Open Access

OBM Genetics

LIDSEN Publishing Inc.

Review

Immunomodulatory Benefits of Probiotic Bacteria: A Review of Evidence

Samson Adedeji Adejumo [1, 2], Angus Nnamdi Oli [3, *], Adekunle Babajide Rowaiye [4, 5], Nwamaka Henrietta Igbokwe [6], Chinelo Kene Ezejiegu [3], Zwanden Sule Yahaya [7]

1. Department of Biological Sciences, University of Illinois, Chicago, 845 West Taylor, 60607, Chicago, Illinois, USA; E-Mail: sadeju2@uic.edu
2. Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Federal University Oye Ekiti, Ekiti State, Nigeria; E-Mail: samson.adejumo@fuoye.edu.ng
3. Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Nigeria; E-Mails: an.oli@unizik.edu.ng; ck.ezejiegu@unizik.edu.ng
4. Department of Pharmaceutical Science, North Carolina Central University, Durham, NC 27707, USA; E-Mail: adekunlerowaiye@gmail.com
5. Department of Medical Biotechnology, National Biotechnology Development Agency, Abuja, Nigeria
6. Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmacy, College of Medicine Campus, PMB 12003, Idi-Araba, University of Lagos, Akoka, Lagos, Nigeria; E-Mail: nigbokwe@unilag.edu.ng
7. Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Kaduna State University, Kaduna, Kaduna State, Nigeria; E-Mail: zwanden.yahaya@kasu.edu.ng

* **Correspondence:** Angus Nnamdi Oli; E-Mail: an.oli@unizik.edu.ng

Academic Editor: Lunawati L Bennett

Special Issue: Pharmacogenomics in Drug Development

OBM Genetics
2023, volume 7, issue 4
doi:10.21926/obm.genet.2304206

Received: April 11, 2023
Accepted: November 28, 2023
Published: December 11, 2023

Abstract

Over the past few decades, probiotics have emerged as a viable medical tool for preventing and/or treating diseases. This narrative review provides recent findings on Probiotics and their benefits on the host immune system. It also highlights the specific mechanisms through which probiotics mediate those benefits. The study also explores the topical or systemic probiotic administration method. Authors screened databases like Google Scholar, Web of Science, PubMed, Scopus, and China National Knowledge Infrastructure database, using various keyword combinations such as: “probiotic” AND “Immunomodulation” OR “probiotic” AND “Immunoregulation” OR “probiotic” AND “Immunostimulation”, for relevant literature written in English only. The review shows that probiotics can regulate the host immune system, including regulating T cells, dendritic cells, intestinal epithelial cells, and several signal pathways, and confer health benefits. Although several clinical trials also revealed the prospects and efficacy of probiotics as immunomodulators and treatment of diseases, there is a need for thorough future investigations on the effectiveness of specific strains of probiotics involved in immunomodulation.

Keywords
Probiotics; immunomodulation; neutriceuticals; short chain fatty acids (SCFA); anti-inflammation; immune cells

1. Introduction

Probiotics are living microbes that, when taken in sufficient quantity as part of a food, exert health benefits on their host, for example, preventing and treating some diseases [1]. Strains of Lactobacillus, Bifidobacterium, Enterococcus, and Saccharomyces are the most extensively studied and commonly used probiotics in humans and animals. However, strains like Pediococcus, Lactococcus, Leuconostoc, and Streptococcus have also been documented for probiotic properties [2-4]. Probiotics are mostly consumed orally as dietary supplements and food (such as cheese and yogurt) or with pharmaceutical preparations [5]; hence, most of their actions are demonstrated in the gastrointestinal tract and play essential functions at various levels in maintaining health [6].

Amongst the various edges related to the consumption of probiotics by man, immune system regulation and modulation have attracted the foremost consideration. Specific bacterial strains of probiotics have been reported in human and animal studies to modulate some aspects of immune responses, both innate and acquired [7]. Reviews have shown that many species of Lactobacillus and Bifidobacterium play essential functions in the immune system by upregulating the cytotoxicity of natural killer cells, macrophages phagocytic action, and mediate adaptive immunity as they crosstalk with dendritic cells as well as enterocytes, Th1, Th2, and Treg cells [4, 8, 9]. Other bacteria species reported for their potential therapeutic benefits in immunomodulation help in maintaining balanced gut microbiota, support gut barrier function and metabolic health, production of beneficial metabolites and overall gut health. These include certain strains of Bacteroides such as *Bacteroidetes uniformis* FGDLZ48B1 and *B. intestinalis* FJSWX61K18. They were reported by Guo et al [10] to decrease systemic inflammation; accelerated the recuperation of tissue structures; enhanced Short-chain fatty acid (SCFA) production and restored beneficial gut

microbiota. The bacterium *Akkermansia muciniphila* is known for its ability to slow down the development and progression of diabetes, obesity, and IBD in mice [11], *Propionibacterium freudenreichii* which prevented intestinal inflammatory diseases by increasing the production of short chain fatty acids (SCFA), inhibited IFNγ secretion, reduced TNFα and induced high IL-10 secretion [12], *Bacillus coagulans* reduced inflammation by way of adjusting the expression of inflammatory genes COX-2 and NF-kB through cytokines, thus triggering a cellular immune response [13], *Pediococcus acidilactici* led to increased transcription of genes related to immunity and antioxidants, and it brought about the suppression of Autoimmune Encephalomyelitis by prompting the production of IL-10-producing regulatory T cells [14], *Clostridium butyricum* exerted an inhibitory effect on gut succinate levels to hinder the growth of *C. difficile* and reduce the presence of TNF-α-producing macrophages in the colon's lumina propria (cLP), leading to a significant reduction in colon epithelial damage [15]. *Escherichia coli* Nissle 1917 ameliorates chronic inflammatory bowel diseases [16].

Despite the various reported breakthroughs on the efficacy of probiotics, there is limited research regarding the mechanism of action of probiotics, coupled with the strain-dependent activity observed in the many probiotics. The molecular bases for their therapeutic efficacy are mainly unknown. This review aims to explore the studies published from 1990 on immunomodulation using probiotics, with particular attention given to the host immune response regulated by probiotics and probiotics' mechanism of action on the host organisms.

2. Concept of Probiotics

Probiotics are usually living microbes advantageous to the health of their host if taken in sufficient doses. Some bacteria that have died and their constituents have also been proven to have some probiotic properties [17]. The most common bacteria with probiotic properties are Bifidobacterium and Lactic acid bacterial strains (LABs) found in various functional foods and dietary supplements [17]. Unlike pathogenic bacteria, probiotics do not cause mononuclear cells to proliferate, nor do they trigger inflammatory action on immune cells [6].

An ideal probiotic for human use should typically be of human or plant origin, non-pathogenic, and able to thrive in intestinal conditions (biliary salts, acidic pH, enzymes, etc.) [17]. Furthermore, a good probiotic should be able to exhibit antagonistic potential against pathogenic microorganisms and stimulate their host's immune system with proven valuable effects on the host [18].

Probiotics have been documented to exert immunomodulatory effects *in vivo* (Table 1), including the production of peripheral immunoglobin, provoking the secretion of IgA, and lowering the production of pro-inflammatory cytokines [4]. Homogenates from probiotics bacteria, such as *Bifidobacterium lactis, Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus, Lactobacillus delbrueckii*, and *Streptococcus thermophiles*, can suppress mononuclear cells multiplication. It was reported in an *in vivo* study that mice fed with *L. fermentum* UCO-979C have substantially improved intestinal IFN-γ production, activated macrophages in the intestine and peritoneum, and enhanced the proliferation of CD4+ T cells in Peyer's patches [2]. Further research has also indicated that *Bifidobacterium bifidum* has a significant effect in improving antibody responses to ovalbumin. Likewise, *Bifidobacterium breve* demonstrated an increased humoral immune response after inducement with IgA [4, 19].

Table 1 *In vivo* evaluation of some probiotics capable of modulating immune response.

Probiotics	Immunological benefits	Site of action	Signaling pathway	References
Lactobacillus rhamnosus GG	Enhanced expression of IL-10 R2	Isolated C57 BL/6J mice partially developed colon	Phospho-STAT3, heightened exhibition of SOCS-3	[20, 21]
Lactobacillus fermentum UCO-979C	Upregulation of intestinal IFN-γ production	Intestinal mucosa of mice	stimulates the NF-kB and MAPK pathways	[2]
	Activates the macrophages in the intestine and peritoneal cavity		Activated $F4/80^{+}CD86^{+}$ macrophages	
	Causes proliferation of Peyer's patches $CD4^{+}$ T cells	Intestinal mucosa of mice	Increased $CD3^{+}CD8^{+}$ T cells and $CD3^{+}CD4^{+}$	
Lactobacillus rhamnosus GG	Lowered stimulation of NFκB via ROS	FHs74 Intestinal cells (human foetal)	TLR, NF-B, MAPK (p38)	[22]
Lactobacillus plantarum (LP) WCFS1	Lowered stimulation of NFκB via ROS	Spleen	Attenuates the Th2 responsiveness	[23]
Lactobacillus reuteri DSM 17938	Generation of regulatory T cells	Isolated rat model	NFκB	[24]
Lactobacillus casei Shirota, B. lactis HN019	Removal of Phosphate moiety/group from IκB	Mononuclear cells	TNFα secretion	[23]
Lactobacillus acidophilus, Duolac ATP	The tumoricidal activity of blood mononuclear cells	Mice	Regulated IL-10 and TGF-β expression	[9, 25]
VSL#3 IBS Probiotics	Activation of IL-4 producing T-cells Tight junction proteins are elevated	Cellosaurus cell line HT-29	ERK and p38 MAPKs are added phosphate moiety/group	[26]

Several kinds of research on the *in vitro* evaluation of probiotics (Table 2) have revealed that different probiotics exert immunological benefits on host organisms by regulating specific

signaling pathways, including various species of Lactobacilli which have demonstrated differential antagonistic effects against other fungi and bacteria pathogens including *C. jejuni* as reported by Taha-Abdelaziz et al. [20]. It is also noteworthy that the reported different probiotics trigger immune responses in different ways [20].

Table 2 *In vitro* evaluation of some probiotics capable of modulating immune response.

Probiotics	Immunological benefits	Site of action	Signaling pathway	Reference
Lactobacillus casei OLL2768	Reduced levels of Interleukins-6, 8, & 1α and MCP-1	Intestinal epithelial cells	NFκB and p38 MAPK	[7]
Lactobacillus rhamnosus GG	TLR2 becomes more sensitivity	Epithelial Cell Line (IPEC)-J2 from pig intestine	TLR signaling	[27]
*Lactobacillus jensenii*TL2937	Stimulate down regulators A20, Bcl-3 and MKP-1	Porcine intestinal cells	TLR4-dependent NFκB and MAPK	[28]
Lactobacillus plantarum (LP) WCFS1	Elevated tight junctional adhesion protein molecules	Caco-2 cells	TLR2 signaling	[24]
Saccharomyces cerevisiae CNCM I-3856	Reduced Interleukins-6 & 8 exhibitions	Intestinal Porcine Epithelial Cell Line (IPEC)-1	Fewer ERK1/2 and p38 are added phosphate moiety/group	
Streptococcus salivarius K12	Inhibit NFκB activity	Cellosaurus cell line HT-29	NFκB	[29]
VSL#3 IBS Probiotics	Tight junction proteins are elevated		ERK and p38 MAPKs are added phosphate moiety/group	[7, 26]
Bacillus subtilis CU1	Increased levels of secretory IgA	stools and saliva	IFN-gamma	[30]

3. Mechanisms of Action of Probiotics

The means through which probiotics interact with the host is multifactorial [6, 25]. The immunostimulatory properties of probiotics have been reported in humans and animals [24]. Figure 1 summarizes the main signaling pathways of probiotics, including the establishment of tighter epithelial barriers, improved intestinal mucosa adhesion, production of anti-microorganism substances, competitive pathogens elimination, affiliated inhibition of pathogen adhesion, and immune system modulation [6, 19, 31, 32].

