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Review

Probiotics against Viral Infections: Current Clinical Trials and Future Perspectives

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Abstract: Viral infections represent a major health problem worldwide. Due to the wide variety of etiological agents and their increasing resistance to anti-virals and antibiotics treatments, new strategies for effective therapies need to be developed. Scientific evidence suggests that probiotics may have prophylactic and therapeutic effects in viral diseases. Indeed, these microorganisms interact harmoniously with the intestinal microbiota and protect the integrity of the intestinal barrier as well as modulate the host immune system. Currently, clinical trials with probiotics have been documented in respiratory tract infections, infections caused by human immunodeficiency viruses, herpes, human papillomavirus and hepatic encephalopathy. However, the benefits documented so far are difficult to extrapolate, due to the strain-dependent effect. In addition, the dose of the microorganism used as well as host characteristics are other parameters that should be consider when advocating the use of probiotics to treat viral infections. This review addresses the scientific evidence of the efficacy of probiotics in clinical strains perspective in viral infectious diseases in the last 10 years.

Keywords: probiotic; virus; clinical trials; infection; therapy

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1. Introduction

Recently, the risk of infections caused by viruses has increased dramatically worldwide [1]. This is mainly due to climate change, global warming and the geographical movement of people and goods [2]. On the other hand, the basis of current therapies to treat these infections are based on antiviral drugs and/or vaccines, which may contribute to the high mutation rates of viruses [3]. In this context, the use of non-pathogenic and beneficial bacteria (i.e., probiotics) represents an attractive alternative to explore new therapies against viral infections [4]. To evaluate the efficacy of probiotics in different diseases, it is necessary to conduct clinical trials, which comprise different stages, such as trial design and registration, enrollment of volunteers, completion of the study and, finally, dissemination of the results [5]. According to the ClinicalTrials.gov database, more than 1178 studies with probiotics were reported in 2020, of which, only few in use for viral infections [6]. Indeed, only about 3.9% of all these clinical trials proposed the use of probiotics as a therapeutic alternative in various viral diseases due to their ability to interact, protect the integrity of the intestinal barrier and modulate the host immune system [7–9]. Therefore, the objective

of this review is to discuss the scientific evidence on the effect of the use of probiotics in some diseases caused by different viruses in the last 10 years.

For this review, a literature search was conducted in PubMed and Google scholar databases and clinical trials (https://clinicaltrials.gov/ (accessed on 31 January 2021), during the period 2010 to 2020. The terms used were: probiotics, clinical trials, viruses and disease or causative agent: viral gastroenteritis, rhinovirus, enterovirus, adenovirus, influenza, coronavirus, bocavirus, human papillomavirus (HPV), human immunodeficiency virus (HIV), herpes, and liver disease. Reports on probiotics, mixtures of probiotics and synbiotics used in the treatment of diseases caused by viruses were included and reviews and meta-analyses were excluded.

2. Probiotics

The International Scientific Association for Probiotics and Prebiotics (ISAPP) has defined probiotics as: "*live microorganisms that, when administered in adequate amounts, confer health benefits*" [10]. To exert these benefits, probiotics must remain viable and available in appropriate amounts to survive the stress of the gastrointestinal tract and reach the small intestine and colon with a recommended number of viable cells above 1×10^6 CFU/g [11]. Typically, probiotics are used in the form of single strains; however, some studies suggest that administration of a mixture of probiotics of different strains, or even administering symbiotic, results in additive or even synergistic effects in terms of bioactivity [12,13]. The term synbiotic describe a "*mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host*" [14]. This combination improves the survival of probiotics strains in the gastrointestinal tract, ensuring a superior effect, compared to the activity of the probiotic or prebiotic alone [15]. In the case of a mixture of probiotic strains, this involves a combination of at least two different strains in equal or different proportions [12]. Probiotics include mainly strains of *Lactobacillus* and *Bifidobacterium*. *Lactobacillus* species include *L. acidophilus*, *L. amylovorus*, *L. brevis*, *L. bulgaricus*, *L. casei*, *L. cellobiosus*, *L. crispatus*, *L. curvatus*, *L. delbrueckii* spp. *bulgaricus*, *L. fermentum*, *L. gallinarum*, *L. helveticus*, *L. johnsonii*, *L. paracasei*, *L. plantarum*, *L. reuteri* and *L. rhamnosus*. *Bifidobacterium* species for instance include *B. adolescentis*, *B. animalis*, *B. bifidum*, *B. breve*, *B. infantis*, *B. thermophilum*, and *B. longum*. Other species of probiotics include *Streptococcus thermophilus*, *Streptococcus salivarius*, *Lactococcus lactis*, *Leuconostoc mesenteroides*, *Pediococcus pentosaceus*, *Pediococcus acidilactici*, *Propionibacterium acidipropionici*, *Propionibacterium freudenreichii*, *Propionibacterium jensenii*, *Propionibacterium thoenii*, *Enterococcus fecalis*, *Enterococcus faecium*, *Bacillus alcolophilus*, *Bacillus cereus*, *Bacillus clausii*, *Bacillus coagulans*, *Bacillus subtilis*, *Escherichia coli* Nissle 1917, and the yeasts *Saccharomyces boulardii* and *Saccharomyces cerevisiae* [16–20]. In addition, thanks to the highlights of studies on the gut microbiota together with the development of new sequencing techniques and bioinformatics tools, it has now been possible to find new "candidate strains" with applications in the food, agricultural, aquaculture and pharmaceutical industries, and which therefore represent a high probiotic potential [21–23]. These bacterial strains, less conventional than those mentioned above, are known as next generation probiotics (NGP), and some examples are: *Sporolactobacillus inulinus*, *Akkermansia muciniphila*, *Feacalibacterium prauznitzii*, *Roseburia hominis*, *Eubacterium* spp. and *Bacteroides* spp. [17]. The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) described guidelines for characterizing microorganisms as probiotics in 2001 [24]. These include: taxonomic identification, functional characterization, and potential health benefits. To determine the beneficial health effects of a probiotic candidate strain, characterization studies and/or assays (such as in vitro cellular models, animal models and human trials) are necessary to determine whether the candidate bacterium provides significant improvement in any of the conditions, symptoms, signs tested, well-being and/or quality of life [24,25]. Although preclinical research provides scientific evidence supporting the use of probiotics and safety, it is essential to establish a proper scientific protocol, such as target population, specific intervention under study, control groups, and safety and efficacy

results [23]. When preparing and developing such trials, some aspects have to be considered, such as the dose and strain of the probiotic as well as the type of population and the medical condition [26]. Currently, some clinical trials have successfully determined the use of probiotics as a therapeutic alternative for the management of some viral infections such as: viral gastroenteritis, respiratory tract infections and liver diseases, as well as herpes, HIV and HPV infections [7].

