

The Effect of Probiotic Bacteria on Enhancing Immune Response and Reducing Pathogenic Infections

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Abstract: Probiotic bacteria raise host resistance to viral pathogens through induction of both innate and acquired immunity and lessen the incidence and severity of bacterial infections of the gastrointestinal and respiratory tracts. Channels used by probiotic bacteria to enhance immune response include stimulation of phagocytic activity by neutrophils, induction of regulated levels of reactive oxygen species via activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complexes, mediation of the production of inflammatory cytokines, and restoration of intestinal microbiota following viral infections. Additional mechanisms of competitive exclusion by cell surface proteins, antimicrobial metabolite secretion, and stimulation of mucin secretion decrease the ability of pathogens to colonize the host, limiting the proliferation of gastrointestinal

and respiratory pathogens.

Probiotics are living microorganisms capable of establishing a beneficial host-microbial relationship following ingestion. Probiotics exhibit promising effects in the prevention of gastrointestinal and respiratory tract infections. Administration of probiotics from genera *Lactobacillus* and *Bifidobacterium* increases innate immune responses to pathogen-associated molecular patterns and signaling through toll-like receptors, stimulating phagocytic and cytolytic activity and increasing pathogen clearance. Probiotic administration increases the production of mucosal immunoglobulin A (IgA) in imperative mucosal sites such as the intestine, respiratory tract, and vagina, assisting in the clearance of foreign pathogens. Probiotic strains from genera *Lactobacillus* and *Bifidobacterium* promote appropriate regulation of the adaptive immune response to infection via mechanisms dependent on antigen-presenting cells of the mucosal immune system and cytokine production by dendritic cells and T cells. Studies from randomized controlled trials and meta-analyses indicate that specific probiotic bacteria can reduce the number of symptoms associated with common acute respiratory infections in a strain-specific manner and reduce the incidence of common acute diarrheal diseases when maintained at sufficient numbers for an appropriate duration.

1. Introduction

Probiotic bacteria exert numerous beneficial effects on human health by effectively improving the balance of intestinal microbial communities. These microorganisms stimulate the activities of various immune cells, including macrophages, natural killer cells, and antigen-presenting cells, and significantly increase the secretion of immunoglobulins, which play a crucial role in immune defense. In addition, probiotics promote the production of anti-inflammatory cytokines while simultaneously inhibiting the expression of pro-inflammatory cytokines, thus helping to maintain a well-functioning immune system. Furthermore, they have a vital role in suppressing the growth of opportunistic pathogens, thereby protecting the body from infections and enhancing intestinal barrier function. This enhancement is achieved through increased mucus production and the upregulation of tight junction proteins that maintain intestinal integrity. Probiotic bacteria also provide a defense against pathogenic viral infections through the mechanism of competitive exclusion of pathogens and the production of various inhibitory substances that deter their growth. Notably, lactic acid bacteria have been shown to reduce the risk of developing acquired immune deficiency syndrome (AIDS) and certain types of tumors. Regular consumption of probiotics leads to the induction of T-helper cell cytokines such as IL-1 α and IL-1 β , as well as stimulating the secretion of immunoglobulin A (IgA) by plasma cells, which collectively help to reduce microbial translocation and bolster overall health. [1]

2. Understanding Probiotic Bacteria

Probiotics are defined as non-pathogenic microorganisms that confer health benefits when administered in adequate quantities [1]. Probiotic bacterial species include certain Lactobacilli, Streptococci, Enterococci, and Bifidobacteria strains of lactic acid bacteria, species within the Enterobacteriaceae family, and Bacilli. Probiotics can be administered as individual strains or as multi-strain or multi-species formulations from these bacterial genera; these preparations can be available as fermented food products, dietary supplements, or pharmaceutical formulations. Probiotics are administered primarily for their beneficial effects on maintenance or restoration of healthy gut microbiota. Consumption of probiotic bacteria leads to an increase of these microorganisms in the intestinal tract, which can help to prevent a decline in bacterial abundance and potentially protect the host against infection [2].

The main mechanisms associated with probiotic action include competitive exclusion of invading pathogens at mucosal surfaces, secretion of antimicrobial factors, enhancement of barrier function, and immunomodulation. Probiotic strains displaying antimicrobial activity secrete antibacterial metabolites such as bacteriocins and lactic acid that inhibit growth and virulence of both Gram-positive and Gram-negative bacteria. Stimulation of innate immune cells by probiotic strains induces production of immunoglobulins, particularly secretory IgA, and various innate immune mediators. In addition, probiotics can activate and attract neutrophils, macrophages, and natural killer cells to sites of infection. Probiotic microorganisms are also able to modulate markers of the adaptive immune system, inducing differentiation and/or generation of several subsets of T effector cells, T regulatory cells, and B lymphocytes. These wide-ranging functional properties enable probiotic strains to potentially confer protection against pathogens via multiple pathways. [3][4][5]

2.1. Definition and Classification

The term probiotic was coined in 1965 by Lilly and Stillwell to describe substances produced by microorganisms that stimulate the growth of other microorganisms. Fuller amended the definition in 1989, describing probiotics as microorganisms that carry a host-wide benefit by enhancing intestinal microbial balance. The World Health Organization (WHO) and the United Nations (UN) currently define probiotics as microbes that exert a positive impact on the host's health when consumed in sufficient quantity. Many bacterial species have been identified as probiotic, but the most widely used are the lactic acid bacteria (LAB) from the Lactobacillus, Bifidobacterium, Enterococcus, and Streptococcus genera [1].

