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Modulatory Effects of Probiotics During Pathogenic Infections With Emphasis on Immune Regulation

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In order to inhibit pathogenic complications and to enhance animal and poultry growth, antibiotics have been extensively used for many years. Antibiotics applications not only affect target pathogens but also intestinal beneficially microbes, inducing long-lasting changes in intestinal microbiota associated with diseases. The application of antibiotics also has many other side effects like, intestinal barrier dysfunction, antibiotics residues in foodstuffs, nephropathy, allergy, bone marrow toxicity, mutagenicity, reproductive disorders, hepatotoxicity carcinogenicity, and antibiotic-resistant bacteria, which greatly compromise the efficacy of antibiotics. Thus, the development of new antibiotics is necessary, while the search for antibiotic alternatives continues. Probiotics are considered the ideal antibiotic substitute; in recent years, probiotic research concerning their application during pathogenic infections in humans, aquaculture, poultry, and livestock industry, with emphasis on modulating the immune system of the host, has been attracting considerable interest. Hence, the adverse effects of antibiotics and remedial effects of probiotics during infectious diseases have become central points of focus among researchers. Probiotics are live microorganisms, and when given in adequate quantities, confer good health effects to the host through different mechanisms. Among them, the regulation of host immune response during pathogenic infections is one of the most important mechanisms. A number of studies have investigated different aspects of probiotics. In this review, we mainly summarize recent discoveries and discuss two important aspects: (1) the application of probiotics during pathogenic infections; and (2) their modulatory effects on the immune response of the host during infectious and non-infectious diseases.

Keywords: antibiotic resistant bacteria, antibiotics alternative, probiotics, pathogenic infections, immunomodulating

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INTRODUCTION

The term probiotic is derived from the Greek word (προβιοτικό: πρό and βἰός) meaning "for life" (1, 2). Probiotics have a very old history since their first description; the first clinical trial investigating the remedial effects of probiotics in constipation was started in 1930 (3). Probiotics have a wide range of applications in poultry, livestock, aquaculture, and also in

humans for the prevention and treatment of disorders, ailments, and infectious and non-infectious diseases (e.g., bacterial, viral, parasitic, or fungal diseases, nervous system disorders, obesity, cancer, and allergic problems), as well as preoperative and postoperative processes. Nowadays, probiotics are an inevitable part of human nutrition with elevated consumption levels through naturally and microbially fermented products with enormous amounts of viable beneficial microbes, such as fermented animal products, fermented fruits and their juices, and various other food products (4). Different probiotics like *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus*, *Enterococcus*, *Vagococcus*, *Bacillus*, *Clostridium butyricum*, *Micrococcus*, *Rhodococcus*, *Brochothrix*, *Kocuria*, *Pseudomonas*, *Aeromonas*, *Shewanella*, *Enterobacter*, *Roseobacter*, *Vibrio*, *Zooshikella*, *Flavobacterium,* and some yeasts are commonly used probiotics to control infectious diseases as well as to improve health and quality of aquaculture production (5, 6). The application of specific probiotics culture in the poultry and livestock industry has become very common in recent days. Many economically important poultry diseases like Salmonellosis, Clostridial diseases, Coccidiosis etc., respond positively during probiotics treatment (7). Genus *Bacillus*, *Pediococcus*, *Lactobacillus*, *Enterococcus*, *Streptococcus*, *Aspergillus*, and *Saccharomyces* are usually used in poultry (1).

To increase meat production and inhibit pathogenic growth, antibiotics are usually supplemented in the feed of poultry and livestock leading to the emergence of antibiotic-resistant bacteria. Antibiotic-resistant bacteria are becoming very common, presenting difficulties to the treatment of clinical infections with current chemotherapeutics, thus effective and novel strategies which will enable the host immune system to combat the infections are urgently needed (8). Probiotics exert beneficial effects to their hosts by diverse mechanisms, e.g., antimicrobial peptide (AMP) production, fatty acids production, stabilization of disturbed intestinal microflora, competitive pathogen exclusion, and modulation of host innate and adaptive immune responses (9). Nowadays, strategies using probiotics as an immunomodulator to control infectious diseases have become popular. Antimicrobial effects of probiotics by modulating the innate and adaptive immune responses of hosts have been extensively reported in numerous *in vitro* and *in vivo* studies.

Immune cells or epithelial cells can express a series of pattern recognition receptors (PRRs). The typical PRRs consist of Toll-like receptors (TLRs), retinoic acid-inducible gene-I-like receptors (RLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), and C-type lectin receptors (10). Pathogen-associated molecular patterns (PAMPs) of probiotics interact with PRRs to initiate appropriate signaling pathways for the expression of different genes and subsequent production of immune mediators, which help the hosts to counteract the pathogenic infections (11). Besides these immune remedial effects, probiotics also provide other health-promoting effects on hosts. Indigenous microbiota possess different biological activities extending from anabolism to catabolism of large molecules, resulting in beneficial effects on host health as well as microbiota themselves. Intestinal microflora can ferment endogenous mucus and indigestible diet residues and produce vitamins, such as vitamin K and B (12). The following sections of this review provide a brief introduction to probiotics and discuss the mechanism of probiotic functions and their application during pathogenic infections.

HISTORY OF PROBIOTICS

In the early 1900s, Louis Pasteur asserted that microorganisms were responsible for food fermentation, while Élie Metchnikoff stated that the increased longevity of individuals living in the rural areas of Bulgaria was closely associated with the daily consumption of fermented dairy products, such as yogurt. He claimed that lactobacilli could mitigate the putrefactive effects of gastrointestinal metabolism, which contributed to diseases and aging. Approximately 2,000 years earlier, Hippocrates claimed that "death sits in the bowl" (13). Fermented foods have a long history; fermented milk can be traced back to the Neolithic age. The fermentation of milk was first reported around 10,000 BC in the Middle East and India, and around 7,000–5,000 BC in Egypt, Rome, Greece, and the rest of Europe. The first appearance of soy sauce is estimated around 4,000 BC and 3,000 BC in China, Japan, and Korea; fermented rice first appeared around 2,000 BC in Asia. Fish sauce originated from northern Africa and South East Asia around 1,000 BC. The use of wine possibly started in North Africa around 3,000 BC, and subsequently expanded in the Middle East, Greece, Egypt, and Rome. The use of beer may have started around 7,000 BC in China and probably around 5,000 BC in Mesopotamia (2, 14) (**Table 1**).

SELECTION CRITERIA AND HEALTH BENEFITS OF COMMONLY USED PROBIOTICS

A number of microbes have been used as probiotics. The number of microbial organisms with probiotic characteristics is remarkable. Among them, lactic acid bacteria (LAB) are a group of non-spore forming, Gram-positive rods or cocci with tolerability to markedly low pH; they are fermenters of carbohydrates and use carbon as final electron acceptors. LAB have a wide range of applications and are the most commonly used probiotics (15, 16). They are classified on the basis of their cellular morphology and glucose fermentation mode, into Phylum-Firmicutes, Class-Bacilli, and Order-Lactobacillales. Currently, the LAB genera include *Lactobacillus*, *Streptococcus*, *Leuconostoc*, *Carnobacterium*, *Lactococcus*, *Aerococcus*, *Enterococcus*, *Pediococcus*, *Oenococcus*, *Weissella*, *Alloiococcus*, *Tetragenococcus*, *Dolosigranulum*, and *Vagococcus* (17, 18). The most frequently utilized genera of bacteria used in probiotic formulations are *Lactobacillus*, *Enterococcus*, *Streptococcus, Bacillus*, and *Bifidobacterium*, as well as some fungal strains of the genus *Saccharomyces*, such as *Saccharomyces boulardii* (*S. boulardii*). Most of these are regarded as the intestinal commensal microbiota (2).

The process for the identification of newly-isolated probiotic candidates is the first problem that needs to be addressed. From isolation to market launching, knowledge needs to be collected

TABLE 1 | Some fermented foods history and origin.

Food origin	Aproximate appearance year	Region
Fermented milk	10,000 BC	Middle East
Product of fermented milk	7,000–5,000 BC	Egypt, Italy, Greece
Mushroom	4,000 BC	China
Wine	3,000 BC	North Africa, Middle East, Europe
Soy sauce	3,000 BC	China, Korea, Japan
Fermented honey	2,000 BC	Middle East, North Africa
Fermented rice	2,000 BC	China, Asia
Fermented malted cereals: beer	2,000 BC	China, Middle East, North Africa
Chees	2,000 BC	China, Middle East
Fermented meats	1,500 BC	Middle East
Bread	1,500 BC	Egypt, Europe
Pickled vegetables	1,000 BC	China, Europe
Fish sauce	1,000 BC	Southesat Asia, North Africa
Sourdough bread	1000 BC	Europe
Tea	200 BC	China

on host health, adhesion properties, and resistance to host biochemical environments. Probiotics must be safe, adhere to the lining of intestinal cells with high survival potential, have an immunostimulatory function, have the ability to colonize the tract lumen, withstand exposure to low pH and bile salt, and should have antipathogenic characteristics (19, 20). Other probiotic properties may be considered for selecting probiotic strains with cognitive effects, such as their ability to lower cholesterol, antioxidant function, or cytotoxic impact on cancer cells. Of note, a prospective probiotic does not need to follow or meet all aforementioned selection criteria (21). **Figure 1** shows some properties of good probiotics.

The microbiota inhabiting the animal body provide crucial services to the ecosystem, such as the production of important resources and bioconversion of different nutrients, which are beneficial for both the host and microbes. Microbiota can execute different crucial biological activities, ranging from anabolism to catabolism of large molecules. These biological activities can be beneficial for host health and the microbes. The metabolic functions of intestinal microflora reduce the energy costs of their host, as they ferment endogenous mucus and indigestible food residues, and also produce vitamins such as vitamin K and B (12). Therefore, due to their biological activities, probiotics have positive health effects on hosts, including reduction of the energy required during digestion and provision of beneficial nutrients. Different kinds of commercially available probiotics products are available to boost the health of adults and children (www.probioticchart.ca, www.usprobioticguide.come) (22).

PROBIOTICS ENCAPSULATION

Because of the substantial decrease in their viability in the harsh gastrointestinal environment of the host (gastric pH, protease, lipase, and peristalsis) and during different food processing and storage conditions (high temperature, pH changes, oxygen, and hydrogen), the possible beneficial health effects of probiotics may not be recognized. A number of systems have been designed to improve orally administered probiotics viable number in gastrointestinal tract (GIT), including coating and embedding systems (23). Microencapsulation is an efficient technique that is used to increase the viability and resistance of probiotics against the harsh environmental conditions of GIT and during storage conditions. Microencapsulation is a physicochemical or mechanical process in which probiotics are usually inserted or coated with food-grade materials like lipids, biopolymers, or other hydrocolloidal materials, providing protection against adverse conditions such as heat shock, low pH, bile salts, cold shock, etc. (24). Several studies have been reported that microencapsulation increases the viability of probiotics Encapsulation of *Bifidobacterium longum* with milk increases its viability during storage time (25). *Lactococcus lactis* subsp. *cremoris* LM0230 encapsulation in alginate increases its stability and viability (26). Similarly, *Lactobacillus rhamnosus* GG encapsulation with pectin increases its viability in simulated GIT conditions. Muhammad et al. (27) reported *Lactobacillus plantarum* KLDS 1.0344 ability to alleviate chronic lead toxicity in mice increases when encapsulated with starch originated from tomatoes (27). The study of Riaz et al. (28) shows that the survival rate under simulated GIT conditions of zein-coated alginate *Bifidobacterium bifidum* significantly increases.

POTENTIAL MECHANISMS OF THE PROBIOTIC FUNCTION

The mechanisms of probiotic function are complex, heterogeneous, and specific to probiotic strains. They include competitive exclusion of pathogens (29), ability to colonize the intestine (30), intestinal barrier function improvement by increasing the expression of tight junction proteins and mucin expression along with the interaction of PAMP to PRRs, AMP production (31), and immune system regulation. Some important mechanisms are briefly discussed below.

Competitive Pathogen Exclusion

This refers to a condition in which one bacterial species has a greater potential to attach the epithelia, through a receptor, than other species (11). The known mechanisms of competitive exclusion mainly include lowering the pH in the lumen, contesting for nutrient utilization, and AMP production against competitors (32). Interaction between molecules distributed in the gut epithelia and the surface of bacterial cells mediates the adhesion and colonization of bacteria. Commensal or probiotic bacteria produce adhesive surface molecules (e.g., enolases, glyceraldehyde-3-phosphate, and pyruvate dehydrogenase) and adhere to the extracellular matrix of the host (33, 34). These adhesive surface molecules assist commensal bacteria and probiotics in contesting and preventing pathogenic bacterial attachment and colonization (35, 36). *Lactobacillus fermentum* (*L. fermentum*) competitively binds to collagen I of host epithelial

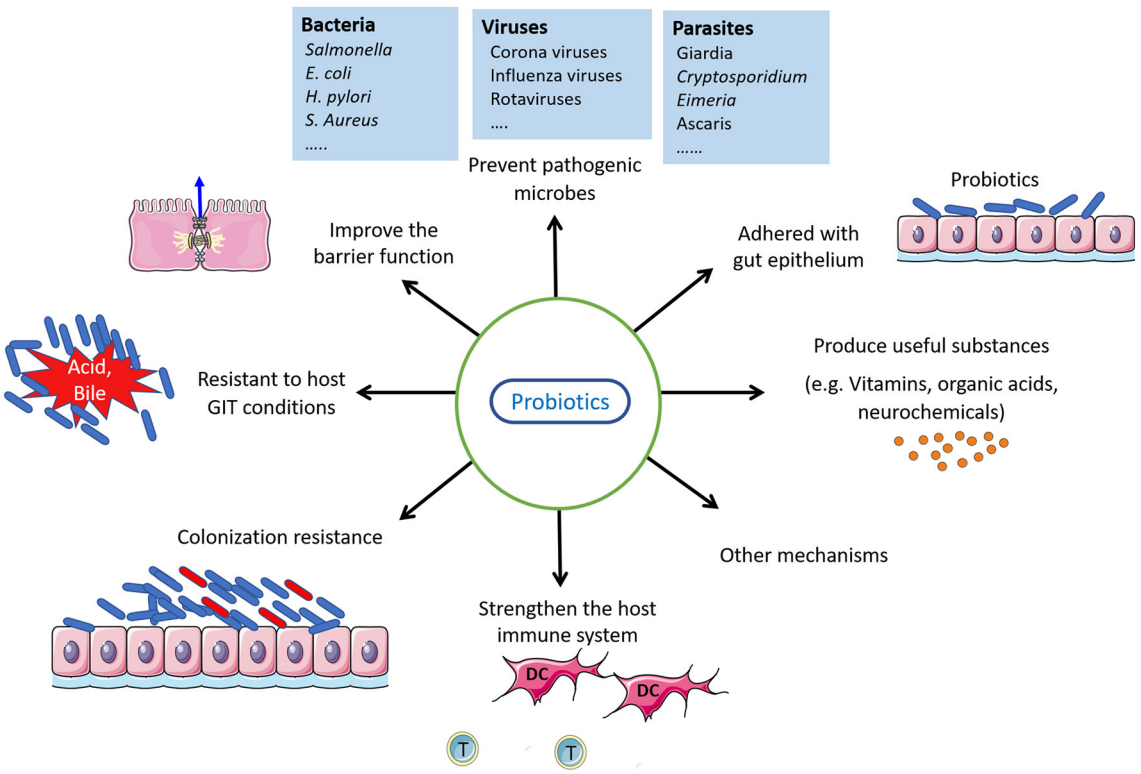

FIGURE 1 | Probiotics properties and their action.

cells by expressing its collagen-binding protein genes and inhibits the binding of *Campylobacter jejuni*. Similarly, *Lactobacillus gasseri* expresses aggregation-promoting factors on their cell surface, which helps in self-aggregation and its binding with the host extracellular matrix fibronectin component. This facilitates the colonization of probiotics and the exclusion of pathogens from the GIT (37). *L. gasseri* also inhibits the adhesion of *Helicobacter pylori* (*H. pylori*) to AGS gastric epithelial cell lines by expressing its Sortase A (srtA) gene, which produces surface molecules that facilitate *L. gasseri* aggregation, as well as binding and adhesion to AGS cell lines (38). Pretreatment with some probiotics impedes pathogenic bacterial attachment to host cell receptor sites by steric hindrance pose, and reduces the colonization of unwanted microbes by producing negative growth factors for pathogens (39). Seaweed *Bacillus* probiotics have good adhesion properties to shrimp intestinal mucosa with competitive exclusion ability and eliminate *Vibrio parahaemolyticus* strain 3HP (40).