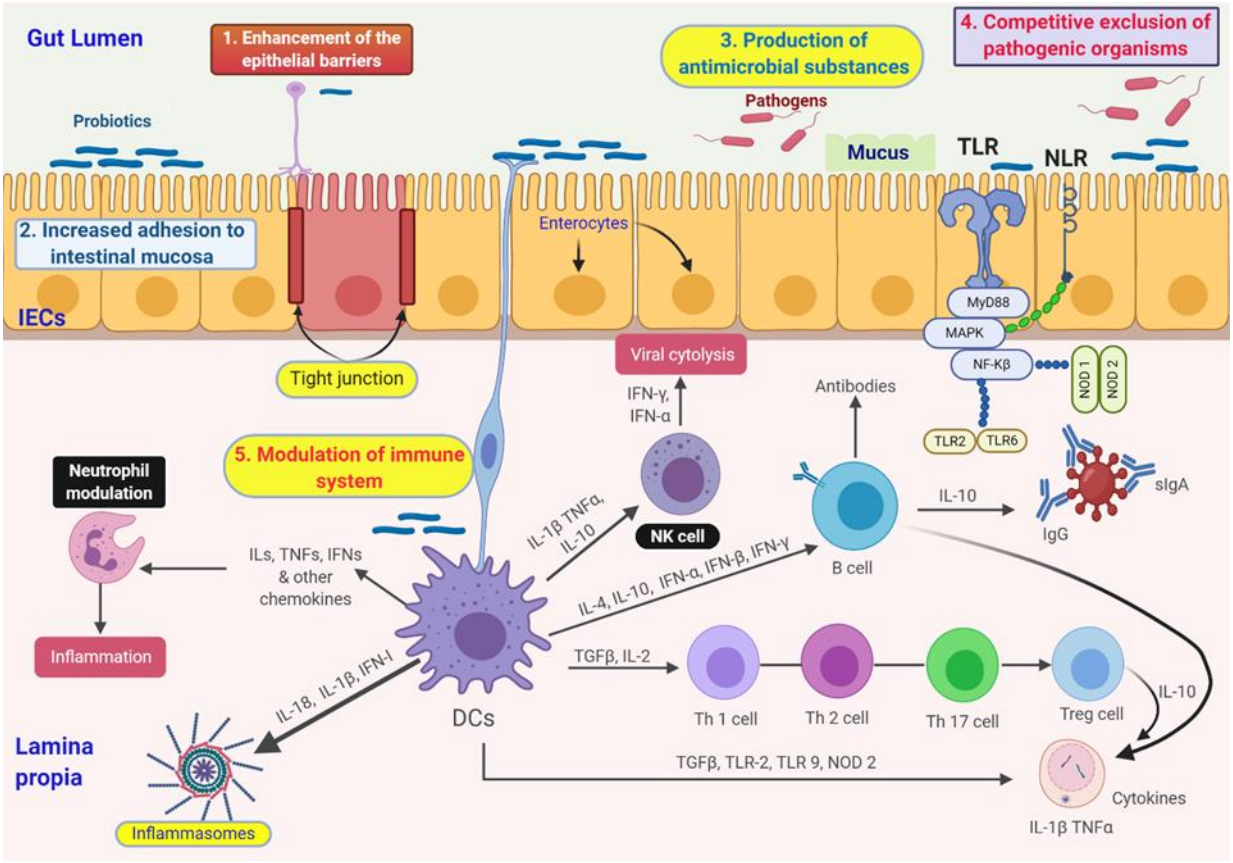

Figure 1 Mechanisms by which probiotics exert their actions (1) Enhancing the epithelial barriers; (2) Enhanced binding to the mucosa of the intestine; (3) Production of antimicrobial substances; (4) Pathogenic organisms are competitively excluded (5) Modulation of the immune system.

3.1 Maintenance of Intestinal Barrier Integrity

The intestinal epithelium is a primary defense mechanism in maintaining epithelial reliability and ensuring host protection from the external environment. The intestinal epithelial barrier defense involves the secretory IgA, mucous layer, the epithelial junction adhesion complex, and antimicrobial peptides. When this barrier function is weakened, pathogens can breach the sub-mucosal layer and trigger inflammatory reactions. Consequently, this can lead to conditions in the intestines, such as inflammatory bowel disease [33]. Intake of these bacteria beneficial to health (probiotic bacteria) has been proven to aid in maintaining intestinal barrier function [34]. Recent findings have shown that probiotic microorganisms can repair damaged barrier function. In Caco-2 cells and T84, for instance, *Escherichia coli* Nissle 1917 (EcN1917) has been associated with preventing the disruption of the mucosal barrier caused by enteropathogenic E. coli and restoring mucosal integrity. This is facilitated by increased PKC and zonula occludens (ZO-2) tight junction protein expression and distribution, which leads to tight junction complex rebuilding [35].

Probiotics can potentially uphold the barrier function and integrity of the mucosal membrane and avert long-term inflammation, protecting the host from various infectious diseases [36]. Probiotics reduce paracellular permeability, provide innate immunity against pathogenic organisms, and improve the physical blockage of the mucous layer [37]. Probiotics can also repair intestinal membrane barriers that gut pathogens have damaged.

3.2 Modulation of Intestinal Epithelial Cells by Probiotic

Intestinal epithelial cells (IECs) are a primary physical barrier separating digested material, intestinal microbes, and the mucosal immune system. The integrity of the intestinal mucosal barrier depends on the strength of tight junctions which are made up of transmembrane proteins [7], whose assembly is dependent on the activation of signaling pathways involving mitogen-activated protein kinase (MAPK). Tight junctions are specialized protein complexes (including claudin, occludin, and Zonulin) that form a barrier between cells lining the intestinal tract, helping to control the movement of molecules and ions across the gut lining. Probiotics have the potential to contribute to maintaining the integrity of tight junctions and the gut barrier through several mechanisms, such as controlling the expression of genes and proteins related to fast junction signaling in intestinal epithelial cells (IECs) [38].

Lactobacillus plantarum, a probiotic strain, was found to induce TLR2 signaling-mediated translocation of Zonula occludens-1 (ZO-1) to the TJ region between epithelial cells in Caco-2 intestinal cells [7]. According to [39], the probiotics' ability to induce intestinal epithelial cell apoptosis can be an excellent way to improve membrane integrity when enteric infections or inflammatory diseases have harmed it.

3.3 Short Chain Fatty Acid Production

Some probiotics, like certain strains of Bifidobacterium and Lactobacillus, can ferment dietary fibers to produce Short-chain fatty acids (SCFAs) like acetate, butyrate, and propionate. SCFAs, particularly butyrate, have been implicated in supporting the integrity of tight junctions, which are critical structures that regulate the permeability of the intestinal barrier. Peng et al. [40] demonstrated the effect of butyrate treatment on the enhancement of AMP-activated protein kinase (AMPK) activity in a Caco-2 cell monolayer model leading to the accelerated assembly of tight junctions promoting the development of the intestinal barrier.

By supporting the function of tight junctions, SCFAs like butyrate help prevent "leaky gut" or increased gut permeability. When tight corners are strong, they limit the passage of potentially harmful molecules from the gut into the bloodstream.

Butyrate has anti-inflammatory effects and can inhibit specific inflammatory pathways. Chronic inflammation can disrupt tight junctions, leading to increased barrier permeability, so reducing inflammation indirectly helps maintain their integrity. SCFAs inhibit the production and expression of pro-inflammatory mediators, including TNF-α, IL-6, and nitric oxide (NO) [41], and enhance the production and activity of the anti-inflammatory cytokine IL-10 [42, 43]. Recent *in vitro* and clinical trials indicated an inverse relationship between the levels of these short-chain fatty acids (SCFAs) within the intestines and the occurrence of medical conditions like colorectal cancer, inflammatory bowel disease (IBD), and diabetes. [44-46]. SCFAs can also modulate the production of prostaglandin E2 (PGE2), an anti-inflammatory prostanoid that can weaken the output of IL-1β and TNF-α by macrophages [47]. Some strains of probiotics, including *Akkermansia muciniphilia*, [48] Bacteroides spp. [49], *Faecalibacterium prausnitzii*, and *Clostridium symbiosum* [50, 51] have been reported to produce SCFAs that are beneficial in sustaining intestinal balance, which is crucial for upholding the host's overall well-being and preventing numerous ailments.

3.4 Improved Intestinal Mucosa Adhesion

Some probiotics can influence the production and composition of the mucus layer that covers the gut lining. A healthy mucus layer contributes to proper interaction between gut microbes and the intestinal epithelium, affecting tight junction function. The ability of probiotics to attach to the mucosal surface of the intestine is a significant requirement for colonizing the host cell and subsequent interaction with the host [52, 53]. It is also essential to regulate the immune system and counter pathogens [52].

Lactic acid bacteria, among other probiotics, have shown various surface features necessary to communicate with intestinal epithelial cells (IECs), which release mucin (The main component of the intestinal mucosa, a complex glycoprotein mixture). The intestinal mucosa thus prevents the adhesion of harmful bacteria to the animal or human cell [52, 54]. *Lactobacillus reuteri* produces Mucus-binding protein (MUB), which plays a vital role in the attachment of microorganisms to their hosts via a lipid moiety or the cell wall [23, 55]. Probiotics have also been reported to result in qualitative modifications in intestinal mucins, thereby preventing pathogen binding [54]. Antimicrobial proteins (AMPS) such as defensins, released by epithelial cells, can also be stimulated by probiotics. Defensins are effective against fungi, viruses, and bacteria and help stabilize the gut barrier function [7].

3.5 Maintenance of Gut Microbial Balance

An imbalance in the gut microbiota (dysbiosis) has been linked to compromised intestinal barrier function. Probiotics can contribute to a balanced microbial ecosystem, which supports gut lining health and tight junctions. The inability to achieve gut homeostasis results in adverse shifts in host metabolism, which are associated with chronic conditions like cancer, cardiometabolic disorders, and Inflammatory Bowel Disease (IBD) [56].

According to Blaabjerg et al. [57], the protective effects of probiotics by maintaining gut homeostasis have been demonstrated in different diseases associated with disruption of the intestinal microbiota. A meta-analysis by [57] reported that combined administration of *Lactobacillus rhamnosus* and *Saccharomyces boulardii* probiotics in clinical trials significantly reduced antibiotics-associated diarrhea by 51% in patients with AAD with no increase in side effects. Krebs [58] investigated the effect of Lactobacillus probiotics in colorectal cancer patients and documented a significant change in intestinal microbiota leading to improved mucosal structure due to increased intake of Lactobacillus. Despite various ongoing research to establish the specific roles and mechanism of actions by which probiotics maintain gut homeostasis, these and other studies have demonstrated that probiotics have potential in the prevention or treatment of human gut microbiome-related diseases.

