




# Role of probiotics to combat viral infections with emphasis on COVID-19

Aravind Sundararaman<sup>1</sup> · Mousumi Ray<sup>1</sup> · P. V. Ravindra<sup>2</sup> · Prakash M. Halami<sup>1</sup> 

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## Abstract

Interspecies transmissions of viruses between animals and humans may result in unpredictable pathogenic potential and new transmissible diseases. This mechanism has recently been exemplified by the discovery of new pathogenic viruses, such as the novel severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) pandemic, Middle-East respiratory syndrome-coronavirus epidemic in Saudi Arabia, and the deadly outbreak of Ebola in West Africa. The SARS-CoV-2 causes coronavirus disease-19 (COVID-19), which is having a massive global impact in terms of economic disruption, and, above all, human health. The disease is characterized by dry cough, fever, fatigue, myalgia, and dyspnea. Other symptoms include headache, sore throat, rhinorrhea, and gastrointestinal disorders. Pneumonia appears to be the most common and severe manifestation of the infection. Currently, there is no vaccine or specific drug for COVID-19. Further, the development of new antiviral requires a considerable length of time and effort for drug design and validation. Therefore, repurposing the use of natural compounds can provide alternatives and can support therapy against COVID-19. In this review, we comprehensively discuss the prophylactic and supportive therapeutic role of probiotics for the management of COVID-19. In addition, the unique role of probiotics to modulate the gut microbe and assert gut homeostasis and production of interferon as an antiviral mechanism is described. Further, the regulatory role of probiotics on gut-lung axis and mucosal immune system for the potential antiviral mechanisms is reviewed and discussed.

## Key points

- Gut microbiota role in antiviral diseases
- Factors influencing the antiviral mechanism
- Probiotics and Covid-19

**Keywords** Probiotics · SARS-CoV-2 · COVID-19 · Gut-lung axis · Zoonosis

## Introduction

Over the past 4 months, the coronavirus disease-19 (COVID-19) has had a massive global impact in terms of economic disruption, the strain on local and global public health resources, and, above all, human health. At the time of writing this review, there were 21,600,000 positive cases and

7,74,000 deaths worldwide. In India, there were 2,600,000 positive cases and 50,921 reported deaths. COVID-19 is caused by highly pathogenic, novel zoonotic severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2) that belongs to the family of SARS-CoVs, which also includes Middle-East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-1. These viruses are enveloped, positive sense single-strand RNA viruses belonging to the large family of *Coronaviridae* and subfamily *Coronavirinae*, which infect birds and mammals. The genome size of these viruses ranges from 26 to 32 kb (Anon 2020a). SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors on cells via its spike (S) glycoprotein. The S protein has two domains S1 and S2. S1 binds to the peptidase domain of ACE2, therefore, termed as the receptor-binding domain (RBD), while S2 catalyses the membrane fusion, thereby releasing the genetic

✉ Prakash M. Halami  
prakashalami@cftri.res.in

<sup>1</sup> Department of Microbiology and Fermentation Technology, CSIR-Central Food Technological Research Institute, Mysuru 570020, India

<sup>2</sup> Department of Biochemistry, CSIR-Central Food Technological Research Institute, Mysuru 570020, India

material into cells (Hoffmann et al. 2020). Inside the cell, the RNA provides the template for structural proteins such as replicase (R1a/ab), envelope (E), spike (S), membrane (M), nucleoprotein (N), and several non-structural proteins (NS1–16), uncharacterized protein 14, protein 9b (Anon 2020b). Of them, non-structural proteins are predicted to participate in the host-protein interactions and modulate host-cell signaling pathways. The incubation period presumed to vary between 2 and 14 days. The current understanding of the mode of transmission is incomplete. However, based on the recent outbreaks in various parts of the world, the common mode of transmission includes droplet transmission when an infected person coughs or sneezes and surface contact of droplets that contain virus followed by touching nose, eyes, and mouth. Evidence also points towards vertical transmission to newborns, also by fecal transmission. The typical clinical symptoms of SARS-CoV-2 infection include dry cough (67%), fever (88%), fatigue (38%), myalgia (14.9%), and dyspnea (18.7%). Other symptoms include headache, sore throat, rhinorrhoea, and gastrointestinal symptoms. Pneumonia appears to be the most common and severe manifestation of the infection (Guan et al. 2020). Currently, there is no vaccine or specific drug for COVID-19. Further, the development of new antiviral presents several challenges and requires a considerable length of time and effort for drug design and validation. Therefore, exploring the repurposing, the use of natural compounds can provide alternatives and can support therapy against COVID-19. Currently, no research supports the use of any supplement as adjuvant therapy for the management of COVID-19 subjects. In addition to the SARS-CoV2, avian influenza, ebola, dengue, and Zika viral infections remain poorly controlled around the world (Liu et al. 2016).

The live microbes, which possess health benefits on the host when administered in appropriately adequate amount, are referred to as probiotics and it includes a number of genera of bacteria and yeasts. Probiotics include *Lactobacillus*, *Bifidobacterium*, *Leuconostoc*, *Pediococcus*, and *Enterococcus*. The normal gastrointestinal microflora of the humans is populated with microflora that belongs to the genus *Lactobacillus* and *Bifidobacterium*. They are safe and widely used in yogurts and other dairy products (López-Moreno and Aguilera 2020). Probiotics play a role in balancing the host defensive immune response, thereby stimulating mucosal barrier function and modulating the immune system (El Hage et al. 2017). Interestingly, intestinal bacteria have been shown to exert the beneficial effects through modulation of vitamin D axis. Through vitamin D axis, probiotics can protect mucosal barrier integrity and suppress gut mucosal inflammation (Li et al. 2015). Further, via vitamin D axis, probiotics can regulate both innate and adaptive immune systems. Its effects include decreasing Th1/Th17 T cells and pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, IFN $\gamma$ , and TNF $\alpha$ , in favor of Th2 response, increasing Treg, downregulating T cell-driven

IgG production, inhibiting DC differentiation, and helping maintain self-tolerance, while enhancing protective innate immune responses (Del pinto et al. 2017). The interactions of gut-lung axis influence probiotics role in respiratory diseases, thereby the immune dialogue remains a two-way process. The lung microbiota protects against respiratory infections, primarily by production of granulocyte-macrophage via IL-17 and Nod2 stimulation. In response to lung infections, gut microbiota plays a crucial role. In vivo studies in germ-free mice showed increased morbidity during acute lung infection (Brown et al. 2017). Similarly, modulation in the severity of *Mycobacterium tuberculosis* infections in lung is correlated with gut microbiota (Namasivayam et al. 2018). Trace elements such as zinc play an essential role in normal growth and development of the host. Zinc has significant effects on intestinal bacterial populations and the immune system by boosting the Th1 immune pathway. The primary mechanism of zinc homeostasis in the body is the gastrointestinal absorption of ingested zinc balanced by the secretion of endogenous zinc into the gut and excretion in the feces (Cummings and Kovacic 2009). The perturbations in zinc homeostasis in human are a critical factor to influence antiviral immunity. The deficiency of zinc leads to the risk of acquiring viral infections as there is an imbalance of the Th1 and Th2 immunity functions, leading to a defect in the Th1 pathway (Giella and DiRita 2012). Leonardi et al. (2013) showed LAB enriched with zinc could be a valuable source of this element in food, because zinc metalloproteins or bioplexes are the best form for absorption by humans.

