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The Effectiveness of Probiotics against Viral Infections: A Rapid Review with Focus on SARS-CoV-2 Infection

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Abstract

Viral infections have gained great attention following the rapid emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic around the globe. Even with the continuous research on developing vaccines and antiviral agents against various viral infections, no specific treatment or vaccine has been approved for many enteric or respiratory viral infections; in addition, the efficiency of currently available treatments is still limited. One of the most reliable and recommended strategies to control viral infections is prevention. Recently, intense studies are focusing on a promising approach for treating/preventing various viral infections using probiotics. As per the World Health Organization (WHO), probiotics can be defined as "live microorganisms which, when administered in adequate amount, confer a health benefit to the host." The use of probiotics is a simple, cost-effective, and safe strategy to prevent viral infections, specifically; respiratory tract and intestinal ones, by different means such as stimulating the host's immune response or modulating gut microbiota. In this rapid review, we emphasize the protective effects of probiotics against viral infections and proposed mechanisms for protection that might offer a novel and cost-effective treatment against current and newly discovered viruses like SARS-CoV-2.

Introduction

The first scientific evidence regarding probiotics was made by Nobel laureate Metchnikoff, who sensed that the intake of non-pathogenic bacteria with yogurt had a positive influence on endogenous bacterial flora and gastrointestinal tract's functionality [1]. The term "probiotics" was first used in 1953 by Werner Kollath to describe inorganic and organic supplements of several foods used to improve the health of malnutrition patients [2]. In 1965, Lilly and Stillwell used the term "probiotics" to describe microorganisms that promote other microbial growth [3]. Later, FAO/WHO has defined probiotics as "live microorganisms which, when administered in adequate amount, confer a health benefit to the host [4]." Figure 1 illustrates some beneficial effects of probiotics on human health.

To be classified as a probiotic, the microorganism should have certain characteristics, such as having a human origin source, being non-pathogenic, being resistant to the intestinal environment, and having a beneficial effect on the immune system. The majority of the probiotic microorganisms are "generally recognized as safe, GRAS" [6]. Most lactic acid bacteria (LAB) and bifidobacteria have been described as probiotics [7], [8]. However, the most common probiotic microorganisms are listed in Table 1.

In addition to their important biological activities, the probiotics were previously defined to have antiviral activities. Ang *et al*. [38] have confirmed in this context that *Lactobacillus reuteri* is capable of protecting human skeletal muscles and colonic cell line against Coxsackievirus A and Enterovirus 71 infections. In addition, Galán *et al*. [39] have proven the antiviral activity of *Lactobacillus casei* and *Bifidobacterium adolescentis* against rotavirus infection. Moreover, *Bacillus subtilis* anti-influenza activity and *Lactobacillus gasseri* anti-respiratory sentential virus potential have also been proved by Starosila *et al*. and Eguchi *et al*., respectively. However, many other studies are being conducted to investigate the efficacy of probiotics against certain viral infections.

At the end of the year 2019, an etiological agent responsible for the outbreak of viral pneumonia was detected in Wuhan, Hubei Province, China, and spread rapidly around the world. Then, this new virus was named by the International Committee on

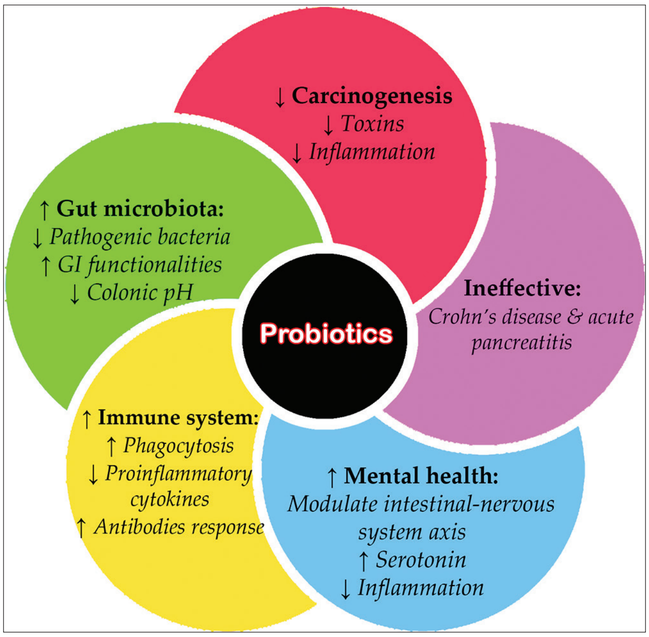

Figure 1: Probiotics' beneficial properties to human health [5]