3.6 Competitive Expulsion of Pathogens

Although the ability of probiotics to outcompete pathogenic bacteria is an active area of investigation, available evidence from recent studies that have explored the effects of probiotics against pathogenic bacteria indicates the potential of probiotics to competitively interact with pathogenic bacteria and contribute to maintaining a balanced gut microbiota, which is essential for maintaining overall health. Probiotic bacteria compete with harmful pathogens for resources

such as nutrients and adhesion sites within the host's body, suppressing pathogen growth and colonization, ultimately promoting a healthier microbial balance and reducing the risk of infections. It has been reported that Lactobacillus GG and *Lactobacillus plantarum* 299V competitively block the sticking of *E. coli* [59]. Some strains of Lactobacilli can block receptor sites obstructing the entrance of pathogens, and specific probiotic metabolites are proposed to be responsible for the modulation of various cell signaling and metabolic pathways [60].

Probiotics compete for attachment, preventing pathogenic bacteria from colonizing sites like colonic crypts, goblet cells, and intestinal villi. Adherence to the surfaces of intestinal epithelial cells represents a significant pathological condition for enteric pathogens. Likewise, resistance to colonization plays a substantial role in the microbiota. Probiotics can bind to intestinal cells via electrostatic interactions or specific surface proteins, allowing them to tie in large quantities and physically block adherence sites, preventing pathogens from binding and subsequently causing infection [37, 60]. Probiotics have been documented to possess more remarkable adherence ability to the epithelial cells than pathogens [61]. *Lactobacillus reuteri* and *Bifidobacterium bifidum*, for example, have been shown to bind to host cell surface glycolipids, preventing pathogens from attaching to the same surface glycolipids [37]. The competitive exclusion of pathogenic organisms by probiotics results from a bacterium-to-bacterium communication in which the pathogenic bacteria and beneficial ones contend for mucosal adhesion sites and the available nutrients [17].

3.7 Production of Antimicrobial Substances

Probiotics inhibit pathogenic bacteria growth by secreting antimicrobial substances such as acetic acid, lactic acid, formic acid, and short-chain fatty acids, which lower the intracellular pH and inhibit pathogen growth [62]. Several probiotics release antimicrobial peptides, such as antimicrobial peptides and bacteriocins. The most frequent method of bacteriocin-mediated destruction of pathogenic organisms, such as the obliteration of target cells, is mediated by the production of pores and/or cell wall inhibition [62, 63]. For instance, nisin forms a complex with Lipid II (a molecule used in synthesizing bacteria's cell walls), thereby preventing cell wall biogenesis of bacilli capable of forming spores. Consequently, the complex clumps together and assimilates peptides, creating pores in the bacterial membrane [64, 65]. Various reports have implicated Lactobacilli as being able to produce substances involved in viral particles inactivation, such as the inactivation of vesicular stomatitis virus and adenovirus by *Lactobacillus rhamnosus* GR-1 and *L. fermentum* RC-14 within a short duration [62].

Several *in vitro* studies have demonstrated the ability of probiotics, such as *Streptococcus salivarius, Lactococcus* sp. HY 499 and Enterococcus faecalis, to inhibit the growth of pathogens including *S. epidermidis, Propionibacterium acnes*, and *S. aureus*, by producing antibacterial proteins (bacteriocins) [65-67]. Muizzuddin et al [68] also reported the activity of *Lactobacillus plantarum* extract in reducing mild acne lesions *in vivo*, improving erythema and skin barrier reconstruction. Examples of bacteriocins synthesized by certain probiotic strains include bifidocin B produced by *Bifidobacterium bifidum* NCFB, lactacin B originating from *L. acidophilus*, plantaricin from *L. plantarum*, and nisin from *Lactococcus lactis* [58].

3.8 Modulation of The Immune System by Probiotics

Probiotics can help fight pathogens by boosting the host immune system. According to evidence, probiotics decimate pathogens in the gastrointestinal tract by stimulating both specific and non-specific immunity, thereby preventing bacteria from causing intestinal diseases [10, 69].

Probiotics can confer immunomodulatory benefits on the host cell by establishing immune interactions with innate immune cells such as epithelial cells, natural killer cells, macrophages, neutrophils, and dendritic cells, as well as with humoral immune cells, including B and T-lymphocytes [70, 71]. Immunomodulatory effects of probiotics include:

- Delivery of anti-inflammatory molecules to the intestines [72].
- Immune response modulation to attenuate allergy [73].
- Stimulation of humoral responses against infection [74].
- Down-regulation of inflammatory substances production [75].

This article mainly discusses The immunomodulatory mechanism in detail as it emphasizes the significance of understanding how probiotics interact with the immune system and their potential impact on health and disease. Understanding how probiotics can influence the immune response can have direct health implications, as it may lead to the development of probiotic-based interventions for various health conditions.

4. Immunomodulatory Functions of Probiotics

Probiotics modulate the immune system by releasing substances with immunomodulatory and anti-inflammatory potentials that can trigger an immune response [75]. Immunomodulation using probiotics is related to the release of cytokines from immune cells. These cytokines (interleukins (ILs), interferons (IFNs), chemokines, tumor necrosis factors (TNFs), and transforming growth factor (TGF) are responsible for the regulation of innate and adaptive immunity [4, 71]. It has also been documented that the immunomodulatory effects of probiotics are related to the probiotic's interactions with various immune cells, such as intestinal epithelial cells (IECs) and dendritic cells with lymphocytes and monocytes/macrophages, among others [76]. The immunomodulatory effects of probiotics on the immune system can be classified as immunostimulatory or immunoregulatory based on the impact of the probiotics on the immune system. While some probiotics have been documented as possessing immunostimulatory potentials by enhancing immune responses, immunoregulatory activities of probiotics help to maintain a balanced and controlled immune system [77]. Some of the specific probiotic strains involved in immunomodulation and immune cell activation are represented in Figure 2.

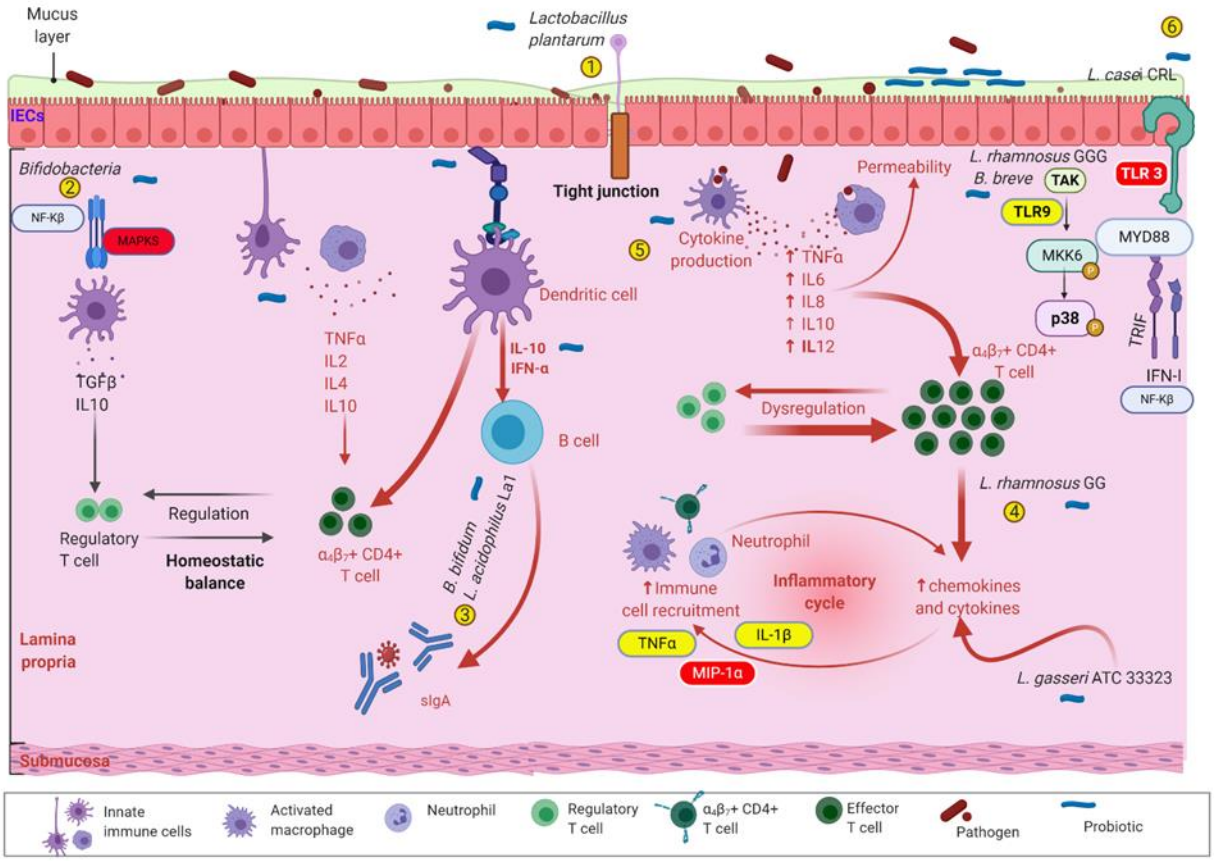

Figure 2 Probiotics Immunomodulation: Probiotics distinctly regulate epithelial cell responses via the stimulation or repression of discrete signaling routes depending on the microbial strain. (1) Activation of tight junction by *Lactobacillus plantarium*; (2) Stimulation of the release of "regulatory cytokines/anti-inflammatory, IL-10 and TGFβ by Bifidobacteria; (3) Stimulation of secretory IgA (sIgA) serum concentration by *B. bifidum* and *L. acidophilus* La1 (4) Reduction of NF-κB stimulation via ROS by *Lactobacillus rhamnosus* GG; (5) *Lactobacillus rhamnosus* GG induces development and the production of Th1-type cytokines and chemokines in human monocyte-derived dendritic cells; (6) Activation of TLR signaling pathway leading to stimulation of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) by *Lactobacillus casei*.

4.1 Immunostimulatory Effects of Probiotics

Several strains of probiotics have been reported to activate and boost the host immune system in recognizing and attacking pathogens, leading to increased production of immune cells, cytokines, and antibodies. These probiotics are often used in immunotherapy to treat certain diseases, including cancer [78].

Several probiotics have also been documented for their ability to modulate innate and adaptive immunity, enhance their activity, and promote a balanced immune response [77].

