PROBIOTIC'S BIOTECHNOLOGY FOR PREVENTION AND TREATMENT OF COVID-19

S. Starovoitova

National University of Food Technologies, Kyiv, Ukraine
Svetik_2014@ukr.net

SARS-CoV-2 infection leads to complicated immunologic and pathophysiologic responses in the host. Along with the phenotypic changes in the host, the gut microbiome is broadly altered in COVID-19 patients. Subsequent blooms of opportunistic bacteria, fungi, and viruses under circumstances of SARS-CoV-2 infection and quiescent/overt gut inflammation in COVID-19 pose further threats to host health and gut microbiota restoration. Such expansions in certain microbial species and decreases in microbiome diversity in conjunction with the impaired host immunity may hinder restoration of the gut normobiota post COVID-19. Consequently, the altered gut microbiome ecology persists even after disease resolution. Overall, the intricate microbiome ecological network in a steady state is significantly weakened in COVID-19, shifting to one predominated by COVID-19-enriched microbes [1].

It is well-known that confounding factors such as treatment and diet can significantly affect the gut microbiome composition. However, due to the acute nature of COVID-19, controlling for these confounding factors or including treatment-naïve COVID-19 patients seems infeasible. Therefore, some of the differences between the microbiomes of COVID-19 and controls, and of those between disease stages (i.e., mild vs. severe COVID-19 cases), could be attributed to treatment regimens and/or diet. SARS-CoV-2 infection might be a crucial contributor to the gut microbiome dysbiosis in patients with COVID-19. Although studies have demonstrated that the infection of SARS-CoV-2 would lead to the altered gut microbiome, the causal relationships among the baseline gut microbiome (before infection) that regulates angiotensin-converting enzyme 2 (ACE2) expression and host immune status, infectivity/severity of SARS-CoV-2, and altered gut microbiome after infection are complicated [2-4].

Compositions of the gut microbiome (baseline) favor the infection of SARS-CoV-2, and subsequent infection of SARS-CoV-2 induces the change of gut microbial ecology. Little is known about the relative contribution of the baseline status of the gut microbiome to the later-on infection and the dynamics of the altered gut microbiome. Beyond that, it is also paramount to further understand how the gut microbiome regulates host immunity against SARS-CoV-2 infection, therefore disease severity, as well as the long-term impact of COVID-19 on the gut microbiota restoration in relation to host health after the pandemic.

Thus, nowadays 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 bacteriotherapeutic 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 microflora. This statement is especially significant for the elderly, whose intestinal flora is less diverse. Especially the number of useful representative's 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 microflora 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 or secondary-tertiary waves [2].

The use of probiotics in COVID-19 patients has been suggested by many investigators, based on the ability of specific probiotics to regulate the immune response (perhaps to calm the "cytokine storm"), or to prevent other types of respiratory infections, including influenza and ventilator-associated pneumonia and to prevent antibiotic associated diarrhea and *Clostridioides difficile* infections [5-7].

Probiotic supplements were considered to be an optimal approach to restore the gut mucosal barrier function in viral pneumonia. Probiotics can bind to Toll-like receptor-4, whose population could increase with the help of inactivated *Lactobacillus salivarius* and fructo-oligosaccharides, thereby competing against harmful bacteria. In addition, probiotics and its metabolic profiles including bacteriocin, hydrogen peroxide, antimicrobial peptides and defensin, help to modulate the local immunity and drive enterocyte and goblet cells to secret mucus as a consequence to strengthen the mucosal barrier at length.

For COVID-19 patients, SARS-CoV-2 binds its spike proteins to ACE2. ACE2 is highly expressed in the bronchi and gastrointestinal tract to facilitate to viral invading and replication. Since the invasive bindings to ACE2, ACE2 located in the gut might not function effectively, potentially altering the symbiotic flora and undermining the intestinal barrier, leading to patients prone to secondary infections. Treatment of an irritant, compared with wildtype littermates, caused gut microbiota alteration to promote profoundly inflammatory reaction in ACE2 mutation mice, which could be directly regulated by microbial agents. Encouragingly, probiotics and prebiotics treatment has been incorporated as adjuvant therapy for critical patients to prevent secondary infections.

