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Kawaljit Kaur *

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Review

Exploring the Diverse Roles of Probiotic Strains in Aging, Cancer, Autoimmune Diseases, and Neurodegenerative Disorders

Kawaljit Kaur

ImmuoLink, LLC, Riverside, CA, USA, 92508; drkawalmann@g.ucla.edu; Tel.: 1-5093395967

Simple Summary

Probiotics are live microorganisms that support health by balancing gut bacteria, boosting immunity and metabolism, and potentially preventing or treating various conditions. Their effectiveness varies by strain and proper use. Advances in microbiome research are leading to personalized probiotic treatments with significant benefits. Different strains play unique roles in aging, cancer, autoimmune diseases, and neurodegenerative disorders. Understanding these strain-specific effects is crucial for personalized healthcare. Studies show probiotics can strengthen immunity, improve gut health, and enhance overall well-being. Tailoring probiotics to individual needs may help address complex health challenges. This review provide overview that each probiotic strain has unique benefits, and targeted use can maximize their therapeutic potential.

Abstract

This review looks at how probiotics affect health issues like cancer, aging, autoimmune diseases, and neurodegenerative disorders, focusing on immune balance through different probiotic strain combinations. It discusses how various combinations activate PBMCs, NK cells, and CD8+ T cells in unique ways. Some combinations are helpful for autoimmune diseases, while others show potential in cancer treatment. Most formulations improve immune balance and aging when used as supplements. The research highlights varying levels of immune cell activation, with certain combinations promoting cell growth and activating NK and CD8+ T cells alongside feeder cells. In cancer-bearing humanized mice, oral administration of specific combinations with NK cell-based therapy enhanced tumor suppression, immune function, and bone health. Cancer patients taking probiotic supplements experienced increased cytokine production and improved PBMC and NK cell cytotoxicity. Probiotics' positive effects are also examined in aging, autoimmune diseases, and neurodegenerative disorders. Overall, the review emphasizes the important role of probiotics in maintaining immune balance and boosting immunotherapy results.

Keywords: NK cells; T cells; CD8+ T cells; immunotherapy; probiotics; cancer; aging; autoimmune; neurodegenerative; cytotoxicity; IFN-γ

1. Introduction and Background

In the early 20th century, Elie Metchnikoff discovered certain strains of gut bacteria essential for maintaining balance in the gut, which he named probiotics [1]. These live, beneficial bacteria, often derived from fermented foods or the gut itself, offer numerous health benefits supported by studies and clinical trials [2,3]. Research shows their potential to address gut issues, obesity, syndrome, allergies, heart disease, and even cancer [4–7]. Probiotics help maintain the intestinal barrier and microbial balance by enhancing proteins and mucus that prevent pathogens and excessive immune responses [8,9]. They interact with immune cells through direct contact and signaling molecules, boosting immunity while maintaining gut tolerance [10]. Probiotics also strengthen defenses against

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infections by activating immune cells and increasing cytokines and antibodies [11]. Additionally, they balance inflammation, helping with conditions like inflammatory bowel disease, allergies, and autoimmune disorders [12–15]. By competing with pathogens and producing antimicrobial agents, probiotics contribute to immune stability [16]. Components like exopolysaccharides, surface proteins, and secreted peptides interact with immune receptors, influencing signaling pathways [17–19]. They also adhere to the gut lining and engage with immune cells via Toll-like receptors (TLRs) like TLR2, TLR4, and TLR9 [12,20].

Probiotics play a crucial role in maintaining immune balance by activating Tregs, which promote tolerance to commensals and food antigens, reducing inflammation and allergic responses [21]. They also impact the differentiation and function of T helper (Th) cell subsets and Tregs, driving immune responses like cell-mediated immunity or tolerance through cytokines like IL-10 and TGF-β [12,20]. Probiotics aid in B-cell maturation into plasma cells that produce secretory IgA (sIgA), essential for defending mucosal surfaces against pathogens [22]. The immune-modulating effects of probiotics depend heavily on the specific strains used, as different species and strains can uniquely affect cytokine responses and immune cell activity. For instance, Lactobacillus strains often enhance Th1-type immune responses, while Bifidobacterium strains typically promote anti-inflammatory effects [23]. Most probiotics are lactic acid-producing bacteria, such as lactobacilli, streptococci, and bifidobacteria, emphasizing their potential for human health [24]. Certain strains, like Lactococcus lactis subsp. Cremoris C60, have even been found to boost antigen presentation by dendritic cells, enhancing cytotoxic T cell responses critical for combating tumors and viruses [25,26].

