

Review

The Antiviral Potential of Probiotics—A Review on Scientific Outcomes

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Abstract: A rich repertoire of research studies on probiotics has been documented as one of the therapeutic agents or adjuvants for vaccines in treating viral infections. It is well known that the immunomodulatory properties of probiotics reduce the severity of viral infections. The efficacy of probiotics alone and combined boost up the host's innate immunity, thereby developing a robust antiviral paradigm. As dietary and therapeutic measures, probiotics potentially work as an alternative for those who lack access to vaccines or antiviral drugs. Potential probiotic mechanisms include competing with pathogens for nutrients and colonization sites, producing antimicrobial metabolites and enhancing protective immune responses. The live probiotics can reach and colonize the host animals' intestines then confer the health benefits by improving the host's natural defence against viral infections. The research studies on probiotics suggest that they reduce the risk of viral infections, yet the innermost mechanisms are still unknown. The reason for scripting this review is to discuss the current developments in probiotic therapeutic measures and their probable insights into antiviral agents.

Keywords: probiotics; antiviral activity; corona virus; immune enhancement



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1. Introduction

Probiotics are defined as “living microorganisms, which provide health benefits on the host beyond natural basic nutrition” [1]. They improve the hosts' intestinal microbial balance when administered in an adequate ratio. The term “probiotic” originated from the Greek word meaning “for life” [2] and was first used by Lilly and Stillwell [3]. The term probiotics is currently used to denote microorganisms (associated with beneficial health effects for humans and animals), which convene the host organism's health if they are consumed in sufficient amounts [4]. Generally, probiotics are well-defined as live microorganisms. The most common microbes that are used as probiotics are lactobacilli and bifidobacteria. Live microbes either from gut commensals or fermented foods or from any other source are not considered as “probiotics” until those live microbial species or strains are isolated, characterized and substantiated with proper evidence of their safety and efficient health benefits with adequate controlled studies. Dead microbes, microbial products and components are not considered as probiotics [5]. Probiotics are consumed through fermented foods such as yogurts or dietary supplements [6]. The probiotics consumption influences the health of the host by inhibiting the local gut mucosal microbial niche [7] and augmenting the indigenous immunological responses [8]. The probiotics intake may stimulate the intestinal microbiota's composition and activity, and its contents [9].

Probiotics may play a beneficial role in several medical conditions [10–15]. The diverse number of microbial species and genera can be executed as probiotics and are indigenous to

the host gastrointestinal tract (GIT). Probiotics can be taken in various forms, such as yogurt, cheese and fermented foods, as a part of a regular diet and therapeutics [16]. A recent study has reported the possible use of probiotic formulations (probiotic-based toothpaste and chewing gum) for periodontal therapy in patients with periodontal disease [17]. Probiotics are used as an adjuvant in the treatments by rebalancing the normal gut microbiota and enhancing the immune response, which indicates probiotics as a promising approach in the prevention of and reduction in clinical symptoms. Probiotics are used in the management and prevention of allergies, antibiotic-associated diarrhea, gastrointestinal disorders and respiratory infections [15]. Based on systemic reviews and meta-analysis by Wang et al. [18] and King et al. [19], the intake of probiotics appears to reduce the incidence of respiratory infections in children [18], reduce the use of antibiotics in infants and children and decrease the risk of common acute infections [19].

Considering the beneficial effects of probiotics in viral infections, specific probiotics have been suggested in alleviating the severity of virulence. Global outbreaks of viral infections initiate the search for probiotic consumption. Since infections were being treated with various antimicrobial medicines, resulting in antimicrobial resistance, the growing world requires frontline drugs for the therapy of a wide range of infectious outbreaks. However, those drugs should have capabilities ranging from immunomodulating properties to encountering the infectious particles.

The widespread illness and mortality caused by viruses worldwide initiates the need for a better understanding of the host immune responses and novel therapeutic or prophylactic interventions. Each available vaccine has limited efficacies; as new strain specific pandemic vaccines are required to be developed to provide optimal protection during every pandemic situation (which is caused by the specific pandemic strain) [20]. Antiviral medicines have restrictions such as instant drug treatments after infection, and the development of new resistance strains [21–25]. Thus, it is desirable to find any other solution that would provide antiviral effects.

The current manuscript summarizes the antiviral potential of probiotics.

2. In Vitro Evidence of the Antiviral Activities of Probiotics

Bifidobacterium adolescentis SPM1005-A treatment reduced the expression of an onco-gene in Human papillomavirus (HPV) type 16 infected SiHa cells. The suppression of E6 and E7 mRNA was observed after probiotic treatment, which was not associated with the morphology of cells and does not exhibit any cytotoxicity. The result suggests that SPM1005-A could be used to prevent HPV-associated cervical cancer [26].

The pre-treatment of feline calicivirus with a cell-free bacterial medium filtrate (CBMF) and a bacterial cell suspension (BCS) of *Lactococcus lactis* subsp. *lactis* LM0230 reduced the feline calicivirus titer (in terms of log₁₀ tissue culture infectious dose (TCID₅₀)) in Crandell-Reese feline kidney cells. About 1.3 and 1.8 TCID₅₀ were observed in the viral infected cells when the virus was pre-treated with CBFM and BCS, respectively. A significant decrease in feline calicivirus titer was not obtained by the pretreatment of the virus with CBFM (adjusted to pH 7). When the kidney cells are co-treated with feline calicivirus and either CBFM (adjusted to pH 7) or BCS, the antiviral activity was increased significantly. There was no cytotoxicity in the cells (uninfected with virus) treated with higher dilutions of CBFM, and with both undiluted and diluted BCS [27].

B. adolescentis inhibited the multiplication of murine norovirus-1 on RAW 264.7 (murine macrophage cell line) cells. The genome copies of murine norovirus-1 collected from the infected RAW 264.7 cells were not reduced, indicating that *B. adolescentis* does not inhibit the murine norovirus-1 from binding to the RAW 264.7 cells. However, the binding of human norovirus GI.1 virus-like particles to human intestinal epithelial cell lines (Caco-2 and HT-29 cells) was reduced by *B. adolescentis*. Similarly, the binding of human norovirus GII.4 virus-like particles to Caco-2 cells was not reduced, while the binding of human norovirus GII.4 virus-like particles to HT-29 cells was reduced. Therefore, the antiviral

effect of *B. adolescentis* against murine norovirus-1 and human norovirus virus-like particles might be based on a different mechanism [28].

