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Mechanisms of action and health benefits of probiotics: a comprehensive review

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Abstract

Probiotics, originating at birth, play a crucial role in the development and maintenance of a healthy and disease-free environment within the gut of both humans and animals. These beneficial microorganisms from fermented, processed, and non-dairy foods provide numerous health benefits, such as stress reduction, disease prevention, immune stimulation, gut microbiota control, nutritional supplementation, diarrheal disease relief, vitamin production, weight management, and anticancer activities. With more health problems on the rise and the negative side effects of conventional medication and antibiotics prevailing, natural supplements such as probiotics are a relief. Probiotics, such as *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*, have been identified as safe and effective candidates for gut health applications. This review addresses the current understanding of the mechanism of action of probiotics, their functions in human health, and their therapeutic potential for various diseases. We emphasize the importance of prioritizing probiotic administration along with conventional medicinal drugs for their wide benefits and fewer side effects. Our findings aim to direct future studies on the modes of action of probiotics against emerging health challenges.

Keywords

probiotics, bacteria, health effects, mechanisms of action, antimicrobial effects, diseases

Introduction

In the early days, a relationship between microorganisms and humans was observed. It is a very interesting fact that humans cannot survive without microorganisms. In the human body, the head to toe is covered with microorganisms, which protect the human body. The gut contains complex, stable, and beneficial microorganisms that help in various ways, such as digestion of food, increasing immunity, and providing many necessary enzymes. Microbiota refers to the various groups of microorganisms, such as bacteria, archaea, eukaryotes, and viruses, that are present under specific conditions. Gut microbiota community composition can be changed due to some factors. In this microbial jungle, a variety of microorganisms (fungi, viruses, bacteria, and even parasites) can inhabit it. It was previously mentioned in the literature, 100 trillion microorganisms reside in the intestine, which is 10 times larger than the cells of the human body [1]. Currently, the good bacteria in the gut have been compromised because of the modern lifestyle, introducing many pathogenic bacteria to the gut, which prevents the beneficial role of good bacteria. It is logical to increase the number of beneficial bacteria to maintain good gut health [2]. Many bacteria help cure diseases by having a symbiotic relationship with the host. These are referred to as probiotics. Probiotics, defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host", Anjana and Tiwari [3] 2022, have been studied for their ability to promote a balanced and diverse gut microbiome, which is essential for maintaining overall health [1]. If a sufficient amount of these bacteria is ingested, they can confer several health benefits, such as those provided by gram-positive bacteria like *Lactobacillus* and *Bifidobacterium* [4]. Overconsumption of antibiotics can disturb gut microbiota functionality, thereby killing beneficial microorganisms. Antibiotics usually fail to differentiate between beneficial and harmful microorganisms. The main reasons for antibiotic resistance are improper use of antibiotics, lack of proper knowledge, and misuse of antibiotics [5, 6]. Frequent use of antibiotics also destroys genital tract bacteria and weakens the immune system. This issue has encouraged researchers to find natural alternatives to restore the good bacteria in the body and treat a variety of gastrointestinal infections [7]. The primary source of gut microbiota is the mother, who transfers the gut microbiome vertically during birth. The composition of the gut microbiota depends on the mother's flora, genetic factors, and medication use. 97% of the gut bacteria are anaerobic, and the majority of strains found are Bacteroidetes (*Porphyromonas*, *Prevotella*, and *Bacteroides*), Firmicutes (*Ruminococcus*, *Clostridium*, *Lactobacillus*, and *Eubacteria*), and Actinobacteria (*Bifidobacterium*) [4, 8–10]. Recent studies have shown that probiotics may help improve immune function, protect against pathogenic bacteria, affect the gut-brain axis, and aid in the adsorption of food and nutrients (Figure 1). In addition, probiotics can play a role in the gut, providing beneficial gut bacteria that create a physical barrier to prevent unwanted bacterial ingestion. Therefore, the benefits of probiotics can be addressed as the prevention of diarrhea, irritable bowel syndrome (IBS), ulcerative colitis, and Crohn's disease. The gut-brain axis is also interconnected, and many studies have suggested that probiotics may help in the management and regulation of mental disorders. A clinical trial with 86 students found that after treatment with probiotics for 28 days, there were improvements in their behavior, such as panic anxiety, neurophysiological anxiety, worries, and mood regulation. In addition, a clinical study reported that probiotic mixed strains of *Lactobacillus reuteri* NK33 and *Bifidobacterium adolescentis* NK98 for 8 weeks improved mental health and sleep [11].

To ensure health benefits, a good amount of probiotics in the gut is required with regular food intake. The strains of probiotics should be from human sources and contain a few major features, such as: 1. benefits to the host, 2. survival in the intestine, 3. it is also used as a feed additive to improve the intestinal epithelial cell (IEC) membrane, 4. creation of antibiotic substances against infections, and 5. stabilizes intestinal microflora. The number of probiotics should be large enough to provide a sufficient number of bacteria in the gut [7]. Lactic acid bacteria (LAB) are good sources of probiotics, except for *Streptococcus* and *Enterococcus*. In many food products, LAB are widely used without any adverse effects. Probiotics are mostly isolated from the human gut, and it is known that large quantities of probiotic consumption are advised as a functional food; for example, *Bifidobacterium* can be found 10^{11} cells/g in the intestine [12, 13]. Probiotics can also increase the metabolism of host tissues, particularly the gastrointestinal mucosa and

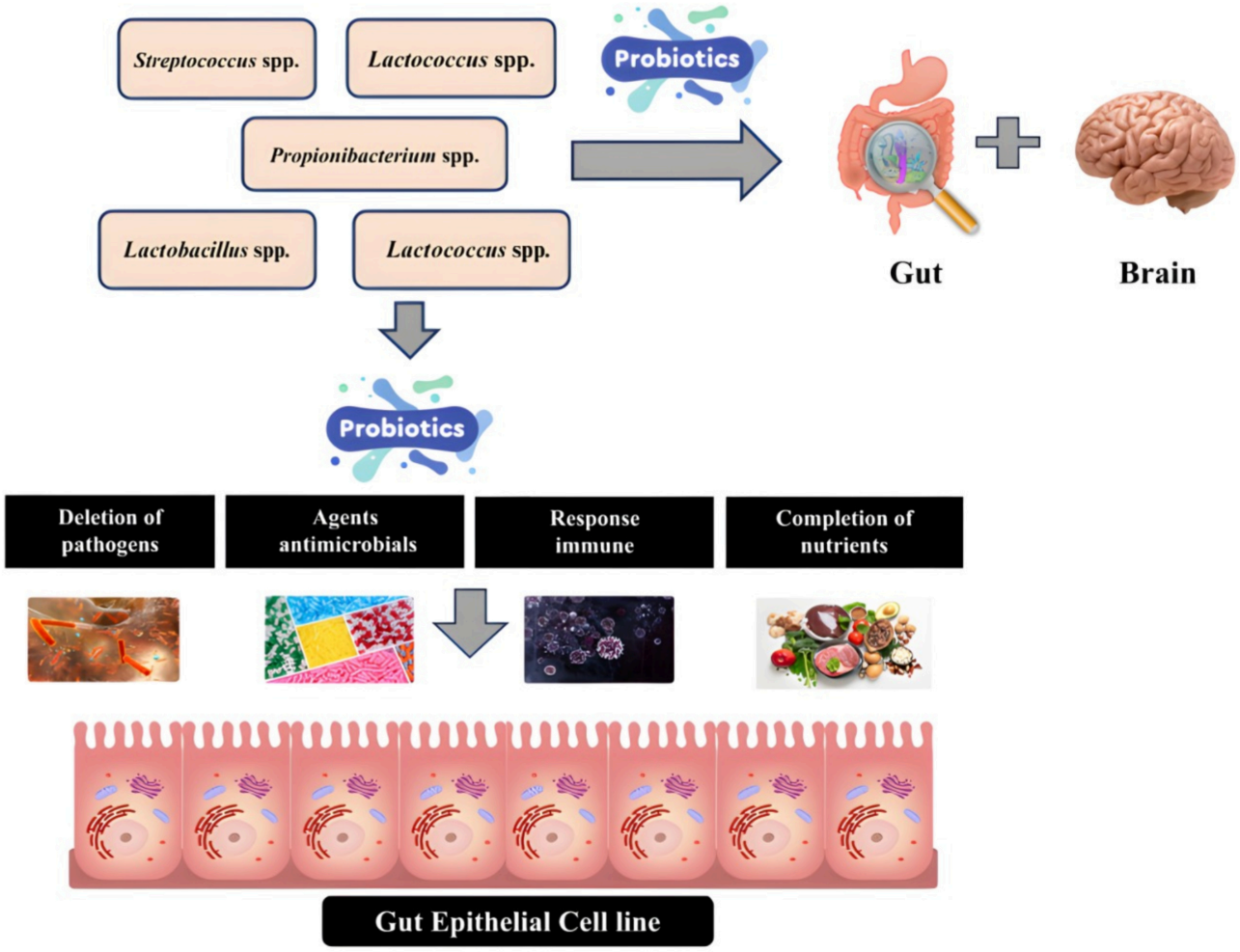

Figure 1. Effect of probiotics on health and the relationship between the brain and gut. Probiotics exert beneficial effects on health by modulating the gut-brain axis and affecting neurotransmitter production and brain function. They achieve this by altering the gut microbiota composition, reducing the abundance of pathogenic bacteria, enhancing the immune system, and improving nutrient absorption. These effects contribute to improved overall health, potentially benefiting neurological and mental health. The authors created the figure on the platform Canva (https://www.canva.com/).

liver [14]. As research continues to uncover the critical link between gut microbiota and host health, the consumption of probiotics has increased significantly. While much attention has been focused on their beneficial functions, potential risks such as infections and the transfer of antibiotic resistance genes to pathogenic bacteria are often overlooked. Some studies have shown that probiotics may have harmful effects on the host. In case of immunocompromised states, *D*-lactic acidosis, brain fogginess, bacteraemia, and antibiotic resistance gene transfer could be found [15]. This review offers a comprehensive exploration of mechanistic approaches and contemporary perspectives on the therapeutic benefits of probiotics in disease prevention and treatment.

Mechanism of action

There are two types of immune responses in the host body: innate and adaptive. The innate immune response is nonspecific defense against pathogens and/or antigens. Components of innate immunity include barriers such as mucous, epithelial cell layer, M cells, goblet cells, dendritic cells (DCs), Paneth cells, natural killer (NK) cells, macrophages, and cytokines. The second line of host defense is the adaptive immune response, which targets pathogens and/or antigens very specifically. Key components of adaptive immunity include T cells, B cells, immunoglobulins (Igs), MHCs, $CD4^+$, interleukin (IL; IL-10, IL-12, IL-1), interferon (IFN), and tumor necrosis factor (TNF) [16]. Mucins are mainly glycosylated proteins that create the mucosa layer, and they also include Igs, glycolipids, glycoproteins, and electrolytes. This gel-like viscous layer covers the intestinal epithelium and functions as a barrier between microbes and the epithelial cell layer. Mucus provides immunity to the host from infectious diseases by preventing bacteria from adhering

to the gut epithelial cells and moving inside the lamina propria. The mucosa and epithelial cell layers provide physical protection against microbes (Table 1) [17, 18]. When probiotics attach to the mucosa and colonize, they act as an extra layer of physical barrier against pathogens (Figure 2). For example, *Lactobacillus* and *Bifidobacterium* are lactic acid, gram-positive, and probiotic bacteria [17]. Probiotic bacteria have proteins and adhesive molecules that are responsible for binding to mucus components. Lipoteichoic acid (LTA) is a cell wall component of probiotic bacteria such as *Bifidobacterium* spp. and *Lactobacilli*. LTA shows antimicrobial activity by producing nitric oxide synthase (NOS) through immune cells, such as macrophages, and inhibits bacterial and viral infection [19, 20]. *Lactobacillus salivarius* REN carries one type of protein called surface layer proteins (SLPs), such as choline-binding protein A [17]. The SLPs remain attached to the extracellular membrane through noncovalent bonds as the first surface components of bacteria, and these proteins also bind to gut epithelial cells. Competitive exclusion occurs when a bacterial species competes for adhesion to a receptor of the gut epithelium [21].

