

Review

# Pharmacological Efficacy of Probiotics in Respiratory Viral Infections: A Comprehensive Review

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**Abstract:** Mortality and morbidity from influenza and other respiratory viruses are significant causes of concern worldwide. Infections in the respiratory tract are often underappreciated because they tend to be mild and incapacitated. On the other hand, these infections are regarded as a common concern in clinical practice. Antibiotics are used to treat bacterial infections, albeit this is becoming more challenging since many of the more prevalent infection causes have acquired a wide range of antimicrobial resistance. Resistance to frontline treatment medications is constantly rising, necessitating the development of new antiviral agents. Probiotics are one of several medications explored to treat respiratory viral infection (RVI). As a result, certain probiotics effectively prevent gastrointestinal dysbiosis and decrease the likelihood of secondary infections. Various probiotic bacterias and their metabolites have shown immunomodulating and antiviral properties. Unfortunately, the mechanisms by which probiotics are effective in the fight against viral infections are sometimes unclear. This comprehensive review has addressed probiotic strains, dosage regimens, production procedures, delivery systems, and pre-clinical and clinical research. In particular, novel probiotics' fight against RVIs is the impetus for this study. Finally, this review may explore the potential of probiotic bacterias and their metabolites to treat RVIs. It is expected that probiotic-based antiviral research would be benefitted from this review's findings.

**Keywords:** probiotics; viral infections; respiratory viral infections; immunomodulatory effects; SARS-CoV-2; probiotics delivery

## 1. Introduction

Mortality and morbidity from influenza and other respiratory viruses are significant causes of concern worldwide [1,2]. A healthy immune system protects against viral infections and reduces susceptibility to subsequent bacterial infections [3,4]. Various variants

of respiratory viruses are the cause of concern globally. As a result, new methods of regulating immune responses are required to defend against emerging respiratory viruses [5]. Probiotics are living microorganisms that, when provided in sufficient proportions, offer health advantages to their hosts, according to the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations [6]. *Lactobacillus* and *Bifidobacterium* are prominent families of bacteria in the gut microbiota [7]. Probiotic formulations are microecological products that improve the intestinal flora's architecture, diminish the growth of harmful microbes, and improve the immune response [8,9]. They modulate innate and adaptive immune responses, facilitating the immune system's development and maturation. Probiotics regulate host-pathogen interactions by initiating the innate immune responses that comprise of Toll-like receptors (TLR), nuclear factor kappa B (NF- $\kappa$ B), mitogen-activated protein kinase (MAPK), and c-Jun NH2-terminal kinase (JNK) pathways. Probiotics such as *Lactobacillus* and *Bifidobacterium* can restore host health by eliminating pathogens and regulating immune responses in intestinal epithelial cells [6,10,11]. Probiotic strains are becoming popular due to their ability to modulate immunological responses, especially in the lower and upper respiratory tracts. Various studies have shown that probiotics regulate allergic reactions and protect the body against viral and bacterial infections [6,12–17].

In the present crisis of COVID-19, the immunomodulatory activities of probiotics may enhance the response to vaccines; therefore, probiotics could be a low-cost method of strengthening vaccination effectiveness and extending the protection period [18,19]. The gut–lung axis has been shown to have a role in improving gut health and homeostasis through the antiviral effects of oral probiotics. While various commercial probiotics have been shown to be beneficial against coronavirus, their efficacy in treating people infected with COVID-19 is still contested [20]. Probiotics have been shown to dramatically boost plasma cytokine levels, influenza vaccination effectiveness, and overall quality of life while decreasing virus titers and the frequency and duration of respiratory illnesses [21]. Probiotics and epithelial cells may directly influence cytokine responses and regulatory T cells [22]. Therefore, probiotics are promising candidates that should be studied for viral infections and immune function modulation.

The gut immune system and treatment duration are linked to immunological disorders. Because probiotics' benefits rely on the strains, clinical research findings have not been conclusive. Identifying specific target populations with greater susceptibilities to the possible impacts of probiotics may be necessary to test the effectiveness of these probiotics. The efficacy of active probiotic strains against RVIs is studied in this review. Moreover, probiotics as a treatment for respiratory infections, their mechanisms of action, clinical studies, probiotic delivery, and implications are also discussed. Conclusively, this study tries to investigate the therapeutic prospects of probiotic microorganisms and their metabolites as a treatment for RVIs. The results of this review are likely to help researchers in the field.

## 2. Materials and Methods

The current comprehensive review compiled the information using diverse computerized databases such as Saudi Digital Library, ScienceDirect, Scopus, Google Scholar, and PubMed. Keywords such as *Bifidobacterium*, *Lactobacillus*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium bifidum*, *Lactobacillus* species, lactic acid bacteria, *Lactobacillus del-brueckii*, *Lactobacillus fermentum*, *Lactobacillus reuteri*, *Lactobacillus johnsonii*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Lactobacillus plantarum*, *Lactobacillus salivarius*, *Lactobacillus helveticus*, *Lactobacillus lactis*, *Lactobacillus casei*, *Lactobacillus acidophilus*, antiviral, health advantages, inflammatory bowel disease, allergies, inflammation, cytokines, allergic diseases, immunomodulatory, anti-inflammatory, anti-viral, innate or adaptive, innate immunity, anti-inflammatory cytokines, immunomodulatory effects, respiratory tract infections, respiratory viral infection, antiviral remedies, influenza, respiratory viruses, viral pneumonia, antiviral mechanism of action, SARS-CoV-2 infection, vaccine development,

and clinical trials were used to search literature with respect to probiotics. Phrases such as “probiotic efficacy against viral infection”, “factors affecting the delivery of probiotics”, “dosage forms contained probiotic microorganism”, “effect of probiotics in the treatment of respiratory viral infections”, “antiviral effects of probiotics”, and “immunomodulatory effect of probiotics” were used to search the literature related to respiratory-related viral infection.

Further information was retrieved from various medicinal books. For the comprehensive aspect, studies published in the last twenty-five years (from 1997 to 2022) were considered; however, there was no time limitation for the comprehensive review. Inclusion criteria were in vitro studies, in vivo studies, clinical studies, cross-sectional studies, cohort-type studies, and studies that addressed the treatment of respiratory viral infection with probiotics. Considering comorbidities, data related to respiratory viral infections and lung disease were included. Only studies available in English were included in this study; however, the selected studies should present reliable methodologies. Exclusion criteria were researched with dubious methods, master’s dissertations, unfinished research, and doctoral thesis.

### 3. Probiotic Bacteria Strains

Probiotics are helpful living bacteria found in people and animals, whereas prebiotics is chemical substances that improve the growth of probiotics. Para probiotics and postbiotics refer to dead or inactivated living cells of probiotics and healthful metabolic products that are produced by the living cells of probiotics, respectively. However, probiotics and prebiotics have been scientifically shown to provide several physiological, functional, nutritional, and immunological advantages [23]. The most often utilized probiotic strains belong to *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* genera. The *Bifidobacterium* strains include *Bifidobacterium longum*, *Bifidobacterium infantis*, and *Bifidobacterium bifidum*. *Lactobacillus* species include *Lactobacillus del-brueckii*, *Lactobacillus fermentum*, *Lactobacillus reuteri*, *Lactobacillus johnsonii*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Lactobacillus plantarum*, *Lactobacillus salivarius*, *Lactobacillus helveticus*, *Lactobacillus lactis*, *Lactobacillus casei*, and *Lactobacillus acidophilus*. Other strains are *Enterococcus faecalis*, *Enterococcus faecium*, *Saccharomyces boulardii*, and *Streptococcus thermophilus* [24–28]. Commonly utilized probiotic strains are shown in Figure 1.