Competitive exclusion of probiotics exerts the beneficial effects on the GIT and other organs of the host, increases the adhesion of probiotics, and performs protective actions against pathogens by competing for binding sites of the host. Furthermore, this adhesion of probiotics increases the opportunity for interaction with the host, which favors the immunostimulatory effects of probiotic surface molecules (ligands for receptors of the host) and their metabolites (41, 42). Therefore, the competitive exclusion properties of probiotics offer several benefits to host health, including the reduction of pathogenic attachment, colonization (many diseases arise because of pathogen colonization), further spread of the pathogen, and pathogenic load in hosts. Furthermore, this property of probiotics enables them to colonize the host GIT, which is necessary for the further beneficial action of probiotics to their hosts.

Intestinal Colonization

The potential of probiotics to colonize the intestine is one of the most important properties recommended by WHO/The Food and Agriculture Organization of the United Nations (FAO). The positive characteristics of probiotics, such as antagonisms to harmful microbes or the modulation of the immune system, are linked to their intestinal colonization, which is investigated *in vitro* using simulated intestinal cells, as *in vivo* investigation is difficult (43). The adhesion of LAB with intestinal cells has been extensively reported. Interaction between molecules distributed on gut epithelia and the surface of bacterial cells mediates the adhesion and colonization of bacteria and is highly variable between different bacterial strains. García-Ruiz et al. (44) reported 0.37–12.2% adhesion of wine-isolated LAB (44) and Pisano et al. (45) reported 3–20% adhesion of LAB (45).

Intestinal Barrier Function

As the intestinal epithelial barrier acts as a physical and biochemical barrier and is important for preventing systemic

entry of toxins, bacteria, and other foreign unwanted compounds, so its integrity and full function are quite important. It has been reported in many studies that LAB can improve intestinal epithelial barrier damage induced by pathogenic infection (46–51). Probiotics possess a diverse mechanism of action to improve the intestinal barrier function and maintain homeostasis. "*Lactobacillus* contains a HSP27-inducible polyphosphate (poly P) fraction. Probiotic-derived polyphosphates, strengthen the epithelial barrier function and keep intestinal homeostasis through the integrin-p38 MAPK pathway" (52). *Lactobacillus casei* DN-114 001 and *Lactobacillus acidophilus* strain LB have the potential to improve intestinal epithelial barrier during *Escherichia coli* infection (53, 54). Strains of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* stimulate tight junction proteins (occludin, claudin-1) results in enhanced barrier stability (55). *L. plantarum* WCFS1 significantly increases occludin and ZO-1 in tight junction vicinity by TLR2 dependent pathway and protect tight junction disruption by toxins, pathogens, and cytokines (49). Qin et al., also showed that *L. plantarum* has protective effects on intestinal barrier by rearranging tight junction proteins (occludin, claudin-1, JAM-1 ZO-1) disturbed by *E. coli* and ameliorates barrier function (50). Another strain of *L. plantarum*, MB452 increases occludin expression and improves intestinal barrier integrity (46). *E. coli* Nissle 1917 (EcN) ameliorates *E. coli* induced intestinal epithelial barrier dysfunction by regulating the expression of occludin and claudin (56). *L. rhamnosus* (LR: MTCC-5897) and *L. fermentum* (LF: MTCC-5898) significantly improve the *E. coli* disturbed tight junction proteins (Occludin, ZO-1, cingulin-1, claudin-1) in Caco-2 cells (57).

Several other reports of Lactobacilli study have also been shown that *Lactobacilli* ameliorate the intestinal barrier damage and pro-inflammatory cytokines production induced by *Salmonella* (47, 58). Probiotics are also effective to improve malnutritional induced intestinal barrier damaged as indicated by the study of Garg et al. on a malnutritional mice model, in which they reported that *Lactobacillus reuteri* LR6 feeding significantly improves the intestinal morphology damaged during malnutrition (59).

Antimicrobial Peptide Production

Different criteria are applied to AMP classification according to their source (animals, fungi, plants, and bacteria), mechanisms of action (AMP acting on cell surface molecules or intracellular components), structure (patterns of covalent bonding), and biosynthetic pathway (non-ribosomally synthesized or ribosomally synthesized) (60). Bacteriocins (AMP from prokaryotes) of LAB are classified into three classes: Class I, post-translationally modified (e.g., lantibiotics); Class II, non-modified, heat stable with size <10 kDa (e.g., pediocin PA1, leucocin A, plantaricin A, and enterocin X); and Class III, heat labile, large peptides with size >30 kDa (e.g., helveticin J) (16). Bacteriocins have low molecular weight and form pores in target cell membranes, leading to the death (61) of pathogenic bacteria, and also act as anti-cancerous agents. Furthermore, bacteriocins also possess immunomodulatory properties with pronounced anti-inflammatory effects during pathogenic infections. As bacteriocins are non-toxic, particularly those derived from LAB, they are used in food preservation. A number of studies showed that certain kinds of probiotics inhibit many types of pathogenic bacteria (*proteus* spp., *E. coli*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Listeria monocytogenes, Citrobacter freundii*, *H. pylori*, *Enterobacter aerogenes*, *Compylobacter jejuni*, *Micrococcus luteus*, *Salmonella* spp., *Shigella* spp., and some fungi) by the action of their bacteriocins (62). Bacteriocins from *Lactobacillus salivarius* inhibit foodborne and other medically important bacteria, such as *Listeria monocytogenes*, many genera of *staphylococcus*, *Neisseria gonorrhoeae*, *Bacillus*, and *Enterococcus*; the bacteriocins kill these bacteria by creating membrane pores and subsequent leakage of cellular material. Further, these bacteriocins also assist *L. salivarius* colonization in the intestine without showing any prominent adverse effects on other lactic acid bacteria (63) *L. plantarum* also exerts antimicrobial activities by producing many types of bacteriocins with antimicrobial effects against food spoilage bacteria, such as *Alicyclobacillus acidoterrestris* (64), *Salmonella* spp., *Listeria monocytogenes*, *Staphylococcus aureus*, and *E. coli*; thus, they may be used as preservatives for pork meat (65). Apart from bacteria, some bacteriocins from *L. plantarum* are also effective against yeast and molds, such as *Fusarium*, *Candida*, *Aspergillus*, and *Mucor* (66). Bacteriocins from other probiotic species markedly induce apoptosis and inhibit tumor formation, cancer cell proliferation, and membrane depolarization of cancer cells during treatment (61). There are different classification systems for AMP and, owing to their diverse mechanism of actions, they have a wide range of applications in humans and animals, as well as aquaculture fields (67). They inhibit growth and even kill diverse pathogens by creating pores in their cell membranes, as well as initiating appropriate immune responses.

Immune Regulation

It is well-established that probiotic bacteria exert an immunomodulatory effect and have the potential to communicate and interact with a series of immune cells (e.g., DCs, lymphocytes, epithelial cells, monocytes, and macrophages). The immune response generally comprises the innate immune response and adaptive immune response. Innate immune response responds to PAMPs distributed on the majority of bacteria (11). The principle immune response to any pathogen is activated following the interaction of PRRs (i.e., TLRs, NLRs, and C-type lectin receptors) with PAMPs and initiates cell signaling. Intestinal epithelial cells are the host cells that most extensively come into contact with probiotics. However, probiotics may also interact with DCs, which play a significant role in the innate immune response and bridge the innate and adaptive immune responses. Through their PRRs, both intestinal epithelial cells and DCs can communicate and react to gut microorganisms (68, 69). Under the effects of probiotics/commensal microbiota, the activated DCs induce the appropriate immune response (e.g., naïve CD4 T cells to Treg cell differentiation), which generally inhibits Th1-, Th2-, and Th17-mediated inflammatory response. Furthermore, probiotics blunt intestinal inflammation (70) by downregulating the expression

of TLRs *via* secretion of TNF-α inhibitory metabolites and inhibition of nuclear factor-κB (NF-κB) signaling in enterocytes (68). Probiotics also modulate the expression of various kinds of cytokine production.

Cytokines Mediated Immune Response and Probiotics

Probiotic benefits related to immunoregulation for the treatment of various diseases have been extensively studied. Immunomodulatory effects of probiotics are mainly due to the induction of the release of cytokines including interleukins, transforming growth factor (TGF), tumor necrosis factors (TNFs), interferons (INFs), and immune cells released chemokines, which further regulate the immune system (71, 72). Immunostimulatory and immunoregulatory actions of probiotics have been reported in various studies. Immunostimulatory probiotics are capable of acting against infection and cancer cells, inducing the release of IL-12, which stimulates the NK cells and produces the Th1 cells. By maintaining the balance between Th1 and Th2, these probiotics also work against allergies. Contrary to this finding, immunoregulatory probiotics are attributed to Treg cells and IL-10 production to blunt excessive inflammatory responses, inflammatory bowel disease, and autoimmune disorders (73, 74). So, probiotics immunomodulatory effects *via* cytokines are strain-specific as indicated by the *in vitro* study of Haller et al. (75) using Caco-2 cells in which they reported that *Lactobacillus sakei* is capable of inducing pro-inflammatory cytokines (IL-1β, TNFα, and IL-8) whereas *Lactobacillus johnsonii* induced anti-inflammatory cytokines (TGF-β) (75). A mixture of *Lactobacillus paracasei* and *L. reuteri* to *Helicobacter hepaticus* IL-10-defcient mice leads to reduced colitis and pro-inflammatory cytokines production (76). Kourelis et al. (77) study on Fisher-344 inbred rats and BALB/c, demonstrated that *L. acidophilus* NCFB 1748 and *L. paracasei* subsp. *Paracasei* DC412 induce specific immune markers and innate immune responses *via* recruiting polymorphonuclear cell and production of TNFα (77). Probiotics-induced cytokines expression for immune system modulation of the host has been briefly discussed in the relevant section.

Toll-Like Receptor-Mediated Immune Response and Probiotics

Toll-like receptors and single-pass membrane-spanning receptors are very important protein receptors expressed on several non-immune (epithelial, fibroblasts) and immune [macrophages, B cells, natural killer (NK) cells, DCs] cells. Activation of the TLR signaling pathway, except TLR3 (78), generally leads to the recruitment of MyD88, which results in activation of the NF-κB and mitogen-activated protein kinase (MAPK) pathway. TLR-induced signaling is also responsible for the maturation of DCs characterized by increased expression levels of DC markers (CD80, CD83, and CD86) and chemokines receptor C-C motif chemokine receptor 7 (CCR7). TLR9 is crucial for the mediation of the anti-inflammatory effects of probiotics, though many other receptors are also involved.

Lactobacilli ligands initiate cell signaling after binding to TLR2 in combination with TLR6, endorsing dimerization and NF-κB activation *via* recruitment of MyD88 (79). Engagement of a bacterial ligand with TLR2 results in cytokine production and increases the transepthelial resistance for conquering microbes (79, 80). Several *Lactobacillus* strains induce their immunomodulatory effects by binding to TLR2, which recognizes peptidogycan (a component of the cell wall of Gram-positive bacteria). An *in vitro* study showed that *L. plantarum* and *L. rhamnosus* increased TLR2 expression in human cells (Caco-2). *L. casei* showed similar effects in *Salmonella*-infected and healthy mice, and induced TLR expression, as well as interleukin-10 (IL-10), interferon-gamma (IFN-γ), and TNF-α production (81, 82).

Numerous other probiotics interact with TLR4 to induce an appropriate immune response. For example, during pre- and post-*Salmonella* challenges in mice, *L. casei* increased the production of IL10, IFN-γ, and IL6, and reduced the levels of TNF-α by interacting with TLR4 (82, 83). Likewise, *L. rhamnosus* GG (heat-inactivated) and *Lactobacillus delbrueckii* subsp. *Bulgaricus* (*L. delbrueckii*) reduce TLR4 expression in DCs (human monocyte-derived) (84). TLR9, another important TLR, identifies bacterial CpG DNA and CpG-ODN (engineered unmethylated oligonucleotide mimics). Unmethylated pieces of DNA comprising CpG patterns produced from probiotics also have the propensity to mediate anti-inflammatory activities *via* TLR9.

In the case of the differentiated epithelium, apical, and basolateral stimulation results in the activation of different signaling pathways. Basolateral TLR9 activation causes activation of the NF-κB cascade by the degradation of IκBα. Of note, apical activation of TLR9 results in the suppression of NF-κB by the aggregation of ubiquitinated IκB in the cytoplasm (85). Apical or basolateral stimulation of these receptors is important and involves different signaling cascades leading to various immune responses. The results from the study conducted by Ghadimi et al. show that polarized T84 and HT-29 cells increase TLR9 expression in a specific manner in response to apically applied natural commensal origin DNA. They reported that when LGG DNA is applied to these cells, it attenuates TNF-α enhanced NF-κB activity by reducing IκBα degradation and p38 phosphorylation (86).

Lactobacillus plantarum-purified DNA also modulates the immune response of host cells by interacting with TLRs, as reported by Kim, whose studies show that *L. plantarum*-purified DNA inhibits LPS induced TNF-α production in THP-1 cells. Furthermore, *L. plantarum*-purified DNA blunt the expression of TLR4, TLR2, and TLR9, which induce NF-κB activation through the LPS signaling pathway, leading to pro-inflammatory cytokines upregulation (87, 88). TLRs are important membrane receptors; most intracellular signaling pathways involve the activation of membrane receptors. Furthermore, TLRs play a key role in the induction of immune response by probiotics through the recruitment of specific intracellular signaling molecules. Depending on their interaction with specific TLRs, probiotics may decrease or increase TLR expression.