The mechanism of how probiotics work on the host organism and immune system is complicated and still not fully elucidated. However, the remedies and effectiveness of vaccines for viral diseases are limited by the high mutation rates of viruses, especially RNA viruses. In this review, we discuss the efficiency of probiotics and their significance in prevention of viral infections. In addition, we provide the significance of microbes in different parts of the body upon viral infections. The future research will potentially focus on treatment of various viral diseases using probiotics or paraprobiotics as the rational adjunctive.

## Lung microbiota and respiratory infection

As compared with the lower gastrointestinal part, the lungs contain about 10 to 100 bacteria per 1000 human cells that is relatively less bacterial biomass (Sze et al. 2012). A cystic fibrosis study reinforces that the gut and the lung microbiota develop at the same time after birth, and it is proved that there is a constant cross talk between these two areas (Marsland et al. 2015). The dynamic composition of the lung microbiome is determined by the incorporation through nutrition, temperature, and quality and quantity of the anti-

inflammatory cells, elimination through cough, mucociliary clearance, innate and adaptive immunity, immigration through micro-aspiration and inhalation of microorganisms, and relative growth within its communities (O'Dwyer et al. 2016; Fanos et al. 2020). The lung is an organ that is continually exposed to microbiota either through inhalation or sub-clinical microaspiration from the beginning of life. The lung and airway microbiome have directly affected immunity against disease or can have an effect of altered local immunity/inflammation during the development of the disease. The upper respiratory tract and oropharynx, where microbes are found in abundance, are not eliminated through host mucosal defense and mucociliary clearance (Wilson and Hamilos 2014), able to reach deep in to the lung. Subclinical aspiration of oropharyngeal contents occurs universally in humans (O'Dwyer et al. 2016). Murine studies have demonstrated bacterial load in the lungs increases over the first 2 weeks of life, and the phyla of organisms found in the lung shifted from *Gamma-proteobacteria* and *Firmicutes* towards *Bacteroidetes* (Frank et al. 2010). The lung environment becomes rich in gut bacteria, such as *Bacteroidetes* and *Enterobacteriaceae*, called “more gut in the lung” (Fanos et al. 2020). Probiotics mainly colonize in the gut, but it has a fundamental impact on the systemic immune responses. It can also colonize and exert the immune responses at distant mucosal sites, including the lung (Tapiovaara et al. 2016; Baud et al. 2020). The study reported that probiotic *Lb. plantarum* GG could colonize in the upper respiratory system, especially where the lymphatic system is available. Researchers have isolated probiotic *Lb. plantarum* DSM9843 from the tonsil epithelium of six individuals after 8 h of per oral consumption of fermented oatmeal gruel enriched with *Lb. plantarum* DSM9843 (Tapiovaara et al. 2016). Such developmental changes in the microbiota were associated with accumulation of T regulatory cell population that could promote tolerance to allergen challenge (Frank et al. 2010). Lung microbiota may specifically regulate lung immunity or the development of bronchial-associated lymphoid tissue against lung infection (O'Dwyer et al. 2016). A human can face different potent organisms, harmful particles, and gases during normal inhalation. Deposition of these harmful organisms, such as molds, bacteria, and viruses, occurs on the airway or alveolar surfaces. Some of these organisms range from less than 3 to 5  $\mu$  that can only penetrate to the deep lung. Cilia and mucus layer prevent pathogens from entering the lung. Once they enter into the lung, the lung's defense mechanisms are activated through the activation of alveolar macrophage (Janssen et al. 2016). Alveolar macrophage with their cell surface receptor binds with the deposited particles, ingest, kill, and digest them. In addition, when the lungs are introduced with such serious infectious particles, white blood cells, especially neutrophils, increase in the circulation that helps to ingest and kill the pathogens. The lung microbiota can protect

against respiratory infections with *S. pneumoniae* and *K. pneumoniae*, triggering the pulmonary production of granulocyte-macrophage colony-stimulating factor (GM-CSF) through the stimulation on interleukin 17 (IL-17) and Nod2 (Mukherjee and Hanidziar 2018). Pro-inflammatory cytokine IL-17 is induced by CD4<sup>+</sup> and CD8<sup>+</sup> T cells of stromal, endothelial, and epithelial cells in response to lipopolysaccharides. IL-17 binds to cell receptors and activates neutrophils, AP-1, and NF- $\kappa$ B activity (Ryzhakov et al. 2011). IL-17 also induces endoplasmic reticulum stress and autophagy via inositol-requiring enzyme 1, inhibiting the reproduction of infectious virus (Kim et al. 2015). Nod-like receptors (NLRs) act as cytoplasmic receptors that support host defense mechanisms through stimulation of NF $\kappa$ B signaling. NF $\kappa$ B controls the transcription of effector genes with the pro-inflammatory cytokine TNF- $\alpha$  and the neutrophil chemokine, IL-8. In reasonable condition, NF $\kappa$ B remains sluggish and binds with inhibitor molecule I $\kappa$ B in the cytoplasm. Upon stimulation, I $\kappa$ B is phosphorylated through IKK, sends the signal for ubiquitination, releases NF $\kappa$ B free from I $\kappa$ B, and uncovers the nuclear localization sequence (NLS) that helps the NF $\kappa$ B p65/p50 heterodimer to travel into the nucleus and acts as a transcription factor at target promoter regions (Llewellyn and Foey 2017). NLRs protect against respiratory pathogen infection via neutrophil induction in the bone marrow, regulate circulatory neutrophil and inflammatory monocyte lifespan, support hematopoiesis, promote lymphoid follicle development, and stimulate adjuvant activity (Brown et al. 2017). Also, the gut microbiota plays a vital role in the response of the lung to bacterial infections. Studies on germ-free mice showed an increase in the morbidity and mortality during the acute pulmonary infection by *P. aeruginosa*, *K. pneumoniae*, and *S. pneumoniae* (Mukherjee and Hanidziar 2018). The World Health Organization as on January 30, 2020 has alarmed a public health emergency of international concern (PHEIC) due to novel coronavirus (CoV) also termed as SARS-CoV-2 which causes severe acute respiratory syndrome. Lung infection with coronavirus involves disruptions of the epithelium in gas exchange areas and associated airways (Fanos et al. 2020). The epithelial cells of the alveoli serve as a SARS receptor with angiotensin-converting enzyme 2 (ACE2), digestion-related enzymes in human enterocytes. Coronaviruses are frequently varying the binding receptor and binding site during their progression (Feng et al. 2020). Viral infection induces alveolar macrophage to form multinucleated giant cells, monocytes, and dendritic cells to act against SARS-CoV. Elevated concentration of pro-inflammatory cytokines, including CXCL10 (IP-10), CCL2 (MCP-1), IL-6, and CXCL8 (IL-8) in serum, was evident when lung is exposed to SARS-CoV infection (Qian et al. 2013). Lung infection with SARS-CoV also leads to marked elevations in mRNA concentrations of interferon- $\beta$ , interferon- $\lambda$ , CXCL10, CXCL11, and IL-6 (Zhaohui et al.