The *Bifidobacterium longum* subsp. *infantis* CECT7210 treatment reduced the replication (~36% reduction in infectious foci) and infection rate (~48% reduction in infectious foci) of rotavirus Wa in the MA-104 and HT-29 cell lines. The co-culturing of CECT7210 and cell lines effectively reduced the viral infectivity [29].

The cell-free metabolites of *Lactobacillus casei* CMPUJ 415, *Lactobacillus fermentum* CMPUJ 413, *Bifidobacterium bifidum* and *B. adolescentis* DSM 20083 were evaluated for the anti-rotavirus activity. The treatment of metabolites of *L. casei* CMPUJ 415 and *B. adolescentis* DSM 20083 effectively reduced the production of NSP4 protein and the release of Ca^{2+} in rotavirus-infected MA104 cells. The results suggested that probiotic bacterial metabolites could suppress the impact of the rotavirus infection by reducing the production of the NSP4 protein and regulate the liberation of Ca^{2+} [30].

Viable probiotic strains such as *B. adolescentis* (DSM 20083), *Bifidobacterium breve* (ATCC 15700), *B. bifidum* (ATCC 11863), *Bifidobacterium dentium* (DSM 20084), *Bifidobacterium lactis* (Lafti B94-DSL), *Lactobacillus acidophilus* (Lafti L10-DSL), *L. casei* (Lafti L26-DSL), *L. fermentum* (ATCC 9338), *Lactobacillus plantarum* (CECT 220) and *Lactobacillus rhamnosus* (ATCC 7469) were screened for in vitro anti-rotavirus activity in MA104 (embryonic Rhesus monkey kidney cell line) cells. The percentage of viral infection was reduced by the *L. casei*, *L. fermentum*, *B. adolescentis* and *B. bifidum* strains in MA104 cells compared to that of the other viable probiotic strains. The antiviral effect of these four probiotic strains were further analyzed using different methods such as (i) exposing the cells with protein-based metabolites of the probiotic strain before viral infection (pre-treatment method), (ii) or after viral infection (post-treatment method) and (iii) the co-incubation method (the co-incubation of protein-based metabolites of the probiotic strain and virus and then the exposure of MA104 cells to the co-incubated mixture). The results indicated that the co-incubation method could protect the cells from viral infection effectively. Notably, *L. casei* and *B. adolescentis* suppressed about 75 and 63% of infectivity, respectively. The results indicated that probiotic supplementations could reduce the infectious rate of rotavirus [31]. Similarly, Han et al. [32] reported that the pre-exposure of probiotic strain *B. longum* BORI to MA104 cells significantly reduced the viral infection, which was attributed to the ability of the probiotic to interfere with the interaction of viruses and host cells. Further, the anti-viral potential of the probiotic strain corresponded to the non-protein, low-molecular-weight bacterial compounds. The study suggested that the probiotic-derived compounds could help to manage the rotaviral infection (Table 1).

Table 1. Antiviral potential of probiotics: in vitro evidences.

Probiotic(s)	Model	Anti-Viral	Findings	Ref.
<i>Bifidobacterium adolescentis</i> SPM1005-A	SiHa cells	Human papillomavirus type 16	↓ expression of E6 and E7 oncogene	[26]
<i>Lactococcus lactis</i>	Crandell-Reese feline kidney cells	Feline Calicivirus	↓ virus titers	[27]
<i>B. adolescentis</i>	Caco-2, HT-29 and RAW 264.7 cells	Norovirus	Inhibit the multiplication of Murine norovirus-1 on RAW 264.7 cells ↓ Binding of human NoV GI.1 VLPs to Caco-2 and HT-29 cells	[28]
<i>Bifidobacterium longum</i> subsp. <i>infantis</i> CECT 7210	MA-104 and HT-29 cell lines	Rotavirus	↓ virus multiplication and infection.	[29]
<i>Lactobacillus casei</i> CMPUJ 415, <i>Lactobacillus fermentum</i> CMPUJ 413, <i>Bifidobacterium bifidum</i> and <i>B. adolescentis</i> DSM 20083.	MA104 cells	Rotavirus	↓ NSP4 production ↓ Ca^{2+} release	[30]
<i>B. adolescentis</i> (DSM 20083) and <i>L. casei</i> (Lafti L26-DSL)	MA104 cells	Rotavirus	↓ Infectivity of virus	[31]

Table 1. Cont.

Probiotic(s)	Model	Anti-Viral	Findings	Ref.
<i>B. longum</i> BORI	MA104 cells	Rotavirus	Inhibit the viral infection	[32]
<i>Lactobacillus rhamnosus</i> GG and <i>L. casei</i> Shirota	Human and animal epithelial cell lines	Rotavirus Transmissible gastroenteritis virus	↑ Release of ROS. Attachment to cell line was varied. ↑ The integrity of the monolayer.	[33]

↑: Increased; ↓: Reduced; ROS: reactive oxygen species; NoVs: Noroviruses; VLPs: Human NoV virus-like particles.