NLR-Mediated Immune Response and Probiotics

In tissues with blunt TLR expression, NLRs are important and present in the cytoplasm. Thus far, more than 20 NLRs have been recognized. Among them, NOD1 and NOD2 are the most studied and important NLRs (89). NOD1 is expressed in many cells and recognizes peptidoglycan moieties (comprising Gram-negative meso diaminopimelic acid). NOD2 is mainly expressed on DCs, lungs cells, macrophages, intestinal cells, buccal epithelium, and Paneth cells. It senses muramyl dipeptide motifs which are present in a wide range of bacteria (90). NOD1 and NOD2 undergo self-oligomerization following recognition by their agonist. This results in the recruitment and activation of receptor interacting serine/threonine kinase 2 (RICK; an adaptor protein, kinase responsible for the regulation of apoptosis *via* CD95), which is necessary for MAPKs and NF-κB activation and the subsequent production of inflammatory mediators such as cytokines and chemoattractants. Another important signaling factor that NLRs trigger is, apoptosis-associated speck-like protein with caspase induction to trigger caspase 1 (CASP1; an adaptor protein required for the functionally effective and mature forms of pro IL18 and pro IL1). NLRs are involved in the formation of the inflammasome that results in CASP1 activation. There are three major inflammasomes named according to the NLRs involved: NOD-like receptor family pyrin domain containing protein 1 (NLRP1), NLRP3, and NLRC4. Murymyl dipeptide, bacterial and viral RNA, and lipopolysaccharides are sensed by NLRP3 (91). Many *Lactobacillus* species exert their immune regulatory effects *via* NLRs. In galactose-1-phosphate uridylyltransferase (GALT) of swine, *L. gasseri* and *L. delbrueckii* increase the expression of NLRP3 *via* TLR and the NOD signaling cascade, leading to appropriate activation of NLRP3. Furthermore, NOD1, NOD2, TLR2, and TLR9 agonists also enhance NLRP3 expression. *L. salivarius* exerts its anti-inflammatory effect by producing IL10 *via* regulation of NOD2 (92, 93). Probiotics modulate systemic and local immune responses of the host in a strain-specific manner by the expression of PAMPS, such as flagellin, lipopolysaccharides, CpG-DNA, and other surface proteins. PAMPs are recognized by PRRs expressed on numerous immune and epithelial cells. TLRs, C-lectin type receptors, and NLRs are the best studied PRRs. PRRs have broad specificity and their limited number can recognize a wide range of PAMPs. Interaction between PAMPs and PRRs results in the activation of multiple molecular signaling cascades that generate a specific cellular response against the encountered microbes.

Probiotics and Regulation of the NF-κB Pathway

The NF-κB pathway is involved in many pathological conditions and controls the expression of many (∼150) pro-inflammatory and anti-inflammatory cytokines genes. These genes are extensively involved in both adaptive and innate immune responses. NF-κB is found in nearly all types of cells (94, 95). Many probiotics regulate the activation of the NF-κB pathway. *L. casei* inhibits *Shigella fexneri*-induced activation of the NF-κB pathway (96). *L. rhamnosus* and *Lactobacillus helveticus* downregulate the Th1 pro-inflammatory response and improve Th2 response during *Citrobacter rodentium* infection (97). *Bifdobacterium lactis* inhibits IκBα degradation during colitis (98). Some researchers have claimed that dietary yeast downregulates TLR2, NF-κβ p65, MyD88, IL8, and IL1β (99). *L. reuteri*, *L. casei*, and *L. paracasei* show anti-inflammatory characteristics *via* NF-κB pathway regulation; for example, *L. reuteri* decreases the expression of inflammatory mRNA cytokines production and increases anti-inflammatory cytokines production, and also improves the production of apoptosis-inhibiting proteins to improve cell survival and its immune response. *L. reuteri* do this by interfering the ubiquitination of IκB and nuclear translocation of p65 (NF-κB subunit), respectively (100–102). *L. casei* and *L. paracasei* hinder the production of pro-inflammatory cytokines by inhibiting the phosphorylation of IκBα and nuclear translocation of p65, and also reverse the degradation of IκBα (103, 104). Similar inhibitory effects on the NF- κB pathway have been shown by *L. plantarum* and *L. brevis*. *L. plantarum* inhibits NF-κB-activating factors by decreasing the binding activity of NF-κB (105), while *L. brevis* prevents interleukin 1 receptor associated kinase 1 (IRAK1) and AKT phosphorylation (106). *Bifdobacterium infantis* and *Streptococcus salivarius* also reduce NF-κB activation (101).

Besides these probiotics have several other mechanisms of action related to antifungal, antibacterial, antiviral, antiparasitic, antiallergic, anti-cancerous, antidiabetic, amelioration of the cardiovascular system, the reproductive system, and the central nervous system which has been briefly discussed in the relevant section.

IMMUNE REGULATION-BASED THERAPEUTIC APPLICATION OF PROBIOTICS DURING INFECTIOUS DISEASES

Probiotics have a wide range of applications covering numerous non-infectious and infectious diseases, including bacterial, viral, parasitic, fungal, and many other non-infectious diseases. They exert anti-pathogenic effects by modulating both the innate and adaptive immune responses of the host.

Bacterial Diseases

Due to the several disadvantages associated with the preventive use of antibiotics, strict controls have been introduced to prohibit or reduce their use during the treatment of bacterial diseases. In the last three decades, the dietary application of feed additives has been attracting attention as a replacement for antibiotics. Probiotics have been among the most effective feed additives for the control or treatment of bacterial diseases (5). Immune modulatory therapies with probiotics for some selected pathogens are briefly discussed below (**Table 2**).

Salmonella Infection

Probiotics may be used as alternatives to the prophylactic use of drugs for the control and prevention of salmonellosis (137). *Salmonella* causes a foodborne disease in both animals and humans with high morbidity (93.8 million human infections) and mortality (155,000 deaths) worldwide annually (138–142).

TABLE 2 | Probiotic therapies during bacterial diseases.

Probiotics	Target bacteria	Study models	Mechanism of action	Effects	References
L. rhamnosus S1K3	*S.* Typhimurium	Caco-2 cells, mice	↑ Claudin-1 ↑ sIgA, sIgA secreting cells Maintain IL-4, IL-12 protein level ↓ TGFβ	↑ Barrier integrity ↓ *Salmonella* count Improves health status	(107)
Multistrain formula consisting of different *Lactobacilli*	*S.* Typhimurium	Chicken	↓ IFN-γ production	↓ *Salmonella* complications ↑ Recovery rate	(47)
L. plantarum LPZ01	*S.* Typhimurium	Chicken	↓ IFN-γ production Regulate miRNA	↓ *Salmonella* load and associated complications	(108)
L. casei DBN023	*S. pullorum*	Chicken	↓ TNF-α and IFN-γ ↑ IL10	↑ Villi height ↑ Muscle thickness ↑ Intestinal immune functions ↓ Mortality ↓ Pathological changes ↓ Inflammation	(58)
L. casei CRL 431	*S.* Typhimurium	Mice	↑ IL10	↓ *Salmonella* associated complications	(82)
S. cerevisiae strain 905	*S.* Typhimurium	Mice	↑ IgA, IgM in serum ↑ Kupffer cells in liver ↓ IL-6, TNF-α, and IFN-γ	↓ *Salmonella* load in Peyer's patches, spleen, mesenteric lymph nodes, liver ↓ Mortality	(109–111)
S. boulardii	*S.* Typhimurium	T84 cells	↓ NF-kB, MAPKs ERK1/2, p38, and JNK activation ↓ IL-8	↓ *Salmonella* associated complications	(112)
L. gasseri Kx110A1	*H. pylori*	THP-1 cells	↓ TNF-α, IL6	↓ *Salmonella* associated complications	(113)
L. fermentum UCO-979C	*H. pylori*	AGS cells	↓ IL8, IL1β, MCP-1	↓ *H. pylori* induced gastric inflammation	(114)
L. acidophilus and *L. rhamnosus*	*H. pylori*	AGS cells	↓ NF-κB and MAPK activation ↓ IL8, IL6, MAP-2, IL1β, TNF-α.	↓ *H. pylori* induced gastric inflammation	(115–117)
L. bulgaricus NQ2508	*H. pylori*	GES-1 cells	↓ TLR4 expression ↓ NF-κB activation ↓ IL8	↓ *H. pylori* induced gastric inflammation	(118)
L. rhamnosus GG	*H. pylori*	AGS and Caco-2 cells	↓ Gastrin-17 ↓ IL8 and TNF-α	↓ *H. pylori* induced gastric inflammation and ulceration	(119)
L. paracasei 06TCa19	*H. pylori*	MKN45 cells	↓ NF-κB and p38 MAPK activation ↓ IL-8 and RANTES	↓ *H. pylori* induced gastric inflammation and ulceration	(120)
S. boulardii	Clostridial infection	BALB/c mice	↑ IgA, IgG, IgM	↓ Clostridial infection severity	(121)
S. boulardii	Clostridial infection	Mice	Inhibits the *Clostridium* toxins A-induced ERK1/2 and JNK/SAPK signaling pathways	↓ Clostridial infection severity	(122)
S. boulardii	Clostridial infection	Rat	Degrades Clostridial toxins by its protease action ↓ Binding of toxins to host cell	↓ Clostridial infection severity	(123)
L. casei BL23	*S. aureus*	Bovine mammary epithelial cells	↓ IL8, IL6, TNF-α, IL1β, and IL1α	↓ Inflammation of the mammary glands	(124)
B. subtilis DS991 EPS	*S. aureus*	C57BL/6J mice	↓ Pro-inflammatory cytokines, chemokines and T-cell activation	↓ Inflammation	(125)
L. salivarius BGHO1	*L. monocytogenes*	Rats	↑ CD14, TNF-α, IL1β ↓ *Listeria* toxins	↑ Protection against *Listeria monocytogenes*	(126)
L. delbrueckii UFV-H2b20	*L. monocytogenes*	Mice	↑ TNF-α and IFN-γ Stimulates macrophages to increase bacterial killing	↑ Lifespan ↓ Bacterial load from liver and spleen ↓ Liver immunopathology	(127)
Heat-killed *Enterococcus faecium* BGPAS1-3 cell wall protein	*L. monocytogenes*	Caco-2 cells	↑ TGF-β and claudin production ↑ TLR4 expression ↓ TLR2 expression	↓ *Listeria monocytogenes* infection	(128)

(Continued)

TABLE 2 | Continued

Probiotics	Target bacteria	Study models	Mechanism of action	Effects	References
Enterococcus faecium JWS 833	*L. monocytogenes*	Mice and peritoneal mouse macrophages	↑ TNF-α, IL1β, Nitric oxide (NO)	↓ *Listeria monocytogenes* complications	(129)
L. fermentum MTCC 5898	*E. coli*	Mice	↑ IFN-γ, TFNα, MCP-1 ↑ IgA, IgG1 ↑ Antioxidant enzymes activity ↓ IL-4 and IL-10	↓ *E. coli* load in liver, spleen, intestine, and peritoneal fluids	(167)
L. rhamnosus MTCC 5897	*E. coli*	Mice	↑ IgA, IgG ↑ Antioxidant enzymes activity	↓ *E. coli* load in liver, spleen	(168)
L. rhamnosus (LR: MTCC-5897)	*E. coli*	Caco-2 cells	↑ Claudin-1, Occludin, ZO-1, Cingulin	↓ Hyperpermeability Maintains barrier integrity	(170)
L. fermentum (LF: MTCC-5898)	*E. coli*	Caco-2 cells	↑ Claudin-1, Occludin, ZO-1, Cingulin	↓ Hyperpermeability Maintains barrier integrity	(57)
L. rhamnosus ACTT 7469	*E. coli*	pig	↓ TLR4 ↓ TNF-α, IL8	↓ *E. coli* associated inflammation	(130)
L. plantarum B1	*E. coli*	chickens	↓ TLR4 expression ↓ IL2, IL4, IFN-γ ↑ Mucosal antibodies (IgA)	↓ *E. coli* associated inflammation	(131, 132)
L. jensenii TL2937	*E. coli*	PIE cells	↓ IRAK-M, BCL3, TOLLIP, A20	↓ *E. coli* associated inflammation	(133)
L. amylovorus DSM 1669	*E. coli*	Caco-2 cells and pig explant	Modulates Tollip and IRAK-M ↓ TLR4 expression ↓ phosphorylation of the IKKα, IKKβ, IκBα, and NF-κB subunit p65 ↓ IL-1β and IL8 production ↑ Hsp72 and Hsp90	↓ *E. coli* associated inflammation	(134)
L. delbrueckii TUA 4408	*E. coli*	PIE cells	↓ MAPK and NF-κB activation	↓ *E. coli* associated inflammation	(135)
L. rhamnosus ATCC 7469	*E. coli*	IPEC-J2 cell model	↑ ZO-1 and Occludin ↓ *TLR4* and *NOD2* mRNA expression	Maintain epithelial barrier ↓ *E. coli* associated deleterious effects	(136)

After attachment and internalization into the lamina propria, *Salmonella* induces an inflammatory response, e.g., release of pro-inflammatory cytokines, followed by inflammation, ulceration, diarrhea, and destruction of the mucosa (143). Persistent infection is established due to the ability of *Salmonella* to evade the host immune system (144). The persistence of infection is further aided by virulent factors of *Salmonella* that are responsible for the clonal deletion of CD^+ T cells (145).

