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PROBIOTICS AS IMMUNOMODULATORS: A COMPREHENSIVE REVIEW OF THEIR ROLE IN ENHANCING IMMUNITY, GUT HEALTH, AND DISEASE MANAGEMENT

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ABSTRACT

Probiotics, defined as live microorganisms conferring health benefits when consumed in adequate amounts, exhibit profound immunomodulatory capabilities. Numerous studies highlight their ability to enhance immune responses by promoting Th1 differentiation, regulatory T-cell populations, and cytokine production, such as IL-10 and interferon-α. Mechanistic insights reveal their interaction with gut epithelial cells, M cells, and immune cells, initiating immune signals and enhancing mucosal and systemic immunity. Probiotics such as *Lactobacillus* strains stimulate phagocytic activity and antibody production, including IgM, IgA, and IgG, reinforcing intestinal barrier function and modulating immune responses to pathogens. Animal studies demonstrate probiotics' protective effects against infections like *C. rodentium* and *Salmonella enterica*, reducing disease severity and improving survival rates. Furthermore, strain-specific responses, including enhanced innate immunity and modulation of cytokine profiles, have been observed. Heat-killed probiotics retain immunomodulatory activity, offering practical advantages such as improved storage and transportation. In immune-compromised hosts, probiotics help restore intestinal homeostasis and reinforce the mucosal barrier, providing therapeutic potential in conditions like HIV and autoimmune diseases. Probiotics also regulate the immune system through pathways involving tight junction proteins, protein kinase C, and MAP kinase, ensuring gut integrity and reducing inflammation. Their strain-dependent effects include both pro-inflammatory and regulatory responses, linked to interactions with pattern recognition receptors. This evidence underscores the therapeutic promise of probiotics in enhancing immunity, protecting against infections, and modulating inflammatory and autoimmune disorders, suggesting their pivotal role in clinical and nutritional applications.

KEYWORDS: Probiotics, Immunomodulation, Gut microbiota, Cytokine production, Mucosal immunity, Lactobacillus strains, Intestinal barrier function, Autoimmune disorders.

I. INTRODUCTION

The WHO/FAO defines probiotics as "live microorganisms that confer a health benefit on the host when consumed in adequate amounts." The study of probiotics began in earnest at the Pasteur Institute in Paris during the early 20th century, led by notable microbiologists such as Henry Tissier and Nobel Laureate Eli Metchnikoff. In 1908, Metchnikoff hypothesized that promoting beneficial gut flora by adjusting stomach pH could mitigate many health issues associated with aging. Although the initial approach of using fermented dairy products to manage pH proved incorrect, Metchnikoff's concept garnered significant attention and spurred further research. By 1953, the term "probiotics" was officially introduced to describe bacterial strains that positively influence digestive health.

Probiotics are primarily bacteria—microscopic, single-celled organisms—and their effects can vary widely depending on the species, strain, and preparation method (Bengmark, 2003). Commonly used probiotic microorganisms include species of *Lactobacillus* and *Bifidobacteria*, as well as the yeast *Saccharomyces boulardii* (Table 1.1) These probiotics are most often consumed in dairy products, fortified foods, or as pharmaceutical formulations. Emerging evidence highlights their numerous health benefits, including alleviating symptoms of lactose intolerance (Alvarez-Olmos & Oberhelman, 2001), preventing acute and traveler's diarrhea (Bengmark, 2003; Blum *et al*., 2000), mitigating antibiotic-associated diarrhea (Blum *et al*., 2002) and rotaviral diarrhea (Dsouza *et al*., 2002), and reducing the recurrence of certain cancers, particularly bladder and colorectal cancer (Elliott *et al*., 2005).

Table 1.1 Different types of probiotics (Rastogi *et al.*,2011).

Lactobacillus species	Bifidobacterium species	Streptococcus species	Saccharomyces species	Others
L. acidophilus	*B. bifidum*	*S. thermophilus*	*S. boulardii*	*Bacillus cereus*
L. casei (rhamnosus)	*B. breve*	*S. salivarius*		*Escherichia coli*
L. fermentum	*B. lactis*			*Enterococcus*
L. gasseri	*B. longum*			*Propionibacterium*
L. lactis	*B. infantis*			*freudenreichii*
L. salivarius	*B. adolescentis*			
L. reuteri				
L. bulgaricus				

II. CHARACTERISTICS OF GOOD PROBIOTICS

Fuller and Perdigon (2001) identified key characteristics that define an effective probiotic strain, emphasizing its ability to provide significant health benefits to the host. The essential features include:

- Non-pathogenicity and Non-toxicity: The strain must be safe for consumption, posing no risk of infection or adverse effects.
- Viability and Abundance: The probiotic should consist of live cells, preferably in high concentrations, to maximize its beneficial impact.
- Survivability in the Gastrointestinal Environment: It must withstand harsh gut conditions, such as low pH and the presence of organic acids, while maintaining metabolic activity.
- Stability and Shelf Life: The strain should remain viable during storage and under diverse field conditions, ensuring consistent efficacy.