Probiotic bacteria employ several mechanisms to confer their health-enhancing effects on the host. First, they improve intestinal barrier function, competing with potential pathogens for adhesion to epithelial cells and mucosa. This competitive exclusion hampers the colonization and overgrowth of invading pathogenic microbes within the gastrointestinal tract. Second, probiotics secrete protective molecules, including inhibitory peptides, organic acids, and short-chain fatty acids, that collectively impede the proliferation of harmful bacteria. Finally, specific probiotic strains actively regulate the host's immune system by interacting with mucosal epithelial cells and antigen-presenting cells. These interactions stimulate innate immune responses and promote adaptive immunity, thereby supporting systemic protection against infectious and allergic conditions. [6][7][8]

2.2. Mechanisms of Action

Enhancement of the host immune response constitutes a principal mechanism by which probiotic bacteria exert beneficial effects [9]. Improved barrier function, competitive exclusion of pathogens, and stimulation of both innate and adaptive immunity contribute [10]. The ability to adhere to and transiently colonise gastrointestinal (GI) surfaces is a key attribute; the adherence of *L. plantarum* 299v to intestinal mannose receptors induces the release of cytokines and chemokines that drive mucosal and systemic immune responses. Interaction with epithelial and immune cells triggers production of soluble factors, including IL-6, TNF- α , and IFN- γ , which modulate expression of defence molecules, antigen presentation, leukocyte recruitment, and activation of effector cells. Probiotics also promote IgA production and elicit a Th1-skewed cellular response, facilitating the clearance of pathogens rapidly and effectively. Furthermore, probiotics hinder pathogens by competing for substrates and receptor sites, thus impeding colonisation and infection.

3. The Immune System: An Overview

The immune system defends against disease-causing agents. Comprising a network of traits, it inhibits accumulation of microorganisms and parasites, guarding an organism's health. It consists of two components: brain-regulated specific and non-specific immunity; and innate and acquired immunity. The former involves brain responses organizing specific and non-specific immunity, while the latter entails developed and expressed immunity acquired through disease exposure or vaccination. Innate immunity uses physical and chemical barriers—mucous and skin—as first-line defenses against injury and pathogen invasion. It includes stored cellular components, such as natural killer cells and phagocytes, and soluble factors like complement components and cytokines. Trained immunity involves epigenetic modifications enabling innate immune cells to mount amplified responses upon reinfection. Adaptive immunity allows development of immunological memory to counter frequently encountered diseases; it comprises cellular and humoral branches. Cellular immunity, mediated by T-cells within lymphoid organs, fights virus-infected cells, tumor cells, and supports antibody production. Humoral immunity involves B-cells producing antibodies that circulate in body fluids to immobilize infective agents [1]. [11][12][13][14]

3.1. Components of the Immune System

The immune system confers host resistance to infection by a wide variety of microorganisms. It is composed of highly specialized cells and organs that inhibit the growth of potentially infectious agents. Typically, the immune system discriminates between self and nonself as the basis for responding appropriately to environmental and microorganism-provided antigens. The immune system can be divided into innate and adaptive immunity. Innate immunity refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body. These mechanisms include physical barriers such as skin, chemicals in the bloodstream, and immune system cells that attack foreign cells in the body. The innate immune system provides an immediate but non-specific response. Cells of the innate system recognize, engulf, and kill pathogens. In response to antigen exposure, activated immune cells release a wide

range of pro-inflammatory mediators such as proteolytic enzymes, cytokines, and prostaglandins. Adaptive (or acquired) immunity refers to antigen-specific immune response. The antigen first contacts the immune system through specialized antigen-processing cells such as macrophages, dendritic cells, or B cells. These cells internalize and degrade the antigen and display antigen fragments on their surface attached to major histocompatibility complex molecules. Subsequently, certain T-helper cells ($CD4^{+}$) recognize the antigen and become activated. The activated T-helper cells coordinate the adaptive immune response that involves the production of antigen-specific immunoglobulins by B cells and the activation of cytotoxic T cells ($CD8^{+}$) that kill infected or cancer cells [15].

3.2. How the Immune System Works

The immune system is designed to prevent pathogenic microbes from invading and replicating within the host while tolerating harmless or beneficial microbes and unwanted immune responses. Innate immunity provides a nonspecific defense against invading pathogens that generally acts within several hours of exposure [16]. Adaptive immunity, also known as acquired immunity, is antigen-specific and includes the development of immunologic memory after initial exposure, resulting in an enhanced response to subsequent exposures to the same antigen. Both the innate and adaptive components of the immune system are complex and multidimensional and are integrated to provide immunity.