When administered in adequate amounts, probiotics have the ability to modulate the expression of immune-related cytokines, including interleukins IL4, IL6, IL12, IFN-γ, and IL1β in lymphoid cells during *Salmonella* infection (47, 107, 108, 142, 146). *L. rhamnosus* S1K3 maintains IL-4 and IL-12 protein levels and reduces TGFβ during the late stage of *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) NCDC infection in mice and also increases the level of IgA secreting cells in lamina propria, IgA in serum, and secretory IgA level in intestinal fluids during *S.* Typhimurium NCDC infection in mice. This probiotic also reduces the *S.* Typhimurium NCDC count in feces, prevents its further spread in the liver, spleen, and intestine of mice, and improves overall health. Furthermore, in an *in vitro* study on Caco-2 cells, *L. rhamnosus* S1K3 improves the tight junction proteins (occludin and claudin-1) (107). The production of IFN-γ, a pro-inflammatory cytokine, is induced by *Salmonella*. IFN-γ delays recovery from intestinal inflammation, boosts inflammatory mediators [TNF, ILβ, inducible nitric oxide synthase (iNOS)], and hampers IL22- and lectin REGIIIβ-mediated antimicrobial defense (147). Probiotics beneficially regulate the immune response of the host and suppress the expression of pro-inflammatory cytokines and subsequent inflammation. IFN-γ is suppressed by the anti-inflammatory action of probiotics, greatly reducing the severity of *Salmonella* infection. During salmonellosis, immune players, macrophages, and monocytes secrete IL6, which serves as a pro-inflammatory cytokine and its expression levels are reduced by *Lactobacillus* spp. for the effective and rapid prevention of *Salmonella* infection in broiler chickens (47). A study conducted by Chen et al. showed that *L. plantarum* (LPZ01) reduces *S.* Typhimurium load, IFN-γ expression, TNF-α level, and associated inflammation in broiler chickens by regulating the expression of certain miRNAs involved in immune regulation and inflammatory responses (108). Supplementations with some probiotics increase the activation of B cells and antibody production by increasing IL10 expression. The latter is an important immunoregulatory and anti-inflammatory cytokine involved in antibody production during *Salmonella* infection. *L. casei* (DBN023) improves, regulates, and enhances intestinal immune functions, while cytokines balance and reverse the

detrimental effects of *Salmonella pullorum*, characterized by higher levels of anti-inflammatory cytokines (IL10) and lower levels of pro-inflammatory cytokines (TNF-α, IFN-γ, and IL17). During prophylactic feeding of probiotics in chicken infected by *Salmonella pullorum*, *L. casei* (DBN023) increases villi height and muscle thickness and reduces *Salmonella pullorum*-associated mortality and pathological changes in intestinal epithelial tissues (58). *L. casei* CRL 431 also increases the expression of IL10 to reduce the severity of *S.* Typhimurium infection in BALB/c mice (82). In this manner, probiotics improve the host immune response by hampering the overexpression of inflammatory cytokines, as well as increasing the expression of anti-inflammatory cytokines and production of anti-*Salmonella* antibodies to blunt the severity of *Salmonella* infection.

Some yeasts are also used as immunobiotics and are effective in reducing *Salmonella* infection. The study by Martins et al. shows that *Saccharomyces cerevisiae strain* 905 (S. *cerevisiae* 905) protects and reduces the mortality of mice, orally challenged by *Salmonella* Typhimurium (109), and also significantly reduces the translocation of *S.* Typhimurium to the liver of gnotobiotic mice, and to other organs (Peyer's patches, the spleen, the mesenteric lymph nodes, and the liver) of the conventional mice. The same author in another study shows that this strain increases the number of Kupffer cells in the liver and induces a higher level of secretory IgA in the intestinal contents and IgA and IgM in the serum of mice (110). Furthermore, this strain reduces pro-inflammatory cytokines (IL-6, TNF-α, and IFN-γ) levels and modulates activation of MAPK (p38 and JNK, but not ERK1/2), NF-κB and activator protein-1, signaling pathways which are involved in transcriptional activation of pro-inflammatory mediator during *Salmonella* infection (111). Another yeast strain *S. boulardii* reduces *S.* Typhimurium induced IL-8 production in T84 cells by exerting its inhibitory effects on *S.* Typhimurium induced activation of the MAPKs ERK1/2, p38, and JNK as well as on activation of NF-kB (112). *S. boulardii* possesses the capability to bind with *S.* Typhimurium leading to reduced organ translocation of this pathogen, which results in decreased activation of MAPK (p38, JNK, and ERK1/2), phospho-IkB, p65-RelA, phospho-jun, and c-fos in the colon and signal pathways, involved in the activation of inflammation, induced by *S.* Typhimurium kB (148). Therefore, yeast can survive in host GIT, colonize there, reduce the pathogenic load from the host, and can modulate the immune response of their hosts toward a beneficial pattern.

A series of studies show that short-chain fatty acids (SCFAs) exert diverse beneficial effects on the health of the host gut and body (e.g., anti-inflammatory effects, prevention of histone deacetylases, and suppression of NF-κB resulting in IL1β downregulation), and play a vital role in maintaining intestinal homeostasis. Many probiotics possess regulatory properties for SCFA and can directly or indirectly increase their production. *L. acidophilus* reduces *S.* Typhimurium-induced inflammation directly by increasing the production of SCFA and indirectly by increasing that of other SCFA-producing gut bacteria (149). Moreover, *L. acidophilus* balances *Salmonella*-induced dysbiosis in infected mice (150).

Other probiotics have also shown beneficial effects on the prevention of *Salmonella* infection and inhibit the pathogenesis of *Salmonella* at initial steps. *L. plantarum* (MTCC5690) improves the intestinal defense through modulation of TLR2 and TLR4, and prevents the colonization and further spread of *Salmonella* in mice (151). Similarly, *E. faecium* (PXN33) in combination with *L. salivarius* (59) also inhibits *Salmonella Enteritidis* colonization in the GIT of poultry (152). Supplementation of probiotics greatly reduced the severity of *Salmonella* infection by their immunomodulatory mechanisms of action. As probiotics decrease the expression of inflammatory cytokines and increase the antibody production and anti-inflammatory cytokine expression during salmonellosis, supplementation can improve the overall health of the host.

Helicobacter Pylori Infection

Helicobacter pylori, a Gram-negative and spiral-shaped pathogenic bacterium, resides in >50% of the population worldwide and causes different diseases characterized by prominent gastric inflammation which is associated with gastric ulcers. The mechanism of *H. pylori*-induced inflammation includes chemokine (IL8)-mediated infiltration of neutrophils, increased RANTES level, and *H pylori* urease-induced degradation of NF-κB inhibitor (IκBα) (115, 120, 153–155). *H. pylori* can survive inside macrophages, arrest phagocytosis, and induce their apoptosis by preventing nitric oxide (NO) production. Furthermore, *H. pylori* stimulates macrophages to secret TNF-α and IL6, which are associated with gastric inflammation, by expressing the TNF-α-converting enzyme17 (ADAM17). ADAM17 is a crucial enzyme for the maturation and functioning of TNF-α and IL6. *L. gasseri* Kx110A1 inhibits these pro-inflammatory cytokines from *H. pylori*-infected THP-1 cells by inhibiting the expression of the *H. pylori* ADAM17 enzyme (113). *L. fermentum* UCO-979C regulates the immune response of host macrophages (HumanTHP-1 cell line) and human gastric epithelial cells (AGS cell line) by stimulating them to secrete specific cytokines and chemokines. Moreover, it significantly increases the secretion of inflammatory cytokines (IL6, TNF-α, and IL1β) in both AGS and macrophages, and the secretion of IL10, IFN-γ, and IL12p70 only in macrophages prior to *H. pylori* challenge. In contrast, it decreases the levels of *H. pylori*-induced inflammatory cytokines [IL8, IL1β, monocyte chemoattractant protein-1 (MCP-1), and IL6] in AGS, and those of TNF-α in both AGS and macrophages. Thus, prior to infection, treatment with *L. fermentum* UCO-979C increases inflammatory cytokines to counter future infections. In contrast, during infection, *L. fermentum* UCO-979C treatment lessens the over-activated immune response of host cells, as also shown by Garcia-Castillo et al. (114). The study reported that *L. fermentum* has the ability to decrease *H. pylori*-associated inflammation by improving TGF-β production in the AGS cell line. TGF-β inhibits NF-κB activation by upregulating the levels of IκBα. Notably, *H. pylori* infection impedes this TGF-β-associated signaling pathway by inducing SMAD7 expression to promote inflammation.

Similar to *L. fermentum, L. acidophilus*, and *L. rhamnosus* also regulate the immune response of host cells and decrease their pro-inflammatory immune response against *H. pylori*. As

shown by their anti-inflammatory effects in AGS cells, in which both probiotics greatly reduced the CagA-induced expression of IL8 by inhibiting its translocation into host cells. CagA is an *H. pylori* virulent factor responsible for inflammation by the degradation of cytoplasmic IκBα and increasing translocation of NF-κB into the nucleus (116, 156, 157). Moreover, *L. acidophilus* activates Th1 response to counter *H. pylori* infection, suppresses *H. pylori*-induced SMAD7 expression as well as the activation of the NF-κB and MAPK signaling pathways, and decreases subsequent inflammatory response (production of IL8, IL6, MAP-2, IL1β, TNF-α, and granulocyte-colony stimulating factor) during *H. pylori* infection (115, 117). *L. bulgaricus* NQ2508 also shows similar anti-inflammatory effects by reducing *H. pylori*-induced IκBα degradation and subsequent IL8 production in the human gastric epithelial cell line-1 (GES-1). It may also secrete some soluble proteins which exert inhibitory effects on TLR4 and inhibit its activation by *H. pylori*. Moreover, it blocks subsequent signaling pathways toward NF-κB activation and its delivery to the nucleus for the transcription of pro-inflammatory cytokines (118). As mentioned above, gastric ulcers and cancer are prominent complications of *H. pylori* infection. They mainly arise due to the over-immune response of host cells and the subsequent production of inflammatory cytokines, which are involved in gastric ulceration. Many probiotics reduce these complications by regulating the *H. pylori*-disrupted immune response. *L. rhamnosus* GG reduces gastric ulceration and cancer induced by *H. pylori via* the IL8/TNF-α/Gastrin-17 pathway. *H. pylori* upregulates Gastrin-17 by increasing the levels of IL8 and TNF-α, which in turn upregulate Gastrin-17. Gastrin-17 typically causes gastric cancer, whereas IL8 and TNF-α cause inflammation and apoptosis leading to ulceration of the stomach. *L. rhamnosus* GG shows significant immunobiotic properties with anti-inflammatory effects and attenuates Gastrin-17 levels by suppressing the expression of IL8 and TNF-α (119, 158–161). Similarly, *L. paracasei* may ameliorate *H. pylori*-induced gastric inflammation by regulating the immune response of host cells. *L. paracasei* 06TCa19 inhibits *H. pylori* CagA-induced p38 and IκBα phosphorylation and increases the levels of these NF-κB inhibitors in MKN45 cells. This results in inhibition of the transcription of the inflammatory chemokine genes (120). Numerous other probiotics are extensively used to ameliorate *H. pylori*-induced complications with the aim to regulate the immune system of the host (162, 163).

Escherichia Coli Infection

Escherichia coli causes different problems for humans and animals. Enterotoxigenic *E. coli* (ETEC) causes diarrhea in piglets and other species by secreting heat-labile and heat-stable toxins. Through a complex mechanism, these toxins activate the chloride channel (cystic fibrosis transmembrane channel) resulting in diarrhea. The *E. coli* causing postweaning diarrhea mostly carries F4 (K88) fimbriae (164). $F4^+$ ETEC increases the expression of membrane and cytoplasmic-associated receptors (TLRs and NLRs), which are involved in the NF-κB signaling pathway and subsequent production of pro-inflammatory cytokines (IL8 and TNF-α) leading to inflammation (130, 164, 165).

Probiotics greatly reduce the expression of these pro-inflammatory cytokines by reducing the interaction of *E. coli* with membrane receptors. *L. rhamnosus* ACTT 7469 weakens the *E. coli*-induced expression of TLR4, TNF-α, and IL8 at the protein and mRNA levels in piglets. Furthermore, *L. rhamnosus* increases the expression of TLR2, TLR9, and NLR in the case of *E. coli* infection in piglets, which results in decreased intestinal inflammation (130). As mentioned above, TLR2 and TLR9 are involved in the anti-inflammatory effects of many probiotics.

Similar anti-inflammatory effects have also been shown by supplementation of *L. plantarum* B1, which reduces *E. coli*-induced inflammation in broiler chickens by decreasing the expression of TLR4 and the levels of cytokines (IL2, IL4, and IFN-γ) involved in inflammation. *L. plantarum* also increases the levels of mucosal antibodies (IgA) (131, 132). Hence, probiotics (mainly, the *Lactobacillus* species), regulate the immune response in a beneficial manner by decreasing the expression of membrane receptors (TLR4) involved in inflammation associated with pathogens. On the other hand, probiotics increase the expression of membrane receptors (TLR2, TLR9) involved in the reduction of pathogen-induced inflammation. Like, *Lactobacillus jensenii* TL2937 in porcine intestinal epithelial cells decreases the expression of TLRs by increasing the negative regulators [IRAK-M, BCL3, toll interacting protein (TOLLIP), and A20] of these receptors and reduces the *E. coli* induced inflammation (133). Another study also reported similar anti-inflammatory effects of other probiotics (*Lactobacillus amylovorus* DSM 1669 and *L. delbrueckii* TUA 4408), including inhibition of ETEC-induced activation of the NF-κB and MAPK pathways *via* negative regulation of TLRs, which results in a decrease of pro-inflammatory cytokines (IL1, IL6, IL-1β, and IL8) and an increase of anti-inflammatory cytokine (IL10) in pig explant, caco-2, and porcine intestinal epithelial cells (134, 135). Amdekar et al. also demonstrated that *Lactobacillus* species play a key protective role against *E. coli*-induced urinary tract infection, and clearance of pathogens by regulating the expression of TLRs (TLR2 and TLR4) and subsequent production of anti-inflammatory cytokines (166). Probiotics induce the expression of different kinds of cytokines involved in host immune response during pathogenic infection by regulating the expression of TLR and their intracellular signaling pathways. They increase the expression of anti-inflammatory cytokines and reduce the inflammatory response of host cells during infection. *L. amylovorus* shows protective and anti-inflammatory effects in pig explants and caco-2 cells against *E. coli* infection and decreases *E. coli*-mediated inflammation by increasing the levels of TLR4 negative regulators (IRAK-M and TOLLIP) and decreasing those of extracellular heat shock proteins (HSP90 and HSP72), which are crucial for TLR4 functioning. This effect leads to inhibition of the *E. coli*-induced increase in the levels of TLR4 and MyD88, phosphorylation of IκBα, IκB kinase α (IKKα), IKKβ, and NF-κB subunit p65, as well as the overproduction of inflammatory cytokines (IL8 and IL1β) (134). Treatment with *L. rhamnosus* ATCC 7469 decreases TLR4 and NOD2 mRNA expression during ETEC infection in IPEC-J2 cell model and reduces the associated inflammatory response of the host. Notably, ETEC induced higher mRNA expression of these membrane

and cytoplasmic receptors that lead to the transcription of inflammatory genes *via* the NF-κB pathway (136).

Some probiotics improve the immune status of aging mice to increase their resistance against infection. The study of Sharma et al. on mice reported that *L. rhamnosus* MTCC 5897 feeding alleviates the imbalance of Th1/Th2 immune response and also increases the activity of antioxidant enzymes (catalase, glutathione peroxidase, and superoxide dismutase) and reduces *E. coli* load in the liver, spleen, and intestines by increasing the level of *E. coli* specific antibodies (IgA and IgG) (167). Similarly, *L. fermentum* MTCC 5898 feeding in aged mice increases their protection against *E. coli* infection by increasing the IgA and IgG1 levels and inflammatory proteins and reduces the *E. coli* load in the intestines, liver, spleen, and peritoneal fluids (168). Other lactobacilli improve the *E. coli* disturbed intestinal barrier function as, *E. coli* significantly decreases the intestinal permeability by decreasing the level of tight junction proteins (Occludin, ZO-1, cingulin-1, claudin-1, etc.) as observed by Bhat et al. in Caco-2 cells (169). *L. rhamnosus* (LR: MTCC-5897) improves these tight junction proteins and significantly reduces the *E. coli* induced hyperpermeability in Caco-2 cells (170). Similar effects were also observed by *L. fermentum* (LF: MTCC-5898) treatment during *E. coli* infection in Caco-2 cells in which *L. fermentum* (LF: MTCC-5898) improves the barrier integrity by reducing *E. coli* induced lower mRNA expression of Occludin, ZO-1, cingulin-1, and claudin-1 (57).