Taxonomy of Viruses as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 19 (COVID-19) [42]. SARS-CoV-2 belongs to the Orthocoronavirinae subfamily of the Coronaviridae family in the order Nidovirales. Coronaviruses named after the distribution of crown-like spikes on the outer surface of the virus particle. In addition, the nucleic material of these viruses is a single-stranded, positive-sensing RNA (+ssRNA) [43], [44].

Table 1: Some major probiotic microorganisms

Microorganism	Genera	Probiotic strains	References
Bacteria	*Lactobacillus*	*L. acidophilus*	[9], [10], [11], [12], [13], [14], [15], [16]
		L. amylovorus	
		L. brevis	
		L. casei	
		L. crispatus	
		L. curvatus	
		L. delbrueckii subsp. *bulgaricus*	
		L. fermentum	
		L. gallinarum	
		L. gasseri	
		L. johnsonii	
		L. paracasei	
		L. plantarum	
		L. reuteri	
		L. rhamnosus	
		L. salivarius	
	Bifidobacterium	*B. adolescentis*	[17], [18], [19], [20], [21], [22]
		B. animalis	
		B. bifidum	
		B. breve	
		B. infantis	
		B. longum	
		B. thermophilum	
	Enterococcus	*E. faecalis*	[23], [24]
		E. faecium	
	Lactococcus	*L. lactis*	[25], [26]
	Leuconostoc	*L. mesenteroides*	[27]
	Pediococcus	*P. acidilactici*	[28]
	Sporolactobacillus	*S. inulinus*	[29]
	Streptococcus	*S. thermophilus*	[30]
	Bacillus	*B. cereus*	[31], [32]
		B. clausii	
		B. pumilus	
		B. subtilis	
	Escherichia	*E. coli* Nissle 1917	[33], [34]
	Propionibacterium	*P. freudenreichii*	[35]
Yeast	*Saccharomyces*	*S. cerevisiae*	[36], [37]
		S. boulardii	

SARS-CoV-2 genome encodes 27 proteins, including capsid (S) and envelope (N). The S-protein binds the angiotensin-converting enzyme 2 (ACE-2) receptor, which is widespread in many human tissues (including the lungs and gut) and can indirectly modulate nutrient transport to the intestine, reduce the bioavailability of vitamins and amino acids essential for the production of antibodies and immune regulation in general [45]. Clinically, SARS-CoV-2 is reported to cause respiratory and gastrointestinal tract symptoms. Although scientists around the world work hard and respond rapidly in developing a new vaccine or antiviral medication for SARS-2, no COVID-19 vaccine or new effective antiviral medicines are approved yet. In such circumstances, the most reliable and recommended strategy to control viral infections is prevention.

In this review, we sought to elucidate the mechanisms through which the probiotics exert their antiviral and preventive potential as well as the possibility of using them to improve the COVID-19 patient's health.

Possible Antiviral Mechanisms of Probiotics

The probiotics' antiviral effects may exert by several mechanisms, including the production of antiviral inhibitory substances, direct interaction with viruses, or by stimulating the immune system [46]. These proposed mechanisms are summarized below.

Production of Viral Inhibitory Substances

A wide range of antimicrobial compounds is produced by probiotics such as organic acids, bacteriocins, hydrogen peroxide (H_2O_2), exopolysaccharides (EPS), and diacetyl. These agents lead to control other microbial growth [47].

