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Review

The effect of probiotics on respiratory tract infection with special emphasis on COVID-19: Systemic review 2010–20

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ABSTRACT

To evaluate the effects of probiotics on respiratory tract infection (RTI) a systematic review of randomized controlled trials (RCTs) from January 2010 to January 2020 was conducted. The PubMed, Google Scholar, Embase, Scopus, Clinicaltrials.gov, and International Clinical Trials Registry Platform databases were systematically searched for the following keywords: respiratory tract infection, probiotics, viral infection, COVID-19, and clinical trial. A total of 27 clinical trials conducted on 9433 patients with RTI plus 10 ongoing clinical studies of probiotics intervention in Coronavirus disease 2019 (COVID-19) were reviewed. The review looked at the potency of probiotics for the hindrance and/or treatment of RTI diseases, this may also apply to COVID-19. The review found that probiotics could significantly increase the plasma levels of cytokines, the effect of influenza vaccine and quality of life, as well as reducing the titer of viruses and the incidence and duration of respiratory infections. These antiviral and immune-modulating activities and their ability to stimulate interferon production recommend the use of probiotics as an adjunctive therapy to prevent COVID-19.

Based on this extensive review of RCTs we suggest that probiotics are a rational complementary treatment for RTI diseases and a viable option to support faster recovery.

Introduction

Respiratory tract infection (RTI) is one of the most common infectious diseases of viral or bacterial origin. The disease is divided into upper respiratory tract infections (URTI) and lower respiratory tract infections (LRTI). The upper respiratory tract includes the nose, sinuses, pharynx, and larynx. Common upper respiratory tract infections include tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, certain types of influenza, and the common cold (Eccles et al., 2007). Symptoms of URTIs include cough, sore throat, runny nose, nasal congestion, headache, low-grade fever, facial pressure, and sneezing. The lower respiratory tract consists of the trachea (windpipe), bronchial tubes, bronchioles, and lungs. Medically, lower respiratory tract infections are more serious and important than upper respiratory tract infections (Van Riel et al., 2006).

Viral pathogens are the most common cause of RTIs; these include rhinovirus, respiratory syncytial virus, influenza virus, human parainfluenza virus, human metapneumovirus, measles, mumps, adenovirus, and coronavirus. Bacterial pathogens causing RTI are less common than viral pathogens but can also cause outbreaks and sporadic cases of respiratory illness; these include *Streptococcus pneumoniae, Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae, Coxiella burnetii,* and *Legionella pneumophila*. Bacterial sinusitis, bronchitis or pneumonia may occur as secondary infections after a viral respiratory infection.

Influenza affects both the upper and lower respiratory tracts and can produce a variety of symptoms including high fever, chills, sore throat, headache, runny or blocked nose, weakness, muscle pain, and diarrhea (Barik, 2012). More than 200 serologically different virus types are responsible for human URTIs, among

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which rhinoviruses are the most common cause (Wang and Liu, 2014).

Coronavirus disease 2019 (COVID-19) is a new pandemic disease caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]). Zoonotic coronaviruses have emerged in recent years and caused human outbreaks such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). The virus enters cells via spike proteins (S) and angiotensin-converting enzyme 2 (ACE2) receptor proteins on host cells. It can affect both upper (sinuses, nose, and throat) and lower (windpipe and lungs) respiratory tracts and cause problems such as acute respiratory distress syndrome (ARDS), respiratory failure, multiple organ failure, or even death (~10%); it represents a global health challenge (Serratosa et al., 2012).

Probiotics have shown a positive response in clinical treatment for several diseases. Inhibition of gastric coronavirus, rotavirus, hemagglutinin type 1 and neuraminidase type 1 (H1N1) influenza virus, and HIV *in vitro* and reduction of viral load *in vivo*, using *Lactobacillus* has been well established (Anwar et al., 2020). Probiotics are defined as live microorganisms that have health benefits for the host and contain immunostimulatory substances such as lipoteichoic acid, peptidoglycan and nucleic acid, which are Toll-like receptor (TLR) ligands, and muramyl dipeptide, which is a Nod-like receptor ligand (Jensen and Thomsen, 2012). Studies have shown antiviral activities of probiotic strains against common respiratory viruses, such as rhinovirus, influenza and respiratory syncytial virus (Luoto et al., 2014). Probiotics affect both the acquired and innate immune systems and reduce the severity of infections in the upper respiratory and gastrointestinal tracts (Khani et al., 2012). Probiotics increase the level of type I interferons; the number and activity of natural killer (NK) cells, T cells and antigen-presenting cells; and the level of specific antibodies in the lungs (de Vrese et al., 2005). Probiotic strains regulate the dynamic balance between immunoregulatory and pro-inflammatory cytokines.

RTIs are the result of an imbalance in the microbial population of the respiratory tract and gastrointestinal tract affecting the lungs mucosa (Kumar et al., 2018). This dysbiosis may subsequently alter immune function and predispose the patient to secondary bacterial infection (Getahun et al., 2010). The gut microbiome has a critical impact on inducing immune responses at distant mucosal sites including the lungs (Abt et al., 2012). Studies have shown that the administration of certain Bifidobacteria or *Lactobacillus* has a beneficial impact on RTIs (Zelaya et al., 2016).

In 1 study the frequency and severity of common cold symptoms in patients with rhinovirus infection were shown to be lower in the *Lactobacillus rhamnosus* (LGG) treated group than in the control group (Kumpu et al., 2015). *Lactobacillus delbrueckii* subsp. *bulgaricus* OLL1073R-1 has been shown to augment NK cell activity and reduce common cold symptoms (Makino et al., 2010). *Lactobacillus paracasei* subsp. *paracasei* (*L. casei* 431) shortened the duration of upper respiratory infection symptoms (Nagai et al., 2011). *Lactobacillus plantarum* L-137 augmented the innate and acquired immune responses in mice and humans and reduced RTIs in the treatment group compared to the control group (Merenstein et al., 2010). *Bifidobacterium animalis* subsp. *lactis* Bl-04 (Bl-04) was shown to decrease the risk of upper respiratory illness in a natural setting (Turner et al., 2017).

Given the results of these studies on the use of probiotics, their use may also play a role in reducing the severity of ARDS, a major complication of COVID-19. The effect of probiotics against several

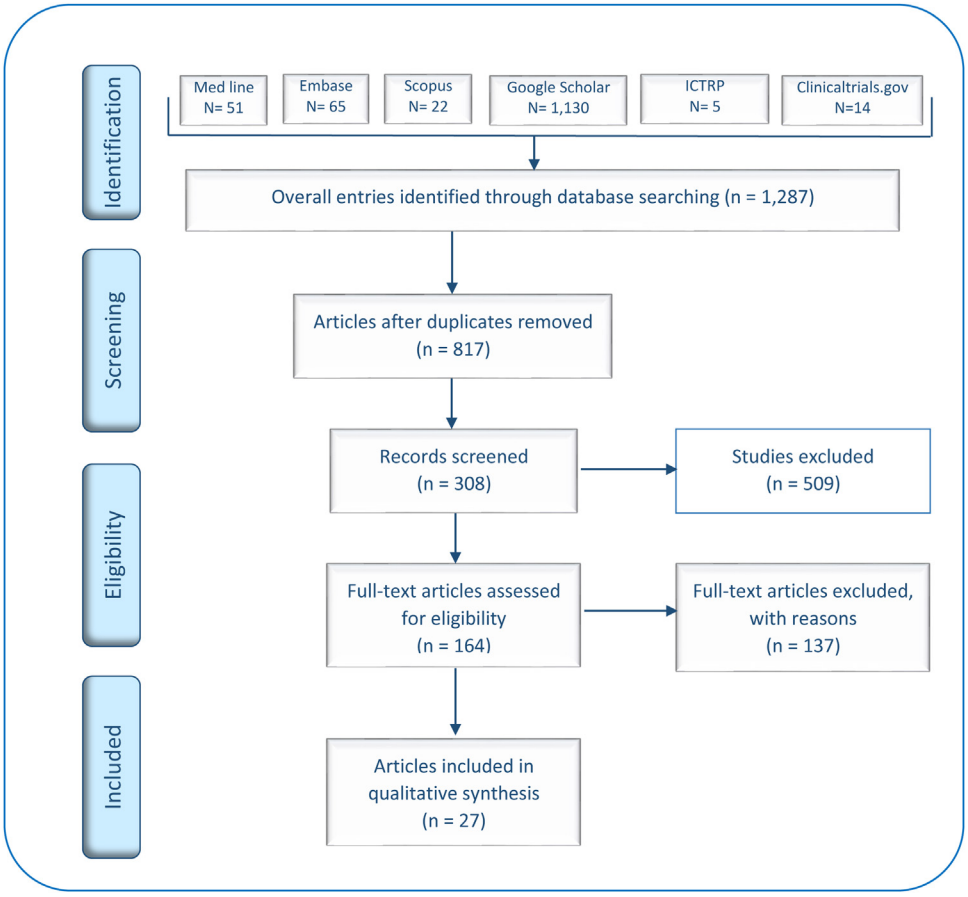

Figure 1. PRISMA flow chart of the study selection procedure

Table 1
The outcomes of different clinical trials assessing the efficacy of probiotics on respiratory tract infections.

