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Probiotics in Gut Health and Immunity: Mechanisms and Clinical Evidence

Michał Filipski, MD

ORCID: https://orcid.org/0009-0005-0966-4246

University Hospital in Wroclaw (USK), Borowska 213, 50-556 Wroclaw, Poland

e-mail: michal.fil9@gmail.com

Bartosz Wróbel, MD

ORCID: https://orcid.org/0009-0006-1156-8568

Hospital of Ministry of the Interior and Administration in Cracow, Kronikarza Galla 25, 30-053 Cracow, Poland

e-mail: bar8tek@gmail.com

Lena Wójcik, MD
ORCID: https://orcid.org/0009-0002-2191-4277
Hospital of Ministry of the Interior and Administration in Cracow, Kronikarza Galla 25, 30-053 Cracow, Poland
e-mail: lenawojcik196@gmail.com
Krzysztof Gadzalski, MD
ORCID: https://orcid.org/0009-0000-6821-3350
St. Raphael's Voivodeship Specialist Hospital in Czerwona Góra, Czerwona Góra 10, 26-060 Chęciny, Poland
e-mail: gadzal99@gmail.com
Konstancja Owczarenko, MD
ORCID: https://orcid.org/0009-0009-2232-7753
Lower Silesian Centre of Oncology, Pulmonology and Hematology, plac Ludwika Hirszfelda 12, 53-413 Wroclaw, Poland
e-mail: konstancja.owczarenko@gmail.com
Kacper Szada-Borzyszkowski, MD
ORCID: https://orcid.org/0009-0006-4967-215X
Lower Silesian Center of Oncology, Pulmonology and Hematology, plac Ludwika Hirszfelda 12, 53-413 Wroclaw, Poland
e-mail: kacperrrada@gmail.com
Corresponding author: Michał Filipski, michal.fil9@gmail.com

Abstract

Background. Probiotics are live microorganisms that support human health mainly by influencing the gut microbiota. They help maintain the integrity of the intestinal barrier and play an important role in regulating immune responses. Their growing clinical relevance is linked to conditions associated with microbiota imbalance.

Aim. The aim of this review was to present the main mechanisms of probiotic action and to assess their clinical effectiveness in selected gastrointestinal, infectious, and allergic diseases.

Material and methods. This narrative review is based on data from randomized controlled trials and meta-analyses focusing on both molecular mechanisms and clinical outcomes of probiotic use.

Results. Probiotics improve intestinal barrier function by supporting tight junction proteins and reducing intestinal permeability. They also modulate immune responses by limiting inflammation and promoting regulatory pathways, including the induction of regulatory T cells. Clinical studies show that multistrain preparations, especially those containing *Lactobacillus* and *Bifidobacterium*, are effective in reducing the risk of antibiotic-associated diarrhea and *Clostridioides difficile* infection. They also help relieve symptoms of functional gastrointestinal disorders and improve outcomes in allergic diseases such as atopic dermatitis and childhood asthma. Overall, probiotics are well tolerated and safe.

Conclusions. Probiotics can be a valuable supportive therapy in disorders related to microbiota imbalance. Further studies should focus on better matching specific strains to individual patients in order to increase treatment effectiveness.

Keywords: probiotics, gut microbiota, intestinal barrier function, tight junctions, regulatory T cells, antibiotic-associated diarrhea, Clostridioides difficile, functional gastrointestinal disorders, atopic dermatitis, childhood asthma, Lactobacillus, Bifidobacterium, immune tolerance, NF-κB pathway, multistrain formulations

1. Introduction

Probiotics, defined by the Food and Agriculture Organization of the United Nations and the World Health Organization as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host." [1]. The human gut microbiota comprises a complex ecosystem of microorganisms that plays a critical role in maintaining gastrointestinal function, metabolic homeostasis, immune tolerance, and protection against pathogenic organisms [2]. Recognition of the role of microflora in health and disease has led to an increased scientific interest in dietary interventions aimed at modulating the composition of microorganisms, particularly through the use of probiotics [3]. Probiotics exert their beneficial effects through multiple mechanisms, including competitive exclusion of pathogens, production of antimicrobial substances, modulation of the immune system, and improvement of gut barrier function [4]. The variability in the efficacy of probiotics across different strains, conditions, and populations requires a rigorous, evidence-based approach to strain selection and clinical applications, with probiotic strains requiring characterization, safety assessment, and confirmation of positive clinical trial results in humans conducted according to generally accepted scientific standards to be qualified as probiotics [5].

