GENERAL REVIEW

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Oral microbiome, COVID-19 and probiotics

Oralni mikrobiom, COVID-19 i probiotici

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Ključne reči:
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Introduction

The COVID-19 pandemic is an ongoing global pandemic that seriously endangers human life and health. Clinical presentation of this disease varies from completely asymptomatic or mild infection to severe complications, post-COVID syndrome, and even lethal outcome [1].

The etiologic agent of COVID-19 disease is the SARS-CoV-2 virus, an RNA-positive single-stranded virus from the *Coronaviridae* family. Even though coronaviruses primarily cause zoonotic infections, there are currently seven strains that can cause an infection in humans [2]. There are five different variants resulting from genetic evolution that have been identified since the onset of the pandemic: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) [3].

The SARS-CoV-2 virus is one of many respiratory viruses where the oropharynx is the primary site of entry and replication [4]. It binds to angiotensin-converting enzyme 2 (ACE-2) receptors *via* its glycoprotein extension (S protein) [4–6]. These receptors are present on the tongue, oral and nasal mucosa, salivary glands, and nasopharynx [7–11]. The study of Xu et al. [12] showed higher ACE-2 expression in small salivary glands than in lungs during COVID-19 disease, proving that salivary glands represent a significant virus reservoir [13].

Since the beginning of the COVID-19 pandemic, basic preventive measures have been applied to prevent the transmission of the virus (hand disinfection, wearing face masks, social distancing, and quarantine). Thirteen different official treatment protocols were introduced, though currently, there is no optimal treatment [1]. Antiviral therapy, vaccines, and immunomodulating agents are widely used in order to reduce disease severity, especially in patients with an increased risk of developing a severe clinical form of the disease [14]. While searching for the most effective treatment against the COVID-19 infection, scientists and clinicians have also applied alternative possibilities for improving immunity [15]. Recent research data have revealed the interaction of intestinal and respiratory systems in immunity induction, acting as local and systematic modulators of inflammation [16].

The human microbiome is important for blocking inflammation and immunity regulation. The impact of oral microbiome (OM) dysbiosis in patients with COVID-19, which can directly or indirectly favor the development of the infection and affect the pathogenesis of the disease, has been recognized. The human microbiome plays a significant role in the immune response of the host to respiratory viral infections. The modulation of local and systemic immune reactions by using probiotics is one of the most promising effects of probiotics on overall human health [15]. The presence and registration of dominant microbial communities in an individual's OM can enable personalized therapy that aims at restoring the microbiome and preventing the occurrence of many diseases in the future [17].

Many studies on COVID-19 published in the past three years have examined the exact mechanism of virus replication at the primary site of infection, as well as the role of OM on SARS-CoV-2 virus binding capacity and infection development [4, 5, 9, 18–25]. The goal of this review was to evaluate the role of OM in the prevention of SARS-Cov-2 virus infection and its impact on the severity of COVID-19 clinical presentation. In addition, the aim of this literature review was to present possible preventive and therapeutic applications of probiotics which were used as one of the

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remedies against SARS-Cov-2 virus infection. This review focuses on the analysis of oral microbiota during the COVID-19 infection and gives us new insights into the relationship between microbiota and probiotics.

Oral microbiome

The human OM is the genome of all microorganisms which inhabit the oral cavity. The term "microbiota" refers to a specific and unique composition of microbial population that affects health and varies from person to person. In many studies, these two terms are equated [26–28].

Oral flora is the second largest and one of the most diverse microbiomes in the human body, right after the intestines, which weigh about 2 kg [29–32]. The composition of oral flora is heterogeneous and contains over 1,000 different bacterial species, viruses, fungi, helminths, protozoa, and archaea that persist in mutual balance but also in symbiosis with the host [23, 33–35]. Each person has a complex of microorganisms, and everyone carries an individual microbiome that develops over a lifetime. The composition and diversity of the OM can be influenced by the following: the duration of pregnancy, delivery method, breastfeeding, genetic factors (sibling microbiota profiles are more similar when compared to the profiles of persons who are not related), environmental conditions (oral hygiene, saliva quality, and quantity), habits (tobacco, alcohol, stress, etc.), diet, certain drugs (antibiotics, antacids, etc.), age (three stages of evolutionary development: childhood, adulthood, and old age), and individual general health [4, 36–42].