3. Probiotics and Antiviral Effects

Currently, viral diseases represent a serious threat to public health and affect the global economy [2,27]. In the world observer the emergence and reemergence of viral diseases we can cite that of HIV in 1981, the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002, H1N1 influenza virus in 2009, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012, Ebola virus in 2013 and the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) in 2019, among others [28]. Vaccines are: "*biological agents that elicit an immune response to specific antigen derived from an infectious disease-causing pathogen*" [29,30], being the main prophylactic strategy against viral infectious diseases [31]. However, vaccines efficacy is limited by recurring doses and high mutation rate of viruses [3]. According to scientific evidence, probiotics may be beneficial adjuvant agents in various diseases caused by viruses [32]. The antiviral effects of probiotics include host–microbiota interaction to maintain the integrity of the intestinal barrier by promoting mucin secretion and restoring tight junctions, inhibition of pathogens growth and colonization through competition for nutrients and binding sites on epithelial cells, production of antimicrobial compounds, such as lactic acid, hydrogen peroxide, bacteriocins, and modulation of the immune system (Figure 1) [8,9,32,33]. The most important effect of probiotics in viral diseases is their ability to modulate the immune system. In fact, probiotics can increase the amount of immunoglobulin A (IgA) in the lamina propria (LP), which contributes to the inhibition of bacterial adherence to epithelial cells and the neutralization of toxins [34]. In addition, probiotics exert immunomodulatory activities through interaction with Toll-like receptors (TLRs), responsible for recognizing pathogen-associated molecular patterns (PAMPs), resulting in the initiation of downstream signaling cascades such as nuclear factor-κB (NF-κβ) [35,36]. Upon recognition of PAMPs (also present in probiotics), second messenger signaling takes place, inducing the expression of the antiviral genes *Mx1* (myxovirus resistance gene) and *OAS1a* (2′-5′oligoadenylate synthetase 1A gene) (Figure 1), which are critical for antiviral responses by inducing type I and type III IFNs response in lung tissue and alveolar macrophages [37]. *Mx1* is broadly inhibitory and acts prior of genome replication at an early post-entry step, preventing viruses (e.g., Influenza A) from reaching their cellular destination [38], whereas OAS proteins are able to synthesize oligomers, which may mediate RNA degradation, contributing to viral RNA decay [38]. After interaction with probiotics, activated antigen-presenting cells induce T-helper type 1 (Th1) cells, which in turn, activate phagocytes and promote virus clearance [39,40]. Upon activation, CD8+ T lymphocytes differentiate into cytotoxic T-lymphocytes (CTLs), which killed virus-infected cells [39–41]. Activation of natural killer cells (NKs), result in interferon-gamma (IFN-γ) expression and activation of antiviral defense [36]. Based on in vitro and in vivo studies confirming the mechanisms of action, probiotics can be considered as a therapeutic alternative for viral infectious diseases [42,43].

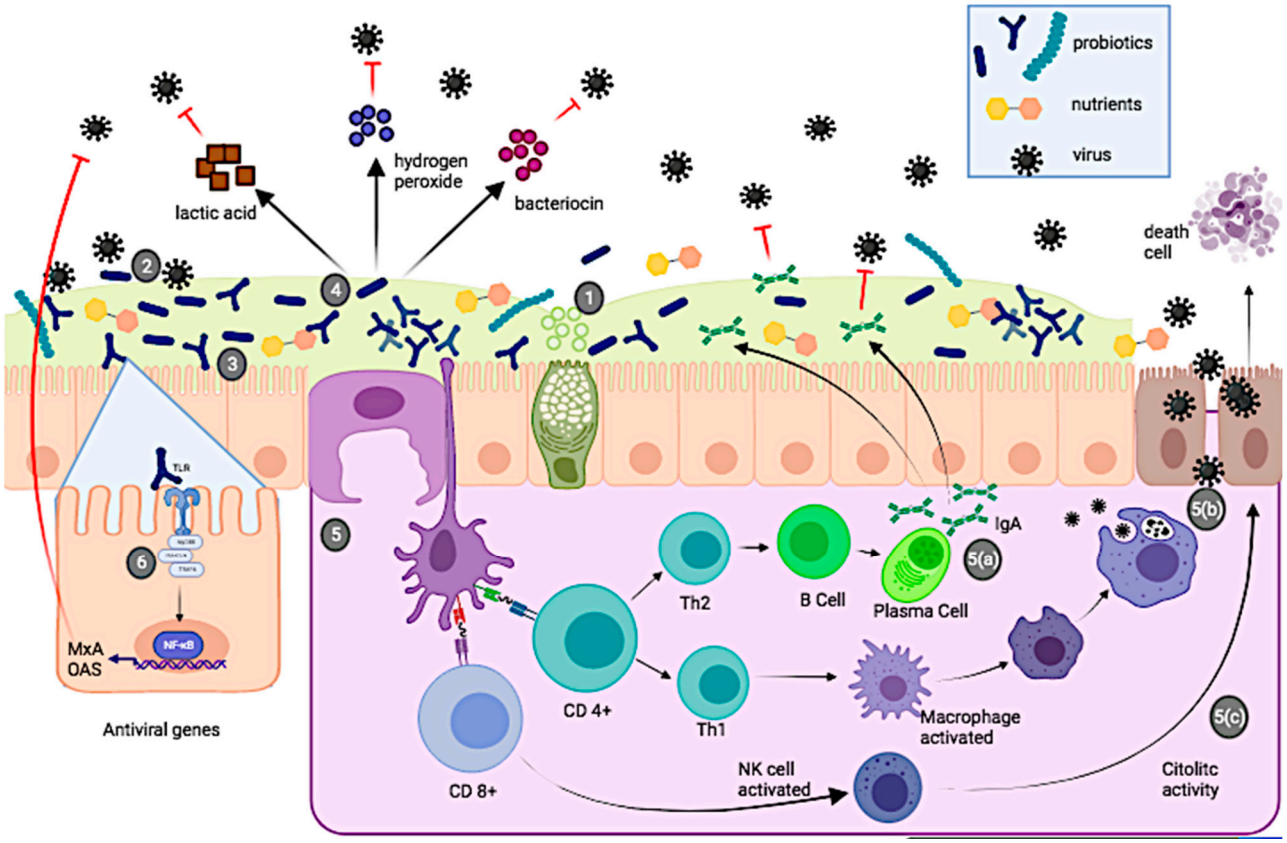

Figure 1. Antiviral effects of probiotics. The major impact of probiotics against viral infections is based on the probiotic-microbiota crosstalk with the aim of maintaining the integrity of the intestinal barrier by: (1) promotion of mucin secretion, (2) adhesion of probiotics to the epithelial surface with the aim of blocking viral attachment either by steric hindrance, covering receptor sites in a non-specific manner, or competing for specific carbohydrate receptors, (3) binding of probiotics directly to epithelial cells, (4) production of antimicrobial compounds such as lactic acid, hydrogen peroxide, bacteriocins and (5) modulation of the immune system [8,9,32,33]. In the case of the immune system these include: 5(a) type 2 T-helper cells (Th2) capable of producing high levels of IgA [34]; 5(b) type 1 T-helper cells (Th1) that will activate phagocytes and promotes virus clearance, and, 5(c) upon activation, CD8+ T lymphocytes differentiate into cytotoxic T lymphocytes (CTLs) which will kill virus-infected cells [39,40]. Probiotics likewise exert immunomodulatory activities through interaction with TLR receptors (6), resulting in the initiation of downstream signaling cascades, such as NF-κβ, which induce the expression of antiviral genes (MxA and OAS) [37]. (This figure was created with Biorender.com, access date: 29 July 2021).

4. Probiotics and Respiratory Tract Infections (RTIs)

Respiratory tract infections (RTIs) represent one of the leading causes of death, ranking third worldwide. The WHO reports that they rank first in the global burden of disease measured each year by the number of disabilities or deaths [44]. Tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, certain types of influenza, and the common cold represent some of the main RTIs [45]. The main causative agents of RTIs are of viral origin and include rhinoviruses, adenoviruses, influenza viruses, respiratory syncytial virus (RSV), and coronaviruses [46]. In terms of mortality, 20% of deaths occur in the post-neonatal stage, caused by lower respiratory tract infections, with RSV and influenza virus as etiologic agents. In adults, the same pattern exists in upper respiratory tract infections (e.g., viral origin), whereas a predominance of agents of bacterial origin has been described in lower respiratory tract infections [47]. In contrast, adenovirus and rhinovirus have a lower mortality [48]. Finally, the incidence of RTIs caused by coronaviruses has increased exponentially and spread fast. Thus, in December 2019, a case of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (the causative agent of COVID-19, [49]) was reported for the first time; and today this disease is considered by WHO as a pandemic.

