest in the use and development of products based on probiotic microorganisms to prevent coronavirus infection. However, the issue of the properties of probiotic microorganisms that are necessary for the prevention or treatment of this particular pathology remains open. Many studies demonstrated that the use of probiotics for the prevention and treatment of coronavirus infection could be effective [1—4].

The key points of SARS-CoV-2 entrance into the human body are receptors expressed on the cell membranes of the lungs and small intestine. The coronavirus is thought to constantly change its patterns to bind to cell receptors in the lungs; however, the receptors for virus binding to cells in the small intestine remain unchanged. It was experimentally proven that in the acute phase of COVID-19, only 10% of patients have the DNA complementary to the virus DNA in their blood; meanwhile, in almost 50% of patients, the DNA is found in fecal samples. Thus, the intestine can be a kind of reservoir for virus replication, which is due not only to the fecal-oral route but also to a wide range of viral load and the severity of the immune response in the same patient during the disease [4, 5].

Intestinal microbiota is known to perform an immunoregulatory function, the effects of which go beyond the gastrointestinal tract, affecting, among others, the lung immune system and forming the microbiota-intestine-lungs axis. That is why qualitative and quantitative changes in the intestinal microbiota composition are closely related to changes in the regulation of the immune response in the lungs [5]. The microbiota composition of patients with the lethal outcome of COVID-19 was studied by fecal samples sequencing. A significant decrease in the level of the main genera of symbiotic bacteria such as *Bifidobacterium* and *Lactobacillus* was found, as well as an increase in the number of opportunistic bacteria, especially representatives of *Corynebacterium* and *Ruthenibacterium* genera. It was suggested that changes in the intestinal microbiota composition posed an additional risk of immune and respiratory disorders caused by COVID-19 in these patients [6, 7].

Immunoregulatory properties are characteristic of many probiotic strains, especially typical representatives of probiotic microorganisms of *Bifidobacterium* and *Lactobacillus* genera. It is known that immunobiotics (a variety of probiotics, the main mechanism of action of which is associated with immunomodulatory properties) affect both innate and adaptive immunity. Therefore, they can be used to prevent many infectious (e.g. clostridial infection) and allergic forms of bronchial asthma or atopic dermatitis diseases. Italian scientists showed that probiotics can be useful in the treatment of COVID-19 owing to their immunoregulatory properties. Also, it was shown experimentally that oral administration of probiotics reduced the risk of death from pneumonia caused by COVID-19 by 20% [1, 3].

Probiotic products are able to block the attachment of the virus also through the process of competition for certain adhesion points.

The role of intestinal microbiome in COVID-19. Each person has a unique qualitative and quantitative composition of bacteria in the intestine — the normal microbiota (normobiota) — which plays a variety of physiological roles, in particular in the modulation of the immune response [8, 9].

It was experimentally shown that the intestinal microbiome can play an important role in the body's fight against coronavirus infection and the prevention of severe course of COVID-19 disease [2, 10—12].

The composition of the intestinal microbiota of patients with COVID-19 correlates with the concentration of some cytokines, chemokines, and markers of inflammation in plasma. This indicates that intestinal microbiota plays a leading role in the modulation of the host's immune response and potentially affects disease severity and the recovery process. Microbial imbalances are found to be also associated with higher levels of cytokines, small molecules which are a natural part of the immune response but can lead to damage if not properly regulated [8, 9, 13].

In particular, a critical decrease in the quantitative composition of several species of bacteria in the intestinal normobiota in patients with COVID-19 is associated with an increase in the concentration of many cytokines [tumor necrosis factor-α (TNF-α), CXCL10, CCL2, and interleukin-10 (IL-10)], indicating that these microorganisms may play a role in preventing over-aggressive inflammation. Such representatives of intestinal commensals, the number of which is significantly reduced in patients with COVID-19, include *Bifidobacterium adolescentis*, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Ruminococcus obeum,* and *Dorea formicigenerans*. For example, *F. prausnitzii* stimulates the production of regulatory colon T-cells in humans, which secrete the anti-inflammatory cytokine IL-10. A high relative amount of *E. rectale* in the intestine is associated with a decrease in the inflammatory process in Alzheimer's disease, while *B. adolescentis* is able to suppress the activation of nuclear factor κB, which promotes the expression of proinflammatory cytokines [13].