Picking the right strain and dosage of probiotic bacteria is essential for achieving immune benefits. The effects of probiotics on immunity largely depend on the specific strains and the overall context, making careful selection key to meeting therapeutic goals. This review looks at how different probiotic formulations activate and boost immune cells, helping maintain immune balance in conditions like cancer, aging, autoimmune diseases, and neurodegenerative disorders.

2. Probiotics Formulation for Cancer Prevention and as Adjuvant Cancer Therapeutics

Cancer is the second leading cause of death globally, with no effective cure currently available, and cancer-related deaths are expected to rise [27]. There is a pressing need for treatments that are highly effective and have minimal side effects [28–30]. Current therapies often impact quality of life due to side effects, drug resistance, and affordability challenges [31]. Interestingly, research suggests probiotics could help in cancer prevention and as an additional treatment. Probiotics contribute to cancer prevention and treatment by influencing immunoglobulin A production, stimulating macrophage activity, and reducing the toxicity of anti-cancer therapies [15,32–35]. Probiotics boost immune responses and support tumor immunity by interacting with dendritic cells, macrophages, natural killer cells, and neutrophils, enhancing their function and cytokine production [12,36]. This activation leads to the upregulation of co-stimulatory molecules on antigen-presenting cells and the release of cytokines to manage inflammation and immune cell recruitment, balancing pro- and anti-inflammatory pathways [26,37–39]. Found in foods and supplements, probiotics enhance innate immunity by activating natural killer cells for antitumor effects and maintaining gut microbial balance [40–44]. They also lower nitric oxide production and reduce pro-inflammatory cytokines [28,30,45–50]. Even inactive probiotics and their byproducts provide similar health benefits, making them valuable in cancer prevention and treatment [51–56].

NK cells are crucial for innate immunity due to their lack of antigen specificity [57–59], while CD8+ T cells play a key role in adaptive cellular immunity, closely interacting with the innate immune system [60,61]. Both cell types are essential in cancer therapy, forming the foundation of current treatments [62,63]. Impaired function of these cells is associated with worse outcomes in cancer patients [64–70]. NK cells also enhance CD8+ T cell responses against viral infections like cytomegalovirus [71,72]. In cancer patients, NK cells show reduced cytotoxicity, IFN-γ secretion, survival, and expansion, linked to lower expression of CD16, NKG2D, and the zeta chain [67,73–79]. CD8+ T cells in cancer patients exhibit

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decreased IFN-γ secretion and reduced expression of CD62L, CD28, CCR7, and CD127 [80]. Probiotics have shown potential by significantly enhancing NK cell cytotoxicity and IFN-γ secretion in both NK and CD8+ T cells [80]. This approach also improves monocytes' ability to synergistically stimulate IFN-γ secretion in NK cells in cancer patients and healthy individuals [81]. Probiotics further impact DCs, regulatory T cells, and NK cells, strengthening intestinal defenses, although the effects vary depending on the probiotic strains used [1,42].

A study examined eight gram-positive bacterial strains, showing that formulations containing Streptococcus thermophilus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, and Lactobacillus bulgaricus stimulated both pro-inflammatory and anti-inflammatory cytokines and growth factors in NK cells [82]. Notably, IFN-γ and IL-1Ra levels significantly increased [82]. This NK cell activation by probiotics supports their anti-cancer effects [73,75,82]. Probiotic-treated NK cells revealed that Lactobacillus species and Streptococcus thermophilus promoted a Th1-type cytokine profile, increasing IL-12 and IFN-γ while decreasing IL-10, whereas Bifidobacterium induced a Th2 profile with higher IL-10 and IL-6 compared to IL-12 and IFN-γ [82]. Another study analyzed probiotic formulations and identified seven gram-positive strains, either as a mix of seven or four: Streptococcus thermophilus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, and Lactobacillus paracasei, or Streptococcus thermophilus, Lactobacillus acidophilus, Lactobacillus plantarum, and Lactobacillus paracasei, which demonstrated anti-cancer and anti-infection effects by increasing IFN-γ and reducing IL-10 [83]. Probiotic bacteria have been utilized to develop NK or CD8+T cell-based immunotherapies, which significantly boost the functional capabilities of these cells [73,75,84,85]. A combination of eight strains (Streptococcus thermophilus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, and Lactobacillus bulgaricus) or seven strains (Streptococcus thermophilus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, and Lactobacillus paracasei) of gram-positive bacteria, along with feeder cells, significantly boosted the growth of NK and CD8+ T cells [86,87].