The most common species of bacteria in the OM are representatives of the genera *Bacteroides*, *Synergistes*, *Gemella*, *Granulicatella*, *Streptococcus*, *Veillonella*, the phyla Actinobacteria, Proteobacteria, Tenericutes, Firmicutes, and Spirochaetes, while oral viruses are mainly composed of eukaryotic viruses such as *Herpesviridae*, *Papillomaviridae*, and *Anelloviridae* [human papillomavirus (HPV), human cytomegalovirus (CMV), herpes simplex virus type-1 (HSV-1), and Epstein-Barr virus (EBV)] [32, 43]. *Myoviridae* and *Podoviridae* belong to lytic viruses (they rapidly degrade their bacterial hosts), while *Siphoviridae* are lysogenic viruses that are in balance with the host bacteria. Oral viruses represent a restricting factor for bacterial growth and can control bacterial oral populations [44, 45]. Research by Peters et al. [46] described 154 species of commensal fungi and confirmed that the *Candida* genus was most commonly present in 70% of healthy patients. Recent studies revealed the commensal presence of different genera of protozoa, helminths, and archaea. Nonetheless, their pathogenic potential in the development of oral diseases is still unexplored [47–49].

Importance of oral microbiome in oral and general health

The oropharyngeal microflora in a healthy host maintains balanced symbiotic relationships defined as "microbial homeostasis" (eubiosis) [32]. The OM is exposed to frequent daily fluctuations that can lead to microbial imbalance (dysbiosis) [50, 51]. Microbial balance in the oral cavity is necessary because it enables equilibrium between beneficial and harmful microorganisms that interact with each other and can have an inhibitory, stimulating, or synergistic effect on each other [32, 50, 51]. The OM contributes to the development of the local immune system. However, its imbalance, along with the complex interaction with the host resistance and various environmental factors, creates conditions for the development of various oral or systemic diseases (Figure 1) [17, 52, 53]. During dysbiosis, the following three changes occur: loss of

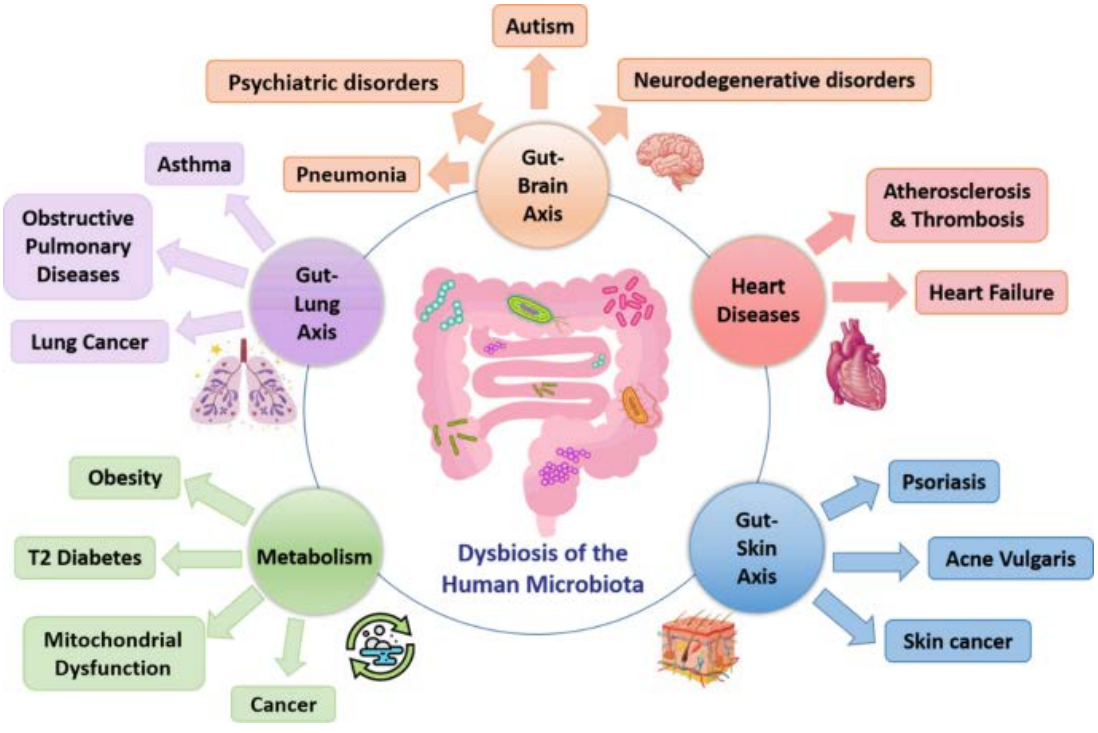

Fig. 1 - Impact of microbiota dysbiosis on the overall health of humans [52].

microbial diversity, loss of beneficial microorganisms, and increase in pathogenic microorganisms that are not mutually exclusive and can occur simultaneously [54]. As a result, potentiating cariogenic and inflammatory bacterial genomes [33, 55] make perfect conditions for the development of diseases such as caries [56–59], periodontal diseases [60–64], and malignant alterations of oral tissues [65–67].