2013). Out of several possible treatments of COVID-19, like nutritional, antiviral, anti-coronavirus, and miscellanea, medication with probiotics, especially bifidobacteria and lactobacilli, provides a significant chance of recovery (Fanos et al. 2020). Probiotics like *Bifidobacteria* or *Lactobacillus* has beneficial effects against influenza virus infection in the respiratory tract (Zelaya et al. 2016). Probiotic consumption improves the level of type I interferons, antigen-presenting cells, NK cells, and T and B cells in the lungs' immune system. Probiotic administration can also improve the pro- and anti-inflammatory cytokines, helping to clear the viral infection by minimizing the cell damage in the lungs (Baud et al. 2020). This suggested mechanisms also can be manifested to prevent the complications regarding COVID-19. Recent studies suggest that the involvement of the gut in COVID-19 is even greater and more prolonged compared with the lung (Xu et al. 2020).

## Nasopharynx microbes

Nasopharynx serves as the predominant niches of various types of both commensals and pathogenic microbiota (Lemon et al. 2010). Microbes vary from smoker to non-smokers, healthy to unhealthy, and aged versus neonatal in terms of membership and distribution (Charlson et al. 2010). Numerous investigations discovered that the nasal microbiome of healthy people is fundamentally composed of the phyla *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* with the genera of *Bifidobacterium*, *Propionibacterium*, *Corynebacterium*, *Dolosigranulum*, and *Moraxella* being prevalent (Huffnagle et al. 2017; Kumpitsch et al. 2019). Numerous pathogenic species, including *Streptococcus pneumoniae*, *Haemophilus flu*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Neisseria meningitidis*, exist in the nasopharynx of apparently healthy people (Allen et al. 2014). Like pathogenic bacteria, some viruses, including rhinoviruses, enteroviruses, coronaviruses, and adenoviruses, have been found in asymptomatic infected people. The Human Microbiome Project's metagenomic studies could advance explicitly distinguish the significant organisms as *P. acnes*, *C. accolens*, *C. kroyenstedtii*, *S. aureus*, and *S. epidermididis* in the nasopharynx (Anon 2012). Among bacteria, *H. influenzae* was the most dominating bacterium, which together with *S. pneumoniae* and *M. catarrhalis* makes up the human nasopharynx microbiome (Bisgaard et al. 2007).

In the presence of *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*, either alone or in a mixture of these organisms, can altogether colonize blood eosinophil and increase IgE counts in youngsters at 4 years old (Bisgaard et al. 2007). Any infections of the upper respiratory tract lead to elaborate connections between bacterial pathogens and viruses, both

synergistic and competitive. Microorganisms in the upper respiratory tract can change bacterial adherence, bacterial colonization, and host immune response. An investigation of the nasopharyngeal microbiota of kids with severe bronchitis demonstrated microbial movements relying upon the viral disease human rhinovirus (HRV) (Heinonen et al. 2016), respiratory syncytial infection (RSV) (Mejias et al. 2013), or co-contamination. The lung microbiota in chronic obstructive pulmonary illness (COPD) patients and healthy people during a rhinovirus challenge demonstrated massive changes after infection (Huang et al. 2017). The mucus layer present in the nasopharynx assists in humidifying the breathed air and traps the entered microorganisms or any foreign molecule (Kumpitsch et al. 2019). This contaminated mucus here and there is passed out through mucociliary clearance (Bustamante-Marin and Ostrowski 2017). Strangely, commensal organisms with immunomodulatory properties are fit for initiating the host's immune reactions and fast protection against pathogens (Michael and David 2013). Probiotic *Lactobacillus* GG, or in the combination of *Lactobacillus* GG with other probiotics, was shown to reduce the occurrence or risk of URI in children (Kumpu et al. 2012).

The human nose and upper respiratory tract efficiently hold the pathogen through invading immunogenic particles and droplets. The pathogen detected by mucosal layers of the gastrointestinal tract (GI), respiratory, urinary, and genital tracts functions as the body's immunologic system (Zhang et al. 2018). The human nose is covered by type 1 mucosal layer consisting of a single layer of epithelial cells, antigen-presenting cell, goblet cells, and specialized lymphoid organs similar to the gastrointestinal tract. After attachment, the pathogenic foreign particle that activates the local mucosal immune system even in the upper respiratory tract especially invades into the lung. Hua et al. (2018) demonstrated that the nasal exposure to coronavirus in the nose and upper airways can immunologically prepare the lungs for more rapid initiation of an innate and adaptive immune response against homologous and heterologous infection. The immune system plays a crucial job in treating severe acute respiratory coronavirus by changes in peripheral blood T lymphocyte subsets and contributes to understanding the disease diagnosis and treatment (Lin et al. 2020). Also, overproduction of cytokines and chemokines, activation of T helper cell-mediated immunity and host inflammatory response, was observed during the acute phase of SARS infection (Russell et al. 2020).

## Gut microbe interaction and immune modulation

The gut is the key habitat where most of the microbes stay in the host symbiotically. In the gut, microbiota plays an indispensable role in maintaining intestinal homeostasis (Kerry

et al. 2018). The gut microbiome includes different microbial communities, not restricting to, of bacteria, viruses, and fungi (Shi et al. 2017). The human gut microbiome consists of around 1000 different species of microbes and varies densities from  $10^4$  to  $10^5$  bacteria per millimeter of the digestive tract in the small intestine and  $10^{11}$  bacteria per gram of luminal content of the colon (Thomas et al. 2017). The composition of the microbiome may differ from person to person, and it depends on environmental changes and genetic inheritance (Harmsen and de Goffau 2016). In sound people, the microbiome principally comprises of four gatherings of microscopic organisms: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* (Gu et al. 2013; Seedorf et al. 2014), in which the two phyla *Firmicutes* and *Bacteroidetes* represent 90% of gut microbiota. Additionally, for the most part, the dominating phyla of the gut are *Bacteroides* and *Firmicutes*, followed by *Proteobacteria* and *Actinobacteria* (Rinninella et al. 2019). In the symbiotic relationship between microbiota and the host, both are mutually beneficial (Parker et al. 2018). Microbiome utilizes the space, nutrient, and breeding environment from the human gut (Chang and Kao 2019). In turn, intestinal microflora helps in carbohydrate fermentation, synthesizes vitamins, and downregulates the intestinal permeability (Kau et al. 2011). The gut microbiota acts as a defense barrier and helps to modify the intestinal immune system. The lower tract microbiome is influenced by various environmental factors. Thus, the cooperation amongst the microbiome and intestinal immune system is indispensable to preserve intestinal homeostasis. When this homeostasis is exhausted by means the balanced gut microbial community change, dysbiosis causes intestinal diseases (Na et al. 2017; Chang and Kao 2019). Studies revealed that the accelerated microbial colonization in the neonatal gastrointestinal tract performs a crucial role in the growth of the gut immune system. The gut microbiome exhibits competition against pathogen binding, their colonization, survival, and direct killing by their metabolites (e.g., organic acid, antimicrobial compounds), and increasing the gut-associated immunity. The probiotic oral administration protects against infection in distant gut mucosa like bronchi and urogenital mucosa (Hao et al. 2011; Barbieri et al. 2017). The risk of *Salmonella enterica* serovar Typhimurium contamination can be minimized by oral administration of probiotics inducing phagocytic and microbicidal action of macrophages (Galdeano et al. 2011). According to Galdeano et al. (2011), the cytokines released by the probiotic act on immune cells inaccessible from the digestive tract. With the production of a specific antibody, probiotics can stimulate the systemic immune response. A sufficient amount of probiotics can stimulate an innate and adaptive immunity of the host. Gut microbiota also has its long-distance health impact on the heart, liver, kidney, and lung immunity (Marsland et al. 2015; Enaud et al. 2020). In the gut-lung axis, distal (gut) immune modulation during respiratory disease is mediated