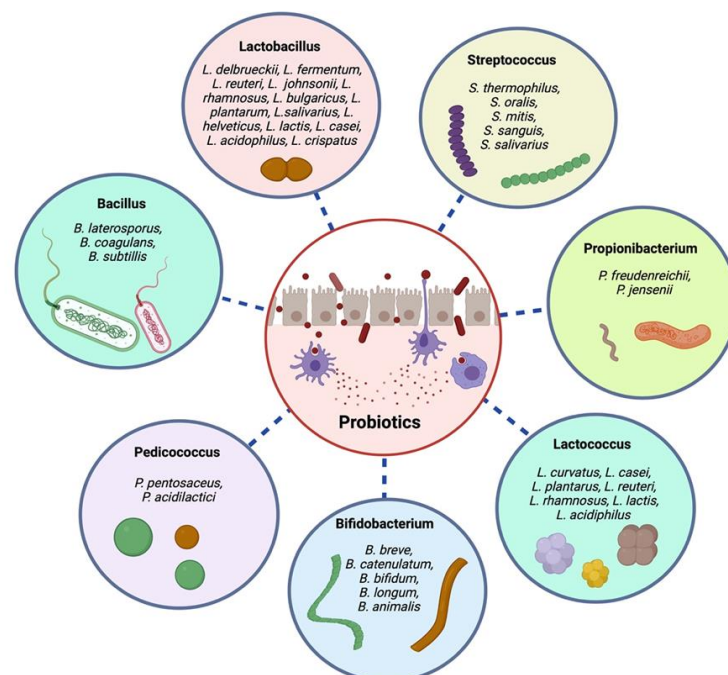


Figure 1. The most often utilized probiotic strains.

#### 4. Probiotic Isolates and Their Health Advantages

Probiotics are fascinating more and more as alternatives to current and traditional medicines. Numerous anticipated mechanisms explore how probiotics work; they depend on probiotic strain, dosage, and intake route [29–31]. The adhesiveness ability of probiotics with the intestine mucosal layer is the most significant for immune system modulation and exhibits antagonistic results, and it has an antagonist effect contrary to pathogens [32–34]. Such precise adhesiveness belongs owing to the interaction between mucin and surface proteins; in that way, probiotics prevent pathogenic bacteria development and multiplication [35].

Furthermore, probiotics produce organic acids and bacteriocins that include lactic and acetic acids, leading to decreased pH intracellularly and raising the ionized organic acids, finally acting as killers of pathogens [36–39]. Probiotic bacteria produce biological activity by conquering pathogen-binding spots [40]. Bacteria interact with each other in their environment through chemical signaling molecules called autoinducers called quorum sensing. Signaling regulates the behavior of enteric microbes responsible for infections and colonization inside the host. *Lactobacillus* releases a molecule that constrains signaling of quorum sensing, directly interacts with signaling, or directly interacts with the *E. coli* O157 gene of bacterial transcription responsible for colonization [38,41–44]. Moreover, probiotic bacteria express their immunomodulatory action by interrelating with epithelial, dendritic cells, monocytes/macrophages, and lymphocytes [45]. These diverse mechanisms of action of probiotics make them the potential agent in preventing and treating numerous diseases such as cancer, diabetes, diarrhea, obesity, cardiac disorders, human immunodeficiency virus (HIV), inflammatory bowel disease (IBS), kidney diseases, allergies, etc. [30,46,47]. These potential health claims fascinate the researchers towards the novel development of probiotics. However, current modern medicine has several minor to significant side effects. The need of the hour is to search for an alternative with fewer side effects that is more therapeutic.

Allergies are some specific conditions produced via hypersensitivity of the immune system [48]. Probiotics treat allergies by curing the impaired digestive system by reducing inflammation, strengthening the gut lining, and stabilizing the immune system. In addition, probiotics alter the antigen's structure and decrease their immunogenicity, pro-inflammatory cytokines generation, and intestinal permeability. Overall, probiotic actions play a significant role in preventing and treating allergic diseases [49–51]. For example, *Lactobacillus* GG and *L. rhamnosus* GG improve the signs of food allergies and substantially decrease the risk of allergic diseases [52]. Furthermore, probiotics are used in irritable bowel syndrome (IBS) through potent mechanisms that reduce epithelial binding and suppress the growth of pathogenic bacteria, antimicrobial constituents' production, immunoregulation, and improved epithelial barrier function and immunoregulation. Thus, these are used to treat Crohn's disease, ulcerative colitis, and pouchitis [53–55].

Cancer is a significant cause of ailment and death across the world. The natural adjuvant is the best key to treating this chronic disease [56–58]. Probiotic bacteria exhibit anticancer effects through a specific group of microbes, including *Bifidobacterium* and *Lactobacillus* species. They reduce the carcinogenic enzyme levels of the colonic through various defensive mechanisms, including antimutagenic organic acids production, improving the host immune system, intestinal permeability regulation, and microflora balance [59–61]. Moreover, evidence recommends that foodstuffs containing probiotic bacteria possibly contribute to cardiac disorder by reducing serum cholesterol levels and controlling blood pressure. Suggested mechanisms involved are cholesterol assimilation, interfering with cholesterol absorption in the gut. In addition, the fermentation process distresses the blood lipids and facilitates an antihypertensive result [62–65]. At the same time, probiotic bacteria have significant effects as anti-inflammatory and immunomodulatory behavior via boosting the dendritic cell's pattern of maturation through discharging tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) interleukin-12 (IL-12) and raising the IL-10 levels besides restraining the generation of pro-inflammatory cells. *Bifidobacteria* persist in the intestines and play a substantial role in health promotion. *Bifidobacteria* induces upregulation of IL-10 secretion by reducing

CD40 and CD80 expression. Subsequently, immunomodulatory and anti-inflammatory activities were observed by enhancing the production of IL-10 [66,67].

Numerous studies discovered about hypoglycemic and anti-diabetic effects of *Lactobacillus* spp. [68]. Probiotics improve antioxidant enzyme actions such as superoxide dismutase, glutathione peroxidase, and catalase. Many strains of lactic acid bacteria (LAB) have revealed antioxidant activities through several mechanisms, including the chelation of metal ions, scavenging of reactive oxygen species (ROS), and enzyme inhibition [69,70]. In this way, probiotics exhibit defensive action through the antioxidant-linked potential measures to counter different diseases. However, probiotics' properties are still a matter of consideration. Additional clinical studies are required to understand the exact mechanism of action of probiotics in different diseases. Different described probiotics available on the market are shown in Table 1.