Organic acids

The important and characterized antimicrobial compounds produced by LAB are acetic, lactic acid, and formic acid [48]. The major end-product of sugar fermentation by LAB is lactic acid which used to inhibit microbial growth by stress resultant from the low pH, which, in turn, makes the environment unfavorable for some pathogenic and spoilage microbial growth [49], [50]. The microbial inhibitory effects of organic acids are mainly caused by their dissociated forms, which, by changing the environment into acidic, interfere with essential metabolic functions [51], [52]. The acidic pH has been reported inactivates human immunodeficiency virus (HIV) and herpes simplex virus 2 (HSV-2) [53], [54]. Such low pH may also participate in alleviating SARS-CoV-2 infectivity.

Bacteriocins

Bacteriocins are extracellular, low-molecular-weight proteins that can inhibit the microbial growth of various pathogens with distinct bacteriostatic and bactericidal effects [47], [55]. The majority of bacteriocins are heat stable and sensitive to certain proteolytic enzymes [56]. Many bacteriocins have accordingly been characterized and purified from LAB and used for a variety of industrial and biomedical applications such as food and biopreservation technology, cancer therapy, antimicrobials, and for maintaining human health [57]. Bacteriocins of LAB have some pivotal properties that gain considerable attention, such as (a) being GRAS, (b) non-toxic, (c) protease-inactivated with a slight effect on the gut microflora, (d) can tolerate pH and temperature ranges, (e) having the ability to inhibit many food spoilage bacteria and food-borne pathogens, (f) having bactericidal potential, and (g) they are usually plasmid-encoded [58].

In the past two decades, bacteriocins have been reported to have antiviral properties [59]. They can bind, at the cellular level, to the cell surface receptors [60]. This, in turn, could reduce the cytopathic effects and intracellular RNA of the virus at a pre-incubation condition [61]. Furthermore, bacteriocins and bacteriocin-like substances can interfere with the enzymatic reactions that are important for viral infection [62]. Wachsman *et al*. have proven the antiviral effect of entertain, a bacteriocin, against strains of HSV-1 and HSV-2 by inhibiting late stages of replication and effect on intracellular replication of the virus. *Lactobacillus delbrueckii* subsp. *bulgaricus* 1043 bacteriocin also has a virucidal effect on influenza virus [63]. Moreover, the virucidal effect of the bacteriocin subtilosin, produced by probiotic *Bacillus amyloliquefaciens* has also been reported against HSV and influenza virus [40], [64]. In this context, bacteriocins produced by probiotics may also have such antiviral activities against SARS-CoV-2.

Hydrogen peroxide

H_2O_2 is a compound with high reactivity at high concentrations and quite toxic to the biological systems [65]. In addition, H_2O_2 represents a strong oxidizing agent that has been shown to damage cellular membranes, DNA, and bacterial proteins [66] and have an inhibitory or lethal effect on microorganisms, depending on certain factors including concentration, temperature, pH, and other environmental factors [67]. LAB can produce H_2O_2 when grown in the presence of oxygen through electron-transporting by different mechanisms involving flavin [68] and because they are catalase-negative, H_2O_2 can accumulate to higher concentration [50]. The induction of stress proteins allows LAB to tolerate higher concentrations than the other types of bacteria [69]. Although H_2O_2 and superoxide radical (O^{2-}) are strong oxidant species and can increase the reactive oxygen species that lead to oxidative stress [70], a recent study by Singh *et al*. has revealed that H_2O_2 production by *Lactobacillus johnsonii* could promote epithelial restoration during colitis [71].

In regards to antiviral activities, H_2O_2, superoxide, and hydroxyl radicals are all suspected for inactivating pathogenic viruses [72]. A previous study has also shown that H_2O_2 has a significant anti-influenza virus activity [73]. Typically, H_2O_2 from *Lactobacillus* has a microbicidal effect in the vagina to protect the female genital tract from microbial infection. It also showed notable activities against type-1 and type-2 HIV [72], [74].