Cells of the innate immune system include granulocytes, monocytes/macrophages, dendritic cells, natural killer cells, and others [17]. The innate immune system also comprises a variety of epithelial barriers, phagocytic cells, pattern-recognition molecules, and the complement system. Cells of the adaptive immune system are predominantly T- and B-lymphocytes. T lymphocytes develop into either cytotoxic or helper cells, which in turn orchestrate the diverse adaptive immune response by the production of cytokines. These cytokines either direct the immune response to predominantly increase the level of cell-mediated cytotoxicity by activating macrophages, natural killer cells, and the complement cascade or to increase the production of antigen-specific antibodies by the B cells.

4. Probiotics and Immune Response

Probiotic bacteria can enhance immune defences in humans and animals through components in their cell walls and secreted factors. *Lactobacillus rhamnosus* GG increases innate immunity by stimulating type 1 interferon production through Toll-like receptor 3 activation, and boosts adaptive immunity by enhancing antigen presentation and regulating T-cell and B-cell differentiation. Colonization with *Lactobacillus* species promotes dendritic cell maturation and induces expression of proinflammatory cytokine genes, improving resistance to infections such as *Vibrio cholerae*. Probiotics influence immune function by modulating both innate and adaptive responses [18].

4.1. Enhancement of Innate Immunity

The intestinal microbiota plays a key role in human health, particularly with respect to immune system development and maintenance of immune homeostasis [17]. Aberrant microbial colonization during neonatal life or gut inflammation leads to disturbed homeostasis. This manifests as abnormal development of lymphoid organs, reduced numbers of T cells, skewing towards a type 2 immune phenotype, and decreased serum immunoglobulin levels. Such dysbiosis renders the host more susceptible to infections and increases the risk of developing disorders such as allergies and auto-immune diseases, as well as metabolic conditions. Administration of probiotic bacteria is therefore a promising strategy to improve immune homeostasis and enhance host health. By normalizing inappropriate or inefficient immune responses, probiotics have the potential to restore the natural balance between host and microbiota in conditions associated with perturbed immune homeostasis. This is particularly relevant in individuals at increased risk of infection due to age, genetics, obesity, malnutrition, stress, or lifestyle. Pre-clinical and clinical

studies have demonstrated that probiotic supplementation confers protection against bacterial and viral infections, as well as allergic disorders primarily affecting the skin and respiratory tract [19]. In immunocompetent healthy human volunteers, treatment with *Lactobacillus* strains has been shown to improve both the percentage and the activity of natural killer cells. The importance of probiotic regulation of the host immune response is well documented, yet open questions remain. Most research has targeted the alleviation or treatment of disease or acute infection, with emphasis on models where immune homeostasis is perturbed, such as asthma, colitis, or infection. Relatively few studies address the situation in non-diseased, healthy subjects. Clearly, immune regulatory effects in pathological situations differ significantly from those required to maintain a state of immune homeostasis. While enhanced immunity may be desirable under conditions of acute infection, downregulation of the response may be required to maintain immune homeostasis in established chronic inflammatory disorders such as IBD or allergy. Maintenance of a homeostatic phenotype while simultaneously boosting immunity presents a paradox that has not previously been addressed. Healthy wild-type mice and non-diseased healthy human volunteers constitute an appropriate system to address this question, distinct from that of clinical intervention. Experiments have therefore been performed in healthy mice, more relevant to the use of probiotics by the general population. Furthermore, studies in humans rely on limited immunological parameters due to ethical constraints and the invasive nature of immunological monitoring. It remains primarily mechanistic animal studies that give the best insight into probiotic-mediated immune modulation.

4.2. Enhancement of Adaptive Immunity

The mammalian immune system is differentiated into innate and adaptive immunity, both of which provide protection against invading microorganisms. Innate immune responses represent the first line of defense and are non-specific; they operate rapidly to prevent infection upon encountering potentially harmful microbes. In contrast, adaptive immunity offers a specific response against invading pathogens while also being capable of generating long-lasting immunological memory; however, this type of immunity is slow to activate. The mammalian immune system is also characterized by an ...The administration of probiotics has been reported to enhance adaptive immune responses. Hundreds of probiotic strains have been documented to exert immunomodulatory effects and augment resistance to pathogenic infections by promoting immune signaling and regulating cytokine production [1]. For example, several species of *Lactobacillus* activate antigen-presenting cells (APC) and increase levels of interleukin (IL)-12, tumour necrosis factor- α (TNF- α), and interferon- γ (IFN- γ) [20]. Moreover, probiotic strains stimulate granulocyte-macrophage colony-stimulating factor, which enhances the function of various immune cells.

5. Probiotics in Disease Prevention

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits on the host [21]. They have been shown to decrease the risk and reduce symptoms of various infections, including in the gastrointestinal and upper respiratory tracts. A synthesis of randomized, placebo-controlled trials demonstrates reduced durations and frequencies of respiratory infections and related symptoms. Probiotics have also lowered the incidence of ventilator-associated pneumonia and decreased upper respiratory-tract infections when included in enteral nutrition for individuals with traumatic brain injuries. Systematic reviews and meta-analyses confirm diminished rates of respiratory-tract infections in both children and adults. Supplementation of the normal flora with lactobacilli has led to quicker recovery from symptoms of bacterial vaginosis. In animal models, probiotic administration has improved resistance to viral and bacterial infections. The protective effect against pathogens is likely mediated by enhanced immune function coupled with the capability of probiotic strains to inhibit adhesion or growth of microbial pathogens. The Live microbes ingested as probiotics also contribute to competitive exclusion of potential pathogens through colonization and production of antimicrobial substances.