**Table 1.** Different described probiotics available on the market.

Brand	Product Benefits	Formulation	Strains
Boldfit	Immune support, digestive balance, weight loss, gut health	Each capsule has 30 billion CFU	<i>L. acidophilus</i> and <i>B. lactis</i>
Carbamide Forte Probiotics Supplement	Metabolism management	Each capsule has 30 billion CFU	<i>L. casei</i> , <i>L. plantarum</i> , <i>L. reuteri</i> , <i>L. salivarius</i> , <i>L. paracasei</i> , <i>B. bifidum</i> , <i>B. berve</i> , <i>B. lactis</i> , <i>S. boulardii</i> , <i>S. thermophilus</i> , and many more
HealthKart	Boost immunity by stimulating the activity of immune cells	Each capsule has 30 billion CFU	14 critical strains such as <i>L. plantarum</i> , <i>L. fermentum</i> , <i>L. reuteri</i> , <i>B. lactis</i> , <i>B. bifidum</i> , <i>B. boulardii</i> , <i>L. casei</i> , <i>L. acidophilus</i> , <i>S. thermophilus</i> , <i>B. berve</i> , <i>L. rhamnosus</i> , <i>B. lactis</i> , <i>L. paracasei</i> , and <i>L.salivarius</i>
Inlife	Digestive support and energy management	Each capsule has 2.75 billion CFU	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus rhamnosus</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium longum</i> , and <i>Saccharomyces boulardii</i>
Jarrow	Improve digestion, metabolism, absorption of nutrients, and immunity	Each capsule contains only about 5 billion CFU	<i>L. rhamnosus</i> , <i>L. helveticus</i> , <i>L. plantarum</i> , <i>L. lactis</i> <i>B. berve</i> , <i>Pediococcus acidilactici</i> , and <i>B. longum</i>
Mountainor	Enhances immunity and digestive health	Each capsule contains a total of 50 billion CFU with 16 carefully selected probiotic strains, which are most beneficial for gut health	It contains most strains from the L, B, and S category
Neuherbs Daily Probiotics	Stomach health support	Each capsule contains 20 billion CFUs	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus fermentum</i> , <i>Lactobacillus rhamnosus</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium longum</i> , and <i>Saccharomyces boulardii</i>
Now Foods	Digestive health support	Each capsule contains 25 billion CFU	The probiotic supplement contains all the necessary and imperative L, S, and B category acid strains

**Table 1.** Cont.

Brand	Product Benefits	Formulation	Strains
Swisse	Boosts immunity, healthy digestion, intestinal balance, growth of good bacteria, bloating, and flatulence	Each tablet contains 35 billion CFU	<i>B. lactis</i> and <i>L. acidophilus</i>
TrueBasics	Immune support	Each capsule contains 30 billion CFU	Lactic acids and <i>L. plantarum</i>
Wow	Immune support	Each capsule contains 20 billion CFU	<i>L. plantarum</i> , <i>L. casei</i> , <i>L. gasseri</i> , <i>B. bereve</i> , <i>B. infantis</i> , <i>L. fermentum</i> , <i>L. paraceti</i> , <i>L. acidophilus</i> , <i>B. bifidum</i> , <i>L. rhamnosus</i> , <i>L. salivarius</i> , <i>S. thermophilus</i> , <i>L. reuteri</i> , and <i>B. lactis</i>

### 5. Probiotics Effect on Viral Replication

Novel infectious illnesses and unexpected pathogenic potential may result from viral transmissions between animals and humans. These illnesses influence human health, the economy, and other aspects of a global society. Fever, dry cough, myalgia, dyspnea, and weariness are some of the symptoms that are associated with these disorders. Other symptoms include sore throat, rhinorrhea, headache, and gastrointestinal disorders. The most prevalent and severe sign of the illness seems to be pneumonia [71]. Unfortunately, there is no specific drug for the treatment of various new emerging viruses. In addition, the drug design and validation process, which is necessary for developing novel antiviral therapies, takes substantial time.

Consequently, repurposing natural compounds may provide alternatives and enhance antiviral treatment options. In addition, the particular function that probiotics play in regulating the microbes in the gut, maintaining gut homeostasis, and generating interferon as an antiviral mechanism is shown. The rapid mutation rates of viruses, particularly RNA viruses, make it challenging to develop effective treatments or vaccinations for viral illnesses. In this section, we evaluated the research on the antiviral effects of probiotics for preventing and treating viral infections based upon the different virus types.

#### 5.1. Human Immunodeficiency Virus (HIV)

An in vitro investigation was conducted to assess the efficacy of LAB isolated from healthy women’s breastfeeding to prevent HIV-1 infection. There were 38 different types of breastmilk bacteria tested in this research investigation. Bacteria that have been heated to death and cell-free liquids from bacteria cultures were tested for their ability to stop HIV-1 infection. Viral isolates with tropism for CXCR4, CCR5, or dual tropism were used in the tests. These findings establish for the first time that commensal LAB isolated from human breastmilk suppresses HIV-1 infection in vitro and indicate that these bacteria may play a role in mucosal protection against HIV-1 in the nursing newborn [72].

#### 5.2. Herpes Simplex Virus (HSV)

HSV-1 and HSV-2 were suppressed dose-dependently by *Enterococcus mundtii* ST4V, isolated from soya beans [73]. Enterocins ST4V and CRL35 inhibited viral particle replication [73,74]. Several vaginal *Lactobacillus* strains were tested in vitro for their ability to protect against the herpes simplex virus type 2 (HSV-2) infection. Bacterial cells that are still alive affect several stages of viral replication. Anti-HSV-2 activity lacked virucidal properties. It was exerted via the action of soluble bacterial factors, which could inhibit the generation of infective virions in the presence of the bacteria. Infected cells fed cell-free lactobacilli supernatants had considerably lower HSV-2 production. Lactic acid effectively inhibited viral intracellular antigen production, and both virucidal efficacy and replication inhibition were associated [75]. HSV-2 replication was inhibited in other investigations by a

non-protein cell wall component of the bacteria *Lactobacillus brevis* [76]. Probiotic strains of *Lactobacillus paracasei* subsp. *rhamnosus*, *Lactobacillus paracasei*, *L. Plantarum*, and *Lactobacillus reuteri* entrapped vesicular stomatitis viruses by adhering to the particles [77].

### 5.3. Swine Influenza Virus

An investigation was conducted to determine the probiotic *Enterococcus faecium* (*E. faecium*) NCIMB 10415's inhibitory impact on replicating two swine influenza virus strains (H1N1 and H3N2) in a continuous porcine macrophage cell line (3D4/21) and MDBK cells. The examinations showed direct adsorptive trapping of SwIV through *E. faecium*. A probiotic microorganism fights influenza viruses in at least two ways: directly interacting with them and boosting the body's natural defenses at the cell level [78]. There are many ways that LAB probiotics can be antiviral: They can interact with viruses directly, make antiviral inhibitory metabolites, and make the immune system work more [79]. A high degree of specificity and selectivity was shown by LAB species for the inhibitory action [80]. IL-10 is an anti-inflammatory cytokine in the human immune response [80,81]. IL-10 was initially identified as a T-helper type 2 (Th2) cell product that suppressed cytokine generation in Th1 cells [82,83]. Additionally, probiotics may inhibit the production of pro-inflammatory cytokines by interfering with the mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF- $\kappa$ B) pathways [84,85].

Observations of virus replication inhibition have been the basis of most bacteria in antiviral activity reports. In addition, the particular function that probiotics play in regulating the microbes in the gut, maintaining gut homeostasis, and generating interferon as an antiviral mechanism is shown. Probiotics activate the macrophages and NK cells, modulate immunoreactions, and enhance the immune reaction to inhibit viruses [86,87]. A study has exhibited that either live LAB or cell-free supernatants (CFS) might restrict the porcine epidemic diarrhea virus (PEDV). The specific mechanism of probiotics is unclear and might be a powerful treatment against a pandemic strain of PEDV [88]. Another study has shown through the mice model that genetically engineered *Lactobacillus casei* oral vaccine effectively stimulates the mucosal SIgA and systemic IgG antibody responses [89]. Many types of research have been conducted to search for desired genes and antigens to fight the PEDV of probiotics [89–92]. In their examination, Liu et al. showed that modified *Lactobacillus plantarum* acted strongly as an antiviral agent in intestinal porcine epithelial cell lines [90]. The rapid mutation rates of viruses, particularly RNA viruses, make it challenging to develop effective treatments or vaccinations for viral illnesses. This is especially the case with RNA viruses. There is still much mystery surrounding the complex mechanism by which probiotics affect the host biology and immune system. Further studies are currently required to determine the precise mechanism of antiviral action.