Outcomes	Intervention	Dose	Probiotics	No. of Participants (Mean age ± SD)	Participants Characteristics	Study Design	Country	Reference
Probiotic was beneficial for children and reduced the severity of common colds	1 sachet/ o. d/ 12wks	1×10^9 CFU	*L. plantarum* HEAL9, *L. paracasei 8700:2*	131 (3.1 ± 1.4)	URTI	RDBPCT	Sweden	Ahrén et al. (2021)
Prebiotics affected intestinal microbiota and maintained antibody titers in elderly individuals	Doses of GOS and BGS used in group F were 4.0 and 0.4 g/day, respectively.	Not reported	Prebiotic	43 (84.5 ± 7.5)	Influenza vaccine	RCT	Nagoya	Akatsu et al. (2016)
Probiotic strains reduced the risk of acquiring common cold infections	O.d/ 12 wks	1×10^9 CFU	*L. plantarum* HEAL 9, *L. paracasei* 8700:2	318 (46.5)	Common cold	RDBPC	Sweden	Berggren et al. (2011)
Probiotics alleviated the symptoms of URTI by improving inflammatory parameters and enhancing immunomodulatory properties.	1sachet /12 wk	1×10^9 CFU	*L. plantarum* DR7	109(≤ 60)	URTI	RDBPCT	Malaysia	Chong et al. (2019)
Lactobacillus GG was as a potentially important adjuvant to improve influenza vaccine immunogenicity	1 capsule/ b. i.d/ 4wks	1×10^{10} CFU	*Lactobacillus* GG	42 (33.5)	Live-attenuated influenza vaccine (LAIV)	RDBPCT	USA	Davidson et al. (2011)
Antigen-specific B and T cell activation following an in vitro recall challenge with the influenza vaccine was not affected by a synbiotic	1 sachet/ o. d/ 8 wks	1×10^9 CFU in 1 g skim milk powder	*B. longum, B. infantis* CCUG 52486	63 older cohorts: (60- 85 y) 62 younger cohort: (18-35 y)	Influenza vaccine	RDBPCT	U.K	Enani et al. (2018)
Probiotics increased the immune response against the influenza vaccine and decreased symptoms associated with respiratory infection	1 capsule/ d/ 2 wks	3×10^9 CFU	*L. coryniformis* K8 CECT5711	98 (83.79 ± 6.5)	Inactivated trivalent influenza vaccine	RDBPCT	Spain	Fonollá et al. (2019)
L. salivarius did not reduce the frequency of URTI and did not affect the levels of salivary antimicrobial proteins or blood leukocyte and lymphocyte subsets counts during a spring period	1sachet/ d/ 16 wks	2×10^{10} CFU	*L. salivarius*	66 (23.9 ± 4.7)	URTI	RDBPCT	UK	Gleeson et al. (2012)
Probiotics reduced plasma CMV and EBV antibody titers as well as URS episode incidence	65 ml milk pot / b.i.d/ 20 wks	6.5×10^9 CFU	*L. casei* strain Shirota	268 (21 ± 3)	URS (CMV, EBV)	RDBPCT	UK	Gleeson et al. (2016)
probiotic reduces the risk of common infections in stressed individuals such as shift workers	2 bottles/b.i. d/12 wks	1×10^{10} CFU 1×10^9 CFU	*L. casei* DN-114 001, *S. thermophiles, L. delbrueckii* subsp. *bulgaricus*	1000 (32)	RGCID	RDBRCT	France	Guillemard et al. (2010)
Probiotics reduced stress-induced gastrointestinal dysfunction and the number of days with common cold or influenza	1 packet/ o. d/ 8 wks	2.5 g and 5 g of galactooligosaccharides	Prebiotic	427 (19.9 ± 0.1)	Cold/flu symptoms	RDBPCT	USA	Hughes et al. (2011)
L. casei 431 dose did not affect the immune response to influenza vaccination but reduced the duration of upper respiratory symptoms	100 mL acidified milk drink / o.d/ 6 wks	1×10^{10} CFU	*L. paracasei* subsp. *paracasei, L. casei* 431	1104 (31.6)	Influenza vaccine	RDBPCT-parallel-group study	Denmark	Jespersen et al. (2015)
Probiotic had no significant effect on preventing influenza or enhancing NK cells activity but increased IFN-γ	112 mL yogurt drink fermented /o.d/ 16 wks	1.12×10^9 CFU	*L. delbrueckii* subsp. *bulgaricus* OLL1073R-1	961 (39.3)	Influenza and the common cold	Randomized, controlled, open-labeled	Japan	Kinoshita et al. (2019)
The occurrence and severity of cold symptoms and the number of subjects with	o.d / 6 wks	1×10^9 CFU	*L. rhamnosus GG*	60 (24.3)	Rhinovirus	RDBPCT	Finland	Kumpu et al. (2015)

Table 1 (*Continued*)