5.1. Reduction of Respiratory Infections

Mucosal surfaces of the respiratory, genitourinary, and gastrointestinal tracts provide an important interface with the environment through which opportunistic pathogens can enter the body and cause disease. Beneficial probiotic bacteria can impede pathogen colonization of these areas by competitive exclusion through competition for nutrients and receptors, by production of antimicrobial substances such as bacteriocins, by modification of the environment, or through modulation of the immune system [22]. Several probiotic *Lactobacillus* strains reduce the incidence or severity of respiratory tract infections and have potential therapeutic application in allergic reactions and asthma. However, important factors such as the most effective strain(s), optimum dosage, length of treatment, and mechanism(s) of action are yet to be conclusively determined. Detection of a respiratory pathogen often induces a cascade of immune signalling molecules, resulting in differential activation of immune pathways. Probiotics delivered to the gut can activate regulatory T cell populations that generate immune signals conveyed to the bone marrow, ultimately resulting in differentiation of macrophages or dendritic cells that migrate to the lungs and enhance respiratory immunity.

5.2. Impact on Gastrointestinal Infections

A considerable number of clinical trials show that probiotic consumption reduces the risk or severity of gastrointestinal infections [2]. Respiratory infections normally receive more attention, yet gastrointestinal infections of viral or bacterial origin constitute a major global health problem. Rotaviruses and other strains of viruses cause significant morbidity and mortality. Therefore, reduction of these diseases provides critical public health benefits. Probiotics may compete for niches or create an inhospitable environment for the pathogens in the gastrointestinal tract [23]. They affect pathogen adhesion and invasion of epithelial cells, sequester essential nutrients, and alter the expression of specific genes that inhibit virulence functions such as toxin secretion. Probiotics may also modify environmental conditions including pH and the thickness and composition of mucus layers to prevent pathogen colonization.

6. Clinical Evidence Supporting Probiotic Use

The prophylactic and therapeutic applications of probiotics are supported by extensive clinical data. Randomized, double-blind, placebo-controlled trials indicate that probiotic supplementation, including strains such as *L. rhamnosus* and *L. reuteri*, reduces the incidence and severity of respiratory tract infections in children [1]. Meta-analyses reveal that infants administered probiotics experience fewer episodes of acute upper respiratory tract infections compared with controls, corroborating findings from multiple systematic reviews conducted between 2011 and 2016.

In addition to respiratory benefits, evidence demonstrates that certain probiotics decrease the duration of diarrheal episodes in pediatric populations. Both single-strain and multi-strain preparations, at concentrations exceeding 5×10^9 colony-forming units per day, effectively reduce the prevalence of antibiotic-associated diarrhea. Strains such as *L. casei* Shirota, *L. delbrueckii* subsp. *bulgaricus* OLL1073R-1, *L. reuteri* DSM 17938, and various *Bifidobacterium* species participate in these protective effects [10].

Probiotic consumption prior to antibiotic treatment is also associated with lowered rates of *Clostridium difficile*-associated diarrhea, highlighting an additional mechanism by which these microorganisms mitigate disease risk. Collectively, the clinical literature substantiates that targeted probiotic supplementation enhances immune function and diminishes the incidence of respiratory and gastrointestinal infections, particularly in vulnerable populations such as children, the elderly, and immune-compromised individuals.

6.1. Randomized Controlled Trials

Randomized controlled trials have examined the immune effects of probiotics in healthy

individuals. One such trial evaluated the consumption of a fermented product containing *Lactobacillus gasseri* CECT 5714 and *Lactobacillus coryniformis* CECT 5711 compared with standard yogurt. Intake of either product increased the proportion of phagocytic cells, including monocytes and neutrophils, along with their phagocytic activity. The probiotic formulation additionally elevated the relative abundance of natural killer (NK) cells and IgA concentrations. Interestingly, these effects were more pronounced after two weeks of treatment than after four weeks, suggesting immune regulation, and the probiotic product conferred greater enhancement of immunity than the control yogurt [24].

A related study investigated the impact of orally administered *Lactobacillus plantarum* WCFS1, *Lactobacillus salivarius* UCC118, and *Lactococcus lactis* MG1363 on systemic T and dendritic cell populations and responses in mice. Both *L. plantarum* WCFS1 and *L. salivarius* UCC118 are recognized probiotic strains, whereas *L. lactis* MG1363 lacks documented probiotic properties. The bacteria were administered over five days, the timeframe required for mice to develop an adaptive immune response. The results revealed strain-dependent modulations of dendritic cells in vitro and in vivo, as well as selective T cell responses observed in vivo and ex vivo [17].