## 6. Immunomodulatory Effects of Probiotic

Probiotics protect the host by regulating, stimulating, and modulating immune responses. To better understand probiotics' immunomodulatory effects, researchers have focused on comprehending their potential better to prevent or relieve some illnesses for which effective medical therapy is currently lacking. It has been proven scientifically that immune cells (T cells and B cells) play a role in adaptive immunity. They protect the body from infections by building memories of the diseases they fight [93]. This section summarizes current research on probiotics' immunomodulatory characteristics.

Probiotics have three functions such as protective, metabolic, and trophic [94]. It is worth mentioning that trophic function has gained attention in immunomodulation investigations. Generally, vertebrates' immune systems may be classified as innate or adaptive. Innate immunity is a type of defense that is not specific. For example, when pathogens are found in the body, it reacts quickly or almost immediately. It also has a pathogen-specific long-term protective memory that helps the adaptive immune system fight and kills pathogens when they return [95]. Adaptive immune responses are triggered when lymphocytes, particularly B and T cells, recognize antigens with their unique recep-

tors. There have been a lot of studies and reports about probiotics in the last few years. They have been found to help the immune system in many ways, including boosting the immune barrier [96,97]. Probiotic homogenates from *Lactobacillus acidophilus*, *Lactobacillus rhamnosus* GG, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Streptococcus thermophiles*, and *Bifidobacterium lactis* have been shown to inhibit mononuclear cell growth [98]. *Bifidobacterium breve* exhibits an elevated humoral immune response following stimulation with IgA, but *Bifidobacterium bifidum* dramatically improves antibody responses to ovalbumin [99].

Additionally, enterocytes and M cells may transport macromolecules, antigens, and microbes through the epithelium via a transepithelial vesicular transport mechanism. Antigenic chemicals boost the body's innate and adaptive immune systems after getting through the intestinal barrier [100]. Strains of probiotic bacteria significantly impact the gut barrier by activating B cells to produce IgA, which helps maintain a healthy gut barrier. Probiotics have been shown to influence the generation of cytokines by APCs, which begins adaptive responses, an in vitro study using enterocyte cells (Caco-2, HT-29, and dendritic cells derived from PBMC). Cytokines also help the body fight off bacteria, fungi, viruses, and other harmful things that try to get in. Based on research undertaken in animal models, it has been shown that specific nuclear-regulated cytokine genes benefit from cytokine-mediated binding and cascade activation by activating or inhibiting particular cell-surface receptors [101–103]. IL-1, IL-8, and TNF- were all increased by *Lactobacillus sakei* in an in vitro investigation involving Caco-2 cells; however, TGF- $\beta$  (anti-inflammatory) production was affected by *Lactobacillus johnsonii*. This study found that interleukin-6 promotes the clonal proliferation of IgA B lymphocytes while stimulating the synthesis of antibodies such as immunoglobulin M and immunoglobulin G and decreasing IgE secretion [104]. Anti-inflammatory cytokines, such as IL-4, IL-5, IL-6, IL-10, and IL-13, are produced by Th2 cells. In addition, B cells, monocytes, DCs, and Tregs induce an adaptive immune response in the body [105,106]. A study was conducted to investigate the effect of *Lactobacillus bulgaricus*, *Lactobacillus casei*, and *Lactobacillus crispatus* on *Escherichia coli* to investigate bacterial modulating effects on cytokine responses. Probiotics interact with immune-competent cells and change the production of proinflammatory cytokines. This is because there was a significant drop in TNF- $\alpha$  output in inflamed mucosa grown with *L. casei* and *L. bulgaricus*. Interleukin-10 mouse models through the *Bifidobacterium infantis* and *Lactobacillus salivarius* were employed to assess their influence on host immune systems in the mucosa and systemic cytokine profiles [107].

Probiotic-treated animals had significantly lower interferon (IFN) and TNF (TNF- $\alpha$ ) levels in their Peyer's patch lymphocytes and spleen cells, respectively [108]. In the p38 MAPK pathway, *Lactobacillus rhamnosus* GG plays a critical function in activating anti-apoptotic Akt/protein kinase B and inhibiting pro-apoptotic factors [109]. *Bifidobacterium* and *Lactobacillus* species were given to rats to evaluate the immunomodulatory effects of probiotics, with overexpression of IL-10 (anti-inflammatory cytokines) and downregulation of TNF- $\alpha$  and IL-6 showing modulation or regulation of immune responses (proinflammatory cytokines). The studies showed that the probiotics significantly increase IgG and IgA concentrations in rats, although this is dose-dependent. Probiotics also can be immunomodulators to interact with epithelium and DCs, macrophages/monocytes, and lymphocytes [110]. Another study discovered that the proinflammatory cytokine TNF- $\alpha$  was significantly lowered by the *Lactobacillus bulgaricus* and *Lactobacillus casei* when interacting with immunocompetent cells. Numerous *Bifidobacterium* and *Lactobacillus* strains have been shown to induce TGF- $\beta$ , IL-6, and IL-10 expression in epithelial cells and promote immunoglobulin synthesis further (IgA). These probiotic bacteria strains make the immunoglobulin receptors on the cells of the intestinal epithelium cells [111]. Studies show that probiotics can only affect cytokines from a single strain. Therefore, combining different probiotic strains to treat inflammation-related tissue damage and gastrointestinal inflammation in humans is beyond the scope of further research.



## 7. Role of Probiotics in Respiratory Tract Infections

Many non-antiviral and antiviral remedies are presently searched to conquer morbidity and mortality correlated with influenza and other respiratory virus infection [112,113]; still, no one is entirely effective in winning the fight against them. Modern medicine and nutraceutical have a broad spectrum of uses in various ailments, including antiviral, immunomodulators, antioxidant, hepatoprotective, anticancer, and cardioprotective [114]. Studies comparing the makeup of the lung microbiome in healthy and diseased states have shown substantial variations [115,116]. Lung disease has reduced bacterial diversity, with a single taxon or small group dominating [117,118]. It has been shown that age-related changes in composition and diversity in the gut microbiota were seen in cross-sectional research involving individuals from various age groups [119]. *Bifidobacteriaceae*, *Bacteroidaceae*, *Ruminococcaceae*, and *Lachnospiraceae* become less common with aging [119–122].

Unique microbial communities reside on the surfaces of mucosal linked with gastrointestinal tract (GT) and respiratory tract (RT), according to studies of the last 15 years, and these communities impact host defense against viral infections. The competent immune system lessens viral infections and the susceptibility to secondary bacterial infection. Antiviral immune responses induced by RVIs related to the change of microbial formation and activity (“dysbiosis”) in the GT and RT might change succeeding immune activity toward secondary bacterial infection or change the dynamics of inter-microbial communication; therefore, potential pathogenic bacterial species proliferation is increased. Thus, examining how respiratory viruses modify the gastrointestinal microbiome is worthwhile. It has been proposed, for example, that there is a link between viral-mediated inhibition of antibacterial immune responses [3]. The density of DNA and RNA viruses in the intestinal virome equals that of bacterial cells. It may result in a 20:1 enhancement in bacterial cells on gut mucosal surfaces and inside mucus layers [123]. Gut microbiome and respiratory infection interactions are bidirectional. Studies have shown that the respiratory virus may change the gut microbiome; it forms adaptive immune responses to fight the respiratory viruses. Antibiotic cocktail pretreatment in mice has raised morbidity from influenza infection [124,125]. Inhibiting severe illness and limiting viral load, the gut microbiota and immune system interact and perform a protective function. Immunity in elderly individuals and infants is weakened. As a result, these two categories have a high mortality rate and are easily infected by viruses.