Exopolysaccharides

Polysaccharides are polymers composed of 20 to 10^7 units of monosaccharides. They range from linear to highly branched structures [75]. However, EPS are long-chain biological polysaccharides produced by microorganisms [76]. It was proven that EPS have important biological activities such as antibiofilm, antitumor, antioxidant, and immunomodulatory effects [77]. EPS from the probiotic *Lactobacillus plantarum* strain N4 (Lp) have been shown to have an inhibitor effect on the transmissible gastroenteritis virus [77]. Furthermore, Callahan *et al*. [78] reported that EPS could block HIV viral entry. Such EPS may also have a preventive or inhibitory role against SARS-CoV-2.

Direct virus-probiotic interaction

Inactivation of viruses by LAB could also occur through adsorption or trapping mechanism [46]. In this mechanism, the interaction between bacteria and viruses is a principal to exhibit the antiviral effect of probiotics [79]. Conti *et al*. (2009) have reported that *Lactobacillus* isolated from vagina have a protective effect against HSV through the adhesive ability of bacteria to reduce the absorption of the virus. Bacterial cells may directly interact with viral particles and lead to trapping them or competition for cell membrane receptors [62]. A previous study stated that the probiotics trap vesicular stomatitis virus (Indiana vesiculovirus) through interaction between *Lactobacillus* cells and the envelope of the virus directly [80]. Similarly, Mousavi *et al*. [81] reported the mechanisms for the antiviral effect of *L. crispatus* toward HSV-2 and concluded that these mechanisms include (a) formation of micro-colonies in the cell surface, cause blocking to the receptors and effect on the entry of virus into the cells and (b) trapping of viral particles by *L. crispatus* that interact directly with an envelope of the virus. Furthermore, *L. gasseri* inhibited HSV-2 through the trapping mechanism [82]. Furthermore, Wang *et al*. (2013) reported the inhibition of influenza viruses by *Enterococcus faecium* through direct interaction. However, such mechanisms may cease SARS-CoV-2 infection or decrease viral load which is a possible factor in the severity of the disease.

Stimulation of immune system

Lactobacilli have distinct antimicrobial and antiviral activities that play an effective regulator to the immune system [83]. Furthermore, they stimulate specific and non-specific responses, including the activation of natural killer (NK) cells, enhancement of the phagocytic activity of peripheral blood leukocytes, regulatory T cells, and interleukin-10. In this regard, the stimulation of nonspecific secretory and specific antibody responses to rotavirus has been recorded [84]. Recent work by Arena *et al*. (2018) has proven that probiotics can exert modulatory effects of the immune system by enhancing the immune defense against viruses such as induction of interleukins, T-helper cells, macrophages, NK cells, and immunoglobulins.

Several studies have evaluated the effect of some immunobiotics against enteric viruses, respiratory viruses, and pathogenic bacteria [85]. In 2010, the administration of *L. pentosus* to mice showed antiviral potential by activation of lung NK cells and decreased allergic reaction [86]. Heat-killed *Lactobacillus rhamnosus* strains administration has also exhibited IFN-α stimulation in respiratory syncytial virus (RSV) infection and decrease a viral load in mice lungs [87]. Moreover, Kawashima *et al*. (2011) have demonstrated that innate and adaptive immune systems are triggered by the probiotic strain, *L. plantarum*, isolated from traditional Japanese fermented food. In addition to its strong IL-12-inducing activity and IgA-inducing activity, viable *L. plantarum* has a high digestive juice resistance, leading to improved Th1 immune response and preventative activity against influenza virus infection. Too, reduction of H1N1 infection in mice by *Lactobacillus fermentum* has also been documented through the same mechanisms [88], [89]. Likewise, *Bifidobacterium longum* showed an anti-H1N1 activity by decreasing the pro-inflammatory cytokines [90]. Finally, enhancing the immune responses using probiotics' supplementation is a well-documented point; however, it may also be an effective way to alleviate COVID-19.

Probiotics and Enteric Viral Infections

The rotavirus, norovirus, adenovirus, and astrovirus are the most common viruses that cause gastroenteritis. The preventive role of probiotics against common types of viral enteritis is discussed below:

Rotavirus infection

The rotavirus infection is commonly responsible for diarrheal disease among children under 5 years of age, particularly in developing countries. Rotavirus infection is also associated with other symptoms such as vomiting, fever, and dehydration which can lead to death [91], [92]. In 2006, the US-FDA approved two oral live vaccines (RotaTeq and Rotarix) to prevent rotavirus infection in infants [93]. However, the rates of morbidity and mortality are still high [91]. In such circumstances, probiotics may consider promising cheap and safe preventive alternatives [94] to be administered to patients.