Maragkoudakis et al. [33] studied the antiviral activity of lactic acid bacteria (LAB) strains such as *L. rhamnosus* GG, *L. casei* Shirota, *L. fermentum* (ACA-DC179, PCA142), *Lactobacillus pentosus* PCA227, *L. plantarum* (ACA-DC146, BFE5092, PCA236, PCS20, PCS22, PCS25 and PCS26), *Enterococcus faecium* (PCK38, BFE900, BFE2207 and PCD71), *Lactobacillus paracasei* subsp. *tolerans* ACA-DC4037 and *Lactobacillus gasseri* PCA185) against the rotavirus RF strain and transmissible gastroenteritis coronavirus using the model (which are derived from healthy tissues) such as intestinal epithelial cell lines such as H4 (Human origin), PSI (Pig origin), GIE (Goat origin) and monocyte/macrophages such as TLT (Human origin), PoM2 (Pig origin) and pig enterocytes (CLAB). The induction of the release of free radicals (reactive oxygen species; ROS), the percentage of surviving cell lines and the ability of LAB to attach to the cell lines were used as a measure to determine the antiviral activity of the LAB strains. The release of ROS (H_2O_2 and NO^-) from cell lines was increased up to 50% when co-cultured with LAB strains, but this induction was probiotic strain-specific and cell line-specific. The percentage of surviving virus infected-cell lines increased by up to 80%, which depended on the LAB strains and cell lines. The ability of LAB strains to attach to the cell lines was LAB-specific. *E. faecium* PCD71, *L. plantarum* ACA-DC146 and *L. paracasei* ACA-DC4037 exhibited a high adhesion capability with cell lines. *L. casei* Shirota showed the potent antiviral activity against transmissible gastroenteritis coronavirus and *L. plantarum* PCA236 showed the potent antiviral activity against both transmissible gastroenteritis coronavirus and rotavirus. The antiviral activity of the other tested strains was dependent on the type of cell lines, virus and LAB strains. The study demonstrated that the LAB strains have the antiviral potential in vitro, which warrants further studies [33].

3. In Vivo Evidence of the Antiviral Activities of Probiotics

The pre-exposure of probiotic strain *Lactobacillus rhamnosus* GG could improve the host's cell mediated-immune system against the H1N1 influenza virus. Specifically, the intranasal intervention of *L. rhamnosus* GG for three days induced pulmonary YAC-1 cell-killing activity and the transcriptional expression of pulmonary IL-1 β and TNF in BALB/c mice, which suggests that probiotic supplementation could protect the host system via a cell-mediated immune response [34].

The BALB/c mice were orally supplemented with *L. rhamnosus* GG and *Lactobacillus gasseri* TMC0356 for nineteen days, and the animals were exposed to influenza virus (5×10^6 PFU per mouse) on day 14. The mice administered with *L. rhamnosus* GG and *L. gasseri* TMC0356 showed a significant reduction in clinical symptoms and viral titer compared to the control group [35].

Park et al. [36] determined the antiviral effect of *Lactobacillus plantarum* (DK119) isolated from the fermented Korean vegetable food "Kimchi". The intranasal or oral administration of *L. plantarum* (DK119) provided greater protection against influenza virus infection in mice.

A few years later, another crew of researchers studied the protective anti-viral effect of heat-killed cells of *L. plantarum* (Lp) isolated from Kimchi. In this study, the crew found that the oral intake of heat-killed Lp (named nF1) could protect mice from the lethal challenges caused by different influenza strains, such as Influenza A and Influenza B, which was detected by determining the number of survival days of the infected mouse. Their observations are reliable that the heat-killed Lp (nF1) treatment significantly reduced viral

load and replication in infected mouse lungs [37]. Altogether, these results recommend the remedial potential of heat-killed *Lp* against influenza.

Thus far, influenza has been an acute fatal respiratory tract infection all over the world. Both younger and elderly individuals are equally prone to risk their lives, despite their feeble immune function. The vaccination for influenza does not provide much prevention because of the peculiar development of their resistive nature and concurrent mutagenesis, which could deliberately change the dominant viral strains. Hence, it is important to initiate convincing new natural alternative defensive procedures in the host system by triggering innate immunity in day-to-day life.

The yogurt fermented with *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 was found to reduce the risk of catching a cold [38]. The probiotic yogurt was orally administered in the quantity of 0.4 mL/day, and the Exopolysaccharides (EPS) isolated from 1073R-1 were also given (20 µg of EPS/day) to BALB/c mice for 21 days before intranasal infusion with influenza virus A/PR/8/34 (H1N1). The anti-influenza virus effects of both yogurt and EPS were exerted by the immunostimulatory effects and NK cell activity in the mice [39].

Some of the species of LAB, such as *L. plantarum* YU [40] and *Lactobacillus casei* Shirota [41,42], have been already testified to have potent anti-influenza virus properties in mice.

Lactobacillus brevis KB290 (KB290), isolated from a traditional Japanese pickle “Suguki”, has immunomodulatory effects. Prophylactically administered KB290 reduced the loss of body weight induced by influenza viral infection. The mice who received KB290 produced a significantly higher level of IFV-specific immunoglobulin IgA in bronchoalveolar lavage fluid and serum interferon α (IFN- α) compared with the controls. KB290 ingestion drastically induced and augmented IFN- α and IFV-specific IgA production [43]. *Lactobacillus gasseri* SBT2055 (LG2055) induced antiviral immunity by enhancing the expression of the antiviral gene, myxovirus (influenza virus) resistance 1 (Mx1), and 29–59 oligoadenylate synthetase 1A (Oas1a) mRNAs in the lungs of the treated mice. Thus, by upregulating the anti-viral genes, LG2055 inhibited the viral replication [44] (Table 2).

Next to the influenza virus, rotavirus is a predominant viral agent that causes severe, dehydrating gastroenteritis in infants and young children [45,46]. LG2055, when orally administered to mouse dams, prevented rotavirus infection in their pups [47]. Pant et al. [48] evaluated the productive results of a combination therapy of immunoglobulins and probiotics against rotavirus in a mouse model. Four-day-old pups of BALB/c mice were administered with *L. rhamnosus* GG (10^8 CFU/dose per day) for three days in combination with or without immunoglobulins (Hyperimmune Bovine Colostrum antibodies; 10 µg per day). The probiotic supplementation reduced the prevalence, severity and duration of diarrhea. The administration of probiotics and immunoglobulin effectively reduced the diarrheal outcome measures, histopathological changes and intestinal viral load. The results suggested that combining probiotics and immunoglobulins could be a potent treatment strategy for rotavirus-mediated diarrhea.