New antiviral treatments are being developed worldwide to reduce RTIs, not only caused by influenza virus infections, but also by adenoviruses and, more recently, by SARS-CoV-2 [50]. In this context, probiotics have been proposed as an alternative for the management of viral RTIs, since these microorganisms increase phagocytic activity, increase the expression of CR1, CR3, FccRI, and FcaR receptors (which are associated with phagocytosis), and increase the microbicidal function of neutrophils [51]. In addition, probiotics increase the level of type I interferons, antigen-presenting cells, NKs, and T- and B-lymphocytes in the lung immune system [51]. In this review, we found in the literature that probiotics have a greater beneficial effect on diseases caused by influenza virus compared to rhinovirus, rotavirus and enterovirus [52], while no positive effects have been reported in otitis media infection (Table 1). It should be noted that different strains of probiotic and synbiotic were used, at different doses and duration of treatment in the different clinical trials reviewed (which have shown a promising therapeutic benefit) (Table 1). In particular, the use of probiotics in influenza virus infections, has been shown to result in a reduction of respiratory symptoms and viral load (Table 1). For instance, ingestion of a strain of *L. brevis* reduces the incidence of influenza, mainly in children not vaccinated against influenza virus (15.7 vs. 23.9 days, $p < 0.001$) [53]. Also, administration of *L. paracasei*, *L. casei*, *L. rhamnosus*, and *L. lactis* strains reduces respiratory symptoms ($p < 0.0059$) and, in particular, the strain of *L. lactis* induces a transcriptional upregulation of the IFN-α gene and the interferon-stimulated gene 15 (ISG15) ($p = 0.019$). In the case of LGG, this strain shows similar protection rates to vaccines against influenza H_1N_1 and B [54–56]. On the other hand, synbiotic administration of *B. longum infantis* and gluco-oligo saccharides (a type of prebiotic) results in an increase in the number of IgA ($p < 0.01$) and IgG memory B cells ($p < 0.001$) and total IgG B cells ($p < 0.001$), following influenza vaccination [52]. In susceptible populations (such as the elderly), *L. rhamnosus* decreases the risk of influenza and other viral respiratory infections (35%); however, no significant difference was reported [57].On the other hand, *L. coryniformis* improves vaccine efficacy ($p = 0.036$) and protects against respiratory infections ($p = 0.007$) [58], while *L. delbrueckii* prevents influenza infection caused by influenza A H_3N_2 virus and increases IgA ($p = 0.04$) and H_3N_2-bound IgA levels ($p = 0.001$) in saliva of early age subjects [59]. In rotavirus infections, administration of *B. animalis* spp. *lactis* decreased rhinovirus replication in nasal secretions, whereas a synbiotic based on LGG and galacto-oligosaccharides (GOS) and polydextrose (PDX) (1:1) reduced the incidence of RTIs in infants receiving prebiotics (rate ratio "RR", 0.24; 95% CI, 0.12–0.49, $p < 0.001$) or probiotics RR, 0.50; 95% CI, 0.28–0.90, $p = 0.022$) compared to placebo, but not rhinovirus viral load [60]. Nowadays, 11 clinical trials on RTIs caused by coronavirus have been reported on the ClinicalTrials.gov platform, but these studies are still in the recruitment phase [61].

Table 1. Probiotics used in clinical trials of respiratory tract infections caused by viruses.

Condition	Virus	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
Healthy adults	- Influenza virus H_1N_1 and B strains and H_3N_2	Adults (18–49 years)	- LGG (1×10^{10} CFU/twice daily)	Oral	28 days	Randomized double-blind placebo-controlled	- Similar protection rates against the vaccine H_1N_1 and B strains in subjects receiving LGG and placebo - For H_3N_2 strain, 84% receiving LGG vs. 55% receiving placebo had a protective titer after vaccination ($p = 0.048$)	[54]
Respiratory tract infection	- Rhinovirus - Syncytal virus - Parainfluenza virus - Enterovirus - Influenza A virus (H_1N_1) - Human bocavirus Adenovirus - Influenza A virus H_3N_2	Children (2–6 years)	- LGG (1×10^{8} CFU/twice daily)	Oral	196 days	Randomized, double-blinded and placebo-controlled parallel group	Reduces respiratory symptoms compared to the placebo (p values no reported) without reducing the number of respiratory viruses	[62]

Table 1. *Cont.*

Condition	Virus	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
Respiratory tract infection	Rhinovirus	Premature newborns (1–3 days)	- 30 days: LGG + ATCC 5310 (1×10^9 CFU) plus 1 × 600 mg of mix PDX (1:1) - 31–20 days: LGG+ ATCC 5310 (2×10^9 CFU) plus 2 × 600 mg of mix PDX (1:1)	Oral	60 days	Randomized, double-blind, placebo-controlled	- The incidence of respiratory tract infections was significantly lower in infants receiving prebiotics (rate ratio "RR", 0.24; 95% CI, 0.12–0.49, $p < 0.001$) or probiotics RR, 0.50; 95% CI, 0.28–0.90, $p = 0.022$) compared to placebo - No significant differences were found in terms of viral RNA load during infection, duration of excretion and severity of rhinovirus infections.	[60]
Respiratory tract infection.	Rhinovirus Enterovirus	Adults (18–28 years)	- LGG (1×10^9 CFU) - *B. animalis* spp. *lactis* BB-12 (2×10^9 CFU)	Oral	150 days	Randomized, double-blind, placebo-controlled	Decrease in the presence of picornavirus after 3 months ($p = 0.0069$) in the probiotic group than placebo; however, the appearance of virus in the asymptomatic population was not reduced	[63]
Otitis media	Rhinovirus Enterovirus	Children (1–5 years)	- LGG ($8–9 \times 10^9$ CFU)	Oral	21 days	Randomized, double-blind, placebo-controlled	No reduction in the presence of rhinoviruses and enteroviruses in children with otitis media	[64]

Table 1. *Cont.*

Condition	Virus	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
Influenza infection	Influenza A virus	Children (6–12 years)	*L. brevis* KB290 (1×10^9 CFU)	Oral	40 days	Open-label and parallel-group	Reduces the incidence of influenza in schoolchildren treatment probiotic than no treatment (15·7 vs. 23.9, $p < 0{\cdot}001$); the effect was especially evident in subjects not vaccinated against influenza.	[53]
Influenza Symptoms	Influenza	Adults (30–59 years)	*L. lactis* spp. *lactis* JCM5805 (1×11^{11} CFU)	Oral	70 days	Randomized double-blind, placebo-controlled	Inhibits symptom incidence days of cough ($p = 0.015$) and feverishness ($p < 0.009$), development by transcriptional upregulation of the IFN-α gene and IFN-stimulated antiviral factor ISG15 (interferon-stimulated gene 15) ($p = 0{\cdot}019$), compared to placebo. No final decrease in viral RNA was observed.	[55]
Respiratory infections	Influenza	Adults (18–60 years)	- *L. paracasei* spp. *paracasei* (1×10^9 CFU) - *L. casei 431* (1×10^9 CFU)	Oral	42 days	Randomized, double-blinded and placebo-controlled parallel group	No effect on the components of the immune response to influenza vaccination was observed, but the duration of upper respiratory symptoms was reduced ($p < 0.0059$).	[56]