by the gut microbiota. The healthy gut microbiome can alter the gut immunity as well as the lung immunity by their gut-lung axis (Fanos et al. 2020). During airway infection of the respiratory tract, body's commensal organisms stimulate the immune response to the local (lung) and distal (gut) sites, considered as gut-lung axis, where gut microbiota modulate pulmonary immune system during this infection (Budden et al. 2017). The gut-lung axis is assumed to be bidirectional, meaning via the blood and lymphatic system where the microbial metabolites endotoxins can impact the lung when inflammation arises; also it can influence the gut microbiome. By this mechanism, there is a possibility of novel SARS-Cov2 that might also affect the alteration of the gut microbiota (Dhar and Mohanty 2020). Gut microbiota showed to involve in many respiratory disease modulation of the lung (Taylor et al. 2016). Probiotics showed significant microbial killing properties through alveolar macrophage, neutrophils, natural killer cells, and increased levels of pro-inflammatory cytokines like TNF- $\alpha$  and IL-6 in the lung (Vieira et al. 2016; Belkacem et al. 2017). The anti-inflammatory cytokines (such as Treg cells and IL-10) also increase with increasing pro-inflammatory cytokines in the lung of infected mice (Khailova et al. 2013). The most important way is that the lymphatic system lies in between the lungs and the intestine. Commensals, their body parts (e.g., lipopolysaccharide), and metabolites (e.g., short-chain fatty acids) translocate through the mesenteric lymphatic system from the gut to the lung using the systemic circulation and regulate the lung immunity (Trompette et al. 2014; Bingula et al. 2017). A recent study revealed that tissue-repairing innate lymphoid cells could migrate from the gut to the lungs, in response to an inflammatory immune response upon IL-25 (Huang et al. 2018). A study reported that *K. pneumoniae* infection was downregulated by the consumption of *Bifidobacterium longum* in mice. Looft and Allen (2012) concluded the reduced level of Lactobacilli and Lactococci and upregulation of *Enterobacteriaceae* in the gut lumen during influenza infection study in a clinical model.

## Mucosal immune response

Dysbiosis of the host immunity can stimulate the body's immune system, i.e., immune organ, soluble cytokines, and cell receptors, and the main backbone of the immune defense. The communication between microbiota and environmental factors affects mucosal immunity (Neish 2014). The mucus layer present on the surface of the gastrointestinal tract, respiratory tract, vaginal tract played the first line of defense, where immunoglobulin A antibody acts as the first line of mucosal immunity (Corthesy 2013). Mucins act as a barrier function of mucus immunity. The foreign particle or pathogen once crosses the mucociliary barrier able to get contact with several soluble antimicrobial peptides present in the mucus, such as

lysozyme, lactoferrin, collectin, and defensins, produced by immune cells of the respiratory tract. These antimicrobial peptides are involved in direct killing of the pathogen or pathogen inhibition through opsonization or recruitment of other inflammatory cells (Das and Thakur 2015; Boyton and Openshaw 2002). Pathogen infection of mucosal epithelial cells introduces monocytes, macrophages, granulocytes, B cells, natural killer cells, and dendritic cells. Initiation of these safe cells relies upon different pattern recognition receptors (PRRs). PRRs including Toll-like receptors (TLR) and nucleotide-binding oligomerization domain-containing protein 2 (NOD-2), C-type lectin-like receptors (CLRs), and cytosolic DNA sensors activated intracellular signalling induce immune responses, through pro- and/or anti-inflammatory or regulatory and/or antiviral chemokines' direct immunogenic responses (Akira et al. 2001; Ausubel 2005; Chaudhuri and Sabroe 2008; Hooper and Macpherson 2010). Pathogen destruction through macrophage and dendritic cells also take part in the innate respiratory mucosal immune system. Alveolar macrophage immediately eliminates the pathogen by emitting NO and reactive oxygen species. Dendritic cells (DCs) assist with perceiving and dispense with the pathogen from various perspectives. DCs play a significant part in viral clearance from the lungs by initiating antiviral CD8<sup>+</sup> cytotoxic T cell response in the lymph nodes (Ho et al. 2011). Dendritic cells are proficiently phagocytized the invading pathogen through transepithelial dendrites (Farache et al. 2013). Dendritic cells also help to block and transcytose the pathogen through epithelial goblet cells and M cells. Invading antigens are transcytosed through M cells to the subepithelial APCs. APCs send the signal to the T cell region of the mucosa-associated lymphoid tissue (MALT) for processed antigen presentation to the B cell. The B cell generates surface immunoglobulin IgA positive (IgA<sup>+</sup>) B cells. Antigen-stimulated T cells and cell surface immunoglobulin enter into the systemic circulation through the lymph nodes. During intracellular immunoglobulin-mediated transport, a virus may be neutralized through it (Das and Thakur 2015). Cytokines derived from epithelia, like TGF-beta, IL-25 and IL-33, play a critical role in the activation of a Th2 or T regulatory mucosal immune response. Severe lung damage with RSV increased neutrophil infiltration and upregulation of TNF- $\alpha$ , IL-13 producing CD4<sup>+</sup> cells in the lung (Stokes et al. 2013). Infection with RSV also upregulate the mucus production due to an increased level of IL-17, a pro-inflammatory cytokine secreted by the activated T cells in the lung (Chen et al. 2003). Probiotic organisms also help in maturation and activation of the mucosal immune system (MIS) by various signal networks mediated by their secreted metabolites, such as organic acid, short-chain fatty acids (SCFAs) (Topping and Clifton 2001; McDermott and Huffnagle 2014), and antimicrobial compounds termed bacteriocins (Galdeano et al. 2019). Several viruses cause respiratory infection to humans (Marsland