Thus, probiotics positively regulate the immune response of host cells at various steps through different mechanisms of action and protect the host from ETEC-induced deleterious effects.

Clostridial Infection

Clostridial species are rod-shaped, Gram-positive toxins and spore-producing bacteria. *Clostridium difficile* is linked to a wide range of clinical problems (171) and produces many toxins (e.g., cytotoxins and enterotoxins), which cause diarrhea (172). It mainly produces the exotoxins TcdA and TcdB with a size of ∼300 kDa. When it binds apically with epithelial gut cells, TcdA causes tight junction interruption and also facilitates the binding of TcdB toxins to the basal lamina. TcdB causes an increase in vascular permeability, release of neurotensin, induction of pro-inflammatory cytokines, fluid secretion, and eventually diarrhea (173).

Probiotics may subside the detrimental effects of clostridial infection by modulating the innate (mucus, lysozymes, and alpha defensin production, and modulation of membrane receptors such as TLRs and NLRs) and adaptive (production of immunoglobulins, anti-inflammatory cytokines, antigen uptake, and modulation of antigen-presenting cells) immune responses and cell signaling pathways (NF-κB and MAPK) of the host (173, 174). *S. boulardii* is a type of yeast that may be used as a probiotic against clostridial toxins. It increases the production of antibodies (IgA, IgG, and IgM) acting as adjuvant in BALB/c mice (121) and has numerous other mechanisms of action associated with immune regulation. It inhibits the activation of the NF-κB and MAPK signaling pathways, and pro-inflammatory cytokine (IL8) production induced by *C. difficile* toxin A in human colonic epithelial cells (NCM460). This toxin activates the extracellular signal-regulated kinase 1/2 (ERK1/2) and stress-activated protein kinases (SAPK)/Jun amino-terminal kinases (JNK) (JNK/SAPK) pathways, resulting in the transcription of pro-inflammatory cytokine (IL8) genes and leading to inflammation. *S. boulardii* inhibits the *Clostridium* toxins A-induced ERK1/2 and JNK/SAPK signaling pathways in mice (122). Furthermore, it degrades *C. difficile* toxins by its protease action and decreases the binding of toxins to host cell (rat ileum) receptors (123).

Staphylococcus Infection

Staphylococcus is a major cause of bovine contagious mastitis and persistent infection in bovine mammary epithelial cells in animals. *Via* upregulation of TLR2 and TLR4, *Staphylococcus aureus* (*S. aureus*) increases the secretion of basic fibroblast growth factor and TGF-β1 through activation of the NF-κB pathway by inhibiting NF-κB inhibitors in bovine mammary epithelial cells (175). Many probiotics are used to treat and control *Staphylococcus* infection. Probiotic *L. casei* (BL23) significantly reduces inflammation of the mammary glands during *S. aureus* infection by suppressing the expression of *S. aureus*-induced pro-inflammatory cytokines (IL8, IL6, TNF-α, IL1β, and IL1α). This results in potent anti-inflammatory effects against *S. aureus* infection in bovine mammary epithelial cells (124). *Bacillus subtilis* has shown protective effects against *S. aureus* infection in mice, by activating macrophages, limiting systemic inflammation induced by *S. aureus*, and decreasing the pathogen load. *Bacillus subtilis*-secreted exopolysaccharides (EPS) have an immunomodulatory function, producing hybrid macrophages (having the functions of both M1 and M2) with anti-inflammatory and bactericidal phagocytic characteristics. These hybrid macrophages limit *S. aureus*—induced T-cell activation and kill *S. aureus* by increasing the levels of reactive oxygen species and decreasing the levels of pro-inflammatory cytokines and chemokines [chemokine (C-C motif) ligand 2 (CCL2), CCL3, CCL4, TNF] (125). Paynich et al. (176) study on mice showed that *Bacillus subtilis*-exopolysaccharides induces anti-inflammatory macrophages (M2), which inhibit T-cell ($CD4^+$ and $CD8^+$) activation by secreting TGF-β and PD-L1 molecules. These molecules have inhibitory effects on $CD4^+$ and $CD8^+$ cells, showing a significant anti-inflammatory property in T cell-dependent immune reaction (176). In this way, probiotics beneficially regulate the immune response of host cells; they activate immune cells to kill *S. aureus* and decrease pathogen-associated inflammation by limiting the overexpression of inflammatory cytokines from pathogen-activated immune cells.

Listeria Monocytogenes Infection

Listeria monocytogenes causes several infections, including maternal-fetal infection, septicemic pneumonia, pleural infection (177), foodborne diseases with a 20–30% mortality rate (178), and neurolisteriosis leading to meningitis and encephalitis (179). Several probiotics (mostly *Lactobacilli* species) are used to protect the host against *L. monocytogenes* infection. *L. salivarius* (BGHO1) therapies against *L. monocytogenes* exert protective effects by modulating the adaptive and innate immune responses during *L. monocytogenes* infection in rats. BGHO1

increases the mRNA expression of CD14, TNF-α, and IL1β and decreases listeriolysin (*Listeria* toxins) in the intestinal tissues. In mesenteric lymph nodes, BGHO1 co-administered with *L. monocytogenes* enhances CD69 and OX-62 mRNA expression (126). *L. delbrueckii* induces the production of TNF-α and IFN-γ, which stimulates the macrophages to kill *L. monocytogenes*. Mice infected with *L. monocytogenes* which received *L. delbrueckii* UFV-H2b20 have a longer lifespan, less liver immunopathology, and less bacterial load in the spleen and liver (127). These probiotics stimulate macrophages by inducing the expression of specific cytokines to increase their bactericidal activities and decrease the level of toxins, as well as assist the host in eliminating pathogens from their body and accelerate recovery.

Heat-killed *E. faecium* BGPAS1-3 cell wall protein, which is resistant to high temperature, has shown protective and strong anti-listeria activity. It stimulates Caco-2 cells to increase TGF-β production. TGF-β exerts protective effects on epithelial tight junctions by upregulating the expression of claudin (128). These innate immunomodulatory effects are achieved by modulation of the MyD88-dependent TLR2 and TLR4 pathways in intestinal cells against *Listeria* infection. *L. monocytogenes* induces TLR2 and suppresses the expression of TLR4 mRNA in Caco-2 cells. Heat-killed BGPAS1-3 decreases the expression of TLR2 mRNA in Caco-2 cells. In contrast, the expression of TLR4 mRNA in Caco-2 cells is increased by both heat-killed and live BGPAS1-3 before and after *L. monocytogenes* infection, respectively. Furthermore, heat-killed or live BGPAS1-3 has inhibitory effects on the expression of IL8 in uninfected and infected *L. monocytogenes* Caco-2 cells (180). Heat-killed and live probiotics, as well as their cellular components, can regulate the immune response of the host through interaction with TLRs, increase the protective innate immune response, and decrease the inflammatory response of host cells. Cho et al. showed the protective and immunomodulatory effects of heat-killed and live *E. faecium* JWS 833 using a *L. monocytogenes* mice model and peritoneal mouse macrophages, respectively. Both heat-killed and live JWS833 show immunomodulatory properties. When administered orally, live JWS833 increases the levels of serum cytokines (TNF-α and IL1β) and NO against *L. monocytogenes* in mice. Heat-killed JWS833 stimulates the macrophages to produce TNF-α, NO, and IL1β (129). Probiotics have diverse immunomodulatory functions, assisting the host to counter pathogenic infections.

Viral Diseases and Probiotics

The threat of viral illness has recently increased significantly due to the changes in the environment (e.g., anthropogenic climate change and increased global movement of passengers and cargo). Viral infections cause variable morbidity and mortality with a detrimental effect on community well-being and cause widespread economic losses. Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which infected millions of people worldwide during the 2019–2020 pandemic is a good example of this global economic loss (181). Thus, finding alternative and effective strategies to prevent viral infections and reducing the morbidity and mortality of viral infections is critical (**Table 3**). Nevertheless, many vaccines and antiviral drugs aiming to be effective in infections are available, but a major challenge is the new viral strains that appeared after mutations, particularly in RNA viruses. It is wise to have some alternative strategies that could be used as supplemental or preventive remedies. To reduce the severity of viral infections and their numbers, a balanced diet including nutrients or food additives that boost and potentiate immune system response, is a beneficial alternative measure. The use of probiotics is one of the dietary approaches used in recent years to increase immunity and decrease the risk of infections (213). Many probiotics (mainly *Lactobacilli* species) are used for the prevention or treatment of viral illnesses. In addition, to alter the crosstalk between gut bacteria and the mucosal immune system, probiotics have many other immune modulatory and non-immune functions to combat viral incursion. The application of probiotics for the control and prevention of clinically important viral diseases is briefly discussed below.

Rotavirus

Bifidobacterium infantis (MCC12) and *Bifidobacterium breve* (MCC1274) modulate immune response during human rotavirus infection in the porcine intestinal epithelial cell line. Both species are able to blunt IL8 production and increase IFN production by increasing the activation of interferon regulatory factor 3 (IRF3) through the suppression of A20 (a zinc-finger protein with negative effects on IRF3 activation) (182). These probiotics activate various interferon-stimulated genes (ISGs), including RNase L ($2^{'}$-$5^{'}$ oligoadenuylate dependent endoribonulecase) and myxovirus resistance protein A (MxA) (183). MxA decreases virus replication by binding with virus nucleoproteins (219). RNase L has antiviral activity and lessens viral replication through the elimination of infected cells by inducing apoptosis and IFN amplification by activating RLRs (220, 221). RLRs are intracellular PRRs involved in virus recognition. *L. rhamnosus* GG (strain ATCC 53103) and *B. lactis* Bb12 enhance the efficacy of human attenuated rotavirus vaccine (AttHRV) during rotavirus infection in gnotobiotic human rotavirus pig model, by increasing T-cells subset ($CD3^{+}$, $CD4^{+}$) in intestinal tissues and T-cells subset ($CD3^{+}$, $CD8^{+)}$ in the blood and spleen. Further, the severity of diarrhea and virus load was also less in vaccinated pigs receiving ATCC 53103 and Bb12 as compared to only vaccinated pigs (184). Similarly, *S. boulardii* and several *Bifidobacterium* and *Lactobacillus* species have anti-rotaviral effects, mitigate the severity and duration of diarrhea, viral shedding, and incidence of infections associated with rotavirus, and modulate the immune response of the host (222–226) *Lactobacillus* species and *Bifidobacterium* in combination with some prebiotics (human milk oligosaccharide, short-chain galactooligosaccharides, and long-chain fructooligosaccharides) show antiviral response. *L. casei* (Lafti L26-DSL) and *Bifidobacterium adolescentis* (DSM 20083) reduced the infectivity of virus in MA104 cells (embryonic Rhesus monkey kidney cells) by interacting with virus protein (NSP4). NSP4 has been characterized as virus toxin and is associated with diarrhea in host (185, 186). *L. rhamnosus* (strain GG) and Gram-negative *E. coli* Nissle (*EcN*) decrease human rotaviral complications by modulating the immune

TABLE 3 | Probiotics therapies during viral diseases.

Probiotics	Target viruses	Study models	Mechanism of action	Effects	References
Bifidobacterium infantis (MCC12)	Rotavirus	PIE cells	↓ IL-8, ↓ A20, ↑ IRF3, ↑ IFN, ↑ ISGs	↓ Virus replication ↑ Infected cells apoptosis	(182, 183)
Bifidobacterium breve (MCC1274)	Rotavirus	PIE cells	↓ IL-8, ↓ A20, ↑ IRF3, ↑ IFN	↓ Virus replication ↑ Infected cells apoptosis	(182, 183)
Bifidobacterium lactis Bb12	Rotavirus	Pig rotavirus model	↑ T cells subset ($CD3^+$, $CD4^+$) ↑ Vaccine efficacy	↓ Virus load	(184)
Bifidobacterium adolescentis (DSM 20083)	Rotavirus	MA104 cells	Interact with virus protein (NSP4)	↓ Diarrhea	(185, 186)
L. rhamnosus GG (strain ATCC 53103)	Rotavirus	Pig rotavirus model	↑ T cells subset ($CD3^+$, $CD4^+$) ↑ Vaccine efficacy	↓ Virus load	(184)
L. casei (Lafti L26-DSL)	Rotavirus	MA104 cells	Interact with virus protein (NSP4)	↓ Diarrhea	(185, 186)
L. acidophilus and *L. reuteri*	Rotavirus	Pig model	↑ Intestinal IgM and IgG ↑ Serum IgM titers ↑ Total intestinal IgA secreting cell response	↓ Virus load	(187)
Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1 fermented yogurt	Influenza virus	96 volunteers	Affect IgA levels in saliva	Help to prevent influenza infection	(188)
L. paracasei	Influenza virus	Mice	↑ IL1α and IL1β before infection ↑ Recruite immune cells before infection ↑ IL10 after infection	↓ Viral load ↓ Morbidity ↓ Mortality	(189)
L. casei DK128	Influenza virus	Mice	↑ IgG1, IgG2a, ↓ IL6 and TNF-α ↑ Monocytes	↓ Inflammation ↑ Host survival rate	(190)
L. plantarum (O6CC2)	Influenza virus	Mice	↑ IFN-a and Th1 cytokines	↓ Infection severity	(191, 192)
L. paracasei CNCM I-1518	Influenza viruses	Mice	↑ Early recruitment of IL-1α, IL-1β Recruit immune cells before infection	↑ Protection against virus	(189)
L. plantarum (AYA)	Influenza virus	Mice	↑ IgA	↓ Infection severity	(193)
L. GG and *L. johnsonii* (NCC 533)	Influenza virus	Mice	↑ IgA, IFN-g	↓ Mortality ↓ Morbidity ↓ Virus titer ↓ Cell death	(194)
Bifidobacterium longum BB536	Influenza virus	Mice	↑ Activities of neutrophils and NK cells.	↓ Weight loss ↓ Virus replication ↓ Infection severity	(195, 196)
L. plantarum (137)	Influenza virus	Mice	↑ IFN-β	↓ Infection severity	(197)
L. delbrueckii ssp. bulgaricus OLL1073R-1 fermented yogurt	Influenza virus	96 volunteers	Affect IgA levels in saliva	Help to prevent influenza infection	(188)
L. acidophilus NCFM and *Bifidobacterium animalis* subsp. *lactis* Bi-07	Influenza virus like symptoms	326 children	–	↓ Fever incidence (53.0%) ↓ Coughing incidence (41.4%) ↓ Rhinorrhea incidence (28.2%)	(198)
Recombinant *L. plantarum*	Corona viruses (TGEV and PEDV)	IPEC-J2	↑ ISGs (OASL, ISG15, Mx1) ↑ B^+IgA^+, IgG ↑ IFN-γ	↓ Infection severity	(199, 200)
L. casei ATCC39392 vaccine	TGEV	Pig model	↑ Antibodies ↑ IL17	↓ Infection severity	(201)
L. plantarum Probio-38 and *L. salivarius* Probio-37	TGEV	ST cell line	Inhibit virus	↓ Infection severity	(202)
cell-free supernatants of *L. plantarum* 22F, 25F, and 31F, live *L. plantarum* (22F, 25F)	PEDV	Vero cells	Antiviral activity	↓ Infection severity	(203)
Mixture of different Lactobacilli and Bifidobacteria	HIV	Clinical trial on 8 human positive patients	↑ Serotonin in blood ↓ Tryptophan in plasma		(204)
L. rhamnsosus GR-1 and *L. reuteri* RC-14	HIV	Clinical trial of 65 confirmed women	–	Improved life quality of women	(205)