This narrative review summarizes current data on the molecular mechanisms by which probiotics exert beneficial effects on health and their clinical efficacy in treatment of major gastrointestinal, immune, and infectious diseases.

2. How Probiotics Promote Gut Health and Immune Modulation

Probiotics exert beneficial effects through multiple interrelated mechanisms that strengthen intestinal barrier function and modulate immune homeostasis. The intestinal epithelial barrier depends on tight junction (TJ) proteins, including claudins, occludins, and zonula occludens-1 (ZO-1), which regulate intercellular permeability and control the flow of pathogens. These proteins form selective barriers that determine whether harmful molecules can pass through the intestinal epithelium [6]. In dysbiotic states, an increase in intestinal permeability precedes gross tissue damage and is associated with the loss of claudin 4 and occludin from tight junction structures, as these proteins relocate from the cell membrane into the cytoplasm. This allows bacterial lipopolysaccharides (LPS) to translocate across the epithelium, triggering systemic inflammation. *Bifidobacterium infantis* prevents these pathological changes by preserving claudin 4 and occludin localization at tight junctions [7]. Similar protective mechanisms have been identified in other *Bifidobacterium* species. Specifically, *Bifidobacterium bifidum* BB1 inhibits TNF-α-induced intestinal epithelial tight junction permeability through toll-like receptor 2-toll-like receptor 6 (TLR-2/TLR-6) heterodimer activation of peroxisome proliferator-activated receptor gamma (PPARγ), which suppresses NF-κB-mediated inflammatory pathways and preserves tight junction protein expression [8]. Beyond barrier function, probiotics induce regulatory T cell (Treg) populations essential for immune tolerance. A probiotic mixture containing five strains significantly increased CD4+Foxp3+ Tregs in mesenteric lymph nodes. This occurred through conversion of conventional T cells, mediated by regulatory dendritic cells expressing IL-10 and TGF-β [9]. The importance of strain combinations is further highlighted by studies demonstrating that individual probiotic strains alone often fail to achieve therapeutic effects. A three-strain Lactobacillus mixture reversed autoimmune encephalomyelitis through synergistic elevation of serum IL-10, with monostrain treatments proving ineffective in diseased mice. The therapeutic efficacy of this probiotic combination was entirely dependent on IL-10-producing Tregs [10].

These findings demonstrate that probiotics strengthen intestinal health through complementary mechanisms: upregulation of tight junction proteins to enhance barrier integrity, suppression of inflammatory signaling pathways, and induction of IL-10-producing regulatory T cells. The simultaneous strengthening of barrier function and promotion of regulatory immune responses indicates these mechanisms work synergistically to establish intestinal homeostasis.

3. Probiotics in Antibiotic-Associated Diarrhea and *Clostridioides difficile* Infection

Antibiotic-associated diarrhea (AAD) and *Clostridioides difficile* infection (CDI) represent common iatrogenic complications of antimicrobial therapy caused by disruption of the indigenous microbiota, with AAD affecting 5-35% of patients receiving antimicrobials. The most severe manifestation, *Clostridioides difficile* infection, represents a serious complication of antibiotic-associated diarrhea and can be fulminant, relapsing, and occasionally fatal. Antibiotic therapy remains the standard treatment for CDI using vancomycin or fidaxomicin, yet paradoxically perpetuates microbiota disruption, creating substantial clinical need for adjunctive antimicrobial strategies [11].

A multicenter randomized controlled trial evaluated a high-dose multistrain probiotic formulation containing *Lactobacillus spp.*, *Bifidobacterium spp.*, *Bacillus coagulans*, and *Saccharomyces boulardii* in 564 adult participants receiving broad-spectrum antibiotics. AAD occurred in 9.2% of the probiotic group compared to 25.3% in placebo, yielding an absolute risk reduction of 16% and a number needed to treat of 6 (95% CI: 4.55-10.49, $p < 0.001$). The studied probiotic mix also demonstrated significantly improved gastrointestinal quality of life compared to placebo. Moreover, investigator efficacy assessment revealed that 91.8% of participants receiving the probiotic formulation experienced an excellent response compared to 59.3% in the placebo group [12]. A 2025 meta-analysis synthesizing 15 randomized controlled trials confirmed that probiotics reduce AAD incidence by 40%. Multistrain formulations showed superior protection (RR = 0.40) compared to dual-strain (RR = 0.9) or single-strain preparations (RR = 0.6) [13]. Notably, a recent meta-analysis including 42 studies and 11,305 participants found that co-administration of probiotics with antibiotics reduced the incidence of diarrhea by 35%. Higher doses and specific strains, particularly *Lactobacillus* and *Bifidobacterium*, were shown to be advantageous in preventing antibiotic-associated diarrhea [14].