6.2. Meta-Analyses and Systematic Reviews

Several comprehensive reviews provide evidence for probiotics' beneficial effects on immunity and infection prevention. A meta-analysis of randomized controlled trials reported that probiotic consumption reduces the incidence, duration, and severity of the common cold [25]. In a randomized, double-blind, placebo-controlled trial, a fermented product containing *Lactobacillus gasseri* CECT 5714 and *Lactobacillus coryniformis* CECT 5711 enhanced innate immune parameters in healthy adults. Compared to a standard yogurt control, the probiotic product led to greater increases in phagocytic activity, natural killer cell numbers, and salivary IgA secretion, indicating strain-specific immune modulation [24]. A further review of preclinical and clinical evidence discussed significant probiotics effects on respiratory infections, allergy, and other conditions, underscoring their role in maintaining immune homeostasis and reducing illness duration [1]. These data highlight the importance of strain selection, dosage, and intervention duration in achieving optimal probiotic effects and underscore the need for additional large-scale human studies.

7. Mechanisms of Probiotics in Infection Control

The beneficial effects of probiotic bacteria in the gastrointestinal tract extend to other body parts when these bacteria or their components enter the systemic circulation or lymphatics, and probiotic bacteria or their components can induce both local and systemic immune responses through their interaction with innate immune cells. Probiotic bacteria can influence infections either by competitive exclusion of pathogens or by production of antimicrobial substances [10]. Preventing attachment to the host is one way that probiotic bacteria exert antimicrobial effects, and there is considerable evidence that probiotic bacteria, through microbial antagonism, can inhibit or reduce the adhesion of various pathogens, including *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Salmonella Enteritidis*, and *Shigella* sp. competitive exclusion of enteropathogens, including *Salmonella*, by probiotic bacteria involves competition for nutrients and for colonization sites. In addition to the direct effects of competitive exclusion, probiotic bacteria secrete several antimicrobial substances. Many *Lactobacillus* species have been shown to secrete one or more antimicrobial substances that appear to play a role in the elimination or inhibition of undesirable microorganisms in the gut.

Both Bifidobacteria and Lactobacilli participate in immune regulation by inducing regulatory T cells; moreover, probiotic bacteria (and other components of the microbiome) interact with a variety of host molecular receptors, such Toll-Like Receptors (TLRs) [2]. Underpinning the maintenance of immunological and metabolic tolerance is the positive effect of micro-organisms on the immune system. The effect of the microbiome is therefore mediated by bacterial factors released from the micro-organisms, stimulating host cells across a plethora of different receptors

and cellular targets.

Several other antimicrobial strategies have been proposed to explain how probiotic bacteria confer host benefits, including detoxification of harmful metabolites and environmental stressors and reduction of gut pH, and these mechanisms may also indirectly contribute to controlling infections. However, the predominant antimicrobial pathways employed by probiotic bacteria are competitive exclusion and the secretion of antimicrobial substances.

7.1. Competitive Exclusion of Pathogens

Probiotic bacteria can prevent the colonization of the host by pathogenic bacteria through competitive exclusion and by the production of inhibitory compounds [2]. Competitive exclusion describes a process whereby pathogenic bacteria compete with other bacteria for the nutrients and adhesion sites needed for survival [26]. Thus, probiotics occupy receptors to discourage colonization by pathogens, as well as effectively outcompete microbes for the available nutrients. The intestinal mucosa provides a readily accessible reservoir of nutrients that are a valuable resource for colonizing bacteria, especially when the metabolism of the host's own mucosal cells produces intermediary metabolites. Bacteria, including commensals, probiotics, and opportunistic species, use this nutrient reservoir and thereby obtain a selective advantage over transient pathogens that are less adapted to this supply of molecules.

Bacterial production of antimicrobial compounds can provide an additional barrier to pathogenic infection. These antimicrobial agents include a wide array of organic acids as well as bacteriocins with variable specificity against common infectious species. Furthermore, strains of *Lactococcus* and *Lactobacillus* produce large quantities of hydrogen peroxide that, unlike other compounds, has a very broad spectrum of action. The metabolic response of commensals and probiotics is generally rapid after a change in nutrient supply from the host or cell-to-cell communication; consequently, growth suppressive and bactericidal effects can be maintained consistently to limit pathogen persistence and colonization of the intestinal tract.

7.2. Production of Antimicrobial Substances

Probiotic strains, such as *Lactobacillus acidophilus*, *Bifidobacterium animalis*, *Lactobacillus plantarum*, and genetically engineered *Lactobacillus casei*, have been reported to produce antimicrobial compounds including bacteriocins, organic acids, and linoleic acids that exert antagonistic activity against various pathogens. For example, *Bifidobacterium animalis* isolated from healthy human feces displayed antagonism against *Bacillus cereus*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. *Lactobacillus acidophilus* showed inhibitory effects toward food-contaminating bacteria. Bacteriocins produced by *Lactobacillus plantarum* have inhibited the growth of *Listeria monocytogenes*. Genetically modified *Lactobacillus casei* that overexpresses linoleic acids limits the growth, survival, and virulence of *Salmonella Typhimurium* and *Enterohaemorrhagic Escherichia coli* [27].

8. Factors Influencing Probiotic Efficacy

The efficacy of probiotics depends on specific bacterial strains and appropriate dosage and duration. These factors determine the effectiveness of a given probiotic in a particular situation, including its influence on immunity, pathogen resistance, and clinical outcome [28]. Not all bacteria within a species possess the same probiotic properties, so the beneficial effects of one strain may not apply to another even when used in a similar manner [2]. Evidence from randomized, controlled human trials shows that probiotics help protect against clinical conditions, especially infectious and inflammatory diseases affecting the gastrointestinal and respiratory tracts. However, the benefits vary depending on the strain, dose, and length of treatment.