The usage of probiotics has extensively grown because of their effect on immune responses, especially for those affected by lower and upper respiratory tract infections. Cytokine storm is an inflammatory reaction of superinduction that has been associated directly with severe complications and viral pneumonia of respiratory diseases. Probiotics as potential immunomodulatory agents and enhance the host’s response to RVIs. Therefore, probiotics’ antiviral properties and immune responses are vital to understanding [108,109,126]. Furthermore, interactions between probiotics and macrophages and dendritic cells were seen in the lamina propria, resulting in NK cell activation, which triggers IFN- $\gamma$  production to defend against viruses. PAMPs of probiotics interact with different TLRs, and NF- $\kappa$ B-mediated antiviral gene expression is incited. Efficient immune cells go to infection sites via circulatory and lymphatic systems to protect against respiratory viruses [5]. The probable antiviral action of probiotics is shown in Figure 2.

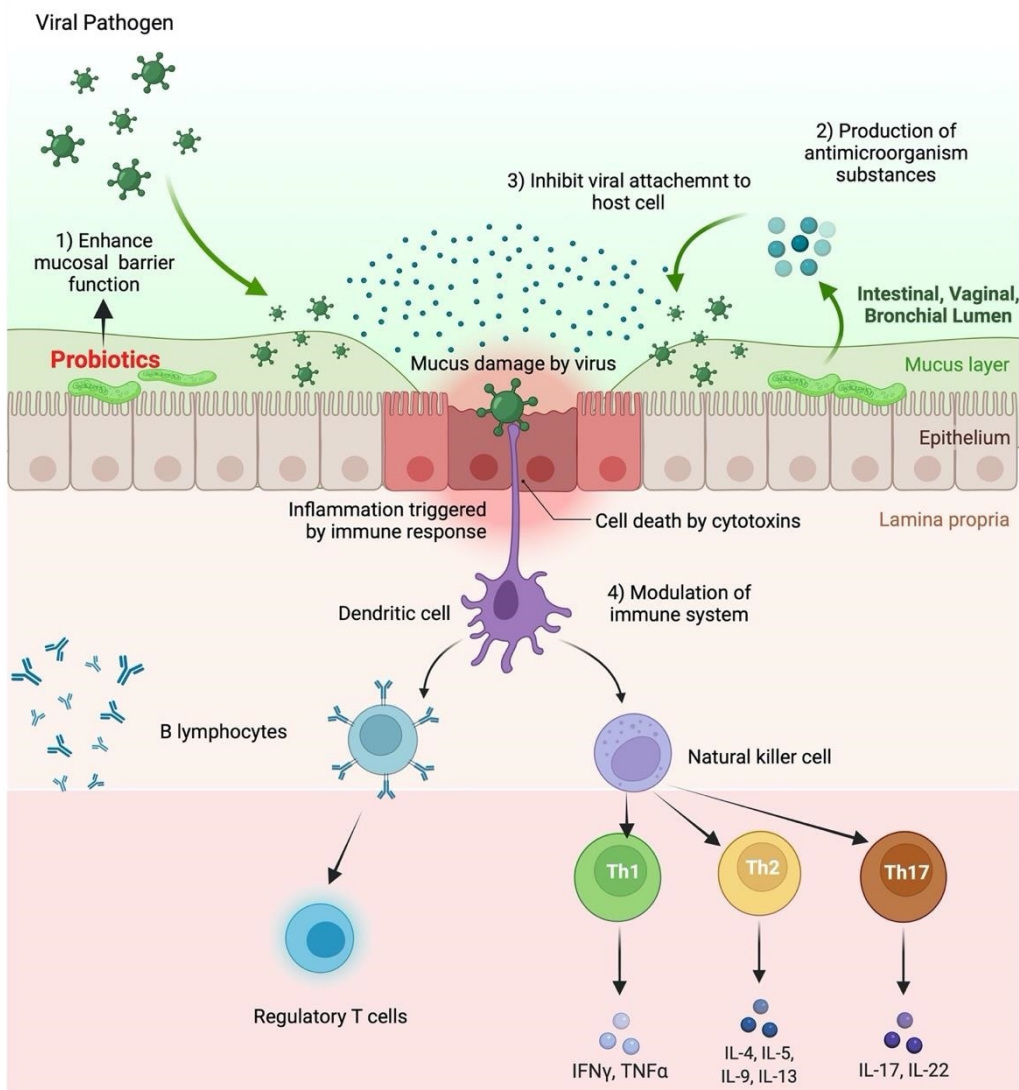


Figure 2. Probable antiviral mechanism of action of probiotics.

### 8. Role of Probiotics in SARS-CoV-2 Infection

In December 2019, the severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2) was discovered in China’s Hubei province, and it causes COVID-19. SARS-CoV are enveloped, positive sense single-strand RNA viruses that belong to the broad family Coronaviridae and subfamily Caronavirinae [127]. COVID-19 has forced us to execute public health measures worldwide as no specific medications are in hand to treat this viral infection [128,129]. The risk of COVID-19 infection is higher than the seasonal flu [130]. COVID-19 is a viral infection that causes respiratory distress but can also induce signs and symptoms related to the gastrointestinal tract. The human gut microbiota regulates immune system homeostasis, which is vital for protecting responses to diverse infections. In addition, lung microbiota and gut have reciprocal interactions called the gut–lung axis (GLA). As a result, metabolites and gut microbiota may trigger any alterations undermining the immune system’s antiviral function against the respiratory virus, including SARA-CoV-2 [131]. Healthy lungs and gut microbiota protect against respiratory tract infection (RTI) related to COVID-19 and the influenza A virus. Thus, any changes in the gut microbiota can impair other organs’ activities [132,133]. Additionally, 33% of patients suffer from irritable syndrome (IBS), and 50% of patients with inflammatory bowel disease (IBD) are sensitive to respiratory ailments without chronic or acute respiratory complications [134,135].

The current pandemic needs alternative treatment to control the high morbidity and mortality rate. We can use previously approved remedies with safety profiles to treat this disease. Probiotics may be available as an alternative treatment with safety profiles. Some studies have been conducted against different strains of SARS-CoV-2, and results show that probiotics can manipulate cytokine storms and modulate immune responses [136,137]. It was found that various commercial probiotics are used and effective against SARS-CoV-2, but the subject of their efficacies is debatable in treating COVID-19 patients now. Nineteen clinical trials were found on ClinicalTrials.gov in the context of probiotics such as mixtures of *Lactobacillus*, *Bifidobacteria*, and *Lactobacillus* to treat COVID-19 patients [89]. The gut microbiota composition can change the prognosis and severity of COVID-19 during hospitalization and alter the immune responses [138]. A microbiome-oriented risk assessment might be used for severe patients' risk profiles [139]. A few components of probiotics could effectively bind the ACE2 receptor proteins and spike proteins (S) to avert the virus from penetrating the host body [140]. It was also found that administering more than twenty probiotics has improved antiviral antibody production and anti-inflammatory interleukin levels and reduced the viral load [5,141–143].