These attributes are critical for the selection and application of probiotics in functional foods and therapeutic interventions.

III. PROBIOTICS AND THE IMMUNE SYSTEM

Gill (2003) and Gill and Guarner (2004) reported that probiotics directly enhance the activity of human dendritic cell (DC) populations, promoting T-helper 1 (Th1) differentiation. In animal studies, probiotic supplementation has been shown to induce regulatory T-cell populations, while human studies demonstrate that probiotic ingestion increases the production of regulatory cytokines, such as interleukin-10 (IL-10), in vitro.

Menard *et al.* (2005) examined the effects of orally administered living lactic acid bacteria (LAB) or their conditioned media on epithelial and immune functions in colitis-prone C57BL/6 IL-10 deficient mice. Their findings revealed enhanced intestinal barrier capacity and stimulation of Th1 immune responses, emphasizing the role of LAB-derived components in host defense mechanisms.

Johnson-Henry *et al.* (2005) investigated the effects of pretreating mice with a mixture of *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* on *Citrobacter rodentium*-induced colonic disease. The study demonstrated that mice receiving probiotics (10^9 cfu/ml) remained healthy, and probiotic pretreatment effectively mitigated the adverse effects of *C. rodentium* infection.

Baken *et al.* (2006) explored the modulation of Th1-mediated immune responses by various probiotic strains. Notably, *Lactobacillus casei Shirota* (LcS) predominantly enhanced innate immune responses and promoted Th1-mediated immune reactivity.

Mason *et al.* (2008) proposed several mechanisms underlying the effects of probiotics on intestinal microflora. These include lowering intestinal pH, releasing gut-protective metabolites, regulating intestinal motility, and increasing mucus production. The gastrointestinal mucosa serves as the primary interface between the external environment and the immune system. A reduction in intestinal microflora can elevate antigen transport, highlighting the crucial role of normal gut microflora in maintaining gut defenses. Nonpathogenic probiotic bacteria interact with gut epithelial cells and immune cells to initiate immune signaling. These interactions occur via M cells in Peyer's patches, gut epithelial cells, and associated immune cells, thereby contributing to intestinal immune regulation.

Seth *et al.* (2008) and Ewaschuk et al. (2008) reported that the immune effects of probiotic bacteria are mediated by soluble peptides secreted into the medium. The biochemical pathways involved in the probiotic effect on tight junction function include protein kinase C and MAP kinase pathways, which influence the redistribution and expression of tight junction proteins such as occludin and claudins.

Kim *et al.* (2009) demonstrated that macrophages cultured with LAB strains exhibited increased production of nitric oxide (NO) and cytokines, including interleukin (IL)-1β, IL-6, IL-12, and tumor necrosis factor-alpha (TNF-α).

Nandakumar *et al.* (2009) concluded that the consumption of beneficial bacteria, such as *Lactobacillus acidophilus* and *Lactobacillus casei*, enhances mucosal immunity and systemic immunity. *Lactobacillus* stimulates phagocytic activity, increases the production of T and B lymphocytes, and enhances antibody production, particularly IgM, IgA, and IgG.

Shiro *et al*. (2011) demonstrated the immunomodulatory effects of LAB on influenza virus (IFV) infection in mice. *Lactobacillus plantarum* was found to protect against body weight loss, reduce viral load in the lungs, and prolong survival time without toxicity in IFV-infected mice. Additionally, LAB reduced the total number of infiltrating cells in bronchoalveolar lavage fluid (BALF), particularly macrophages and neutrophils. LAB also enhanced the production of interferon-alpha and Th1 cytokines through intestinal immunity while reducing TNF-α levels in the early stages of infection.

Ou *et al*. (2011) investigated the immunomodulatory properties of heat-killed LAB, emphasizing their benefits such as extended shelf life, easier storage, and convenient transportation. Their results indicated that LAB adhesion decreased with increased temperatures, though immunomodulatory activity remained unaffected. Notably, Th1-associated cytokines increased, while Th2-associated cytokines decreased. Similarly, Bhatia and Pawan (2007) reported that non-viable bacteria could also enhance immune responses.

Cunningham-Rundles *et al.* (2011) demonstrated that probiotics protect the gut surface and may delay the progression of Human Immunodeficiency Virus type 1 (HIV-1) infection to Acquired Immunodeficiency Syndrome (AIDS). They showed that probiotics promote growth in infants with congenital HIV-1 infection, stabilize CD4+ T cell numbers in HIV-1-infected children, and likely protect against inflammation and chronic immune activation of the gastrointestinal immune system.

Castillo *et al.* (2011) evaluated the effects of orally administered *Lactobacillus* on cytokine production and Toll-like receptor (TLR) expression in mice infected with *Salmonella enterica serovar Typhimurium.* The results demonstrated that *L. casei* modulates cytokine profiles, enhancing immune responses and mitigating infection severity.