8.1. Strain-Specific Effects

Bifidobacterium strains can elicit specific immunomodulatory effects, including both pro-inflammatory and anti-inflammatory responses, underscoring the importance of strain specificity

in probiotic function. The capacity to utilize complex carbohydrates confers a competitive advantage in establishing resilience within the gut, yet individual strains differ in their mechanisms of colonization resistance and immune modulation, as indicated by differential microbiome alterations and enzymatic capabilities [29]. Variation in immunomodulatory properties among strains of the same species suggests that factors beyond phylogeny govern host interactions. Cell wall components such as peptidoglycan and lipoteichoic acid serve as microbe-associated molecular patterns recognized by pattern recognition receptors, while surface molecules including exopolysaccharides and pili further contribute to strain-specific immune effects. The efficacy of specific bifidobacterial strains in enhancing immune responses and combating pathogens has been demonstrated in diverse contexts, ranging from general mucosal immunity to the mitigation of acute infectious diarrhea in children [30]. Because different strains can exert markedly distinct immunomodulatory and protective effects, identification of host-compatible strains therefore emerges as a critical strategy to optimise probiotic interventions [20].

8.2. Dosage and Duration of Intake

A key consideration in probiotic use involves the selection of an appropriate dose and duration of consumption. An assessment of 94 randomized controlled trials included in a recent meta-analysis revealed a wide variation in dosage, spanning from as little as 10^8 to as high as 10^{11} colony-forming units (CFU) [31]. Similarly, the period over which probiotics were administered also differed considerably across studies [30]. These disparities underscore the need for further research to identify an optimal dose and timeframe that maximise the beneficial effects of probiotics. Meanwhile, higher dosages and formal guidance on duration should be taken into account when considering probiotic regimens.

9. Safety and Side Effects of Probiotics

Numerous probiotics have been classified as Generally Recognized As Safe (GRAS) by the U.S. Food and Drug Administration. These include *Lactobacillus* species such as *L. acidophilus*, *L. casei*, *L. fermentum*, *L. lactis*, *L. plantarum*, *L. reuteri*, *L. rhamnosus*, and *L. salivarius*. The long history of probiotic use through the human food chain without significant adverse side effects has supported this GRAS status. Nevertheless, it is important to acknowledge that adverse effects, although rare, cannot be entirely excluded. Common side effects associated with probiotic consumption include bloating, gas, dry mouth, thirst, upset stomach, and changes in bowel movement frequency or consistency. More serious effects have been primarily reported in immuno-compromised or seriously ill individuals [1]. A separate systematic review and meta-analysis of randomized controlled trials examining probiotic use in patients with inflammatory bowel disease did not provide a clear explanation for negative effects, highlighting the need for additional research to clarify the safety profile and identify optimal species, strains, and dosages [32].

9.1. General Safety Profile

Probiotic microorganisms are generally recognized as safe for consumption by food and pharmaceutical authorities worldwide, with no reports of adverse events due to their ingestion in the general population [1]. The administration of probiotics may cause mild adverse effects, such as flatulence or changes in intestinal transit. Rarely, when probiotic bacteria reach the bloodstream, they may lead to cases of bacteremia and/or sepsis. The time for probiotics to exert a beneficial effect varies widely according to the bacterial species administered, the dosage and regimen, the health status of the host, and the formulation of the product.

9.2. Potential Adverse Effects

Probiotic microorganisms are usually considered safe, although probiotic-associated bacteremia or fungemia have been described. Occasionally, patients at risk of bacterial or fungal translocation may exhibit adverse effects from probiotics. Moreover, side effects such as headaches and gastrointestinal symptoms (irritable bowel syndrome, nausea, or dyspepsia) may also occur [1]

10. Probiotics in Different Populations

Probiotics exert benefits for the general population, but evidence from studies on children, older people, and immuno-suppressed patients indicates particular effects in these high-risk groups. These cohorts are more susceptible to infectious diseases and often undergo high rates of antibiotic use and hospitalisation. Intervention studies confirm population-group differences in response to probiotic administration and provide important insights into the mechanisms whereby specific probiotics produce beneficial effects [21].

10.1. Children and Infants

The term “probiotic” was first used by Lilley and Stillwell in 1965 to describe substances secreted by one microorganism stimulating the growth of another. In 1974, Parker proposed the definition “organisms and substances which contribute to intestinal microbial balance.” Following the introduction of the use of live microbial feed supplements in animal husbandry that improved feed efficiency and growth performance by Fuller in 1989, probiotics were defined as live microbial food supplements which beneficially affect the host by improving its microbial balance and have been further updated by the Food and Agriculture Organization, (FAO), and World Health Organization, (WHO) (FAO/WHO, 2001). These definitions are, however, often debated and questioned, as they rather reflect the effects or the potential mood of future rather than strictly defining probiotics based on certain criteria. Probiotics for human use include members of the *Lactobacillus* genus (e.g., *L. acidophilus*, *L. gasseri*, *L. casei*, *L. bulgaricus*, *L. johnsonii*, and *L. reuteri*), *Bifidobacterium* genus (e.g., *B. bifidum*, *B. longum*, *B. infantis*, and *B. breve*), certain species of *Streptococcus*, *Enterococcus*, *Bacillus*, and *Escherichia* (Table 10.1). The two genera, *Lactobacillus* and *Bifidobacterium*, dominate the probiotic market and together constitute the majority of commercially available probiotics [33]. The proposed mechanisms of their probiotic action include maintenance of microbial balance of the gastrointestinal tract, antagonism towards pathogens, and stimulation of the immune system [34].