Outcomes	Intervention	Dose	Probiotics	No. of Participants (Mean age ± SD)	Participants Characteristics	Study Design	Country	Reference
rhinovirus infection was reduced in the group receiving live *L. rhamnosus* GG but not significantly compared to the group receiving inactivated strain,								
Probiotics played a role against viruses causing common cold, but did not reduce viral occurrence in symptomatic conscripts	1 tablet/ b.i. d/ 12 and 21wks	5×10^9 CFU	*L. rhamnosus* GG, *B. animalis* subsp. *lactis* BB-12	982 (19.3)	URTI	RDBPCT	Finland	Lehtoranta et al. (2014)
Bifidobacteria provided benefit related to cold/flu outcomes during acute stress	1 capsule/ o. d/ 6 wks	3×10^9 CFU	*L. helveticus* R0052, *B. longum* subsp. *infantis* R0033, *B. bifidum* R0071	583 (19.8 ± 0.1)	Cold/flu symptoms	RDBPCT	USA	Langkamp-Henken et al. (2015)
Gut microbiota modification with specific prebiotics and probiotics reduce the risk of rhinovirus infections	Mix with 10 mL of breast milk or formula/o.d /0 to 4 wks	1 × 600 mg	prebiotics (a mixture of polydextrose) + galacto-oligosaccharidesnhj	94 (32 + 0 to 36 + 6 weeks	RVIs	RDBPCT	Finland	Luoto et al. (2014)
	Mix with10 mL of breast milk or formula/o.d /4 to 8 wks	2 × 600 mg						
	Mix with 10 mL of breast milk or formula/o.d /0 to 4 wks	1×10^9 CFU	*L. rhamnosus* GG ATCC 53103					
	Mix with 10 mL of breast milk or formula/o.d /4 to 8 wks	2×10^9 CFU						
L. bulgaricus augmented natural killer cell activity and reduced the risk of catching the common cold in elderly individuals	90 g yoghurt/ o. d/8 -12 wks	2.5 -3.5 × 10^8 CFU 6.3 –8.8 × 10^8 CFU	*L. bulgaricus* OLL1073R-1, *S. thermophilus* OLS3059	85 (74.5)	Respiratory tract infections	Not report	Japan	Makino et al. (2010)
Non-viable *L. paracasei* MCC1849 had no significant effect on immune parameters	1 jelly/o.d/ 6 wks	1×10^{10} CFU	*L. paracasei* MCC1849	45 (89.0 ± 5.4)	Viral vaccine	RDBPCT	Japan	Maruyama et al. (2016)
probiotics reduces the incidence of influenza and fever, probably by potentiating innate immunity	1sachet /o. d/14 weeks	1×10^{11} CFU	*B. longum* BB536	27 (86.7 ± 6.6)	Influenza vaccination	RDBPCT	Japan	Namba et al. (2010)
Probiotics combination reduced the symptoms of the common cold and school absenteeism	1 capsule/ b. i.d//12 wks	1×10^{10} CFU	*L. acidophilus, B. bifidum*	80 (12)	Common cold	RDBPCT	Thailand	(Rerksuppaphol and Rerksuppaphol, (2012)
Probiotics improved immune function by augmenting systemic and mucosal immune responses to challenge	1 capsule/o. d/ 6 wks 1acidified dairy drink /o. d/ 6 wks	1×10^9 CFU	*B. animalis* subsp. *lactis,* BB-12 *L. paracasei ssp. paracasei, L. casei* 431	211(37.3 ± 13.9)	Influenza vaccination	RDBPCT	Italy	Rizzardini et al. (2012)
L. pentosus b240 reduced the incidence rate of the common cold in elderly adults and improved resistance against infection by mucosal immunity	1 tablets/ o. d /20 wks	Low dose: 2×10^9 CFU High dose: 2×10^{10} CFU	*L. pentosus* strain b240	300 (70.8 ± 3.4)	Common cold	RDBPCT	Japan	Shinkai et al. (2013)
Probiotics reduced influenza-like illness via the enhancement of an IFN-α-mediated response to the influenza virus	100 mL of JCM5805 yogurt/ o.d/ 10 wks	1×10^{11}CFU	*L. lactis* subsp. *lactis* JCM5805	92 (46)	Influenza-like illness	RDBPCT	Japan	Sugimura et al. (2015)
Probiotics affected the innate immunity in the	1sachet/ o. d/ 4 wks	2×10^9 CFU	*B. animalis* subsp. *lactis* Bl-04	190 (22 ± 6)	Rhinovirus-A39	RDBPCT	USA	Turner et al. (2017)

Table 1 (*Continued*)

Outcomes	Intervention	Dose	Probiotics	No. of Participants (Mean age ± SD)	Participants Characteristics	Study Design	Country	Reference
nose and responded to rhinovirus infection								
Probiotic reduced the incidence of influenza in schoolchildren	80 mL drinks/ 5 d per wk/ 8 wks	6×10^9 CFU	*L. brevis* KB290	1783 (6–12 years)	IFV	Open-label, parallel-group trial	Japan	(Waki et al., 2014)
Probiotics reduced influenza and other respiratory viral infections	2 capsule/ d/ 24 wks	1×10^{10} CFU	*L. rhamnosus* GG	209 (85.5 ± 7.1)	RVI	Randomized, double-blind, placebo-controlled pilot trial.	Canada	Wang et al. (2018)

URTI: upper respiratory tract infections; URS: upper respiratory tract infection symptoms; IFV: Influenza virus; RVI: respiratory viral infections; RDBPCT: randomized double-blind placebo-controlled trial; RCT: randomized controlled trial; b.i.d.: twice daily, wks: weeks, d: days, o.d: once daily, SD: standard deviation

coronavirus species has been reported in various studies, however, these effects and mechanisms have not yet been examined for the new SARS-CoV-2 (Din et al., 2020).

Data show that SARS-CoV-2 causes gastrointestinal complications and probiotics appear to be able to reduce the dissemination of coronavirus via the gut, however, these probiotic strains have not yet been administered to the respiratory tract (Seo et al., 2010). Direct inhibition seems to be impossible at this site. Host-microbe, microbe-microbe and immune-microbe interactions could influence the course of respiratory diseases (Gonzalez-Ochoa et al., 2017). An imbalance between anti-inflammatory and pro-inflammatory cytokines, leading to a cytokine storm, contributes to the development of COVID-19 (Rizzardini et al., 2012). Some probiotic components could bind to spike proteins (S) and ACE2 receptor proteins and prevent the virus from entering the host body (Anwar et al., 2020). The use of probiotics could be effective in reducing other respiratory infections as well as COVID-19.

This systematic review aimed to evaluate the outcomes of clinical trials assessing the efficacy of probiotics in the treatment of respiratory infections over the past 10 years.

Materials and methods

Guidelines

This systematic review followed the guidelines established by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Moher et al., 2009).

The keywords, including respiratory tract infection, probiotics, viral infection, COVID-19, and clinical trial, were searched in the PubMed, Google Scholar, Embase Scopus, Clinicaltrials.gov, and International Clinical Trials Registry Platform databases. Papers published in English from January 2010 to January 2020 were further assessed based on their title, abstract and main text to ensure their relevance to the present study. Data extraction was conducted by 2 independent researchers. Papers indexed in 2 or more databases were considered only once. The reference lists of the selected papers were investigated to identify any further relevant papers. A third researcher checked the results to ensure that all the eligible papers were evaluated.

The extracted data were organized based on the name of authors, country, date of publication, type of clinical trial, size of the sample, diagnostic criteria, characteristics of patients, the period of study, genus and species of probiotics used, dose of probiotics used, side effects of probiotics, and outcomes of treatment. A Chi-square test was used to analyze the qualitative variables. Data were analyzed using SPSS software Version 24.0 (IBM, NY), and a P value ≤ 0.05 was considered statistically significant.

The inclusion criteria for considering full-text publications were: (i) papers published during the last 10 years; (ii) clinical trial studies; and (iii) clinical trial studies conducted on patients with RTI.

The exclusion criteria were: (i) animal experiments; (ii) congress papers; (iii) reviews, meta-analysis, case reports, letters to the editor, and correspondence; (iv) clinical feature summary; (v) non-English papers; and (vi) studies with no clear information.

Results

A total of 1268 papers were retrieved from the Google Scholar, Medline, Embase, and Scopus databases. Figure 1 shows a schematic representation of the search method used in this review. In the second phase, after removing duplicates, 77 papers remained, of which 50 were excluded based on their title and abstract, and 27 selected for detailed full-text evaluation and analysis. The outcomes of the clinical trials that assessed the efficacy of the probiotics in the treatment of RTIs are shown in Table 1. The largest number of studies were conducted in Japan (7/27 studies, 3293/9433 patients). In total 73% of the patients surveyed were women (Figure 2) with an age range of infant to 89 years. The specimens included blood, serum and nasopharyngeal swab.

Of the 27 clinical trials, 23 were conducted on the efficacy of probiotics in the treatment of RTI, 1 on synbiotic efficacy, 2 on prebiotics efficacy, and 1 on probiotic and prebiotic efficacy separately. Of the 15 different probiotic strains studied, *Lactobacillus* species were studied more than Bifidobacteria, and *L. paracasei* and *L. rhamnosus* (15%) were the most common probiotic strains used. The frequency of the different types of probiotic species studied is shown in Figure 3. The prescribed doses of these strains were between 1×10^9 and 1×10^{11} (average dose: 5.05×10^{10}) colony-forming units (CFU) for 6 and 24 weeks.

Of the 27 clinical trials reviewed, 9 examined a combination of multi-strain probiotic bacteria, 15 examined mono-strain probiotic bacteria and, as mentioned above, 2 trials were conducted on prebiotics efficacy and 1 on probiotic and prebiotic cocktails. In 9 studies, a combination of 2 probiotic bacteria was used, while in 2 studies, a combination of 3 probiotic bacteria was used.