Many oral microorganisms enter the digestive tract through saliva, thus changing the intestinal microbiome, which plays an important role in digestion and absorption of nutrients, formation of a protective barrier against pathogens, development and regulation of the immune system, enzyme and vitamin production, control of inflammatory reactions, and neuro and psychological regulation [35]. Consequently, the connection between the oropharyngeal and intestinal microbiome sheds new light on inflammatory processes and their therapy. The link between oral and general health is well documented in the literature [35, 50, 52, 68–76]. Chronic oral infections lead to the release of proinflammatory mediators, i.e., cytokines that further propagate inflammatory processes and increase the risk of muscle and digestive problems [61, 72], bronchopulmonary diseases [37, 73], rheumatoid arthritis (RA) [53, 67], complications during pregnancy and childbirth [38, 41, 64, 71, 75], cardiovascular diseases [61, 67, 69, 70, 75, 76], obesity [42], liver disease [67], oral cancer [65], pancreatic cancer [77], type 2 diabetes [67, 68], Parkinson's disease [74], psychiatric disorders [78], and colorectal cancer [67]. Each disease is characterized by unique oral and intestinal microbial changes [79]. Microbiome rebalancing is closely related to the recovery from the primary disease, which proves the significant role of the microbiome in healing [72, 80].

Maintaining good oral hygiene is, therefore, important in controlling oral bacterial status, maintaining or restoring symbiotic homeostasis, as well as preventing the spread of oral pathogens to other parts of the body [81–83].

Disruption of the oral microbiome during and after SARS-CoV-2 virus infection

Human OM can have a great influence on the regulation of innate and acquired immunity to viral infections [4], which is especially important for viruses that enter the body through the oropharynx [5, 23, 84–86]. Aerosol respiratory viruses encounter the OM of the upper respiratory tract and favor its dysbiosis and disease progression [87, 88] (e.g., the microbiome in patients with influenza is characterized by the abundance of genus *Pseudomonas*) [75]. Oral dysbiosis promotes respiratory infections directly by increasing pathogenic bacteria and aspirating oral pathogens into the respiratory organs. Indirectly, it alters the immune response of respiratory epithelium and promotes the adhesion of pathogens, cytokine secretion, and production of enzymes that interfere with pathogen clearance [23, 89]. Even in the case of SARS-CoV-2 virus infection, oral dysbiosis may favor the development of infection by these mechanisms [4]. On the other hand, OM can also contribute to the regulation of immunity and inflammation blockade [13, 30, 84, 90]. The study of Pfeiffer and Sonnenburg [91] showed that oral microbiota commensals could also produce antiviral compounds (defensins) against several viral genera (*Adenovirus*, *Herpesvirus*, *Papillomavirus*, *Orthomyxovirus*, and *Coronavirus*).

The oropharyngeal and intestinal microbiota have the possibility of co-infection with microorganisms originating from the oral cavity. The correlation between the imbalance of OM and the increased number of dysbiotic species may serve as predictive factors for COVID-19 disease [5, 35, 79, 92–104]. Ward et al. [24] showed that the severity of COVID-19 disease could be predicted according to the composition of the intestinal or OM. Two pathogens, *Porphyromonas endodontalis* in oral and *Enterococcus faecalis* in the intestinal microbiome, may serve as a predictor of the severity of SARS-CoV-2 infection. The authors suggested that the key to prioritizing patients who need urgent treatment is the identification of biomarkers that can predict clinical outcomes of COVID-19 disease [24].