Laboratory studies show that people with COVID-19 have a significantly altered microbiome composition. People with a poorly functioning intestine are more likely to develop a severe course of COVID-19 because the violation of the qualitative and quantitative composition of the microbiota facilitates the infection of cells of the gastrointestinal tract with coronavirus.

In an experimental study, patients with COVID-19 were shown to have a reduced quantitative composition of some intestinal bacteria species, which is known to alter the human immune response. Changes in the bacterial composition were observed for at least a month after recovery, which indicates the association of dysbiotic intestinal microbiome with immune health issues after COVID-19 [2, 8, 10—12].

Intestine-lungs-brain axis. Being in direct antagonism with pathogenic bacteria, probiotics enhance the immune status of the body and the barrier function of the mucous membrane as well as inhibit bacterial adhesion and invasion of the intestinal epithelium. The intestine-lungs axis is involved in an infectious process caused by pathogenic bacteria and viruses, as the intestinal microbiota enhances the activity of alveolar macrophages, in this way protecting the host from pneumonia. The existence of the intestine-lungs-brain axis through communication mediated by a complex of neural, immunological, and neuroendocrine connections is experimentally proven.

Pattern recognition receptors (PRRs) are essential for the development of innate immune response. Probiotics regulate innate immune cells through interactions between cell wall components or metabolites with the PRR of the host. However, probiotic bacteria activate dendritic cells (DC) and macrophages and enhance the adaptive immune response. PRR expression breaks out in the lung cells during inflammatory processes. The most studied PRR for pathogen recognition are Toll-like receptors (TLRs), which are membrane glycoproteins. The appearance of TLR4 signaling molecules in pulmonary stromal cells is critical in the inflammatory process of the airways. However, it is probiotics that can reduce inflammation by limiting the expression of TLR4 [14].

The biological role of intestinal microbiota and its effect on lung diseases (asthma, chronic obstructive pulmonary disease, chronic bron-

chitis, emphysema, lung cancer, pneumonia, viral and bacterial infections) is experimentally proven. Viral infections of the respiratory tract cause disorders of the intestinal microbiota [10]. A study in China confirmed that SARS-CoV-2 infection affects the balance of physiological intestinal normobiota, especially the reduction in the number of *Bifidobacterium* and *Lactobacillus* genera [7]. Another study has shown that the share of COVID-19 patients with antibiotic-associated diarrhea was 36% [15]. These studies indicate an urgent need to maintain the balance of normobiota in patients with COVID-19.

Intestine-lungs axis and COVID-19. The intestine and the lungs are compartments of the host's body, populated by microbiota; however, the lungs, unlike the intestine, contain much less normobiota. There is a two-way connection between lungs and intestine, i.e., there is an intestine-lungs axis. It is believed that inflammation in the gastrointestinal tract leads to pneumonia due to this connection. One of the mechanisms of bidirectional interaction between the lungs and intestinal microbiota is that increase in the permeability of the gastrointestinal tract can lead to the migration of intestinal microbiota into the lungs, modulating their normobiota and the corresponding immune responses. In addition, representatives of the intestinal microbiota and their metabolites (lipopolysaccharides or short-chain fatty acids) are also involved in this bidirectional interaction. It was suggested that COVID-19 may disrupt the lung microbiota, modulate the intestinal normobiota, and, as a consequence, lead to gastrointestinal symptoms. In addition, the symptoms of gastrointestinal disease associated with COVID-19 may be due to the same embryonic origin of the gastrointestinal and respiratory tracts. So, they are structurally similar and interact equally in physiological and pathological conditions [16, 17].

The intestinal microbiota regulates the immunity balance not only in the intestine but also in other organs. Changes in the intestinal normobiota can lead to respiratory diseases [4]. The researchers concluded that the administration of probiotics (intranasally or orally) increases immunity and reduces the level of the virus in the lungs. This supports communication between the intestine and the lungs [11].