Total effects of probiotics on the immune response

Of the 27 clinical trials, 3 showed that probiotics did not play a significant role in boosting the immune system and improving the

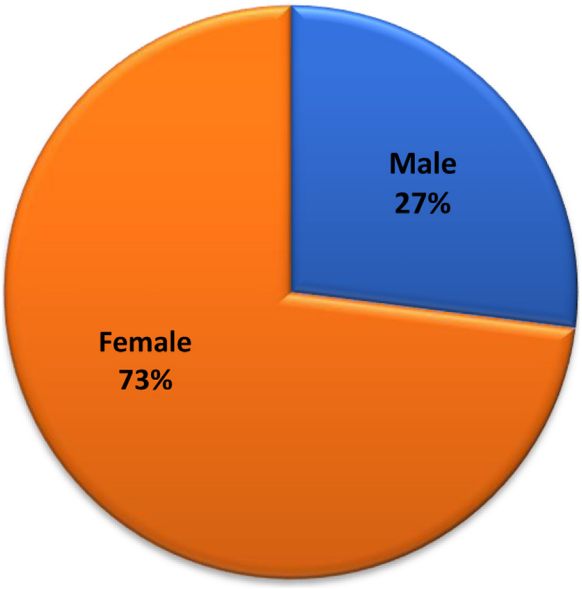

Figure 2. The frequency of RTI among male and female patients

body's defenses against diseases (Enani et al., 2018; Gleeson et al., 2012; Lehtoranta et al., 2014).

In 1 study, the probiotic intake was reported to increase the population of NK T cells compared to the control group (40.9 vs. 24.1) as well as the expression of the memory marker CD45R0 on the surface of CD8+ lymphocytes. The plasma levels of cytokines in various categories, anaphylatoxins, pro-inflammation and other cases, were also studied. The plasma concentrations of complement C4a and C5a, cytokines (interleukin-(IL)1β, IL-6, IL-8, IL-12, IL-5, and IL-10), and tumor necrosis factor α (TNF-α) were evaluated in the probiotic and control groups. In general, the level of cytokines increased in the probiotic groups due to the use of probiotics. However, the IL-6 level in the probiotic groups was higher than in the control groups.

Effects of probiotics on the immune response to influenza vaccination

Of the 27 clinical trials, 7 were conducted on the effects of probiotics and 1 on the effects of prebiotic compounds to improve vaccine performance. The findings on the effects of probiotics on the immune response to influenza vaccination are shown in Table 2. Patients in these studies were distributed into control and probiotic groups. The mean age of the patients was 59.7 years, ranging from 18 to 99 years; 60% of patients were female. The most common probiotic species studied was *Lactobacillus*, 2 studies evaluated *Bifidobacterium longum*, and 1 evaluated a combination of *Lactobacillus* and *Bifidobacterium.*

On average, the probiotic groups consumed capsules containing 1×10^9 to 1×10^{11} CFU of probiotic strains daily for 28 to 98 days. The vaccination was conducted by medical services with a vaccine containing inactivated trivalent (H1N1, H3N2, and B) influenza virus. The antibody titers against the 3 viral antigens included in the vaccine were evaluated at baseline and 2, 6, 8, and 10 weeks after influenza vaccination. Seroconversion was defined as the proportion of vaccinated individuals achieving a haemagglutination inhibition titer of >1:40 against at least 1 of the viral subtypes included in the vaccine. The present study results showed a significant increase in total plasma immunoglobulin(Ig)G titer in the probiotic groups compared to the control groups (14.27 and 10.67, respectively). The seroconversion against at least 1 of the antigens in the vaccine was 4.94 times higher in the probiotic groups than in the control groups (Table 2).

Evaluation of the immune benefits of 2 probiotic strains of *B. animalis* subsp. *lactis* BB-12 and *L. paracasei* subsp. *paracasei*, *L. casei* 431 in an influenza vaccination model indicated that an increase in specific IgG was greater in both probiotic groups vs. the control (Rizzardini et al., 2012).

Adverse events (AEs)

There was no significant difference between the 2 study groups (probiotic groups vs. control groups) in terms of the incidence of AEs (Turner et al., 2017; Wang et al., 2018). However, there were more gastrointestinal-related AEs in the control groups (41.8%) compared to the probiotic groups (32.25%). The most common gastrointestinal-related AEs in the control groups were nausea (16.74%), diarrhea (3.59%), vomiting (16.9%), abdominal pain (3.83%), then flatulence (3.62%), while in the probiotic groups the incidence of AEs was nausea (5.72%), diarrhea (7.93%), vomiting (3.9%), abdominal pain (2.85%), and flatulence (2.07%). Non-gastrointestinal AEs including rhinorrhea, headache, cough, muscle aches, sore throat weakness, chills, and fever were lower in the probiotic groups (11.87%) compared to the control groups (22.5%).

Microbiota

The review of fecal recovery results of various studies indicated that the count of 2 important *Lactobacillus* species significantly increased in the probiotic groups (Akatsu et al., 2016; Berggren et al., 2011). A significant increase was reported in the number of *L.*

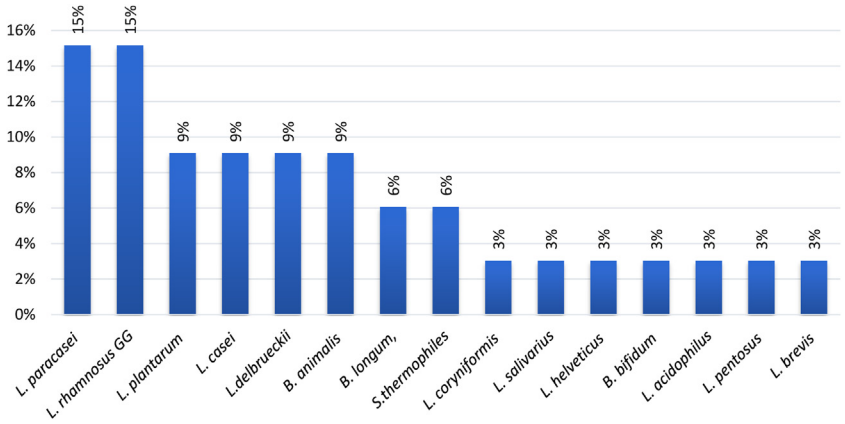

Figure 3. The frequency of probiotics used in different trials for patients with RTI

Table 2
Effects of probiotics on the immune response to influenza vaccination.