For *Clostridioides difficile* infection prevention, a meta-analysis of 16 randomized trials in hospitalized patients demonstrated that probiotics administered concurrently with antibiotics reduced CDI incidence by 63%, with a number needed to treat of 14 to prevent one CDI case. Notably, efficacy was greater with *Lactobacillus*-based formulations compared to *Saccharomyces boulardii* preparations. The subgroup analysis by study quality revealed that good-quality trials demonstrated significant reductions in both AAD and CDI with probiotic use[15]. A randomized controlled trial reported exceptional primary *Clostridioides difficile* infection prevention efficacy with a combination of *Limosilactobacillus reuteri* LMG P-27481 and *Lacticaseibacillus rhamnosus* GG ATCC 53103 co-administered with antibiotics in 113 hospitalized adults, achieving 0% *C. difficile* infection incidence in the probiotic group compared with 11% in controls, alongside prevention of vomiting and diarrhea. The probiotic group also showed significant reduction in diarrhea and vomiting. This superior outcome likely reflects complementary mechanisms: *L. reuteri* produces reuterin, an antimicrobial metabolite antagonistic to *C. difficile*, while *L. rhamnosus* GG generates lactic acid and bacteriocins antagonistic to *C. difficile* growth [16].

Despite promising results, optimal dosage regimens, duration of treatment, and identification of patient populations most likely to benefit from specific probiotic strains remain areas requiring further investigation.

4. Probiotics in Gastrointestinal Functional Disorders

Functional gastrointestinal disorders, defined by the Rome IV criteria as gastrointestinal symptom clusters without identifiable morphologic or physiological abnormalities, represent a growing clinical challenge affecting a substantial part of the global population. Among the most prevalent FGIDs are functional constipation (FC), functional diarrhoea (FDr), and irritable bowel syndrome (IBS), all of which share common pathophysiological mechanisms including dysbiosis, altered gut microbial environment, abnormal GI motility, brain-gut disturbances, and low-grade intestinal inflammation [17]. Emerging evidence demonstrates that targeted probiotic interventions can modulate these pathophysiological mechanisms and provide clinically meaningful symptom relief through restoration of gut microbiota balance and enhancement of intestinal barrier function.

A randomized controlled trial in 140 adults with functional constipation or functional diarrhoea showed that four weeks of multi-strain probiotic supplementation significantly reduced gastrointestinal symptom scores. In FC subjects, weekly stool frequency increased from 3.3 to 6.2 times per week with normalized stool consistency, while FDr subjects experienced decreased stool frequency from 12.7 to 9.8 times per week. Both groups demonstrated significant increases in serum IgA and interferon-γ, reduced inflammation markers, and enhanced short-chain fatty acid production. Additionally, both groups showed significant improvements in anxiety, depression, and perceived stress scores, with no serious adverse events reported [18]. Additional evidence comes from a double-blind randomized controlled trial in 187 adults with functional constipation or functional diarrhea consuming symbiotic fermented milk containing *Lactobacillus plantarum* ST-III and inulin. In FC participants, intestinal health significantly improved from day 3 of intervention. In FDr participants, stool consistency normalized by day 14. Both groups demonstrated increased Bifidobacteria and Lactobacillus populations, reduced pathogenic bacteria, and elevated short-chain fatty acids and secretory immunoglobulin A levels [19]. These results confirm that both probiotic and symbiotic formulations effectively normalize bowel function and modulate microbiota in functional bowel disorders.

