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Review

Systematic Review of Probiotics and Their Potential for Developing Functional Nondairy Foods

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Abstract: The gastrointestinal tract is an environment that hosts various microorganisms, including pathogens. Generally, pathogenic bacteria enter the host body through food and the gastrointestinal tract. These pathogenic bacteria can colonize or infiltrate host cells and tissues, causing various infectious diseases. In recent years, the protective role of probiotic bacteria against gastrointestinal pathogens has been carefully investigated. Probiotics have been found to modulate intestinal microbial flora and play a significant role in the gastrointestinal tract's function, especially by inhibiting the growth of pathogenic bacteria. However, the mechanism of action of probiotics has yet to be sufficiently proven and recognized. Several important mechanisms support the antagonistic effects of probiotics on various microorganisms, which is achieved, for example, through the production of different antimicrobial compounds, such as bacteriocins, various organic acids, antibiotics, antimicrobial proteins, and exopolysaccharides; mucosal barriers with mucosa and bacteria binding blockers; competition for nutrient uptake; and strengthening of the immune system. Accordingly, this review summarizes the recent studies that have examined the mechanism of action of probiotic bacteria and their beneficial effects in preventing pathogenic bacterial growth and improving gastrointestinal functions. Comprehending their mechanisms of action allows the selection of appropriate probiotic strains for specific applications in gastrointestinal dysfunction.

Keywords: probiotic; immunomodulatory; pathogen; fermentation

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1. Introduction

Probiotics can be defined as live microorganisms that exert beneficial effects on health beyond those inherent to essential nutrition when ingested in adequate quantities. The most common bacteria related to probiotic activity are *L. acidophilus*, *L. casei*, *L. reuteri*, *L. plantarum*, *L. casei* GG, *Bifidobacterium brevis*, *B. longum*, *B. infantis*, *B. animalis*, and *S. thermophilus*, and some varieties of yeast, such as *Saccharomyces boulardii* [1].

Many probiotic bacteria are part of the intestinal microbial flora. Some of them are increasingly inoculated into food to increase its nutritional content and protect the intestines to maintain intestinal microbial balance, improve intestinal microbial flora intestinal health, and increase the strength of the host immune system [2]. The mechanisms of action that are involved include induction at a pH below 4, inhibition of the growth of pathogenic bacteria, production of lactic acid, a decrease in intestinal permeability, an increase in lactase activity, competitive effects on other pathogenic bacteria, and reductions in digestion time. Furthermore, the advantageous effects of probiotic bacteria with respect to improving host health include decreasing the inflammatory response of the intestine [3], reducing cholesterol through its absorption [4], changing the microbial flora by suppressing the growth of pathogenic bacteria through the synthesis of antimicrobial compounds [5], neutralizing unwanted compounds (enterotoxins, ammonia, and toxic biological amino acids), intensifying immunity (lymphocyte and macrophage activity) and enhancing intestinal immune

response [6], decreasing lumen pH and inhibiting *Helicobacter* growth, and suppressing bacterial growth through direct binding to Gram-negative bacteria [7].

For these reasons, many probiotic bacteria (*L. acidophilus*, *Bifidocaterium* spp., *L. casei*, and *S. salivarius* spp. *thermophilus*) have been incorporated into commonly consumed dairy products to exert specific effects on the intestine, influencing intestinal mucus production and reducing permeability or increasing local or systemic immunity. After consumption, probiotic bacteria can survive in the severe conditions in the stomach and gastrointestinal tract (this may include probiotics capable of resisting acid, enzymes, oxygen, and bile). Antibiotic resistance may also assist them in surviving in the presence of medication and other antimicrobial compounds. They have the strength to stay in the gastrointestinal tract by passing through the upper gastrointestinal tract and adhering to the surface of the gastrointestinal mucosa, which prevent their washing away by bowel movements, enabling their permanent and temporary substantiation and accelerated reproduction in the gastrointestinal tract. They function in the intestine and increase their probability of survival in the intestine by producing inhibitory metabolites or antagonists against carcinogenic and pathogenic bacteria and exert various therapeutic effects by stabilizing the microbial flora of the intestine so that they can affect host health positively [8].

Appropriate amounts of these probiotic bacteria should be available in food and consumed daily to obtain the health effects provided by probiotics (Table 1) [9]. Consequently, probiotics' impact on the host depends on the probiotic, type of infection, dosage, and treatment duration. The effective dose in humans is 10^7–10^9 CFU/mL, which can be achieved by consuming at least 100 g of 10^6–10^7 CFU/mL of the product daily [10].

Criteria and safety assessments are needed for the selection of new probiotic strains, including identifying and characterizing nonpathogenic strains with antagonistic properties against pathogens in the host or other pathogen control systems; therefore, probiotic bacteria must have a human origin and be subject to safety assessment to ensure that they are nontoxic, nonmutagenic, nonpathogenic, nonsensitive. Consumers must also be able to tolerate food with a high number of cells that exhibit durability in such products. However, how these particular actions work and how the host controls them are still being determined. Therefore, how to select probiotics for use is still poorly understood [11].

Most studies carried out in humans have been based on probiotics isolated in feces. What happens in the upper reaches of the colon, cecum, or ileum can be very different. On the other hand, viability could be better in the dairy products in which probiotics have been incorporated. To properly assess the viability of these probiotic bacteria, it is necessary to be rigorous with respect to the methodology used to evaluate them. Furthermore, viability can be improved with the proper selection of acid- and bile-resistant strains; the use of impermeable oxygen containers, two-stage fermentation, and microencapsulation; the incorporation of micronutrients such as peptides and amino acids; and sonication of the bacteria, such as in yogurt. Research on the mechanisms of action of probiotics; the repercussions of their use regarding immunity, the intestine, and allergy; and their favorable nutritional effects continues, requiring the efforts of gastroenterologists, allergists, immunologists, nutritionists, and the dairy-products industry [12–15]. Comprehending the mechanisms of action of probiotic bacteria will allow the selection of the appropriate probiotic strains for specific applications in gastrointestinal dysfunction, so this review discusses recent findings on the mechanisms of action of probiotic bacteria against pathogenic bacteria.

Table 1. Health effects of some probiotics.

Probiotic	Health Effect	Reference
L. plantarum	Relief of irritable bowel syndrome (IBS).	Stevenson et al., 2014 [16]
	Reduction of LDL-cholesterol. Reduction in the recurrence of diarrhea due to *Clostridium difficile*.	Nordström et al., 2021 [17]

Table 1. *Cont.*

Probiotic	Health Effect	Reference
L. casei	Immune modulation.	Galdeano et al., 2015 [18]
L. rhamnosus	Treatment of acute rotavirus and antibiotic-associated diarrhea.	Guandalini et al., 2017 [19]
	Treatment and prevention of allergies.	Tomaro-Duchesneau et al., 2014 [20]
L. acidophilus	Activation of the immune system in patients with IBS.	Öhmanet et al., 2009 [21]
	Reduction of serum cholesterol.	Lee et al., 2010 [22]
	Reduction in rotavirus and antibiotic-associated diarrhea.	Ahmadi et al., 2015 [23]
L. salivarius	Relief of IBS symptoms and modulation of the intestinal microbiota.	Sierra et al., 2010 [24]
L. reuteri	Reduction in rotavirus and associated diarrhea.	Urbanska et al., 2016 [25]
	Immune modulation.	Engevik et al., 2021 [26]
Bifidobacterium breve	Immune modulation and stimulation. Reduction in IBS symptoms.	Choi et al., 2022 [27]
B. animalis	Increased IgA secretions.	Solano-Aguilar et al., 2018 [28]
B. longum	Allergy treatment.	Miraglia Del Giudice et al., 2017 [29]
Escherichia coli Nissle 1917	Fewer relapses in IBS disease. Immune modulation. Recovery from ulcerative colitis. Exclusion of *E. coli* pathogens.	Schultz et al., 2017 [30]
B. lactis	Reduction in the frequency of rotavirus and traveler's diarrhea. Inhibitory effects against *Helicobacter pylori*.	Cruchet et al., 2015 [31]
S. thermophilus	Improvement in lactose intolerance. Prevention of rotavirus diarrhea	Kora, 2022 [32]

2. Probiotics and Gut Microbiota

The intestinal microbiota is dispersed throughout the digestive system, and the highest concentration of microorganisms and metabolic activity are found in the large intestine [33]. The microbiota population of an average adult is presented in Figure 1. Diet is the main factor that influences the intestinal microbiota; additionally, diseases and genetic factors influence microbiota composition, and there has been extensive research on the role of antibiotics in the gut microbiota [34]. The primary function of the intestinal microbiota is to recover energy from digested food in the gastrointestinal tract through fermentation processes. Different groups of bacteria collaborate, mainly lactic acid bacteria, to degrade the organic matter in digested food. It is estimated that about 7 to 8% of the total daily energy is derived from the fermentation of the intestinal microbiota [35]. Other beneficial aspects of the fermentation processes include stimulating the immune system response and inhibiting the growth of pathogens. Furthermore, the microbiota strongly stimulates the maturation of the lymphoid tissue associated with the intestine [36]. The intestinal microbiota provides an essential stimulus for the immune system's maturation and the development of its functions. It influences several intestinal functions, playing vital roles in nutrition, maintaining the integrity of the epithelial barrier, and developing mucosal immunity [37,38].