(Continued)

TABLE 3 | Continued

Probiotics	Target viruses	Study models	Mechanism of action	Effects	References
L. plantarum 299v	HIV	Clinical trial of 14 children	Stabilize $CD4^+$ T cells numbers	↓ Inflammation	(206)
S. boulardii CNCM I-745	HSV-1	Mice	↑ Anti-inflammatory cytokines ↓ pro-inflammatory cytokines	↓ Gastrointestinal dysfunctioning	(207)
L. rhamnosus BMX 54	Human papillomavirus (HPV)	Clinical trial of 117 women	–	Favors recreation of vaginal balance, may be useful to control HPV infection	(208)
Bifidobacterium bifidum	HPV	Mice	↑ IL2 ↑ IFN-γ	↓ Virus complication, prevent tumor growth	(209)
L. reuteri RC-14 and *L. rhamnosus* GR-1	HPV	Clinical trial of 180 women	–	↓ Abnormal cervical smear rate, no effect on virus clearance	(210)
L. rhamnosus PTCC 1637 and *E. coli* PTCC 25923	Herpes simplex virus-1	African green monkey kidney cells	↑ Viability of macrophages Competitive adhesion with cells	↑ Virus elimination Antiviral effects	(211)
Enterococcus faecalis FK-23	Hepatitis C virus	*In vitro* trial of 39 positive patients	↓ Alanine transferase	Improve health	(212)
Bifidobacterium bifidum 2-2, *Bifidobacterium*. *bifidum* 3-9, *L. gasseri* TMC0356, *L. casei* TMC0409, *L. rhamnosus* LA-2 *L. rhamnosus* (LGG), Streptococcus thermophilus TMC1543	Enteric common infectious diseases	Bovine intestinal epithelial cell line	↑ TLR3 activation ↑ IFN β	↑ Protection against enteric viruses	(213)
L. fermentum PCC, *L. casei* 431 and *L. paracasei*	Upper respiratory tract viruses and influenza viruses	Clinical trial of 136 volunteers	↑ Serum IFN-γ ↑ Intestinal IgA	↓ Symptoms of flue and respiratory tract infection incidence	(214)
L. plantarum DR7	Upper respiratory tract virus's infection	Clinical trial of 209 adults	↑ IL-4, IL-10, CD44, CD117 ↓ IFN-γ, TNFα, CD4, CD8	↓ Nasal symptoms and frequency of URTI ↓ Oxidative stress ↓ Plasma peroxidation	(215)
Bifidobacterium bifidum G9-1 (BBG9-1)	Rotavirus	BALB/c mice	Induced mucosal protective factors	Improve lesion and diarrhea	(216)
L. helveticus R0052 and *L. rhamnosus* R0011	Rotavirus, Adenovirus, Norovirus	Clinical trial of children (816)	–	No beneficial effects	(217)
L. paracasei N1115	Upper respiratory tract viruses	274 clinical volunteers' trial	May stimulate T cell immunity	Protection against acute respiratory tract infection	(218)

response and interacting with rotavirus. In the pig rotavirus model, *EcN* and *L. rhamnosus* GG induced higher total IgA levels in the intestine and serum post- and pre-human rotavirus challenge, respectively, and reduced viral shedding. *EcN* can regulate the expression of cytokines (IL6 and IL10) and bind with rotavirus protein 4 to reduce rotavirus attachment to the host cells (227, 228). In the rotavirus gnotobiotic pig model, *Lactobacilli* species (*L. acidophilus* and *L. reuteri*) significantly increased total intestinal IgM and IgG and serum IgM titers and total intestinal IgA secreting cell responses (187). Furthermore, Azevedo et al. (229) demonstrated that these probiotics (*L. acidophilus* and *L. reuteri*) significantly increased Th1 and Th2 cytokines in human rotavirus infected pigs, and also help in maintaining immunological homeostasis during human rotavirus infection by regulating the production of TGF-β. Different probiotics have anti-rotavirus activities involving various immunomodulatory mechanisms. *Bifidobacterium* stimulates ISGs and lowers various pro-inflammatory cytokines, while *Lactobacillu*s increases anti-rotavirus antibodies and reduces rotavirus-associated complications.

Influenza Virus

A randomized controlled trial on 96 elderly people showed that a yogurt fermented with *L. delbrueckii ssp. bulgaricus* OLL1073R-1 (1073R-1-yogurt) affected the level of influenza A H3N2 bound IgA levels in saliva (188). *L. acidophilus* NCFM and *Bifidobacterium animalis* subsp. *lactis* Bi-07 reduce the incidence of coughing (41.4%), rhinorrhea (28.2%), and fever (53%) in a double blind placebo controlled study on 326 children during the winter season (198). Different clinical trial studies on children, elderly people, adults, and animals compiled by Lehtoranta et al. (230) shows that probiotic administration reduced the risk respiratory viruses including influenza viruses. In mice, *L. paracasei* showed anti-influenza effects and beneficially modulated the immune response against influenza infection, while reducing the viral load, morbidity, and mortality. *L. paracasei* increases the levels of pro-inflammatory cytokines (IL1α and IL1β) and recruitment of immune cells before infection. This accelerates viral clearance and reduces the levels of inflammatory cytokines [macrophage inflammatory protein-1α (MIP1α), IFN-γ, MCP-1, and MIP1β] after influenza

infection. Moreover, *L. paracasei* has shown anti-inflammatory characteristics at the late stage of infection by increasing the levels of IL10 (189). Heat-killed *L. casei* DK128 shows similar anti-inflammatory effects against influenza infection by decreasing influenza virus-induced pro-inflammatory cytokines (IL6 and TNF-α), monocytes, and activated NK cells in the lungs of mice, thereby preventing pulmonary inflammation. Furthermore, DK128 increases the levels of antibodies (IgG1 and IgG2a) against the influenza virus at an earlier time point and provides cross-immunity against secondary heterosubtypic influenza infection with improved health and survival rate in mice (190). *L. plantarum* (O6CC2) beneficially modulates the host immune response during influenza infection in mice by increasing the production of IFN-α and Th1 cytokines (IL12 and IFN-γ) as well as the expression of Th1 cytokine receptors which potentiate NK cell activity at the early stage of influenza infection in mice. Of note, NK cells are an important line of defense during this early phase (191, 192). At the late stage of infection, *L. plantarum* (O6CC2) decreases IL6 and TNF-α production to control influenza-mediated inflammation. Furthermore, O6CC2 decreases neutrophil and macrophage infiltration to overcome the inflammatory response to influenza infection (231). *L. plantarum* (AYA) has shown protective immunological effects against influenza virus infection by increasing production of mouse mucosal IgA (193). *L. GG* and *L. johnsonii* (NCC 533) are also associated with increased IgA production (232, 233). *B. longum* (MM-2) has shown anti-influenza activity by enhancing the innate immunity through increases in the expression of NK cell activator genes (IFN-g, IL2, IL12, IL18) activities. This probiotic reduces mortality, morbidity, virus titer, cell death, virus-induced inflammation, and the expression of mRNA for pro-inflammatory cytokines (IL6, TNF-α, IL1β, MIP2, and MCP-1) in mice infected with influenza virus (194). Similar immune regulatory and anti-influenza effects of *Bifidobacterium* have been observed by other researchers. *B. longum* BB536 enhances the activities of neutrophils and NK cells, reduces fever in human beings (195), reduces IL6 and IFN-γ at the late stage of infection, and prevents body weight loss and virus replication in the lungs of mice infected with the influenza virus (196). *L. plantarum* (137) induces higher type-1 interferon (IFN-β) levels in the serum of mice at the early stage of influenza infection (197). Notably, innate immunity of type-1 interferon is involved in countering viral infection at the early stage (234). In the case of the influenza virus infection, gut microbiota have preventive effects and modulate type I IFNs (235). These IFNs are involved in innate immunity during viral infection with antiviral activities, as well as the degradation and inhibition of viral nucleic acids and viral gene expression, respectively (236, 237). These studies showed that various probiotics show anti-influenza activities along with immunoregulatory effects during infection.

Coronavirus

Coronavirus disease 2019 (COVID-19) was officially declared as a pandemic by WHO on March 11, 2020 (238). SARS-CoV-2 was first identified in Wuhan city (China) in December 2019 (239) in patients with pneumonia and rapidly spread to 216 countries (240, 241). Coronaviruses (CoVs) belong to the family Coronaviridae and genus coronavirus order Nidovirales and subfamilies: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus (242). Subfamilies alphacoronavirus and Betacoronavirus originate from mammals mainly bats, and Gammacoronavirus and Deltacoronavirus subfamilies originate from pigs and birds (243). In SARS-CoVs virion envelop, there are three main structural proteins—protein S (Spike), protein M (membrane), and protein E (envelop). Protein S (Spike) facilitates the SARS-CoVs adherence and fusion (52). All CoVs are positive sense, single stranded RNA, and pleomorphic viruses with typical crown shape peplomers of 27–32 kb and 80–160 nM size (239, 244). Genomic structure analysis showed that the viruses belong to β-coronavirus including MERS-CoV and SARS-CoV with high mutation rates because of RNA dependent DNA polymerase transcription error (242), which is also the main target of drug discovery (245). Pathogenesis of SARS-CoV-2 includes binding of its spikes proteins (S) to Angiotensin-Converting-Enzyme-2, which are highly expressed in lungs as well as in esophagus and enterocytes in the colon and ileum, to get entry into the cells for infection (246). TMPRSS2 is a protein, which helps the "S" proteins of SARS-CoV-2 to get entry into cells, is also highly expressed in absorbent enterocytes (247). Clinical signs of COVID-19 disease are different ranging from asymptomatic to non-specific flu and severe pneumonia, Middle Eastern respiratory syndrome (MERS) (248), and life-threatening consequences like acute respiratory distress syndrome and different organ failure. It can also affect neurological, gastrointestinal, and hepatic systems (249). According to data from Wuhan city in China, 14% of the infected cases were severe, 4% died, and 5% needed intensive care (250).

In spite of the different measurements including hygienic improvement, screening, and social distancing, COVID-19 is rapidly spreading and progressing worldwide (22, 240), while the search for effective drugs and vaccine therapies is underway. Scientists are battling against the time needed to develop a vaccine, but it is hard to make an efficient and safe product as rapidly as the virus is spreading (251). Thus far, there are no effective drugs available for SARS-CoV-2. However, according to genomic structure analysis and its similarity with SARS and MERS, certain drugs (e.g., lopinavir, ritonavir, and nitazoxanide) may be applicable (252). At the same time, several studies have compiled alternative data related to general viruses management and treatment (253–258) including nutritional supplements like vitamins and some other immune boosts medicine (259). Some *in silico* data are in favor of probiotics use for the treatment of COVID 19 as data indicate that probiotics derived molecules like lactococcin Gb (*L. lactis*), subtilisin (Bacillus amyloliquefaciens), sakacin P (*L. sakei*) may inactivate "S" glycoprotein and its receptors molecules i.e., Angiotensin-Converting-Enzyme-2 (260). Similarly, several other studies have published their data regarding the use of probiotics for the general management of viral diseases as it is indicated by some clinical evidence that some kinds of probiotics are helpful in preventing bacterial and viral infections like respiratory tract infections, sepsis, and gastroenteritis. Viruses account for over 90% of upper RTIs as etiological agents. Many studies have

recorded the positive effect of probiotics on the protection of upper respiratory tract infections. Reduced risk of getting upper respiratory tract infections in probiotic supplementations was recorded in a meta-analysis study of 12 randomized control trials involving 3,720 children and adults. It was observed in 479 adults of a randomized, double-blind, placebo-controlled intervention study that *B. bifidum* MF 20/5, *L. gasseri* PA 16/8, and *B. longum* SP 07/3 along with mineral and vitamins reduced the duration of fever and common cold (22). *Streptococcus salivarius* strain K12 may possibly reduce the severity of COVID-19 complications by its ability to maintain stable upper respiratory tract microbiota. As advanced studies have shown that lung microbiota have an important role in the homeostasis of immune responses (261), and its dysbiosis makes the patient more vulnerable to viral infections. In the case of COVID-19, a significant difference in lung microbiota has been observed in patients with COVID-19 and normal persons (262). Probiotic consumption triggers pro- and anti-inflammatory cytokines production to clear the viral infection, reduce the cell damage in the lungs, and improve the levels of T cells, B cells, NK cells, and type 1 interferons in the immune system of the lungs, and it may help to prevent COVID-19 complications (261).

Probiotics and recombinant probiotics with antiviral effects are effectively used to combat and minimize the detrimental effects of other coronaviruses, such as alphacoronaviruses—particularly transmissible gastroenteritis virus (TGEV) and porcine epidemic diarrhea virus (PEDV)—which cause substantial economic losses in the pork meat industry. Recombinant *L. plantarum* inhibits TGEV and PEDV infections in the IPEC-J2 cell line by enhancing ISGs (OASL, ISG15, and Mx1) which have strong antiviral effects (199). Recombinant *L. plantarum* (containing the surface S antigen of TGEV) elicits an immune response characterized by higher numbers of activated DC cells, $B^{+}IgA^{+}$ cells, secretory IgA (sIgA), serum IgG, IFN-γ, and IL4 which help the host to combat TGEV (200). Similar effects were observed by Jiang and colleague who reported that a recombinant *L. casei* ATCC39392 vaccine modulates the immune response against TGEV infection, induces IL4, mucosal (IgA), and systemic (Ghosh and Higgins) antibodies, and polarized Th2 immune response with enhanced the expression of IL17 against TGEV in a pig model (201). Similarly, immune protective effects with the elicitation of sIgA and IgG production against PEDV have also been shown by a *L. casei*-based vaccine, consisting of a DC-targeting peptide attached to the PEDV core antigen (263). Antibiotics and porcine bile-resistant *L. plantarum* Probio-38 and *L. salivarius* Probio-37 have shown antiviral effects *in vitro* ST cell line and inhibit TGE coronavirus without cytotoxic effects (202). Another study shows that cell-free supernatants of different LAB (*L. plantarum* 22F, 25F, and 31F) and live *L. plantarum* (22F, 25F) have anti PEDV activity with any cytotoxic effects on Vero cells (203). *E. faecium* has protective effects against enteropathogenic coronavirus TGEV and hinders the virus entry into cells by interacting with cell surface molecules, reducing viral structural proteins, and inducing antiviral NO (264, 265). Furthermore, *E. faecium* stimulates an antiviral response by increasing the expression of IL8 and IL6 mRNA (266), which contribute to the immune regulation against many other enteric pathogens (267). Studies show that *E. faecium* (probio-63) and *E. faecalis* (KCTC 10700BP) suppress coronavirus growth, responsible for porcine epidemic diarrhea (268, 269). These findings indicate that probiotics have antiviral effects, and stimulate the immune response of the host against viruses. Many probiotics enhance vaccine efficacy; some probiotics inhibit virus entry into cells and also stimulate the production of different cytokines during viral infection.