The rotavirus-specific B cell responses were found to be induced by the virulent Wa strain of human rotavirus with or without LAB (1:1 mixture of *L. reuteri* and *L. acidophilus*; Oral dose: 10^3 at 3 days of age; 10^4 at 5 days of age; 10^5 at 7 days of age; and 10^6 CFU at 9 and 11 days of age) colonization in gnotobiotic pigs infected with human rotavirus. The LAB colonization did not reduce human rotavirus shedding [49] (Table 2). Since LAB intervention alone is not as efficient in enhancing the induction of intestinal B cell responses against human rotavirus infection [49], the Yang group studied the adjuvant effect of LAB by assessing the B cell and T cell response induced by the attenuated Wa strain of the human rotavirus vaccine (oral dose) with *L. acidophilus* or without LAB in neonatal gnotobiotic pigs [50]. The LAB intervention effectively boosted the intestinal (IgA, IgG) antibody secreting cell responses and the serum Ig (IgA, IgG, IgM) titers in vaccinated gnotobiotic pigs. The LAB colonization delayed the onset of virus shedding in feces but did

not affect the virus fecal shedding. Thus, the study suggested that LAB supplementation possesses an essential role in enhancing host immunity [50].

Table 2. The antiviral potential of probiotics based on in vivo studies.

Model System	Probiotic(s)	Duration of Probiotic Exposure	Findings	Ref.
BALB/c mice	<i>Lactobacillus rhamnosus</i> GG	3 days (pre-exposure)	Activates the lung natural killer ↑ Cell-mediated immune responses	[34]
BALB/c mice	<i>L. rhamnosus</i> GG and <i>Lactobacillus gasseri</i> TMC0356	19 days (pre-exposure)	↓ Clinical symptom scores ↓ Pulmonary virus titers	[35]
BALB/c mice	<i>Lactobacillus plantarum</i> DK119	Oral administration for 10 days (pre-exposure) and 14 days (post exposure)	↓ lung virus loads ↑ Cytokines IFN-γ and IL-12	[36]
BALB/c mice	<i>L. plantarum</i> (Lp) heat-killed LP (nF1)	14 days (pre-exposure) and 14 days (post exposure)	↓ viral replication in the lungs of mice ↑ number of days of survival	[37]
BALB/c mice	<i>Lactobacillus delbrueckii</i> ssp. <i>bulgaricus</i> OLL1073R-1	21 days (pre-exposure)	↑ Anti-influenza virus IgA and IgG1 ↑ Natural killer (NK) cell activity	[39]
BALB/c mice	<i>Lactobacillus brevis</i> KB290 (KB290)	14 days (pre-exposure)	↑ Influenza specific IgA levels ↑ Serum interferon-α level	[43]
C57BL/6N mice	<i>Lactobacillus gasseri</i> SBT2055 (LG2055)	21 days (pr-exposure)	↓ Lung virus loads ↑ Expression of antiviral genes Mx1 and Oas1a	[44]
Gnotobiotic (Gn) pigs	<i>Lactobacillus acidophilus</i> NCFM™	exposure at 3, 5, 7, 9 and 11 days of age	↑ Intestinal IgA and IgG ↑ Serum IgA, IgM and IgG titers	[49]

↑: Increased; ↓: Reduced.

4. Clinical Studies on the Antiviral Potential of Probiotics

The intervention of probiotic *Lactobacillus casei* Shirota effectively cleared the HPV infection and increased the clearance of HPV-associated cervical lesions in patients with HPV and low-grade squamous intraepithelial lesions. A six-month intervention of *L. casei* Shirota showed a significant impact in controlling the HPV infections, which provides new treatment and management strategies to control cervical cancer [51].

The supplementation of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 (mixture of 1:1 of GR-1 and RC-14; 5.4×10^9 CFU of LAB per capsule per day) did not influence the high-risk-HPV clearance rate in women. Meanwhile, a probiotic intervention significantly reduced the mildly abnormal initial cervical smears and unsatisfactory smears in the study subjects [52] (Table 3).

The supplementation of fermented milk containing *L. casei* Shirota (4×10^{10} cells per 80 mL per day) for three months significantly reduced the duration of fever in older adults, who were suffering from norovirus gastroenteritis. There was no difference in the incidence of infection, but probiotic milk consumption improved the microbiota of the subjects. The concentration of fecal *Bifidobacterium* and *Lactobacillus* were increased, and the fecal *Enterobacteriaceae* load was reduced during the intervention. The concentration of fecal acetic acid was also significantly increased in the probiotic-supplemented group compared to the placebo. The results suggested that the continuous consumption of fermented milk containing *L. casei* Shirota could reduce the number of fever episodes but could not prevent the viral infection [53].

Table 3. The results of clinical studies on the antiviral potential of probiotics.