Reference	Vaccine Content	Probiotics& Dosage	Probiotic& Vaccination time	Immunological Parameters		Effects of Probiotics on Response to Vaccine
				Probiotic Group	Control Group	
Namba et al. (2010)	A/[H1N1] A/[H3N2] B	1×10^{11} CFU of BB536 daily for 5 weeks	2 w before vaccination	IgA (mg/dL): 419 IgG (mg/dL): 1630 IgM (mg/dL):88 NK cell activity (%): 26 Neutrophil bactericidal activity (%): 88.9 A/H1N1 antibody titer (log):0.8 A/H3N2 antibody titer (log):1.5 B antibody titer (log):0.5	IgA (mg/dL): 418 IgG (mg/dL): 1620 IgM (mg/dL):89 NK cell activity (%): 37 Neutrophil bactericidal activity (%): 92.7 A/H1N1 antibody titer (log):1.3 A/H3N2 antibody titer (log):0.6 B antibody titer (log):1.1	The proportion of subjects who contracted influenza was significantly lower in the BB536 group than in the placebo group. The proportion of subjects with fever was also significantly lower in the BB536 group than in the placebo group. In the BB536 group, the NK cell activity and the bactericidal activity of the neutrophils were significantly higher at week 5 than before BB536 administration.
Fonollá et al. (2019)	A/[H1N1] A/[H3N2] B	*L coryniformis* 3×10^9 CFU	2 w before vaccination	IgA (mg/dL): 4.13 IgG (mg/dL): 10.5 IL-4 (pg/mL): 0.78 IL10 (pg/mL): 3.47 TNF-α (pg/mL): 7.07	IgA (mg/dL): 3.91 IgG (mg/dL): 10.28 IL-4 (pg/mL): 0.94 IL-10 (pg/mL): 2.47 TNF-α (pg/mL): 4.93	The percentage of responders to vaccination was higher in the probiotic group than in the control group, and the incidence of respiratory symptoms associated with respiratory infections was also significantly lower (p = .007)
Akatsu et al. (2016)	A/[H1N1] A/[H3N2] B	Prebiotics, GOS and BGS	The doses of GOS and BGS were 4.0 g/day. Influenza vaccines were given at week 4	IgG (g/dL): 1.5 IgA (mg/dL): 374 IgM (mg/dL): 105 H3N2:7	IgG (g/dL): 1.5 IgA (mg/dL): 367 IgM (mg/dL): 108 H3N2: 1	Higher H3N2-specific IgG levels were observed 3 w after vaccination (p = .090)
Davidson et al. (2011)	A/[H1N1] A/[H3N2] B	L.GG. 1×10^{10} CFU	Immediately after probiotics	15% seroconversion for strain H1N1, 45% for strain H3N2, and 41% for strain B. There was no difference in seroconversion rates due to H1N1 and B strains between the treatment and placebo groups from baseline.		Increase in hemagglutinin titers in response to H3N2 strain 4 w after vaccination (p = .048).
Jespersen et al. (2015)	A/[H1N1] A/[H3N2] B	*L. paracasei* subsp. *paracasei, L. casei* 431 1×10^{10} CFU	3 w after probiotics	H1N1: 448 H3N2: 536 B: 475	H1N1: 445 H3N2: 526 B: 465	There was no difference in A/H1N1, A/H3N2, and B strains-specific IgG levels 3 w after vaccination (p-values NS). There was no difference in seroconversion rates 3 w after vaccination (p-values NS).
Maruyama et al. (2016)	A/[H1N1] A/[H3N2] B	*L. paracasei* 1×10^{10} CFU	3 w after probiotics	IgG (g/L): 14.4 IgA (g/L): 2.85 IgM (g/L): 0.90 NK activity (%): 33.8 Neutrophil bactericidal activity (%): 99.1 Neutrophil phagocytic activity (%): 93.4	IgG (g/L) = 14.9 IgA (g/L): 3.04 IgM (g/L): 0.90 NK activity (%): 29.4 Neutrophil bactericidal activity (%): 98.5 Neutrophil phagocytic activity (%): 92.6	There was no difference in A/H1N1, A/H3N2, and B strains-specific IgG levels 6 w after vaccination (p = .643, .767, .828). There was no difference in total IgA, IgG, IgM levels 6 w after vaccination (p = .632, .821, .329). There was no difference in NK-cell activity, neutrophil bactericidal and phagocytic activity 6 w after vaccination (p = .814, .217, .560)
Rizzardini et al. (2012)	A/[H1N1] A/[H3N2] B	BB-12, *L. paracasei* subsp. *paracasei*, *L. casei* 1×10^9 CFU	2 w after probiotics	IgG (BB-12): 81.1 IgG (*L. casei* 431): 28.6	IgG (BB-12): 20.8 IgG (*L. casei* 431): 18.5	Vaccine-specific plasma IgG in both probiotics groups was significantly greater, salivary vaccine-specific IgA was greater but not significant. No difference was found for salivary vaccine-specific IgA or IgM but was significantly greater in total
Enani et al. (2018)	A/[H1N1] A/[H3N2] B	*B. longum* bv. Infantis 1×10^9 CFU with a prebiotic	4 w after probiotics	IgA memory: 14.3 IgG memory: 13 NCS memory: 46.6 Total IgA: 22.4 Total IgG: 20.6	IgA memory: 19 IgG memory: 16.6 NCS memory: 60.3 Total IgA: 27.7 Total IgG: 24.9	Vaccination (time effect) increased the number of memory, IgA + memory, IgG + memory, NCS memory, and total IgG + B cells in young subjects

plantarum (6.9×10^5 and 6.4×10^5 cells/g in the probiotic and control group, respectively) and *L. paracasei* (from 9.7×10^4 to 1.4×10^6 and 1.8×10^6 cells/g in the probiotic and control groups, respectively) after 2 and 12 weeks.

The *Lactobacillus* and *Bifidobacterium* count in the probiotic group increased (≥10-fold) while the *Bacteroides* count in the probiotic group after 8 weeks was significantly lower than in the control group. There was no significant difference in the count of *Clostridium leptum*, Enterobacteriaceae, and *Enterococcus* between the control and probiotic groups (Berggren et al., 2011).

Clinical and respiratory symptoms

Incidence, prevalence and duration of respiratory infection symptoms were significantly lower in the probiotic groups, especially sore throat and cough. The incidence of local respiratory

Table 3
Ongoing clinical trials studies of probiotic intervention for the management of the COVID-19.

Study Start Date/ Reference	Country	Study Design	Participants Characteristics	No. of Participants (age)	Probiotics	Days	Dose (CFU)		Comparators	Outcomes
November 16, 2020/ NCT04621071	Canada	RDBPCT	COVID-19 patients that Self-caring at home	84(≥18)	2 strains of probiotics	25	1×10^{10}	Oral, o.d /2capsule	placebo	Duration and severity of symptoms, effect on oral and fecal microbiota
May 4, 2020/ NCT04390477	Spain	OLRCT	COVID-19 patients requiring hospitalization	40(≥18)	Probiotics	30	1×10^{9}	Oral, o.d/ 1capsule	No Intervention	Cases with discharge to ICU or home, evolution of mortality and safety of treatment, detection of new cases of SARS-Cov-2 infection among healthcare personnel
July 16, 2020/ /NCT04458519	Canada	Single-blinded, randomized, prospective trial	COVID-19 patients that Self-caring at home	40(18–59)	Probiorinse of *Lactococcus Lactis* W136	14	2.4×10^{9}	Nasal irrigation/ b.i.d	Saline solution	Change in severity of COVID-19 infection, number of days with any symptom of anosmia, number of days where rescue medication is required
April 24,2020/ /NCT04366180	Spain	RDBPCT	Active healthcare personnel without COVID-19	314(≥20)	*Lactobacillus* K8	60	3×10^{9}	Oral/o.d/ 1 capsule	placebo	Incidence of SARS CoV-2 infection in healthcare workers, evaluation of clinical symptoms and medical treatment
April 1, 2020/ /NCT04666116	Spain	SBRCT	COVID-19 patients admitted with infection secondary	96(18–99)	Probiotics	365	N. D	N. D	No dietary supplementation	Viral load during the period of admission to the nasopharyngeal smear, evaluation of clinical indicator, analytical parameters, mobility, microbiome analysis in feces
August 19, 2020 /NCT04517422	Mexico	RDBPCT	COVID-19 patients requiring hospitalization	300(18–60)	*L. plantarumL. plantarum* CECT7481 *L. plantarum* CECT 7484 CECT 7485 *P. acidilactici* CECT 7483	30	N. D	Oral/ capsule	Placebo	Severity progression of COVID-19, stay at ICU, mortality ratio, lung abnormalities, viral load, levels of immunoglobulins, gastrointestinal manifestations, fecal microbiome, adverse events, change in serum biomarkers
March 26, 2020/ NCT04366089	Italy	SBRCT	COVID-19 patients requiring hospitalization	152(≥18)	*S. thermophilus* DSM322245 *B. lactis* DSM 32246 *B. lactis* DSM 32247 *L. acidophilus* DSM 32241 *L. helveticus* DSM 32242 *L. paracasei* DSM 32243 *L. plantarum* DSM 32244 *L. brevis* DSM 2796	21	2×10^{11}	Oral/ b.i.d/ 6 sachets	Standard of care	Delta in the number of patients requiring orotracheal intubation despite treatment, delta of crude mortality and mobility, delta in the value of interleukin (IL)-1, IL-6, IL-10, TNF-alpha, cluster of differentiation, fecal calprotectin, lipopolysaccharide, zonulin, alpha1-antitrypsin
June 24, 2020/ NCT04399252	United States	RDBPCT	People with household	1000(≥1)	*L. rhamnosus* GG	28		Oral/o.d/ 2 capsule	Placebo	Change in Shannon diversity, change in

Table 3 (*Continued*)

Study Start Date/ Reference	Country	Study Design	Participants Characteristics	No. of Participants (age)	Probiotics	Days	Dose (CFU)		Comparators	Outcomes
			contact of COVID-19							Shannon diversity in patients that develop COVID-19
2020-07-18/ IRCT20101020004976N6	Iran	RDBPCT	Personnel of the emergency department in contact with hospitalized COVID19 patients	80(≥18)	Lactocare® synbiotic	30	N. D	Oral/ o.d/ 1 capsule	placebo	fever, findings of CT scan and CXR, number of lymphocytes, WBC and infection by COVID-19, cough and sore throat, nausea, vomiting and diarrhea
CHICTR2000029974	China	OLRCT	Mild or moderate novel coronavirus pneumonia (NCP) patients	300(≥18)	probiotics	N. D	N. D	N. D	standard treatment	Cough, all-cause mortality, time to effervescence, time to clinical recovery, Gastrointestinal symptom, chest CT, mechanical ventilation, SARS-CoV-2 RT-PCR

RGCID: respiratory and gastrointestinal common infectious diseases; RDBPCT: randomized double-blind placebo-controlled trial; OLRCT: open Label randomized controlled trial; SBRCT: single-blinded randomized controlled trial; SBRPT: Single-blinded randomized prospective trial; b.i.d.: twice daily, wks.: weeks, d: days, o.d: once daily.

symptoms (sore throat, cough, and/or nasal congestion) was approximately 42% lower in the probiotic groups compared to the control groups (P = 0.007) (Wang et al., 2018).