In individuals consuming Bifidobacterium, DCs showed increased expression of anti-tumor immunity-related genes, enhancing T cell activation [88,89]. Lactobacilli play a key role in stimulating immune responses by influencing DCs, NK cells, and Th1 cells [28,90–92]. Lactic acid bacteria boost host immunity by producing IL-2, which activates NK cells [93]. Consuming Lactobacillus acidophilus is associated with higher serum levels of IFN-γ, IL-10, and increased CD4+ and CD8+ T cells [94–96]. Oral administration of B. longum and B. breve to melanoma-bearing mice significantly reduced tumor volume, showing effects similar to PD-1 therapy alone. When combined with PD-1 therapy, these probiotics further reduced tumor volume [88,97]. Probiotic-fed humanized mice exhibited improved NK-mediated cytotoxicity, increased IFN-γ secretion across tissues, and reduced tumor load, and also restored bone formation [74,98,99]. Colorectal cancer patients experienced significant reductions in various cytokines when treated with probiotics [50]. In mice with breast tumors, oral L. acidophilus administration reduced tumor burden and affected cytokine production [100,101]. Lactobacillus plantarum and Lactobacillus salivarius show potential in preventing oral and colon cancers by modulating immune responses and suppressing COX-2 expression in tumors [102–104]. Bifidobacterium longum, Lactobacillus acidophilus, and Lactobacillus plantarum consumption has shown promise in preventing and inhibiting cancers like colon, breast, liver, intestines, lungs, oral cavity, and pancreas [28,50,89,94–96,103–116]. These findings highlight the potential of probiotics in cancer treatment, showcasing their ability to modulate immune responses for therapeutic benefits [111,114,115,117].

Probiotics also have shown efficacy as adjuvant therapeutics, offering protection against chemotherapy and radiation side effects like diarrhea, fever, and disruptions to intestinal microbiota in cancer patients. These advantages not only enhance patients' quality of life but also help prevent interruptions or halts in treatment [118–125]. These results highlight that probiotics not only provide

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therapeutic benefits against cancer but also improve outcomes when paired with other cancer treatments.

3. Probiotics Formulation to Restore Immune Function in Older Individuals

Aging brings about immunosenescence, characterized by a decline in both innate and adaptive immune functions, increased systemic inflammation, and alterations in the composition and diversity of gut microbiota [126,127]. It significantly affects innate immunity, causing changes in the number, characteristics, and functionality of immune cells, which are closely linked to various diseases and infections [128–136]. These changes increase susceptibility to infections, chronic diseases, and reduced vaccine effectiveness. In older adults, diminished immune function leads to higher risks of infections, cancer, autoimmune disorders, Alzheimer's disease, atherosclerosis, vision problems like age-related macular degeneration, cardiovascular issues, coronary heart disease, liver fibrosis, neurodegenerative diseases, and exposure to pathogens [133–138]. Additionally, cytokine levels, especially IFN-γ, are notably lower in the immune cells of older individuals [139,140].

The gut microbiota is essential for immune regulation, with aging-related dysbiosis playing a major role in immune dysfunction [141,142]. Probiotics can restore gut microbial balance, enhance innate immunity, such as natural killer (NK) cells, and regulate inflammation [8,143]. NK cells are thought to significantly influence longevity, as their proper function protects the elderly from infections, cancer, autoimmune disorders, and neurodegenerative diseases [133]. Aging leads to decreased NK cell function, contributing to age-related health issues [133–136]. NK cells are vital for fighting these illnesses and activating adaptive immune cells, ensuring a robust immune system in old age [129,140]. Additionally, NK cell proliferation declines in the elderly. Research by Chuang Guo et al. found that the proinflammatory CD52+ NK cell subset increases in older adults, facilitating infection spread [144]. Feeder cells, which support NK cell activation and growth, also lose effectiveness in older individuals due to reduced ligand expression and factor secretion [140]. However, in vitro treatment with probiotics, alone or with feeder cells, has restored NK cell numbers and function in the elderly [140]. Probiotic supplements have been found to moderately improve immune markers and boost NK cell function, an essential part of innate immunity, in healthy older adults [20]. Studies show that probiotics significantly enhance NK cell cytotoxic activity in individuals aged 60 and above, helping with early infection defense and tumor surveillance [145]. They also lower chronic low-grade inflammation, prevent infections, and promote healthy aging [145]. Probiotics increase anti-inflammatory cytokines like IL-10 and TGF-β while reducing pro-inflammatory markers such as IL-6 and CRP, combating chronic inflammation [12,146]. These treatments can activate T and B cells, improve immune monitoring, reduce the occurrence and severity of colds and gut infections, and strengthen vaccine responses [146].