4.1.1 Macrophage Activation

Macrophages are immune cells that are crucial to the body's defense against infections and other foreign invaders. They are known for engulfing and destroying pathogens such as bacteria, viruses, and fungi. Probiotics can stimulate macrophage activity, enhancing their ability to recognize and eradicate pathogens. This can lead to improved pathogen clearance and immune response. Probiotics can influence the polarization of macrophages. Certain strains of probiotics are documented to trigger macrophages into adopting the M1 phenotype to eliminate intracellular pathogens. Conversely, other probiotic types can prompt M2 macrophages, eliciting an anti-inflammatory response depending on the microenvironment [79, 80]

Ji et al [81] reported the impact of the probiotic Bacillus amyloliquefaciens (Ba) on the polarization of bone marrow-derived macrophages (BMDMs) toward both M1 and M2 phenotypes. They said that *Bacillus amyloliquefaciens* (Ba) modulated the polarization of M1 macrophages and bolstered their phagocytic activity as manifested by the increased ability of the macrophages to capture soluble antigens through the upregulation of IL-6, TNF-α, iNOS, and IL-1β mRNA genes, along with an elevation in nitric oxide (NO) production [82].

Other studies have documented the *in vitro* ability of various probiotic strains to stimulate nitric oxide production and improve the phagocytic activity of macrophages [82-84].

4.1.2 Natural Killer (NK) Cell Activation

Natural Killer (NK) cells serve a crucial role in the immune response against tumors and viral inversion. Natural killer cells can differentiate between healthy and abnormal cells with changed or missing primary histocompatibility complex class I molecules [85]. Once the abnormal cells are recognized, NKs induce the production of immune mediators such as TNFα and IFNγ or by cytolysis of infected or altered cells directly [17]. DC regulation caused by LAB might influence the activity of natural killer cells and, subsequently anti-viral and/or anti-tumor immune responses. Likewise, the use of *Lactobacillus casei* Shirota (LcS) by patients who already had their colonic polyps surgically removed substantially lowered the relapse of colorectal cancer [17]. It was reported that LcS induced TNFα and IL-12 production, which correlates with Natural Killer activity [17]. Human DCs exposed to LAB can cause stimulation, rapid multiplication, and cell-killing effects in NK cells and resultant NK-derived Interferon-γ production [17].

The specific action of Lactobacillus bacteria on Natural Killer cells is boosting their anti-tumor responses. This agrees with other studies that indicated that supplementing with LcS increased NK cell activity *in vivo* due to IL-12 production [86].

4.1.3 Modulation of Neutrophils

Neutrophils are phagocytic natural immune cells capable of engulfing pathogens. Probiotics specifically modify neutrophil effector responses by stimulating a wide range of pathogen-sensing signaling pathways that depend on the kind of microbial strain [87]. The central mechanism of probiotics on neutrophils includes hydrolytic enzyme activity, reactive oxygen species production during phagocytosis, chemokine-mediated recruitment, formation of Neutrophil extracellular trap, and inflammatory cytokine secretion.

L. rhamnosus GG was reported to prevent Neutrophil extracellular trap formation and consequently lowered reactive oxygen species (ROS) production, leading to delayed tissue damage due to chronic inflammatory reaction [88]; the ability of L. rhamnosus GG to reduce the generation of reactive oxygen species (ROS) is accountable for the inhibitory effect of NFκB. Again, *L. gasseri* ATC33323 cell-wall extract increased the release of MIP-1α, MCP-1, TNFα, and IL-1β in a Sprague-Dawley rat model of sepsis [89]. However, neutrophil signaling modulation by probiotics is in its early stage, and it can be summarized that its effect on various cells and pathways is determined by the strain involved and the reactions being investigated [90].

4.1.4 Modulation of Inflammasomes

Inflammasomes are large intracellular multiprotein complexes involved in innate immunity by coordinating the maturation of Interleukins-1β and -18 when there are threat signals [91]. They are essential in maintaining intestinal homeostasis and are implicated in chronic inflammation of the human intestine. Inflammasomes recognize and respond to pathogen-associated molecular patterns (PAMPs), such as bacterial flagellin, and damage-associated molecular patterns (DAMPs), such as uric acid crystals. Inflammasomes are also involved in immunological responses against viruses by stimulating type I interferon release and pyroptosis [92, 93]. Because of their capacity to control the production and out of the pro-inflammatory cytokine, Interleukin-1β, probiotics aid in the control of the assembly, release, and inflammasome's activity necessary for the interleukin-1β and-18 processing via the caspase-1 pathway. Therefore, probiotic organisms can modulate inflammations and defense against viruses by modifying selectively interleukin-1β and -18 and type-I interferons via the signaling aggregation and effects of different inflammasomes [94].

4.1.5 Secretory IgA Modulation (sIgA)

Probiotics can influence the production and modulation of secretory immunoglobulin A (sIgA), a vital component of the immune system that is pivotal in protecting mucosal surfaces, including those in the gut, respiratory tract, and other mucosal tissues. Immunoglobulin A helps neutralize pathogens and toxins at mucosal surfaces, preventing them from entering the body. Probiotics promote the production of IgA, thereby enhancing the integrity of mucosal barriers [95-98].

Mucosal B cells in the lamina propria adjacent to mucosal surfaces secrete sIgA, an antibody that plays a crucial role in mucous membrane immunity. sIgA helps translocate IgA dimers to the interior surfaces of epithelial cells [99]. The secretory component in the intestinal lumen enables the binding of sIgA to the mucus layer site, where the IgA results in the immune exclusion of antigens present in the mucosa [100]. Probiotics stimulate sIgA production, thereby improving barrier function [101]. A much older research report confirmed that ingesting fermented milk containing L. acidophilus La1 and B. bifidum after immunization against Salmonella enterica serovar Typhimurium Ty21 caused a spike in IgA serum concentration [102].

While the impacts of probiotics vary based on the specific strains, recent research findings suggest that the application of specific probiotic strains, like Lactobacillus and Pediococcus, could have a positive impact on IgA secretion and function by directing dendritic cells to enhance IL-6 and IL-10 secretion [77]. The increased production of IgA may contribute to the protection of barrier functions in the body's mucosal surfaces, such as the gut and respiratory tract. Research has indicated that providing infants with formula supplemented with specific strains of

Lactobacillus and Bifidobacteria can increase the number of IgA-producing cells specific to cow milk antigens in their blood [74].

4.2 Immunoregulatory Effects

4.2.1 Modulation of Cytokine Activities

Cytokines are signaling molecules that regulate immune responses, inflammation, and various physiological processes. Probiotics can influence the balance of cytokines produced by immune cells, helping to promote a balanced immune response. Probiotics regulate mucosal immune responses in strain-dependent ways by prompting the production of different B-cell growth factors including cytokines IL-4, IL-5, and IL-13 [71, 72]. Probiotics can trigger acquired immune responses via cytokine production and create a network of signals amongst the immune cells [73]. Some probiotics also activate cytokine production via immune-modulatory pathways [4]. Other probiotics, especially strains of Bifidobacteria and Lactobacillus, can trigger the activation of anti-inflammatory/regulatory cytokines like IL-10 and TGFβ, which are linked to the suppressive function and tolerance of regulatory T cells (Tregs) [7].

Activation of Anti-Inflammatory Cytokines. Many probiotics have been shown to stimulate the generation of anti-inflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). These cytokines play a role in controlling the immune response and curbing excessive inflammation [103]. IL-10 is the most essential anti-inflammatory cytokine and a pluripotent cytokine in the human immune system [104]. It acts on APCs and/or directly on Treg cells to trigger the differentiation of IL-10-producing T cells. IL-10 is a broad effector molecule capable of eliciting a significant effect on human immune responses and affecting the physiology of varied subpopulations of immune cells in several ways [104, 105]. Interleukin-10 ensures that human B cells rapidly multiply, differentiate, and thrive and induces IgG and IgA generation by B cells.

In a clinical trial among ulcerative colitis, patients who were administered a probiotic combination containing *Enterococcus faecalis, Lactobacillus acidophilus*, and *Bifidobacterium* reported a reduced recurrence level of ulcerative colitis flare-ups [106]. The mixture enhanced the expression of IL-10 and decreased TNF-α and IL-1β expression. L. casei CRL 431 nasal therapy improved immunological response to *Streptococcus pneumoniae* infection as shown in the proliferation of IL-10, IL-4, IgA, and TNF-α in the respiratory tract [107].

Inhibition of Pro-Inflammatory Cytokines and NF-κB Activation. Probiotics can decrease inflammation and support immune balance by attenuating the activity of nuclear factor-kappa B (NF-κB) [108]. Nuclear Factor-kappa B (NF-κB) constitutes a protein complex that holds a crucial function in governing the expression of genes implicated in immune responses, inflammation, cell survival, and diverse physiological processes. NF-κB regulates the expression of genes that encode pro-inflammatory cytokines (such as TNF-α, IL-6), chemokines, and adhesion molecules. This contributes to the initiation and amplification of the immune response. Some probiotics have been shown to downregulate NF-κB activation, leading to reduced expression of pro-inflammatory cytokines and a dampened inflammatory response [109].

The immunoregulatory effects of probiotics on suppressing the NF-κB pathway have been documented in individuals diagnosed with ulcerative colitis (UC), a significant type of inflammatory bowel disease. Hegazy et al. [110] administered *Lactobacillus delbruekii and Lactobacillus fermentum* probiotics to patients suffering from moderate UC initially confirmed with evidence of colonic mucosal injury and inflammation and led to increased colonic MPO activity, elevated fecal calprotectin levels, and heightened expression of TNF-α and NF-κB p65 proteins within the colon. At the end of the 8-week intervention, the probiotics significantly ameliorated the inflammation by decreasing the colonic concentration of IL-6, expression of TNF-α and NF-κB p65 [110].

L. casei and L. paracasei probiotics were reported to inhibit the generation of pro-inflammatory cytokines by preventing the phosphorylation of IκBα, hindering the nuclear movement of p65, and reinstating the degradation of IκBα [111, 112]. *L. plantarum and L. brevis* have also demonstrated similar inhibitory impacts on the NF-κB pathway. L. plantarum achieves this by reducing the binding activity of NF-κB. [113], meanwhile, *L. brevis* hinders the phosphorylation of interleukin 1 receptor-associated kinase 1 (IRAK1) and AKT [114]. *Bifidobacterium infantis* and *Streptococcus salivarius* likewise decrease the activation of NF-κB [109]. These are clear evidence of probiotics' ability to inactivate pro-inflammatory cytokines and maintain a stable immune system.

4.2.2 Toll-like Receptor Modulation (TLRs)

Probiotics can modulate Toll-like receptors (TLRs) as part of their interactions with the immune system and the gut microbiota [115]. TLRs are a category of pattern recognition receptors (PRRs) essential for detecting pathogen-associated molecular patterns (PAMPs) present in various microorganisms. Activation of TLRs triggers immune responses and contributes to the defense against infections [116]. The TLR signaling pathway leads to the aggregation of myeloid differentiation primary response 88 (MyD88) that stimulates the mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF–κB) signaling routes [7, 114]. A study showed that L. casei CRL 431 successfully activated TLR4 in healthy mice and can be applied as a surveillance apparatus for disease-causing bacteria [90]. TLR4 stimulation induces pro-inflammatory mediators, regulates TLR2 expression, and results in the mobilization of inflammatory cells and the induction of the proper spleen responses. TLRs' functions ultimately result in the regulation of bacterial replication [117].