Table 1. Mechanisms of action of probiotics to improve host immunity.

Antimicrobial activity	Barrier functions	Immunomodulation
Changing luminal pH	Increased mucus production	Epithelial cells
Secreting antimicrobial peptides	Increased barrier stability	Dendritic cells
Inhibit microbial invasion		Macrophages
Blocking microbial adhesion		B cells & T cells

Since probiotic bacteria compete for epithelial colonization by SLP, oral uptake of probiotics can prevent pathogenic bacteria from colonizing the gut. For example, *Lactobacillus helveticus* R0052 has been shown to prevent *Escherichia coli* from adhering to Caco-2 cells [22]. These bacteria also carry Mub and MucBP, which are mucin-binding proteins linked to cell wall peptidoglycan and adhere to mucins. However, Mubs are available in pathogenic bacteria, such as *Listeria monocytogenes*, which are exclusively present in LAB, such as *Lactobacillus* and *Bifidobacterium*, found in the human gut. According to Zhang et al. [23] (2015), cell wall-anchored proteinases A (CwaA) were found to be potential adhesins of *Lactobacillus plantarum*, and the responsible genes could improve the adhesion ability of probiotics [23]. The filamentous structures on the bacterial body surface are called fimbriae or pili. The main role of pili is to adhere to other bacteria and the gut epithelial layer. For example, *Lactobacillus* species have SpaCBA, which was first found in *Lactobacillus rhamnosus* LGG. SpaCBA is a combination of three parts: SpaC, a mucus-binding molecule that plays an important role in adhesion to the Caco-2 gut epithelial layer [17]. Fibronectin is a glycoprotein found in the gut epithelium as an extracellular matrix in both solid and insoluble forms. Fibronectin-binding proteins (FBPs) are present in pathogenic bacteria and probiotics and are responsible for invading the host epithelial layer [19]. *Lactobacillus acidophilus* is widely used as a probiotic in dairy products. In a study, *L. acidophilus* lost its mucin-binding ability after deletion *of* the *fbpB* gene in vitro [24]. After successful pathogen adhesion, capsular polysaccharides (CPSs) play a vital role in the gut microenvironment. CPS is a bacterial surface polymer of monosaccharides formed via glycosidic bonds. A previous study showed that CPS5 of *Bacteroides thetaiotaomicron* increased its tolerance to antibiotics and colonized the mouse gut [22]. Probiotic bacteria also show antagonistic behavior against pathogens by lowering the pH level, reducing bacterial translocation, and producing defensins in the intestine. For example, *L. acidophilus* carries several acid-induced genes to survive in acidic conditions in the intestine [25]. Probiotics also exhibit antimicrobial activity by altering the mucus composition of the mucosal barrier. Moreover, probiotics also release some components in the biological metabolic system, such as organic acids and bacteriocins, which can trigger immune responses, such as apoptosis and inflammation [9, 26, 27]. After binding to the mucosa and colonization, probiotics induce IgA production through B cell stimulation without changing the $CD4^+$ T cell number and prevent pathogens from reaching the epithelial layer. For example, *Lactobacilli* can induce B cell clonal expansion by producing IL-6, which increases IgAs. Overall, the adhesion of probiotics to the intestinal layer, induction of IgAs, and colonization play vital roles in improving immunity by preventing the colonization of pathogens. This is how probiotics provide primary immunity to prevent and improve immunity [16].

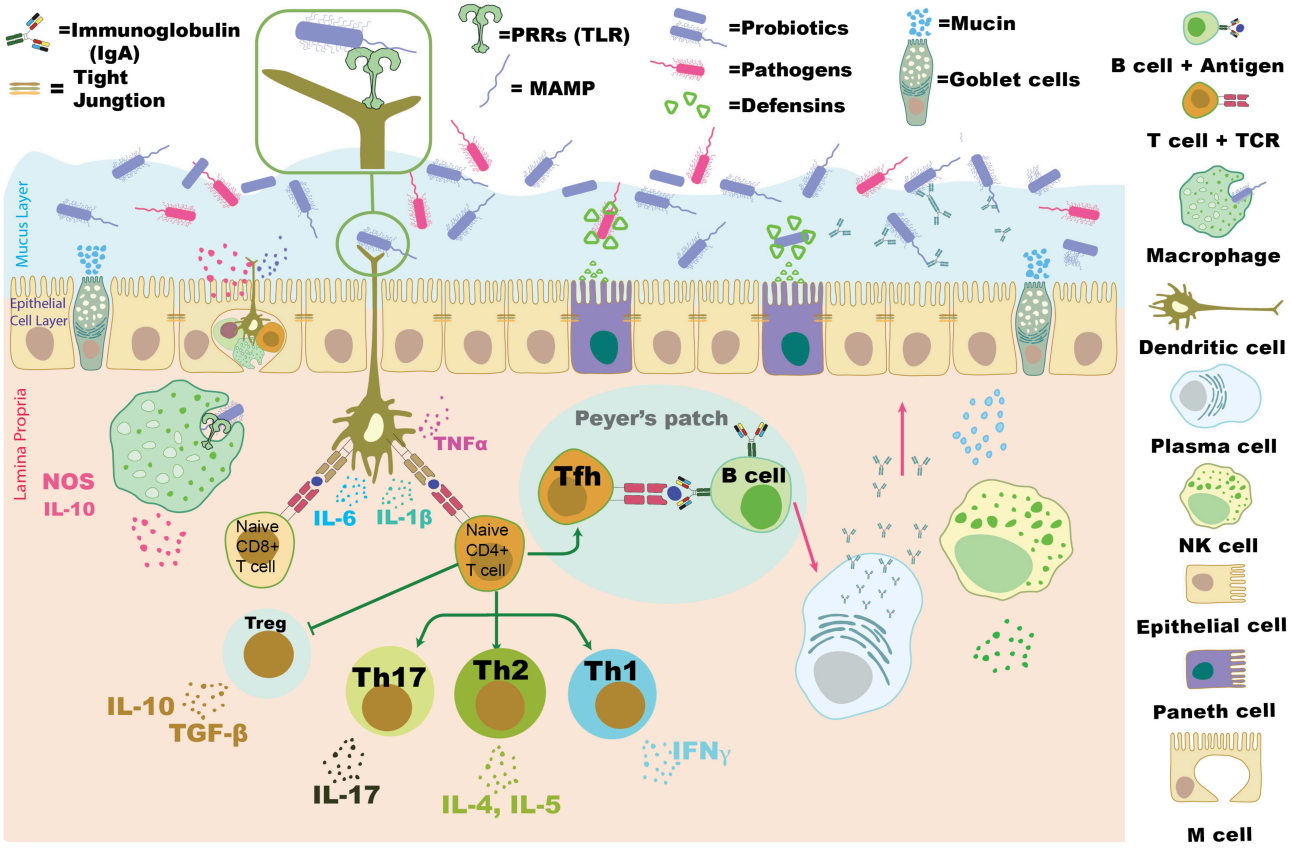

Figure 2. Mechanism of actions of probiotics to boost immunity against pathogens. The authors created the figure on the platform Canva (https://www.canva.com/). Firstly, oral uptake of Ps binds with ML by different binding proteins and colonizes there. As a result, pathogenic bacteria cannot colonize. Ps changes luminal pH, increases antimicrobial peptides, and promotes competitive exclusion. GCs release mucin to create ML. GCs are found in the ECL, which also contains Paneth's cells, which secrete defensins. ECL also contains M cells, which provide permeability to bacteria and/or antigens. In the lamina propria, the antigen will be phagocytosed by APC such as macrophages and DCs. These cells can bind with bacterial MAMPs (flagellin) through PRRs (TLRs), which will produce cytokine responses. Meanwhile, antigens will be represented to naïve TCs by the APCs. Then TCs will differentiate into Th1, Th2, Th17, and Treg, etc., and secrete cytokines. Then, TCs represent antigen to the BCs, and later BCs become mature Ig (IgA) producing plasma cells and memory cells. Finally, IgA moves through the epithelium to the mucus layer and prevents pathogens. Overall, the whole immune system will be triggered by Ps, which are non-pathogenic to the host, but the biological system is ready to act against pathogens and/ or antigens. PRRs: pattern recognition receptors; TLR: Toll-like receptor; NK: natural killer; NOS: nitric oxide synthase; IL-10: interleukin-10; TNF: tumor necrosis factor; IFN: interferon; Ps: probiotics; TCs: T cells; BCs: B cells; MAMPs: microbe-associated molecular patterns; APC: antigen-presenting cell; ML: mucus layer; DCs: dendritic cells; GCs: goblet cells; ECL: epithelial cell layer.

IECs play an important role in regulating intestinal mucus secretion by goblet cells [21]. Structurally, the intestinal epithelial barrier (IEB) contains goblet cells and Paneth cells, which produce antimicrobial peptides and defensins. Additionally, the IEB contains M cells or microfold cells, which are responsible for capturing and transporting bacterial cells or antigens from the intestinal lumen surface to the lymphoid tissue. The activity of M cells triggers transcytosis, thereby stimulating various underlying immune cells, including DCs, intraepithelial DCs, macrophages, plasma cells, lymphocytes, and NK cells to activate host defense mechanisms [16]. The IEB's robustness is also maintained by the tight junctions (TJs), which is a protein complex. If the properties of the TJ are altered, the IEB functionality is disrupted, resulting in a leaky gut condition, which is responsible for IBS. Many compounds from the diet improve IEB's functionality. Moreover, many studies have proven that probiotics, such as *L. rhamnosus*, *Lactobacillus casei* DN-114001, and *L. plantarum* MB452, are found to protect intestinal epithelium from pathogens by upregulating ZO-1, which can stabilize TJs and improve IEB functions [17]. Probiotics have been proven to stimulate immune cells, innate immunity, followed by releasing cytokines and chemokines through T cells, and increase intestinal IgA and Treg cells [27, 28]. Probiotic bacteria are recognized by Toll-like receptor 2 (TLR2) and TLR4 on DCs, which are also present on epithelial cells [21]. Probiotics are also able to activate the host's adaptive immunity by elevating the B cells' clonal expansion and increasing IgA production. Because of the probiotics, IL-10 and IFN-γ numbers also increase and are involved in the

immunomodulation process [29]. Whole recognition procedure for pathogenic bacteria and probiotics by the epithelial cells is different; probably it depends on the numbers and kinds of microbe-associated molecular patterns (MAMPs) [17]. Pathogens stimulate proinflammation by NF-κB transcription activation, and probiotics prevent IB factor degradation as represented in an article where an experiment was conducted with nonpathogenic *Salmonella pullorum* [21].