Haran et al. [23] described how the dysbiosis of the inflammatory type of OM, characterized by the members of genera *Prevotella* and *Veillonella*, may play an important role in prolonging the duration of COVID-19 symptoms. The genus *Veillonella* are gram-negative anaerobic cocci that produce large amounts of lipopolysaccharides and may be an additional co-infectious agent (especially *Veillonella dispar* and *Veillonella infantium*) [98]. The genus *Prevotella* is highly inflammatory and affects the promotion of SARS-CoV-2 infection, thus worsening the severity of the COVID-19 clinical presentation [105–107]. Haran et al. [23] emphasized the importance of the presence of gram-negative bacteria with a liposaccharide component in the capsule (*Leptotrichia* and various species of genus *Veillonella*) which can have proinflammatory effects and cause systemic damage and neuroinflammation. Due to OM dysbiosis and the presence of pathogens that promote chronic inflammation (*Leptotrichia*, *Prevotella*, and *Fusobacterium*), myalgic encephalomyelitis and symptoms of neurological diseases (confusion, disorientation, slow thinking, and poor concentration after six months) may occur in COVID-19 [102–104]. The present commensals (*Prevotella* and *Neisseria*) in OM can act as a local probiotic and counteract the SARS-CoV-2 virus [17]. Likewise, the higher relative abundance of the *Rothia* genus in the patient's oral flora affects the occurrence of COVID-19 complications [108].

Ren et al. [79] identified specific microbial markers of oral microbiota in patients with COVID-19 but also in recovered patients. The results of this study showed compositional and functional changes in OM of COVID-19 patients. During infection, there is an overall decrease in the diversity of oral microorganisms. The number of bacteria that produce lipopolysaccharides was increased, while the number of bacteria that produce butyric acid was decreased. Thus, by secreting lipids into the bloodstream, microbiome dysbiosis may affect the progression of COVID-19. Ren et al. [79] also noticed a better prognosis in patients with severe COVID-19 who had an OM enriched with *Streptococcus* (*S. parasanguinis*). Oral dysbiosis persisted even after the recovery from COVID-19 infection when a constant increase in *Porphyromonas* and *Haemophilus* gen-

era and a decrease in *Leptotrichia*, *Megasphaera*, and *Selenomonas* (*Megasphaera* is a cariogenic bacterium) [106] genera was detected.

Furthermore, an imbalance in the relative numbers of different bacterial strains and the genera *Enterococcus* and *Enterobacter* were present only in patients with COVID-19 (not observed in the control group of healthy patients) [5]. Ward et al. [24] showed that higher quantities of *Porphyromonas endodontalis* are correlated with an increase in severe stages of COVID-19, while higher quantities of *Muribaculum intestinale* are linked with moderate cases. Cox et al. [95] also highlighted the impact of coinfections on the clinical presentation and mortality of patients with COVID-19. They indicated an association between cariogenic and oral pathogenic bacteria and complications of COVID-19. According to the earlier literature evidence, these bacteria are involved in the pathogenesis of respiratory and chronic inflammatory systemic diseases (type 2 diabetes mellitus, hypertension, cardiovascular disease), which are also the most common comorbidities associated with the risk of severe complications and death from COVID-19 [97, 109, 110]. Marouf et al. [101] also observed an abundance of periodontopathogenic bacteria in COVID-19 patients and demonstrated that the presence of periodontitis was associated with a 3.5-fold higher risk of admission to intensive care units, a 4.5-fold higher risk of assisted ventilation, and an 8.81-fold higher risk of mortality independent of other concomitant risk factors. On the other hand, numerous studies reported that interventions aimed at boosting oral hygiene in patients with pneumonia have significantly improved the clinical picture and reduced mortality [23, 35, 105, 107].

The exact genome of oral flora in patients with COVID-19 is still the focus of scientific interest. Iebba et al. [20] were among the first who had described the bacterial component of OM in patients with COVID-19, pointing to the importance of fungi and viruses in defining individual sensitivity. By examining an oropharyngeal swab, Ai et al. [93] found that more than half of COVID-19 patients had co-infection with another virus, such as influenza A or B, rhinoviruses, enteroviruses, or respiratory syncytial virus. Soffritti et al. [5] investigated an association between OM profile and severity of COVID-19 clinical presentation and observed a significant increase in *Herpesviridae* viruses, EBV, and HSV-1. EBV infection in patients with COVID-19 has been associated with an increased risk of severe COVID-19 symptoms as well as a fatal outcome [96, 99].