Probiotics and Parasitic Diseases

Probiotics are widely applicable to the treatment and prevention of parasitic infections (**Table 4**). Oral administration of *L. rhamnosus* MTCC 1423 during Giardia infection in mice modulates both cellular and humoral immune responses, enhances sIgA, IgA^{+} cells, $CD4^{+}$ T lymphocytes, and anti-inflammatory cytokine IL10, and decreases pro-inflammatory cytokine IFN-γ (277). *E. faecium* SF 68 stimulates an anti-giardia immune response, increases $CD4^{+}$ T cells and the production of anti-giardia antibodies (intestinal IgA and serum IgG), and reduces the parasitic load (278). *Lactobacillus* and *S. boulardii* also have positive effects in the treatment of giardiasis, minimizing interaction between the host and pathogen, reducing parasite load, and modulating the immune response of the host. *L. johnsonii* La1 (NCC533) reduces active trophozoite of Giardia intestinalis strain WB and infection duration in *Meriones unguiculatus* (286). Recombinant *L. plantarum* NC8 (containing *Eimeria tenella* protein) induced a higher percentage of a T-cell subset ($CD3^{+}$, $CD4^{+}$, and $CD8^{+}$) and antibody levels, provided protection against *E. tenella* infection in chickens, and reduced lesion, cecum damage, and oocyst shedding (270). *L. salivarius*, *L. johnsonii*, and *S. cerevisiae* provided protection against *Eimeria* infection in chickens; reduced oocyst count, improved weight gain and FCR, and stimulated the immune response with higher antibodies (IgM and IgG) titer and lymphoproliferative response (271). Pender et al. revealed that chickens receiving supplementation of commercially available probiotics; Primalac W/S (*L. acidophilus*, *L. casei*, *E. faecium*, and *B. bifidium*) showed lower mortality, higher body weight, and fewer *Eimeria maxima*-, *Eimeria tenella*-, and *Eimeria acervulina*-induced lesions; however, there was no effect on the immune response (272). Lactic acid from *L. acidophillus* stimulates the host immune response during *Cryptosporidium* infection, increasing the number of lymphocytes, levels of complement proteins (C3, C4), and antibodies (IgM, IgG), as well as reducing oocyst shedding from infected rabbits (273). *L. casei*, Bifidium bacteria, and *E. faecalis* exert protective effects during *Cryptosporidium parvum* infection and greatly reduce parasite load and oocyst shedding from the intestine of infected mice (287–289). In contrast, Oliveira and Widmer demonstrated that some commercially available probiotics enhanced the severity of cryptosporidia infection by altering the intestinal environment in favor of *C. parvum* proliferation (290). *Bifidobacterium animalis subspecies lactis* strain Bb12 stimulates local immune response during *Ascaris suum* infection in juvenile pigs and production of anti-parasite antibodies (IgA in serum and IgG1 and IgG2 in ileal fluid) and glucose uptake

TABLE 4 | Probiotics therapies during parasitic diseases.

Probiotics	Parasites	Study models	Mechanism of action	Effects	References
Recombinant *L. plantarum* NC8	*Eimeria tenella*	Chicken	↑ $CD3^+$, $CD4^+$, $CD8^+$ ↑ IgA, IgM and IgG	↓ Lesion ↓ Cecum damage ↓ Oocyst shedding ↓ Inflammation	(270)
L. salivarius, *L. johnsonii*, and *S. cerevisiae*	*Eimeria tenella, Eimeria maxima, Eimeria necatrix*	Chicken	–	↓ Oocyst count ↑ Weight gain ↑ FCR	(271)
Primalac W/S (*L. acidophilus*, *L. casei*, *Enterococcus faecium*, and *Bifidobacterium bifidium*)	*Eimeria maxima*, *Eimeria tenella*, and *Eimeria acervulina*	Chicken	–	↓ Lesion	(272)
L. acidophillus lactic acid	*Cryptosporidium parvum* oocysts	Rabbit	↑ Complement proteins (C3, C4) ↑ Lymphocytes ↑ IgM and IgG	↓ Parasitic load	(273)
Bifidobacterium animalis	*Ascaris suum*	Juvenile pigs	↑ IgA in serum ↑ IgG1 and IgG2 in ileal fluid	↓ Parasitic complications	(274)
L. rhamnosus	*Ascaris suum*	Pigs	↑ TLR9 expression ↑ TNF-α, IFN-γ, and IL10	↓ Parasitic allergic complications	(275, 276)
L. rhamnosus	*Giardia intestinalis* (Portland strain I)	BALB/c mice	↑ sIgA, IgA^+ cells, $CD4^+$ ↑ T lymphocytes ↑ IL10 ↓ IFN-γ	↓ Giardia infection severity Restore intestinal morphology	(277)
Enterococcus faecium SF68	*Giardia intestinalis* H7 (ATCC 50581)	Mice	↑ Intestinal IgA ↑ Serum IgG ↑ $CD4^+$ T cells	↓ Parasitic load	(278)
L. plantarum, *L. reuteri*, *L. casei*, and *L. acidophilus*	*Schistosoma mansoni*	Mice	↑ IgM ↓ AST, LDH, and gGT	↓ Parasitic complications ↓ Spleen and liver weight	(279)
L. sporogenes	*Schistosoma mansoni*	Mice	↓ Schistosomiasis cytokine-induced chromosomal aberration	↓ Chromosomal aberration	(280)
L. plantarum	*Trichinella spiralis*	Mice	↑ Serum IFN-γ	↓ Larval count ↓ Inflammation	(281)
L. fermentum, *Enterococcus faecium*, *Enterococcus durans*	*Trichinella spiralis*	Mice	↑ Phagocytic activity of leukocytes	↑ Protection	(282)
L. casei	*Trichinella spiralis*	Mice	↑ IgA and IgG	↑ Protection	(283)
L. rhamnosus (JB-1)	*Trichuris muris*	Mice	↑ IL10 ↑ Mucus-secreting goblet cells	↑ Larval removal	(284)
S. boulardii	*Toxocara canis*	Mice	↑ IL12 and IFN-γ	↑ Protection	(285)

(274). Similarly, *L. rhamnosus* modulates the expression of TNF-α, TLR9, IFN-γ, and IL10 gene, which results in decrease in eosinophil action and allergic skin reaction induced by *Ascaris suum* in the pig model (275, 276). Many probiotics are effective against schistosomiasis; *Zymomonas mobilis* stimulates immune response and provides 61% protection during schistosomiasis (291). *L. plantarum*, *L. reuteri*, *L. casei*, and *L. acidophilus* stimulate IgM antibodies against *Schistosoma mansoni* infection in mice (279). *L. sporogenes* reduces schistosomiasis cytokine-induced chromosomal aberration in mice (280). During trichinellosis (*Trichinella spiralis* infection in mice), *L. plantarum* increases the levels of IFN-γ and reduces larval count (281). *L. fermentum*, *E. faecium*, and *Enterococcus durans* enhance the activity of phagocytes during *Trichinella spiralis* infection in mice (282). *L. casei* induces IgA and IgG during *T. spiralis* infection in mice (283, 292). In trichuriasis mice model, *L. rhamnosus* (JB-1) increases IL10 and mucus-secreting goblet cells, resulting in the faster removal of larvae (284). *E. faecalis* CECT7121 (*Ef*7121) and *S. boulardii* are associated with larvicidal activity and high production of IL12 and IFN-γ, respectively, during *Toxocara canis* infection in mice (285, 293). Different probiotics have different mechanisms of action during parasitic infections. They reduce complications, regulate cytokine production, and facilitate the production of anti-parasitic antibodies. However, it has been shown that some probiotics enhance the parasitic infection as indicated in the study by Dea-Ayuela and colleague on mice in which they reported that *L. casei* decreases cytokines (IFN-γ, TNF-α, IL-4, and Il-13) and antibodies (fecal IgA) against *Trichuris muris*, increasing the susceptibility of *T. muris* infection. This *L. casei* associated increased susceptibility to infection may be related to deactivation of TNF-α dependent Th2 effector responses against *T. muris* due to the strong inhibitory effect of *L. casei* on this cytokine (294).

PROBIOTICS THERAPIES IN NON-INFECTIOUS DISORDERS

Probiotics improve the central nervous system and mental function with beneficial effects reported in anxiety, Alzheimer's disease, depression, schizophrenia, and autism (295). In an autism spectrum disorder mice model, an *L. reuteri* diet led to a behavioral improvement in an oxytocin-dependent manner (296). Probiotics can alter the composition of gut microbiota (297), which in turn acts on the gut–brain axis by secreting neuroactive substances (298) and significantly influences and regulates cerebrovascular diseases, neurodegeneration, and mental dysfunction (299). *B. infantis* reduces stress by increasing the levels of tryptophan in plasma, decreasing the levels of serotonin in the frontal cortex, and regulating the hypothalamic–pituitary–adrenal axis. *L. rhamnosus* JB-1 decreases the expression of gamma aminobutyric acid receptor and corticosterone levels in mice, which are induced during stress (300–302). Moreover, *B. longum, L. helveticus*, and *L. plantarum* reduce anxiety (303). *L. fermentum* NCIMB can produce ferulic acid, which is a strong antioxidant that can stimulate the proliferation of the nervous system stem cells and be used to treat neurodegenerative disorder, diabetes, and obesity. In mice, feeding ferulic acid ameliorates Alzheimer's disease symptoms, oxidative stress, and neuroinflammation (65). Thus, probiotics have positive effects on brain function, by affecting the functions of the nervous system as well as some related hormones and their receptors (**Table 5**). However, a detailed study of the effects of probiotics on the nervous system is needed to support the currently available evidence.

Different probiotics regulate obesity (323), which predisposes individuals to different diseases, such as non-alcoholic fatty liver diseases, cardiovascular diseases, diabetes, cancers, and some disorders related to the immune system (324). *L. plantarum* CBT LP3 and *B. breve* CBT BR3 reduce obesity related marker, and *L. rhamnosus*, *E. faecium*, *L. acidophilus*, *B. bifidum*, and *B. longum* decrease low-density lipoprotein cholesterol, total cholesterol and oxidative stress level in an *in vivo* human trial (320). *B. bifidum* W23, *B. lactis* W51&W52, *L. lactis* W19&W58, *L. brevis* W63, *L. casei* W56, *L. acidophilus* W37, and *L. salivarius* W24 regulate the obesity by decreasing triglyceride, total cholesterol, homocysteine, and TNF-α level in a randomized double-blind placebo-controlled trial on 50 women who were obese (321). Indigenous microbiota play a key role in obesity by harvesting energy for the host through different metabolic pathways. Probiotics change the composition of gut microbiota, thereby influencing obesity (12). Gut microbiota contribute to obesity *via* several potential mechanisms, such as lipogenesis, carbohydrate fermentation, and energy storage, and through numerous pathways (e.g., different hormones, metabolites, and neurotranmitters), which regulate energy balance and food intake (**Table 5**).

Probiotics also reduce the risk of cancer by different mechanisms of action, which include the exclusion of oncogenic bacteria, improvement of epithelial barrier function, increase of tumor cell death by apoptosis, production of immune-modulating metabolites (acetate, butyrate, propionate, conjugated linoleic acids, etc.), increase of cytokine production with an antitumor response, and TLR modulation. Butyrate regulates cell proliferation, differentiation, and apoptosis (325), it can stimulate anti-inflammatory cytokines and IL10 production and decrease the production of inflammatory cytokines *via* inhibition of NF-κB. Furthermore, butyrate regulates apoptosis-regulating proteins [CASP7, CASP3, BCL2 antagonist/killer (BAK), and BCL2], suppresses COX2 activity, stimulates the production of AMPs, and increases glutathione-S-transferase. These effects lead to downregulation or upregulation of genes related to the apoptosis, proliferation, and differentiation of cells (326, 327). Propionic acids and acetic acid have also shown anti-inflammatory activities by suppressing NF-κB activation and modulating the expression of pro-inflammatory genes (328). Some probiotics (*Lactobacilli*, *bifidobacteria*, and *streptococcus*) can produce conjugated linoleic acid, which has pro-apoptotic and anti-proliferative activities. This is achieved by increasing the expression of peroxisome proliferator-activated gamma receptor (PPARγ), which is involved in immune function and apoptosis. Some probiotics show their anti-cancerous activities *via* cation exchange between their peptidoglycan and the carcinogenic compound. Furthermore, probiotics decrease the COX2 enzyme-mediated production of prostaglandins, which increases the risk of colorectal cancer (329, 330). Probiotics can increase the production of immunoglobulins, such as IgA, generating an anti-inflammatory environment. IgA does not provoke activation of the complement system and acts as a barrier to reduce contact between the carcinogenic compound in the lumen and colonocytes, thereby reducing the risk of cancer (331). A prospective study involving 82,220 individuals showed that individuals who consume yogurt and sour milk are less susceptible to bladder cancer. An Italian cohort study on 45,000 volunteers of a 12-year follow up without comparative group, reports that yogurt consumption decrease in colorectal cancer (332). *L. casei* administration in humans for 4 years showed less recurrence of adenoma atypia, and probiotics with oligofructose-enriched inulin preparation reduce DNA damage in colonic epithelial cells and HT29 cells (322). Animal studies supported the beneficial effects of yogurt against genotoxic amines and cancer of the bladder and colon. In a breast cancer mice model, *L. acidophilus* isolated from yogurt promoted the proliferation of lymphocytes and decreases tumor growth (323) (**Table 5**). Hence, probiotics reduce the risk of cancer by different mechanisms. Some probiotics assist in excluding the oncogenic bacteria, while others inhibit inflammatory pathways and increase apoptosis of tumor cells. Furthermore, probiotics stimulate the production of immune-modulating metabolites involved in cell growth, proliferation, and apoptosis.