Probiotics and DCs

DCs are also called detector cells because of their receptors that bind with a specific part of the pathogens. DCs are found in the mucosa and gut-associated lymphoid tissue (GALT). These cells also catalyze signalling pathways, such as c-type lectin receptors and pattern recognition receptors (PRRs), such as TLRs, that modify their characteristics and release cytokines [27]. Probiotics contain MAMPs that bind with PRRs of DCs and stimulate the cells to protect the IEB [22]. After DCs start phagocytosis and get antigen from the mucus or lamina propria, they migrate to the lymph nodes. Finally, DCs can induce T cells and elicit the immune response [19]. Bacterial cell wall components take part in immunity regulations by the DCs. Bacterial antigen presentation by the gut CD11cþ DCs is dependent on MHC-II molecules, which are vital for Th17. In the case of immune response, there are associations found with CPS A, *Bacteroides fragilis*, and TLR2 of DCs. Where DCs have been demonstrated to prevent intestinal colitis and release IL-10. For instance, a direct association has been demonstrated between specific fragments of *Bacteroides fragilis* capsular polysaccharide A (PSA) and TLR2 on mouse plasmacytoid DCs. These plasmacytoid DCs have been shown to express proteins that protect the gut against colitis and to promote IL-10 secretion by $CD4^+$ T cells following exposure to capsular PSA [19].

Probiotics and macrophages

Macrophages have three main functions: phagocytosis, microbiocidal activity, and cytokine production. These functionalities increase with the presence of probiotics [29]. Probiotics can influence immunity indirectly or directly through stimulation of cytokine elevation, such as ILs, IFNs, TGFs, TNFs, and chemokines by macrophages. *L. casei* CRL 431 was found to produce IL-10 by macrophages [16]. Macrophages can perform phagocytosis of pathogens and are found in the intestinal subepithelial part, where antigens pass through the epithelium. Macrophages contain PRRs (TLRs), similar to DCs, that bind to MAMPs on pathogens. Macrophages work as antigen-presenting cells (APCs) [17]. Macrophages are secondary APCs that represent antigens to the memory T cells and are typically found in either of two subclasses: 1. M1 macrophages are involved in immunogenic activation and proinflammatory responses derived from TNF, IL-1, IL-6, IL-8, and IL-12; and 2. M2 macrophages are associated with mucosal homeostasis and tolerance, and activated by anti-inflammatory or regulatory cytokines such as IL-10, TGF, and IL-1Rα. These subclasses are potential targets of probiotics, such that M1 macrophages are inhibited in inflammatory pathologies and M2 macrophages are inhibited in suppressor pathologies, such as in mucosal cancers [20].

LTA, the cell wall of gram-positive bacteria, can induce nitric oxide (NO) synthase in macrophages and kill the virus, while also increasing receptors such as FcγRIII (CD16) and TLRs for phagocytosis. These APCs also participate in T cell responses by secreting cytokines and differentiate into subtypes of $CD4^+$ T cells such as Th1, Th2, or Th17. T cells binding with APCs is vital for the host's adaptive immunity [19]. *L. plantarum* was found to increase IL-10 production and secretion in the macrophages which has been obtained from the colon after inflammation. On the other hand, *L. rhamnosus* GG increased IFN, IL-12, and IL-18 [21].

T cells and probiotics

T cells are part of the adaptive immune response, which shows interactions with probiotics [26]. T cells are also found in the lamina propria. T cells and related inflammation become activated after DCs with antigen reach the lymph nodes. T cells regulate the adaptive immune system of the intestine through IgA secretion. Research indicates that elevation of Treg function is probably linked to the positive effects of probiotics on

conditions such as allergies. Previous study results showed probiotics can regulate immune modulator secretion by innate immune cells, such as DCs, and regulate T cells. For example, many types of pathogen-associated molecular pattern molecules (PAMPs) are expressed by the *Lactobacilli* strains, which can stimulate cytokine production, and later these bind to the PRR on APCs. These cytokines work as an important signal for T cells and induce cytokines, such as Th1, Th2, Th17, or T regulatory cell responses [19]. Overall, probiotics are capable of increasing Tregs, which are important for inflammation regulation [27].

B-Lymphocytes and probiotics

The GALT is a part of the mucosa-associated lymphoid tissue (MALT). GALT plays the most important part of the immune system. It presents a big source of B-cells and T-cells, which later move to the area where they show necessary immune responses. The intestine is responsible for containing around 75% B cells that produce IgA. Probiotics are responsible for the maturation of IgA-producing plasma cells (differentiated from B cells). Where IECs produce cytokines and chemokines and create a microenvironment in the intestinal lamina propria, where clonal expansion of B cells occurs and increases IgA production. IgAs move to the mucosa through the intestinal epithelial layer and later control bacterial adhesion to the host gut epithelium [27]. This is how B cells play an important role in adaptive immunity through secreting antibodies. B cells are found to prevent excessive immune response and control it by IL-10. A study found that, after *Lactobacillus gasseri* SBT2055 oral administration, the production of IgA was triggered and increased IgAþ cells in Peyer's patches and lamina propria. In another human experiment with probiotics, *Bifidobacterium animalis* with xylooligosaccharide decreased CD19 expression in B cells, which gave a clear picture of the good outcomes of immune system modulations caused by the correctly chosen probiotics and/or prebiotics [19]. Moreover, in another study, after admission of *L. rhamnosus* GG to an infant with acute gastroenteritis elevated nonspecific adaptive immune response that increased IgG, IgA, and IgM. *Bifidobacterium bifidum* potentially improves antibody production. *L. acidophilus*, *L. bulgaricus*, *Streptococcus* (*S.*) *thermophilus*, *B. bifidum*, and *Bifidobacterium infantis* containing yogurts induced IgA response against the cholera toxin in mice [21].

Probiotic delivery to the target site

Mechanisms of probiotic delivery

The microencapsulation technique is a widely used method of probiotic delivery. This method is used to avoid severe physicochemical stresses during processing, such as acidity, high temperatures, various digestive enzymes, microbiota, and passing through the gut. Because biological processes can decrease the viability of probiotics when they are consumed orally [30, 31]. Probiotic delivery mechanisms are crucial for ensuring the viability and effectiveness of probiotics in therapeutic applications. Various innovative strategies have been developed to enhance the stability and bioavailability of probiotics during their passage through the gastrointestinal tract (GIT). To introduce a new probiotic delivery, there are some barriers that need to be overcome by probiotic bacteria; these are given below.

Chemical reactions

For probiotic delivery, bacteriocins, bile salts, sugars, antimicrobials, gastric juice, and digestive enzymes can be counted as intestinal chemical barriers in the gut environment [31, 32]. Interactions with antimicrobials and bacteriocins are very challenging barriers to probiotics' viability. Moreover, gastric acid is also an equally difficult barrier for probiotic delivery. Because H^+ (proton) in gastric juice can change membrane permeability and deactivate the probiotic, and bile salts are responsible for dissolving lipids and membranes that cause leakage of probiotic cell membranes, ultimately, losing its viability. In the case viability of probiotics at the time of storage, there are two factors that work as barriers: oxygen levels and redox potential. Especially during storage, some probiotics are less oxygen-tolerant and unable to survive without anaerobic conditions; for example, *Bifidobacteria* are less oxygen-tolerant than *Lactobacilli*. As a result, specialized packaging is required based on probiotics. The viability of probiotics also depends on the

water availability. A low acidic environment can also affect a probiotic's viability, such as fruit juice with low pH and high organic content, providing enough stress that makes the probiotic's survival a challenge. As a result, the encapsulation process could be used to improve the probiotic delivery system [33].

Physical factors

In the intestinal tract, food transport, breakdown, and processing occur within a very limited time. This limits the probiotics' retention in the gut and, as a result, adhesion to the mucosa and growth is reduced [32]. Critical physical parameters influencing probiotic viability during storage include temperature control, oxygen exposure, and moisture content (water activity, aw). These factors must be carefully optimized to maintain microbial stability and metabolic integrity. If probiotics are stored at freezing temperatures, the cell membrane will be damaged, which will raise the concern of viability. Probiotic viability may be adversely affected by osmotic stress occurring at the time of thawing, resulting in their death. Maintaining optimum fermentation temperature is also important for viability; the majority of *Lactobacillus* spp. The optimum range is 30°–43°C. For industrial and experimental use, the drying method is very effective in cost reduction of transportation and frozen storage. There are many ways of drying, but spray-drying, freeze-drying, and vacuum-drying are highly used [31].

Host biological and microbial factors

After oral ingestion of probiotics, they face a consequence when they reach the gut called colonization resistance. It occurs when probiotics reach the gut and fail to gain a competitive advantage over native microbes. Since adhesion, nutrient uptake, and required conditions play a major role in colonization, sometimes probiotics might fail to survive the gut. The chosen probiotics also show antagonism against microbes that later cause difficulties in cell viability, such as competition for nutrients, coaggregation with pathogens, and stimulation of immunity. The intestinal pathological microenvironment works as a barrier to probiotics. For instance, in the gut, numerous immune cells, such as macrophages, neutrophils, leukocytes, DCs, etc., can increase ROS levels, which can damage bacterial cell membranes and inactivate probiotics. Moreover, the gut mucus layer plays a major role in the immune system, which acts as a layer where probiotics adhere, colonize, and reproduce. If orally ingested probiotics pass through the epithelium and reach the blood and transfer to the organs, it will cause serious health concerns for the host [31, 32].

Strategies for enhancing probiotic delivery

Targeted delivery of probiotics in the gut is crucial for maximizing their therapeutic potential, particularly in treating conditions like inflammatory bowel disease (IBD) and ulcerative colitis. Orally administered free or unprotected probiotics are susceptible to degradation in the human GIT due to enzymes such as lysozymes in saliva, acidic conditions in the stomach, digestive enzymes in the small intestine, etc. Therefore, probiotic delivery systems must improve the stability of probiotics during food processing and digestion and increase the chances of viable probiotics reaching and colonizing the large intestine. Encapsulation involves a coating that can protect probiotics from antimicrobial effects by resisting extreme conditions in the lumen of the gut as well as stabilising mucoadhesion, thus facilitating colonization and repopulation by healthy microbes [33, 34]. Encapsulation of probiotics increases their viability as they travel through the digestive system compared to naked probiotics. A study by Pan et al. [35] (2022) demonstrated that Gram-positive and Gram-negative bacteria can be protected against six different clinically relevant antibiotics. In the biological system, encapsulation can even absorb antibiotic molecules. Protected probiotics were able to colonize in the intestinal tract of rats that were treated with levofloxacin. This antibiotic causes antibiotic-associated diarrhoea, and probiotics were able to reduce it and improve symptoms caused by diarrhoea [35]. Typically used materials include alginate-pectin (PEC) microgel [36], chitosan-alginate [37], cellulose sulfate [38], etc. Huang et al. [39] (2023) found that in situ cultivation of probiotic microcapsules increased the loading capacity of viable cells after encapsulation and improved the survival of cells during gastrointestinal digestion. Various innovative methods have been developed for creating stable encapsulation and have been coupled with strategies that enhance the efficacy of probiotics reaching target locations during gastrointestinal transit.

Microencapsulation materials

The materials used to coat probiotics in encapsulated delivery systems must satisfy a number of criteria; they should be food-grade, be able to adequately protect probiotics during transit in the GIT while also releasing them at the targeted site, as well as be economical. In addition to the materials described in Table 2, many researchers have used combinations of different construction materials for probiotic encapsulation. Such combinations often utilize the most advantageous features of the individual materials, resulting in overall improved functionality.