*Bifidobacterium* spp. and *Lactobacillus* spp. are vital traditional probiotics that can regulate a varied gut ecology in flight against SARS-CoV-2. The results of clinical trials and circumstantial evidence provide the foundation for the argument for using probiotics to treat SARS-CoV-2. In the gut microbiota, *Lactobacillus* may cause eubiosis via its antiviral properties, which can have an anti-inflammatory impact and help avoid superinfections. Probiotics have exhibited prospects for lessening the severity of symptoms and viral pathogenicity of COVID-19 and significant nourishing help for patients, but clinical approaches ought to be developed. Therefore, shortly can be enlightened on probiotics' preventative or medicinal role. The possible role of probiotics in SARS-CoV-2 infection is shown in Figure 3.

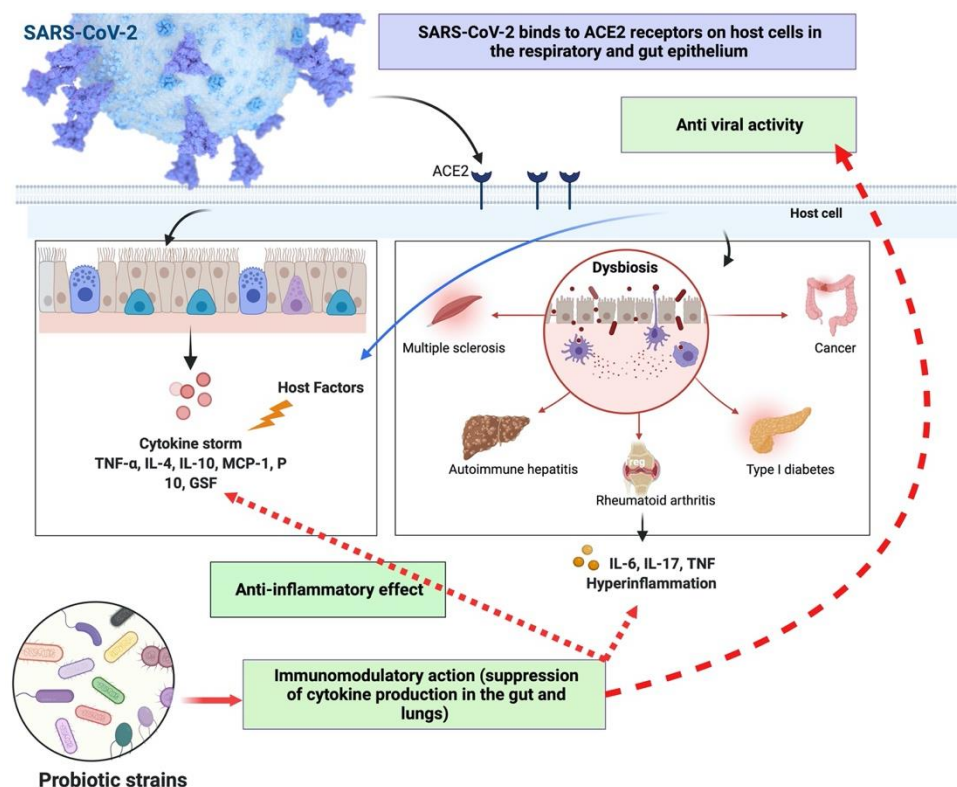


Figure 3. The possible role of probiotics in SARS-CoV-2 infection.

## 9. Clinical Trial on Probiotics' Role in Respiratory Viral Infections

Immunity and airway physiology could be modulated by intestinal microbiota through the gut–lung axis. The microbiome analysis of COVID-19 patients showed a specific intestinal dysbiosis in COVID-19 disease pathophysiology. COVID-19 might be controlled by managing the intestinal microbiome; therefore, the probiotic's role is crucial in the present epidemic, but probiotics' grounds for treating COVID-19 are indefinite. Researchers used an in vitro cytokine response test to analyze the immune system of probiotic lactic acid bacteria used to control COVID-19 in a single-arm, double-blinded, prospective experiment. The emphasis of the study was to evaluate the effectiveness of *Bifidobacterium longum*, *Lactobacillus plantarum* (*L. plantarum*), and *Lactococcus lactis* ssp. *lactis*, against infection with respiratory RNA viruses. Twenty qualified volunteers were enrolled, and 18 of them finished the intervention. In vitro cytokine response assay showed a high innate cytokine index for all subjects by *L. plantarum*. From sixteen to eighteen subjects showed a rising level of cytokine index with significant differences in the fold change. At last, it was concluded in this trial that *L. plantarum* exhibited immunomodulatory effects and mimicked the blood cytokine responses developed by the initial immune response to viral infection. The trial outcomes confirmed that *L. plantarum* might be the potential alternative to manage COVID-19 [144].

In clinical trials on diabetes type 2 patients, it was found that fermented milk containing *L. acidophilus* (*L. acidophilus*) LA5 and *Bifidobacterium lactis* Bb12 control anti-inflammatory cytokines and help to improve blood sugar levels [145]. It also reported that probiotics reduce blood sugar levels and insulin resistance by improving inflammation. Yogurt with *L. acidophilus* strain La-5 and *Bifidobacterium animalis* (*B. animalis*) remarkably decreases HbA1c levels [68]. A clinical study showed that a lessening level of probiotics such as *Bifidobacterium* and *Lactobacillus* is the cause of the imbalance of intestine microbiota among some patients with COVID-19, which leads to secondary infection due to bacterial translocation [146]. Another study was conducted on 42 participants of two nursing homes with ages  $\geq 65$  years and administered jelly of 10 billion heat-killed *L. paracasei* or placebo for six weeks. Administration of the influenza vaccine is performed after three weeks of jelly intake. The outcomes have shown no significant variation between the groups in immune parameters with antibody responses against the vaccinations [147]. Studies have proven that intake of probiotics is good for lessening the RI symptoms and modulating the immune response. Therefore, RDBPC parallel-group trial was conducted to examine this activity. *L. casei* 431 and *L. paracasei* were received by 1104 healthy adults. After 21 days, participants were vaccinated with the seasonal influenza vaccine. The trial's findings revealed that *L. casei* 431 had no meaningful influence on immunological responses to influenza vaccination but did alleviate UR symptoms [148].

According to the research, age-related immunological dysregulation increases infection rates and lowers vaccine efficiency. In a clinical trial, *L. casei* Shirota reduced respiratory symptoms in senior nursing home residents and boosted their immune response to influenza vaccination [149]. A clinical examination was conducted to examine whether a daily probiotic dairy drink may improve the immunological response to influenza vaccination in healthy senior volunteers over 70. Anti-influenza antibodies were more significant in the probiotic product group than in the control group. Individuals over 70 may benefit from frequent use of a specific probiotic product demonstrated to enhance particular antibody responses to influenza vaccination in this age range [150]. The studies enlisting the probiotic efficacy against viral infection are summarized in Table 2. According to our research evaluation, probiotics seem to be a cost-effective method of enhancing vaccination effectiveness and extending protection. Therefore, studies in the future should concentrate on finding the most promising strains, dosages, and timing of vaccination.