Table 1. *Cont.*

Condition	Virus	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
Rotavirus Infection	Rotavirus	Adults (18–65 years)	- LGG (1×10^9 CFU)	Oral	42 days	Randomized, controlled, pilot trial	No significant differences in viral load were shown	[65]
Rotavirus Infection	Rotavirus	Adults (18–60 years)	- *B. animalis* spp. Bl-04 (2×10^9 CFU)	Oral	5 days	Randomized controlled trial	Decreases rhinovirus replication in nasal secretions ($p = 0.03$) and reduce virus titer in nasal lavage ($p = 0.04$). However, not influence on the inflammatory response to rhinovirus infection	[66]
Elderly in nursing homes	Influenza	Elderly (≥65 years)	- LGG (1×10^{12} CFU)	Oral	182 days	Randomized, double-blind, placebo-controlled	Reduces the risk of influenza and other viral respiratory infections by up to 35%, but no significant difference was reported	[57]
Aging	Influenza	Adults (60–85 years)	*B. longum infantis* CCUG 52,486 (1×10^9 CFU) plus gluco-oligosaccharides 8 g/day	Oral	42 days	Randomized, double-blind, placebo-controlled	Vaccination increased numbers of IgA memory ($p < 0.01$), IgG memory ($p < 0.001$) and total IgG B cells ($p < 0.001$) in young subjects, but not shows same effects in older subjects	[52]
Elderly in nursing homes	Influenza	Elderly (≥65 years)	*L. coryniformis K8* CECT5711 (3×10^9 CFU)	Oral	14 days	Randomized, double-blind, placebo-controlled	Increases immune response to flu vaccine ($p = 0.036$) and decreases symptoms associated with respiratory infections ($p = 0.007$) compared to placebo	[58]

Table 1. *Cont.*

Condition	Virus	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
Health workers	Influenza	Adults (20–71 years)	- *L. delbrueckii* spp. *bulgaricus* OLL1073R-1, *S. thermophilus* (1.1×10^9 CFU)	Oral	112 days	Randomized controlled	Probiotic intake shows a significant preventive effect against influenza or NK cell activity. However, increase in the production of IFN-γ (2.69 to 6.21 pg/mL, $p = 0.03$)	[67]
Elderly in nursing homes	Influenza	Elderly (mean 87.35 years)	- *L. delbrueckii* spp. *bulgaricus* OLL1073R-1 (1.1×10^8 CFU)	Oral	84 days	Randomized, double-blind, parallel-group	Prevents infection caused by influenza A virus subtype H3N2 and increasing IgA ($p = 0.04$) and H3N2-bound IgA ($p = 0.001$) levels in saliva	[59]

5. Probiotics and Human Immunodeficiency Virus (HIV)

HIV infects the cells of the immune system, altering or disabling their function [68]. In addition, this virus produces a gradual deterioration of the immune system, which progressively loses CD4+ T lymphocytes, affecting the lymphoid tissue of the intestine, which has a high lymphocyte content, leading to high virus replication [69,70]. HIV infection is also characterized by generating a state of dysbiosis of the gut microbiota, with increased levels of *Erysipelotrichaceae*, *Enterobacteriaceae*, *Desulfovibrionaceae*, *Fusobacteria*, *Pseudomonas aeruginosa* and *Candida albicans* and decreased levels of *Bifidobacterium*, *Lactobacillus*, *Lachnospiraceae*, *Ruminococceae*, *Bacteroides* and *Rikenellaceae* [71–75]. This intestinal dysbiosis severely compromises basic gut functions, such as efficient nutrient absorption and maintenance of intestinal barrier function, and may contribute equally to pathology and disease progression [71]. Antiretroviral therapies (ART) are used to control HIV infection. ART reduces the viral load at the systemic level; however, they may also have side effects, such as diarrhea and other gastrointestinal symptoms leading to treatment interruption [76,77]. The use of probiotics has been proposed as a therapeutic alternative in HIV-infected individuals, as these microorganisms can help restore the host gut microbiota, improving mucosal barrier functions and modulating the immune system [73]. Therefore, it is believed that probiotics could be a cost-effective and clinically efficient strategy to reduce HIV-related morbidity and mortality [76]. In the clinical trials reviewed, probiotics were administered either as a single strain, a mixture of probiotics, or as probiotics supplemented with micronutrients (Table 2). Administration of single strains, such as *B. coagulans*, increased the percentage of CD4+ T cells ($p = 0.018$), and showed a decrease in inflammation by correlating D-dimer with CRP and sCD14 with tumor necrosis factor (TNF)-α [70,78]. In addition, Villar-Garcia et al. [79] observed in a study in 2015, that administration of *S. boulardii* decreased microbial translocation and expression of the inflammation marker IL-6. For their part, Serrano-Villar et al. [80] conducted a similar study in 2019 administering *S. boulardii*; however, the authors did not find any improvement in the number of circulating T cells neither at the level of inflammation nor immune activation. In the case of probiotic mixture, we found five clinical trials using different probiotics and all studies have beneficial effects on HIV infection (Table 2). Schuther et al. [75] evaluated strains of *P. pentosaceus*, *L. mesenteroides*, *L. paracasei* and *L. plantarum* strains and observed that supplementation with these bacteria effectively increases the levels of probiotic species (*L. plantarum* $p = 0.001$ and *P. pentosaceus* $p = 0.036$) in the gut during chronic HIV-1 infection. However, plasma CD14 and C-reactive protein levels were not affected during treatment. In another study, d'Ettorre et al. [81], *L. plantarum*, *S. thermophilus*, *B. breve*, *L. paracasei*, *L. delbrueckii* spp. *bulgaricus*, *L. acidophilus*, *B. longum* and *B. infantis*, can improve immune function by increasing the percentage of Th17 cell subsets ($p = 0.059$) and reducing the frequency of CD8+ lymphocytes (without reaching significance). Similar results were obtained by Ishizaki et al. [78], indeed, they observed that *L. casei* Shirota strain increased CD4+ cell count ($p < 0.01$), especially Th17 ($p < 0.05$) and decreased CD8+ cells (27.5% to 13.2%, $p < 0.001$). Other authors evaluated the effect of the administration of *L. plantarum*, *S. thermophilus*, *B. breve*, *L. paracasei*, *L. delbrueckii* spp. *bulgaricus*, *L. acidophilus*, *B. longum*, and *B. infantis* on neuropsychological performance: this clinical trial indicated that patients receiving probiotics showed an improvement in neurological cognitive functions, such as abstract reasoning, as well as short-term ($p = 0.0058$) and long-term memory ($p = 0.0019$) [82]. Furthermore, d'Ettorre et al. [83] observed that the administration of *S. salivarius*, *B. breve*, *B. infantis*, *B. longum*, *L. acidophilus*, *L. plantarum*, *L. casei*, *L. delbrueckii*, and *Streptococcus. faecium* provides a specific benefit in HIV-infected patients during antiretroviral treatment by reducing immune activation on CD4 T-lymphocytes. Probiotic intake also reduces systemic inflammation (CRP plasma levels, $p = 0.006$) (Table 2). Finally, the administration of probiotics and micronutrients (i.e., vitamin A-1500 IU, vitamin E-5.7 IU, niacinamide-3.8 mg, vitamin B1-0.3 mg, vitamin-B12 0.6 µg, vitamin B6-0.3 mg, vitamin C-21 mg, Fe-3.3 mg, Se-13.8 µg, Zc-2.4 mg DHA (omega-3 fatty acid from fish oil) 13 mg and EPA (omega-3 fatty acid from fish oil) 19 mg), showed an increase in CD 4+ lymphocyte

population, while micronutrients (Cu-25 µg, Zn-5 mg, Se-10 µg, I-38µg, vitamin A-1250 IU, vitamin B1 and B2- 0.75 mg, vitamin B6-0.5 mg, vitamin B5-1.25 mg, vitamin B12-0.5 µg, vitamin D-100 IU and vitamin E-2.5 IU), help to significantly delay the progression of advanced stage of the disease, according to WHO clinical staging [84,85]. Further research on the benefits of probiotics is ongoing, but we can conclude that evidence from current clinical trials may have a beneficial effect when administered with ART therapies.

Table 2. Probiotics used in clinical trials to treat human immunodeficiency virus (HIV) infections.