The benefits vary depending on the probiotic strain used. Lactobacillus acidophilus helps balance gut bacteria and boost immunity during illness or antibiotic use [16]. Lactobacillus fermentum strengthens the immune system and helps prevent gastrointestinal and respiratory infections [147,148]. Lactobacillus casei/paracasei have anti-inflammatory properties, support the gut barrier, and aid in immune modulation [149]. Lactobacillus plantarum promotes immune response and reduces gut inflammation [150]. Lactobacillus rhamnosus enhances gut health, strengthens immune defenses, and eases digestive discomfort. Bifidobacterium longum reduces inflammation, protects against intestinal infections, and supports immune balance [151]. Bifidobacterium bifidum improves digestive health and boosts the immune system. Bifidobacterium lactis helps prevent infections and supports vitamin production [152]. For individuals over 60, typical probiotic doses range from 1 billion to 50 billion CFU (colony-forming units) daily, depending on the strain and health condition. Studies show supplementation duration usually varies between 3 to 12 weeks, with longer courses potentially needed for lasting effects [153]. Probiotic formulations can be single-strain or multi-strain combinations, often including both Lactobacillus and Bifidobacterium species for synergistic benefits. Probiotics are generally safe for healthy elderly individuals [153].

Gerobiotics are an intriguing new kind of probiotics and related biotics designed to tackle aging-related issues like cellular senescence, mitochondrial dysfunction, and chronic inflammation [154–156].

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They go beyond gut health, offering potential anti-aging and immune-boosting benefits [154]. Early studies suggest that strains like Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium longum, and Lactobacillus helveticus may help improve aging processes and strengthen immunity [157].

4. Probiotics Formulation for Autoimmune Disease Therapeutics

Autoimmune diseases occur when the immune system becomes overactive and mistakenly attacks the body's own tissues [158]. Studies show that gut microbiota dysbiosis, an imbalance in the intestinal microbial community, is connected to the onset and progression of autoimmune conditions such as type 1 diabetes, rheumatoid arthritis, lupus, and multiple sclerosis [158]. Probiotics offer a promising way to manage gut microbiota, restoring balance by promoting beneficial microbes and outcompeting harmful ones [159]. They help strengthen the gut barrier by improving tight junctions, reducing gut permeability ("leaky gut"), and lowering exposure to inflammatory triggers [160,161]. Probiotics also regulate immune responses by balancing T-helper cells (e.g., increasing anti-inflammatory Treg cells while reducing Th17/Th1-driven inflammation) and modulating cytokines (e.g., boosting IL-10 and TGF-β while decreasing TNF-α and IL-6) [23]. Additionally, they interact with immune cell receptors (TLRs) to refine immune activation and produce helpful metabolites like short-chain fatty acids (SCFAs) that reduce inflammation [162].

Various probiotic strains hold promise for supporting patients with autoimmune diseases through their differentiation effects [163]. Lactobacillus species such as L. casei, L. rhamnosus, L. acidophilus, and L. reuteri are known for their immunomodulatory and barrier-strengthening properties [157]. Bifidobacterium species, such as B. bifidum and B. animalis, promote Treg induction and help reduce pro-inflammatory responses [164]. Bacillus coagulans has been associated with easing arthritis symptoms and systemic inflammation [165]. Next-generation probiotics (NGPs), developed through sequencing and bioinformatics, leverage synthetic biology and gene editing for targeted therapeutic applications [166]. Probiotic formulations may involve single-strain or multispecies blends tailored to specific autoimmune conditions [167]. Research in animals and humans indicates probiotics can delay or prevent autoimmune diabetes in NOD mice, lower inflammatory cytokines, and reduce joint damage in rheumatoid arthritis [153,168]. They also improve gut microbiota composition in conditions like systemic lupus and multiple sclerosis. However, results vary based on strain, disease, and study design [169,170]. While meta-analyses highlight their adjunctive benefits, probiotics are not yet standard primary treatments [171]. The functional state of NK cells is crucial in infection control, disease progression, and prognosis. NK cell dysfunction has been linked to the development of autoimmune diseases, with changes in NK cell number or function impacting the entire immune system [133,172]. One study showed a probiotic formulation with three gram-positive bacterial strains enhanced IL-10 levels in PBMCs and NK cells, providing benefits for autoimmune diseases compared to other combinations [83].