**Table 2.** The studies enlisting the probiotic efficacy against viral infection.

Participants	Interventions	Comparison	Outcomes	Study Design	Reference
18	<i>L. plantarum</i> , <i>Bifidobacterium longum</i> , and <i>Lactococcus lactis</i> ssp.	<i>L. plantarum</i> , <i>Bifidobacterium longum</i> , and <i>Lactococcus lactis</i> ssp.	As an anti-COVID-19 probiotic, <i>L. plantarum</i> should be consumed daily	A single-arm, double-blind, prospective trial	[144]
20 infants	<i>Bifidobacteria</i> ( <i>B. longum</i> / <i>B. infantis</i> and <i>B. breve</i> )	<i>Bifidobacteria</i> and placebo	Antipoliiovirus reaction could be improved by intestinal <i>Bifidobacteria</i>	RPC trial	[151]
Infants (6 months of age)	Probiotic strains	Probiotics and placebo	Probiotics may boost the immune system’s response to Hib vaccination	RDPC, allergy- prevention trial	[152]
60	<i>Lactobacillus plantarum</i> CECT 7315/7316	<i>Lactobacillus plantarum</i> CECT 7315/7316 and placebo	It possesses immunostimulant properties and can improve influenza vaccine effectiveness in the elderly	RDPC, human trial	[153]
211	<i>Bifidobacterium animalis</i> ssp. <i>lactis</i> (BB-12 <sup>®</sup> ) & <i>Lactobacillus paracasei</i> ssp. <i>paracasei</i> ( <i>L. casei</i> 431 <sup>®</sup> )	BB-12 <sup>®</sup> (capsule) or <i>L. casei</i> 431 <sup>®</sup> and placebo	Immune function may be improved by using BB-12 <sup>®</sup> or <i>L. casei</i> 431 <sup>®</sup>	RDPC, parallel-group study	[154]
42	<i>Lactobacillus paracasei</i>	<i>Lactobacillus paracasei</i> or placebo	Immune markers showed no significant changes	RDPC	[147]
1104 healthy adults	<i>L. paracasei</i> and <i>L. casei</i> 431	<i>L. paracasei</i> and <i>L. casei</i> 431 or placebo	<i>L. casei</i> 431 has no significant effect on influenza vaccination but lessens the period of URSs	RDPC, parallel-group study	[148]
15 adults	<i>Lactobacillus</i> in Jelly	<i>Lactobacillus</i> and placebo	<i>Lactobacillus</i> in Jelly improves the influenza vaccine effectiveness in the elderly	RPC trial	[155]
737 healthy people aged ≥ 65	<i>L. casei</i> Shirota	<i>L. casei</i> Shirota and placebo	It reduces respiratory symptoms and boosts the immune response to the influenza vaccine	RDBPC trial	[149]
308 elderly	<i>L. casei</i> DN-114 001	<i>L. casei</i> and placebo	Boost specific antibody responses to influenza vaccination	Two RDMC studies	[150]

Abbreviations: RDBPC—randomized, double-blind, placebo-controlled; RPC—randomized, placebo-controlled; UR—upper respiratory; IR—immune responses; URSs—upper respiratory symptoms; RMDC—randomized multicenter, double-blind, controlled; GI—gastrointestinal.

### 10. Scope of Prebiotics or Probiotics and Vaccine Development to Prevent Viral Infections

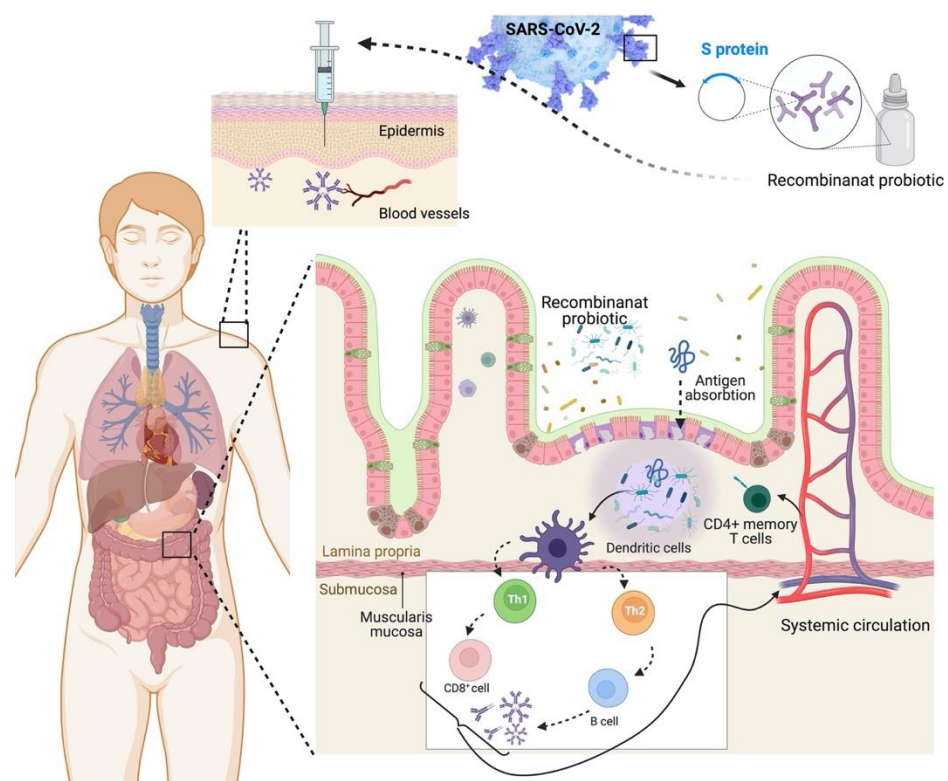
Prebiotics are a form of dietary fiber demonstrated to boost antibody levels after immunization. Epidemiologic studies have observed that the estimation of intake of prebiotics is complex, but quantifying dietary fiber is a routine process [156]. This section investigates the immunogenicity of prebiotics and probiotics. Prebiotics and probiotics are related in terms of their advantages. Many vegetables and fruits are a source of prebiotics, specifically those containing complex carbohydrates, such as resistant starch and fiber [157].

These complex carbohydrates are not digestible; therefore, they pass on by the digestive system as food for various microbes and bacteria. Prebiotics are similar to fertilizers in that they encourage the growth of beneficial bacteria in the digestive tract. Prebiotics has many beneficial effects that support a healthy gut for a better digestive system, lessen adverse antibiotic effects, and promote other benefits. However, it is found that less research has been conducted on prebiotics than on probiotics. Microbiome therapy describes the consumption of a mixture of prebiotics and probiotics. Prebiotic fibers assist feed and potentiate probiotic bacteria. The combination of these two enhance probiotics' effectiveness.

Infectious illness prevention relies heavily on vaccines, which are unlikely to change soon [158]. Prebiotics alter the immune responses to the allergy and cause a lower incidence of dermatitis. Many studies have exhibited that prebiotic carbohydrate affects vaccine-specific antibody response to develop the immune system in healthy infants. A prebiotic mixture of long-chain fructo-oligosaccharides and short-chain galacto-oligosaccharides (scGOS) might work especially by stimulating or down-regulating Th1 and Th2 actions, respectively [159]. Current studies have indicated particular activities on normal T cells with upregulation and downregulation of Th1 and Th2, respectively [160–162]. Probiotics enrich adaptive and innate immunity [131,163].