Condition	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
HIV Infection	Adults (mean 48 years)	- *L. rhamnosus* CAN-1 (1×10^9 CFU) plus micronutrients (vitamin A- 1500 IU, vitamin E- 5.7 IU, niacinamide-3.8 mg, vitamin B1- 0.3 mg, vitamin- B12 0.6 µg, vitamin B6-0.3 mg, vitamin C- 21 mg, Fe- 3.3 mg, Se-13.8 µg, Zc-2.4 mg DHA (omega-3 fatty acid from fish oil) 13 mg, and EPA (omega-3 fatty acid from fish oil) 19 mg).	Oral	30 days	Randomized, double-blind, three-period cross-over controlled	Increases immune function and CD 4+ lymphocyte count, with micronutrient alone 41 cells/µL, probiotic + micronutrient +19 cells/µL and probiotic alone—7 cells/µL, in HIV-positive individuals. However not shows significant difference.	[84]
Chronic HIV infection	Women (mean 47.5 years)	- *P. pentosaceus* (1×10^{10} CFU) - *L. mesenteroides* (1×10^{10} CFU) - *L. paracasei* spp. *paracasei* (1×10^{10} CFU) - *L. plantarum* (1×10^{10} CFU)	Oral	28 days	Randomized, placebo-controlled	Increases the levels of probiotic species (*L. plantarum* $p = 0.001$ and *P. pentosaceus* $p = 0.036$) in the gut during chronic HIV-1 infection. However, plasma CD14 and C-reactive protein levels were not affected during treatment	[75]

Table 2. *Cont.*

Condition	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
Chronic HIV infection	Adults (37–72 years)	- *B. coagulans* GBI-30, 6086 (2×10^{12} CFU)	Oral	90 days	Double-blind placebo-controlled	Increases the percentage of CD4+ T cells (p = 0.018), and shown inflammation decrease by correlation between D-dimer with CRP and sCD14 with tumor necrosis factor (TNF)-α.	[70]
HIV infection	Children (≤15 years)	- *L. sporogens* (2.5×10^{10} CFU) plus micronutrients (Cu- 25 µg, Zn- 5 mg, Se- 10 µg, I- 38µg, vitamin A-1250 IU, vitamin B1 and B2- 0.75 mg, vitamin B6- 0.5 mg, vitamin B5- 1.25 mg, vitamin B12- 0.5 µg, vitamin D- 100 IU, and vitamin E- 2.5 IU)	Oral	90 days	Randomized control study	Increases CD4+ T cells compared to control group (p = 0.0022). In addition, micronutrient supplementation shows a significant delay (p = 0.049), in the progression of the advanced stage of the disease, according to WHO clinical staging	[85]
HIV infection	Adults (18–80 years)	- *S. salivarius* (2.0×10^{11} CFU) - *B. breve* (9.3×10^{10} CFU) - *B. infantis* (9.3×10^{10} CFU) - *B. longum* (9.3×10^{10} CFU) - *L. acidophilus* (2.0×10^{9} CFU) - *L. plantarum* (2.2×10^{11} CFU) - *L. casei* (2.2×10^{11} CFU) - *L. delbrueckii* (3.0×10^{11} CFU) - *S. faecium* (3.0×10^{7} CFU)	Oral	336 days	Unspecified	Provides a specific benefit in HIV-infected patients during antiretroviral treatment, reduced immune activation on CD4 T-lymphocytes. Probiotics intake reducing systemic inflammation (CRP plasma levels, p = 0.006)	[83]

Table 2. *Cont.*

Condition	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
HIV infection	Adults (≥18 years)	Visbiome®: *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii*, *B. breve*, *B. infantis*, *B. longum*, and *S. thermophilus* (4.5×10^{11} CFU/packet)	Oral	168 days	Prospective, double-blinded, randomized, placebo-controlled, multicenter pilot studies	Reduces inflammation and improves gut immune health; moreover, it was safe and tolerated by HIV patients.	[86]
Neuropsychological performance in HIV-infected patients	Adults (≥18 years)	Vivomixx®; Visbiome®: *L. plantarum*, *S. thermophilus*, *B. breve*, *L. paracasei*, *L. delbrueckii* spp. *bulgaricus*, *L. acidophilus*, *B. longum*, and *B. infantis* (4.5×10^{11} CFU)	Oral	180 days	Longitudinal, nonrandom-ized designed, single-arm, pilot study	Improvement of neurological cognitive functions, such as abstract reasoning and short-term (p = 0.0058) and long-term memory (p = 0.0019). However, no direct effect on viral load was observed	[82]
HIV infection	Adults (≥18 years)	- *L. plantarum*, *S. thermophilus*, *B. breve*, *L. paracasei*, *L. delbrueckii* spp. *bulgaricus*, *L. acidophilus*, *B. longum*, and *B. infantis* (1.8×10^{12} CFU)	Oral	180 days	Longitudinal pilot study	- Increase significantly *Bifidobacteria* spp. Compared to their basal level (p = 0.019). - Reduces the frequency of CD8+ lymphocytes (not shows significant difference) and increases the percentage of Th17 cell subsets (p = 0.059). - Restore the physical and immunological integrity of the intestinal mucosal barrier in HIV patients	[81]

Table 2. *Cont.*

Condition	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
HIV infection	Children (9 months–5.8 years)	- *L. casei* Shirota (6.5×10^9 CFU)	Oral	56 days	Nonrandomized, open-labeled, prospective study	Significantly increase in CD4+ cells count ($p < 0.01$), especially Th17 ($p < 0.05$), and decrease in CD8+ cells (27.5% to 13.2%, $p < 0.001$). However, it was not associated with an increase in plasma HIV load or serious adverse events	[78]
HIV infection	Adults (≥18 years)	- *S. boulardii* (250 g)	Oral	336 days	Pilot Multicenter randomized, placebo-controlled, double-blind	Did not improve the number of circulating T cells, inflammation or immune activation	[80]

6. Probiotics and Gastrointestinal Infections

Gastroenteritis is a common infectious syndrome which represents the leading cause of hospitalization in children, causing more than 200,000 deaths per year worldwide. Gastrointestinal infection is characterized by nausea, vomiting, diarrhea, anorexia, weight loss, and dehydration [87,88]. The main causative agent of gastroenteritis is rotavirus, followed by norovirus and adenovirus [89,90]. Rotavirus is an RNA virus belonging to the Reoviridae family, which causes more than half a million deaths annually and more than 2 million hospitalizations worldwide [90]. Novovirus belongs to the family Caliciviridae and is a highly infectious RNA virus [91], since only 100 virons are needed to cause an infection, and because of its resistance to various antiseptic agents [92]. Treatment for gastrointestinal diseases consists of controlling hydration and preventing complications. Dehydration is controlled with a course of oral solutions and a return to normal feeding. However, they are not fully effective in shortening the duration of diarrhea or eliminating the causative agent [90]. According to the guidelines of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Pediatric Infectious Diseases (ESPID), the use of probiotic strains of LGG and *S. boulardii* is recommended for the treatment of diarrheal diseases in children [93]. Indeed, oral administration of LGG in infancy reduces the secretion of anti-inflammatory substances, induces the production of oxygen free radicals and the production of bactericidal substances [94]. While administration of *S. boulardii* results in increased levels of IgA and IL-10, directly participating in the immunomodulatory response to intestinal infections. In addition, beneficial effects have been attributed in the prevention of *Clostridium difficile* infections and antibiotic-associated diarrhea [94]. Taken together, these activities could be responsible for their effects in preventing diarrhea caused by rotavirus, so the administration of these probiotics is often recommended [87,95]. The probiotics shown in Table 3 were administered orally, mainly targeting children, and only one study was conducted in older adults. Regarding the beneficial effects of probiotics on viral gastroenteritis, *L. plantarum*, *S. boulardii*, *B. longum*, and *L. acidophilus* were observed to have effects on rotavirus. Administration of *L. plantarum* inhibits rotavirus growth, in addition to reducing virus titer ($p < 0.001$), diarrhea episodes and Vesikari score [87], while administration of *S. boulardii* produced a decrease in