Many researchers have studied the preventive role of certain probiotics against rotavirus, such as *Bifidobacterium* and *Lactobacillus* affirmed their role in antagonizing rotaviruses [95]. Erdoğan *et al*. [96] have reported that the treatment of acute rotavirus gastroenteritis with *Bifidobacterium lactis* B94 and oral rehydration could significantly reduce the diarrheal period in children aged from 5 months to 5 years old. Later, in 2017, Park *et al*. [97] reach similar results after administering *B. longum* BORI and *L. acidophilus* AD031 to infants infected with rotavirus. A more recent study has proven that specific probiotic strains such as *Lactobacillus salivarius* PS2, *L. acidophilus* NCFM, *Bifidobacterium breve* M-16V, and *Lactobacillus helveticus* R0052 have the ability to reduce the severity of rotavirus infection [98].

Supporting the theory that probiotics can stimulate the host's immune system, Sindhu *et al*. [99] have mentioned that the consumption of *L. rhamnosus* (LGG) can modulate both innate and adaptive immune system's responses by increasing levels of serum IgG during infection with rotavirus. On the other hand, Fernandez-Duarte *et al*. [100] suggested that *B. adolescentis* and *L. casei* could block rotavirus adherence to the MA104 cells. While, a recent study indicated that non-protein components with low-molecular-weight derived from *B. longum* BORI act as anti-rotaviral substances [101]; however, more studies are required to specify active compound to completely elucidate the underlying mechanism of action.

Noroviruses infection

Human norovirus can also cause gastroenteritis and generally lasts for 2–3 days and accompanied by vomiting, nausea, and diarrhea [102]. Infants, elderly, and immunocompromised patients are the risk groups. Although acute diarrhea is generally self-limiting and may disappear within a few days [103], [104], dehydration in toddlers and young infants remains the major risk factor.

Developing vaccines and antiviral drugs against human norovirus are still under experiments [105]. Studies indicated that probiotics might act as adsorbents for P particle, a nano-scale sized particle in norovirus capsid and critical for the host's immune response and receptor binding [106]. For example, *Enterobacter cloacae* which are a commensal bacterium could bind to human norovirus through surface histo-blood group antigen and inhibit virus infectivity when tested in pigs [107], [108]. Another study showed that P particle attachment to epithelial cells could be inhibited by the presence of *L. casei* BL23 and *Escherichia coli* Nissle 1917 [109]. Accordingly, and to avoid developing severe forms of SARS-CoV-2, enhancing a healthy diet with probiotics may represent a good strategy.

Probiotics and Respiratory Viral Infections

While many researchers have concentrated on the use of probiotics to treat or prevent intestinal infections, recent research has focused on the effectiveness of probiotics on humans against respiratory viral infections [110], which are a serious cause of morbidity and mortality around the world [111]. The causative agents of respiratory viral infections in humans are over two hundred different types of pathogenic viruses, including RSV, human rhinoviruses (common cold), human enteroviruses, influenza viruses, adenoviruses, parainfluenza viruses, and coronaviruses. Symptoms of these infections vary from mild respiratory symptoms to severe diseases [112], [113], [114], [115]. Below, evidence-based probiotics' effects against common infections are highlighted below:

RSV infection

One of the most common respiratory viruses that almost all children are infected with by the age of 2 years is RSV. The symptoms can vary from mild symptoms to severe infection of the lower respiratory tract, bronchiolitis, and pneumonia with an increasing risk of developing asthma and persistent wheezing [116], [117]. Elderly and immunocompromised individuals are most at risk to be infected with RSV [118], [119]. No RSV vaccine has been approved so far, and specific antiviral medicines against RSV are still limited. Several probiotics are therefore proposed to prevent RSV infection as prophylactic or antiviral agents. For example, Tomosada *et al*. (2013) have found that TLR3/RIG-I antiviral respiratory immune response is modulated by intranasal administration of two different commensal strains of *L. rhamnosus* (*L. rhamnosus* CRL1505 and *L. rhamnosus* CRL1506) and increased infant mice resistance to RSV in comparison with a control group. In addition, recent research has shown that the RSV titer in the lungs can be significantly reduced with no weight loss in mice after viral infection when *L. gasseri* (LG2055) is administered orally [41].