Subjects	Study Type	Probiotic(s)	Dose & Duration	Findings	Ref.
Women (Probiotic group, $n = 24$; Age = 31.4 ± 8.4 years old) (Control group, $n = 27$; Age = 32.1 ± 8.3 years old) (with HPV + low-grade squamous intraepithelial lesion)	Controlled pilot study	<i>Lactobacillus casei</i> Shirota	6 months	↑ Clearance of cytological abnormalities ↑ HPV clearance rate	[51]
Women with HPV infection (Probiotic group, $n = 62$; Control group, $n = 59$) (Age ~30 to 65 years old)	Randomized, double-blinded, placebo-controlled	<i>Lactobacillus rhamnosus</i> GR-1 and <i>Lactobacillus reuteri</i> RC-14	5.4×10^9 CFU per capsule per day; probiotic intake continued until negative HPV testing	No change in HPV clearance rate. ↓ Mildly abnormal initial cervical smear and unsatisfactory smear.	[52]
Elderly people (Probiotic group, $n = 39$; Control group, $n = 38$) (Average age = 84 years old)	An open case-control	Fermented milk containing <i>L. casei</i> Shirota	4×10^{10} cells per day; 3 months	↓ Fever duration ↑ Fecal <i>Bifidobacterium</i> and <i>Lactobacillus</i> load ↓ Fecal Enterobacteriaceae load ↑ Fecal acetic acid content	[53]
Children (Probiotic group, $n = 97$ (49 females, 48 males); Age = 3.7 ± 1.3 years old) (Control group, $n = 97$ (42 females, 55 males); Age = 3.8 ± 1.4 years old)	Randomized, double-blinded, placebo-controlled	Milk containing <i>L. rhamnosus</i> GG	10^8 CFU per day (400 mL per child); 28 weeks	↓ Respiratory symptoms	[54]
Healthy subjects (Probiotic group, $n = 137$ (90 females, 47 males); Age = 46.5 years old) (Control group, $n = 135$ (90 females, 45 males); Age = 43.7 years old)	Randomized, double-blind and placebo-controlled study	<i>Lactobacillus plantarum</i> HEAL 9 and <i>Lactobacillus paracasei</i> 8700:2	10^9 CFU per day; 12 weeks	↓ Common cold episodes and symptoms ↓ Pharyngeal symptoms ↑ B lymphocytes proliferation	[55]
Healthy adults (Probiotic group, $n = 25$ (10 females, 15 males); Control group, $n = 25$ (9 females, 16 males)) (Age = 33 ± 7.7 years old)	Randomized, double-blinded, placebo-controlled	<i>Lactobacillus fermentum</i> CECT5716	10^{10} CFU per day; 2 weeks before and after vaccination	↑ Natural killer cells count ↑ T-helper type 1 cytokine concentrations ↑ IgA & IgM ↓ Incidence of an influenza-like illness	[56]
Healthy adults (Probiotic group, $n = 548$ (308 females, 240 males); Age = 31.6 years old) (Control group, $n = 551$ (338 females, 213 males); Age = 31.3 years old)	Randomized, double-blinded, placebo-controlled	Milk containing <i>L. casei</i> 431	$\geq 10^9$ CFU per day; 42 days (vaccination after first 21 days)	↓ Duration of upper RTIs	[57]
Healthy adults ($n = 62$ (39 females, 23 males); Age = 26 ± 4 years old) and older ($n = 63$ (45 females, 18 males); Age = 69 ± 5 years old) subjects	Randomized, double-blinded, placebo-controlled	<i>Bifidobacterium longum</i> bv. <i>infantis</i> CCUG 52,486 and gluco-oligosaccharide	10^9 CFU per day, and 8 g of prebiotic per day; 8 weeks (vaccination after first 4 weeks)	↑ Influenza vaccine-specific antibodies	[58]
Patients infected with the H7N9 influenza virus	Retrospective study	<i>Clostridium butyricum</i> , <i>Bacillus subtilis</i> and <i>Enterococcus faecium</i>	10^7 CFU/tablet/thrice a day (<i>C. butyricum</i>); (or) 10^8 CFU/capsule/thrice a day (<i>B. subtilis</i> , and <i>E. faecium</i>)	↑ Diversity in the microbiota. <i>B. subtilis</i> and <i>E. faecium</i> supplementation ↓ the secondary infection.	[59]
Healthy men ($n = 5$) and women ($n = 5$); (Average age = 44 years old)	Single-arm, controlled study	<i>Bacillus coagulans</i> GBI-306086.	2×10^9 CFU per day; 30 days	↑ TNF- α production	[60]
Older adults (Probiotic group, $n = 100$ (74 females, 26 males); Age = 85.2 ± 7.1 years old) (Control group, $n = 96$ (58 females, 38 males); Age = 85.9 ± 7 years old)	Randomized, double-blinded, placebo-controlled pilot study	<i>L. rhamnosus</i> GG	10^9 CFU per capsule/2 capsules per day; 6 months	↓ Respiratory viral infections	[61]

Table 3. Cont.

Subjects	Study Type	Probiotic(s)	Dose & Duration	Findings	Ref.
Pediatric patients with viral gastroenteritis (Probiotic group, $n = 13$ (6 females, 7 males); Age range = 3 to 59 months old) (Control group, $n = 16$ (5 females, 11 males); Age range = 5 to 73 months old)	Randomized, double-blinded, placebo-controlled	<i>B. longum</i> , <i>Bifidobacterium lactis</i> , <i>L. rhamnosus</i> , <i>L. plantarum</i> , <i>Pediococcus pentosaceus</i> and <i>Lactobacillus acidophilus</i>	10^9 CFU (10^8 CFU/each strain) per sachet, twice a day; 1 week	↓ Duration of diarrhea	[62]
Children with acute rotaviral gastroenteritis (Low dose probiotic group, $n = 9$; High dose probiotic group, $n = 8$; Control group, $n = 6$) (Average age = 33.2 months old; 10 females, 13 males)	Open-label randomized trial	<i>L. rhamnosus</i> 35	2 or 6×10^8 CFU per day; 3 days	↓ Fecal rotavirus shedding	[63]
Children (Standard therapy + probiotic group, $n = 40$; Control (standard therapy + placebo) group, $n = 40$) (Age = 3 to 36 months old)	Randomized, double-blinded, placebo-controlled	Bifilac™	1 sachet, 3 times per day; 14 days	↓ Episodes and duration of diarrhea ↓ Degree of dehydration ↓ Duration of rotaviral shedding	[64]
Preterm infants (Probiotic group, $n = 21$ (7 females, 14 males); Prebiotic group, $n = 23$ (12 females, 11 males); Placebo group, $n = 24$ (5 females, 19 males))	Randomized, placebo-controlled trial	<i>L. rhamnosus</i> GG, galactooligosaccharide and polydextrose mixture	Probiotic dose = 1×10^9 CFU per day (for 30 days) and 2×10^9 CFU per day (for 31–60 days); Prebiotic dose = 1×600 mg/day (for 30 days) and 2×600 mg/day (for 31–60 days)	↓ Incidence of RTIs	[65]
Healthy subjects (Probiotic group, $n = 58$ (39 females, 19 males); Age = 22 ± 6 years old) (Control group, $n = 57$ (33 females, 24 males); Age = 23 ± 7 years old)	Randomized, double-blinded, placebo-controlled	<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BI-04	2×10^9 CFU; 28 days	↓ CXCL8 response to rhinovirus infection. ↓ Nasal lavage virus titer and shedding of virus in nasal secretions.	[66]
Endurance athletes (Probiotic group, $n = 126$ (53 females, 73 males); Age = 20.3 ± 0.2) (Control group, $n = 117$ (48 females, 69 males); Age = 20.6 ± 0.2)	Randomized, double-blinded, placebo-controlled	<i>L. casei</i> Shirota	6.5×10^9 CFU per day; 20 weeks	↓ Plasma CMV and EBV antibody titers	[67]
HIV patients (Probiotic group, $n = 22$ (2 females, 20 males); Age = 49.45 ± 7.75 years old) (Control group, $n = 22$ (5 females, 17 males); Age = 45.5 ± 7.75 years old)	Randomized, double-blinded, placebo-controlled	<i>Saccharomyces boulardii</i>	6×10^7 live cells per capsule/2 capsules 3 times per day; 12 weeks	↓ Plasma levels of Lipopolysaccharide-binding protein, and IL-6	[68]
HIV patients (Probiotic group, $n = 22$ (2 females, 20 males); Age = 49.45 ± 7.75 years old) (Control group, $n = 22$ (5 females, 17 males); Age = 45.5 ± 7.75 years old)	Randomized, double-blinded, placebo-controlled	<i>S. boulardii</i>	56.5 mg live cells per capsule/2 capsules 3 times per day; 12 weeks	↓ Load of Clostridiaceae family.	[69]
HSV-2 patients ($n = 53$)	Randomized, double-blinded, placebo-controlled	<i>Lactobacillus brevis</i> strains	2×10^9 CFU per capsule/2 capsules per day; 6 months	↓ Recurrence genital HSV-2 infection.	[70]