Changes have also been observed in the fungal part of the microbiome, with the appearance of *Aspergillus*, *Nakaseomices*, and *Malassezia spp*., *Candida albicans*, *Saccharomyces cerevisiae*, *Aspergillus fumigatus*, and *Malassezia restricta* (OM of healthy patients consists only of *Candida* and *Candida cerevisiae*, *Aspergillus fumigatus*, and *Malassezia restricta*) [5]. According to Jasinski-Bergner et al. [109], these changes in COVID-19 patients could be an inducing factor influencing the onset of SARS-CoV-2 virus infection because dysbiosis facilitates the activation or reactivation of oral pathogens, which can further impair proper immune control and lead to deterioration of immune response effectiveness.

Ward et al. [24] found that the composition of OM has a high accuracy of COVID-19 severity prediction (84% accuracy of predicting fatal outcome).

Application of probiotics

With the emergence of increasing antibiotic resistance, new concepts for the prevention and therapy of multidrug-resistant infections are proposed by causing the microbiological shift of the endogenous microbiota. For this reason, research into bactericidal action and antiviral factors of probiotics became the focus of modern interest [107, 111–113].

Positive effects of probiotics are primarily observed in the treatment of gastrointestinal infections but also in the prevention of various pathological conditions in the field of gastroenterology, allergology, internal medicine, oncology, oral medicine, pediatrics, infectiology, and psychiatry [104–107, 109–114].

Modern therapeutic procedures have introduced changes in treatment protocols with a tendency to establish a healthy environment to prevent the development of opportunistic infections and recover the OM. Probiotics are living microorganisms (so-called "good" bacteria) that, if applied in an adequate amount, could establish and maintain the ecological balance of microflora. They are safe, non-pathogenic, non-invasive, and non-carcinogenic strains that can perform recolonization and restore symbiosis between the host and the disturbed microbiota [115]. Several bacterial genera are most often used as probiotics: *Bifidobacterium*, *Lactobacillus*, *Bacillus*, and *Pediococcus*. The strains used most often *are Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*. In addition, fungi can be used as probiotics [112–115].

Probiotics act in complex multifactorial ways. Probiotic bacteria can interfere with the absorption process by directly binding to the virus or inhibiting the entry into the epithelial cells by blocking the host receptor [25]. Probiotics can also compete with nutrient pathogens, produce antimicrobial agents, strengthen the intestinal epithelial barrier, and modulate the immune system of the host [116–118]. The performance of probiotics can be twofold – immunostimulatory and immunoregulatory. A group of immunostimulatory probiotics affects the proliferation of T helper (Th) 1 cells and stimulates the production of interleukin (IL)-12, which induces the production of interferon-gamma (IFN-γ) in natural killer cells. Immunoregulatory probiotics stimulate regulatory T cells but also suppress proinflammatory responses by inducing IL-10 [117]. Experimental animal models showed that balancing cellular and humoral immune responses mitigates the effects of a "cytokine storm" [25, 119].

The significant role of probiotics in maintaining homeostasis of the upper respiratory tract microbiome was proven in multiple studies. In addition, it was revealed that oropharyngeal probiotics are very effective in maintaining immune

system stability and protecting against viral infections [120–122]. Direct and indirect efficiency of various probiotic strains (e.g., *Lactococcus lactis* JCM 5805 and *Bacteroides breve* IIT4064) has been proven against influenza virus [123]. Probiotic bacteria release various substances, such as bacteriocins, biosurfactants, lactic acid, hydrogen peroxide, nitric oxide, and organic acids, which can inhibit virus proliferation [25]. *Lactobacillus* genus produces lactic acid as an antiviral inhibitory metabolite, thus preventing secondary infections [124]. Furthermore, like the genus *Bifidobacterium*, *Lactobacillus* genus can capture the virus and interfere with the binding of the virus to the receptors of the host cell [125, 126]. Nisin and peptide P18 are bacteriocins with antiviral effects against influenza A virus [127]. Apart from bacteriocin production, the antiviral ability of oropharyngeal probiotics is also maintained by the stimulatory effect on the innate immune response, which is manifested by an increase in the IFN-γ levels in human saliva ten hours after oral administration of *Streptococcus salivarius* (strain K12) lozenge [128]. Probiotic strains of genera *Lactobacillus* and *Bifidobacterium* (such as *Lactobacillus reuteri* ATCC 55730, *Lactobacillus paracasei*, *Lactobacillus casei* 431, *Lactobacillus fermentum* PCC, and *Bifidobacterium infantis* 35624) are significant factors in generating immunomodulatory responses during various infections [25, 129]. In addition, probiotic bacteria have antioxidant potential in neutralizing free radicals. The strains *Lactobacillus rhamnosus* GG, *Lactobacillus plantarum* CAI6, *Clostridium butyricum* MIIAIRI 588, and strains in VSL#3® increase total antioxidant capacity [130]. Moreover, by participating in the formation of redox homeostasis, probiotics can inhibit the progression of COVID-19 disease [25].