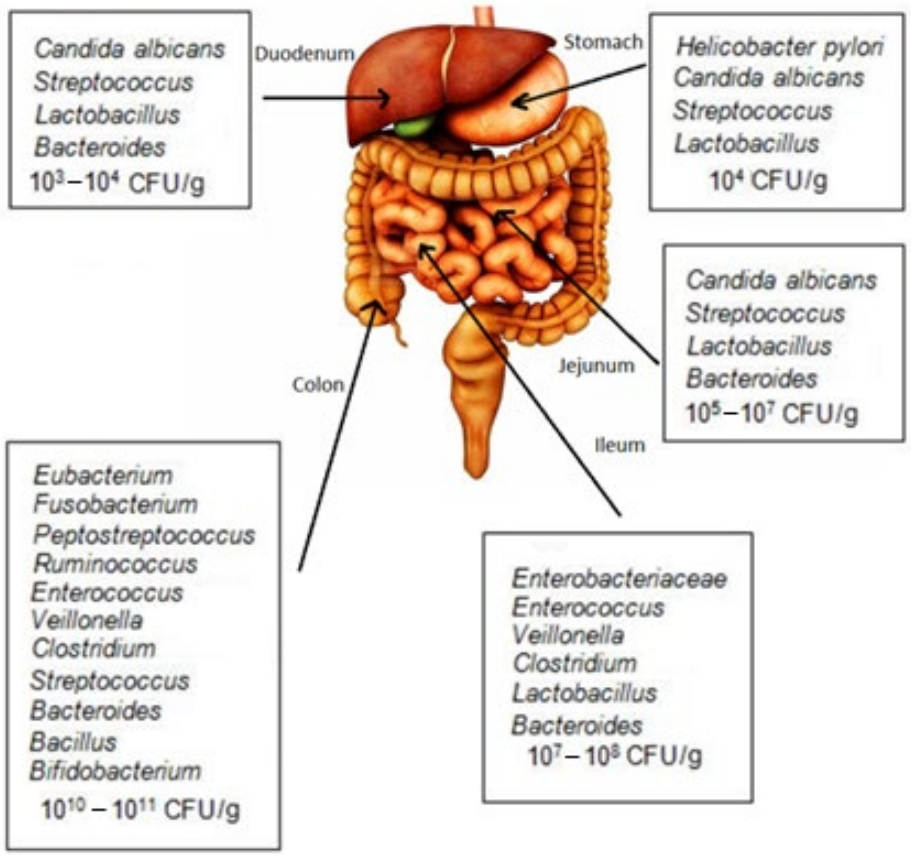
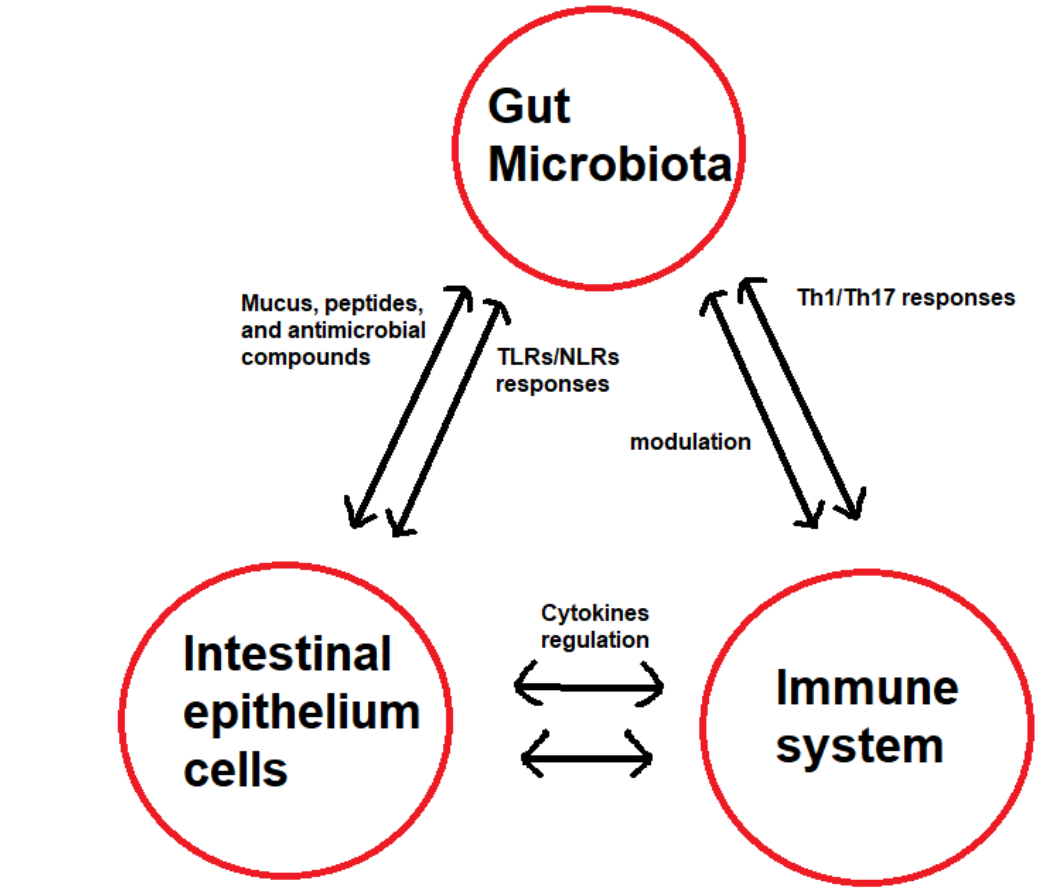


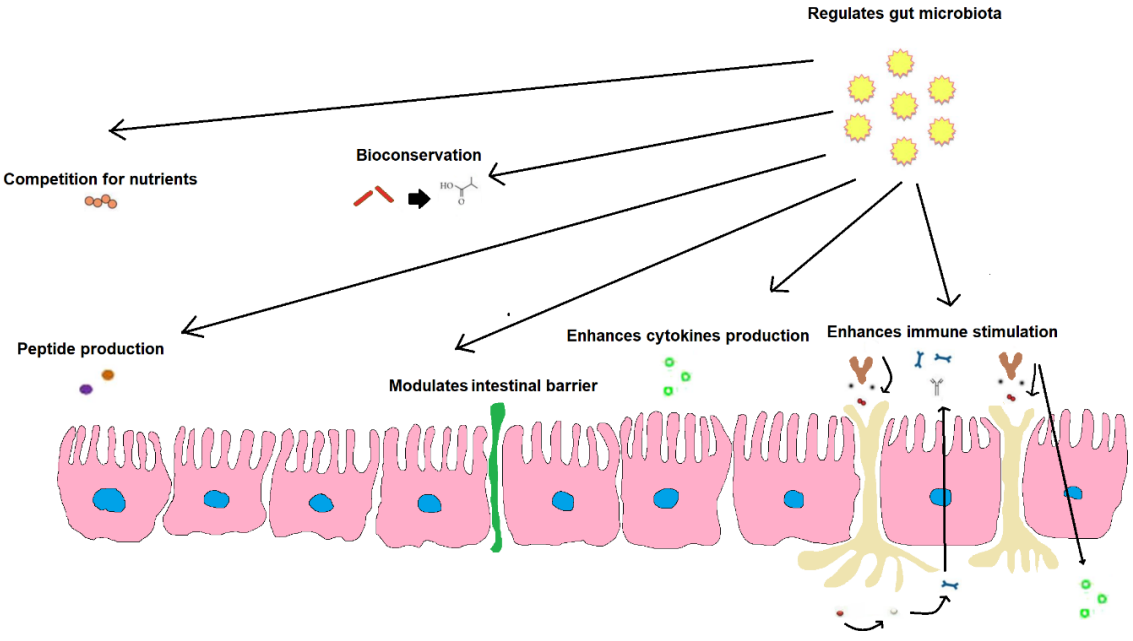
Figure 1. Microbiota composition in different parts of the digestive system.