↑: Increased; ↓: Reduced; CFU: Colony-forming unit; TNF-α: Tumor necrosis factor-alpha; HPV: Human papillomavirus; RTIs: Respiratory tract infections; CMV: Cytomegalovirus; EBV: Epstein–Barr virus; CXCL8: Chemokine (C-X-C motif) ligand 8; HIV: Human immunodeficiency viruses; HSV-2: Herpes simplex virus type 2.

The children (2–6 years old) were supplemented with milk containing *L. rhamnosus* GG 10^8 CFU per day (400 mL) for 28 weeks. The respiratory viral diversity was assessed. The results indicated that probiotic supplementation did not affect the viral load and diversity

in children, whereas the days of respiratory symptoms were reduced compared to the control. The results suggested that *L. rhamnosus* GG was not effective in reducing the viral load in children [54].

The supplementation of *Lactobacillus plantarum* HEAL 9 and *Lactobacillus paracasei* 8700:2 (10^9 CFU per day for 12 weeks) reduced the incidence of the common cold and its symptoms significantly in healthy subjects compared to the placebo (control) group. The total cold symptoms score and pharyngeal symptoms were also reduced during the probiotic treatment. Moreover, the probiotic supplementation improved the B lymphocytes count in healthy subjects. The results suggested that the consumption of *L. plantarum* HEAL 9 and *L. paracasei* 8700:2 could prevent or nullify the severity of the common cold [55].

The co-adjuvant ability of *Lactobacillus fermentum* CECT5716 for an anti-influenza vaccine has been reported by Olivares et al. [59]. The healthy subjects ($n = 25$; 10 females, 15 males) were orally supplemented with *L. fermentum* (10^{10} CFU per day) for 28 days in addition to an anti-influenza vaccination (vaccination on day 14). Two weeks after vaccination, the concentrations of natural killer cells, T-helper type 1 cytokine concentrations, antigen specific IgA and total IgM were increased significantly compared to the placebo control ($n = 25$; 9 females, 16 males). The vaccination boosted immunity, whereas the probiotic supplementation further improved the immune system. The incidence of influenza-like illness was much lower in the probiotic-supplemented group during the five months after vaccination. The results suggested that the consumption of probiotics could enhance systemic immunity against viral infection [56].

The effect of the supplementation of fermented milk containing *L. casei* 431 on the immune response to influenza vaccination in healthy adults (18–60 years old) was investigated. The consumption of probiotic milk (10^9 CFU per day) for 42 days did not affect the immune response in healthy subjects, whereas the duration of upper RTIs was reduced. There were no notable changes in the incidence and severity of the infection. The results suggested that *L. casei* 431 could reduce the number of episodes of upper RTIs in healthy adults [57].

The supplementation of *Bifidobacterium longum* bv. *infantis* CCUG 52486 (10^9 CFU per day) and gluco-oligosaccharide (8 g per day) for eight weeks increased the total antibody titers, influenza-vaccine-specific IgA, IgM and IgG levels in both adult and older subjects. The antibody titer and vaccine-specific immunoglobulin levels were slightly lower in older subjects compared to adults. The senescent ($CD28^-CD57^+$) helper T cells and plasma anti-CMV IgG levels were higher at baseline in the intervention group, which biased the outcome of the study. The study suggested that aging is associated with antibody response to influenza vaccination and the symbiotic supplementation did not improve the situation. Moreover, the study evidenced that the randomization of study subjects is a critical step in randomized, double-blinded, placebo-controlled pre-clinical studies [58].

Hu et al. [59] studied the effect of *Clostridium butyricum*, or *Bacillus subtilis*, and *Enterococcus faecium* supplementation on microbial diversity and preventing the risk of secondary infection in patients who are suffering from an H7N9 influenza viral infection. The results showed that the probiotic intervention improved the diversity and evenness of microbiota. The supplementation of *C. butyricum* did not prevent the incidence of secondary infection, but the *B. subtilis* and *E. faecium* intervention reduced the secondary infection in H7N9-infected patients. The authors claimed that *B. subtilis* and *E. faecium* supplementation could ameliorate secondary infection in H7N9-infected patients.

The antiviral potential of GanedenBC³⁰ (*Bacillus coagulans* GBI-306086) has been evaluated in healthy subjects in terms of immune activation. The healthy subjects were supplemented with 2×10^9 CFU of probiotics for 30 days. The changes in the levels of TNF- α and IFN- γ have been determined at baseline and after 30 days of study. The results showed that the level of TNF- α was increased upon adenovirus and influenza A (H3N2 Texas strain) exposures, whereas there were no significant changes in the IFN- γ level. There were no adverse effects during the study. The results suggested that GanedenBC³⁰ may be a safe and potent probiotic for the treatment of respiratory viral infection [60].