Table 2. Some materials are used for the encapsulation of probiotics.

Component	Advantage	Disadvantage	Probiotic	Therapeutic effect of strain(s)	Reference
Proteins					
Milk proteins (whey protein and/or casein)	Acid-stable; pepsin-resistant; bile salt-resistant; enzyme-activated controlled release in intestine; exceptional film-forming properties	Potential allergen	*Lactobacillus rhamnosus* GG, *Bifidobacterium longum* 1941, *Lactobacillus delbrueckii* ssp. *bulgaricus*, *Streptococcus thermophilus*	Preventing diarrhoea, primary rotavirus infection, and atopic dermatitis	[40–42]
Plant proteins [zein (corn protein) and/or soy protein]	Enhanced protection due to forming a hydrophobic shell; pH and thermal stability	Might aggregate and compromise stability	*Bacillus subtilis* 168	Increasing abundance of beneficial gut bacteria	[43, 44]
Gelatin	Improved antioxidant property; mucoadhesion can potentially enhance probiotic delivery	Denatures at high temperatures	*Lactobacillus rhamnosus* GG *Bifidobacterium bifidum* *Lactobacillus acidophilus* *Bacillus coagulans* *Saccharomyces boulardii*	Gut disease prevention, such as IBS, IBD, diarrhea prevention. Improving immune modulation, such as allergy, inflammation. Vaginal or urinary tract infection improved by *Lactobacillus* strain	[45]
Albumin (egg white protein)	Gelling and cross-linking ability; specific site-targeting properties	Potential allergen; pH sensitive	*Lactobacillus acidophilus* TISTR 1338	Preventing diarrhoea, treating *Helicobacter pylori*, improving respiratory tract infections, lowering serum cholesterol levels and improving the host's lactose tolerance levels	[46, 47]
Silk fibroin	Resistant to gastric acid and bile acid; resistant to enzymatic action; improved adhesion to IECs	Can be brittle	*Lactobacillus plantarum*, *Enterococcus faecium* KCTC 13115BP (EF-3), *Streptococcus thermophilus* KCTC 14471BP (ST-27), *Bifidobacterium animalis* subsp. *lactis* KCTC 13116BP (BL-5), *Bifidobacterium bifidum* KCTC 13114BP (BB-1), *Lactobacillus acidophilus* KCTC 13117BP (LA-7)	Reducing diarrhea, inhibiting pathogenic bacteria, reducing blood cholesterol, and improving liver cirrhosis and obesity	[48, 49]
Polysaccharides					
Alginate	High encapsulation efficiency; significant increase in the survival rate of probiotics; cost-effective	Reduced probiotic protection at low pH	*Saccharomyces cerevisiae* strains, *Saccharomyces boulardii*, *Enterococcus faecium*, *Bacillus licheniformis*, fruit-derived lactic acid bacteria (LAB)	Preventing and treating diarrheal diseases (acute infantile diarrhoea, antibiotic-associated diarrhoea, nosocomial infection); preventing systemic infection; managing IBD;	[50]

Table 2. Some materials are used for the encapsulation of probiotics. (*continued*)

Component	Advantage	Disadvantage	Probiotic	Therapeutic effect of strain(s)	Reference
				immunomodulation; prevention and treatment of allergies; anticancer effects, treating high cholesterol, and relieving lactose intolerance	
Chitosan	The only commercially available water-soluble cationic polymer, quick biodegradation	Reported to have some antimicrobial and antifungal actions; therefore can be used as the shell but not the capsule during encapsulation strategies	*Lactobacillus* and *Bifidobacterium* spp.	Boosting host immunity; improving growth of targeted microorganisms; eliminating harmful bacteria	[51]
Pectin	Itself a prebiotic, meaning it can be fermented by beneficial bacteria in the gut, further supporting their growth and activity; resistant to enzymatic digestion in the stomach and small intestine	Might modify probiotics' metabolism	*Lactobacillus plantarum*	Protection against intestinal epithelial barrier disruption	[52, 53]
Carrageenan	Improved probiotic survival in acidic conditions	No significant resistance to bile salts	*Lactobacillus plantarum*	Enhancing gut health by securing a good number of probiotic bacteria in the GI tract in highly acidic conditions	[54]
Gellan and/or xanthan gum	Excellent gelling and malleability properties; biocompatible and biodegradable; heat and acid-stable	May be unstable in physiological conditions	*Lactobacillus paracasei* 28.4	Antifungal activity against *Candida albicans* in the oral cavity	[55, 56]
Cellulose	Cheap; can be used to make pH-responsive capsules when complexed with other materials	It can lead to structural defects when used in complexes	*Lactobacillus* spp., *Bifidobacterium* spp.	Treatment of severe skin infections and chronic wounds	[57]
Starch and/or dextran	Acid-resistant	Can be unstable under thermal stress; can form irregular aggregates	*Lactobacillus rhamnosus*	Enhancing probiotic stability and viability under simulated gastrointestinal conditions	[58]
Pullulan	Itself a potential prebiotic; increased probiotic viability after acid and bile exposure	Can be expensive	*Lactobacillus acidophilus* NRRL-B 4495	Preventing and treating gastrointestinal infections and diarrhoea; stimulating immune responses that promote the effects of vaccination or even prevent certain allergic symptoms	[59, 60]
Lipids					
Plant oils (olive, sunflower, soybean, corn)	Improved survival in gastric and pancreatic juices	May interfere with probiotic survivability	*Candida adriatica*, *Candida diddensiae*, *Nakazawaea molendini-olei*, *Nakazawaea wickerhamii*,	Synthesizing polyunsaturated fatty acids (PUFAs), which provide health benefits	[61]

Table 2. Some materials are used for the encapsulation of probiotics. (*continued*)

Component	Advantage	Disadvantage	Probiotic	Therapeutic effect of strain(s)	Reference
			Wickerhamomyces anomalus, *Yamadazyma terventina*		
Dioleoylphosphatidic acid and cholesterol	Preserves the native viability and biosafety of naked probiotics	Might induce an inflammatory response	*Escherichia coli* Nissle 1917 (EcN)	Preventing and treating *Salmonella typhimurium* (STm) and dextran sulfate sodium (DSS) induced colitis	[62]

IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; IECs: intestinal epithelial cells.

Microencapsulation techniques

Encapsulation refers to the preparation of "carrier" capsules made of solid, liquid, or even gaseous components that are able to release their contents in a controlled manner. Nano- (< 0.2 μm), micro- (0.2–5,000 μm) encapsulation are the most common size-based types for ingestion [63]. Probiotics can be encapsulated either via physical (spray drying, freeze drying, spray chilling, spray cooling, extrusion, fluidized bed drying, electrospraying, and electrospinning) or chemical (coacervation, ionic gelation, and molecular inclusion) means [64].

Spray drying is mainly used to protect the heat-sensitive prebiotics and involves dissolution, emulsification, or dispersion of the probiotic in an aqueous or organic solution containing an encapsulating agent, followed by spraying the mixture in a drying chamber. The droplets from the spray dry instantly, resulting in encapsulated particles that are collected. *L. plantarum* and *L. rhamnosus* have been viably encapsulated with this technique [65, 66]. This technique is fast and has a low operational cost, and is therefore easily scalable. However, the simple particles produced might provide limited protection to probiotics.

Spray cooling is similar to spray drying, but instead of forming particles by evaporation, they are formed by cooling such that the matrix material solidifies around the probiotics [67]. *Saccharomyces boulardii*, *L. acidophilus*, and *B. bifidum* have been encapsulated using the spray chilling or cooling technique [68]. This technique is appropriate for heat-sensitive probiotics and is also easily scalable.

Freeze drying or lyophilization is suitable for thermally sensitive bioactives and involves rapid freezing followed by dehydration. Freeze drying has been used to stabilize *L. rhamnosus*, *L. acidophilus*, *Lactococcus lactis*, *L. plantarum*, and *L. acidophilus* [66, 69–71]. A study was started on a microencapsulated probiotic delivery method for *L. plantarum,* which would be cryoprotected by microcapsules of chitosan-inulin complex. It was freeze-dried so that probiotics can get maximum viability. It was assessed by using in vitro low pH intestinal tract conditions and stored at various temperatures. A Box-Behnken experimental design includes different concentrations of $CaCl_2$, chitosan, and inulin used as encapsulant components for developing *L. plantarum* microcapsules. Under optimum conditions, 68.33% cell viability was achievable, but the study showed that *L. plantarum* with small microbeads could elevate the probiotic viability to around 108 log CFU/mL. Efficacy of freeze-dried, microencapsulated *L. plantarum* was reported to be dependent on a number of factors, including cell viability during drying, gastrointestinal treatment, refrigerated storage conditions, and the physicochemical properties of the powders used [71, 72]. Lyophilization results in a long shelf life; however, the process is expensive and slow, which might limit scalability.

Fluidized bed coating is often combined with spray drying technology and involves depositing a coating agent (which could include aqueous solutions of gums, starch, cellulose, or proteins) on the surface of the bioactive [73]. *Enterococcus faecium* IFANo.045 and *L. plantarum* IFANo.278 have been coated with this technique using cellulose [74]. *L. plantarum* NCIMB 8826 has been coated using alginate-chitosan [75]. This technique results in a uniform coating and can be tuned to create multi-layer capsules; however, the equipment cost is high.

Extrusion involves mixing bioactives into a hydrocolloid solution, which is then extruded through a nozzle into a curing solution (e.g., $CaCl_2$, $AlCl_3$, or $FeCl_2$) such that the initial mixture turns into a gel and pellets are created [76]. Various polysaccharides (most commonly sodium alginate) can be used for extrusion encapsulation and determine the size, shape, and viability of the encapsulated material [77]. *L. plantarum* 15HN has been encapsulated with this technique using alginate, an alginate-psyllium blend, and an alginate-fenugreek blend [78] while *L. acidophilus* La-14 has been encapsulated using a calcium chloride solution [79]. Alginate combined with natural polysaccharides and fructo-oligosaccharides has been used to encapsulate strains of *L. casei* 01 and BGP 93 via extrusion [76]. This technique uses relatively simple equipment; however, the process is slow, which may lead to low scalability.

Ionic gelation utilizes the electrostatic interactions between opposite charges involving at least one polymer and is most often used to prepare alginate particles [80]. The use of chitosan as a coating material on alginate beads containing the bacterium *Bifidobacterium longum* has been shown to improve its survival in gastric fluid and high-temperature conditions [81]. Different probiotics have been encapsulated via the ionic gelation process, such as *L. casei*, *L. rhamnosus*, *L. plantarum*, *Pediococcus pentosaceus*, *Lactobacillus fermentum*, and *L. acidophilus* [82–89]. Positively charged chitosan and negatively charged alginate can be used to coat *E. coli* Nissle 1917 for protection [33, 90] while encapsulated *L. acidophilus* can be encapsulated with carboxymethyl cellulose and chitosan to enhance their vitality in the GIT [33, 91]. This technique is also relatively simple and low cost, and can be easily scaled.