Probiotics and COVID-19

The proven effectiveness of probiotics both in the treatment and prevention of viral infections was the rationale behind their use in patients with SARS-Cov-2 virus infection [25, 28, 131–135].

In the last three years, studies dealing with the importance and benefits of probiotics in the prevention and treatment of COVID-19 have been conducted (Table 1) [21, 135-143]. The use of probiotics, along with other therapies, led to a shorter and easier clinical presentation, with reduced severity of gastrointestinal and respiratory symptoms, a lower percentage of smell and taste disorders, and less frequent symptoms of post-COVID syndrome [125–143]. However, in patients on corticosteroid therapy, probiotic supplemental therapy is contraindicated due to their primary disease [135].

The first study that proved the positive effects of probiotics in the treatment of COVID-19 infection was the 2020 Wuhan study [21]. The use of the probiotic strain ENT-K12 (*Streptococcus thermophilus*) among medical workers in institutions for COVID-19 treatment has reduced the possibility of respiratory infection and lethal outcomes by 80%. This probiotic strain locally releases two antibiotics (salivaricin A2 and B) and reduces the possibility of colonization of β-hemolytic group A streptococci, including *Streptococcus pyogenes* (a bacterial pathogen that causes coinfection during viral infection). The use of probiotics has also reduced the use of antibiotics among the respondents by more than 90% [21].

Block [144] suggested the concomitant use of probiotics in patients with COVID-19, treated with azithromycin, to reduce the risk of hypercolonization of *Candida albicans* strains. Nutritional support with probiotic strains of *Lactobacillus acidophilus*, *Bifidobacterium*, and *Saccharomyces boulardii*, along with minerals and vitamins, has reduced the complications of massive antibiotic therapy [145–147].

D'Ettorre et al. [135] compared the incidence of respiratory failure and control of symptoms, after probiotic therapy, with different *Streptococcus*, *Lactobacillus*, and *Bifidobacterium* strains. The use of probiotics was associated with a lower risk of respiratory failure and faster control of COVID-19 symptoms (especially diarrhea). In patients with a severe clinical picture, the immunomodulatory effects of probiotics may be relevant for the prevention of acute respiratory distress syndrome and multiple organ failure as a complication of cytokine storm [135].

Ceccarelli et al. [147] observed a lower mortality rate after the use of probiotic strains of genera *Streptococcus*, *Bifidobacterium*, and *Lactobacillus* during COVID-19, but with longer hospital stays. However, research by Bozkurt and Bilen [142] showed that in patients with moderate and severe COVID-19 symptoms, an additional therapeutic dose of the probiotic strain *Bifidobacterium animalis* resulted in a shorter hospital stay and lower mortality rates.

Probiotics mechanism of action in COVID-19

The mechanism of probiotic protection against SARS-CoV-2 infections is based on general effective principles, such as inhibition of pathogen adhesion and antimicrobial and immunomodulatory specific properties of different probiotic strains [118, 145, 148]. These mechanisms can enhance the elimination of the SARS-Cov-2 virus but also act preventively by suppressing bacterial coinfections that correlate with COVID-19 (Figure 2) [118, 148, 149].

During fermentation, probiotic strains produce specific bioactive peptides that block ACE-2 enzyme receptors, thus preventing the SARS-CoV-2 virus from binding to these active sites [4, 150, 151]. The remnants of dead probiotic cells can act as ACE-2 inhibitors as well. These bioactive peptides may modulate blood pressure due to the inhibition of the conversion of angiotensin-I to angiotensin-II. The possible effect of these peptides on reducing the progression of COVID-19 is still being examined [152]. The concept of using ACE-2 receptor-blocking drugs as a treatment modality for COVID-19 was first proposed by Fernandez-Fernandez [151]. Imai et al. [152] reported that the usage of ACE blockers had a positive effect on the reduction of respiratory distress syndrome. The study by Singh and Rao [25] confirmed that by binding mucosal cell receptor and ACE-2, probiotic strains interfere with coronavirus and block its binding, while an increase of innate immunity is stimulated by releasing intestinal mucins from mucosal cells and producing secretory antibodies (IgA). The authors stated that the key role in combati-

Table 1

Review of clinical studies which used probiotics in the prevention and therapy of COVID-19 disease *