Lin *et al.* (2011) examined probiotics' regulatory effects on T-cell-mediated immune responses, showing that high concentrations ($\geq 1 \times 10^6$ CFU/ml) inhibit mitogen-induced cell proliferation and arrest the cell cycle at the G0/G1 stage in mitogen-stimulated spleen cells and human peripheral blood mononuclear cells (PBMCs). Lower concentrations ($<1 \times 10^6$ CFU/ml) enhanced interferon-gamma (IFN-γ) production and suppressed interleukin-4 (IL-4) production. Randhawa et al. (2011) further demonstrated that *Lactobacillus delbrueckii 405* and *Lactobacillus casei subsp. casei* 17, individually and in combination (10^9 cells/ml), synergistically lowered cholesterol levels and enhanced immune system activity.

Evrard *et al*. (2011) highlighted the complex and strain-specific effects of probiotics on the immune system, noting that their response remains controversial. Some probiotic strains modulate cytokine production by dendritic cells (DCs) in vitro, inducing either a regulatory or pro-inflammatory response. These outcomes appear to be linked to specific interactions between bacterial strains and pattern recognition receptors. Their results demonstrated that probiotics could induce dose-dependent immunomodulation of human DCs, particularly at higher doses.

Fanning *et al.* (2012) explored the role of *bifidobacterial* surface exopolysaccharides (EPS) in promoting beneficial host-commensal interactions. Their findings revealed that EPS plays a pivotal role in immune modulation and pathogen protection. Specifically, EPS helps commensal bacteria remain immunologically silent while simultaneously conferring protection against pathogens, underscoring its importance in maintaining host-microbiota homeostasis.

Kaur and Bhatia (2012) investigated the immune-modulatory potential of four *Lactobacillus acidophilus* strains in Swiss albino mice. Their results showed that immunomodulation by *L. acidophilus* is strain-specific. They suggested that orally supplemented *L. acidophilus* could indirectly influence T-lymphocyte activity by stimulating other immune cells, such as phagocytes.

Stoeker *et al.* (2013) addressed the association between HIV infection and intestinal mucosal dysfunction, emphasizing the therapeutic potential of probiotics to enhance mucosal barrier function in HIV-positive individuals. Their study involved administering *Lactobacillus acidophilus* to cats with chronic feline immunodeficiency virus (FIV) infection. The findings revealed that FIV infection significantly affected transcellular transport across the intestinal epithelium but not paracellular transport. Probiotic treatment in FIV+ cats led to cytokine release changes and altered mucosal leukocyte percentages, effects absent in FIV- cats. This suggested a novel role for FIV in upregulating transcellular transport and highlighted the therapeutic potential of probiotics in restoring intestinal homeostasis.

Kwon *et al.* (2013) examined the immunomodulatory effects of a probiotic mixture, IRT5, on experimental inflammatory disorders. Their study demonstrated that pretreatment with IRT5 significantly suppressed the development of experimental autoimmune encephalomyelitis (EAE), a T cell-mediated autoimmune disease of the central nervous system. Additionally, IRT5 treatment in ongoing EAE delayed disease onset. Probiotic administration inhibited pro-inflammatory Th1/Th17 polarization while promoting IL-10-producing and/or Foxp3+ regulatory T cells in the peripheral immune system and at inflammatory sites. These findings suggest that IRT5 probiotics have potential therapeutic applications in modulating T cell-mediated neuronal autoimmune diseases, such as multiple sclerosis.

Collectively, these studies underscore the strain-specific and context-dependent effects of probiotics on immune modulation, highlighting their potential as therapeutic agents for various immune-mediated conditions.

IV. CONCLUSION

The research on probiotics underscores their multifaceted role in modulating the immune system, enhancing gut health, and mitigating inflammatory and autoimmune conditions. Probiotics, particularly various strains of *Lactobacillus* and *Bifidobacterium*, demonstrate significant immunomodulatory effects by promoting Th1 responses, stimulating regulatory cytokines like IL-10, and enhancing both mucosal and systemic immunity. They interact with gut epithelial and immune cells, facilitating pathogen defense and maintaining intestinal homeostasis.

Mechanistic studies reveal that probiotics influence immune signaling through pathways such as protein kinase C and MAP kinase, which regulate tight junction integrity and cytokine production. The strain-specific effects of probiotics, including heat-killed variants, highlight their potential for practical applications, offering advantages like prolonged shelf life without compromising immunomodulatory efficacy.

In disease models, probiotics have shown promise in attenuating infections like *C. rodentium* and *Salmonella enterica*, enhancing host resistance, and reducing disease severity. Their therapeutic potential extends to immune-compromised conditions, such as HIV and autoimmune diseases, where they help restore gut integrity and balance immune responses. Probiotic mixtures like IRT5 have demonstrated efficacy in suppressing pro-inflammatory polarization and promoting regulatory T cells, suggesting their utility in managing T cell-mediated diseases.

Overall, probiotics represent a valuable tool in enhancing immunity, protecting against pathogens, and mitigating inflammatory disorders. Their strain-specific responses and wide-ranging health benefits position them as a cornerstone for developing novel therapeutic strategies and functional food products aimed at improving human health.

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