Oral administration of probiotics during a viral lung infection can prevent the development of intestinal infection and dysbiosis. This approach helps to fight viral lung infections by reducing inflammation or acting directly on the virus by circulating bacterial metabolites. The metabolites produced by intestinal bacteria move through the bloodstream to modulate the immune response in individual organs. They play a key role in the communication between intestinal microbiota and lungs.

The intestinal microbiota produces a number of different metabolites, in particular postbiotics, such as folate, indoles, γ-aminobutyric acid, serotonin, secondary bile acids, desaminothyrosine, and short-chain fatty acids. The main metabolite for use in pulmonary viral infections is butyrate; the secondary ones are bile acids and desaminothyrosine.

Butyrate, propionate, acetate, etc. are short-chain fatty acids produced by the intestinal microbiota from indigestible fibers. They are able to regulate inflammation in the host and modulate immunity against pathogens. Besides immunomodulatory properties, butyrate is an important source of energy for the proliferation of colon cells and supports the barrier function of intestine. Butyrate and propionate help increase the level of inflammatory Ly6C monocytes in the lungs during the flu. These monocytes differentiate into activated macrophages that are responsible for reducing neutrophils production. The decreased level of neutrophils leads to a decrease in influenza-mediated pulmonary immunopathology [18].

Desaminothyrosine is a metabolite of intestinal normobiota, which is formed in the process of the metabolism of flavonoids. These flavo-

noids activate the secretion of type 1 interferon and protect against influenza by increasing α/β-interferon receptors, etc. [19].

In the liver, cholesterol is converted into primary bile acids, which are further degraded by intestinal bacteria into secondary bile acids (deoxycholic, lithocholic, or ursodeoxycholic), the role of which in the anti-inflammatory action has been shown experimentally, especially in the innate immune system [20].

It was experimentally proven that probiotics based on living cells of *L. rhamnosus*, *Bifidobacterium* sp. as well as inactivated by heating *Enterococcus faecalis*, along with prebiotic compounds such as inulin, polysaccharides, and oligosaccharides, play a crucial role in the treatment of viral pneumonia. These prebiotics and probiotics help ~~to~~ reduce viral load, which leads to increased overall survival through activating antiviral cytokines IFN-α, IFN-γ, IL-1β, and IL-12, as well as suppressing inflammatory cytokines IL-6 and TNF-α [21].

IL-12 and IL-6 are typical activators of the Th1 and Th2 immune responses, respectively. In severe influenza infections, there is a noticeable shift in the polarization of Th from Th2 to Th1 [22]. However, during treatment with pro- and/or prebiotics, this inflammatory-oriented polarization can be reversed by the up-regulation of IL-12 and the down-regulation of IL-6.

It was found that pro- and prebiotics can attract Treg cells and increase the concentration of IL-10 to achieve an antiviral effect, preventing excessive inflammatory responses by inhibiting the production of inflammatory cytokines TNF-α and IL-6.

The intestinal microbiota is able to protect against secondary infections caused by entheogenic endotoxemia during severe viral pneumonia. The intestinal mucosal barrier consists of mucus, symbiotic microorganisms, and tight contacts between intestinal epithelial cells and mucosal immune cells and prevents opportunistic infections.

Probiotic therapy is considered to be the optimal approach to restoring the barrier function of the intestinal mucosa in viral pneumonia. Probiotics can bind to TLR-4, the population of which increases significantly during therapy with a synbiotic complex of inactivated cells *L. salivarius* and fructooligosaccharides. In addition, probiotics, as well as their metabolic profiles, including bacteriocins, hydrogen peroxide, antimicrobial peptides, and defensins, help to modulate local immunity and cause enterocytes and goblet cells to secrete mucus, consequently strengthening the mucosal barrier over the entire surface [9, 21, 23].