Human rhinoviruses (HRV)

Rhinoviruses are the leading causes of common cold in humans [120]. Severe symptoms typically include irritation, pneumonia, bronchiolitis, asthma, and chronic obstructive pulmonary disease [121]. There is currently no approved antiviral treatment or vaccine for HRV infection. However, research articles have documented that various probiotics could reduce the risk of HRV disease. In a preterm population, the incidence of HRV infection was reduced significantly during the 1st year of life through using polydextrose and *L. rhamnosus* [122]. Kumpu *et al*. [123] found that receiving *L. rhamnosus* GG (live or heat-inactivated) decreased the incidence and severity of common cold symptoms caused by rhinoviruses. However, the dose of probiotic bacterial strains, side effects, and accurate mechanism against HRV is inadequately reported and needs further investigation [124], [125].

Influenza virus infection

Another viral agent responsible for thousands of human and animal deaths annually is the influenza virus. Influenza viruses are a group of RNA viruses, which belong to the family Orthomyxoviridae. There are four types of influenza viruses A, B, C, and D. Mainly, humans are infected with type A and B [126]. Influenza A viruses are responsible for several pandemic outbreaks worldwide [127]. Although the vaccine is available but with new viral strains evolving rapidly and variations between circulating viruses and vaccines created, the efficiency of the influenza virus vaccine decreases [128], [129]. Therefore, the efforts rely on the use of probiotics to reinforce and improve the host's immune system against viral infection. The use of yogurt fermented by *L. delbrueckii* ssp. *bulgaricus* OLL1073R-1 (R-1) might prevent infection caused by respiratory or influenza viruses through polysaccharides secretion, which improves immune system's functions and activates the NK cells [130], [131]. In a mouse model, *L. acidophilus* can regulate NK T-cells and prevent influenza virus infection [132]. Furthermore, the *B. bifidum*'s effect on improving immune response to the influenza virus in a recent study on BALB/c mice infected with lethal influenza A (H1N1) has been evaluated by Mahooti *et al*.

[133]. Furthermore, findings revealed a strong induction of both humoral and cellular immunity, drop in the level of IL-6, and increased survival rate in mice receiving *Bifidobacterium* than those of the control group.

Adenoviruses infection

Adenoviruses represent group of Rowavirales that belong to the non-enveloped double-stranded linear DNA viruses. Adenoviruses can cause various clinical syndromes in humans in addition to keratoconjunctivitis, including gastrointestinal and urogenital infections [134]. Various antiviral drugs such as ribavirin, ganciclovir, and cidofovir have shown variable activities against severe human adenovirus infections especially in immunocompromised organ transplant recipients. However, the efficiency of these drugs is limited to the ability of the virus to develop resistant strains in addition to their side effects [135]. Therefore, it is safer to stimulate the immune system and increase resistance to adenovirus infections through probiotics and their metabolic products [136]. *In-vitro* MTT assay against human adenovirus type 5 was used to examine the cytotoxicity of six EPSs produced by various LAB. The results showed that EPS 26a produced by *Lactobacillus* sp. have a significant antiviral activity through the formation of non-infectious virus progeny [137].

Probiotics and COVID-19

In response to the emerging threat posed by SARS-CoV-2, the WHO announced a Public Health Emergency of International Concern a pandemic on March 11, 2020. Infection with SARS-CoV-2 causes coronavirus disease 19 (COVID-19), which has been characterized by fever, respiratory, and gastrointestinal symptoms, along with other less common symptoms [138]. No vaccine or antiviral drug for SARS-CoV-2 has been yet approved. However, faced with this pandemic, new answers and ways of addressing these problems are needed.