Complex coacervation involves the continuous stirring of three chemically immiscible parts such that the base substance diffuses into the coating solution and an outer layer solidifies around the bioactive via chemical or physical crosslinking reactions [65, 92, 93]. This process utilizes polysaccharides such as gum arabic (GA), chitosan, mesquite gum, PEC, alginate, xanthan gum, carrageenan, and carboxymethyl cellulose, as well as proteins including gelatin, whey protein, casein, albumin, and plant-derived proteins such as pea protein. or soy protein [65]. *L. rhamnosus* GG has been encapsulated by whey protein isolate-high melting point fat shortening oil (SO) and GA through complex coacervation [94]. Other probiotics encapsulated via the complex coacervation process include *L. plantarum*, *L. casei*, *Lactobacillus paracasei*, *Bifidobacterium lactis*, *L. acidophilus*, and *L. reuteri* [92–97]. This technique can be used to create sophisticated assemblies that are optimized for controlled release of probiotics in target locations of the GIT. However, optimization can be time-consuming and may limit scalability.

Electrospraying and electrospinning. Electrodynamic (EHD) is a technique that produces nano or microscale fibers by electrospinning and electrospraying that can be used for various applications, such as good stabilization and controlled release of sensitive components like essential oils, peptides, proteins, etc. Electrospinning and electrospraying are versatile, flexible, mild, and straightforward techniques which have emerged as techniques for probiotic stabilization in the last few years [98]. From these techniques, nano- or microscale fibers and spheres are made. The mechanism works as polymer solution extrusion is performed using a syringe pump equipped with a needle. Upon droplet formation at the needle tip, a Taylor cone develops. Subsequently, jet ejection occurs from the apex of the cone, followed by the deposition of the resulting fragmented droplets onto the collector. It was found that the survival rate of probiotic strain increased to 89.26% after using electrospinning, and when *L. rhamnosus* 1.0320 was kept for 21 days of storage, the survival rate was 84.63% by using polyvinyl alcohol (PVA)/PEC as the wall material. In another study, it was mentioned that the survivability was 90.07% and 91.96% in simulated gastric and intestinal fluids with PVA/PEC in the wall material [64]. In another study, the encapsulation of *L. plantarum* in electrosprayed whey protein concentrate (WPC) microcapsules demonstrated enhanced viability when fresh cultures were used instead of freeze-dried cultures. Compared to free cells, WPC encapsulation significantly improved bacterial survival during storage at elevated relative humidity (53%). Additionally, suspending the bacteria in the surfactant Tween 20® increased the production yield of electrosprayed capsules. The viability of encapsulated *L. plantarum* was further assessed under in vitro digestion conditions and compared to freeze-dried samples. Encapsulation provided notable protection, with the majority of viability losses occurring during the gastric phase (pH 3) due to acidic degradation. Minimal

differences in viability between encapsulated and freeze-dried bacteria were observed after the intestinal phase, likely because the capsules were fully disrupted by this stage. The marginal disparity may also be attributed to the inherent acid resistance of this particular strain. To enhance the protection of *L. acidophilus* under moist heat conditions, multilayered microcapsules were fabricated using a combination of electrospraying and fluidized bed coating. The core material, composed of alginate and glycerol, was electrosprayed into a shell solution of egg albumen (EA) and stearic acid (SA), followed by fluidized bed coating with cassava starch granules during drying. The encapsulation efficiency exceeded 90%, and cell viability was further improved by increasing the SA concentration. Although encapsulated cells exhibited a viability loss of only 0.6 log CFU/g, long-term stability studies are required to fully assess the efficacy of these microcapsules in probiotic preservation. Electrospun and electrosprayed structures are known to exhibit favourable mucoadhesive properties (Moreno et al. [99], 2018), which can significantly prolong the gastrointestinal residence time of probiotics and enhance their interactions with the gut microbiota. In a recent study, mucoadhesive electrosprayed microcapsules composed of alginate-starch and chitosan-coated alginate, loaded with *L. plantarum*, were evaluated for gastrointestinal delivery. The researchers employed an in vitro fluorescence imaging-based flow-through test using ex vivo porcine gastric epithelial mucosa to assess mucoadhesion. The chitosan-coated alginate particles demonstrated strong retention on gastric mucosa, comparable to that of pure chitosan controls. In contrast, alginate-starch particles (used as a negative control) exhibited weak retention, attributed to the non-ionic nature of starch and its inherently poor mucoadhesive properties [100].

Responsive coating strategies

Responsive coating strategies for probiotics aim to enhance their survival and targeted delivery within the human GIT by overcoming challenges like inactivation during processing, storage, and passage through the harsh acidic environment of the stomach and the presence of bile salts in the small intestine. pH-responsive coatings are designed to be stable in the acidic environment of the stomach but dissolve as the pH increases in the intestine, allowing for the release of the probiotics at the target site. Luo et al. [101] 2022 reported the oral delivery of probiotics based on a pH-sensitive trigger mechanism, based on mucosal adhesion, enzyme degradation, spore or biofilm formation, or a redox-responsive trigger mechanism. Enzyme-responsive coatings are designed to be degraded by specific enzymes present in the gut, ensuring the release of probiotics at the desired location. Altogether, a combination of factors must be taken into consideration to ensure protected travel through the digestive system and the controlled release of probiotics at the target location. These factors include the characteristics of the probiotics themselves (such as initial quantity, particle size, diffusivity, partition coefficient, and concentration gradient), the properties of the carrier matrix or encapsulation system [including original size, shape and structure, porosity, pore formation and closure, and the (non)flocculated state of emulsion droplets], as well as external factors such as the surrounding environment and conditions within the GIT (e.g., the oral cavity and transit of the bolus into the stomach), chime going to the small intestine, and indigestible ingredients going to the colon [102, 103].

Probiotics as an antimicrobial agent

Probiotics, particularly LAB, produce various antimicrobial substances that play a crucial role in inhibiting pathogenic bacteria. These substances include bacteriocins, organic acids, hydrogen peroxide, and other metabolites, which collectively contribute to their antimicrobial properties, which contribute to the health benefits associated with probiotics.

Production of antimicrobial substances

Bacteriocins and organic acids

By producing antimicrobial compounds like bacteriocins and organic acids, probiotics help suppress the growth of harmful bacteria. These compounds can alter the gut environment, making it less favourable for pathogen survival [104, 105]. LAB strains have been shown to produce antimicrobial activities with

inhibition zones ranging from 15–17 mm against urinary tract infection (UTI) isolated *E. coli*, effectively reducing pathogen numbers and biofilm formation. Bacteriocins are ribosomally synthesized antimicrobial peptides that exhibit a broad spectrum of antimicrobial activity against various pathogens. The producer microbes of bacteriocins benefited from surviving in a highly populated microenvironment produced by various microorganisms [106]. They function by disrupting bacterial membranes, inhibiting cell wall biosynthesis, and causing leakage of cellular contents, forming pores in the target cell membranes, leading to cell lysis and causing cell death [107]. For example, probiotic strains like *Weissella confusa* and *L. plantarum* have shown strong antibacterial effects against drug-resistant bacteria [104, 105].

Short-chain fatty acids (SCFAs) and other metabolites

SCFAs: Probiotics metabolize prebiotics and dietary fibers to produce SCFAs, including propionic and butyric acids. These acids are crucial for gut health, providing energy to colonocytes and modulating immune responses. SCFAs, particularly butyrate, enhance gastrointestinal barrier function, modulate inflammatory responses, increase resistance to pathogenic colonization, and regulate enteroendocrine signalling and energy homeostasis. The primary substrates for microbial synthesis of SCFAs in the human colon are dietary fibers, which are intricate carbohydrates resistant to host enzymatic digestion. The daily fiber intake by American adults today is merely 21–38% of USDA recommended intake, and this represents a significant nutritional deficiency. Prebiotic supplementation is now a specific therapeutic strategy to enhance the production of colonic SCFA through selective manipulation of commensal microbiota, with the possibility of conferring health benefits mediated by these microbial metabolites [108].

Neuroactive metabolites: In the gut, trillions of microbes form a gut microbial community, and they can produce thousands of unique small molecules or metabolites that can eventually affect the host. In general, among the common metabolites, many SCFAs, bile acids, choline, vitamins, amino acids, and neurotransmitters such as serotonin, dopamine, and γ-aminobutyric acid (GABA) are found. The bidirectional communication network between the gut microbiota, GIT and central nervous system constitutes the brain-gut-microbiome axis (BGMA). Gut microbial communities influence host physiology through both central (neural) and peripheral (circulatory) pathways. Microbial metabolites permeate the intestinal barrier and transmit signals to the CNS either through vagal afferents or systemic circulation across the blood-brain barrier (BBB). These bioactive molecules, classified as postbiotics, hold therapeutic potential in their ability to modulate disease phenotype, microbial populations, and host metabolic pathways. Conversely, disruption of gut microbial homeostasis and postbiotic signaling has been implicated in the pathogenesis of systemic diseases, including metabolic syndrome, cardiovascular disease, and neurological disorders. Some probiotics, such as *Lactobacillus* and *Bifidobacterium*, can produce neurotransmitter-like compounds such as GABA and serotonin, which may influence the gut-brain axis and cognitive functions [109]. SCFAs exert pleiotropic effects on central nervous system function by modulating BBB integrity, regulating the neuroimmune response, and modulating neuronal gene expression. Notably, the gut enterochromaffin cells generate approximately 90% of the body's serotonin, and microbiota-derived signals from the gut are essential to regulate its synthesis. Microbial compositional changes that reduce serotonin bioavailability have been implicated in the pathophysiology of depression and anxiety disorders, among a constellation of other neuropsychiatric disorders. Moreover, gut microbiota communicates with the CNS through immunological and neural pathways. Microbial dysbiosis can cause immune activation with elevated circulating proinflammatory cytokines (e.g., IL-6, TNF-α). These mediators may disrupt neuronal function through either systemic circulation or vagal afferent signaling, establishing a mechanistic link between gut microbiota disturbances and neurodegenerative processes characteristic of Alzheimer's and Parkinson's disease [110].

Amino acid metabolites: Probiotics can also produce amino acid derivatives like indole-3-lactic acid, which have potential health benefits, including anti-inflammatory effects [111].

Other methods of antimicrobial effects by probiotics

Competition with pathogens for resources and adherence sites

Probiotics employ several mechanisms to compete with pathogens for resources and adherence sites in the human gut, thereby promoting gastrointestinal health. Probiotics compete with pathogens for binding sites on the intestinal epithelium, effectively preventing pathogen adhesion. For instance, *L. plantarum* FS2 has been shown to inhibit the adhesion of diarrhoeagenic *E. coli* by pre-infecting the host cells, thereby preventing pathogen attachment [12]. *E. coli* Nissle, via Curli, Type 1 and F1C fimbriae, might colonize the intestine through increased adherence to the mucosa and prevent the adhesion of other pathogens [112]. The ability of probiotics to adhere to the gut lining is crucial for their colonization and competitive exclusion of pathogens. This adhesion is often strain-specific, as demonstrated by various LAB strains that exhibit different levels of adhesion and competition against pathogens like *Salmonella enteritidis*, *E. coli*, *Cronobacter sakazakii*, *Campylobacter jejuni*, and *Listeria monocytogenes* [113]. Probiotic bacteria can also provide protection against pathogens by limiting the availability of nutrients to pathogens and preventing their proliferation. For example, *E. coli* HS and *E. coli* Nissle utilize multiple sugar molecules and prevent their uptake by pathogenic *E. coli* [114]. Across species, a commensal strain of *E. coli* was able to delay the intestinal colonization and translocation of the pathogen *Salmonella typhimurium* in GF mice, possibly due to competition for nutrients [115]. It has also been shown that the intestinal microbiota can provide colonization resistance to infection with *Citrobacter rodentium*, a mouse pathogen used to model infection with diarrheagenic *E. coli* strains, including enterohemorrhagic EHEC and enteropathogenic *E. coli* (EPEC), by competing for similar carbohydrates [116].