In patients with COVID-19, SARS-CoV-2 binds its adhesion proteins to angiotensin-converting enzyme 2 (ACE2). ACE2 is highly expressed in the bronchi and gastrointestinal tract, which promotes the penetration and replication of viruses [21, 24]. Because invasive binding occurs with ACE2 (located in the intestine), their effective functioning can be disrupted, potentially leading to changes in the symbiotic microorganisms and undermining the intestinal barrier, which in turn leads to the predisposition of patients to secondary infections. Encouraging is the fact that treatment with pro- and prebiotics is included as adjuvant therapy for critically ill patients to prevent secondary infections in the fourth trial version of the COVID-19 Diagnosis and Treatment Plan of the National Health Commission of China [25].

In this fashion, rational pre- and probiotic therapy can limit inflammatory reactions, stimulate both innate and adaptive cellular immunity to protect against viral attacks and prevent secondary infections.

Reduction of "cytokine storm" in COVID-19 with the aid of probiotic products. Cytokine storm is an aggressive inflammatory reaction that occurs in some COVID-19 patients and is caused by the production of a large number of pro-inflammatory cytokines [6]. This phenomenon can damage the lungs, gastrointestinal tract, liver,

kidneys, microcirculation, and eyes. Scientific studies prove that probiotics can regulate functional immune cells, mucosal cells, and epithelial cells of the human intestinal tract. Probiotics play a functional role in restoring and maintaining a complete balance between necessary and unnecessary mechanisms, taking into account all immune responses (innate and adaptive) [26].

Regulation of the immune response by probiotics is always carried out by the implementation of their biological interactions with the following formations:

- epithelial cells of the intestinal tract;
- dendritic cells;
- follicle-associated epithelial cells;
- macrophages;
- T- and B-lymphocytes;
- gene expression;
- signal paths [9, 23].

In case vaccination is not possible, the best approach to fight SARS-CoV-2 infection is to improve the immune system using bacteriotherapeutic products of different types and generations (probiotics, prebiotics, synbiotics, parabiotics (dead or inactivated probiotics), postbiotics (beneficial metabolites of probiotic microorganisms), symbiotics, immunobiotics, etc.), which can minimize the inflammatory process caused by COVID-19 [2]. Immune benefits of probiotics in the COVID-19 treatment may be associated with the development of mucosal immunity by stimulating the secretion of immunoglobulin A (IgA), improving the biological functions of phagocytosis, macrophages, and regulatory cells. In addition, probiotics and some nutrients (vitamins, trace elements, and nutraceuticals) may enhance immune function and affect the obstruction and management of SARS-CoV-2 viral infection [27].

Potential mechanisms of probiotics' action in the prevention of COVID-19. The following main mechanisms of COVID-19 prevention by probiotics have been experimentally proven:

- improving the intestine epithelial barrier;
- competition with pathogens for nutrients;
- attachment to the intestine epithelial wall;
- production of antipathogenic elements;
- strengthening of the host immune system [1, 3, 4, 13—17, 26, 28].

Intestinal microbiota significantly affects the host's systemic immune response and the immune responses of nearby areas of the mucosa, such as the lungs. The use of certain strains of bifidobacteria and lactobacilli can have a positive effect on the removal of the influenza virus from the respiratory tract.

Some probiotic strains can raise the level of first-type interferon, as a result of increasing the number and function of antigen-presenting cells, natural killer cells, and T-cells, as well as a result of increasing the level of certain antibodies. Probiotic strains are able to increase the stability of pro-inflammatory and immunoregulatory cytokines, which help to get rid of viruses. Such strains may be promising for the prevention of acute respiratory distress syndrome, which is the main obstacle to COVID-19 [17]. Probiotic strains are able to strengthen bottlenecks, for example, they can act as fuel for colonocytes, which can reduce the invasion of SARS-CoV-2 by increasing the level of butyrate. Probiotic strains have antiviral properties. However, none of these mechanisms and effects have been confirmed for COVID-19. Nevertheless, the use of antiviral properties of probiotics against COVID-19 should not be abandoned, as far as positive results of their antiviral activity against other coronavirus strains have been obtained. Moreover, patients with COVID-19 very often suffer from secondary bacterial infections [23].