The nursing home residents were supplemented with the probiotic strain *L. rhamnosus* GG (10^9 CFU per capsule/two capsules per day) for six months, and then its impact on influenza and other viral infections was analyzed. Probiotic intervention showed about 15% of viral infections among the study subjects of probiotic group, whereas the placebo group showed 22.9% of infection among the study subjects. Although the probiotic group showed some protective activity against viral infection, further studies are needed to confirm the findings with a larger group of people [61].

The probiotic strains with in vitro antiviral activity have been studied for the efficiency to reduce the symptoms of viral gastroenteritis in pediatric patients. A mixture of *B. longum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *L. rhamnosus*, *L. plantarum* and *Pediococcus pentosaceus* strains were supplemented to patients (10^9 CFU twice a day) for one week. These strains effectively reduced the duration of diarrhea compared to the placebo control without any adverse effects, which suggested that the use of potent probiotics could nullify the severity of viral gastroenteritis in children [62].

The effect of *L. rhamnosus* 35 supplementations on fecal rotavirus shedding was studied in children with acute rotaviral gastroenteritis. The children were administrated with 2 or 6×10^8 CFU of *L. rhamnosus* 35 or a placebo for three days. The fecal samples were analyzed for the changes in the viral particle count compared with the baseline. There was no change in the placebo and the 2×10^8 CFU treated group in terms of fecal viral shedding. However, the supplementation of 6×10^8 CFU *L. rhamnosus* 35 for three days reduced about 86% of the fecal viral shedding in children. The results indicated that the dose of probiotic supplements has a vital role in treatment efficiency [63].

The supplementation of BifilacTM for 14 days significantly reduced the number of episodes and the mean duration of diarrhea in children (3–36 months old). Additionally, the dehydration rate, the need for rehydration and intravenous fluid therapy reduced when compared to the placebo. Importantly, the BifilacTM supplementation reduced the rotaviral shedding significantly. The study claimed that the use of BifilacTM is safe and adjuvant for acute rotaviral treatments [64].

The influence of the supplementation of a probiotic (*L. rhamnosus* GG) and prebiotics (galactooligosaccharide and polydextrose mixture) on rhinovirus infection-associated respiratory tract infections (RTIs) in preterm infants has been studied. *L. rhamnosus* GG (1×10^9 CFU per day for 30 days, and 2×10^9 CFU per day for 31–60 days) and a mixture (1:1) of galactooligosaccharide and polydextrose (1×600 mg/day for 30 days, and 2×600 mg/day for 31–60 days) were supplemented to infants. During the 60 days of the intervention period, the incidence, duration and severity of the RTIs were measured. The probiotic and prebiotic supplemented group showed a significantly low frequency of RTIs compared to the placebo group. Similarly, the number of RTI episodes were reduced in the probiotic and prebiotic supplemented groups. There were no adverse effects and no change in rhinovirus RNA shedding, viral RNA load or the severity of rhinovirus infection among the study subjects. The results suggested that the use of prebiotics and probiotics could prevent rhinoviral infection by modulating the composition of gut microbiota [65].

The effect on the response of chemokine (C-X-C motif) ligand 8 (CXCL8) to rhinovirus infection in probiotic (*Bifidobacterium animalis* subspecies *lactis* B1-04)-supplemented healthy subjects have been studied. The supplementation of B1-04 at a concentration of 2×10^9 CFU per day for 28 days significantly reduced the CXCL8 response against the virus. Additionally, the nasal lavage virus titer and viral shedding in nasal secretions were reduced considerably in the probiotic-treated subjects compared to the control. The study also stated that lower respiratory inflammation was not influenced by the intervention of B1-04. The supplementation of B1-04 could have an effect on innate immunity and protects against rhinovirus infection [66].

Endurance athletes were supplemented with *L. casei* Shirota (6.5×10^9 CFU per day) for 20 weeks, and the changes in upper RTI symptoms and plasma Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) antibody titers were assessed. The results revealed that the supplementation of *L. casei* Shirota did not influence the incidence and number of episodes

of upper RTIs symptoms. The probiotic intervention significantly reduced the plasma level of CMV and EBV antibody titers, which shows that the probiotic supplementation could improve the immunity against respective viral infection [67].

Villar-García et al. [68] reported that *Saccharomyces boulardii* supplementation (6×10^7 CFU per day; 56.5 mg live cells per capsule; two capsules three times per day) for 12 weeks significantly reduced the plasma level of the Lipopolysaccharide-binding protein and IL-6, which indicates that yeast intervention reduces bacterial translocation and systemic inflammation in patients [68]. The effect of the supplementation of *S. boulardii* on gut microbial composition and systemic inflammatory status in HIV patients has been reported by the Villar-García group [69]. The study showed that the members of *Clostridiaceae* family species were lower in the feces of the probiotic-treated subjects, and *Lachnospiraceae* genus and Proteobacteria abundance were also changed with respect to probiotic intervention. These candidates were closely associated with the incidence of systemic inflammation. Thus, the study results revealed that the supplementation of *S. boulardii* could improve the inflammatory state of HIV patients via the positive regulation of gut microbial composition [69].

Mohseni et al. [70] compared the efficiency of use of multi-strain probiotics and acyclovir in genital herpes simplex virus type 2 (HSV-2)-infected female subjects. A six-month supplementation of probiotics (2×10^9 CFU per capsule/two capsules per day) or acyclovir (400 mg twice daily) showed the impact on the median time to the first and second recurrence of infection. Although acyclovir treatment prolongs the time taken for the reappearance HSV-2 infection compared to the probiotic group, some of the adverse effects were noticed in the acyclovir treated groups, whereas there were no clinically important effects in the probiotic-treated group. The study showed that use of multi-strain *Lactobacillus brevis* could be a safe and alternative therapeutic candidate to suppress the recurrence of genital HSV-2 infection in women [70].