Modulation of host immune response

Probiotics can stimulate the host's immune system, enhancing the production of secretory IgA and anti-inflammatory cytokines, which help in the defence against pathogens. Secretory IgA is thought to have multiple functions including binding to and neutralizing foreign antigens from pathogenic agents/toxins (such as by protecting the intestinal epithelium from cholera toxin), modulating the adhesion of bacteria to intestinal epithelium (such as by enhancing *Lactobacillus* and *Bifidobacterium* probiotic adhesion) and production of epithelial Ig receptors, leading to a higher state of epithelial immunologic alertness [177]. The interaction between probiotics and the host's immune system can also lead to the regulation of pro-inflammatory cytokines, thereby maintaining gut homeostasis and preventing pathogen colonization. Probiotics can regulate innate immune cells such as macrophages, DCs, and NK cells to enhance antimicrobial activity by stimulating the production of cytokines, notably IL-12 and IFN-γ [118–120]. Moreover, in another study, after admission of *L. rhamnosus* GG to an infant with acute gastroenteritis elevated nonspecific adaptive immune response that increased IgG, IgA, and IgM. *B. bifidum* potentially improved antibody production. *L. acidophilus*, *L. bulgaricus*, *S. thermophilus*, *B. bifidum*, and in mice, *B. infantis*-containing yogurts stimulated an IgA response against the cholera toxin [21].

While in vitro and preclinical studies demonstrate probiotic strains exhibit direct antimicrobial activity against pathogenic bacteria through competitive exclusion, bacteriocin production, and pH modulation [16], clinical guidelines emphasize that their primary therapeutic value lies in mitigating antibiotic-associated complications. The Maastricht Consensus (2018) positions probiotics as adjuvant therapy specifically to reduce antibiotic side effects, including microbial dysbiosis and intestinal inflammation [121], rather than as standalone antimicrobial agents. This distinction should be incorporated when valuating probiotic mechanisms of pathogen inhibition [122]. Factors such as antibiotic resistance and individual microbiota deviations can influence the success of probiotic interventions. Therefore, a deeper understanding of host-microbe interactions and the development of tailored probiotic therapies are essential for optimizing their use in gastrointestinal health.

Examples of antimicrobial activities of probiotic strains

***Lactobacillus* spp.**: *L. rhamnosus* exhibits significant antimicrobial activities, making it a promising candidate for combating various pathogens, including antibiotic-resistant strains. This probiotic

demonstrates inhibitory effects against a wide range of bacteria and fungi through multiple mechanisms. One such mechanism is the production of bacteriocins, proteinaceous toxins that inhibit the growth of similar or closely related bacterial strains. For instance, the *L. rhamnosus* VHProbi M14 strain contains 23 bacteriocin-related genes, contributing to its broad-spectrum antimicrobial activity such as against *Streptococuus mutans* and *Fusobacterium nucleatum* under mixed culture conditions [123]. These antimicrobial properties translate into diverse applications in food and health. In food preservation, *L. rhamnosus* has been used to inhibit foodborne pathogens in products like yogurt, demonstrating its potential as a natural preservative [124]. Clinically, the strain LR-R3 has shown antagonistic activity against carbapenem-resistant *Acinetobacter baumann*ii, making it a viable therapeutic alternative in nosocomial infections [125].

***Bifidobacterium* spp.**: *Bifidobacterium breve* for example exhibits significant antimicrobial activities through the production of metabolites, modulation of host immune responses, and maintenance of gut microbiota balance, making it a critical player in inhibiting pathogenic bacteria and promoting gut health. Its antimicrobial properties are largely attributed to bacteriocin production, which provides a competitive advantage by inhibiting harmful bacteria while preserving the beneficial microbiota balance. Additionally, *B. breve* modulates the host immune system, enhancing immunity and reducing inflammation. For instance, the strain *B. breve* CCFM1310 increases Ig secretion, repairs spleen injury, and modulates cytokine expression in immunosuppressed mice, thus improving the immune response [126]. Exopolysaccharides (EPS) produced by *B. breve* also play a role by preventing DC maturation and $CD4^+$ T-cell activation, supporting immune evasion and maintaining host-microbe mutualism [127]. A list of some probiotics, their functions, and uses is given below (Table 3).

Table 3. List of probiotics, functionalities, and uses [16, 128].

Probiotics	Functionalities or used for
Bifidobacterium adolescentis	Constipation
Bifidobacterium animalis	Folic acid and organic zinc production, normal DNA synthesis, immunity, and cell division, protecting DNA, lipid, and protein oxidative damage, normal bone maintenance, fertility and reproduction, gastrointestinal discomfort reduction, leaky gut, strengthening immunity, antioxidant activity, cardiovascular health, cholesterol lowering
Bifidobacterium longum	IBS-related gastrointestinal discomfort reduction, intestinal microbiota rebalance, EPS production, constipation, kidney stones incidence reduction, obesity treatment, and cholesterol management
Bifidobacterium infantis	Immune stimulation improves lung function
Bifidobacterium bifidum; *Bifidobacterium infantis*	Cardiovascular health: cholesterol lowering
Bifidobacterium breve	Constipation, anti-inflammatory, gastrointestinal discomfort, inhibiting pathogens, obesity treatment, cystitis, and kidney stones incidence reduction
Bifidobacterium lactis	Antioxidant activity
Lactobacillus plantarum	Gut-brain axis, healthy aging, immune system, sleep regulation, mood modulation
Lactobacillus acidophilus	Intestinal microbial rebalance, reducing intestinal inflammation, kidney stones incidence, reducing allergy, intestinal dysbiosis caused by antibiotic therapies, increasing chemotaxis of polymorphonuclear cells, and preventing diarrhea prevention
Lactobacillus crispatus	Treatment of conditions caused by an imbalance of the skin microbiota
Lactobacillus reuteri	Protects DNA, proteins, and lipids, maintenance of normal immunity and bone
Lactobacillus delbrueckii	Intestinal microbial rebalance, lactose digestion, inhibition of pathogens and different gas-producing coliforms, allergy, treating intestinal dysmicrobisms for antibiotic therapies use, diarrheal
Lactobacillus fermentum; *Lactobacillus crispatus*	Inhibits *Candida* strains, treats vulvovaginal candidiasis (VVC), restores physiological gut barrier, cardiovascular health, lowers LDL-C, antioxidant properties
Lactobacillus gasseri	Weight management, vaginal health, rebalance healthy vaginal microbiota
Lactobacillus paracasei	Reduces intestinal inflammation, kidney stones incidence reduction, has immunomodulatory activity, helps the normal function of the neuron system, multiple sclerosis therapy and psychological function
Lactobacillus pentosus	Antipathogenic activity
Lactobacillus reuteri	Reuterin production and vitamin B12, an immunostimulant, reduce intestinal inflammation, kidney stones incidence reduction

Table 3. List of probiotics, functionalities, and uses [16, 128]. (*continued*)

Probiotics	Functionalities or used for
Lactobacillus rhamnosus	Rotaviral diarrhea, gastroenteritis, anti-inflammatory activity, inhibition of pathogenic bacteria
Lactobacillus salivarius	Inhibits *Enterococcus faecium*, *Neisseria gonorrhoeae*, *Enterococcus faecalis*, *Cutibacterium acnes*, and *Candida,* prevents urogenital infections, restores intestinal microbial balance, pediatric gastroenteritis and ability to adhere on intestinal mucosa
Streptococcus thermophilus	Lactose digestion, EPS production, gut permeability, diarrhea
Lactobacillus brevis	Neurotransmitter synthesis, immune stimulation, reduces symptoms of rotavirus diarrhea, salivary cytokine release
Lactobacillus casei	Antitumor properties
Lactobacillus helveticus	Cholesterol management and antioxidant
Hafnia alvei	Next generation weight management probiotic
Bacillus mesentericus	Immune stimulation

EPS: exopolysaccharides; IBS: irritable bowel syndrome; LDL-C: low density lipoprotein cholesterol.

Side effects and limitations of probiotics

Before a bacterial strain can be considered appropriate to use as a probiotic, it must be ensured that it is harmless to the host, non-toxic, non-pathogenic (including not being an opportunistic pathogen), be genetically stable and not have any genotoxic properties [129]. The bacteria should also be resistant to the adverse conditions in the GIT, must efficiently adhere to the gut lining and should have a short generation time. Despite best attempts, limitations remain in the use of probiotics, and it is difficult to find a single ideal probiotic. For example, LAB are known to produce different varieties of bacteriocins with excellent antimicrobial properties; however, these bacteria are sensitive to digestive enzymes and must be protected by artificial encapsulation techniques [130]. Furthermore, the bacteriocins produced by these LAB may become toxic to humans at high concentrations already been seen. This risk is further complicated by the possibility of horizontal gene transfer of bacteriocin-associated genes as well as other virulence factor genes within the gut microbiome. This risk is most likely to be developed via long-term colonizing probiotics and other potential risks include disruption of the microbiome (e.g., through displacing a microbe typically performing a necessary function) and breaching of the gut barrier to access systemic circulation. For example, an increase in *Lactobacillus*-associated bacteremia was reported among intensive care unit patients receiving probiotics in a Boston hospital [131]. A specific *Bifidobacterium* strain has been reported to modify SCFA production in the gut and may be involved in antibiotic-associated diarrhea [132]. Individuals who use venous catheters or have severe diseases have been reported to be affected by *Saccharomyces fungemia*. Immunocompromised individuals as well as individuals with gut dysbiosis and/or impaired intestinal barriers are at an especially higher risk of side-effects associated with probiotics [129]. Populations at risk include the pregnant, newborns and the elderly as well as those undergoing chemotherapy, those who have had an organ transplant and those with HIV/AIDS [129, 133]. Theoretically, possible side-effects include systemic infections, unwanted metabolic activities, overstimulation of the immune system, and gene transfer [133]. In 100 studies of probiotic use during pregnancy, 11 reported gastrointestinal problems, nausea, and headache that might be caused by the treatment, but no serious health concerns of mother or infant were reported [131]. SCFAs produced via probiotic metabolism could also affect various organs such as the brain and liver [132]. *L. paracasei* bacteremia was reported in and 8-month-old infant girl being treated with probiotics [16]. Immunocompromised individuals must be adequately assessed prior to being administered with probiotics, even for supposedly “safe” probiotics. Some individuals may also experience relatively minor and temporary symptoms such as bloating or flatulence, but consumer concern may create an unfavorable view of probiotic use for all [129]. Conversely, probiotics can also reduce the side effects of other treatments even in compromised individuals. For example, a meta-analysis of probiotic use during cancer treatment reported that oral probiotics significantly decreased the side effects associated with radiotherapy and chemotherapy compared to placebo groups [133]. Another study in children being treated with chemotherapy for acute leukemia

reported improved gastrointestinal symptoms when taking probiotics [134]. Due to the high variability in the target population, there is mixed evidence of probiotic benefits as well as drawbacks; therefore, a comprehensive safety evaluation is necessary for the full understanding of the effects of probiotics [133].