Quality of life (QOL)

Patients' QOL was assessed by interview with questions associated with lifestyle and health status. Questions covered the following items were asked twice, once before the start and once after the end of the treatment course: physical functioning, group performance, body pain, general health perception, vitality, social functioning, the role of emotion, and mental health. The post-intervention score of the general health perception subscale in the probiotic groups was significantly improved compared with the control groups (King et al., 2014).

Virological findings and probiotic intervention

Of the 27 clinical trials reviewed, 4 detected effects of probiotics on reducing viral load (Gleeson et al., 2016; Kumpu et al., 2015; Lehtoranta et al., 2014; Turner et al., 2017). The immune response to viral infections was significantly increased in the probiotic-treated groups. Probiotics also decreased viral titer in the respiratory system and the proportion of subjects shedding the virus in nasal secretions (56% in the probiotic groups, 91% in the control groups).

In a trial by Lehtoranta et al. fewer viruses were detected in the probiotic group than in the control group, including picornavirus, influenza A and B viruses, respiratory syncytial viruses (A and B), human parainfluenza viruses type 1 to 4, adenovirus, and human metapneumovirus. The number of picornaviruses (mainly respiratory viral) in the probiotic group was 3 times lower than in the control group (P = 0.0069) of the study (Lehtoranta et al., 2014).

Many studies have shown the role of probiotics in reducing respiratory infections, however, there are also some studies suggesting the opposite. For example, Gleeson et al. showed that the incidence of URTI symptoms was unexpectedly low (mean 0.6 per individual), and there was no significant difference between the probiotic and control groups. The duration and severity of URTI symptoms were not influenced by probiotics (Gleeson et al., 2012).

Turner et al. (2017) indicated that there was no significant difference between the probiotic (*B. animalis* subsp. *lactis* Bl-04) and control groups in terms of the serum level of CXCL10, IL-6, GCSF, CXCL8, IL-1β, and CCL2; decrease in viral titers (RV-A39); and shedding of virus in nasal secretions (P = 0.02) (Turner et al., 2017).

Ongoing clinical studies of probiotics effects in COVID-19

Probiotics have been considered in clinical trials to reduce the clinical presentation and severity of COVID-19. To the best of the authors' knowledge, no published studies have so far reported the use of probiotics as a supportive treatment for the management of COVID-19.

There were 10 ongoing clinical studies (commencing between January 2020 and January 2021) identified on probiotic intervention in COVID-19, these are shown in Table 3. Some of these studies did not specify the exact type of probiotic being studied but most examined lactobacilli. Scientists in Canada are exploring whether probiotics could potentially reduce the duration and severity of symptoms and rebalance oral and fecal microbiota. Also in Canada, a study on the effect of *Lactobacillus lactis* W136 on the severity of COVID-19 infection is considering the number of days with any symptom of anosmia and the number of days where rescue medication is required. Researchers from Spain are conducting 3 separate research studies to determine the effect of probiotics on: (i) incidence of SARS-CoV-2 infection in healthcare workers; (ii) patient viral load, clinical indicators, mobility, and microbiome analysis in feces; and (iii) patient mortality and safety of treatment. A study in Mexico is looking at the combined effect of *L. plantarum* CECT7481, *L. plantarum* CECT 7484, *L. plantarum* CECT 7485, and *Pediococcus acidilactici* CECT 7483 on the severity and progression of COVID-19, including duration of stay in the intensive care unit, mortality ratio, lung abnormalities, viral load, levels of immunoglobulins, gastrointestinal manifestations, fecal microbiome, AEs and serum biomarkers. Scientists in Italy are exploring whether specific strains of *Streptococcus thermophilus* DSM322245, *Bifidobacterium lactis* DSM 32246, *B. lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *L. paracasei* DSM 32243, and *L. plantarum* DSM 32244 could affect the number of patients requiring orotracheal-intubation despite

treatment; mortality and mobility; values of IL-1, IL-6, IL-10, TNF-α, cluster of differentiation, fecal calprotectin, lipopolysaccharide, zonulin and alpha1-antitrypsin. Researchers from Iran are investigating the effect of Lactocare® symbiotic on fever, findings of computed tomography scan and chest x-ray, number of lymphocytes, white blood cell count and infection by COVID-19, cough and sore throat, nausea, vomiting, and diarrhea. Researchers in Belgium, the United States and China are also looking at probiotics for improving treatment for COVID-19 patients.

Discussion

Previous studies have reported that the total annual cost of non-influenza-related viral respiratory tract infections approaches US $40 billion (Berggren et al., 2011). One of the most important causes of respiratory infections is influenza, which is the leading cause of morbidity and mortality in the USA among VRTIs, leading to approximately 19 000–36 000 deaths and 200 000 surplus hospitalizations per year (Davidson et al., 2011; Fiore et al., 2010). COVID-19, a respiratory viral infection, has swiftly extended into a global pandemic with significant health and economic burden. To date, there is no approved remedy or prophylactic remedial strategy for COVID-19. The overall cost of SARS-CoV-2 to the global economy has been estimated to be between US$30 billion and US $100 billion. Treatment of this respiratory disease is often symptomatic and oxygen therapy is the mainstay of treatment for patients with severe infections. In cases of oxygen-resistant respiratory failure, for controlling septic shock, mechanical ventilation may be necessary (Lythgoe and Middleton, 2020).

Other COVID-19 treatments used so far include systemic corticosteroids not recommended for the treatment of viral pneumonia or ARDS. Methods such as lopinavir/ritonavir (100/400 mg every 12 h), chloroquine (500 mg every 12 h), and hydroxychloroquine (200 mg every 12 h) have been suggested for treatment. Treatments reducing the period of infection, the rate of infection, the severity of symptoms, and the mortality rate are of chief interest for individuals, the entire society, and treatment staff. Unreflective or inappropriate administration of antibiotics should be avoided. Professionals are proposing diverse alternative drugs like Ayurveda, Siddha, herbal medicines, and other related therapeutic approaches to control COVID-19 (Hu et al., 2020).

This review aimed to comprehensively evaluate the effectiveness of probiotics in the control, prevention, and/or treatment of RTIs, which may also be effective against COVID-19. Most applications and studies on probiotics are confined to the gastrointestinal tract because of their significance and traditional use in this area. However, recent RCTs on the use of probiotics on RTIs have emerged because of their broad range of applications and their potential effectiveness in the control or therapy of some infections, including allergic and atopic dermatitis (Prince, 2020). Our review of previous studies showed that probiotics' impact on common URTIs or viral infections was widely evaluated in RCTs and in numerous reviews and meta-analyses (e.g. King et al., 2014; Prince, 2020; Shin et al., 2015). This systematic review aimed to evaluate the outcomes of clinical trials assessing the efficacy of the probiotic in RTI treatment over the past 10 years.

Of the 27 clinical trials reviewed, 3 studies showed that probiotics did not play a significant role in boosting the immune system and improving the body's defenses against diseases. The discrepancies in response to probiotic treatment in different studies might be due to the differences in the characteristics of the host (age, sex and lifestyle), differences in URTI incidence, insufficient number of subjects, the season of study, the dose of regimens, duration of treatment, severity of the disease, the single or multi-strain formulation used, delivery modes, and so on, which require further detailed investigation.