Creating probiotic formulations for autoimmune disease treatment involves selecting strains with known immunomodulatory benefits, ensuring they survive and thrive in the right locations, and tailoring them to the host and microbiome's specific needs [173,174]. These formulations often blend strains like Lactobacillus, Bifidobacterium, and Bacillus, sometimes enhanced with technologies like nano-encapsulation or genetic engineering to improve their impact. While promising, current research indicates that probiotics are most effective as supplementary therapies rather than standalone treatments until more clinical studies are completed [173].

5. Probiotics Formulation for Neurodegenerative Disorder Therapeutics

Neurodegenerative diseases such as Alzheimer's, Parkinson's, Amyotrophic lateral sclerosis (ALS), and Huntington's are progressive conditions with complex origins, including protein buildup, oxidative stress, neuroinflammation, mitochondrial dysfunction, and immune system issues [175,176]. The gut microbiome significantly influences these diseases via the microbiota–gut–brain axis,

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impacting neuroinflammation, gut barrier integrity, immune responses, and neurotransmitter production [177–179]. Dysbiosis, or an imbalance in gut bacteria, is often observed in these disorders [173,180]. It includes an increased presence of pro-inflammatory strains like Streptococcus, Alistipes, Ruminococcus, Enterococcus, and Desulfovibrio, alongside a reduction in beneficial butyrate-producing bacteria such as Faecalibacterium, Lachnospira, Roseburia, Blautia, and Prevotella [173,180].

Probiotics provide therapeutic benefits by replenishing beneficial bacteria, boosting neuroprotective metabolites like butyrate, and offering anti-inflammatory and antioxidant effects [143,177]. They help maintain gut and blood-brain barrier integrity, influence neurotrophic factors and neurotransmitter pathways such as brain-derived neurotrophic factor (BDNF), serotonin, and gamma-aminobutyric acid (GABA), and support microglial balance [181–183]. Probiotics reduce proinflammatory pathways, enhance vagus nerve signaling for improved brain communication and emotional regulation, and combat oxidative stress through antioxidant defenses, which is vital for neurodegenerative disorders [184,185]. Moreover, they may prevent the buildup of harmful protein aggregates like amyloid-β and α-synuclein via immune modulation, improve gut barrier function, lower systemic proinflammatory endotoxins, and positively affect BDNF to promote neurogenesis and synaptic plasticity [8].

Combining multiple probiotic strains like Lactobacillus and Bifidobacterium species can synergistically improve motor and cognitive symptoms in Parkinson's disease models [186,187]. For effective results, a sufficient dose (usually ≥10^9 CFU per strain per dose) is crucial, and spore-forming bacteria like Bacillus subtilis add stability and improve gastrointestinal survival. Probiotic formulations targeting neurodegenerative diseases should aim to restore gut microbiome balance, enhance butyrate-producing bacteria, and reduce inflammation [188,189]. Studies have suggested the potential implications of probiotics in depression treatment [190]. Both clinical and preclinical studies highlight their exciting potential.

6. Conclusions

Probiotics are widely recognized for their positive impact on gut microbiota health, with recent studies highlighting their broader role in health and disease. They help restore immune function in aging and conditions like cancer, autoimmune, and neurodegenerative disorders. In cancer therapy, probiotics support immune balance and reduce chemotherapy and radiotherapy side effects. Combining probiotics with checkpoint inhibitors shows potential for improving patient outcomes. Research has shown probiotics can activate and expand anti-cancer immune cells such as NK and CD8+ T cells. They boost immune cell cytotoxic activity, IFN-γ secretion, CD8+ T cell numbers, and immune cell recruitment in tumors, enhancing the fight against cancer. Additionally, probiotics aid in restoring immune function in aging and other chronic diseases.

Conflicts of Interest: The authors declare that the work reviewed in this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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