Hence, it can be concluded that the intestinal microbiome may play a key role in the severity of COVID-19, possibly through modulation of the host immune response.

However, the composition of the intestinal microbiota is very heterogeneous in the human population. Moreover, changes in the microbiota composition in patients with COVID-19 may differ over the biogeographical locations of pa-

tients. Nevertheless, studies of changes in intestinal microbiota in combination with immune dysregulation revealed that intestinal microorganisms are likely to be involved in modulating host inflammatory responses during COVID-19.

Thus, the intestinal microbiota can affect the immune response, thereby influencing disease progression. Both overactive and insufficient immune response may be associated with intestinal microbiota status, which can lead to serious clinical COVID-19 complications. Accordingly, the unhealthy status of the microbiota may be a risk factor.

Since the microbiota can be maintained by using adequate, safe, and relatively inexpensive probiotics (pro-, pre-, post-, para-, synbiotics, immunobiotics, functional foods enriched with probiotic microorganisms, etc.), their use should be considered as an adjunct treatment to limit the progression of COVID-19 in infected patients, or as a prophylactic strategy for uninfected people at risk during the expansion of COVID-19 or secondary-tertiary waves [1, 3, 4, 8, 9, 13—17, 21, 26, 28—31].

Diet, environmental factors, and genetics play an important role in the formation of intestinal microbiota which can affect immunity. In the elderly, the diversity of intestinal microbiota decreases; therefore COVID-19 mainly leads to death in elderly patients. This fact again is indicating the role of intestinal microbiota in this disease. Improving the intestine microbiota profile through the use of probiotics, especially immunobiotics, individual nutrition, and supplements enriched with probiotic microorganisms that are known to improve immunity, may be one of the prophylactic ways to minimize the effects of this disease in the elderly and patients with immune risk.

Promising are new tests of the efficiency of personalized functional foods, including the use of prebiotics, probiotics, immunobiotics, etc., along with current methods of treatments.

Conclusions. Determination of the potential role that intestinal normal microflora plays in the pathogenesis of COVID-19 may allow the use of a microbiome risk profile to identify individuals at risk of severe disease or inflammation. Along with this, a rational combination of probiotic products, prebiotic compounds, and functional foods enriched with probiotic microorganisms, together with up-to-date methods of treatment can significantly improve and accelerate the recovery of patients with COVID-19.

REFERENCES

1. Ceccarelli G, Borrazzo C, Pinacchio C, Santinelli [L], Innocenti GP, Cavallari [EN], et al. Oral bacteriotherapy in patients with COVID-19: a retrospective cohort study. Front Nutr. 2021; 7:1—8.
2. Conte L, Toraldo DM. Targeting the gut—lung microbiota axis by means of a high-fibre diet and probiotics may have anti-inflammatory effects in COVID-19 infection. Ther Adv Respir Dis. 2020; 14:1—5.
3. d'Ettorre G, Ceccarelli G, Marazzato M, Campagna G, Pinacchio C, Alessandri F, et al. Challenges in the Management of SARS-CoV2 Infection: The Role of Oral Bacteriotherapy as Complementary Therapeutic Strategy to Avoid the Progression of COVID-19. Front Med. 2020; 7(389):1—7.
4. Gautier T, David-Le Gall S, Sweidan A, Tamanai-Shacoori Z, Jolivet-Gougeon A, Loréal O, Bousarghin L. Next-Generation Probiotics and Their Metabolites in COVID-19. Microorganisms. 2021; 9:1—13.
5. Gohil K, Samson R, Dastager S, Dharne M. Probiotics in the prophylaxis of COVID-19: something is better than nothing. 3 Biotech. 2021; 11(1):1—10.
6. Huang C, Wang Y, Li X, Lu Y, Zhu X, Li Y, et al. Inical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020; 395:497—506.
7. Xu K, Cai H, Shen Y, Ni Q, Chen Y, Hu S, et al. Management of corona virus disease-19 (COVID-19): the Zhejiang experience. J Zhejiang Univ. (medical science). 2020; 49(1):147—157.
8. Starovoitova SO, Antonyuk MM. Vzayemozv'yazok normobioty kyshechnyku ta osoblyvosti perebihu Covid-19. In: Aktual'ni pytannya diahnostyky COVID-19: zb. materialiv Vseukrayins'koyi naukovo-praktychnoyi konferentsiyi, m. Rivne; 2021, Feb 18—19; Rivne: KZVO «Rivnens'ka medychna akademiya», 2021. p. 109—113. Ukrainian.