rotavirus viral load [96]. Also, the administration of these microorganisms helps to reduce fever ($p < 0.05$) and in terms of restoration of gut microbiota, a significant increase in the levels of *Bifidobacterium* ($p < 0.01$) and *L. casei* subgroup ($p < 0.01$), was obtained when *L. casei* Shirota strain was administered in older adults [91] (Table 3). Other studies showed that LGG increased IgG serum levels in children with rotavirus diarrhea (456 vs. 2215 EU, $p = 0.003$) and improved intestinal permeability ($p = 0.027$) [97], while *B. longum* and *L. acidophilus* decreased rotavirus infection in vitro ($p < 0.0001$) [98] (Table 3). Probiotics were also found to have direct effects on diarrhea symptoms and fever. Thus, administration of *L. rhamnosus* or probiotic mixtures of *C. butyricum*, *E. faecalis* and *B. mesentericus* [99] or *B. longum*, *B. lactis*, *L. acidophilus*, *L. rhamnosus*, *L. plantarum* and *P. pentosaceus*, leads to a reduction of diarrhea episodes [98] (Table 3). Finally, only one clinical trial was found in which no beneficial effects on rhinovirus clearance were observed when *L. rhamnosus* and *L. helveticus* were administered [100]. Therefore, the current evidence suggests that supplementation with probiotics or a probiotic mixture may have a significant effect on reducing symptoms of rotavirus gastroenteritis (Table 3).

Table 3. Probiotics used in clinical trials in gastroenteritis viral.

Condition	Agent	Population (Age Range)	Probiotics & Dose	Route	Duration	Type of Study	Results	Ref.
Acut ediarrhea	Rotavirus	Children (1–23 months)	- One probiotic: *S. boulardii* (4×10^{10} CFU) - Mix of probiotics: *L. acidophilus* (6.6×10^{7} CFU), *L. rhamnosus* (3.6×10^{7} CFU), *B. longum* (8.7×10^{6} CFU) and *S. boulardii* (1.3×10^{7} CFU)	Oral	5 days	Randomized double-blind controlled	- *S boulardii* diminished diarrhea in (58 vs. 84.5 h, $p = 0.04$) and fever (18 vs. 67 h, $p = 0.0042$) compared with the control. No decrease in rotavirus load when *S. boluardii* was used. - Mixed probiotic administrations decrease the duration of vomiting (0 vs. 42.5 h, $p = 0.041$) compared to oral rehydration solution	[96]

Table 3. *Cont.*

Condition	Agent	Population (Age Range)	Probiotics & Dose	Route	Duration	Type of Study	Results	Ref.
Gastroenteritis	Norovirus	Elderly (mean 84 years)	- *L. casei* Shirota (4×10^{10} CFU)	Oral	90 days	Open study	- Contributes positively to the relief of fever ($p < 0.05$), caused by norovirus. - Restored the intestinal microbiota, significantly increased levels of *Bifidobacterium* ($p < 0.01$) and *L. casei* subgroup ($p < 0.01$). However, it does not provide protection against viral gastroenteritis	[91]
Acute Gastroenteritis	Rotavirus	Children (6 months–5 years)	- LGG (1×10^{10} CFU)	Oral	28 days	Randomized, double-blind, placebo-controlled	- Improved intestinal permeability in children with rotavirus ($p = 0.027$) - Increased IgG levels response in children with rotavirus diarrhea (456 vs. 2215 EU, $p = 0.003$) - Reduce episodes of diarrhea in children with rotavirus gastroenteritis (25% vs. 46%, $p = 0.048$), but not showed in *Cryptosporidium* gastroenteritis.	[97]

Table 3. *Cont.*

Condition	Agent	Population (Age Range)	Probiotics & Dose	Route	Duration	Type of Study	Results	Ref.
Gastroenteritis	Rotavirus	Children (3 months–14 years)	- *C. butyricum* (2.0×10^7 CFU) - *E. faecalis* (3.17×10^8 CFU) - *B. mesentericus* (1.1×10^7 CFU)	Oral	7 days	Single-center, open-label, randomized, controlled trial	Reduction in the duration of diarrhea in children ($p < 0.0001$). In pregnancy, no decrease in viral load after probiotic treatment was observed	[99]
Gastroenteritis	Rotavirus	Children (3 months–7 years)	- *B. longum*, *B. lactis*, *L. acidophilus*, *L. rhamnosus*, *L. plantarum*, *P. pentosaceus* (1.1×10^9 CFU/g; 1×10^8 CFU/strain)	Oral	7 days	Randomized, double-blind	Decreases the duration of diarrhea, compared with a placebo (6.1 vs. 7.2, $p = 0.030$), without any adverse effect. *B. longum* and *L. acidophilus* inhibited rotavirus infection in vitro	[98]
Acute diarrhea	Rotavirus	Children (3 months–5 years)	*S. boulardii* (500 mg/day)	Oral	5 days	Randomized and controlled	Probiotics intake significantly decrease to diarrhea (60 vs. 89 h; 95% CI: −41.2 to −16.8) and the duration of hospitalization (74 vs. 91 h; 95% CI: −33.46 to −0.54), compared with a control group. However, fever, vomiting and viral load were not reduced	[101]

Table 3. *Cont.*

Condition	Agent	Population (Age Range)	Probiotics & Dose	Route	Duration	Type of Study	Results	Ref.
Gastroenteritis acute	Rotavirus	Children (3–48 months)	- *L. rhamnosus* R0011 and *L. helveticus* R0052 (4.0×10^9 CFU) (95:5)	Not specified	5 days	Multi-center, double-blind trial, randomized	No beneficial effects were shown. Administration did accelerate clearance of rhinovirus associated with viral gastroenteritis	[100]
Gastroenteritis	Rotavirus	Children (14–40 months)	*L. plantarum* LRCC5310 (dose: not specified)	Not specified	Not specified		Inhibits rotavirus growth, reduces virus titer ($p < 0.001$), and improves gastroenteritis symptoms such as diarrhea and Vesikari score	[87]

7. Probiotics and Human Papillomavirus (HPV)

HPV is the main etiological agent of cervical lesions and is closely associated with the development of benign lesions, intraepithelial neoplasms and cervical cancer (CxCa) [102]. HPV infections usually clear without any intervention within a few months after contact, and approximately 90% clear within two years. However, some HPV infections can persist and progress to CxCa. Worldwide, this type of cancer is the fourth most common cancer in women, with an estimated 570,000 new cases in 2018 and more than 311,000 deaths per year [103]. To date, the main therapies used for precancerous HPV lesions are cryotherapy, ablation, and the electrosurgical excision procedure, which involves the removal of abnormal cells or lesions [104]. Despite the use of these treatments, high rates of HPV recurrence have been observed, as the virus remains in clinically normal skin and/or membranes and mucous membranes [104,105]. According to evidence, probiotic consumption may have a significant effect on HPV clearance [106], by leading to a balanced vaginal microbiota, decreasing rates of mildly abnormal and unsatisfactory cervical smears or increasing clearance of low-grade squamous intraepithelial lesion abnormalities, and reducing genital risk in women with high-risk HPV [106–108]; however, the mechanism by which probiotics may exhibit these beneficial effects has not yet been elucidated. Verhoeven et al. [108], administered *L. casei* Shirota (1×10^{10} CFU/day) orally, in patients with HPV-related precancerous lesions, interestingly, women consuming these probiotics were twice as likely to eliminate cytological abnormalities compared to the control group (60% and 31%, respectively). Furthermore, they observed a 26% clearance of HPV in women who received *L. casei* Shirota compared to the control group (19%) [108]. In another study by Palma et al. [106], short- and long-term vaginally administration of *L. rhamnosus* BMX54 (1×10^4 CFU/tablet) was evaluated in women with HPV infections and bacterial vaginosis: BMX54 restored the vaginal microbiota by generating a state of bacterial equilibrium (eubiosis), which reduces bacterial vaginosis characterized by a decrease in *Lactobacillus* spp. and increase in *E. coli*, *Gardnerella* spp., *Chlamydia*, *Ureaplasma* spp., and *Streptococcus* spp. [106,109]. HPV infection was confirmed by polymerase chain reaction (PCR) for subtypes including HPV-16 and -18. Patients who consumed probiotics for a long period had a total HPV decrease of 31.2% ($p = 0.044$), suggesting that probiotics use reduces HPV-

related cytological abnormalities by up to 2-fold ($p = 0.041$) (Table 4) [106]. Ou et al. [107], investigated the influence of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (5.4×10^9 CFU) on genital risk reduction in women with high-risk HPV; however, no significant difference in HPV clearance rate was found, despite the decrease in cervical smear abnormalities (Table 4) [107].