The exact mechanisms of action of probiotics on RTI are not yet known. The action of probiotics seems to be specific to particular species and strains. There appear to be several mechanisms in probiotic function, depending on the probiotic's specifications and target diseases. However, it seems that probiotics have a similar effect in general so that many of the mechanisms of anti-inflammatory actions of probiotics in the gut system might be applied to the respiratory tract (Prince, 2020). Inflammation plays a fundamental role in the pathogenesis of COVID-19; an imbalance between pro-inflammatory and anti-inflammatory cytokines, resulting in a cytokine storm, is currently considered a major factor in the expansion and development of COVID-19 (Hao et al., 2015). Thus, the homeostatic balance between Treg (IL-10) and Th17 (IL-17) cells is disturbed in COVID-19. Intestinal epithelial cells could secrete and reply to different cytokines via the presentation of CD1d, as an MHC-like molecule producing anti-inflammatory cytokine IL-10 since the activation of STAT3 (Hao et al., 2015).

Dendritic cells (DCs), a heterogeneous family of immune cells, are one of the key factors in regulating immune responses by linking innate and acquired immune responses through accurately recognizing pathogenic and endogenous inflammatory signals. They are subdivided into plasmacytoid DCs (pDCs), myeloid DCs (mDCs) and CD8 dendritic cells. pDCs are a rare and essential subset acting as a "control tower" in viral infections by producing a large number of interferons (IFNs) (Lythgoe and Middleton, 2020). In macrophage cell culture *L. rhamnosus* LC705 hinders influenza A viral replication and viral protein production by inducing type I interferon-related gene activation (Lythgoe and Middleton, 2020). In some studies, the probiotic *L. lactis* JCM5805 has been reported to decrease common cold symptoms and activate human pDCs among peripheral blood mononuclear cells, especially in a subgroup of healthy candidates initially demonstrating low pDC activity (Rizzardini et al., 2012).

The role of pDCs and type 1 IFNs in viral and bacterial infections is complex: pDCs use specific TLRs to detect bacteria and viruses. Among TLRs, TLR9 diagnoses microbial nucleic acids through detecting unmethylated CpG motifs of DNA, and TLR7 recognizes microbial RNA or synthetic guanosine analogs. The activation of pDCs by TLR ligand binding contributes to the production of type 1 IFNs as the first-line defense against infection, which acts through blocking viral replication. The production of type 1 IFNs is often associated with viral infections, and it is well known that pathogenic bacteria stimulate IFN-α production. However, non-pathogenic bacteria including probiotics used in food preparation, have been less intensively studied regarding their potency to stimulate DC-mediated IFNs induction. In a study, various lactic acid bacteria were examined for their ability to stimulate pDCs-mediated IFN-α production, leading to the identification of *L. lactis* JCM 5805 probiotic as a strong stimulator of type 1 IFN production (Kawai and Akira, 2011; Prince, 2020; Swiecki and Colonna, 2015).

Another important factor playing an important role in regulating the antiviral immune responses is NK cells; the cytotoxic activity of NK cells involved in host defense against viral infections is stimulated by IFN-α. Rask et al. showed that the use of *L. paracasei* increased the count of NK T cells ($P = 0.06$) as well as the expression of the memory marker CD45R0 on the surface of CD8+ lymphocytes. In this study, an increase was observed in the phagocytic activity of polymorphonuclear leukocytes and monocytes isolated from patients treated by either *L. paracasei* ($P = 0.05$) or *L. plantarum* strains ($P = 0.06$) compared to placebo (Rask et al., 2013). Charlson et al. injected *L. rhamnosus* GG strains to mice nasally for 3 days to provoke the cytotoxic activity of pulmonary NK cells and then infected them with influenza virus H1N1, resulting in a significant increase in the secretion of IL-1 and TNF-α. They concluded that these effects could be the cause of better

survival of treated mice (60%) after 15 days compared with the control mice (20%) (Charlson et al., 2011). Several RCTs have shown different effects of probiotic strains on different innate immune markers (Cox et al., 2010; Olivares et al., 2007; Rautava et al., 2006; Schiffrin et al., 1995). However, a typical viral infection challenge in the immune system increases the cascade of immune functions by increasing cytokines, NK activity and phagocytosis in the early days of infection, which are gradually replaced by viral antigen-specific T cells responses (Burleson and Burleson, 2007; Calder, 2007). The liberation of soluble agents by probiotics could increase the processes of immune cells or epithelial cells that subsequently affect immune cells. Also, probiotics could regulate the activity of the immune system near or far from the target organ (Darbandi et al., 2019; Shin et al., 2015).

Many clinical trials have shown that probiotics stimulate the antibody response to viral vaccination (Aubin et al., 2008; Boge et al., 2009; Davidson et al., 2011; Namba et al., 2010). In this review, the most common probiotic species studied in vaccination was found to be *Lactobacillus*, while 1 study examined *B. longum*, and 1 study examined the effect of a combination of *Lactobacillus* and *Bifidobacterium*. Namba et al. used *B. longum* BB 536 strain as an adjuvant to enhance the immune response to the influenza vaccine, which resulted in the enhancement of antibody titers and cell-mediated immunity when administered to the elderly (Namba et al., 2010). De Vrese et al. also reported similar results, indicating an enhancement in poliovirus-neutralizing antibody and poliovirus-specific IgA and IgG titers when LGG was administered 1 week before oral administration of the polio booster (de Vrese et al., 2005). Evaluation of the immune benefits of 2 probiotic strains of *B. animalis* subsp. *lactis* BB-12 and *L. paracasei* subsp. *paracasei, L. casei* 431 in an influenza vaccination model by Rizzardini et al. indicated that an increase in specific IgG was significantly greater in both probiotic groups compared to the placebo group. A significant increase in both IgG1 and IgG3 after probiotic supplementation in this research suggests that the activities of both T-helper (Th)1 and Th2 lymphocytes are boosted, as IgG1 and IgG3 are considered to be more representative of Th2 and Th1 responses, respectively. In addition to being preferentially associated with Th1 and Th2 T-cell subsets, IgG1 and IgG3 are also correlated with optimal activation of supplement and phagocytosis by macrophages, respectively (Rizzardini et al., 2012).

The results of the previous studies on humans and animals support the function of different *Lactobacillus* strains in the prevention of influenza infection. In a study on a mouse model of H1N1 influenza infection, intranasal disposal to LGG for 3 days was significantly associated with a lower frequency of accumulated symptoms and also a higher survival rate compared to control mice (Harata et al., 2010). In another study on the same mouse model of influenza infection, oral administration of LGG or *Lactobacillus* TMC0356 for 19 days resulted in lower clinical symptom scores and pulmonary viral titters in comparison with control mice (Kawase et al., 2010).

Based on the safety measures of the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, the annual influenza vaccination is currently recommended for all adults and children >6 months (Fiore et al., 2010). Although the highest morbidity and mortality rates are among young children and the elderly, studies have shown that the influenza vaccination in healthy adults reduces both direct and indirect medical costs such as visiting a doctor, prevents co-infections with bacteria and viruses, and use of antibiotics. Therefore, probiotic use is recommended to further increase immunization of vaccination (Nichol et al., 1999; Wilde et al., 1999). A study by the North Carolina State University on Coronavirus disease is engineering *L. acidophilus* probiotics expressing SARS-CoV-2 proteins to be tested as potential vaccines (Hu et al., 2020).