10.2. Elderly Individuals

In elderly individuals, age-related changes in gut microbiota and immune function increase susceptibility to intestinal infections [35]. Characterization of fecal bacterial communities in healthy and hospitalized elderly volunteers using real-time PCR revealed pronounced differences, indicating a dysbiosis associated with aging. Studies investigating the effects of prebiotic compounds, such as bifidogenic growth stimulators and galacto-oligosaccharides, as well as fermented milk products, have demonstrated modulation of intestinal microbiota and enhancement of the antibody response to influenza vaccine in elderly patients. Moreover, supplementation with heat-killed *Enterococcus faecalis* T-110 in aged hamsters improved gut immunity, altered gut flora composition, and reduced intestinal infection incidence, suggesting that probiotic interventions can bolster host defenses in advanced age [36]. These findings support the use of probiotics and prebiotics as strategies to restore microbial balance and enhance immune function in the elderly, thereby reducing the burden of infectious diseases.

10.3. Immunocompromised Patients

Immunocompromised patients are extremely sensitive to adverse consequences from probiotic bacteria. Such patients rely on a stronger immune response to control infection, but probiotic bacteria can disseminate throughout their immune system despite control by white blood cells [17]. Several well-characterized probiotic strains have caused systemic infection in the immunocompromised. However, the majority of studies still show an increase in beneficial clinical outcomes. Immunocompromised states include breast cancer, human immunodeficiency virus infection, diabetes, steroid or immunosuppressive therapy, and premature infants.

11. Future Directions in Probiotic Research

While several probiotic strains have been investigated for their immune-enhancing capacity, many

remain unexplored. In the near future, researchers may consider developing probiotic preparations capable of modulating the gut-brain axis—termed psychobiotics—to improve digestive and immunological functions. In addition, probiotic-genome analyses could facilitate the development of individualized probiotic therapies tailored to specific diseases, offering potentially safer alternatives to conventional treatments [1].

11.1. Novel Probiotic Strains

Lactococcus lactis 11/19-B1 is a novel strain isolated from the surface of a kiwi fruit harvested in Japan. It has been characterized in detail and evaluated for probiotic potential by comparison with three other *L. lactis* strains (JCM5805, NBRC12007, ATCC19435) and two well-known probiotic strains, *Lactobacillus bulgaricus* LB-12 and *Bifidobacterium lactis* Bb-12 [37]. Such bacteria have traditionally been used as starters in the manufacture of fermented milk products such as cheese and buttermilk. Genera that include probiotic strains include *Lactococcus*, *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Enterococcus*, *Streptococcus*, *Pediococcus* and *Leuconostoc*. Probiotics must be safe for use in humans and animals and should possess: antimicrobial activity against human and/or animal pathogens, absence of any virulence factors, no production of biogenic amines, sensitivity to antimicrobials used in human and/or veterinary medicine, tolerance to gastric acid and bile, and ability to adhere to intestinal mucosa. The novel strain possesses the required biological safety, along with marked antimicrobial activities, high β -galactosidase activity, strong adhesion to intestinal cells and a marked ability to stimulate innate immunity.

11.2. Personalized Probiotic Therapy

Given individual variations in microbiota composition and probiotic responses, a personalized approach to probiotic therapy is gaining popularity [1]. Probiotics have shown immunomodulatory effects and a promising potential to help prevent allergic and inflammatory disorders by shifting immune responses towards anti-inflammatory pathways [2]. Probiotic supplementation augmented local and systemic immune reactions whilst maintaining intestinal immune homeostasis, proposing particular benefit in managing irritable bowel syndrome (IBS) symptoms [38].

12. Regulatory Aspects of Probiotic Products

The development of probiotic products is subject to the regulatory frameworks governing foods, food supplements, dietetic foods, and medicinal products. These frameworks establish general requirements and specific restrictions concerning the use of probiotics and the enumeration of viable cells they contain. Because most probiotic products fall under the category of foods, regulations additionally address labeling, presentation, and advertising, including the substantiation of health claims. The European Commission issued a recommendation in 2002 that serves as a basis for determining whether a food can be marketed as a probiotic. In 2016, the International Probiotics Association outlined several guidelines: the probiotic microorganism should be properly identified; the product must contain a viable count of the specified probiotic organisms throughout the shelf life; clinical studies demonstrating health benefits in the target host should be preferably performed; and a suitable dose of the probiotic(s) should be delivered. If health claims are made, the product must comply with applicable regulations such as Commission Regulation (EC) No 1924/2006 [24] [1] [30].