Probiotics can help the cells of the intestinal immune system so that they respond appropriately to external stimuli. This is crucial to avoid inappropriate immune responses, such as allergies or autoimmune diseases. These cells monitor pathogen entry and coordinate defense via the innate immune system, including macrophages, neutrophils, eosinophils, natural killer cells (NKCs), intestinal epithelial cells (IECs), and M cells [37]. Dendritic cells are crucial for the development of an efficient adaptive immune response. Most cells recognize bacterial antigens through the toll cell surface receptors that specifically interact with bacterial walls and antigens [39]. The main idea is that probiotics can affect the mucosal immune system by improving the entire innate immune system. Probiotics have been reported to modulate innate and acquired immunity [39].

Probiotics can also interact with endogenous bacteria and mucosal cells to induce or modulate the immune response. The innate immunity system regulates infections until the adaptive immune response can take over; therefore, it must perfectly discriminate between self and nonself by activating cell receptors, leading to intracellular signaling and cytokine induction. Thus, with the participation of IECs, the intestinal microbiota and the immune system can maintain a balance, which is exemplified in Figure 2a. The probiotics that colonize the intestine are responsible for helping with many biological processes, such as in the fermentation of substances that cannot be digested and in the synthesis of necessary vitamins. Still, probiotics are also part of the first line of defense of the intestinal barrier, which is the selective barrier responsible for preventing harmful substances and pathogenic bacteria from passing into the blood and allowing necessary nutrients, electrolytes, and water to pass through (Figure 2b).



(**A**)



(**B**)

Figure 2. (**A**) Relationship between the intestinal microbiota, immune system, and intestinal epithelium cells. (**B**) Mechanisms through which gut microbiota regulates the intestinal barrier via nutrients completion, bio-conservation of nutrients, peptide production, immune system stimulation, and cytokines modulation.

3. Stability and Survival of Probiotic Bacteria during Crossing through the Gastrointestinal Tract

Low pH and pepsin's antimicrobial properties prevent the entry and survival of probiotic bacteria in the intestine [40]. Consequently, survival in such critically acidic conditions is one of the most significant physiological challenges that probiotic cultures must endure when orally administered. To address this challenge, probiotics can be combined with other food products to enable such microorganisms to survive during the digestive process (Figure 3). Probiotic bacteria must survive the gastric barrier and the small intestine environment, which are significant obstacles for probiotic strains for them to pass through the gastrointestinal tract and produce the desired health benefits. Although the small intestine's pH (7 to 8) does not significantly threaten probiotic survival, pancreatin and bile salts in the small intestine may have deleterious effects by inhibiting probiotic bacterial growth. Studies investigated four strains of *Enterococcus faecium*, which survived properly at pH 4 and lost some viability at pH 3, but none survived at pH 2. Additionally, all four strains of *Enterococcus faecium* were resistant to bile salts. These results imply that all four *Enterococcus strains* may be immune to the effects of pepsin during gastric transfer and are resistant to the pancreatic digestive processes [41].

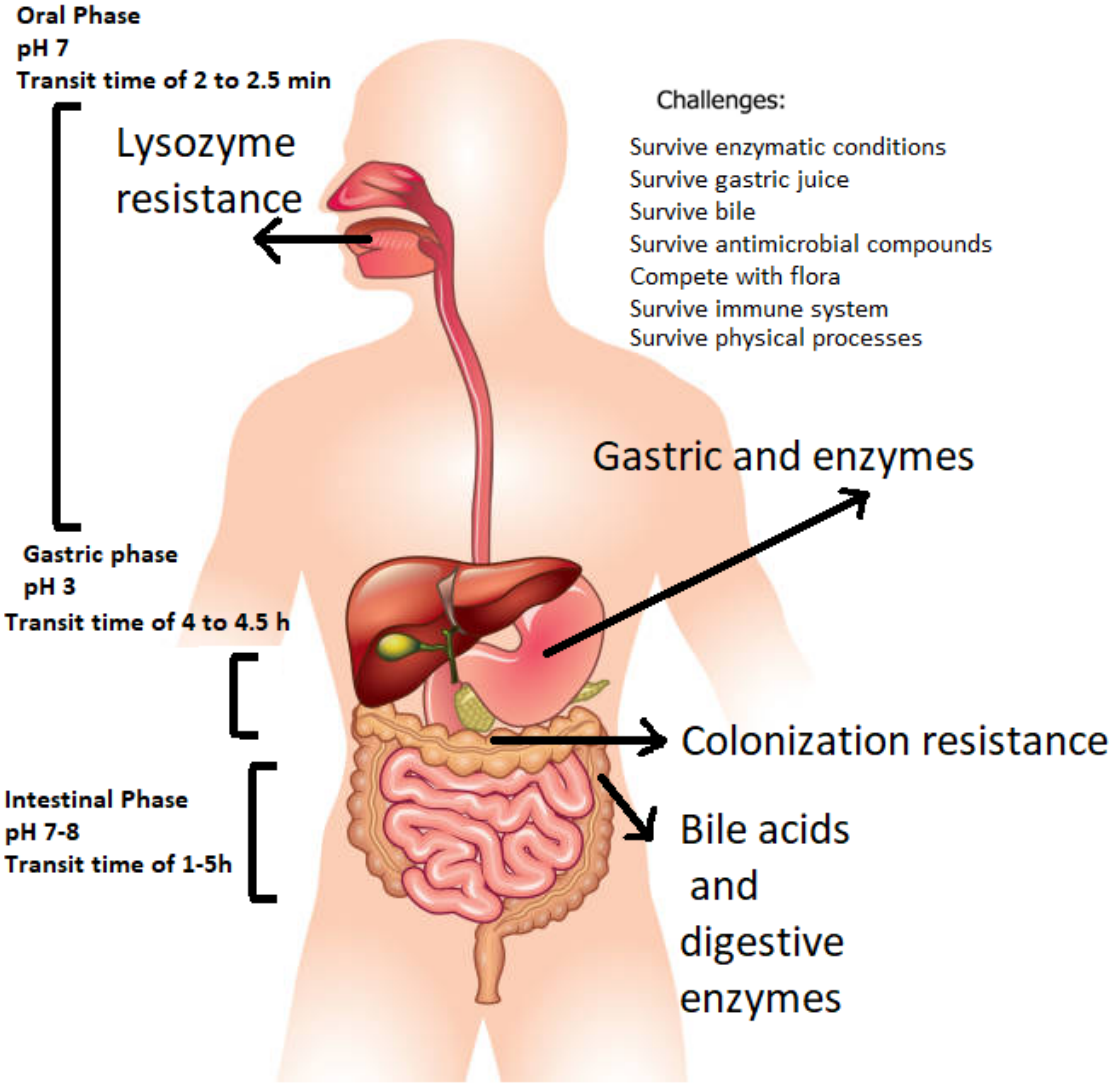


Figure 3. Challenges facing probiotic bacteria in the gastrointestinal tract and digestive system.

4. Mechanism of Action of Probiotics to Inhibit Food-Borne Pathogens

The protective role provided by probiotic bacteria against gastrointestinal pathogens and their mechanisms of action have been thoroughly investigated. Probiotics interact at all levels of the gastrointestinal tract, including the epithelial layer, the mucosal layer, and gut-associated lymphoid tissue (GALT). These interactions are considered a criterion for selecting new probiotic strains for human consumption. The specific pathways and critical mechanisms that affect probiotics' effects are still unknown [42]. Nevertheless, some mechanisms of action have been identified (Figure 4). The mechanisms of action involved include induction at a pH lower than 4, inhibition of the growth of pathogenic bacteria by producing bacteriocins, lactic acid production, decreased intestinal permeability, increased lactase activity, competitive effects on other pathogenic bacteria through adherence, inhibition of rotaviruses, increased production of T-helper cells, and increased production of immunoglobulin A (Figure 4).