Strengthening the immune system is well-known to be an effective and successful way for a healthy lifestyle. This, in turn, oriented attention to the pivotal role of a healthy immune system to face SARS-CoV-2 infection [139]. Open literature search revealed that immune system function is largely improved by a healthy diet. Accordingly, a diversified diet with a broad nutrient profile may prevent and even reduce the vulnerability during COVID-19.

Adjuvants against COVID-19 could be healthy food choices, micronutrients, bioactive compounds, and probiotics [140]. In particular, the potential benefits of probiotics in other coronavirus strains were thoroughly documented [141]. Some probiotics may also play a positive role in the treatment of COVID-19 patients due to their antiviral activity, ability to modulate inflammation, restore gut microbiome, ready availability, generally safe, inexpensive, and easily administered [142]. There are no guidelines on strain, dose, and duration of the probiotics consuming yet. However, *Lactobacillus* and *Bifidobacterium* can be safely used in different clinical situations.

A recent study by Aanouz *et al*. (2020) [143] on computational and molecular dynamics obviously demonstrates the antiviral activity of plantaricins, a bacteriocin, which blocks viral entry by binding with RdRp, RBD, and ACE2 through multiple mechanistic approaches by metabolic product of *L. plantarum*. Blocking the main structural protein S is critical and can be one of the best targets since it plays a key role in the life cycle of SARS-CoV-2. Moreover, Anwar *et al*. (2020) [144] have suggested that plantaricin metabolites may be a preventive option before the latest antiviral medication specific to COVID-19 has been discovered. Other studies are being carried out across the globe to decide whether modifying the gut microbiota through the diet will contribute to our COVID-19 care, and in recent times, Baud *et al*. (2020) [145] have suggested certain probiotic strains that are evidence-based and that are important in reducing the pandemic burden. Apart from boosting the immune system, specific therapeutic strategies may be advised for the prevention of cytokine storm such as the use of probiotics for patients with gastrointestinal symptoms linked to COVID-19 and those with milder systemic symptoms [146].

Different patients' responses to infection may depend on variations in the composition of their microbiota and correction with probiotics may help to minimize the need for intensive care [147]. Dhar and Mohanty (2020) have identified the potential role of intestinal microbiota in determining better immune and respiratory function in such patients [148]. Too, number of authors discussed the idea of significant positive modulation of respiratory function by probiotics/synbiotics supplementation, starting from previous studies on the close associations between gut microbiota and lung function. In general, that finding indicates that probiotics are essential and useful supplements to patients and confirm the role of our microbiota in sustaining and eventually restoring a healthy quality of life.

For better understanding, the presented knowledge must be more deeply validated before they can be implemented in standard protocols for COVID-19 patients, assess also the true impact of SARS-CoV-2 on gut microbiota, and also take into account the possible role of gut virobiota, which seems to have a specific role in the homeostasis of gut microbiota [149]. Moreover, interactions between SARS-CoV-2 and the gut microbiome and resident virobiota could influence the ability of this new coronavirus to infect and disseminate the intestinal cells more easily and explain how probiotics could have a COVID-19 resistance [150].

In addition to their benefits to humans, probiotics may also participate in certain clinical presentations related to life-threatening outcomes such as bloodstream infections [151], [152]. However, neither mortality nor adverse health complications were ascribed to the clinical use of probiotics. Furthermore, additional studies are demanded to better understand their safety, behavior in the food matrix, and their survival and colonization in the gastrointestinal tract using expressly designed *in vivo* models.

Conclusions

With no approved vaccine or antiviral drugs for some viral disease, including COVID-19, establishing effective means to protect humans from viral infections still a bit challenging. Of the safest, affordable, and easy to consume, agents are probiotics. Enhancing the host immune system with probiotics is widely studied. They were known with their multifunctional effects, which can act as adjunctive therapy for the prophylaxis of a large number of viral infections. Finally, research needs to progress to establish probiotic scientific guidelines for the prevention and/or treatment of COVID-19.

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Authors' Contribution Statement

All authors have equally contributed to this work and approved it before submission.

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