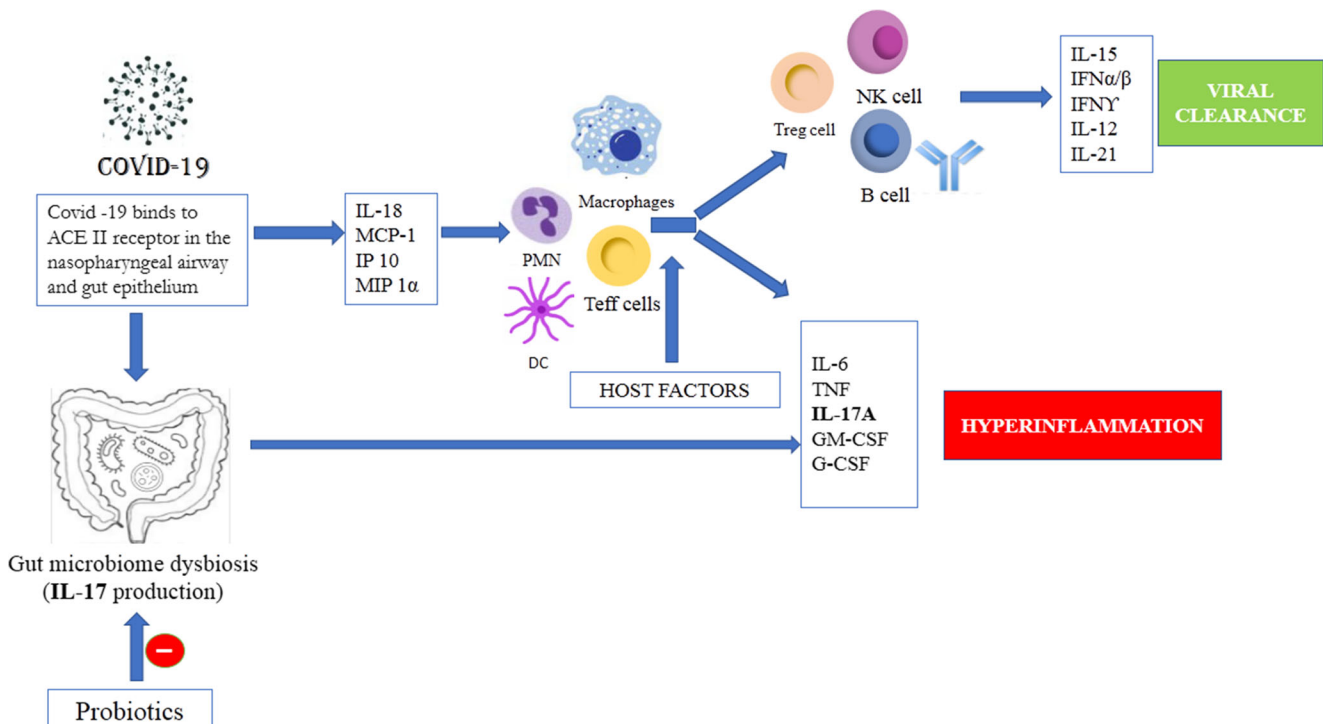
et al. 2015). Probiotic bacteria also could bind to an invading virus, thus inhibiting virus attachment to the host-cell receptor (Salminen et al. 2010). Probiotic medication helps to fortify mucosal immunity and provide restriction against respiratory viral infection (Marsland et al. 2015).

## Probiotic as immune enhancers

Probiotics exert several health beneficial effects to the host by several potential systems through the local immunity (by keeping up gut wellbeing and gut wall integrity) and systemic immunity (by enhancing specific and non-specific immune system). The application of probiotics is efficient and competent for several ailments, including virus infection (Kanauchi et al. 2018). Over a century ago, Nobel Prize winner Elie Metchnikoff performed a series of trials showing that ingesting lactic acid-producing microbes improves illness like digestive and respiratory tract disorders (Gordon 2008). Probiotics modulate the host's innate immune system by enhancing phagocytic activity, leucocytes (polymorphonuclear and monocytes), and expression of some receptors (CR1, CR3, Fc $\gamma$ RI, and Fc $\alpha$ R) that are associated with phagocytosis, and increases the microbicidal function of neutrophils (Hao et al. 2011). The number and the activity of natural killer (NK) cells are also significantly improved in the blood (Grudzien and Rapak 2018). Toll-like receptor (TLR) signalling by commensal organisms exhibits a significant effect for preserving the host's intestinal homeostasis by enhancing gut barrier function and improving the local immune response (Belkaid and Hand 2014).

Probiotics also can induce APCs derived pro- and anti-inflammatory cytokine (for example, IL-10, IL-12, IL-17, TNF- $\alpha$ , interferon- $\alpha$ ) production against foreign particles through activation of adaptive immunity. Intestinal inflammation regulatory pro-inflammatory cytokines, chemokines and their receptors are inhibited by anti-inflammatory cytokine IL-10, produced by different immune-activated cells (Azad et al. 2018). Probiotics provide two different immunomodulatory effects: one is the immunostimulatory effect, which activates IL-12 production, induces NK, Th1, and Th2 cells, and acts against infection and allergy; and another type is immunoregulatory effect, which induces IL-10 and Treg cell activation by Th2, DCs, B cells, and monocytes for adaptive immunity of the host (Chiba et al. 2010) (Fig. 1). A recent animal and human clinical study showed the increased level of IFN- $\gamma$ , IL-2, tumor necrosis factor (TNF)-, serum IgA, and IgA-secreting cells in response to immune function of *Lactobacillus* or *Bifidobacterium* strains (Zhang et al. 2018).

With the enhancement of gut immunity, probiotic consumption may also decrease the risk or can modify respiratory health infection (Wang et al. 2016). Probiotics stimulate lung immunity by enhancing T regulatory response in the airway.



**Fig. 1** The mechanism involved upon host infected by COVID-19. Pro inflammatory cytokines and interferons are released, and viral cellular translation is suppressed to induce viral clearance as a part of the host immune response and an antiviral state in adjacent epithelial cells. Viral clearance occurs in lung and gut epithelium depending on the immune status of the host. However, probiotic consumption improves

inflammation by regulation of immune response in gut through various signalling pathways and helps improve gut dysbiosis caused by SARS-CoV2 and hastens recovery in patients. ACE II, angiotensin-converting enzyme II; PMN, polymorphonuclear granulocyte; DC, Dendritic cells;  $T_{EFF}$  cell, T effector cell;  $T_{reg}$  cell, regulatory T cell; NK, natural killer

The LABs directly enter into the circulation from the gut to the lung and exerts different immunomodulatory action. Oral consumption of *Lactobacilli* can modulate cytokine profiles systemically (Mortaz et al. 2013). Another study showed that *Lactobacillus* GG and *Lb. casei* strains, *Shirota* (LcS) and DN114001, can prevent and treat the microbial infections in the gastrointestinal and respiratory tract with influenza (Mortaz et al. 2013). A community study in both elderly and kids has shown that probiotics *Lb. paracasei*, *Lb. casei* 431, and *Lb. fermentum* PCC may decrease the occurrence, duration, and symptoms of flu and respiratory tract infections by increasing the level of IFN-g in the blood and sIgA in the gut (Zhang et al. 2018). The IFN-g induces bactericidal function of macrophages, induces B cell–opsonizing activity, and increases complement-fixing antibodies that lead to adaptive-mediated immunity (Marshall et al. 2018). Consumption of *Bifidobacterium* and *Lactobacillus* was found to improve the upper and lower respiratory tract infections in children and young population (Rautava et al. 2009; Smith et al. 2013). Consumption of *Bifidobacterium breve*–augmented anti-influenza IgG could successfully protect respiratory tract infections in mice against influenza (Yasui et al 1999).