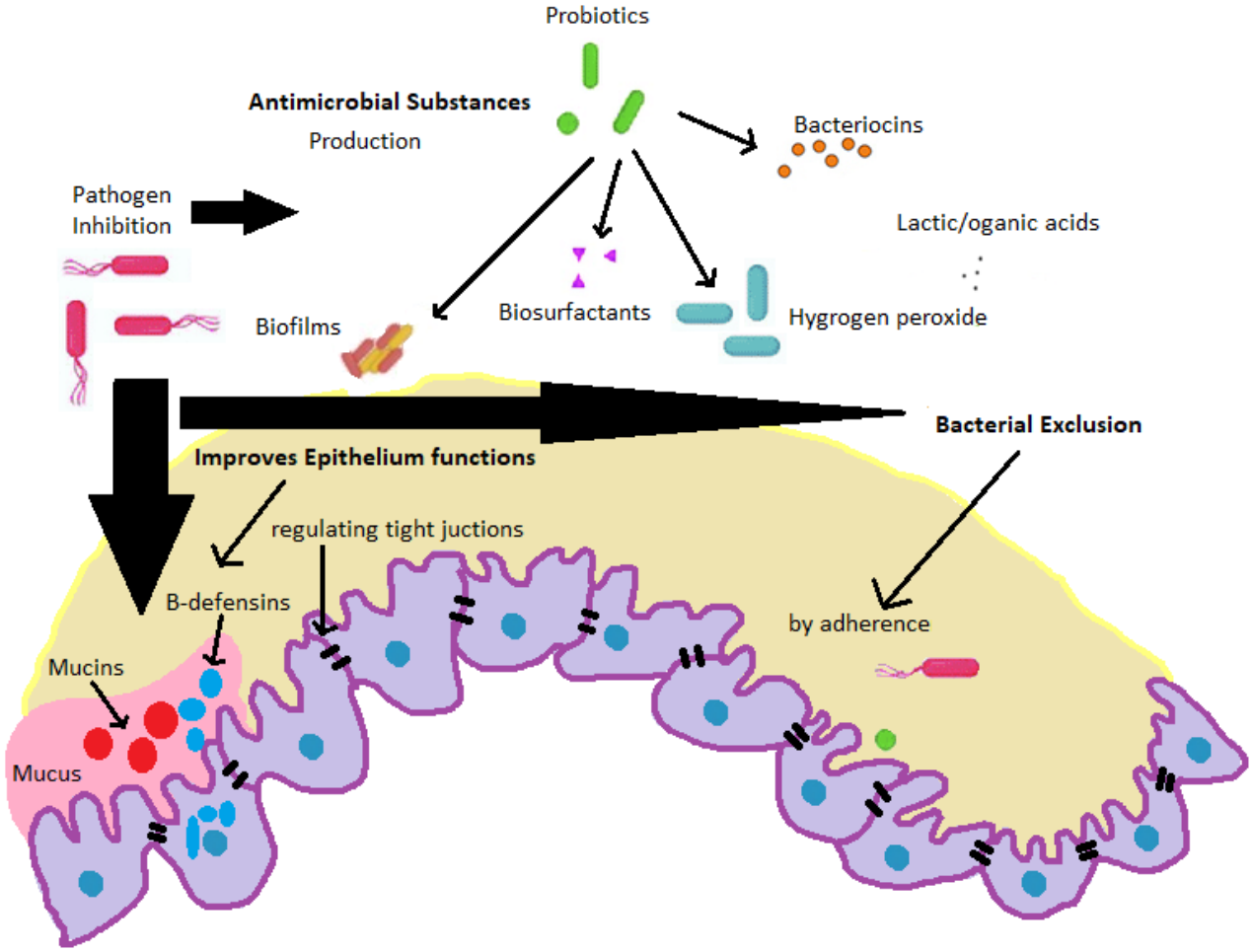


Figure 4. Mechanism of action of probiotics in inhibiting pathogenic bacteria.

4.1. Competition with Pathogens for Binding Sites and Food Sources

Competitive deprivation is referred to as a condition in which one bacterium competes more actively for gut receptor sites than other microorganisms [43]. Probiotics compete with pathogenic bacteria for gut nutrients, minerals, and receptors to activate mucosal immunity [44].

In addition, probiotics compete with bacterial binding sites on intestinal epithelial surfaces. Probiotics are chosen based on their ability to bind in the human intestinal mucosa via adherence. The adhesion and colonization of pathogenic bacteria on the human mucosa may cause infections [45]. Specific requirements must be considered when a

microorganism is selected as a probiotic. Consequently, the first stage for *Lactobacillus* strains is adhesion to intestinal epithelial cells for colonization and further interaction with the gut, critical for inhibiting pathogenic bacteria and enhancing immune system function [45]. Additionally, evidence demonstrates that *Lactobacillus delbrueckii* efficiently inhibits *Escherichia coli* adhesion to Caco-2 cells [46].

Consequently, Consequently, *Lactobacillus delbrueckii* can help to prevent and treat the gastrointestinal infections caused by *Escherichia coli* [46]. *Lactobacillus delbrueckii* has a high adhesion capacity in the gut, so can compete with binding sites to pathogenic bacteria with receptors in epithelial cells, block contact between epithelial cells and pathogenic bacteria, and eventually protect epithelial cells. The adhesion mechanism of probiotics is complicated and needs to be better understood. One theory explains adhesion as a specific interaction between bacterial surface components and their receptors in gut epithelial cells [47]. Adhesion could involve electrostatic and hydrophobic interactions with lipoic acids and particular structures such as polysaccharides and lectins. Probiotics communicate directly with epithelial cells at the cell surface through compounds such as DNA, lipoic acids, complex polymers, and polysaccharides. Additionally, probiotics communicate indirectly with epithelial cells by producing bioactive metabolites. Furthermore, cell surface proteins have been determined to promote adhesion to surfaces that facilitate attachment to the mucosal layer. The role of exopolysaccharides produced by some probiotic strains in promoting adhesion has also been investigated carefully [48]. Probiotics compete for food sources and utilize the nutrients consumed by pathogenic bacteria to grow and multiply and contend with pathogenic bacteria. Consequently, food competition among probiotics, intestinal pathogens, and microbial flora may play a significant role. Various studies have revealed that probiotics such as *Lactobacillus rhamnosus* GG and *Lactobacillus plantarum* can inhibit the growth of enteropathogenic *Escherichia coli* in the gastrointestinal tract [49,50]. Also, this can happen with *Clostridium difficile*, a pathogenic microorganism that grows on monosaccharides. Probiotic bacteria are more effective than *Clostridium difficile* in fermenting monomeric glucose, sialic acid, and N-acetyl glucosamine in the colon, inhibiting *Clostridium difficile* growth [51].

Another example is the probiotic *Bifidobacterium adolescentis* S2-1, which competes with *Porphyromonas gingivalis* for vitamin K and inhibits *P. gingivalis* growth [52]. Probiotic bacteria can also alter the physical environment so that pathogenic bacteria cannot survive. Probiotic strains of *Lactobacillus paracasei* and *Lactobacillus rhamnosus* possess inhibitory effects on *Salmonella typhimurium* and *Listeria monocytogenes* via biofilm formation, displaying strong competition, deprivation, and displacement mechanisms towards pathogens [53].

4.2. Preventing the Adhesion of Pathogenic Bacteria to the Intestinal Epithelium by Producing Inhibitory Agents

Probiotics can prevent gastrointestinal infections due to their ability to produce substances with antimicrobial properties that inhibit pathogenic bacteria growth by improving the intestinal mucosal barrier functions by secreting intestinal protective metabolites such as arginine, glutamine, short-chain fatty acids, and conjugated linoleic acids. A broad range of antipathogenic compounds, such as bacteriocins, ethanol, organic acids, diacetyl, acetaldehydes, hydrogen peroxide (H_2O_2), and peptides, are produced by probiotics [54,55]. These compounds, especially peptides and bacteriocins, increase the membrane permeability of target cells, which polarizes the membrane and, ultimately, leads to cell death. The production of H_2O_2 by probiotics causes the oxidation of sulfhydryl groups. Consequently, the denaturation of membrane lipids by several enzymes increases pathogenic microorganisms' membrane permeability and their decay. Organic acids, especially acetic acid and lactic acid, are the main antimicrobial compounds that have a strong inhibitory effect against pathogenic Gram-negative bacteria such as Helicobacter pylori, decreasing intracellular pH [56].