The discussion over the superiority of different species/strains of probiotics is very complex. Because of the strain-specific abilities of probiotics and the different categories of patients, a specific probiotic might not be suitable for all patients (Zocco et al., 2006). Most probiotic products include species of *Lactobacillus* and *Bifidobacterium* genera, which modulate the gut microbial population and enhance intestinal barrier function (Kleerebezem and Vaughan, 2009; Li et al., 2016). It is believed that probiotics could modulate intestinal microbiota and stabilize the beneficial microbial population by competing with pathogenic bacteria for nutrients and adhesion sites and producing metabolites. Yoshimatsu et al. showed that probiotic therapy was most beneficial for patients who initially had cluster-I microflora rather than cluster-II flora (Yoshimatsu et al., 2015). In a study, the effects of LGG on the prevention of experimental rhinovirus infections in healthy volunteers were investigated. The severity of cold symptoms and the frequency and number of patients with rhinovirus infection in the LGG group were lower than in the control group, although there was no significant difference between the study groups (Kumpu et al., 2015; Van Puyenbroeck et al., 2012). A placebo-controlled phase 2 trial at Duke University will measure if the probiotic *L. rhamnosus* GG has a function in hindrance and cure of COVID-19 infection (Prince, 2020). In another study, children with cryptosporidium diarrhea infection given LGG showed a significant improvement in intestinal permeability (Hu et al., 2020). The exact mechanism of action of probiotics on the immune system is not fully understood. However, LGG has been shown to modulate innate and adaptive immune responses by increasing serum IgG and IgA levels and targeting intestinal pathogens such as rotavirus (Kumpu et al., 2015; Prince, 2020).

Most studies on microbiota in the human body have been conducted on the intestinal tract, however, studies on the respiratory tract are expanding and advancing owing to novel biotechnologies (Gollwitzer and Marsland, 2014). It is hard to assure that respiratory microbiota constituents and mechanisms are analogous to intestinal microbiota in expanding and protecting the immune activities of the lung. There is some evidence to suggest that there are relationships between the respiratory microbiota and many lung diseases and that changes in respiratory microbiota could cause illness in a human. Thus, it could be suggested that probiotic bacteria potentially control the intestinal inflammatory responses by confirming the gut mucosal barrier and the microbial environment as well as by degrading enteral antigens and changing their immunogenicity (Darbandi et al., 2019). The results of another study showed that inter-personal diversity in the gut microbiome will affect the effectiveness of suggested microbiota interventions for SARS-CoV-2 infection. Since the onset of COVID-19 different antiviral drugs have been studied to treat the SARS-CoV-2 virus; on 1 May 2020, an antiviral drug called Remdesivir became the first US Food and Drug Administration-approved emergency drug to treat COVID-19 (Grein et al., 2020). Although the results of the observations do not provide any direct evidence of the interaction of the intestinal microbiome with Remdesivir, some observe that there is a history of modification of the intestinal microbiome by other antiviral drugs (Domínguez-Díaz et al., 2019).

No published studies have reported the use of probiotics as a supportive treatment for the management of COVID-19 (Table 3). However, the International Scientific Association of Probiotics and Prebiotics has highlighted that scientists and clinicians globally are investigating the relationship between the gut microbiome and susceptibility to COVID-19 and assessing the role of various probiotics strains to lower viral load via different mechanisms (Hu et al., 2020).

Most of the properties of probiotics are strain-specific and multi-species probiotics may be more efficient than mono-species probiotics in the treatment of certain clinical conditions. For example, Rerksuppaphol et al. reported that administration of a 2-strain probiotic combination (*L. acidophilus* 10^9/ capsule and *B. bifidum* 10^9/ capsule) to school children aged 8–13 twice daily for 3 months during winter resulted in a significant decrease in respiratory symptoms including fever and cough as well as the length of absenteeism from school compared to placebo (Rerksuppaphol and Rerksuppaphol, 2012). Although there are conflicting data regarding the effects of probiotics on RTI treatment (Jespersen et al., 2015; Kinoshita et al., 2019; Kumpu et al., 2015), 8 extensive studies reviewed in the current research showed that the probiotic cocktail VSL#3 could successfully induce RTI remission among patients.

The results of many studies suggest that probiotics as health supplements and treatment agents are safe (Ahrén et al., 2021). However, the side effects of probiotics should be controlled when used in a specific population. According to the literature search, 2 trials showed side effects of probiotic consumption. Ahrén et al reported that there was no significant difference between the study groups in the incidence and the overall number of side effects reported by children. However, more gastrointestinal side effects in the probiotic group compared to the control group seem to be explained by a higher frequency of vomiting, an AE was also reported in other studies following the administration of probiotics to young children (Ahrén et al., 2021).

Ongoing studies in different countries are looking at whether probiotic strains, especially lactobacilli, in the respiratory tract can decrease viral activity through multifactorial function, barrier and anti-inflammatory, and the risk of secondary bacterial infections for COVID-19 patients. Scientists are also developing special strains of lactobacilli with immunostimulants to support the intranasal SARS-CoV-2 immunization or potentially for a genetically engineered antigen-producing organism for vaccine transfer. Another RCT showed the role of the gut microbiota in rendering a good antibody response against influenza, demonstrating that gut microbiota could change the response for vaccines (Hagan et al., 2019).

Many studies have shown that a mixture of probiotics or prebiotic-synbiotic combinations could improve RTIs and clinical symptoms in treated patients in all age groups. For example, a clinical study by Sazawal et al. on 1-4 year-old children reported the beneficial effect of adding prebiotics oligosaccharide and *B. lactis* HN019 to milk in preventing and controlling severe respiratory infections and preventing diarrhea in this group (Sazawal et al., 2010). Similarly, a RCT showed that consumption of a probiotics-containing dairy drink was able to reduce the occurrence of dysentery episodes by 21% (95% CI: 0–38%; $P = 0.05$); pneumonia by 24% (95% CI: 0–42%; $P = 0.05$); severe acute lower respiratory infection by 35% (95% CI: 0–58%; $P = 0.05$); and the duration of disease severity and high fever by 16% (95% CI: 5–26%, $P = 0.004$) and 5% (95% CI: 0–10%; $P = 0.05$), respectively (Guillemard et al., 2010; Makino et al., 2010).

The optimal combination and dose of probiotics for the treatment of diseases has not yet been determined. However, it is commonly asserted that 10^8–10^9 CFU/g of probiotic should be used daily to deliver a minimum concentration of 10^6 viable cells into the intestine to exert positive effects on the host (Knorr, 1998; Neffe-Skocińska et al., 2018). In the RCTs assessed in this review, probiotics were administered at doses between 1×10^9 to 1×10^{11} CFU for 6 and 12 weeks. From treatment results of patients with RTI, the best-recommended dose was 5.05×10^{10} CFU/g an average, showing good efficacy in reducing respiratory symptoms, reducing the duration of the disease, and increasing immunity. Some studies have shown that a probiotic dose higher or lower than 5.05×10^{10} CFU/g is only effective in increasing QOL and response to general symptoms (Lorenzo-Zúñiga et al., 2014). Not all the probiotic effects on human health seem to be related to the viability of bacteria since even heat-killed probiotic bacteria or probiotic-derived DNA were shown to have the potency to improve significant health problems (Arimori et al., 2012; Hirose et al., 2006; Merenstein et al., 2010).

Conclusion

We conclude from the literature review that the benefit of probiotics and synbiotics as prophylactic and complementary treatment in patients with RTI is a promising preventive strategy to reduce the severity of respiratory infection symptoms, reduce the duration of disease, improve QOL, and induce and maintain remission in patients with RTI. Therapeutic strategies such as the optimal dose, duration or specific probiotic species to be used are yet to be agreed upon.

This systematic review of broad clinical-based studies with multi-center activities from different countries will progress our understanding for determining the potential use of probiotics and/or prebiotics in the context of SARS-CoV-2.

Author Contributions

Atieh Darbandi, Malihe Talebi, and Maryam Kakanj initiated the idea of this study. Arezoo Asadi and Roya Ghanavati contributed to data collection, interpretation and final approval of data for the work. Atieh Darbandi and Roghayeh Afifirad developed the first and final draft of the manuscript. Amir Darb Emamie developed the second draft of the manuscript. All figures and tables were designed and checked by Atieh Darbandi and Arezoo Asadi. Malihe Talebi and Maryam Kakanj critically reviewed and revised the manuscript. All authors reviewed and contributed to the revisions and finalized the drafts.

Conflict of interest

The authors report no conflict of interest.

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Ethical approval

The ethical committee of Iran University of Medical Sciences provided and endorsed the ethical approval for this study (IR.IUMS.REC.1399.1046).

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