However, overexpression of TLRs can lead to inflammation and potentially contribute to various immune-related disorders. Some probiotics have been reported to downregulate the expression of certain TLRs, which can help prevent excessive immune activation and maintain immune homeostasis, such as *Clostridium butyricum* TO-A, which was reported to downregulate TLR4 mRNA and protein levels when combined with butyrate in HT-29 cells [118]. Other strains of probiotics can also interfere with TLR signaling pathways, leading to reduced activation of downstream inflammatory responses. This can help modulate the immune response and prevent exaggerated inflammation. According to Finamore et al [119], through an *in vitro* experiment involving human intestinal Caco-2/TC7 cells and intestinal explants from 5-week-old crossbreed piglets treated with enterotoxigenic *Escherichia coli* (ETEC) K88, *Lactobacillus amylovorus* has demonstrated its capacity to inhibit TLR4 inflammatory signaling pathway. The observation revealed that *Escherichia coli* (ETEC) K88 suppressed the activation of various stages within the

TLR4 signaling pathway by inhibiting the phosphorylation of key activators of NF-κB signaling, including the IKKα, IKKβ, IκBα [119].

4.2.3 Nucleotide-Binding Oligomerization Domain-Like Receptor Modulation

Nucleotide-binding oligomerization-domain-like receptors or NOD-like receptors (NLRs) are another set of membrane-bound receptors found in the cytoplasm and are essential in tissues with low levels of TLR expression [117]. There are more than 20 different NLRs, but NOD1 and NOD2 are the most characterized [117, 120]. Some probiotics, such as *L. delbrueckii* subsp, can enhance NLR expression. *L. bulgaricus* NIAI B6 and L. gasseri JCM1131 T were reported to enhance NLRP3 expression in adult and newborn swine gut-associated lymphoid tissue (GALT), indicating that immunobiotic Lactobacillus strains upregulate NLRP3 expression using the signaling pathway mediated via TLR and NOD, causing NLRP3 stimulation in porcine Gut-associated lymphoid tissue (GALT) [121]. It has also been predicted that NLRP3 plays a significant function in the modulation of inflammation in the human intestine, as seen in Crohn's disease, and that the expression of dysregulated NLRP3 disrupts immune homeostasis linked to human auto-inflammatory disorders [105].

4.2.4 Modulation of Dendritic Cells

Probiotics can influence the maturation and function of dendritic cells. Dendritic cells are known for their characteristic branched projections and are responsible for sending antigen material and presenting it to the surface of immune system B or T cells. T cells develop in response to cytokine, distinct regulatory T cells, and TH1, TH2, and TH17 subpopulations Raphael et al. [12]. DCs are fundamental in producing immune responses and are found in several gastrointestinal tract locations. DCs regulate the differentiation of Th1 and Th2 responses, either by their cytokines or by providing co-stimulation for T cells, which can then multiply and develop cytokines and chemokines [4, 122, 123].

DCs can direct naive CD4+ T cell differentiation into Th1, Th2, or Th3. In the presence of *L. rhamnosus*, DCs reduced the rapid multiplication of T cells (immature and memory) and the release of Interleukins -2, 4, and 10 upon anti-CD3/anti-CD28 activation [7]. Also, oral consumption of *L. rhamnosus* induced the differentiation of CD4+ to Th1 and Th2 cells *in vivo* [124].

Probiotics modulate DC responses by stimulating different pathogen-sensing signaling pathways, including TLR9, TLR2, and NOD2, in a strain-specific manner [7].

4.2.5 Regulatory T Cells (Tregs)

Tregs are a specialized subset of CD4+ T lymphocytes that play a crucial role in immune regulation and maintaining self-tolerance [125]. They are essential for preventing excessive immune responses against self-antigens and maintaining immune balance. Tregs exert their regulatory effects through multiple mechanisms. They secrete anti-inflammatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which dampen immune responses [126,127]. Tregs also interact directly with other immune cells to suppress

their activation. Probiotics have demonstrated the ability to enhance the formation and function of Tregs, which are immune cells specialized in suppressing excessive immune responses.

Zhao et al [128] used combined probiotics comprising of Bifidobacterium, Lactobacillus, and Enterococcus to upregulate the abundance of CD4 + CD25 + Foxp3 + T cells in mesenteric lymph nodes in addition to the reported upregulation of interleukin (IL)-2, IL-4 and IL-10 expression in colonic tissues from colitis mice. In the same study, it was reported that the combined Bifico probiotics were able to downregulate interferon-γ and TNF-α.

5. Concerns About the Safety of Probiotics

Probiotics are typically considered to be safe for a healthy population. The safe use of probiotics has been evaluated in various reviews and clinical trials to establish the possible side effects on the host cells. No harmful effects have been observed in controlled clinical trials, according to the available data with the most used strains of Lactobacilli and Bifidobacteria [129].

Since humans began to consume fermented milk as a food, LAB, which includes various Enterococcus, Streptococcus, and Lactobacillus species, has been consumed regularly and is considered safe to use even though they are opportunistic pathogens [130]. *Lactobacillus acidophilus*, for example, has been utilized as a probiotic to boost the immune system and treat several diseases such as Canker sores, Hives, Fever blisters, Cancer, and General digestion problems [131]. However, caution should be taken in administering probiotics in immunocompromised individuals such as infants, patients with catheters inserted into large veins, patients who recently had surgery, or patients with severe medical conditions. When administered in adequate proportion to the right individuals, probiotics can be a handy therapeutic tool. However, if taken without indications and administered unregulated, probiotics may result in a harmful effect on the host [132].

Probiotic use has been linked to the production of toxic substances, infections, hyper-regulation of the immune system, and antibiotic resistance genes transfer from probiotic microorganisms to other microorganisms in the digestive tract [133-136].

5.1 Immune System Deviation or Hyperactivation in Immuno-Suppressed Individuals

Probiotics can trigger allergic reactions in the host cell and cause mild gut problems such as bloating, diarrhea, stomach upset, or gas, particularly when newly consumed. However, these symptoms do not usually last long once the body gets used to the probiotics [137].

The microbiota in the intestine is essential for optimal immunological function, particularly in providing innate immunity, establishing germinal centers within lymphoid follicles, and forming and maintaining oral tolerance to dietary antigens. Introducing probiotic strains may alter the existing intestinal microbiota's initial configuration and result in significant adverse immunomodulatory effects.

For instance, it was reported that Probiotic Lactobacillus species increased the Th1 cytokine interferon γ production in some human clinical trials and was shown to inhibit Th2 cytokine activity *in vitro* [138]. The overproduction of Th1 interferon γ may harm the fetus's survival during pregnancy.

5.2 Mutagenesis/ Microbial Resistance

After administration, Probiotics can develop in the host gut and become less effective and perhaps even harmful by introducing drug-resistant strains. The response of probiotic organisms to different stressors was analyzed using laboratory mice and showed that probiotics can cause the host system to develop antibiotic resistance [139].

Likewise, there are concerns regarding the possibility of probiotic strains from pathogenic origin transferring antibiotic-resistance genes to the host intestinal microbiota. This poses a significant threat since a majority of Lactobacillus strains are particularly resistant to common antibiotics such as vancomycin, tetracycline, chloramphenicol, and erythromycin, raising severe concerns about the spread of resistance to more dangerous organisms like *Staphylococcus aureus* and enterococci [140].

5.3 Undesirable Metabolic Events

The gut microbiota plays a crucial role in the host's metabolic functions, such as glucose homeostasis, complex carbohydrate digestion, and lipid metabolism. Introducing probiotic microorganisms can disrupt the normal metabolic activities in the intestinal mucosal and have consequential effects on the entire organism. However, such undesirable effects seem temporary until the internal environment reaches a homeostatic balance [141].

5.4 Intestinal Side Effects

While it has been reported that probiotics positively impact human health, it is essential to be cautious about taking probiotic supplements. This is especially important for individuals with underlying medical issues, including those with immune-compromised systems, pregnant women, sick infants, and those recovering from previous surgery. Evidence suggests that taking probiotics can lead to harsh side effects, including dangerous infections, in the individuals mentioned above.

Minor gastrointestinal problems such as taste disturbance, flatulence, soft stools, nausea, and abdominal cramping have also been reported in people using probiotics. Using probiotics to prevent Clostridioides difficile-related diarrhea revealed that patients who were given probiotics were 18%-20% less likely than controls to have these side effects [142].

5.5 Virulent Trait Expression

Probiotic strains tend to return to a virulence state, particularly those of pathogenic origin, when under favorable conditions. One of the main concerns about probiotics' safety is their capacity to attach to the intestine's mucosal surfaces, which is crucial for their function. On the other hand, attachment to the intestinal mucosa may enhance the risk of bacterial virulence and translocation. The potency of probiotics may, therefore, also increase their pathogenicity. A study conducted by Apostolou et al [143] supports the link between mucosal adherence and pathogenicity in Lactobacillus spp. Lactobacillus spp. According to the researchers, blood culture isolates attach to the intestine's mucosal surface in larger numbers than isolates of human feces or dairy foods. Probiotics have also been shown to cause sepsis in murine experiments. For example, Wagner et al [144] investigated and colonized athymic mice with various human isolates of *Bifidobacterium animalis, L. reuteri, L. acidophilus*, and LGG. While the probiotics did not cause

any harmful effects in the mice, colonization with LGG and *L. reuteri* strains resulted in the mortality of specific athymic neonatal mice. This research indicates that neonates lacking proper immune defenses might face an elevated likelihood of experiencing probiotic-related sepsis.

5.6 Excessive Immune System Stimulation in Vulnerable Hosts

Some research has found that probiotics can cause severe infections and other side effects. Probiotics have been associated with an increased risk of autoimmune inflammation and other autoimmune illnesses in some people because of excessive stimulation of immunological responses. This is more prevalent in people with immune system disorders, those who have previously undergone surgery, and those who are incredibly sick [145].

Probiotics can collaborate with commensal bacteria to cause an immune problem and can directly impact the host. One of the significant challenges for future study is to understand these connections. Other significant challenges include understanding their mechanisms of action, knowing more specifically the probiotic strains capable of conferring which health benefits, and determining the concentration needed to achieve those effects [146].

6. Conclusion

The immunomodulatory benefits of probiotics have been demonstrated in several pieces of research, as reported in this review, which has recently gained much attention in maintaining intestinal homeostasis and inducing the mucosal immune system. Available research findings indicate that probiotics have multidimensional Immunomodulatory beneficial effects on human health.

The activities of these probiotics are experienced within the intestinal epithelial cells, dendritic cells, neutrophils, and macrophages. Nonetheless, it's crucial to highlight that the therapeutic advantages of probiotics are unique to specific strains. Hence, the outcome of one strain cannot be extended to another. Most currently available probiotic strains have varying limitations ranging from non-specificity of probiotics for various pathogens, poor activities, low-stress tolerance, and difficulty in establishing the appropriate dosage. Despite the promising potential, this, in addition to some of the reported safety concerns, has hampered the wide use of probiotics in clinical settings.

Therefore, there is a need for more research to fully establish the safety concerns regarding the wide use of probiotics in treating diseases. This further necessitates the need for future research to aggressively focus on producing cheap, bioengineered probiotics that are both safe and effective and continuous research on new biotherapies for the prevention and treatment of diseases. Furthermore, we can explore how various strains influence host immune responses, shedding light on the presently ambiguous mechanisms through which probiotics modify signaling processes within host cells. This involves identifying distinct probiotic reactions, significant effector molecules, and the altered signaling events within host cells that play a role.