Reference	Country	Study type	Subjects	Probiotic strain	Intervention	Main results
d'Ettorre et al. [135]	Italy	Single group	70 patients with COVID-19 hospitalized	*Streptococcus thermophilus* DSM 32345, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lacticaseibacillus paracasei* DSM 32243, *Lactiplantibacillus plantarum* DSM 32244, *Levilactobacillus brevis* DSM 27961, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247	Daily oral 2.4 billion CFUs bacteria for a period of 14 days	Probiotic intervention demonstrated a significant improvement in clinical conditions among patients with COVID-19.
Tang et al. [136]	The United States	Double-blinded, randomized, placebo-controlled trial	1,132 individuals with household contacts who tested positive for COVID-19	*Lacticaseibacillus rhamnosus* GG (ATCC 53103)	Daily oral *Lacticaseibacillus rhamnosus* GG or placebo for a period of 28 days	Low-cost and safe probiotics can serve as a rapid intervention strategy in the prevention or reduction of symptoms of pandemic diseases.
Endam et al. [137]	Canada, Saudi Arabia, and the United States	Prospective randomized clinical trial	23 individuals between 18–59 years of age received late PCR positive tests for SARS-CoV-2	*Lactococcus lactis* W136	Nasal irrigations through a buffered isotonic solution containing 2.4×10^9 CFUs of *Lactococcus lactis* W136 or buffered isotonic saline isolated for two weeks (twice a day)	Probiotic intranasal intervention was correlated with a reduced number of patients showing moderate/severe symptoms of fatigue, loss of smell perception, and sensation of breathlessness, and by decreased percentage of individuals with moderate/severe facial pain or sore throat.
Gutierrez-Castrellon et al. [138]	Mexico and Spain	Single-center, quadruple-blinded randomized clinical trial	300 outpatients with symptomatic COVID-19 (ages 18–60) with positive nucleic acids test for SARS-CoV-2	*Lactiplantibacillus plantarum* KABP022, KABP023 and KAPB033, *Pediococcus acidilactici* KABP021	Daily ingestion of 10^9 CFUs for a period of 30 days	Remission was achieved by 53% of probiotic group compared to 28% in placebo group.
Mozota et al. [139]	Spain	Single group	29 residents of a nursing home who tested positive for COVID-19	*Ligilactobacillus salivarius* MP101	Daily consumption of 10^9 CFUs of *Ligilactobacillus salivarius* MP101 per unit of product (125 g)	Certain immune factors can be utilized as possible nasal or fecal biomarkers of benefits of probiotic strain supplementation in the diet of elderly people infected with SARS-CoV-2.
Wang et al. [21]	China	Retrospective study	138 patients	5×10^7 CFUs of live *Bifidobacterium longum*; live *Lactobacillus bulgaricus* and *Streptococcus thermophilus* (should not be lower than 0.5×10^6 CFUs)	Four doses at a time, 3 times a day	Compared to the control group, patients treated with probiotics showed a significantly reduced time for achieving a negative nucleic acid test while the inflammation indexes, including PCT and CRP, were significantly reduced.
Wang et al. [140]	China	Randomized controlled clinical trial	200 frontline medical staff	One billion CFUs of *Streptococcus thermophilus* ENT-K12 over shelf-life	Slowly dissolving oral lozenge	Significantly reduced incidence of respiratory tract infections by 64.8%, reduced the time experiencing respiratory tract infections and oral ulcer symptoms

Table 1 (continued)

Wang et al. [140]	China	Randomized controlled clinical trial	200 frontline medical staff	One billion CFUs of *Streptococcus thermophilus* ENT-K12 over shelf-life	Slowly dissolving oral lozenge	Significantly reduced incidence of respiratory tract infections by 64.8%, reduced the time experiencing respiratory tract infections and oral ulcer symptoms by 78%, shortened the sick-leave days by 95.5%, and reduced the time under medication in cases when there was no record of antibiotic and anti-viral drug intake in the probiotic group.
Li et al. [141]	Wuhan, China	Retrospective single-center study	311 COVID-19 patients	*Lactobacillus rhamnosus* GG	Daily oral administration per 32 days	Moderates immunity and decreases the incidence of secondary infection in COVID-19 patients.
Bozkurt and Bilen [142]	Turkey	Retrospective study	44 moderate/severely ill adults	One trillion CFUs *Bifidobacterium* BB-12 strain	Oral administration in 250 mL water. Total doses were divided into three parts and administrated to patients for 3 days	Lower mortality, shortening the length of stay in hospital, early radiologic improvement and decrease plasma IL-6 level in moderate/severe SARS-CoV-2 patients in the probiotic group.
Wischmeyer et al. [143]	The United States	Randomized, double-blind, placebo-controlled trial	182 participants	*Lactobacillus rhamnosus* GG	Daily oral use for 28 days	Prolonged time for development of COVID-19 infection, reduced incidence of symptoms and changes to gut microbiome structure when used as post-exposure prophylaxis within seven days after probiotic exposure.