Compared with the healthy adults and the elderly, the immunocompromised elderly population contain reduced diversity and a lower number of the intestinal microbial community

of *Firmicutes*, *Bifidobacteria*, *Clostridium*, *Faecalibacterium*, *Prausnitzii*, and *Blautia coccoides*–Eubacterium rectal and higher occurrence of *Enterobacteriaceae* and *Bacteroidetes* (O’Toole and Claesson. 2010). *Firmicutes* and *Bacteroidetes* symbolize 93% of the total intestinal microflora in a healthy individual (Rondanelli et al. 2015). The number of intestinal organisms and its composition reduce with increasing the age, with induced numbers of facultative anaerobes and Gram-negative bacteria (mainly *Enterobacter*), and decrease in the mucosal architecture. This microbial composition shifting occurs due to living environment, malnutrition, health condition, and different drug administration such as antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) (Mäkivuokko et al. 2010). The 16S rDNA sequencing of 18 older adults taking NSAIDs showed the changes in the significant microbial phyla, such as a lower number of *Firmicutes* and an increasing number of *Bacteroidetes* (Mäkivuokko et al. 2010). The intestinal transit time also depends on the increasing age and health condition. In the case of immunocompromised subject, the intestinal transit time is more, and fecal bacterial cell mass is less compared with the healthy people (Patel et al. 2013). Therefore, variation in the microbial arrangement in the intestinal lumen may lead to decreased immune system function and a higher incidence of gastrointestinal infections in the elderly than in the young. The main immunological

changes associated with aging involve reductions of efficiency of the immune responses mediated by B and T cells (Rondanelli et al. 2015), because the number of lymphocytes in the peripheral blood along with CD3<sup>+</sup> T and CD8<sup>+</sup> T decreases with the increasing age (Pu et al. 2017).

Aging affects both innate and adaptive immune responses. Elderly appearances lack immunological ability like a decrease in phagocytosis, alteration of cellular migration, changes in cell populations and numbers, and decreased antibody production that reduced efficacy to resist infection (Patel et al. 2013). Appropriate probiotics significantly can boost immunity in the elderly (Hamilton-Miller 2004). Administration of a modified diet with proper nutritional food habits may modulate the microbial community. The use of probiotics is safe and represent beneficial provision to prevent or treat various elderly disorders (Blaut et al. 2006). The efficiency of treatment of older adults with *Bif. lactis* DN173010 and *Lb. casei Shirota* is responsible for the production of short-chain fatty acids like butyric acid, propionic acid, lactic acid and decreased the colonic pH value that increased the peristalsis in the colon which is capable of decreasing the intestinal transit time (Patel et al. 2013). A 12-week study of oral administration of the yogurt supplemented with *Lb. paracasei* N1115 can significantly reduce the risk of upper respiratory tract infection (URTI) in the mid-aged and elderly by stimulation of the T cell immunity, and the frequency of URTI in the subjects compared with the control group (Pu et al. 2017). Administration of a fermented dairy product containing the probiotic strain *Lb. casei* DN-114 001 could decrease the duration of common infectious diseases (CID) of the airways, especially in rhinopharyngitis in the elderly in comparison with the control group (Guillemard et al. 2010). Probiotic *Lactobacillus* GG helps in significant modulation of allergic reaction related to atopic eczema (Ozdemir and Goksu Erol 2013). Harata et al. (2010) studied that intranasal spray of *Lactobacillus* GG could regulate respiratory immune system in mice against H1N1 influenza virus infection. Probiotics are also responsible for reducing the risk of chances of ventilator-associated pneumonia; other respiratory infection in healthy and diseased person and 40–60% virus infected chronic obstructive pulmonary diseases (COPD) are prevented by administration of probiotic (Mortaz et al. 2013).

Probiotic consumption decreases the risk of respiratory tract infection in children (Araujo et al. 2015). Typical upper respiratory tract infection and certain types of influenza include the following: tonsil, pharynx, larynx, and sinuses (Eccles et al. 2007; Thomas and Bomar 2020). Indications of critical upper respiratory tract infections can include runny nose, headache, cough, nasal congestion, sore throat, low-grade fever, sneezing, and facial pressure (Van Riel et al. 2006). The utilization of probiotics fundamentally diminishes the danger of the basic cold and lessens the duration of the manifestations of respiratory tract infections (Wang et al.

2016). In addition, probiotics showed a significant role to in competitively colonizing in the gut to exclude pathogens, modulating the gut barrier function and permeability. It has been shown earlier that probiotics can increase the neutrophil, leukocyte, and natural killer cell counts and activity, as explained earlier. A study showed that probiotics modulate the expression of interleukin (IL)-10 and decrease the inflammatory cytokine expression, such as tumor necrosis factor- $\alpha$ , IL-1b, and IL-8 (Oliva et al. 2012), increase salivary immunoglobulin A levels and produce bacteriocins, and ultimately exert the antimicrobial activity (Fooks and Gibson 2002). A meta-analysis showed that administration of *Lb. rhamnosus* GG prevented RTIs (Liu et al. 2013). Another meta-analysis evaluated the effectiveness of probiotics on the duration of respiratory illness episodes in children grouped with adults and restrained to the examinations using *Lactobacillus* and *Bifidobacterium* strains (King et al. 2014). Tabbers et al. (2011) showed curing of nosocomial infection by using *Bifidobacterium animalis* subsp. *lactis* strain BB-12. BioGaia's strain *L. reuteri* DSM 17938 has been shown to protect against upper respiratory tract infection and gastrointestinal problems in children aged 6 months to 3 years old (Gabryszewski et al. 2011).

## Zinc bioavailability and immune system

Zinc in large portion of the cell's metabolic process is utilized as a fundamental cofactor for metallo-enzymes. It is found essential for membrane integrity, DNA synthesis, and cell multiplication, particularly the immune cells (Hojyo and Fukada 2016; Read et al. 2019). Zinc additionally assists with improving the host's reaction to numerous infections and assumes a significant role in maintaining the host homeostasis (Fukada and Kambe 2014). Zinc administration was suggested to improve the T cell-mediated function, an increment in IL-2 mRNA levels, and to reduce production of the pro-inflammatory cytokine, DNA, TNF- $\alpha$ , and lipid oxidation (Barnett et al. 2010). The unavailability of zinc is correlated with the hindered cellular immunity and its deficiency has been observed to reduce the number of B and T lymphocytes, particularly CD4<sup>+</sup>, and activation of Th1 cytokine. Zinc also stabilizes the cell membrane, and its deficiency disrupts the intestinal mucosa, reduces brush border enzymes, and increases mucosal permeability, macrophage function, and the intestinal secretion of water through the cytokine production, intracellular killing, and phagocytosis (Shankar and Prasad 1998).