Probiotic bacteria also produce antibiotics. Rutarin is an antibiotic with inhibitory properties against Gram-positive and Gram-negative bacteria, yeast, fungi, protozoa, and

viruses [57]. Some nonpathogenic *Escherichia coli* strains produce an antimicrobial protein called colicin, which can restrain the growth of *Escherichia col* [58]. Bacteriocins are generated by many Gram-positive and Gram-negative bacteria [59]. The bacteriocins produced by Gram-positive bacteria (usually *lactobacilli*) have an inadequate range of activity. They have antimicrobial activity against strains that similar to the bacteriocin producer, but some bacteriocins additionally inhibit food-borne pathogenic bacteria such as *Listeria monocytogenes* [60]. Many bacteriocins show intense activity against pathogenic bacteria such as *Bacillus*, *Listeria*, *Clostridium*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *enterococci*.

Unlike antibiotics, which target specific enzymes, most bacteriocins kill target cells by producing cavities and penetrating the cytoplasmic membrane. This creates the need for pathogens to produce resistance to bacteriocins. There are reports of some bacteriocins appearing on Gram-negative bacteria, but the outer membrane of Gram-negative bacteria acts as a barrier to foreign agents. Bacteriocins typically have an insignificant inhibitory effect on Gram-negative bacteria [61]. Factors such as bacteriocin concentration, purity, and the target bacterium's physiological stage are crucial for bacteriocin's bactericidal inhibitory effect [60]. Bacteriocins cause cavities in the two phospholipid layers of membranes by causing proton motility, discharging ATP, and leaking nutrients, which damage the integrity of the cell [62]. Similarly, bacteriocins have several different mechanisms of action, including changes in enzymatic activity, inhibition of spore germination, and inactivation of anionic carriers, achieved by creating specific and nonspecific pores in the membrane [60]. Therefore, bacteriocin biosynthesis by lactic acid bacteria is one of the beneficial antimicrobial properties that are essential for eliminating pathogenic bacteria from fermented foods and the gastrointestinal tract [63,64]. Few studies have been conducted on cell aggregation between probiotic and pathogenic bacteria, demonstrating that proteins in the supernatant of probiotic bacteria are involved in cell aggregation and are frequently surface proteins [65]. One of these proteins is the APF protein, recognized as an efficient surface protein in *lactobacilli* cell aggregation [66].

Iron plays an essential role in bacteria's metabolism, enhancing its growth and function as a regulator of gene expression [67]. Therefore, iron siderophore production was also described as an antimicrobial agent of probiotics to inhibit the adhesion of pathogenic bacteria, which is a chelator with a high affinity for iron [68]. Furthermore, iron availability influenced the growth of *Salmonella typhimurium* [69]. Moreover, the probiotic *Escherichia coli Nissle* reduced the growth of *Salmonella typhimurium* in the gut [70].

Exopolysaccharides (EPSs) are extracellular biopolymers produced by many lactic acid bacteria and *bifidobacteria*. The exopolysaccharides produced by intestinal lactobacilli and *bifidobacterial* can enhance intestinal mucosa adhesion [71]. Also, the EPSs produced by *bifidobacterial* can regulate intestinal microbial flora by emerging as fermentable substrates. On the other hand, bacterial EPS can slow bacteriophages' activity [71]. Probiotic bacteria can produce decongested bile acids derived from bile salts. Decongested bile acids show stronger antibacterial activity than the bile salts synthesized by the human organism [71]

4.3. Organizing a Mucosal Barrier with Mucin Secretion

As the first line of defense, the mucosal immune system is essential to protect against invasive pathogens. The mucosal immune system is composed of physical components (mucosa), molecules (antimicrobial proteins), and cellular components that operate synergistically to prevent microbes from invading [72]. The upper layer consists of a carpet of mucus, cilia immersed in a layer of periciliary fluid, epithelial cells, ciliated cells, and a mucus-secreting cell (goblet cell) with mucin granules (Figure 5).

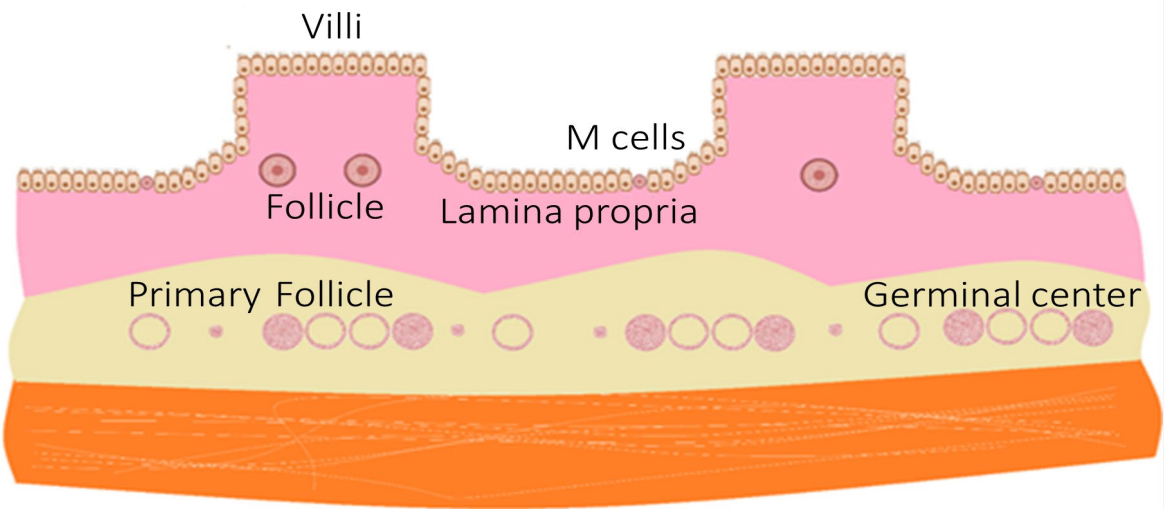


Figure 5. Mucosal barrier composition.

The intestinal mucosa is a barrier, and the gel layer embraces the epithelial tissue. Mucins are a group of high-molecular-weight glycoproteins, and they are critical components of the mucosal layer in epithelial tissues. Subsequently, one of the physiological changes potentially caused by probiotics in epithelial tissues is that they stimulate mucus production.

The mucosa is the internal layer that covers the body cavities exposed to the digestive tract. This includes the oral cavity, pharynx, esophagus, stomach, small intestine, and large intestine [73]. Mucin is one of the most vital bacterial fermentation substrates, resulting in fermentation products of short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate [74].

Butyrate fuels enterocytes for up to 70% of the energy needed and helps regulate and promote epithelial cell growth [75]. Studies have revealed that probiotics can improve mucosal and epithelial barrier functions by producing short-chain fatty acids, including butyrate, a key molecule in maintaining intestinal homeostasis [76]. Specifically, butyrate induces the differentiation of macrophages, which have potent bactericidal activity against pathogens, by reducing mTOR kinase activity and inhibiting histone deacetylase, increasing the secretion of antimicrobial peptides. SCFAs help maintain the proper pH in the intestinal lumen, which is fundamental for activating bacterial enzymes and metabolizing foreign and carcinogenic compounds in the gut. Also, they increase peristaltic motility and reduce the transfer time of intestinal secretions by lowering the intestinal lumen's pH [77].

Probiotics can increase mucus secretion and attract water to the colon by freeing the bile salts, softening the stool, and helping expel stool [78]. Secretory immunoglobulin A (SIgA), produced by the intestinal mucosa, can prevent the invasion of pathogens and have an essential protective effect on the intestinal mucosa [79]. Probiotics also stimulate the gut defense pathways by promoting the production of defensins, which are cationic antimicrobial peptides that are produced in several cell types, such as Paneth cells, which are in the small intestinal crypts and intestinal epithelial tissues. These peptides, or low-molecular-weight proteins, are active against bacteria, fungi, and viruses and modulate the functions of the intestinal barrier. *Bifidobacterium longum* and probiotics stimulated the secretion of defensins from epithelial cells to help treat patients with ulcerative colitis [80]. On the other hand, probiotics have been investigated in biochemical pathways, being found to inhibit β glucuronidase activity to enhance the production of folate, which eventually regulates DNA methylation patterns, protecting the genome's integrity [81].

4.4. Immunomodulation

Probiotics create a natural barrier (Figure 6) against pathogenic bacteria and inhibit the bacteria from attaching to the intestinal epithelial cells, thus increasing immunity

due to their ability to adhere to the intestinal mucosa. Immunomodulation can occur through direct or indirect mechanisms. The direct mechanisms involve the interaction of an immunomodulator and its metabolite with a component of the immune system's cell. Therefore, the modulatory stimulus directly causes a favorable modification in the functions of the cells of the immune system (Figure 6). This principle is fundamental in many cases to inhibit and treat infections and restore microbial balance in the intestine [38]. Furthermore, probiotics can stimulate the gut immune system by inactivating virulence-favorable conditions [82].