Many probiotics have beneficial effects on allergies (**Table 5**). *L. rhamnosus* (MTCC5897) fermented milk (PFM) feeding in newborn mice alleviates allergic symptoms by shifting Th2 to Th1 pathway by decreasing albumin specific antibodies (IgE, IgG, and IgG1), ratio of IgE/IgG2a and IgG1/IgG2a and IL-4, and by increasing IFN-γ, IgA^+ cells, and goblet cells (304, 333).

TABLE 5 | Probiotics therapies in non-infectious diseases.

Probiotics	Disease	Study models	Major finding	References
L. rhamnosus (MTCC5897) fermented milk (PFM)	Allergy	Mice	↑ IgA^+ cells in small intestine ↑ Goblet cells number ↓ Ovalbumin-specific antibodies (IgE, IgG, IgG1) ↓ Ratio of IgE/IgG2a and IgG1/IgG2a ↓ Allergic symptoms	(304)
L. plantarum 06CC2	Allergy	Mice	↓ Ovalbumin-specific IgE ↓ Total IgE ↑ Antiallergic IL-4 and IFN-γ ↓ Allergic symptoms	(305)
Bifidobacterium infantis CGMCC313-2	Allergy	Mice	↓ IL4, IL13 ↓ IgE, IgG1 ↓ Allergic symptoms	(306)
Enterococcus faecalis FK-23	Allergy	Mice	↓ IL-17 ↓ $CD4^+$ cells ↓ TH17 development ↓ Allergic symptoms	(307)
Staphylococcus succinus 14BME20	Allergy	Mice	↓ IgE level in serum ↓ Inflammatory cells flux into lungs ↑ $CD4^+CD25^+Foxp3^+$ regulatory T (Treg) ↑ DCs ↑ IL-10	(308)
Clostridium butyricum CGMCC0313	Allergy	Mice	↓ β-lactoglobulin-mediated intestinal anaphylaxis Inverts the imbalance between Th1/Th2 and Th17/Treg cells ↑ forkhead box P3 (FOXP3) Treg cells ↑ TGF-β and IL10	(309)
L. acidophilus KLDS 1.0738	Allergy	Mice	↓ Inflammatory cells ↓ IgE production ↓ IL6 levels ↓ Th17 response ↑ Treg cells, CD25, FOXP3 ↓ TGF-β	(310)
L. fermentum MTCC: 5898-fermented milk	Cardiovascular	Mice	↓ TNF-α and IL-6 ↓ Coronary artery risk index ↓ Atherogenic index ↓ Triacylglycerols, low-density lipoprotein cholesterol, hepatic lipids ↓ Lipid peroxidation	(311)
L. rhamnosus MTCC: 5957 and *L. rhamnosus* MTCC: 5897	Cardiovascular	Wistar rat	↓ TNF-α and IL-6 ↓ hyperlipidemia ↓ Hepatic lipids ↓ Lipid peroxidation ↑ Antioxidant activities	(312)
L. plantarum	Cardiovascular	Meta-analysis of randomized controlled trials of 653 participants	↓ Diastolic and systolic blood pressure ↓ Total serum cholesterol ↓ Low-density lipoprotein cholesterol levels ↓ Atherosclerosis index ↓ Hepatocyte steatosis risk	(313, 314)
L. fermentum CECT5716 and *Bifidobacterium breve* CECT7263	Cardiovascular	Wistar Kyoto rats	↓ Hypertensions ↓ Endothelial dysfunctioning ↓ Increased blood pressure	(315)
L. rhamnosus GR-1 *L. plantarum* 299v	Cardiovascular	rats	↓ Risk of myocardial infarction Improve ventricular function ↓ Infarct size ↓ levels of leptin	(316, 317)
L. rhamnosus MTCC: 5957, *L. rhamnosus* MTCC: 5897, and *L. fermentum* MTCC: 5898	Diabetes	Wistar rat	Improve glucose metabolism (fasting blood glucose, glycated hemoglobin, serum insulin) Improve serum inflammation status (TNF-α and IL-6) Improve serum lipid profile	(318)

(Continued)

TABLE 5 | Continued

Probiotics	Disease	Study models	Major finding	References
L. plantarum, *L. helveticus*, *L. lactis*, *L. pentosus*, *L. paracasei*, *L. paracasei sbusp.tolerans*, *L. mucosae*, *L. rhamnosus*, *L. harbinensis*, *L. hilgardii*, *Issatchenkia orientalis*, *Candida ethanolica*, *Kluyveromyces marxianus*, and *Pichia membranifaciens*	Diabetes	db/db mice and C57BL/KS	Prevent pancreatic cell apoptosis *via* upregulation of the PI3K/AKT pathway and increase GATA like protein 1 (GLP1) production. GLP1 induces insulin secretion by upregulating the G protein-coupled receptor 43/41 (GPR43/41), proconvertase 1/3 and proglucagon activity	(319)
L. fermentum NCIMB	CNS	Mice	↑ Ferulic acid ↓ Alzheimer's disease symptoms ↓ Oxidative stress and neuroinflammation	(65)
L. reuteri	CNS	Mice	Behavioral improvement	(296)
L. rhamnosus JB-1	CNS	Mice	↓ Gamma aminobutyric acid receptor and corticosterone levels	(300)
L. rhamnosus, *E. faecium*, *L. acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*	Obesity	*In vivo* human trial	↓ Low density lipoprotein cholesterol ↓ Total cholesterol ↓ Oxidative stress	(320)
Bifidobacterium bifidum W23, *Bifidobacterium lactis* W51&W52, *L. lactis* W19&W58, *L. brevis* W63, *L. casei* W56, *L. acidophilus* W37, and *L. salivarius* W24	Obesity	*In vivo* human trial	↓ Homocysteine ↓ Triglyceride ↓ Total cholesterol ↓ TNF-α	(321)
L. plantarum CBT LP3, *Bifidobacterium breve* CBT BR3	Obesity	*In vivo* human trial	Reduced obesity marker	(320)
L. fermentum NCIMB 5221	Obesity	–	↑ Ferulic acid ↓ Obesity	(65)
L. fermentum NCIMB	Cancer	AGS, HeLa, MCF-7, and HT-29 cells	↓ Risk of cancer	(65)
L. casei	Cancer	Colonic epithelial cells and HT29 cells	↓ Adenoma atypia ↓ DNA damage	(322)
L. acidophilus	Cancer	Breast cancer mouse model	↓ Tumor growth	(323)

Bifidobacteriales, *Bacteroidales*, and *Lactobacillale*s in the gut affect the activities of inhaled allergens. *Bifidobacteriales* and *Lactobacillales* suppress allergen sensitization and are effective against allergic rhinitis (334). *B. infantis* CGMCC313-2 represses allergen-mediated inflammatory cells, IL4, IL13, IgE, IgG1, and blunt inflammation during allergy in mice model (306). *E. faecalis* FK-23 inhibits the development of Th17 cells in the intestine, spleen, and lungs of infected mice by inhibiting the expression of TGF-β and IL6 mRNA, thereby facilitating to reduce ovalbumin-induced allergic complication (307). *Staphylococcus succinus* 14BME20 has also shown antiallergic potential; it significantly decreases the influx of inflammatory cells into the lungs, suppresses airway hyperresponsiveness, and reduces the serum IgE and Th2 cells cytokines production in an ovalbumin mice model (308). *Clostridium butyricum* CGMCC0313 increases forkhead box P3 (FOXP3) Treg cells, TGF-β, and IL10, inverts the imbalance between Th1/Th2 and Th17/Treg cells, and reduces β-lactoglobulin-mediated intestinal anaphylaxis, thereby contributing to the reduction of the risk of allergy in mice (309). Orally administered *L. acidophilus* KLDS 1.0738 ameliorates allergic symptoms by increasing Treg cells, CD25, FOXP3, and TGF-β mRNA expression, and inhibiting inflammatory cells, IgE production, IL6 levels, and Th17 response in mice (310).

Many probiotics are used for the prevention and treatment of diabetes (**Table 5**). *L. rhamnosus* MTCC: 5957, *L. rhamnosus* MTCC: 5897 and *L. fermentum* MTCC: 5898 feeding Improves glucose metabolism (fasting blood glucose, serum insulin, and glycated hemoglobin), oxidative stress (glutathione peroxidase, superoxide dismutase, catalase activity, and thiobarbituric acid reactive substances,) serum inflammation status (TNF-α and IL-6) and serum lipid profile in diabetic rats, and also significantly reduces mRNA expression of gluconeogenesis related genes (pepck and g6pase) (318). *L. acidophilus* KLDS 1.0901 shows antidiabetic characteristics by reducing glycosylated hemoglobin, fasting blood glucose level, and increasing the level of glucagon-like peptide 1 in the serum of mice. Further, *L. acidophilus* KLDS 1.0901 increases glutathione peroxidase and superoxide

dismutase activities and also increases the level of glutathione with the reduction of malondialdehyde level in mice serum (335). Similarly, *L. paracasei* 1F-20, *L. fermentum* F40-4, *Bifidobacterium animalis* subsp. *lactis* F1-7 also exhibit the potential to manage the diabetic problem as shown by the *in vitro* study of Zhang et al. (241) using CACO-2, STC-, RAW246.7, and HepG2 cells in which these probiotics increase glucagon-like peptide 1 and peptide YY hormones and decrease IL-6 and TNF-α levels (336).

Different species of other *Lactobacilli* and yeast strains act also as antidiabetic, preventing pancreatic cell apoptosis *via* upregulation of the PI3K/AKT pathway and increased GATA-like protein 1 (GLP1) production. GLP1-induced insulin secretion by upregulating the G protein-coupled receptor 43/41 (GPR43/41), proconvertase 1/3, and proglucagon activity in mice (319). GLP1 is an antidiabetic hormone involved in glucose homeostasis, and reduction of glucagon secretion and appetite (337–339). Many probiotics improve glucose metabolism (340) and inhibit NF-κB pathway overactivation. NF-κB is associated with diabetes and its inhibition leads to improvement in insulin sensitivity (94, 309). Probiotics reduce the risk of diabetes by regulating different cellular signaling pathways and the expression of sugar metabolism hormones.

Some probiotics improve sperm maturation; *L. casei* and *B. lactis* enhanced the maturation of sperm in diabetic rats and decreased their glucose levels (341). *L. rhamnosus* increased the mRNA expression of androgen receptors α and β, activin and progesterone receptor 1, serum follicle-stimulating hormone, luteinizing hormone, and testosterone. These effects were associated with improvement in spermatogenesis, sperm motility, and sperm production, along with a decrease in the percentage of immotile sperm (342, 343). *Bacillus amyloliquefaciens* has shown similar beneficial effects on semen density, live sperm, and overall quality in breeder chicken (344).

Probiotics are also widely applied to cardiovascular diseases; they significantly decrease hypertension, oxidative stress, blood pressure, inflammatory mediators, and cholesterol levels (311, 345–348). It is observed that cholesterol-enriched fed mice show significantly higher levels of serum triacylglycerols, total cholesterol, low-density lipoprotein cholesterol, atherogenic index, lipid peroxidation, coronary artery risk index, and IL-6 and TNF-α in the liver whereas significantly lower levels of catalase, anti-oxidative enzymes activities, glutathione peroxidase, and superoxide dismutase in the kidney and liver. Whereas, *L. fermentum* MTCC: 5898-fermented milk improves these adverse physiological conditions (311). Similarly, feeding of *L. rhamnosus* MTCC: 5957 and *L. rhamnosus* MTCC: 5897 maintains healthy liver and kidney conditions of Wistar rats by increasing antioxidant activities and by decreasing lipid peroxidation, diet-induced hypercholesterolemia in the feces, kidney, liver, and blood of the rats. These probiotics also reduce the expression of mRNA of the TNF α and IL-6 inflammatory markers (312).

Lactobacillus plantarum has shown beneficial effects during the meta-analysis of a randomized controlled trial of 653 participants having cardiovascular diseases, lower diastolic and systolic blood pressure (313), total serum cholesterol, low-density lipoprotein cholesterol levels, atherosclerosis index, and hepatocyte steatosis risk. Furthermore, *L. plantarum* decreases liver triglyceride and cholesterol, whereas it increases cholesterol in feces and excretion of bile acid (314). *In vivo* study of Robles-Vera et al. (315) showed that *L. fermentum* CECT5716 and *Bifidobacterium breve* CECT7263 feeding prevent the development of hypertension, endothelial dysfunctioning, and increase in blood pressure in rats (315). *L. rhamnosus* GR-1 and *L. plantarum* 299v reduce the risk of myocardial infarction, improve ventricular function, and reduce the infarct size by decreasing the levels of leptin in rats (316, 317). Probiotics also decreased the levels of toxic circulating metabolites (indoxyl-sulfate and p-cresyl sulfate) associated with cardiovascular diseases and reduced mortality in patients undergoing dialysis (349). Probiotics exert beneficial effects on cardiovascular diseases through different mechanisms of action (i.e., improving the ratio of low-density and high-density lipids, lowering cholesterol levels, improving endothelial function, and regulating the immune cells) (**Table 5**).

CONCLUSIONS AND FUTURE PROSPECTS

Due to increasing antibiotic-resistant bacteria and antibiotic side effects, the use of antibiotics as a feed supplementation is prohibited in many countries. China also bans the supplementation of growth-promoting antibiotics in animal feed since January 1, 2021. Probiotics are considered as a good alternative for antibiotics, providing an alternative treatment option. Probiotics are widely used in human aquaculture, livestock, and poultry to promote health and counteract enteric pathogens. Probiotics are widely used for the management and treatment of bacterial, viral, parasitic infections as well as non-infectious disorders like mental disorders, cancer, allergies, and metabolic disorders. Concerning their mechanisms of action, probiotics have immunomodulatory and many other mechanisms of action, and work in diverse ways to exert beneficial effects on their hosts, if applied properly. However, concerning the safety and efficacy of probiotics, recent screening techniques rely on the capacity of microbes to elicit cytokine production mostly through cell lines or *ex vivo* isolated residual immune cells, even though they do not reflect the phenotype of intestinal cells. Awareness of the capability and usage of probiotics to improve the microbiota equilibrium in the host gut, to serve as immunomodulators, growth promoters, and to inhibit pathogenic infections is crucial from a practical point of view. It will help to make more progress by investigating more expertise, knowledge, and research on the understanding of probiotics, their specific mechanism of action, and their complete applicability for the safety of the host. More importantly, the safety of probiotics during application should also be carefully considered and strictly evaluated in the future in case of the emergence and spread of antibiotic-resistant bacteria between hosts. Thus, high-throughput validation approaches, as well as comprehensive and credible clinical, *in vivo*, and *in vitro* research on probiotic administration are

warranted to clearly illustrate the advantages and adverse effects of probiotics.

AUTHOR CONTRIBUTIONS

SC and LL designed, modified, and reviewed the manuscript. AR and GZ wrote the manuscript. All authors contributed to the article and approved the submitted version.

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