8. Probiotics and Hepatic Encephalopathy (HE)

HE is a reversible syndrome of brain function defined as: "*an alteration in the function of the central nervous system due to liver failure*". This disease includes a wide spectrum of mental and motor disorders observed in patients with hepatic failure [110]. Mental status changes in HE include memory impairment, euphoria or anxiety, inattention, decreased reaction time, sensory abnormalities, poor concentration, inappropriate behavior, confusion and disorientation. In addition, changes in motor function also include rigidity, induced speech, rest and movement disorders such as tremor, asterixis, hyperreflexia or hyporeflexia. However, the prevalence of HE in patients with liver cirrhosis ranges from 30% to 84% [111], and at least 50–70% of patients with cirrhosis will show abnormalities on psychometric tests and many will have significant functional impairment [112]. On the other hand, patients with hepatitis B virus (HBV)-induced cirrhosis harbor a higher amount of *E. faecalis*, and lower numbers of *Enterobacteriaceae* and *Bifidobacterium*, *Lactobacillus*, *Pediococcus*, *Leuconostoc* and *Weissella* [113]. This structural change in the gut microbiota causes the elevation of ammonia and a disruption of the intestinal barrier; directly affecting the gut-brain axis (and thus behavioral), thus favoring the development of HE [114]. The administration of lactulose and antibiotics is the main treatment for HE. Lactulose is a synthetic, nonabsorbable disaccharide that has multiple effects on the gut microbiota; indeed, it decreases urease enzyme activity and pH, which in turn will decrease ammonia production and absorption in the intestine. Antibiotic use includes neomycin and metronidazole, which are effective in reducing the population of gram-negative and anaerobic urease-producing bacteria. These treatments are effective, but may have toxic side effects, in addition to being expensive [115]. Malaguarnera et al. [116] tested the efficacy of *Bifidobacterium* spp. in combination with fructo-oligosaccharides (FOS) and lactulose in patients with HE caused by HBV, HCV and cryptogenic cirrhosis. Synbiotic intake significantly ($p < 0.001$) reduced ammonia levels (50.2 mmol/L) compared to lactulose intake (61.4 mmol/L) and an improvement in traceability tests ($p < 0.05$), symbol digit modalities ($p < 0.001$) and block design ($p < 0.001$). In addition, no adverse effects were observed compared to those who consumed only lactulose (Table 4). Xia et al. [111] investigated the role of *C. butyricum* (1×10^7 CFU/g) and *B. infantis* (1×10^6 CFU/g) in the treatment of minimal hepatic encephalopathy (MHE), in patients with HBV-induced liver cirrhosis. The groups receiving the probiotic improved in psychometric, digit symbol, and the number connection tests. In addition, they observed that probiotics modified the diversity of the intestinal microbiota, finding an increase in *Clostridium* cluster I and *Bifidobacterium*, while the amount of *Enterococcus* and *Enterobacteriaceae* decreased. The increase in *Clostridium* cluster I and *Bifidobacterium* was related to an improvement in the integrity and maintenance of the intestinal barrier. Furthermore, this improvement of the intestinal barrier had significant effects on decreasing the blood ammonia concentration of the treated-group compared to the control group (76.4 vs. 152.0 µmol/mL, $p = 0.032$), which effectively improves the clinical symptoms of MHE (Table 4) [111]. Although improvements in HE symptoms through modulation of the gut microbiota and decreased urease enzymatic activity produced by pathogenic microorganisms in the gut were observed in both clinical trials, no direct effects of probiotics on inhibition of HBV and HCV viruses were observed. For now, and based on the results obtained in clinical trials, probiotics cannot be recommended for the treatment of most liver disorders; indeed, evidence only suggests their use in MHE. Finally, although probiotics have had positive effects over HBV infections in in vitro tests [117], the exact mechanism conferring these effects has not yet been elucidated.

9. Probiotics and Herpes Simplex-2 (HSV-2) Infection

Genital herpes is a sexually transmitted disease caused mainly by herpes simplex virus type 2 (HSV-2) and, to a lesser extent, by herpes simplex virus type 1 (HSV-1), both belonging to the family Herpesviridae (DNA viruses) [118]. HSV-2 infection is a worldwide problem and WHO estimates that 13% of the population aged 15–49 years is infected with HSV-2. Genital herpes infections are often asymptomatic or show mild symptoms that go unnoticed. However, clinical studies show that up to one-third of people with HSV-2 infection may have symptoms, characterized by one or more vesicles, genital and/or anal ulcers, accompanied by other symptoms such as fever, pain, and lymphadenopathy. HSV-2 infection (for which there is currently no cure) is life-threatening and is almost exclusively sexually transmitted [119]. Treatment for this type of infection consists of the use of antivirals drugs; however, although they can reduce the intensity and frequency of symptoms, they cannot reduce HSV-2 transmission [119,120]. A potential therapeutic alternative to combat HSV-2 infections would be the use of probiotics, due to their ability to secrete bacterial metabolites (e.g., lactic acid, hydrogen peroxide, andbacteriocin), modulate the immune system (Figure 1), and restore the vaginal microbiota [121]. Mohseni et al. [122], conducted a clinical trial in which they observed the effect of probiotics on herpes infections. The researchers administered vaginal capsules of *L. brevis* CD2, *L. brevis* KB290 and *L. brevis* SBC8803, in women with HSV-2 infections and compared it with the control group (which was orally administered 400 mg of acyclovir). The results show that both treatments produce similar effects: the probiotic decreases the healing time of the lesion as well as the acyclovir treatment (6.5 vs. 5.2 days, $p = 0.06$). Furthermore, treatment with all three *L. brevis* strains shows a significant role in suppressing recurrent HSV-2 infection ($p = 0.03$). This finding is quite interesting, since a probiotic therapy is cheaper (than the use of a drug) and has no side effects (headache, nausea, diarrhea and abdominal pain) (Table 4) [122]. According to the literature, there are very few clinical trials focused on the use of probiotics to treat HSV-2 infections. Therefore, there is a need for more clinical trials that consider the co-administration of probiotics and retroviral drugs, the duration of probiotic treatment, sample size and route of administration.

Table 4. Probiotics used in clinical trials in HPV infection, hepatic encephalopathy (HE) and Herpes Simplex-2 (HVS-2) Infection.