A meta-analysis of oral zinc supplementation in patients' with acute respiratory infections observed reduced symptoms and duration of common cold infection (Science et al. 2012). Another study on supplementation of zinc in kids having pneumonia indicated vital reduction of sick conditions



(Rerksuppaphol and Rerksuppaphol 2019). Zinc helps to inhibit viral protease and interferes in physical processes such as virus attachment, infection, and coating (Read et al. 2019). Respiratory epithelial barrier contains tight junction and adhesion junction, where E-cadherin and  $\beta$ -catenin act as the major transmembrane molecules. Deficiency of zinc leads to proteolytic degradation of E-cadherin and  $\beta$ -catenin molecules leading to increased leakage across the upper and alveolar lung epithelial cell (Gammoh and Rink 2017). Zinc depletion also induces abandoned neutrophil migration around the disrupted tight junction with inducing chemokine production, ultimately causing lung disease. Zinc can inhibit several viral respiratory tract infections, including herpes simplex virus (HSV) and the non-enveloped rhinovirus (Suara and Crowe 2004). Respiratory syncytial virus (RSV) is the most significant viral agent for acute respiratory tract infection (ARI), also prevented by zinc salts by preventing cell-to-cell spread in in vitro culture conditions. Zinc supplementation with vitamin A is effective in thwarting acute respiratory disease (ARI), just as diarrhea (Cuevas and Koyanagi 2005). Supplementation of 10–20 mg zinc sulfate/day showed a significantly reduced risk of treatment failure to severe acute lower respiratory tract infection among children in India (Basnet et al. 2012). Another study revealed that increasing plasma zinc levels with daily intake of 10 mg zinc gluconate could decrease the incidence of acute lower respiratory tract infection (Overbeck et al. 2008). Zinc is reported to inhibit RNA-dependent RNA polymerase activity of several viruses including coronavirus, arterivirus, rhinovirus, and hepatitis C virus (Kar et al. 2019). In order to deliver zinc in highly bioavailable form, probiotic strains *Lb fermentum* SR4 and *Lb rhamnosus* GG (LGG) were studied for their ability to accumulate zinc. The results demonstrated that higher bioavailability of Zn was chelated by SR4 and LGG up to 57% and 48%, respectively, when compared with the commercially available inorganic ( $ZnSO_4$ ) and zinc gluconate forms (Lule et al. 2020). te Velthuis et al. (2010) revealed that the combination of  $Zn^{2+}$  and pyrithione (PT) at low concentrations inhibits the replication of SARS coronavirus (SARS-CoV). A study showed consumption of up to 50 mg zinc per day suppresses pandemic COVID-19 viral replication by improving the host's resistance against the viral infection (Razzaque 2020). However, zinc maintains direct antiviral features, through activation of innate and acquired (humoral) antiviral responses (Maywald et al. 2017; Read et al. 2019).

## Role of vitamin D to fight against viral infections

Vitamin D, which is predominantly present in the skin, is significant in calcium reabsorption in the intestine and kidney by activating transcellular calcium transport. The active form

of vitamin D, 1,25-dihydroxyvitamin D (1,25OHD, also called VDR) hormone regulates gene expression especially in immune function and inflammation (Gunville et al. 2013). Vitamin D functioning of immune system helps maintain tight junctions, gap junctions, and adherens junctions. Viral disease affects the junction integrity thereby increasing the rate of infections in the host (Rossi et al. 2020). Deficiency of vitamin D may reduce 25-hydroxyvitamin D (25OHD) levels thereby affecting the host. Probiotic bacteria have been characterized to produce vitamins and positively influencing the composition of the gut microbiota and immune system (Hill et al. 2014). Probiotic bacteria, mostly belonging to the genera *Lactobacillus* and *Bifidobacterium*, confer a number of health benefits, by acting against vitamin delivery and protecting from deficiency (Jayawardena et al. 2020). The higher dietary intakes of fat-soluble vitamins, especially vitamin D, are associated with reduced microbial diversity of *alpha-Proteobacteria* predominantly comprising human pathogens (Steinert et al. 2020).

Studies have demonstrated the significances of vitamin D directly or indirectly in combatting the infection caused by viruses such as rotavirus (Zhao et al. 2019), dengue (Martinez-Moreno et al. 2020) and influenza (Urashima et al. 2010). In COVID-19, rise in case fatality rates (CFR) in oldsters may be due to the reduction in serum 25OHD concentrations with age (Razdan et al. 2020). The reduced production of vitamin D is a result of lower levels of 7-dehydrocholesterol in the skin due to the less time spent in the sun. Immunomodulatory effects of vitamin D acts on both the innate and adaptive immune systems thereby reducing risk of infection and fatality. In COVID-19 patients, the innate immune system generates pro-inflammatory and anti-inflammatory cytokines in response to viral and bacterial infections (Huang et al. 2020). Vitamin D is a modulator of adaptive immunity. The 1,25OHD suppresses T helper cell type 1 (Th1)-mediated responses, by repressing production of inflammatory cytokines IL-2 and interferon gamma ( $INF\gamma$ ) (Lemire et al. 1985). Additionally, 1,25OHD promotes cytokine production by the T helper type 2 (Th2) cells, which helps enhance the indirect suppression of Th1 cells by complementing this with actions mediated by a multitude of cell types. Furthermore, 1,25OHD promotes induction of the T regulatory cells, thereby inhibiting inflammatory processes. COVID-19 infection initiated increased secretion of the Th2 cytokines (e.g., interleukins 4 and 10) that suppress inflammation, which differs from SARS-CoV infection (Huang et al. 2020). SARS-CoV and MERS-CoV differ from CoV infections by producing storms of pro-inflammatory cytokine.

This section defends the role of higher 25OHD concentrations in reducing risk of infection and death from acute respiratory tract infections (ARTI), including CoV and pneumonia. The peak season for ARTIs is generally when 25OHD concentrations are lowest. Thus, vitamin D supplementation may

**Table 1** List of probiotics and their mode of action in stimulating immune response against viral infections

Microbe	Type of infection/virus	Mode of action	References
<i>Lb. plantarum</i> NCIMB 8826	RSV, pneumovirus,	TLR-dependent inflammatory response	Al Kassaa et al. 2014
<i>Lb. casei</i> DN-114001	RTI, rhinopharyngitis, influenza	Enhanced defensin expression and innate immunity	Guillemard et al. 2010
<i>Lactobacillus rhamnosus</i> M21	Pneumonia, influenza	Increases interferon- $\gamma$ and interleukin-2	Song et al. 2016
<i>Bifidobacterium infantis</i> BB-12	URTI	IL-17 inhibitory effect	Smith et al. 2013
<i>Bifidobacterium animalis</i>	URTI	Prevents replication on virus, anti-interleukin-17	Smith et al. 2013
<i>Lactobacillus plantarum</i>	Gastroenteritis coronavirus (TGEV)	Diminishes granulocyte, reduces virus recovery	Yang et al. 2017
<i>Lactococcus lactis</i> JCM 5805	RTI, common infectious disease	Activates plasmacytoid dendritic cell	Kokubo et al. 2019
<i>Lactobacillus plantarum</i> CRL1506	Gastroenteritis coronavirus (TGEV)	Diminish inflammatory-mediated tissue damage	Yang et al. 2017
<i>Bacillus subtilis</i> OKB105	Gastroenteritis coronavirus (TGEV)	Inhibits viral adherence by competitive inhibition	Wang et al. 2017