Synergistic effect of probiotics with conventional drugs

Synergism in biology describes a situation where two or more drugs, chemicals, or biological structures work together to produce an effect greater than the sum of their separate effects [135]. For instance, "Antibiotic A" reduces bacterial growth by 40% and "Antibiotic B" by 30% when each of these is consumed alone. Here, the total effect of their separate effects is (Antibiotic A + B) = 70%. If both antibiotics are used together and used to reduce bacterial growth by more than 70% then this effect will be considered as "synergistic effects". From the perspective of probiotics, synergistic effects have been found in many studies, which could be a new strategy to find improved treatments for diseases. Chloroquine is an antiparasitic drug that can prevent malarial infection. In a study, Mahajan et al. [136] (2021) showed that conventional medicine combined with probiotics have better beneficial effects than both of these separate effects. To exemplify, chloroquine and *L. casei* together were able to reduce maximum parasitic growth.

Probiotics and antibiotics

The relationship between probiotics and antibiotics is complicated. Probiotics have been shown to bolster the efficacy of antibiotic therapies by preserving the balance of gut microbiota, which is frequently disrupted by antibiotic administration. This maintenance of microbial equilibrium helps mitigate the colonization of multidrug-resistant bacteria. Wieërs et al. [137] (2021) demonstrated that probiotic interventions reduced the prevalence of resistant pathogens such as *Pseudomonas aeruginosa* and AmpC-producing enterobacteria. Cell-free supernatants of some probiotic strains have been shown to have synergistic effects with antibiotics like ceftazidime and gentamicin against resistant bacteria like *Staphylococcus aureus* and *E. coli*. El Far et al. [138] demonstrated how probiotics can increase the effectiveness of antibiotics against resistant pathogens. Probiotics are used together with antibiotics to treat *Clostridium difficile* infections, although their specific functions and best ways to administer them are still being studied [139].

Probiotic synergism has some risk factors; one is the possible spread of antibiotic resistance genes, especially in *Lactobacillus* strains. It can spread these genes to harmful bacteria and endanger public health [140]. Concerns regarding the possibility of antibiotic resistance genes spreading up the food chain are raised by the discovery of these genes in probiotics used in veterinary settings, such as in broiler chickens [141]. It was reported that *Lactobacillus* species are susceptible to common antibiotics, for example, tetracycline, erythromycin, and chloramphenicol, by inhibition of protein synthesis. Also, it was found that they are susceptible to penicillin but highly resistant to cephalosporins. Intrinsic resistance to colistin was found in many different types of lactobacilli [142]. *Lactobacillus* species tend to show intrinsic resistance against ciprofloxacin, co-trimoxazole, and nalidixic acid, which are not transferable horizontally [143]. Numerous *Lactobacillus* strains exhibit intrinsic vancomycin resistance and are commonly employed as probiotics for the prevention of *C. difficile* infection [144]. Nawaz et al. [145] (2011) demonstrated that *Lactobacillus* strains, while lacking the acquired resistance gene *van(B)*, exhibited intrinsic vancomycin resistance. The possible ways of getting antibiotic resistance in LAB are intrinsic, acquired, and/or mutational with transposons and conjugative plasmids. In LAB, the most common resistant genes are *tet(M)* and *erm(B).* In addition, *erm(A)*, *erm(C)*, *erm(T)* are also found in lactobacilli and *S. thermophilus* [146]. In one study, it was found that LAB was found resistance against vancomycin, streptomycin, gentamicin, teicoplanin, kanamycin, bacitracin, furantoin, norfloxacin, sulfadiazine, cefoxitin, metronidazole, and trimethoprim [147]. Imperial and Ibana [148] (2016) reported intrinsic resistance in the LAB against bacitracin, kanamycin, teicoplanin, vancomycin, and betalactams. *Lactococcus* spp., *Leuconostoc* spp., and *Lactobacillus* spp. are found to be highly resistant to cefoxitin [148]. In another article, Sharma et al. [149], 2014 mentioned many species of lactobacilli, except *L. delbrueckii* subsp. *L. bulgaricus*, *L. acidophilus*, *L. johnsonii*, and *L. crispatus*, are intrinsically resistant to glycopeptides [149]. *Bacillus*, *Streptococcus*, and

Enterococcus species exhibit broad-spectrum antibiotic resistance, likely attributable to their transferable resistance gene. In contrast, *Bifidobacterium* and *L. lactis* display minimal resistance, potentially due to the absence of transferable genes. These findings highlight the distinct and complex antibiotic resistance profiles among probiotic species, which may be determined by their respective resistance gene repertoires [147]. Probiotics also influence the host immune system and engage with gut microbiota, potentially mediating antibiotic resistance. For this reason, their use should be carefully considered, especially in susceptible groups like infants [150]. Probiotic and antibiotic use in early life can drastically change the ecology of gut microbes, affecting long-term health outcomes. This emphasizes the significance of using probiotics and antibiotics sensibly to maximize benefits and minimize risks [151]. Studies have confirmed that probiotics are effective in the treatment of *Helicobacter pylori*. In a previous study it was checked the relation between probiotic and antibiotic combination and antibiotic single treatment for 0–4 weeks and 4–8 weeks, respectively. The data showed that there is an effect of antibiotic (amoxicillin + clarithromycin) with or without probiotic administration, which can significantly affect the eradication. Administration of probiotics together with antibiotics may reduce the beneficial effect of probiotics. The reason behind it may be that the antibiotic can affect the live cells of probiotics. It is recommended to maintain an interval of at least 2 h between taking probiotics and antibiotics, even though in this study they did not mention the most suitable time for probiotic administration. For example, with *H. pylori,* the co-administration of probiotics can help in the self-protection rather than reducing the *H. pylori*. So after the eradication of *H.* pylori, probiotic uptake can be more beneficial for health. Many researchers advised that the course for probiotic use should be 2 weeks [152].

Probiotics and chemotherapy

According to current research, probiotics can effectively reduce gastrointestinal toxicity caused by chemotherapy, especially mucositis and diarrhea. According to a systematic review and meta-analysis of 23 randomized controlled trials, probiotics can help prevent diarrhea brought on by chemotherapy and radiation therapy, particularly high-grade diarrhea [153, 154]. Probiotic supplementation has been shown to lessen the severity and duration of chemotherapy-induced diarrhea in experimental models, including rats given FOLFOX chemotherapy [155]. Inhibition of the TLR4-NF-κB signaling pathway, which lowers inflammation and shields the intestinal mucosa, is one of the mechanisms behind these effects [156]. In order to prevent diarrhea and other gastrointestinal issues, probiotics also improve the function of the mucosal barrier and heal damaged jejunal villus [130].

Since side effects are uncommon and probiotics are generally regarded as safe, they are a good choice for cancer patients looking to modify their gut microbiota [157]. Furthermore, they encourage the synthesis of SCFAs, which support gut health and have anti-inflammatory qualities [158]. Even though the evidence is in favor of their use, the results are still controversial, and more excellent randomized controlled trials are required to verify their safety and effectiveness in relation to different cancer types and chemotherapy regimens [159]. There is still much to learn about the best probiotic strains, dosages, and treatment durations [160].

Probiotics and antifungal agents

Probiotics and antifungal medications have shown promise for working together, especially when it comes to reducing fungal biofilms and enhancing therapeutic results. Probiotics that have demonstrated strong growth inhibition and antibiofilm activity against *Candida albicans* include *L. rhamnosus* and *Pediococcus acidilactici*. The presence of SCFAs in probiotic supernatants, such as lactate and acetic acid, is partially responsible for this effect [161]. Moreover, probiotics can increase the effectiveness of antifungal medications when combined with them. As an illustration of their potential in biotherapeutic products, synbiotic cultures of *Lactobacillus crispatus* and *L. reuteri* in combination with plant extracts have demonstrated potent inhibitory effects on *Candida* biofilms [162]. The mechanisms behind this synergy include damage to the cell wall and membrane. Here, antifungal medications and synthetic antimicrobial peptides cause structural damage to *Candida* species, increasing the effectiveness of the drug [163].

Increased oxidative stress is another mechanism, as antifungal treatments such as direct current in combination with antifungals cause biofilm structures to be disrupted, oxidative stress to rise, and intracellular drug concentration to rise, all of which intensify antifungal effects [164].

Effects of probiotics on various diseases

One significant characteristic of probiotics is their antibacterial or antagonistic activity, which includes the synthesis of antimicrobial substances, the competitive exclusion of pathogens, the improvement of the function of the intestinal barrier, and other benefits. In therapeutic and nutritional settings, probiotic bacteria are essential and useful. The ability of different probiotics and their metabolites to prevent and treat various infections, illnesses, and disorders was reviewed in this study. Fibrocystic, diabetes, acne, colon cancer, cardiovascular disease, UTIs, atopic eczema syndrome, food allergies, and obesity are among the problems that were observed. Probiotics may be a good option because increased use of medication treatment has raised concerns about drug resistance.

Chronic and acute infectious diseases

Probiotics can aid in the treatment of a number of infectious diseases, including respiratory conditions, diarrhea, and UTIs [165, 166]. Probiotics combat intestinal infections by increasing both specific and non-specific immune responses, gut acidification, competition for resources and binding sites, and chemical production [166]. Probiotic cures are an intriguing alternative because uropathogenic microorganisms and other bacteria may become resistant to antibiotics as a result of antibiotic treatment for UTIs [167]. Using *Lactobacilli* probiotics may help increase the urogenital flora and offer protection from UTIs because *Lactobacilli* predominate in the urogenital flora of healthy premenopausal women [18]. Probiotics can also be used to treat diseases like SIBO and chronic bacterial infections like *H. pylori* and *C. difficile* [168]. *Lactobacilli*, *Bifidobacterium*, *Bacillus licheniformis*, and *Saccharomyces* have been effective in resolving the digestive problems associated with *H. pylori* because they can inhibit the urease function of *H. pylori* and generate reactive oxygen species that damage the bacterial cell wall and membranes [169].

Cystic fibrosis

Cystic fibrosis (CF) is a mutation in the fibrocyctic membrane regulator gene, a hereditary disease. It may start in the gastrointestinal epithelium line and respiratory system then can spread to other organs of the body. In one study conducted in 2010 with CF patients were given probiotics daily that contained (*L. acidophilus*, *L. bulgaricus*, *B. bifidum*, and *S. thermophiles*) and it was found that there was a beneficial effect. According to the results, probiotics may have an inhibitory effect on pulmonary deterioration in CF patients and reduce the rate of pulmonary exacerbations. They also mentioned that probiotics may help reduce gastric inflammation in CF patients and enhance intestinal health [170].

Immune system and gut health

Probiotics play a vital role in immune system boosting. When taken in conjunction with a balanced diet, probiotics can help boost the body's defenses against inflammation and infections. Because they promote the growth of beneficial microorganisms in the gut microbiome, probiotics are essential for maintaining proper digestive function. Additionally, probiotic bacteria ferment carbohydrates to produce organic acids like lactic and acetic acids. These organic acids help maintain an acidic environment in the stomach, which encourages the growth of good bacteria and prevents the formation of harmful ones. There are many other ways in which probiotics can improve immunity and gut health. *L. plantarum* BMCM12, for example, secretes extracellular proteins that reduce pathogen adherence and protect the intestinal barrier. One of the vital benefits of probiotics is pathogen's competitive exclusion, such as *E. coli* Nissle 1917 (EcN) can prevent enterohemorrhagic *E. coli* (EHEC) growth by releasing the DegP protein. Additionally, *H. pylori* can be prevented to bind with epithelial cells by probiotics that secrete antibacterial compounds [171, 172]. IBS is a prevalent brain-gut axis disorder with complex, multifactorial pathophysiology. The emerging evidence bestows prominent significance on gut microbiota in the modulation of subjective symptom presentation in

patients with IBS. Meta-analysis of 15 clinical trials (n = 1,793 IBS patients) depicted notable relief in abdominal pain and global severity symptom scores following probiotic treatment. Similarly, IBD, like Crohn's disease and ulcerative colitis, is due to a dynamic interplay between genetic predisposition, environmental triggers, immune dysregulation, intestinal barrier defect, and microbial dysbiosis. Therapeutic application of some microbial species has been established in preclinical research: *B. infantis* and *B. bifidum* inhibited inflammatory markers and clinical symptoms through IL-10-mediated immunomodulation [11].