Beyond functional constipation and diarrhea, probiotics demonstrate broader therapeutic efficacy in irritable bowel syndrome (IBS). A 2024 systematic review and network meta-analysis synthesizing 54 randomized controlled trials identified probiotics as significantly superior to placebo for symptomatic improvement in IBS, indicating a 47% reduction in symptoms (OR = 0.53, 95% CI: 0.48-0.59). Among the probiotic strains evaluated, Bifidobacterium species and Lactobacillus species emerged as the dominant therapeutic agents, with outcome-specific efficacy depending on IBS presentation. Fecal microbiota transplantation demonstrated comparable efficacy to probiotics. Across all interventions reviewed, no serious adverse events were documented, confirming the favourable safety profile of probiotic interventions for IBS [20]. Subsequent investigation further elucidates the mechanisms through which probiotics exert therapeutic effects in IBS. A recent double-blind randomized controlled trial involving 120 IBS patients across all subtypes demonstrated that 12 weeks of multistrain probiotic supplementation (*Lactobacillus* and *Bifidobacterium* strains) significantly reduced IBS Symptom Severity Scale scores beginning at week 8, with continuous improvement through week 12. Critically, reductions in symptom scores were positively correlated with increased fecal short-chain fatty acid levels (acetate, propionate, and butyrate). Simultaneously, intestinal barrier integrity improved significantly, with decreased intestinal permeability and increased tight junction proteins. Inflammatory markers including C-reactive protein, interleukin-6, tumor necrosis factor-α, and fecal calprotectin decreased significantly [21].

5. Probiotics in Allergic Diseases and Immune Tolerance

Allergic diseases, including food allergy, atopic dermatitis, asthma, and allergic rhinitis, reflect a failure of immune tolerance mechanisms. In allergic pathogenesis a dysregulated immune response driven predominantly by T helper 2 (Th2) cells dominates, releasing pro-allergic cytokines (IL-4, IL-5, and IL-13), which probiotics can suppress. Additionally, emerging evidence indicates that Th17 cells contribute to allergic inflammation through secretion of pro-inflammatory interleukin-17, with probiotics shown to suppress these responses in splenic CD4 T cells. The breakdown of intestinal immune tolerance precipitates allergic sensitization. The intestinal bacterial flora plays a crucial role in oral tolerance induction, probably by affecting the development of the immune system at the neonatal stage [22].

Probiotics modulate dysregulated allergic responses through a fundamental mechanism involving dendritic cell (DC) reprogramming and regulatory T cell (Treg) induction. Selected probiotic strains, particularly *Lactobacillus rhamnosus* and *Bifidobacterium* species, are efficiently internalized by dendritic cells via pattern recognition receptors including TLR2 and NOD2. This engagement triggers a partial maturation of the cells rather than full pro-inflammatory activation, directing DCs toward a tolerogenic phenotype characterized by reduced co-stimulatory molecule expression (low CD40, CD86) and high production of immunoregulatory molecules including IL-10, TGF-β, and indoleamine 2,3-dioxygenase (IDO)[23]. Conversion of T cells into Foxp3^{+} Tregs is directly mediated by regulatory dendritic cells that express high levels of IL-10, TGF-β, COX-2 and IDO, which endow them with potent tolerogenic properties. In vivo, oral administration of a defined probiotic mixture (IRT5) increased CD4^{+}Foxp3^{+} Tregs in mesenteric lymph nodes. This expansion of Tregs was accompanied by broad hyporesponsiveness of T and B cells, with reduced Th1, Th2 and Th17 cytokine production without apoptosis induction. Probiotics-induced regulatory dendritic cells and Tregs translated into clear therapeutic effects, as IRT5 suppressed experimental inflammatory bowel disease, atopic dermatitis and rheumatoid arthritis [9].

In a randomized, double-blind, placebo-controlled trial involving children and adolescents with mild-to-severe atopic dermatitis, daily administration of a multistrain probiotic mixture (*Lactobacillus rhamnosus* HN001, *L. acidophilus* NCFM, *L. paracasei* Lpc-37, and *Bifidobacterium lactis* HN019) for 6 months significantly reduced SCORAD scores (SCORing Atopic Dermatitis severity index) compared with placebo. This clinical improvement was evident from the third month of treatment and persisted for at least 3 months post-treatment. Additionally, the probiotic group required topical immunosuppressants less frequently and probiotics were well-tolerated without severe adverse events [24]. Similar clinical benefits have been observed in younger children with atopic dermatitis comorbid with cow's milk protein allergy. In a randomized, double-blind, placebo-controlled trial in infants under 2 years with atopic dermatitis and confirmed cow's milk protein (CMP) allergy, oral administration of a probiotic mixture (*Lactobacillus rhamnosus* ŁOCK 0900, *L.*