be started through vitamin-producing probiotics on a regular basis to raise 25OHD concentrations above 40–60 ng/ml. However, for treatment of patients infected with COVID-19, a higher dose might be useful (Jeyaraman et al. 2020). Further study on vitamin supplementation by probiotics needs to be evaluated using a large population of healthy individuals comprising equal number of male and female volunteers. This will also enlighten the differences in immune response during infections. On 23 March 2020, Dr. Tom Frieden, Former Director, Center for Disease Control and Prevention, has proposed using vitamin D to combat the COVID-19 pandemic (<https://www.foxnews.com/opinion/former-cdc-chief-tom-frieden-coronavirus-risk-may-be-reduced-with-vitamin-d>).

## Probiotics and control of viral infections

The immune-suppressed patient encounters dysbiosis in the gut microbiota thereby leading to the accumulation of pathogens in the intestinal tract. Infections caused by intestinal bacteria are among the most difficult and challenging to treat, with great potential to become life threatening. In the case of viral infections in humans, respiratory tract epithelium is an entry gate. The first level of protection in the host is by tenacious mucus through motion of the cilia in the columnar epithelium, secretory immunoglobulin A limits in the respiratory tract secretion. The influence of viral infection on the dendritic cells (DC) leads to a cascade of reactions with an activation of CD4<sup>+</sup> and CD8<sup>+</sup> cells and subsequent development of specific T and B cell-mediated immunity.

Probiotics, besides being beneficial bacteria, also possess antiviral activity. Probiotics are chosen as alternatives as they act as natural immune enhancers (Lakshmi et al. 2013). Probiotics and their metabolites may also indirectly interfere with the virus by altering the state of cells, stimulating innate and/or adaptive immunity. They exert antiviral activity by (1) direct probiotic–virus interaction, (2) production of antiviral

inhibitory metabolites, and (3) stimulation of the immune system. Lactic acid bacteria (LAB) and their bacteriocins serve as antiviral agents (Al Kassaa et al. 2014). LAB are known to synthesize exopolysaccharides (EPS), which may confer health benefits to people such as immunomodulatory, antitumor, antibiofilm, and antioxidant activities. One such strain, *Lb. plantarum* CRL1506, upon oral administration demonstrated antiviral properties, through diminish inflammatory-mediated tissue damage (Yang et al. 2017). Analysis of *Lb. plantarum* metabolites showed major presence of sugars, thus indicating the major antiviral active substances may be polysaccharides. Previous studies have also demonstrated colonization of the epithelium with the lactobacilli sterically hindered the adhesion of virus to the surface. Callahan et al. (1991) reported that sulfated exopolysaccharides inhibit the adherence of HIV to the target cells, thus blocking viral entry in to the host. Similarly, *Bacillus subtilis* OKB105 and surfactin have been found to have antiviral activity against TGEV entering the porcine intestinal epithelial cells by adsorbing virus particles and blocking viral attachment by competitive inhibition (Wang et al. 2017).

Probiotics and paraprobiotics of *Lb. plantarum* or *Lb. reuteri* against the pneumonia virus diminished granulocyte recruitment and expression of multiple pro-inflammatory cytokines and reduced virus recovery. This indicates the mechanism of action may be TLR independent (Gabryszewski et al. 2011). A clinical trial of *Lb. plantarum* HEAL 9 and *Lb. paracasei* 8700:2 in healthy individuals reduced the risk of acquiring common cold infections and pharyngeal symptoms (Berggren et al. 2011). A study conducted by Kokubo et al. (2019) showed *Lactococcus lactis* LC plasma affects plasmacytoid dendritic cell activation. This attenuates muscle degenerative genes and the concentration of fatigue-controlled cytokine transforming  $\beta$ -growth factor. *Lb. rhamnosus* M21 upon treatment for pneumonia in mice showed increased levels of interferon- $\gamma$  and interleukin-2, which are representative cytokines of type I helper T cells (Song et al. 2016)

(Table 1). Application of probiotics has demonstrated clinical potential in animal experiments. Various strains of *Lactobacillus* spp. and *Bifidobacterium* spp. through oral or intranasal administration have shown suppression of infection symptoms against viral infections including influenza (Kawahara et al. 2015; Zolnikova et al. 2018). These decrease the virus load titers and increase T helper cells in the lung parenchyma. In another study, simultaneous administration of *Lb. rhamnosus* and *Bif. lactis* has increased IFN- $\gamma$  and interleukin (IL)-4, IL-10, and IL-6 in the bronchoalveolar lavage and activity of phagocytic cells (Gill et al. 2001; Di Cerbo et al. 2016). As a result, probiotics can cause destruction of viral nucleic acid and limit a virus replication. However, the question about probiotic properties, for a prevention or treatment choice against SARS, MERS, and COVID-19, remains open. Further research needs to be focused on the clinical trials for probiotic administration as an adjuvant therapy for the management of COVID-19 patients.

## Conclusions

The safety of probiotics including lactobacilli and bifidobacteria has been demonstrated by numerous clinical studies. Current evidences show probiotics and probiotic-derived factors have promise for enhancing health benefits and regulation of host homeostasis, including immune health. Protection from viral infection has shown as a benefit of probiotic action. The probiotics exert their beneficial effects through modulation of host immune responses, maintain gut homeostasis and produce interferon thereby suppressing the virus induced cytokine storm. Although a few randomized controlled trials showed that administration of probiotics could thwart ventilator-associated pneumonia in COVID-19 patients, the efficacy in reduction of mortality remains uncertain. Lactobacilli and bifidobacteria have shown a promising beneficial effect and administration of them can overcome the gut dysbiosis induced by the SARS-CoV2 infection. Hence, it is reasonable to change the microflora with administration of probiotics and thus potentially improve the host immune status. Yet, the immune stimulation and cytokine expression is strain specific, and may vary according to consortia of the probiotic bacteria. It is likely that a novel and more targeted approach to modulation of gut microbiota as one of the therapeutic approaches of COVID-19 and its comorbidities will be necessary.

As probiotic research goes into the next stage, mechanism of each probiotic action is to be elucidated for effective clinical use. This leads to potential demand for personalized medicine. Future clinical trials may characterize baseline individual microflora and their genetic pattern of responses upon probiotic introduction, therefore revealing the potency of probiotic application in human disease prevention and treatment. In addition, as a part of translational and clinical research, biomarkers are to

be identified for the evaluation of therapies, including probiotics in hosts. This indeed confirms that immune stimulation through probiotics potentially promote prolonged resistance to virus infections and diseases in humans.

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## Compliance with ethical standards

**Ethical statement** This article does not contain any studies with human participants or animals performed by any of the authors.

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