7. Limitations of the Review

This is a narrative review on the immunomodulatory effects of probiotics as documented by various authors and comprised of several claims and reports that have not been independently

proven by clinical trials and, therefore, may not truly serve as scientific evidence for the reported effects. It was also observed that there were claims and counterclaims on the impact of certain strains of probiotics. For instance, some authors reported upregulation, while others documented downregulation of similar signaling pathways by the same bacteria species. It is vital to state that the probiotic strains employed for various therapeutic purposes should undergo several animal studies and human clinical trials to validate their safety and suitability claims. However, the findings documented in this review have opened opportunities for future research exploring probiotics' various reported mechanisms and beneficial effects for best clinical decisions.

Acknowledgments

Authors are thankful to https://biorender.io/ for making their platform available for designing the figures. Authors also acknowledge Dr Jarrad Hampton-Marcell lab at University of Illinois Chicago for access to the lab tools during this research.

Author Contributions

ANO conceptualized the work, ANO, SAA, ABR and ZSY drafted the main manuscript, SAA designed the figures with Biorender Licence provided by Dr Jarrad Hampton-Marcell lab at University of Illinois Chicago, USA, NHI and CKE: assisted in literature search as well as revised the manuscript for intellectual content. All authors saw and approved the final manuscript. All authors approved the final version of the manuscript.

Funding

The authors did not receive any funding for this research and the writing of this manuscript.

Competing Interests

The authors declare that they do not have any conflicts of interest to disclose.

Availability of Data and Materials

The data that substantiate the conclusions drawn in this paper are accessible through the articles cited in the reference list.

References

1. Abatenh E, Gizaw B, Tsegay Z, Tefera G, Aynalem E. Health benefits of probiotics. J Bacteriol Infec Dis. 2018; 2: 8-27.
2. Garcia Castillo V, Komatsu R, Clua P, Indo Y, Takagi M, Salva S, et al. Evaluation of the immunomodulatory activities of the probiotic strain *Lactobacillus fermentum* UCO-979C. Front Immunol. 2019; 10: 1376.
3. Kerry RG, Patra JK, Gouda S, Park Y, Shin HS, Das G. Benefaction of probiotics for human health: A review. J Food Drug Anal. 2018; 26: 927-939.
4. Azad MA, Sarker M, Wan D. Immunomodulatory effects of probiotics on cytokine profiles. Biomed Res Int. 2018; 2018: 8063647.

5. Fenster K, Freeburg B, Hollard C, Wong C, Rønhave Laursen R, Ouwehand AC. The production and delivery of probiotics: A review of a practical approach. Microorganisms. 2019; 7: 83.
6. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients. 2017; 9: 1021.
7. Llewellyn A, Foey A. Probiotic modulation of innate cell pathogen sensing and signaling events. Nutrients. 2017; 9: 1156.
8. Aziz N, Bonavida B. Activation of natural killer cells by probiotics. For Immunopathol Dis Therap. 2016; 7: 41-55.
9. Kim DH, Chung WC, Chun SH, Han JH, Song MJ, Lee KW. Enhancing the natural killer cell activity and anti-influenza effect of heat-treated Lactobacillus plantarum nF1-fortified yogurt in mice. J Dairy Sci. 2018; 101: 10675-10684.
10. Guo H, Yu L, Tian F, Zhao J, Zhang H, Chen W, et al. Effects of Bacteroides-based microecologics against antibiotic-associated diarrhea in mice. Microorganisms. 2021; 9: 2492.
11. Rodrigues VF, Elias Oliveira J, Pereira ÍS, Pereira JA, Barbosa SC, Machado MS, et al. Akkermansia muciniphila and gut immune system: A good friendship that attenuates inflammatory bowel disease, obesity, and diabetes. Front Immunol. 2022; 13: 934695.
12. Gaucher F, Kponouglo K, Rabah H, Bonnassie S, Ossemond J, Pottier S, et al. Propionibacterium freudenreichii CIRM-BIA 129 osmoadaptation coupled to acid-adaptation increases its viability during freeze-drying. Front Microbiol. 2019; 10: 2324.
13. Madempudi RS, Ahire JJ, Neelamraju J, Tripathi A, Nanal S. Randomized clinical trial: the effect of probiotic Bacillus coagulans Unique IS2 vs. placebo on the symptoms management of irritable bowel syndrome in adults. Sci Rep. 2019; 9: 12210.
14. Arani MM, Salati AP, Keyvanshokooh S, Safari O. The effect of Pediococcus acidilactici on mucosal immune responses, growth, and reproductive performance in zebrafish (Danio rerio). Fish Physiol Biochem. 2021; 47: 153-162.
15. Hagihara M, Ariyoshi T, Kuroki Y, Eguchi S, Higashi S, Mori T, et al. Clostridium butyricum enhances colonization resistance against Clostridioides difficile by metabolic and immune modulation. Sci Rep. 2021; 11: 15007.
16. Olier M, Marcq I, Salvador Cartier C, Secher T, Dobrindt U, Boury M, et al. Genotoxicity of Escherichia coli Nissle 1917 strain cannot be dissociated from its probiotic activity. Gut microbes. 2012; 3: 501-509.
17. Plaza Diaz J, Ruiz Ojeda FJ, Gil Campos M, Gil A. Mechanisms of action of probiotics. Adv Nutr. 2019; 10: S49-S66.
18. Plaza Díaz J, Ruiz Ojeda FJ, Gil Campos M, Gil A. Immune-mediated mechanisms of action of probiotics and synbiotics in treating pediatric intestinal diseases. Nutrients. 2018; 10: 42.
19. Dudek Wicher R, Junka A, Paleczny J, Bartoszewicz M. Clinical trials of probiotic strains in selected disease entities. Int J Microbiol. 2020; 2020: 8854119.
20. Taha Abdelaziz K, Astill J, Kulkarni RR, Read LR, Najarian A, Farber JM, et al. In vitro assessment of immunomodulatory and anti-Campylobacter activities of probiotic lactobacilli. Sci Rep. 2019; 9: 17903.
21. Liu J, Gu Z, Song F, Zhang H, Zhao J, Chen W. Lactobacillus plantarum ZS2058 and Lactobacillus rhamnosus GG use different mechanisms to prevent Salmonella infection in vivo. Front Microbiol. 2019; 10: 299.

22. Riehl TE, Alvarado D, Ee X, Zuckerman A, Foster L, Kapoor V, et al. Lactobacillus rhamnosus GG protects the intestinal epithelium from radiation injury through release of lipoteichoic acid, macrophage activation and the migration of mesenchymal stem cells. Gut. 2019; 68: 1003-1013.
23. Mu Q, Tavella VJ, Luo XM. Role of Lactobacillus reuteri in human health and diseases. Front Microbiol. 2018; 9: 757.
24. Bermudez Brito M, Borghuis T, Daniel C, Pot B, de Haan BJ, Faas MM, et al. L. plantarum WCFS1 enhances Treg frequencies by activating DCs even in absence of sampling of bacteria in the Peyer Patches. Sci Rep. 2018; 8: 1785.
25. Kim HW, Hong R, Choi EY, Yu K, Kim N, Hyeon JY, et al. A probiotic mixture regulates T cell balance and reduces atopic dermatitis symptoms in mice. Front Microbiol. 2018; 9: 2414.
26. Chen ZY, Hsieh YM, Huang CC, Tsai CC. Inhibitory effects of probiotic Lactobacillus on the growth of human colonic carcinoma cell line HT-29. Molecules. 2017; 22: 107.
27. Gao K, Wang C, Liu L, Dou X, Liu J, Yuan L, et al. Immunomodulation and signaling mechanism of Lactobacillus rhamnosus GG and its components on porcine intestinal epithelial cells stimulated by lipopolysaccharide. J Microbiol Immunol Infect. 2017; 50: 700-713.
28. Sato N, Garcia Castillo V, Yuzawa M, Islam MA, Albarracin L, Tomokiyo M, et al. Immunobiotic Lactobacillus jensenii TL2937 alleviates dextran sodium sulfate-induced colitis by differentially modulating the transcriptomic response of intestinal epithelial cells. Front Immunol. 2020; 11: 2174.
29. Wan ML, Forsythe SJ, El Nezami H. Probiotics interaction with foodborne pathogens: A potential alternative to antibiotics and future challenges. Crit Rev Food Sci Nutr. 2019; 59: 3320-3333.
30. Lefevre M, Racedo SM, Ripert G, Housez B, Cazaubiel M, Maudet C, et al. Probiotic strain Bacillus subtilis CU1 stimulates immune system of elderly during common infectious disease period: A randomized, double-blind placebo-controlled study. Immun Ageing. 2015; 12: 24.
31. Meybodi NM, Mortazavian A. Probiotic supplements and food products: A comparative approach. Biochem Pharmacol. 2017; 6: 1000227.
32. Bron PA, Kleerebezem M, Brummer RJ, Cani PD, Mercenier A, MacDonald TT, et al. Can probiotics modulate human disease by impacting intestinal barrier function? Br J Nutr. 2017; 117: 93-107.
33. Farré R, Fiorani M, Abdu Rahiman S, Matteoli G. Intestinal permeability, inflammation and the role of nutrients. Nutrients. 2020; 12: 1185.
34. Wang J, Ji H, Wang S, Liu H, Zhang W, Zhang D, et al. Probiotic Lactobacillus plantarum promotes intestinal barrier function by strengthening the epithelium and modulating gut microbiota. Front Microbiol. 2018; 9: 1953.
35. Alvarez CS, Giménez R, Cañas MA, Vera R, Díaz Garrido N, Badia J, et al. Extracellular vesicles and soluble factors secreted by Escherichia coli Nissle 1917 and ECOR63 protect against enteropathogenic E. coli-induced intestinal epithelial barrier dysfunction. BMC Microbiol. 2019; 19: 166.
36. Milner E, Stevens B, An M, Lam V, Ainsworth M, Dihle P, et al. Utilizing probiotics for the prevention and treatment of gastrointestinal diseases. Front Microbiol. 2021; 12: 689958.