Probiotics and prebiotics could be an inspiration for healthcare givers when treating viral pneumonia. This therapy could limit inflammatory responses, stimulate both innate and adaptive immune cells to defend against the viral attacks and preventing secondary infections. Our findings implied a promising target and encourage probiotics or prebiotics to be incorporated into regular treatments for patients infected with respiratory virus, particularly for the patients with severe viral pneumonia [5-7].

There is extensive research investigating the biological roles of the gut microbiota in influencing lung disorders that include asthma, chronic obstructive pulmonary disease, chronic bronchitis, emphysema, lung cancer, pneumonia, pleural effusion, viral and infection. It is also recognized that viral infections in the respiratory tract cause a disturbance in the gut microbiota. The most important probiotics that could be related to decreasing the burden of the COVID-19 pandemic, which included *Lactobacillus casei*, *Lactobacillus gasseri*, *Bifidobacterium longum*, *Bifidobacterium bifidum*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, *Bifidobacterium breve*, *Pediococcus pentosaceus*, and *Leuconostoc mesenteroides*. All these probiotics have been added to several products such as DanActive/Actimel fermented drink (Danone), Tribion harmonis (Merck), Shirota, Morinaga, and Medipharm. A recent study conducted in China confirmed that COVID-19 infection affects the balance of natural microbiota in the human intestine based on the observation of reduced counts of *Bifidobacterium* spp. and *Lactobacillus* spp. in patients infected by COVID-19 [4].

It has also been reported that COVID-19 can cause severe hypoxemia and changes in the balance of gut microorganisms. On the other hand, a significant reduction of probiotics (*Bifidobacterium* spp., *Lactobacillus* spp., and *Eubacterium* spp.) was found to significantly increase the number of pathogens (such as *Corynebacterium* spp., *Actinobacteria* spp., and *Ruthenibacterium* spp.) reported that COVID-19 can cause disorders in the human stomach and intestines, however, there is no scientific evidence about the role of COVID-19 in host-microbial flora disorders. Some probiotics that belong to the genus of *Lactobacillus* and *Bifidobacterium*

biological activity to control the gastrointestinal dysbiosis caused by the severe acute respiratory syndrome coronavirus 2 [1, 4, 5].

Protection by probiotics includes synthesis of antimicrobial agents, immune-modulatory responses, and enhancement of innate host defense. Certain probiotics also have anti-viral effects, including against coronavirus. *Enterococcus faecium* inhibits replication of enteropathogenic coronavirus transmissible gastroenteritis virus (TGEV) in swine testicular cells. This involves direct interference of virus attachments, adsorptive trapping or virus particle inactivation through surface components of the probiotics and stimulating the synthesis of pro-inflammatory cytokines IL-6 and IL-8 and nitric oxide. Probiotics can also interfere with ACE 2, the primary host receptor of the SARS-CoV-2. For instance, during milk fermentation, *Lactobacillus helveticus* and *Lactobacillus casei* release peptides with high affinity for ACE. Bovine milk fermented with *Lactobacillus* species yields fermented products enriched with ACE-inhibitory peptides, of which many are resistant to GI digestion and inhibit ACE in the renin-angiotensin system (RAS). In vitro and in vivo experiments have demonstrated antihypertensive effects of fermented milk products [6].