9. Starovoitova SA, Karpov AV. Immunobiotiki i ikh vliyaniye na immunnuyu sistemu cheloveka v norme i pri patologii. Biotechnology. Theory and Practice. 2015; 4:10—20. Russian.
10. Dhar D, Mohanty A. Gut microbiota and Covid-19 — possible link and implications. Virus Res. 2020; 285:198018.
11. Dumas A, Bernard L, Poquet Y, Lugo-Villarino G, Neyrolles O. The Role of the Lung Microbiota and the Gut-Lung Axis in Respiratory Infectious Diseases. Cell Microbiol. 2018; 20:e12966.
12. Yeoh YK, Zuo T, Lui GC-Y, Zhang F, Liu Q, Li AYL, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut. 2021; 70(4):698—706.
13. Kurian SJ, Unnikrishnan MK, Miraj SS, Bagchi D, Banerjee M, Reddy BS, et al. Probiotics in prevention and treatment of COVID-19: current perspective and future prospects. Archives of Medical Research. 2021; 16:1—13.
14. Stavropoulou E, Bezirtzoglou E. Probiotics as a weapon in the fight against COVID-19. Frontiers in Nutrition. 2020; 7:1—4.
15. Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. Lancet Gastroenterol Hepatol. 2020; 5(7):644—645.
16. Olaimat AN, Aolymat I, Al-Holy M, Ayyash M, Ghoush MA, Al-Nabulsi AA, et al. The potential application of probiotics and prebiotics for the prevention and treatment of COVID-19. Science of Food. 2020; 4:1—7.
17. Zafar N, Aslam MA, Ali A, Khatoon A, Nazir A, Tanveer Q, et al. Probiotics: Helpful for the prevention of COVID-19? Biomedical Research and Therapy. 2020; 7(11):4086—4099.
18. Dang AT, Marsland BJ. Microbes, Metabolites, and the Gut—Lung Axis. Mucosal Immunol. 2019; 12:843—850.
19. Lobel L, Garrett WS. Take DAT, Flu! Immunity. 2017; 47(3):400—402.
20. Hang S, Paik D, Yao L, Kim E, Trinath J, Lu J, et al. Bile Acid Metabolites Control TH17 and Treg Cell Differentiation. Nature. 2019; 576:143—148.
21. Wang F, Pan B, Xu S, Xu Z, Zhang T, Zhang Q, et al. A meta-analysis reveals the effectiveness of probiotics and prebiotics against respiratory viral infection. Bioscience Reports. 2021; 41(3):BSR20203638.
22. Graham BS, Johnson TR, Peebles RS. Immune-mediated disease pathogenesis in respiratory syncytial virus infection. Immunopharmacology. 2000; 48:237—247.
23. Kullar R, Johnson S, McFarland LV, Goldstein EJC. Potential Roles for Probiotics in the Treatment of COVID-19 Patients and Prevention of Complications Associated with Increased Antibiotic Use. Antibiotics. 2021; 10(4):1—10.
24. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020; 81:537—540.
25. General Office of the National Health Commission Notice on the issuance of COVID-19 diagnosis and treatment plan (for trial version 4) [EB/OL]. State Administration of Hospital Administration. 2020. http://www.nhc.gov.cn/yzygj/s7653p/202001/4294563ed35b43209b31739bd0785e67.shtml.
26. Khaled JMA. Probiotics, prebiotics, and COVID-19 infection: A review article. Saudi Journal of Biological Sciences. 2021; 28:865—869.
27. Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, Ranasinghe P. Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. Diabet Metabol Syndrome Clin Res Rev. 2020; 14(4):367—382.
28. Mirzaei R, Attar A, Papizadeh S, Jeda AS, Hosseini-Fard SR, Jamasbi E, et al. The emerging role of probiotics as a mitigation strategy against coronavirus disease 2019 (COVID-19). Archives of Virology. 2021; 166(7):1819—1840.
29. Rosa RB, Dantas WM, do Nascimento JCF, da Silva MV, de Oliveira RN, Pena LJ. In Vitro and In Vivo Models for Studying SARS-CoV-2, the Etiological Agent Responsible for COVID-19 Pandemic. Viruses. 2021; 13(379):1—29.
30. Soloveva IV, Ilyicheva TN, Marchenko VYu, Pyankov OV, Tochilina AG, Belova IV, et al. Genome Features and In Vitro Activity against Influenza A and SARS-CoV-2 Viruses of Six Probiotic Strains. BioMed Research International. 2021; Article ID 6662027:1—11.
31. Zuo T, Wu X, Wen W, Lan P. Gut Microbiome Alterations in COVID-19. Genomics Proteomics Bioinformatics. 2021; 21:1—25.