12.1. Regulatory Frameworks

Probiotic bacteria contribute to several probiotic functions .

Health-beneficial probiotics are monitored by guidelines set forth by authoritative organizations, such as the Food and Agriculture Organization of the United Nations and the World Health Organization . These guidelines recommend adequate labeling of probiotic products with the genus, species, and strain designation; viable number of each probiotic strain at the end of shelf life; recommended serving size to deliver the effective dose of probiotics related to clinical trials; health claims based on scientifically recognized and accepted clinical data; appropriate storage

conditions; and corporate contact details to ensure consumer protection, awareness, and full disclosure .

The Food and Drug Administration (FDA) in the United States requires probiotic products to meet safety and health requirements to assure safety, quality, suggested uses, and truthfulness of claims made on their labels and products . The FDA employs certain regulatory levels for probiotic products, as specific to their application, to ensure consumer protection.

Probiotic products classified as conventional foods and beverages or dietary supplements are regulated by the Center for Food Safety and Applied Nutrition (CFSAN) under the Food Drug and Cosmetics Act and the Dietary Supplements Health and Education Act (DSHEA). In the United States, the use of the term probiotic is generally considered a structure-function claim and cannot be made in reference to the treatment or prevention of diseases. Structure-function claims require a disclaimer stating that the products are not intended to diagnose, treat, prevent, or cure diseases . Safety evaluation of probiotic strains used in foods and dietary supplements is an integral part of the regulatory system in the country. Strain safety assessment generally complies with the guidelines of the Scientific Committee on Animal Nutrition of the European Commission 2011, published by the International Life Sciences Institute in ILSI Europe 2013 and subsequently updated by the Public Health Agency of Canada in 2013 . Regulatory authorities in several European countries require the competent authority to designate commercial strains of probiotics as food additives. Innovations in the safety assessment of the biological forms of probiotics, bacteriophages, and extracellular membrane vesicles are being introduced to complement current systems for assessment of gut health .

12.2. Labeling and Health Claims

Probiotics are products formulated to contain viable, defined, beneficial microorganisms that, when ingested in adequate numbers, alter the microflora of the host and exert health-promoting effects [1]. Multiple national and international bodies regulate advertising and labeling of foods and foods for special dietary uses, including for probiotic products. Regulation of probiotic product labeling and advertising falls primarily under the auspices of federal, state, and local consumer protection and unfair competition statutes, along with general food and drug legislation. In the United States, regulations pertaining to foods and dietary supplements—covering both nutrient content and health claims—are issued by the Food and Drug Administration (FDA). These regulations stipulate that labeling must be truthful and not misleading, enable consumers to obtain facts and interpret them in relation to their own health, and contain no implied claims that the product can be used for therapeutic purposes if such claims cannot be substantiated by authoritative evidence.

Labels and labeling for probiotic products should comply with pertinent regulations including those by the FDA, the Office of Regulatory Affairs (ORA), the Federal Trade Commission (FTC), the National Advertising Division of the Council of Better Business Bureaus, and the Dietary Supplement Health and Education Act, among others. Food and dietary supplement labels, including written, printed, or graphic material on the container, wrapper, or as a tag, must furnish the information described for food labeling and disclaimers for dietary supplements [24]. A number of regulations restrict or prohibit specific claims, further disallowing false or misleading statements and unverifiable testimonials. Health claims on probiotic products are permitted only if substantial scientific evidence exists to demonstrate that the claim is truthful and not misleading and that the substance plays a role in maintaining body structure and functionality [39]. Under these circumstances, the claim must be approved by the FDA or, for substances with generally recognized as safe (GRAS) status, by the Food Safety and Inspection Service of the U.S. Department of Agriculture (FSIS-USDA). Claims of *in vitro* physiological effects with no direct relevance to human experience or intervention and with insufficient credible association between the substance and human health must be avoided. Notably, no health claims applicable to probiotic products have received FDA approval, resulting in the absence of such claims on product labels

and marketing materials. Furthermore, there is no organized global regulatory framework specifically addressing probiotic health claims, and marketing practices in certain jurisdictions may not fully align with the evidence submitted to regulatory agencies or consumer protection bodies. [40][41][42]

13. Conclusion

Probiotic bacteria represent a promising approach for the enhancement of the immune response and the prevention of pathogenic infections, particularly following oral intake. When administered at appropriate dosages and for suitable durations, probiotics can significantly influence immunomodulation. *Bifidobacterium* and *Lactobacillus* strains demonstrate particular efficacy in augmenting innate and adaptive immunity, while species such as *Enterococcus*, *Streptococcus*, *Pediococcus*, and *Leuconostoc* are more closely associated with infectious disease control and inflammation resolution. Among all probiotics, several well-studied strains clearly exhibit direct effects on disease burden and mortality rates. The prevention of infectious diseases is achieved by strengthening the response of the host immune system, and probiotic strains display remarkable potential in establishing this protective environment. Competitive adherence and colonization of critical surfaces, such as mucous membranes or epithelial linings, serve as initial lines of defense. The production of antimicrobial substances, including bacteriocins and short-chain fatty acids, further reinforces the inhibition of pathogen growth.

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