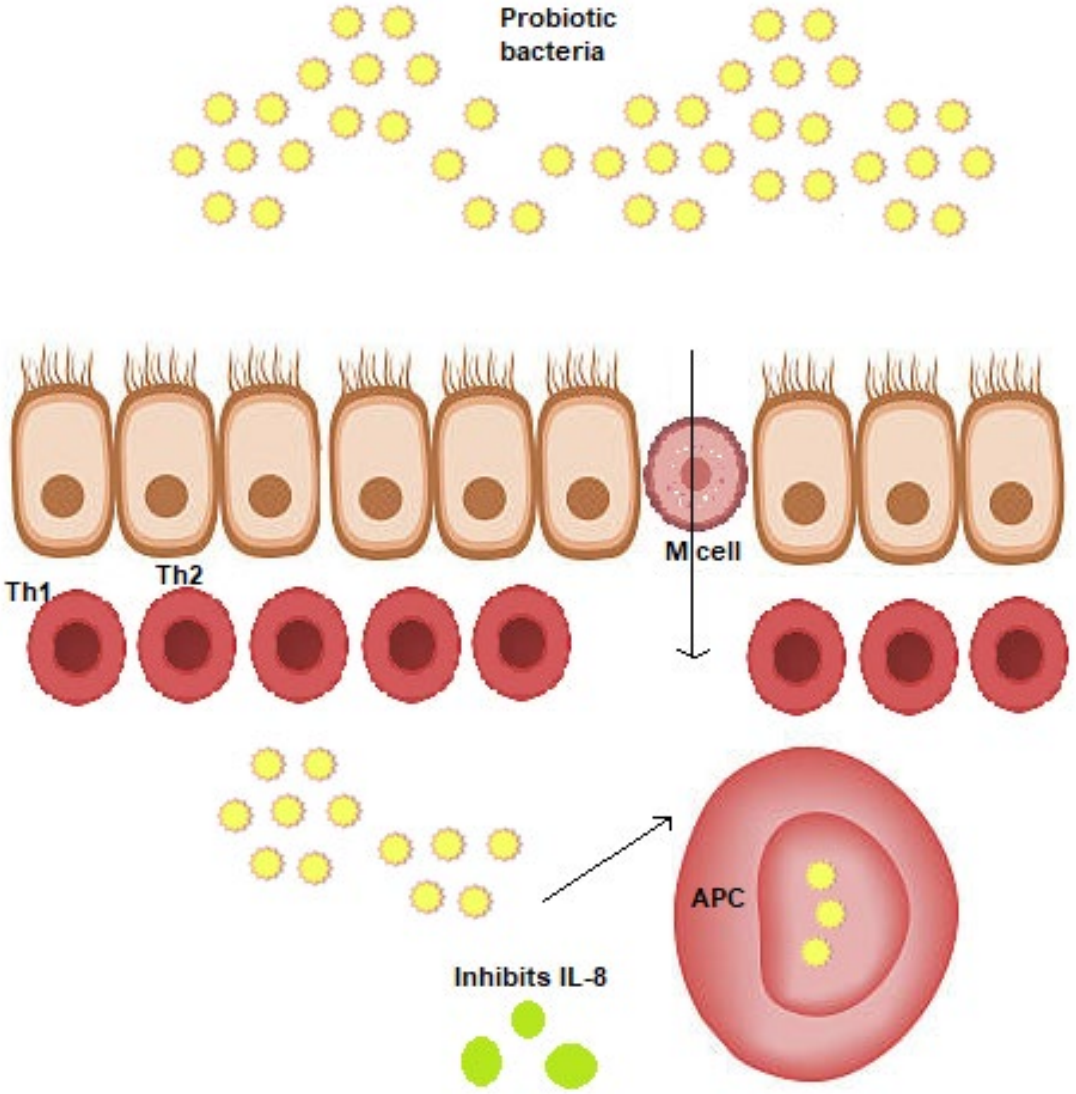


Figure 6. Immunomodulatory effect of probiotics.

The gastrointestinal tract has the biggest gathering of lymphatic tissue, so is the location where the human body has the highest immune capacity. The immunizing ability of *Lactobacillus* strains is used as a standard to evaluate probiotics. Immune cells are the first to respond to various pathogens, tumors, or threats. The gut's microbial flora regulates the immune system by producing molecules with immune and anti-inflammatory functions. Probiotic bacteria interact with epithelial cells, dendrites, monocytes, macrophages, and lymphocytes [83]. Humans have developed a very complex systemic and mucosal immune system. Mucosal immunity can be recognized as the first line of defense that decreases the need for systemic immunity [84]. Probiotics can modulate the mucosal and systemic immune systems [85].

The innate immune system is inherited and protects the gut against infection by other pathogens. The innate immune system is the first line of defense against natural killer (NK) cells as the primary cell involved in the spontaneous identification and degradation of invasive targets (virus-infected cells, tumor cells, bone marrow stem cells, and embryonic cells). Intrinsic immune responses play a considerable role as the first line of defense and promote developed immune responses. Several strains of *lactobacilli* improve the innate and acquired immune response by stimulating dendritic cell (DC) maturation. Consequently, many reports indicate that lactic acid bacteria like *Lactobacillus* and *Bifidobacterium* efficiently strengthen innate and acquired immunity, preventing gastric mucosal allergies and defending against intestinal pathogen infections [86].

Lactobacillus strains can intensify specific acquired immune responses in mice (Paturi). The immune response efficiency depends on the B and T lymphocytes that bind to particular antigens. The initial response to pathogens is caused by pattern recognition receptors (PRRs), which bind to pathogen molecular patterns (PAMPs) [87]. The innate immune system recognizes a large group of components, such as lipopolysaccharides (LPSs) and lipoic acid, through pattern recognition receptors (PPRs), such as adaptive immune responses via antigen-presenting cells (APCs). Furthermore, it enables them to identify foreign substances that induce immunological defense mechanisms, like producing pro-inflammatory and anti-inflammatory cytokines [87]. Macrophages, dendritic cells (DCs), and B cells express Toll-like receptors (TLRs) [88]. The activation of TLRs starts with the dendritic response, which produces cytokines and regulates the cell surface [89]. TLRs recognize bacterial cells and APCs and utilize them at the immune system's convenience [89].

Probiotics can stimulate the immune system by absorbing antigens from dead cells. The consumption of nonliving cells significantly decreases cytokine production compared to the consumption of live probiotic bacteria [90]. Probiotic bacteria can interact with epithelial mucosal cells by communicating with immune cells in the receptor and improving mucosal immune response. Dead bacteria have multiple interactions with immune cells, and they are quickly cleared from the intestinal lumen [91]. Probiotics stimulate immune responses by activating T cells, which are utilized to produce cytokines, increase Th1 responses, and weaken Th2 responses [91].

Probiotics can restore compromised NK cell activity and increase the production of antibodies, mainly IgG, IgM, and interferon-γ. Probiotics can restore and promote macrophages' activity toward the phagocytosis of pathogens, promoting and strengthening phagocytic agents that terminate toxic agents, reactive oxygen intermediates, and lytic enzymes in various inflammatory reactions. Probiotics can increase the production of mucosal antibodies, especially IgA, and increase the secretion of immunoglobulin, reducing the number of pathogenic microorganisms in the intestine and improving the composition of the microbial flora [92]. Probiotics modulate the intestinal microbial composition by keeping balance and suppressing the growth of potentially pathogenic bacteria in the gut. It was reported that *Lactobacillus acidophilus* or *Lactobacillus casei* reduced fecal coliform growth [93]. Probiotics also alter gut microbial flora to specific beneficial bacteria, including *Prevotella* and *Oscillibacter*. These bacteria were recognized to produce anti-inflammatory metabolites [94].

The gastrointestinal microflora interacts with epithelial cells and the immune system. The cytokine response is initiated by interleukin-8 (IL-8) release, which drives neutrophils' and monocytes' migration into the mucosa. Monocytes and dendritic cells in the lamina propria layer can induce tumor necrosis factor (TNF-α), IL-1, and IL-6. IL-1 and IL-6 stimulate CD41 T cells (type 1), creating various cytokines, including IL-4, IL-5, IL-6, and γ-interferon [95]. Moreover, probiotic bacteria can neutralize the inflammatory response to infections and are considered essential mediators in regulating the gastrointestinal tract. This role may be critical in alleviating the gastrointestinal and inhibiting inflammatory conditions after infection, including irritable bowel syndrome in the gastrointestinal tract [96].