37. Mathipa MG, Thantsha MS. Probiotic engineering: Towards development of robust probiotic strains with enhanced functional properties and for targeted control of enteric pathogens. Gut Pathog. 2017; 9: 28.
38. Gou HZ, Zhang YL, Ren LF, Li ZJ, Zhang L. How do intestinal probiotics restore the intestinal barrier? Front Microbiol. 2022; 13: 929346.
39. Koh A, De Vadder F, Kovatcheva Datchary P, Bäckhed F. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. Cell. 2016; 165: 1332-1345.
40. Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. J Nutr. 2009; 139: 1619-1625.
41. Vinolo MA, Rodrigues HG, Hatanaka E, Sato FT, Sampaio SC, Curi R. Suppressive effect of short-chain fatty acids on production of proinflammatory mediators by neutrophils. J Nutr Biochem. 2011; 22: 849-855.
42. Park JS, Lee EJ, Lee JC, Kim WK, Kim HS. Anti-inflammatory effects of short-chain fatty acids in IFN-γ-stimulated RAW 264.7 murine macrophage cells: Involvement of NF-κB and ERK signaling pathways. Int Immunopharmacol. 2007; 7: 70-77.
43. Chakravortty D, Koide N, Kato Y, Sugiyama T, Mu MM, Yoshida T, et al. The inhibitory action of butyrate on lipopolysaccharide-induced nitric oxide production in RAW 264.7 murine macrophage cells. J Endotoxin Res. 2000; 6: 243-247.
44. Huda Faujan N, Abdulamir AS, Fatimah AB, Anas OM, Shuhaimi M, Yazid AM, et al. The impact of the level of the intestinal short chain fatty acids in inflammatory bowel disease patients versus healthy subjects. Open Biochem J. 2010; 4: 53-58.
45. Vernia P, Caprilli R, Latella G, Barbetti F, Magliocca FM, Cittadini M. Fecal lactate and ulcerative colitis. Gastroenterology. 1988; 95: 1564-1568.
46. McIntyre A, Gibson PR, Young GP. Butyrate production from dietary fibre and protection against large bowel cancer in a rat model. Gut. 1993; 34: 386-391.
47. Cox MA, Jackson J, Stanton M, Rojas Triana A, Bober L, Laverty M, et al. Short-chain fatty acids act as antiinflammatory mediators by regulating prostaglandin E2 and cytokines. World J Gastroenterol. 2009; 15: 5549-5557.
48. Reichardt N, Duncan SH, Young P, Belenguer A, McWilliam Leitch C, Scott KP, et al. Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. ISME J. 2014; 8: 1323-1335.
49. Vital M, Howe AC, Tiedje JM. Revealing the bacterial butyrate synthesis pathways by analyzing (meta) genomic data. MBio. 2014; 5: e00889.
50. Dwivedi M, Kumar P, Laddha NC, Kemp EH. Induction of regulatory T cells: A role for probiotics and prebiotics to suppress autoimmunity. Autoimmun Rev. 2016; 15: 379-392.
51. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol. 2014; 12: 661-672.
52. Monteagudo Mera A, Rastall RA, Gibson GR, Charalampopoulos D, Chatzifragkou A. Adhesion mechanisms mediated by probiotics and prebiotics and their potential impact on human health. Appl Microbiol Biotechnol. 2019; 103: 6463-6472.
53. La Fata G, Weber P, Mohajeri MH. Probiotics and the gut immune system: Indirect regulation. Probiotics Antimicrob Proteins. 2018; 10: 11-21.

54. Muscariello L, De Siena B, Marasco R. Lactobacillus cell surface proteins involved in interaction with mucus and extracellular matrix components. Curr Microbiol. 2020; 77: 3831-3841.
55. Somashekaraiah R, Shruthi B, Deepthi BV, Sreenivasa MY. Probiotic properties of lactic acid bacteria isolated from neera: A naturally fermenting coconut palm nectar. Front Microbiol. 2019; 10: 1382.
56. Marteau P, Seksik P, Jian R. Probiotics and intestinal health effects: a clinical perspective. Br J Nutr. 2002; 88: S51-S57.
57. Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the prevention of antibiotic-associated diarrhea in outpatients-a systematic review and meta-analysis. Antibiotics. 2017; 6: 21.
58. Krebs B. Prebiotic and synbiotic treatment before colorectal surgery-randomised double blind trial. Coll Antropol. 2016; 40: 35-40.
59. Mohapatra AR, Jeevaratnam K. Inhibiting bacterial colonization on catheters: Antibacterial and antibiofilm activities of bacteriocins from Lactobacillus plantarum SJ33. J Glob Antimicrob Resist. 2019; 19: 85-92.
60. Van Zyl WF, Deane SM, Dicks LM. Molecular insights into probiotic mechanisms of action employed against intestinal pathogenic bacteria. Gut Microbes. 2020; 12: 1831339.
61. Adriana N, Ilona M, Katarzyna Ś, Zdzisława L, Elżbieta K. Adherence of probiotic bacteria to human colon epithelial cells and inhibitory effect against enteric pathogens-In vitro study. Int J Dairy Technol. 2016; 69: 532-539.
62. Hernández González JC, Martínez Tapia A, Lazcano Hernández G, García Pérez BE, Castrejón Jiménez NS. Bacteriocins from lactic acid bacteria. A powerful alternative as antimicrobials, probiotics, and immunomodulators in veterinary medicine. Animals. 2021; 11: 979.
63. Simons A, Alhanout K, Duval RE. Bacteriocins, antimicrobial peptides from bacterial origin: Overview of their biology and their impact against multidrug-resistant bacteria. Microorganisms. 2020; 8: 639.
64. Kamel DG, Hammam AR, Alsaleem KA, Osman DM. Addition of inulin to probiotic yogurt: Viability of probiotic bacteria (Bifidobacterium bifidum) and sensory characteristics. Food Sci Nutr. 2021; 9: 1743-1749.
65. Oh S, Kim SH, Ko Y, Sim JH, Kim KS, Lee SH, et al. Effect of bacteriocin produced by Lactococcus sp. HY 449 on skin-inflammatory bacteria. Food Chem Toxicol. 2006; 44: 552-559.
66. Kober MM, Bowe WP. The effect of probiotics on immune regulation, acne, and photoaging. Int J Womens Dermatol. 2015; 1: 85-89.
67. Bowe WP, Filip JC, DiRienzo JM, Volgina A, Margolis DJ. Inhibition of propionibacterium acnes by bacteriocin-like inhibitory substances (BLIS) produced by Streptococcus salivarius. J Drugs Dermatol. 2006; 5: 868-870.
68. Muizzuddin N, Maher W, Sullivan M, Schnittger S, Mammone T. Physiological effect of a probiotic on skin. J Cosmet Sci. 2012; 63: 385-395.
69. Stavropoulou E, Bezirtzoglou E. Probiotics in medicine: A long debate. Front Immunol. 2020; 11: 2192.
70. Kobayashi Y, Sugahara H, Shimada K, Mitsuyama E, Kuhara T, Yasuoka A, et al. Therapeutic potential of Bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease. Sci Rep. 2017; 7: 13510.
71. Maldonado Galdeano C, Cazorla SI, Lemme Dumit JM, Vélez E, Perdigón G. Beneficial effects of probiotic consumption on the immune system. Ann Nutr Metab. 2019; 74: 115-124.

72. Cristofori F, Dargenio VN, Dargenio C, Miniello VL, Barone M, Francavilla R. Anti-inflammatory and immunomodulatory effects of probiotics in gut inflammation: A door to the body. Front Immunol. 2021; 12: 578386.
73. Huang J, Zhang J, Wang X, Jin Z, Zhang P, Su H, et al. Effect of probiotics on respiratory tract allergic disease and gut microbiota. Front Nutr. 2022; 9: 821900.
74. Fang H, Elina T, Heikki A, Seppo S. Modulation of humoral immune response through probiotic intake. FEMS Immunol Med Microbiol. 2000; 29: 47-52.
75. Sundararaman A, Ray M, Ravindra PV, Halami PM. Role of probiotics to combat viral infections with emphasis on COVID-19. Appl Microbiol Biotechnol. 2020; 104: 8089-8104.
76. D'Amelio P, Sassi F. Gut microbiota, immune system, and bone. Calcif Tissue Int. 2018; 102: 415-425.
77. Mazziotta C, Tognon M, Martini F, Torreggiani E, Rotondo JC. Probiotics mechanism of action on immune cells and beneficial effects on human health. Cells. 2023; 12: 184.
78. Górska A, Przystupski D, Niemczura MJ, Kulbacka J. Probiotic bacteria: A promising tool in cancer prevention and therapy. Curr Microbiol. 2019; 76: 939-949.
79. Gordon S. Alternative activation of macrophages. Nat Rev Immunol. 2003; 3: 23-35.
80. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol. 2004; 25: 677-686.
81. Ji J, Hu SL, Cui ZW, Li WF. Probiotic Bacillus amyloliquefaciens mediate M1 macrophage polarization in mouse bone marrow-derived macrophages. Arch Microbiol. 2013; 195: 349-356.
82. Park SY, Ji GE, Ko YT, Jung HK, Ustunol Z, Pestka JJ. Potentiation of hydrogen peroxide, nitric oxide, and cytokine production in RAW 264.7 macrophage cells exposed to human and commercial isolates of Bifidobacterium. Int J Food Microbiol. 1999; 46: 231-241.
83. Kim DW, Cho SB, Lee HJ, Chung WT, Kim KH, Hwangbo J, et al. Comparison of cytokine and nitric oxide induction in murine macrophages between whole cell and enzymatically digested Bifidobacterium sp. obtained from monogastric animals. J Microbiol. 2007; 45: 305-310.
84. Marranzino G, Villena J, Salva S, Alvarez S. Stimulation of macrophages by immunobiotic Lactobacillus strains: Influence beyond the intestinal tract. Microbiol Immunol. 2012; 56: 771-781.
85. Abel AM, Yang C, Thakar MS, Malarkannan S. Natural killer cells: Development, maturation, and clinical utilization. Front Immunol. 2018; 9: 1869.
86. Maekawa T, Ida M, Furukawa Y, Kitagawa Y, Yasui K. Supplementation with Lactobacillus pentosus strain S-PT84 and vitamin B mixture enhances natural killer cell activity in healthy humans. J Prob Health. 2016; 4: 134.
87. Wang Y, Liu H, Zhao J. Macrophage polarization induced by probiotic bacteria: A concise review. Probiotics Antimicrob Proteins. 2020; 12: 798-808.
88. Vong L, Lorentz RJ, Assa A, Glogauer M, Sherman PM. Probiotic Lactobacillus rhamnosus inhibits the formation of neutrophil extracellular traps. J Immunol. 2014; 192: 1870-1877.
89. Xu X, Hicks C, Li Y, Su J, Shiloach J, Kaufman JB, et al. Purified cell wall from the probiotic bacterium Lactobacillus gasseri activates systemic inflammation and, at higher doses, produces lethality in a rat model. Crit Care. 2014; 18: R140.