5. Anti-Corona Viral Activity

The microorganisms inhabiting the digestive system gained increased attention due to their contribution toward the prophylactic or therapeutic benefits to the host [71]. Coronaviruses infect different animal species and predominantly result in respiratory and enteric infections. They are the positive-sense single-stranded RNA viruses from the *Coronaviridae* family and the *Coronavirinae* subfamily, which is a large group of microorganisms that infect vertebrates [72,73]. The interspecies transmission of these viruses between animals and humans may result in impulsive transmissible diseases. Emerging and re-emerging viral infections affect the health and wellbeing of people across the globe.

Along with other viral infections, the coronavirus gained much attention over the past year. To control the mass infection, studies for vaccine development, medications and treatments were initiated. However, the new antiviral drugs oblige the need for more time for designing, validation and clinical trials. Henceforth, the consumption of natural compounds can be considered as an alternative therapy for coronavirus infection [72]. It is a well-known fact that, currently, there exists no treatment specifically for the coronavirus [74]. Diet management with appropriate nutrients with anti-viral properties can improve immunity. Similar to other viruses' inherent property, coronaviruses also evolve themselves and frequently change their binding patterns in the lungs; hence, the target varies, but it remains constant in the small intestine [75].

After the COVID-19 outbreak, Chinese researchers have examined some changes in COVID-19 patients' microbiota. The complete analysis of microbiota from COVID-19 patients revealed a significant decrease in symbiotic bacterial families bifidobacteria and lactobacilli and an increase in the opportunistic bacteria *corneibacterium* and *Ruthenibacterium* [76]. This microbiota imbalance or dysbiosis in the intestine results in immune impact [77]. Yeoh et al. [78] investigated two-hospital cohort studies with COVID-19 patients ($n = 100$; 47 females and 53 males) using the obtained blood, stool samples and their records compared to the non-COVID-19 subjects ($n = 78$; 45 females

and 33 males). The study reported that gut microbiota composition is associated with the elevated plasma levels of inflammatory markers (cytokines, chemokines) and blood markers (aspartate aminotransferase, C reactive protein, gamma-glutamyl transferase and lactate dehydrogenase) in COVID-19 patients, indicating that the gut microbiome is linked to the magnitude of COVID-19 severity via the modulation of host immune responses. *Bifidobacteria*, *Eubacterium rectale* and *Faecalibacterium prausnitzii* were found to be low in the samples of the patients with COVID-19, even after disease resolution [78]. A recent systemic review reported by Yamamoto et al. [79] stated that COVID-19 patients with an abundance of opportunistic pathogens showed alterations in both the respiratory tract microbiome and faecal microbiome [79]. Wu et al. [80] studied the dynamics of the oral and gut microbiota before and after disease resolution in COVID-19 patients ($n = 53$) and also studied the alterations in oral and gut microbiota compared with the healthy individuals ($n = 76$), using their throat swab and faecal samples. Both the alpha and beta diversity indexes indicated that the oral and gut microbiome were altered, which is associated with the viral load in the COVID-19 patients. Several bacteria, such as *Granulicatella* and *Rothia mucilaginosa*, were found to be increased in the oral and gut microbiota of the COVID-19 patients. This study also stated that the oral and gut microbiome is associated with the magnitude of COVID-19 severity, suggesting that microbiome-based interventions could be more effective in preventing and treating COVID-19 infections [80]. The idea of using oral bacteriotherapy can help this situation. Some of the strains, such as *Lactobacilli* and *Bifidobacteria*, possess protective roles against the span of viruses, including influenza virus, rhinovirus, respiratory syncytial virus, adenovirus and pneumovirus [81,82].

Ettorre and his colleagues documented that the bacterial formulation with suitable biochemical and immunological profiles triggers protective functions. The bacterial product they used for their study enhances the synthesis of nuclear factor erythroid 2p45-related factor (Nrf2) and its target, Heme oxygenase-1 (HO-1), which shows the antiviral activity by reducing oxidative stress [83]. Another virus from the Coronaviridae family, the Enteropathogenic coronavirus transmissible gastroenteritis virus (TGEV), has also been studied in effect with *Enterococcus faecium* [84]. Chai et al. [84] also concluded that all the TGEV structural proteins were effectively reduced after *E. faecium* treatment [84]. In addition to these available studies, it is important to look forward to a prominent probiotic to suppress the viral growth, to interlude the attachment of virus particles to host cells, to inactivate the viral surface components, or to inhibit the active virulent proteins with minimal or without any damage to the host system.

6. Conclusions

Despite the efficacy of vaccines against viral infections, there has been a profound interest in alternative therapies with nominal cost and potential antiviral properties and with, indeed, no side effects to the host system. Probiotics initially act by colonizing persistently in the host and then modulating the commensal microbiota to restore the normal microbiota balance in the host system, exhibiting an immunomodulatory effect by enhancing the antiviral immune response and/or activating other protective mechanisms by upregulating the antiviral response of non-immunological host mechanisms, which are considered as the indirect mechanism exhibited by the probiotics to eradicate the viral infections. Producing metabolites that have the ability to restrict the viral multiplication or metabolites that are competing against the pathogens is the direct mechanism of probiotics to eradicate pathogens. In the present review, we cumulatively proposed the choice of using the varied number of probiotics to fight as anti-viral warriors and to enhance the host immune system to safeguard against various viral infections. We have listed the advantages of probiotics by including in vitro, in vivo and clinical studies about the antiviral properties of numerous probiotics. Additionally, we clearly stated the results of each study we have listed above. The use of probiotics in a therapeutic approach could reduce the use of antibiotics. In addition to these, more studies about probiotic's abilities are necessary to prove the unverified beneficial mechanisms of uplifting innate immunity; also, the

identification of virus-specific host immunoglobulins and cytokines would bolster the benefits of probiotics in viral infections. Therefore, more knowledge is required to define the role of probiotics as therapeutics in viral infections, as only a few research reports are available and yet more must be investigated, such as the direct mechanism of probiotics producing metabolites that have the ability to restrict viral multiplication to prevent or nullify the complicated viral infections with the use of probiotics as an adjuvant to the therapeutic approach.

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