Furthermore, probiotics regulate immune responses by modulating the inflammation caused by pathogens and inhibiting the production of inflammatory cytokines. Some

probiotics have been reported to inhibit pathogenic bacteria by attaching to the intestinal epithelium and decreasing the expression of inflammatory cytokines caused by pathogens. It was reported that 11 strains of probiotic bacteria could inhibit *Escherichia coli* adhesion to Caco-2 cells and inhibit the IL-8 production caused by *Escherichia coli* in HT-29 cells [97]. *Lactobacilli* strains can modulate proinflammatory responses (TNF-α and IL-8) and anti-inflammatory responses (IL-10) in HT-29 and Caco-2 cells [98]. Furthermore, some strains of *Lactobacillus* can reduce the secretion of proinflammatory cytokines (IL-8) and increase the secretion of anti-inflammatory factors (IL-10) on intestinal epithelial cells [99]. Some probiotic strains are commonly considered as stimulating IL-12 production, increasing Th1 cell growth, and strengthening the immune system to prevent infections and cancers, while other strains essentially produce IL-10.

Probiotics can stimulate the growth of T-regulatory cells and immune responses. Probiotics can help treat inflammatory diseases such as allergies, irritable bowel syndrome (IBD), and autoimmune diseases [37]. The ratio of Th1 and Th2 cells is essential for the natural immune response [100]. Moreover, IFN-γ is a subset of cells (Th1) in the immune system response, which plays a crucial role in improving inflammatory responses [99]. Th1 moderates cellular immunity, capturing intracellular bacteria and viruses and secreting IFN-γ cytokines by Th2 responding to humoral immunity and IL-4 secretion [101].

Some studies confirmed that some probiotics improve local immunity and IFN-γ production, inhibiting allergy-related IL-4 secretion [37]. *Lactobacillus casei Shirota* (LcS) strengthens the immune system by stimulating the overproduction of IL-12 [37]. Moreover, LcS regulates the inflammatory responses of cytokines to macrophages and T cells in Peyer patches. *Lactobacillus casei shirota* modulates the production of IL-12 by improving macrophage activity [102]. Probiotics have antiviral properties that improve the cytotoxic potential of NK cells and the capacity for macrophage phagocytosis.

Probiotic cell wall components such as lipoic/lipotic acid in Gram-positive bacteria (*bifidobacterial* and *lactobacilli*) can inhibit the enzyme NO synthase by macrophages secreting tumor necrosis factor (TNF-α), which increases the activity of critical phagocytic receptors such as FcγRIII and TLR [103]. Probiotics can potentially interfere with virus replication by improving mucosal barrier function and producing innate and adaptive immune responses [104]. Table 2 illustrates the immunomodulatory effect of various probiotics.

Table 2. Immunomodulatory effect of various probiotics.

Probiotic	Immunomodulatory Effect	Reference
Lactobacillus gasseri	Modulation of intestinal epithelial cell proliferation and apoptosis	Di Luccia et al., 2022 [105]
Lactobacillus rhamnosus	Enhances phagocytic capacity	Sheih et al., 2001 [106]
Bifidobacterium lactis	Enhances phagocytic capacity	Maneerat et al., 2013 [107]
Bifidobacterium breve	enhances B cell proliferation with increased IgA	Rigo-Adrover et al., 2016 [108]
Streptococcus thermophilus	Stimulation of cytokine production in clonal macrophage and T-cell models	Dargahi et al., 2016 [109]
Lactobacillus acidophilus	Stimulation of cytokine production in clonal macrophage and T-cell models	Lee et al., 2016 [110]
Lactobacillus casei	Modulation of IgG secretory cells	Escamilla et al., 2012 [111]

5. Development of Nondairy Foods with the Incorporation of Prebiotics and Probiotics

Until a decade ago, yogurt and fermented milk were the most commercially widespread probiotic foods. However, new alternatives are being investigated, and some are entering the market to offer a wider variety of flavors and textures and even more suitable food matrices for these microorganisms. Among these alternatives are desserts, powdered milk for newborn babies, ice cream, butter, mayonnaise, and various types of cheese [112]. The use of milk as a basis for the development of probiotic foods is generally accepted by consumers due to its characteristic known flavors and aromas [113]. From the point of view of convenience as a substrate for probiotics, it has been well documented that milk-derived

substrates are the most acceptable media for the growth of probiotic microorganisms. In general, the main point to be considered when incorporating probiotics into foods is the selection of a probiotic strain compatible with the characteristics of the food matrix that favors its growth and survival. Other criteria to consider include ensuring that the food processing, packaging, and environmental conditions compatible with the survival of the probiotic to ensure product quality during the supply chain and storage. The addition of probiotics into food products must also not have adverse effects on the flavor or texture of the product [113].

Consumers' new behavioral trends and demands are leading to the setting guidelines in the use of food matrices other than the dairy matrix for these microorganisms, encouraging researchers and industry to explore new food matrices. The growth in the number of vegetarian and plant-based consumers is driven by health considerations such as avoiding the consumption of foods with cholesterol. Consumers who are lactose-intolerant or allergic to dairy proteins are also motivated to use nondairy alternatives [114]. Nevertheless, the application of probiotic cultures in nondairy media represents a great challenge since their viability depends on various interacting factors such as pH, hydrogen peroxide production, sugar concentration (osmotic stress), water activity, metabolites, storage temperature, oxygen levels, and the presence of competing and inhibitory microorganisms [115]. Tables 3 and 4 illustrate recent studies on nondairy food fortified with probiotic microorganisms and methods for incorporating probiotics into food matrices.

Table 3. Non-dairy food fortified with probiotic microorganisms.

Food Type	Food Matrix	Probiotic Microorganism	Growth Level	Reference
Fruit based	Apple juice, apple soaked in apple juice, apple soaked in dried apple juice	*L. casei spp. rhamnosus*	1.9×10^8 CFU/mL 4.5×10^5 CFU/g 1.8×10^8 CFU/g	Betoret et al. (2003) [116]
	Homogenized banana pulp	*L. acidophilus* CCRC 10695b free cells and cells immobilized on κ-beads carrageenan and Ca-alginate	8698–9716 log CFU/mL	Tsen et al. (2009) [117]
	noni juice	*Lactobacillus casei* and *Lactobacillus plantarum* and *Bifidobacterium longum*	close to 10^9 CFU/mL	Wang et al. (2009) [118]
	Granada juice	*L. paracasei*, *L. acidophilus*, *L. delbruekii* and *L. plantarum*	$2.9–9 \times 10^8$, $3.07–9 \times 10^8$, $3.6–9 \times 10^8$ and $3.9–9 \times 10^8$ CFU/mL respectively	Mousavi et al. (2011) [119]
	Melon juice	*L. casei* B-442	8.93 log CFU/mL (20 h fermentation) 8.3 log CFU/mL at end of 42 days of storage	Vidal Fonteles et al. (2011) [120]
Vegetable based	Juice for drinking	*L. acidophilus* LA 39 *L. casei* A4, *L. delbrueckii* D7, *L. plantarum* C3	$1.0–9.0 \times 10^9$ CFU/mL after 72 h of fermentation	Yoon et al. (2004) [121]
	Red beet juice	*L. acidophilus* LA 39, *L. casei* A4, *L. delbrueckii* D7, *L. plantarum* C3	$9.2 \times 10^8–27.8 \times 10^8$ CFU/mL	Yoon et al. (2005) [122]