90. Kovtun A, Messerer DA, Scharffetter Kochanek K, Huber Lang M, Ignatius A. Neutrophils in tissue trauma of the skin, bone, and lung: Two sides of the same coin. J Immunol Res. 2018; 2018: 8173983.
91. Schmitz S, Werling D, Allenspach K. Effects of ex-vivo and in-vivo treatment with probiotics on the inflammasome in dogs with chronic enteropathy. PLoS One. 2015; 10: e0120779.
92. Shrivastava G, León Juárez M, García Cordero J, Meza Sánchez DE, Cedillo Barrón L. Inflammasomes and its importance in viral infections. Immunol Res. 2016; 64: 1101-1117.
93. Kopitar Jerala N. The role of interferons in inflammation and inflammasome activation. Front Immunol. 2017; 8: 873.
94. Ryan N, Anderson K, Volpedo G, Varikuti S, Satoskar M, Satoskar S, et al. The IL-33/ST2 axis in immune responses against parasitic disease: potential therapeutic applications. Front Cell Infect Microbiol. 2020; 10: 153.
95. Mantis NJ, Rol N, Corthésy BJ. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. Mucosal Immunol. 2011; 4: 603-611.
96. Kotani Y, Kunisawa J, Suzuki Y, Sato I, Saito T, Toba M, et al. Role of Lactobacillus pentosus Strain b240 and the Toll-like receptor 2 axis in Peyer's patch dendritic cell-mediated immunoglobulin A enhancement. PLoS One. 2014; 9: e91857.
97. Kawashima T, Ikari N, Kouchi T, Kowatari Y, Kubota Y, Shimojo N, et al. The molecular mechanism for activating IgA production by Pediococcus acidilactici K15 and the clinical impact in a randomized trial. Sci Rep. 2018; 8: 5065.
98. Rautava S, Arvilommi H, Isolauri E. Specific probiotics in enhancing maturation of IgA responses in formula-fed infants. Pediatr Res. 2006; 60: 221-224.
99. Li Y, Jin L, Chen T. The effects of secretory IgA in the mucosal immune system. Biomed Res Int. 2020; 2020: 2032057.
100. Rios D, Wood MB, Li J, Chassaing B, Gewirtz AA, Williams IR. Antigen sampling by intestinal M cells is the principal pathway initiating mucosal IgA production to commensal enteric bacteria. Mucosal Immunol. 2016; 9: 907-916.
101. Wu Y, Nie C, Luo R, Qi F, Bai X, Chen H, et al. Effects of multispecies probiotic on intestinal microbiota and mucosal barrier function of neonatal calves infected with e. Coli k99. Front Microbiol. 2022; 12: 813245.
102. Link Amster H, Rochat F, Saudan KY, Mignot O, Aeschlimann JM. Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. FEMS Immunol Med Microbiol. 1994; 10: 55-63.
103. Plaza Díaz J, Ruiz Ojeda FJ, Vilchez Padial LM, Gil A. Evidence of the anti-inflammatory effects of probiotics and synbiotics in intestinal chronic diseases. Nutrients. 2017; 9: 555.
104. Schülke S. Induction of interleukin-10 producing dendritic cells as a tool to suppress allergen-specific T helper 2 responses. Front Immunol. 2018; 9: 455.
105. Alehashemi S, Goldbach Mansky R. Human autoinflammatory diseases mediated by NLRP3-, Pyrin-, NLRP1-, and NLRC4-inflammasome dysregulation updates on diagnosis, treatment, and the respective roles of IL-1 and IL-18. Front Immunol. 2020; 11: 1840.
106. Orel R, Trop TK. Intestinal microbiota, probiotics and prebiotics in inflammatory bowel disease. World J Gastroenterol. 2014; 20: 11505-11524.

107. Shonyela SM, Wang G, Yang W, Yang G, Wang C. New progress regarding the use of lactic acid bacteria as live delivery vectors, treatment of diseases and induction of immune responses in different host species focusing on lactobacillus species. J Prob Health. 2017; 5: 187.
108. Zhang S, Paul S, Kundu P. NF-κB regulation by gut microbiota decides homeostasis or disease outcome during ageing. Front Cell Dev Biol. 2022; 10: 874940.
109. Kaci G, Lakhdari O, Doré J, Ehrlich SD, Renault P, Blottière HM, et al. Inhibition of the NF-κB pathway in human intestinal epithelial cells by commensal Streptococcus salivarius. Appl Environ Microbiol. 2011; 77: 4681-4684.
110. Hegazy SK, El Bedewy MM. Effect of probiotics on pro-inflammatory cytokines and NF-κB activation in ulcerative colitis. World J Gastroenterol. 2010; 16: 4145-4151.
111. Lee JM, Hwang KT, Jun WJ, Park CS, Lee MY. Antiinflammatory effect of lactic acid bacteria: Inhibition of cyclooxygenase-2 by suppressing nuclear factor-kappaB in Raw264. 7 macrophage cells. J Microbiol Biotechnol. 2008; 18: 1683-1688.
112. Sun KY, Xu DH, Xie C, Plummer S, Tang J, Yang XF, et al. Lactobacillus paracasei modulates LPS-induced inflammatory cytokine release by monocyte-macrophages via the up-regulation of negative regulators of NF-kappaB signaling in a TLR2-dependent manner. Cytokine. 2017; 92: 1-11.
113. Petrof EO, Claud EC, Sun J, Abramova T, Guo Y, Waypa TS, et al. Bacteria-free solution derived from Lactobacillus plantarum inhibits multiple NF-kappaB pathways and inhibits proteasome function. Inflamm Bowel Dis. 2009; 15: 1537-1547.
114. Jang SE, Hyam SR, Han MJ, Kim SY, Lee BG, Kim DH. Lactobacillus brevis G-101 ameliorates colitis in mice by inhibiting NF-κB, MAPK and AKT pathways and by polarizing M1 macrophages to M2-like macrophages. J Appl Microbiol. 2013; 115: 888-896.
115. Palm NW, de Zoete MR, Flavell RA. Immune-microbiota interactions in health and disease. Clin Immunol. 2015; 159: 122-127.
116. Duan T, Du Y, Xing C, Wang HY, Wang RF. Toll-like receptor signaling and its role in cell-mediated immunity. Front Immunol. 2022; 13: 812774.
117. Cortes Perez NG, de Moreno de LeBlanc A, Gomez Gutierrez JG, LeBlanc JG, Bermúdez Humarán LG. Probiotics and trained immunity. Biomolecules. 2021; 11: 1402.
118. Isono A, Katsuno T, Sato T, Nakagawa T, Kato Y, Sato N, et al. Clostridium butyricum TO-A culture supernatant downregulates TLR4 in human colonic epithelial cells. Dig Dis Sci. 2007; 52: 2963-2971.
119. Finamore A, Roselli M, Imbinto A, Seeboth J, Oswald IP, Mengheri E. Lactobacillus amylovorus inhibits the TLR4 inflammatory signaling triggered by enterotoxigenic Escherichia coli via modulation of the negative regulators and involvement of TLR2 in intestinal Caco-2 cells and pig explants. PLoS One. 2014; 9: e94891.
120. Wu Q, Liu MC, Yang J, Wang JF, Zhu YH. Lactobacillus rhamnosus GR-1 ameliorates Escherichia coli-induced inflammation and cell damage via attenuation of ASC-independent NLRP3 inflammasome activation. Appl Environ Microbiol. 2015; 82: 1173-1182.
121. Zhen Y, Zhang H. NLRP3 inflammasome and inflammatory bowel disease. Front Immunol. 2019; 10: 276.
122. Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine. 2015; 74: 5-17.

123. Berraondo P, Sanmamed MF, Ochoa MC, Etxeberria I, Aznar MA, Pérez Gracia JL, et al. Cytokines in clinical cancer immunotherapy. Br J Cancer. 2019; 120: 6-15.
124. Ludwig IS, Broere F, Manurung S, Lambers TT, Van der Zee R, Van Eden W. Lactobacillus rhamnosus GG-derived soluble mediators modulate adaptive immune cells. Front Immunol. 2018; 9: 1546.
125. Loubet P, Ranfaing J, Dinh A, Dunyach Remy C, Bernard L, Bruyère F, et al. Alternative therapeutic options to antibiotics for the treatment of urinary tract infections. Front Microbiol. 2020; 11: 1509.
126. Sanjabi S, Zenewicz LA, Kamanaka M, Flavell RA. Anti-inflammatory and pro-inflammatory roles of TGF-β, IL-10, and IL-22 in immunity and autoimmunity. Curr Opin Pharmacol. 2009; 9: 447-453.
127. Ahmad R, Oli AN, Etando A, Sharma P, Sinha S, Chowdhury K, et al. Lactic acid bacteria fermented foods: Impact on immune system and consequences over type 2 diabetes mellitus. J Appl Pharm Sci. 2023; 13: 018-056.
128. Zhao HM, Huang XY, Zuo ZQ, Pan QH, Ao MY, Zhou F, et al. Probiotics increase T regulatory cells and reduce severity of experimental colitis in mice. World J Gastroenterol. 2013; 19: 742-749.
129. Zheng PX, Fang HY, Yang HB, Tien NY, Wang MC, Wu JJ. Lactobacillus pentosus strain LPS16 produces lactic acid, inhibiting multidrug-resistant Helicobacter pylori. J Microbiol Immunol Infect. 2016; 49: 168-174.
130. Arshad FA, Mehmood R, Hussain S, Khan MA, Khan MS. Lactobacilli as probiotics and their isolation from different sources. Br J Res. 2018; 5: 43.
131. Shi LH, Balakrishnan K, Thiagarajah K, Ismail NI, Yin OS. Beneficial properties of probiotics. Trop Life Sci Res. 2016; 27: 73-90.
132. De Simone C. The unregulated probiotic market. Clin Gastroenterol Hepatol. 2019; 17: 809-817.
133. Rao SC, Athalye Jape GK, Deshpande GC, Simmer KN, Patole SK. Probiotic supplementation and late-onset sepsis in preterm infants: A meta-analysis. Pediatrics. 2016; 137: e20153684.
134. Kothari D, Patel S, Kim SK. Probiotic supplements might not be universally-effective and safe: A review. Biomed Pharmacother. 2019; 111: 537-547.
135. Cohen PA. Probiotic safety-no guarantees. JAMA Intern Med. 2018; 178: 1577-1578.
136. Žuntar I, Petric Z, Bursać Kovačević D, Putnik P. Safety of probiotics: Functional fruit beverages and nutraceuticals. Foods. 2020; 9: 947.
137. Jakubczyk D, Górska S. Impact of probiotic bacteria on respiratory allergy disorders. Front Microbiol. 2021; 12: 688137.
138. Pohjavuori E, Viljanen M, Korpela R, Kuitunen M, Tiittanen M, Vaarala O, et al. Lactobacillus GG effect in increasing IFN-γ production in infants with cow's milk allergy. J Allergy Clin Immunol. 2004; 114: 131-136.
139. Crook N, Ferreiro A, Gasparrini AJ, Pesesky MW, Gibson MK, Wang B, et al. Adaptive strategies of the candidate probiotic E. coli Nissle in the mammalian gut. Cell Host Microbe. 2019; 25: 499-512.
140. Plavec TV, Berlec A. Safety aspects of genetically modified lactic acid bacteria. Microorganisms. 2020; 8: 297.

141. Han S, Lu Y, Xie J, Fei Y, Zheng G, Wang Z, et al. Probiotic gastrointestinal transit and colonization after oral administration: A long journey. Front Cell Infect Microbiol. 2021; 11: 609722.
142. Goldenberg JZ, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev. 2017; 12: CD006095.
143. Apostolou E, Kirjavainen PV, Saxelin M, Rautelin H, Valtonen V, Salminen SJ, et al. Good adhesion properties of probiotics: A potential risk for bacteremia? FEMS Immunol Med Microbiol. 2001; 31: 35-39.
144. Wagner RD, Warner T, Roberts L, Farmer J, Balish E. Colonization of congenitally immunodeficient mice with probiotic bacteria. Infect Immun. 1997; 65: 3345-3351.
145. Veckman V, Miettinen M, Pirhonen J, Sirén J, Matikainen S, Julkunen I. Streptococcus pyogenes and Lactobacillus rhamnosus differentially induce maturation and production of Th1-type cytokines and chemokines in human monocyte-derived dendritic cells. J Leukoc Biol. 2004; 75: 764-771.
146. Huang YF, Liu PY, Chen YY, Nong BR, Huang IF, Hsieh KS, et al. Three-combination probiotics therapy in children with salmonella and rotavirus gastroenteritis. J Clin Gastroenterol. 2014; 48: 37-42.