Received 27.10.2021

С.О. Старовойтова[1], В.В. Біла[2],
О.М. Демченко[2], М.Я. Співак[3]

[1] Національний університет харчових технологій,
вул. Володимирська, 68, Київ, 01601, Україна
[2] Комунальне некомерційне підприємство «Перинатальний центр м. Києва»,
вул. Предславинська, *9, Київ, 03150, Україна*
[3] Інститут мікробіології і вірусології ім. Д.К. Заболотного НАН України,
вул. Академіка Заболотного, 154, Київ, 03143, Україна

РОЛЬ КИШКОВОГО МІКРОБІОМА ТА ЙОГО ВІДНОВЛЕННЯ ПРИ COVID-19

Сьогодні, під час пандемії, викликаної вірусом SARS-CoV-2, коли немає чітких терапевтичних стратегій профілактики та лікування, слід звернути увагу на альтернативні методи терапії, які можуть включати в себе використання бактеріотерапевтичних препаратів на основі пробіотичних мікроорганізмів — представників нормобіоти господаря. Експериментальні дані показують, що зміни імунного балансу у пацієнтів із SARS-CoV-2 можуть бути опосередковані відповідними змінами мікробіоти кишківника господаря. Це твердження особливо актуальне для людей похилого віку, у яких кишкова біота менш різноманітна, особливо зменшується кількість її корисних представників, що призводить до більшої чутливості старшого покоління до SARS-CoV-2. Склад та функція кишкової мікробіоти можуть бути потенційним біологічним механізмом, відповідальним за різноманітність сприйнятливості різних груп людей до SARS-CoV-2. Показано двонаправлений зв'язок через вісь кишечник-легені за рахунок розчинних мікробних метаболітів, що транспортуються кровотоком. Представники облігатної мікробіоти кишечника продукують безліч дифузних метаболітів з імуномодулювальними властивостями. Враховуючи потенційні позитивні ефекти бактеріотерапевтичних препаратів та функціональних продуктів харчування, збагачених пробіотичними мікроорганізмами, можна розглянути можливість їх використання у якості лікувально-профілактичних засобів при інфекції, викликаній SARS-CoV-2. Оскільки мікробіоту можна підтримувати за допомогою адекватних, безпечних та відносно недорогих пробіотичних препаратів (про-, пре-, пара-, пост-, синбіотики, імунобіотики, функціональні продукти харчування, збагачені пробіотичними мікроорганізмами тощо), використання їх слід розглядати як додаткову терапію для обмеження прогресу COVID-19 в інфікованих пацієнтів або як профілактичну стратегію для неінфікованих людей, які перебувають у групі ризику під час поширення SARS-CoV-2.

Ключові слова: *мікробіота, пробіотики, мікробіота, SARS-CoV-2, нормобіота, пробіотичні мікроорганізми.*