Diabetes

Diabetes is defined as a condition where there are elevated blood sugar levels and the pancreas cannot produce the hormone insulin, which helps transport glucose from food to reach cells and give us energy. Both type 1 and type 2 diabetes could occur from a genetic background. Type 2 diabetes causes insulin shortage, insulin resistance, or high blood glucose, which is a metabolic disease [173, 174]. Probiotics have been found to be an alternative way to reduce glucose levels in diabetic mice and postpone the consequences and issues associated with diabetes [175–177]. In many researches, it has been proven that probiotics can decrease blood glucose levels in people [178–181]. For six weeks, Ejtahed et al. [178] used yogurt made with *L. acidophilus* and *B. lactis* in 3.98×10^9 CFU to treat type 2 diabetes. According to the results, its antidiabetic effect may make it useful as a treatment [182]. In addition, 20 individuals with type 2 diabetes mellitus who consumed 200 milliliters of soy milk per day enriched with *L. plantarum* A7 (2×10^7 CFU) have been observed that a decrease in fasting plasma glucose compared to control [180]. In another trial, 68 adults with type 2 diabetes mellitus who took probiotic supplements containing *L. acidophilus*, *Lactobacillus lactis*, *Lactobacillus bifidum*, *Lactobacillus longum*, and *Lactobacillus* at a dose of 3×10^{10} CFU in 250 mL water twice a day for 12 weeks showed a decrease in fasting plasma glucose, fasting plasma insulin, hemoglobin A1c, homeostatic model assessment of insulin resistance [181]. Therefore, it can be said that probiotics can be used as therapy for both type 1 and type 2 diabetes by decreasing inflammation and beta cell death, respectively.

Skin diseases (anti-aging)

Skin is the most important outer barrier of the human body. There are a lot of factors, including intrinsic (hormonal and genetic) and extrinsic (environmental: pollution, smoking, radiation, etc.), that cause skin aging rapidly. Due to the increased metalloproteinase activity, the capacity to inhibit ROS increases the pH of the skin, and it elevates skin aging. Research showed probiotics and their metabolites play a role in changing the pH of the skin. During metabolism, probiotics produce acidic molecules and can lower the pH of the skin and help in controlling enzymatic activity, limiting the harmful bacterial growth in the skin, thus maintaining a good skin condition [182–184]. The aging process, along with environmental stress, ROS, and cellular damage, may hamper the natural antioxidant defense system. It was observed by the researchers that probiotics can reestablish these factors and slow down the aging process effectively [183]. Also, probiotics showed a reduction in the negative effects of UV exposure. For instance, people were given *L. johnsonii* and carotenoids for ten weeks before being exposed to both simulated and natural sunlight. Results showed that experimental supplementation improved immune system homeostasis recovery following UV-ray [185]. exposure and decreased UV-induced "*Langerhans* cell density" when compared to a placebo. Human volunteers who consumed 10^{10} CFUs/day of *L. plantarum* HY7714 for 12 weeks saw improvements in skin elasticity, gloss, and moisture content, as well as a reduction in the depth of wrinkles [186].

Cardiovascular disease

A series of abnormal events that arise in the blood circulatory system involving veins, capillaries, and arteries is known as cardiovascular disease. If it happens, it is treated with medication, lifestyle changes, and sometimes surgery. Intestinal microflora can act as a fat-reducing factor, and with probiotic strains, blood lipid levels, such as low density lipoprotein cholesterol (LDL-C), can be controlled, which is a primary risk factor [187–189]. The endothelium, which creates the inner layer of blood vessels, helps in regulating

healthy blood pressure in the human body with the production of sufficient NO, but the is some circumstances low level of NO or a lack of NO production leads to endothelial dysfunction, thus leading to cardiovascular disease [190].

Probiotics were previously found to be useful in reducing cholesterol in a group of people who consumed fermented yogurt [191]. Furthermore, the gut microbiome modulates cardiovascular health by metabolizing dietary components into bioactive compounds, such as SCFAs and trimethylamine *N*-oxide (TMAO). These metabolites influence critical physiological processes, including cholesterol metabolism, blood pressure regulation, and endothelial function [192]. Probiotics have been shown in studies to lower cholesterol levels. For instance, live *L. fermentum* 11976 significantly decreased the levels of LDL-C, triglycerides, and total cholesterol in hypercholesterolemic hamsters [193]. Together with other beneficial food ingredients, these bacteria alter metabolic pathways by reducing the synthesis of endogenous cholesterol [194] and digesting dietary fiber to produce SCFAs. Reducing and managing the degree of inflammation in inflammatory markers [195] is another consequence. In one study, rats were supplied with a high-cholesterol diet and also in addition, supplemented with lyophilized *L. plantarum* MA2 showed comparable outcomes to those fed a high-cholesterol diet alone, with a significant reduction in total cholesterol, LDL-C, and triglyceride levels [196]. Recent research has connected improved lipid profile levels to the mechanism of reducing inflammation. Emerging evidence indicates that specific gut microbiota compositions are linked to elevated blood pressure and reduced responsiveness to antihypertensive therapies, whereas other microbial profiles may confer protection against cardiovascular risk factors [31].

Respiratory disease

There is clinical emerging evidence supporting the therapeutic use of probiotics for allergic rhinitis (AR) and other respiratory diseases. In a randomized controlled trial, *L. paracasei* LP-33 was found to significantly improve nasal symptom scores in AR subjects. Probiotics have been found to have general efficacy against viral respiratory infections, including influenza and COVID-19, through multiple mechanisms: 1. Antimicrobial production: *Bacillus* subtilis 3 synthesizes aminocoumarin, a crucial antibiotic that repels respiratory pathogens and enhances host immunity. 2. Barrier reinforcement: *L. rhamnosus* GG reinforces epithelial strength in intestinal and pulmonary tissues, as confirmed in human trials. 3. Immunomodulation: Probiotic strains increase regulatory T cell counts and reduce pro-inflammatory cytokines (IL-6, TNF-α) in systemic infections. These properties make probiotics suitable adjuvants to SARS-CoV-2 and ventilator-associated pneumonia (VAP). Through the exclusion of pathogens by competitive exclusion and maintenance of microbiota homeostasis, probiotics can reduce VAP incidence without adding to antibiotic resistance [185].

Cancer

Probiotics are very promising adjuvant drugs in cancer treatment due to their ability to modulate gut microbiota and locally and systemically enhance immune responses. The therapeutic effectiveness of probiotics, as demonstrated by preclinical studies, in inhibiting tumor development, growth, and metastasis in various cancer models, including chemically-induced and transplantable tumors is remarkable. The anti-carcinogenic effect is exerted through multiple mechanisms whereby metabolites from the probiotics, like bacteriocins, immunomodulatory peptides, and SCFAs, are key. These substances regulate major oncogenic pathways by competing exclusion of procarcinogenic pathogens, butyrate production augmentation, carcinogenic bile acid inhibition, and binding of diet-derived mutagens. At the molecular level, probiotics inhibit NF-κB-dependent proliferative markers (cyclin D1, COX-2) and anti-apoptotic proteins (Bcl-xL, Bcl-2), promote pro-apoptotic TRAIL signaling and mTOR/4EBP1-mediated cell cycle arrest. They also inhibit tumor angiogenesis and aberrant crypt foci formation. These mechanisms, being multifaceted, provide the foundation for the use of probiotics as non-invasive adjuvants to conventional cancer therapy, particularly in microbiota-associated cancers [31].

Conclusions

It is understood from the best knowledge of the literature that probiotics play roles in various fields, like the effect on intestinal flora, providing nutrient values, strengthening immunity, and annihilating pathogens. The connection between probiotics and human health and disease has been recognized since ancient times. Gut microbiome research is confronted with many challenges, in that variation in sample collection, processing, and analysis methodologies leads to conflicting results between studies. Although some molecular pathways mediating the therapeutic potential of probiotics have been unravelled, compelling clinical evidence of their efficacy in autoimmune and inflammatory diseases remains limited. Moreover, while preclinical studies using animal models have provided valuable mechanistic data, a central need is to validate these findings in human clinical studies in order to assess translational feasibility.

Probiotic research has garnered increasing attention to combat the broadening difference between production capability and consumer demand. Optimized microbial strains, along with specially tailored dietary preparations, are being formulated to enhance their therapeutic efficacy. Some health findings on the effectiveness of probiotics remain inconclusive and require additional scientific evidence. The mechanisms of action of probiotics on host health discussed in this review include modulation of the intestinal microbiota, competitive inhibition of pathogenic microorganisms through effective binding, enhancement of the IEB, and regulation of the host immune system. However, further research is needed to uncover additional mechanisms underlying probiotic function. The review also highlights the therapeutic prospects of beneficial bacterial strains, with their expanding contribution to modern medicine. Mechanistic studies demonstrate that probiotic bacteria exclude pathogens from colonization through competition for intestinal niches and nutrients and by modulating host mucosal immunity. In vivo and in vitro evidence points to the accumulation of deep interactions between these microbes and adaptive immune responses, which has promoted increasing research into their therapeutic uses for the modulation of a wide range of disease states. So far, despite having some negative effects, still probiotics can still be considered as a health benefit supplements for human. Further research into bacterial strains and metabolites affecting immune function may provide important insights for the prevention and management of immune disorders and other diseases.

Abbreviations

APCs: antigen-presenting cells

AR: allergic rhinitis

BBB: blood-brain barrier

CF: cystic fibrosis

CPSs: capsular polysaccharides

DCs: dendritic cells

EPS: exopolysaccharides

GA: gum arabic

GABA: γ-aminobutyric acid

GALT: gut-associated lymphoid tissue

GIT: gastrointestinal tract

IBD: inflammatory bowel disease

IBS: irritable bowel syndrome

IEB: intestinal epithelial barrier

IEC: intestinal epithelial cell

IFN: interferon

Igs: immunoglobulins

IL: interleukin

LAB: lactic acid bacteria

LDL-C: low density lipoprotein cholesterol

LTA: lipoteichoic acid

MAMPs: microbe-associated molecular patterns

NK: natural killer

NO: nitric oxide

NOS: nitric oxide synthase

PEC: pectin

PRRs: pattern recognition receptors

PSA: polysaccharide A

PVA: polyvinyl alcohol

SA: stearic acid

SCFAs: short-chain fatty acids

SLPs: surface layer proteins

TJs: tight junctions

TLR2: Toll-like receptor 2

TNF: tumor necrosis factor

UTI: urinary tract infection

VAP: ventilator-associated pneumonia

VVC: vulvovaginal candidiasis

WPC: whey protein concentrate

Declarations

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Author contributions

STA: Conceptualization, Writing—original draft, Writing—review & editing, Formal analysis, Project administration, Supervision. ABHR: Conceptualization, Writing—original draft, Writing—review & editing, Formal analysis, Project administration. MUA: Conceptualization. MTK: Writing—original draft. JFJ: Data curation. MMI: Writing—original draft. MARR: Conceptualization. MAU: Conceptualization, Writing—review & editing. All authors read and approved the submitted version.

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