Condition	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
Cervical lesion	Women (mean 31.75 years)	*L. casei* Shirota (1×10^{10} CFU/day)	Oral	6-month	Prospective controlled pilot	Reduces twice as likely to clear cytological abnormalities compared than control (60 vs. 31%, $p = 0.05$)	[108]

Table 4. *Cont.*

Condition	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
HPV-infection	Women (>18 years)	*Lactobacillus rhamnosus* BMX54 (1×10^4 CFU/tablet)	Vaginal	Short-term 3 months Long term 9 months	Randomized, pilot study	Short-term restore the vaginal microbiota generating a state of bacterial balance. The patients who used probiotics long-term, decrease in HPV clearance (31.2% vs. 11.6%, $p = 0.044$) and reduce HPV-related cytologic abnormalities compared with short-term (79.4% vs. 37.5%, $p = 0.041$)	[106]
Genital high-risk by HPV-infection	Women (30–65 years)	*Lactobacillus rhamnosus* GR-1 *Lactobacillus reuteri* RC-14 (5.4×10^9 CFU)	Oral	Not specified	Randomized, double-blinded, placebo-controlled trial	Reduces genital risk in women with high-risk HPV ($p = 0.006$); however, no significant differences were found in the HPV clearance rate	[107]
Hepatic encephalopa-thy (HE)	Adults (unspecified age)	*Bifidobacterium* plus fructo-oligosaccharide (FOS)	Oral	60 days	Unspecified	Reduces significant ammonia levels (50.2 vs. 61.4 mmol/L, $p < 0.001$) compared with lactulose treatment and an improvement in traceability tests ($p < 0.05$), symbol digit modalities ($p < 0.001$) and block design ($p < 0.001$)	[116]

Table 4. *Cont.*

Condition	Population (Age Range)	Probiotic & Dose	Route	Duration	Type of Study	Results	Ref.
Minimal hepatic encephalopathy (MHE)	Adults (unspecified age)	*C. butyricum* (1.0×10^7 CFU) *B. infantis* (1×10^6 CFU)	Oral	3 months	Unspecified	- Improvement in psychometric tests, the digit symbol test and the number connection test - Modified the diversity of the intestinal microbiota, finding an increase in *Clostridium* cluster I and *Bifidobacterium* ($p < 0.05$) and decrease *Enterococcus* and *Enterobacteriaceae* ($p < 0.05$) - Shows lows ammonia levels in the probiotics group than control group (76.4 vs. 152.0 µmol/mL, $p = 0.032$)	[111]
Genital Herpes Infections	Women (17–57 years)	*Lactobacillus brevis* CD2 *Lactobacillus brevis* KB290 *Lactobacillus brevis* SBC8803 (2×10^9 CFU/capsule)	Oral	6 months	Randomized double-blind controlled trial	-Probiotic decrease lesion healing time in comparison with aciclovir-treatment (6.5 vs. 5.2 days, $p = 0.06$). - Suppress recurrent herpes virus infection ($p = 0.03$). - Moreover, probiotic therapy has no side effects (headache, nausea, diarrhea and abdominal pain).	[122]

10. Discussion

In this review, we found and discussed a total of 40 clinical trials evaluating the effect of probiotics on viral infections. Calculating the percentage of each clinical trial for each viral disease, and considering as 100% the total of selected studies, we found that RTIs showed the highest percentage of studies (40%), followed by HIV infections (25%), and gastrointestinal infections (20%) and finally HE and HSV-2 infections, which showed 5% and 2.5%, respectively. These percentages are probably related to the incidence of viral diseases. RTIs are the diseases in which most studies use probiotics as adjuvant therapy

(Figure 1). This is probably because they are the most common infections and have a high impact on health and economy worldwide, as is the case with influenza and SARS-CoV-2.

Scientific evidence suggests that the use of probiotics in viral infections may enhance the immune system response, leading to health benefits [15,16,123–125]. Although the antiviral mechanisms produced by probiotics are not fully understood [123], a potential antiviral effect of these microorganisms is usually associated with improvement of the barrier function of the intestinal mucosa, production of antimicrobial substances (hydrogen peroxide or organic acids) and modulation of the immune system [32,123].

Moreover, the effects of probiotics may also include enhanced phagocytic activity, increased secretion of immunoglobulins (IgA, IgG, and IgM) and increased cytokine production (interleukins, TNF-α, and interferon-α) [126]. In the case of SARS-CoV-2 infection, disease progression, generates an increase in free radicals, causing cell damage and triggering a storm of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-2, IL-6, IL-7, and granulocyte colony stimulating factor (G-CSF), affecting the balance of the gut microbiota (i.e., reduction of *Bifidobacterium* spp. and *Lactobacillus* spp. counts) [127]. In this sense, probiotics could restore the altered intestinal microbiota and modulate the immune system, so they could be useful to generate health benefits in this disease [15,16,123–125]. Furthermore, probiotics co-administered with retroviral drugs could enhance the beneficial health effects, as together they could restore the structure, function and integrity of the gastrointestinal mucosa. These beneficial effects are offered by probiotics together with modulation of the immune system (by increasing the CD4+ lymphocyte population, especially Th17, and decreasing the number of CD8+ lymphocytes), inhibition of epithelial invasion and prevention of microbial translocation of pathogens and production of metabolites of health concern [32,70,78,79]. In clinical trials, the rationale for the use of probiotics for HPV elimination is probably based on the interaction of such microorganisms (e.g., *Lactobacillus* spp. mainly) with the vaginal microbiota, resulting in an increased innate and adaptive immune response and a probable direct antiviral effect. On the other hand, clinical trials demonstrating the effect of probiotics in liver diseases were only observed in HE, since, probiotics used in HBV infections were performed in in vitro tests. In such assays, probiotic strains that inhibit HBV do so by an antiviral mechanism associated with the Mx GTPase pathway. However, it is very likely that it will not be possible to perform a similar evaluation in clinical trials, due to the site of infection, which does not allow adequate interaction with probiotics. Finally, several probiotics have been used in viral diseases, as they are low cost and non-invasive. Yet, available probiotics are still limited and research with different probiotic strains and NGP should continue.

Although probiotics are an interesting alternative and represent an emerging multi-billion-dollar industry, regulatory authorities must implement adequate legislation to establish standardization, good quality manufacturing practices, evaluation of efficacy, and studies to document any potential adverse effects [128,129]. Currently, probiotics are regulated as dietary supplements, so proof of efficacy is not mandatory [128,130]; however, this could change in the short time, as countries are starting to discuss the legal framework for probiotic [130]. A study by Phavichitr et al. [131] showed that probiotics shortened the duration of hospitalization of children, but without a significant impact on total expenses. Probiotics may be an economically attractive intervention for disease prevention, however, information on cost-effectiveness is still very scarce and only future clinical studies will be able to provide such an answer in terms of cost [132]. For instance, European Food Safety Authority (EFSA) and the US Food and Drug Administration(FDA) have not yet approved any probiotic formulation as a therapy [128,130]. Regarding the side effects of probiotics (which by definition seems to be somewhat contradictory), the risk of infection by any microorganism considered as a probiotic is very low, but their administration in particular cases must be extremely careful, for example in people with long-term hospitalizations, suppressed immune systems or in post-surgery patients [133–135].

11. Conclusions

Recently published studies have shown that probiotics have beneficial effects against various viral infections (i.e., hepatic encephalopathy and respiratory, gastrointestinal, HIV, HPV and HVS-2 infections). However, the probiotic effect attributed to one strain cannot be extrapolated to other strains of the same species. The potential antiviral effect associated with probiotics includes: (1) interaction and modification of the host microbiota, (2) adhesion of probiotics to the epithelial surface, which may block viral attachment and compete for specific carbohydrate receptors, (3) production of antimicrobial compounds such as lactic acid, hydrogen peroxide, and bacteriocins, and (4) modulation of the immune system. On the other hand, clinical trials are not harmonized in terms of dosage, sample size and control groups, route of administration and duration of probiotic treatment. Therefore, standardization of protocols will allow better selection of strains, and data recorded, as well as their outcomes, will be very helpful for outgoing and future studies.

Finally, probiotics represent an interesting and promising strategy for health promotion and could be used as adjuvants in therapies against viral infections in order to improve the effect of vaccines. Since probiotics are not considered drugs, it is necessary to maintain strict control in legal regulation, sufficient scientific evidence on efficacy and safety, and post-marketing documentation of possible undesirable effects for consumers. In conclusion, we believe that the application of probiotics and NGP in COVID-19 and other diseases requires further investigation, as the evidence suggests a promising effect.

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