Table 3. *Cont.*

Food Type	Food Matrix	Probiotic Microorganism	Growth Level	Reference
	Peanut milk	*B. pseudocatenulatum* G4	7.12–8.39 log CFU/mL	Mustafa et al. (2009) [123]
	Cabbage juice	*Lactobacillus casei* A4, *Lactobacillus debrueckii* D7, and *Lactobacillus plantarum* C3	$17.5 \pm 7.05 \times 10^8$ 72 h	Yoon et al. (2006) [124]
	Carrot juice with fructooligosaccharides	*Lactobacillus* delbrueckii subsp. bulgaricus (classified as DSM 20081 and ATCC 11842)	5.0–5.2 $\times 10^9$ CFU/mL	Nazzaro et al. (2008) [125]
		Lactobacillus rhamnosus (DSM 20711)	4.8–5.2 $\times 10^9$ CFU/mL	
Other grains and cereals	Nonfermented soy frozen dessert	*Lactobacillus acidophilus* MJLA1, *L. rhamnosus* 100-C and *Bifidobacterium lactis* BDBB2 *L. paracaseissp. paracasei* Lp-01 and *B. lactis* Bb-12 *Saccharomyces boulardii* 74012	>107 CFU/g after 28 weeks −20 °C	Heenan et al. (2004) [126]
	Soy milk	*L. delbrueckiissp. bulgaricus* Lb1466	7.88 log CFU/mL	Donkor et al. (2007) [127]
		S. thermophilus St1342	8.24 log CFU/mL	
		L. acidophilus L10	7.37 log CFU/mL	
		L. acidophilus La4962	8.81 log CFU/mL	
		B. lactis B94	8.44 log CFU/mL	
		B. longum Bl536	9.54 log CFU/mL	
		L. casei L26	9.13 log CFU/mL	
		L. casei Lc279	8.88 log CFU/mL	
	Soy milk supplemented fructooligosaccharides (FOS), inulin, mannitol, maltodextrin and pectin	*Lactobacillussp.* FTDC 2113, *Lactobacillus acidophilus* FTDC 8033, *Lactobacillus Acidophilus* ATCC 4356, *Lactobacillus casei* ATCC 393, *Bifidobacterium* FTDC 8943 and *Bifidobacterium longum* FTDC 8643	All strains showed viability exceeding 7 log CFU/mL after 24 h.	Yeo and Liong, (2010) [128]
	Soy milk with strawberry puree	*L. lactis* ATCC11545 and *L. lactis* LL3.	After fermentation and for 3 weeks at 6 °C the counts were greater than 8 log CFU/mL	Beasley et al. (2003) [129]
	Cereal pudding (corn and rice flour)	*Lactobacillus acidophilus* La5 and 1748, *Bifidobacterium animalis* Bb12, and *Lactobacillus rhamnosus GG*	highest growth of L. rhamnosus GG 8 log CFU/g, in 12 noon	Helland et al. (2005) [130]

Table 3. *Cont.*

Food Type	Food Matrix	Probiotic Microorganism	Growth Level	Reference
	Rice enzymatically treated with saccharolytic enzymes and formulated with 3% casein, 3% soybean oil and 0.4% calcium lactate, pectin and strawberry	*Lactobacillus acidophilus* and *L. casei* subsp. *Rhamnosus*	7.6×10^7 CFU/g.	WoonyaratanakoRnkit and Wongkhalaung (2000) [131]
	Drink based on oat flour (5.5%); saccharose (1.5%); combination aspartame, sodium cycle, and saccharin	*Lactobacillus plantarum* B28	7.5×10^{10} CFU/mL 6–8 h	Angelov et al. (2006) [132]
	Dilutions of commercial oat flours Adavena® M40 (M40 product) and Adavena® G40 (G40 product)	*Lactobacillus reuteri* ATCC 55730, *Lactobacillus acidophilus* DSM 20079 and *Bifidobacterium bifidum* DSM 20456	*L. reuteri* ATCC 55730 maintained the highest feasibility (10^8 CFU/mL) after 30 days at 6 °C	Martensson et al. (2002) [133]
	Drink based on malt	*Lactobacillus reuteri*,	8.41 log CFU/mL. 30 h	Kedia et al. (2007) [134]
	Soy milk supplemented with group vitamins b	*Lactobacillus acidophilus* ATCC 314, *L. acidophilus* FTDC 8833, *L. acidophilus* FTDC 8633 Y and *L. gasseri* FTDC 8131	Greater 7 log CFU/mL	Ewe et al. (2010) [135]

Table 4. Methods for incorporating probiotics into food matrices.

Incorporation Method	Probiotic Strain	Matrix Medium	Reference
Surface adhesion via fermentation	*L. plantarum* (ITM21B) *L. paracasei* (IMPC2.1)	Artichoke	Valerio et al. (2006) [136]
	L. plantarum strain (L4), *L. mesenteroides* (LMG 7954)	Cabbage (fermented cabbage)	Beganovic et al. (2011) [137]
	L. paracasei (IMPC2.1)	Table olives	Lavermicocca et al. (2005) [138]
Vacuum impregnation	*S. cerevisiae* (CECT 1347) *L. casei* spp. *rhamnosus* (ECT 245)	Apple	Betoret et al. (2003) [116]
	L. rhamnosus (CECT 275)		Puente et al. (2009) [139]
Immersion of matrix in solution with microorganisms and incubation	*L. casei*	Apple and quince	Kourkoutas et al. (2005) [140]
	L. rhamnosus (GG)	Apple	Alegre et al. (2011) [141]
	B. lactis (Bb-12)	Apple/papaya	Tapia et al. (2007) [142]
Coatings based on alginates and gellan (edible films)	*L. acidophilus* (La-5) *B. lactis* (Bb-12)	Strawberry	Moayednia et al. (2010) [143]
Incorporation as immobilized cells	*L. acidophilus* (BCRC 10695)	Apple puree	Tsen et al. (2004) [144]
		Tomato juice	Tsen et al. (2008) [145]

Table 4. *Cont.*

Incorporation Method	Probiotic Strain	Matrix Medium	Reference
	L. rhamnosus, *B. longum*, *L. salivarius*, *L. plantarum*, *L. acidophilus*, *L. paracasei*, *B. lactis* (Bi-04, Bi-07)	Orange and apple juice	Ding and Shah, (2008) [146]
	L. acidophilus (BCRC 10695)	Tomato juice	King et al. (2007) [147]
		Banana's mashed	Tsen et al. (2003) [148]
Fermentation	*L. acidophilus* (LA 39), *L. plantarum* (C3), *L. delbrueckii* (D7), *L. casei strain* (A4)	Red beet juice	Yoon et al. (2005) [122]
	L. delbrueckii (DSM 20081), *L. rhamnosus* (DSM20711)	Carrot juice	Nazzaro et al. (2008) [125]

6. Side Effects of Probiotics

The consumption of probiotic yogurt has benefits; for example, it can cause an increase in the number of T cells in women. T cells play an essential role in cellular immunity. Daily consumption of this type of probiotic can also lower cholesterol levels. Nevertheless, probiotics in the form of supplements have several side effects, including headaches, allergic reactions, infections, and digestive disorders that can lead to bloating, stomach aches, and diarrhea [149].

An overdose of probiotics is a rare event in a healthy adult. This is because probiotics are living microorganisms that, in normal quantities, are present in the human body and play a fundamental role in the health of the digestive system. They help maintain a healthy intestinal bacterial balance, boosting the immune system and facilitating digestion. The medical community agrees that probiotic supplements are safe for most people when taken directly. Probiotic supplements typically contain between 1 and 10 billion colony-forming units (CFUs) per dose. A higher number of CFUs is not necessarily associated with greater health benefits. There is a limit beyond which an increase in probiotics does not produce additional beneficial effects but may have unintended consequences. Researchers still need to reach consensus on the optimal daily dose of probiotics. This is primarily because the optimal dose may vary depending on the individual's age, general health, the type of probiotic strain, and the specific reasons for taking probiotics. However, staying within the suggested range is important. The consumption of excess probiotics, although rare, can cause digestive complaints such as bloating, gas, and diarrhea. People with weak immune systems, such as those with HIV/AIDS or those who have recently received a transplant, have a slightly higher risk of developing infections when consuming high-dose active probiotics cells [149]. In conclusion, while a probiotic overdose is extremely rare, it is always important to follow the recommended doses on product labels and consult a doctor or dietitian before starting any probiotic supplementation.

7. Conclusions

Probiotic bacteria can modulate critical immune responses related to gut-associated lymphoid tissue (GALT). Probiotics have been incorporated into various food matrices, including nondairy products, in recent years due to their beneficial impacts on human health. Probiotics have notable potential for prophylactic or therapeutic applications in various gastrointestinal disorders. These bacteria have long been proposed for use to increase intestinal health. *Lactobacillus* and *Bifidobacteria* strains have been mainly considered to help treat gastrointestinal disorders. The aim is to potentiate the immune response and synthesize compounds such as short-chain fatty acids, lactic acid, and bacteriocins, promoting the probiotic bacteria's capacity to compete with pathogenic microorganisms for adhesion

sites. Understanding the mechanisms of action permits the selection of suitable probiotic strains for specific applications in gastrointestinal disorders. Nevertheless, the mechanisms of action are not well understood and more research is encouraged to comprehend the role pf probiotics in gastrointestinal disorders.

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