COVID-19 – corona virus disease-19; CFUs – colony forming units; PCR – polymerase chain reaction test; CRP – c-reactive protein; PCT – procalcitonin; IL – interleukin; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2.
***Modified Table of Xavier-Santos et al. [134]**

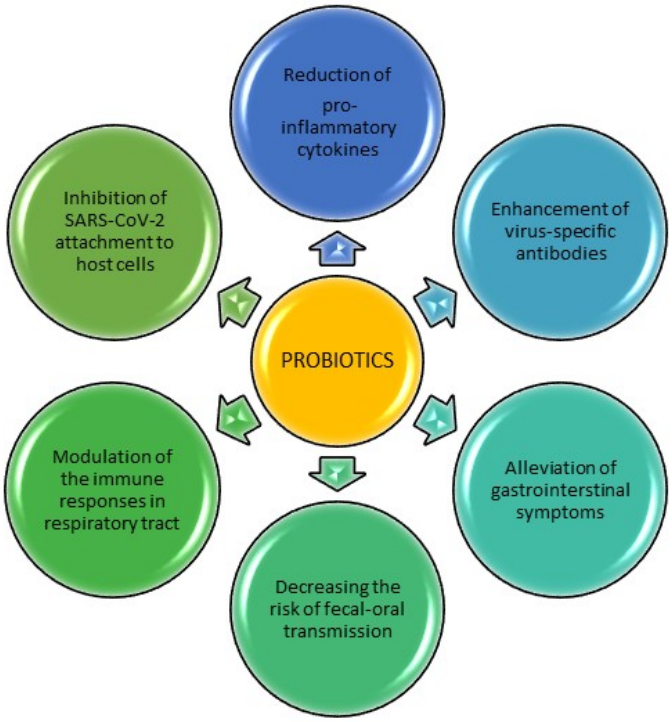

Fig. 2 - Antiviral mechanisms of probiotics against SARS-CoV-2 infection.

ng coronavirus proliferation is played by modulation of immune responses and balance of acquired immunity, production of inflammatory cytokines, the proliferation of B cells that produce specific antibodies, and activation of cytotoxic T lymphocytes that participate in the adaptive immune response [27]. Baindara et al. [126] also showed that some probiotics improved the regulatory activity of T cells and reduced the production of proinflammatory cytokines. In addition, the antiviral effect of probiotics may be achieved by a large number of secreted specific metabolites and bacteriocins [153].

Strengthening the immune response during incubation and the initial phase of COVID-19 disease is crucial in eliminating the virus and preventing the progression of the disease. The use of certain strains of *Bifidobacterium* or *Lactobacillus* has a great influence on the elimination of the SARS-CoV-2 virus from respiratory organs [154]. The use of probiotics, along with adequate treatment for COVID-19, can significantly reduce the occurrence and duration of various systemic diseases [154, 155].

The limitations of this comprehensive literature review arise due to the high heterogeneity of studies that investigated the change and impact of oral microbiota during COVID-19 without knowing the previous status of patients' OM and because patients with different immune statuses used different probiotic strains.

It should be emphasized that introducing targeted drugs and beneficial bacteria was of great importance in restoring the damaged microbiome. Further research should be directed to discovering the most effective probiotic strains, doses, and formulations, as well as the interaction of probiotics and microbiomes. In addition, the influence of environmental factors on the oropharyngeal microbiome, as well as possible coinfection, should be further investigated.

Conclusion

After an extensive review of the literature, it was concluded that numerous clinical studies showed that OM might influence resistance to primary infection and be a predictor for disease severity and complications during COVID-19. The use of probiotic strains can inhibit the adhesion of pathogens, improve the barrier function of the intestine and strengthen the immune response. Through these mechanisms, probiotics can reduce the progression and the development of more severe forms of the disease, shorten the hospital stay and reduce the frequency of post-COVID syndrome.

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