As known, COVID-19 is a multi-organ phenomenon, requiring appropriate systemic inflammatory control for overall survival. Besides, COVID-19 infection expresses new presentations, such as pediatric multisystem inflammatory syndrome, which includes features like Kawasaki disease. “Cytokine storm” or the excessive release of inflammatory cytokines is the reason for severity and death of COVID-19 patients. Therefore, anti-cytokine therapy for the suppression of the hyper inflammatory states is a recommended strategy to treat severe COVID-19. So far, many preclinical studies with probiotics have focused on influenza and pneumonia, demonstrating benefits from oral or nasal administration of probiotics, which prolonged survival, reduced weight loss, diminished viral loads in the lung, and minimized bronchial epithelial damage. Protection was mediated by immune regulation, distinguished by potent viricidal properties by early recruitment of innate immune system through alveolar macrophages, NK lymphocytes and heightened proinflammatory cytokines such as TNF- α and IL-6, etc. This inflammatory boost is followed by a rapid decline, attributed to enhanced anti-inflammatory mediators like Treg cells and IL-10 in the lungs, diminishing lung injuries. Moreover, probiotics’ ability to modulate vitamin D/VDR and balancing the composition and growth of gut microbiota, together suggest the immunomodulatory potential in ameliorating the cytokine storm. Therefore, the use of probiotics with anti-inflammatory effects could maintain the equilibrium of intestinal microecology and prevent secondary infection in COVID-19 [2, 6, 7].

Conclusions.

In view of probiotics supplementation could reduce the severity of COVID-19 morbidity and mortality. Probiotics can inhibit cytokine storm by simultaneously boosting the innate immunity and evading the exaggeration of adaptive immunity, which is challenged to respond quickly to the viral onslaught. Probiotics-induced suppression of the inflammatory cytokine response may prevent both the severity and the occurrence of ARDS, making probiotics an attractive adjunct. Inventing effective therapy will transform the impact of the pandemic on lives as well as economies across the globe. Therefore, supplementation of probiotics in high risk and severely ill patients, and frontline health workers, might limit the infection and flatten the COVID-19 curve.

Thus, the design of different generations of probiotic drugs (pro-, syn-, para-, postbiotics and imunobiotics, etc.) for the prevention and treatment of SARS-CoV-2 infection is a timely and promising issue in modern biotechnology. As well as a rational combination of probiotic drugs and functional foods enriched with probiotic microorganisms, along with modern treatments can significantly improve and accelerate the recovery of patients with COVID-19.

Literature

1. Zuo T., Wu X., Wen W., Lan P. Gut Microbiome Alterations in COVID-19. // Genomics Proteomics Bioinformatics. – 2021.- Vol. 21. – P. 1-25. DOI: 10.1016/j.gpb.2021.09.004

2. Старовойтова С. О. Взаємозв'язок пробіотиків та SARS-COV-2 (Covid-19) in vivo // Наукові праці НУХТ.- 2021. - Том 27, №4. – С. 53- 62. DOI: 10.24263/2225-2924-2021-27-4-7.

3. Mirzaei R., Attar A., Papizadeh S., Jeda A.S., Hosseini-Fard S.R., Jamasbi E. et. al. The emerging role of probiotics as a mitigation strategy against coronavirus disease 2019 (COVID‑19). // Archives of Virology. -2021. – Vol. 166, № 7. P. 1819-1840. DOI: 10.1007/s00705-021-05036-8.

4. Khaled J.M.A. Probiotics, prebiotics, and COVID-19 infection: A review article. // Saudi Journal of Biological Sciences. – 2021. – Vol. 28. – P. 865-869. DOI: 10.1016/j.sjbs.2020.11.025.

5. Kullar R., Johnson S., McFarland L.V., Goldstein E.J.C. Potential Roles for Probiotics in the Treatment of COVID-19 Patients and Prevention of Complications Associated with Increased Antibiotic Use. // Antibiotics. – 2021. – Vol. 10, № 4. – P. 1 – 10. DOI: 10.3390/antibiotics10040408.

6. Zafar N., Aslam M.A., Ali A., Khatoon A., Nazir A., Tanveer Q. et. al. Probiotics: Helpful for theprevention of COVID-19? // Biomedical Research and Therapy. – 2020. – Vol. 7, № 11. – P|. 4086-4099.

7. Kurian S.J., Unnikrishnan M.K., Miraj S.S., Bagchi D., Banerjee M., Reddy B.S. et. al. Probiotics in prevention and treatment of COVID-19: current perspective and future prospects. // Archives of Medical Research. – 2021. – Vol. 16. – P. 1-13. DOI: 10.1016/j.arcmed.2021.03.002.