Antibody responses to vaccines may be affected by probiotics due to their immunomodulatory activity. Therefore, the administration of probiotics in allergy-prone infants has increased. A systematic review was conducted to examine the effect of probiotics on RTI from January 2010 to January 2020. The results of this review concluded that probiotics could significantly raise cytokine levels in the plasma, improve the quality of life, and enhance the effect of the influenza vaccine by lessening the titer of viruses and duration and occurrence of RI. These immune-modulating and antiviral effects and their capability to provoke interferon production suggest using probiotics as an auxiliary cure to control COVID-19. Probiotics could be an appropriate therapy for RTI and a feasible option to help faster recovery with increased vaccine effect [21]. The immunomodulatory impacts of probiotics could affect the response to vaccines. Another systematic review analyzed the randomized placebo-controlled human research to examine probiotics' consequences on humoral vaccine reactions. In this, 3812 enrolled people were examined through 26 studies to explore the outcome of 40 distinct probiotic strains on the reaction to 17 diverse vaccines. Probiotics have been demonstrated to have a beneficial effect in half of the investigations. The beneficial effect of vaccine response was most robust for parenteral influenza and oral vaccinations. There was a considerable variation between the selection of probiotics, dose, strain, purity, viability, and timing and duration of administration. The findings of this analysis indicated that probiotics are a very affordable intervention that may be used to increase vaccination efficacy and duration of protection [18].

Probiotics enriched the response to the influenza vaccine. Therefore, future researchers must search for the most favorable strains, timing, and administration doses concerning vaccination. *B. lactis* and *L. paracasei* (109 CFU) were administered for six weeks, and it increased the Influenza specific IgG, IgG1, and IgG3 levels ( $p \leq 0.01$ ). Higher seroconversion rates for influenza-specific IgG, IgG1, and IgG3 ( $p < 0.010$ ) and higher influenza-specific IgA levels in saliva were noted 4 weeks following trivalent inactivated influenza vaccination (TIV) (*B. casei*  $p = 0.017$ , *B. lactis*  $p = 0.035$ ) [154]. The live-attenuated influenza vaccine (LAIV) protects against influenza by activating the immune system's mucosal mucosa. It is proven by the studies conducted on animals and adults that probiotics enhance the immune response when the vaccines are delivered mucosally [164]. From individual to individual, the immune response to vaccines differs. Therefore, the duration of the protection and efficacy against the various strains must examine. The above-discussed studies claimed that probiotics might enhance the vaccine efficacy and prolong the protection in the present scenario. Future research should confirm the optimal strains, timing, and administration doses of vaccination. The possible scope of probiotics in vaccine development against viral infections is shown in Figure 4.



**Figure 4.** The possible scope of probiotics in vaccine development against viral infections.

### 11. Factors Affecting the Delivery of Probiotics

Probiotics efficiency depends on these microorganisms' physiology, activity, and viability. In addition, not all bacteria are similar in terms of their advantages and ways of action. Therefore, not all probiotics are equivalent. Probiotic strains may have a wide range of beneficial benefits on the host, and most probiotic products have been developed using *Lactobacillus* and *Bifidobacterium* species to withstand the challenges of preparation, storage, and delivery [165]. Probiotic must be resilient enough to withstand the rigors of the manufacturing process without losing much of its vitality. The survival of microorganisms is affected by various physical and chemical conditions such as desiccation, oxygen exposure, humidity, osmotic pressure, and high temperature. In addition, various microbial species are affected by the severe GI conditions defined by low stomach pH and bile salts in the small intestine [166]. On the other hand, numerous *Lactobacillus* and *Bifidobacterium* species are microaerophilic and aero-tolerant and relatively tolerant of various environmental changes encountered during preparation, storage, and GI transportation, which, when combined with well-defined cultivation methods, makes them preferable probiotics products [167]. These microbes are hard to work with because they are prone to oxygen and often in gastric environments after indigestion [168,169]. Difficulties hinder next-generation probiotics in preserving these susceptible microorganisms' viability via typical preparation, storage, and administration procedures. The capacity of a probiotic strain to outcompete another strain within a certain niche is thus required for the establishment of a probiotic in the gut to be long-lasting [170,171].

Oxygen-sensitive bacteria respond best to freeze-drying processing. It is necessary to desiccate oxygen-sensitive microorganisms to store them for an extended period [165]. Probiotic concentrations of  $10^6$  CFU/mL in the small intestine and  $10^8$  CFU/mL in the colon have been shown to have therapeutic benefits [172]. Several requirements must be satisfied to convey probiotic advantages to the consumer properly. From raw materials to the finished product must be monitored and documented for quality assurance, and this must be performed on time. The development of consumer products requires con-

siderable expertise and experience. In the past, probiotic *Lactobacillus* and *Bifidobacteria* have been added to fermented dairy products, which have a short shelf-life and need refrigeration. Dietary supplements and “dry” food matrices may now include probiotics, which are projected to remain stable at room temperature and humidity for up to 24 months. High-quality probiotics may be effectively included in various delivery methods if the manufacturing process, product formulation, and strains are chosen correctly [173].

To produce the next generation of probiotics, new or improved methods of the microbial production cycle are required. Oral administration is the most effective when the intended site is in the GI. Other options include rectal and vaginal [24,59,170,172]. As a result of their high sensitivity to oxygen and the potential for gastrointestinal disorders after ingestion, working with these bacteria is complex. The difficulties in preserving the survival of these sensitive bacteria via typical preparation, storage, and distribution procedures pose a barrier to the commercialization of this sort of next-generation probiotics. A suppository base, such as silicon dioxide, microcrystalline cellulose, rice maltodextrin, magnesium stearate, methylcellulose, and hydroxypropyl, is added to improve the performance of the probiotic diluent, coating agent, lubricant, binder, and sweetening agent. An oral probiotic composition should help prevent or cure respiratory infections. Understanding the function of the oral microbiota in infectious disease is critical for developing therapeutics for preventing and treating respiratory illnesses. However, further research is needed to determine the clinical effectiveness of delivery-related characteristics.

## 12. Conclusions

One of the most prevalent viral or bacterial infections is RVI. Because of an unbalanced microbial population in the digestive and respiratory systems, people are susceptible to RVIs. As far as the lungs are concerned, the gut microbiota plays a vital role in triggering immunological responses. Probiotic strains exhibit antiviral activity against common respiratory viruses. *Lactobacillus* and *Bifidobacteria* have been demonstrated to help in RVIs. Probiotic therapy may be advantageous in reducing disease-induced inflammation while also strengthening mucosal immunity and limiting the transmission of viral infections. Several research findings on probiotics suggest that their administration may also be beneficial in lowering the severity of RVIs and the significant difficulties associated with COVID-19. Probiotics can be used as a complementary therapy to reduce the mortality rate of COVID-19. The supplementation of probiotics may be beneficial in viral illnesses by enhancing immunity. An oral probiotic composition should help prevent or cure respiratory infections. Understanding the function of the oral microbiota in infectious disease is critical for developing therapeutics for preventing and treating respiratory illnesses. According to this review’s findings, probiotics’ immunomodulatory properties may help treat respiratory viral infections. Current microbial product processing procedures are not well adapted to produce next-generation probiotics; thus, improvements or new processing methodologies are required. Oral administration of next-generation live probiotics has received little research. However, further research is needed to determine the clinical effectiveness of delivery-related characteristics and the optimal dosage for each strain in various therapeutic settings. In our analysis of trials, probiotics seem to be a cost-effective method of enhancing vaccination effectiveness and extending protection. Future research should determine the most effective strains, dosages, and administration schedules concerning vaccinations. Finally, probiotic-based antiviral research is expected to benefit from this review’s findings.

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