rhamnosus ŁOCK 0908, and *L. casei* ŁOCK 0919) for 3 months alongside CMP elimination diet significantly improved AD symptoms compared with placebo. Specifically, the proportion of children achieving ≥30% SCORAD reduction (clinical improvement) was higher in the probiotic group (83.3% vs. 66.2%), with even stronger effects in allergen-sensitized patients (91.7% vs. 64.6%). Both groups showed sustained SCORAD reductions after 9-month follow-up [25]. Extending these skin-focused benefits to respiratory allergies, a randomized trial in school-aged children with asthma demonstrated that supplementation with *Lactobacillus paracasei* LP, *L. fermentum* LF, or their combination for 3 months significantly reduced asthma severity and improved Childhood Asthma Control Test (C-ACT) scores. The mixed-strain (LP+LF) group showed the strongest effects, with increased peak expiratory flow rates and reduced serum IgE levels, alongside good tolerability and >93% compliance [26].

6. Conclusion

This comprehensive review demonstrates that probiotics exert multifaceted beneficial effects on gut health and immunity through interconnected mechanisms that strengthen intestinal barrier integrity via tight junction preservation, suppress NF-κB-mediated inflammatory pathways through TLR2/TLR6-PPARγ signaling, and promote regulatory immune responses via induction of IL-10/TGF-β-producing CD4+Foxp3+ Tregs that establish immune tolerance in mesenteric lymph nodes. These strain-specific actions synergistically restore microbial homeostasis disrupted by dysbiosis, antibiotics, or allergic inflammation. Clinically, multistrain formulations containing *Lactobacillus* and *Bifidobacterium* species consistently demonstrate efficacy across diverse conditions, including prevention of antibiotic-associated diarrhoea and *Clostridioides difficile* infections, symptom relief in functional gastrointestinal disorders, and meaningful improvements in allergic diseases such as atopic dermatitis and childhood asthma. These benefits reflect probiotics' unique capacity to restore microbial homeostasis, modulate dendritic cell function toward immune tolerance, and reduce reliance on topical immunosuppressants while maintaining an excellent safety profile without serious adverse events.

While current high-quality randomized controlled trials and meta-analyses provide robust evidence for probiotics as valuable adjunctive therapies, future research should prioritize large-scale, long-term studies incorporating microbiota profiling to identify responder populations, optimize strain-specific dosing regimens, and elucidate mechanisms of sustained immune tolerance. Such a precise approach should position probiotics as a cornerstone intervention for preventing and managing microbiota-driven immune dysregulation across clinical practice.

Disclossure

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Author Contributions:

Conceptualization: Bartosz Wróbel, Lena Wójcik, Michał Filipski

Methodology: Bartosz Wróbel, Lena Wójcik, Krzysztof Gadzalski

Software: Not applicable.

Check (Validation): Bartosz Wróbel, Michał Filipski, Krzysztof Gadzalski

Formal analysis: Lena Wójcik, Kacper Szada-Borzyszkowski, Konstancja Owczarenko

Investigation: Bartosz Wróbel, Lena Wójcik, Kacper Szada-Borzyszkowski, Konstancja Owczarenko, Krzysztof Gadzalski, Michał Filipski

Resources: Bartosz Wróbel, Lena Wójcik, Kacper Szada-Borzyszkowski, Konstancja Owczarenko, Krzysztof Gadzalski, Michał Filipski

Data curation: Bartosz Wróbel, Lena Wójcik, Kacper Szada-Borzyszkowski, Konstancja Owczarenko, Krzysztof Gadzalski, Michał Filipski

Writing - rough preparation: Bartosz Wróbel, Lena Wójcik, Kacper Szada-Borzyszkowski, Konstancja Owczarenko, Krzysztof Gadzalski, Michał Filipski

Writing- review and editing: Bartosz Wróbel, Michał Filipski

Visualization: Bartosz Wróbel

Supervision: Michał Filipski

Project administration: Bartosz Wróbel, Michał Filipski

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