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Review

Probiotics in the Management of Autoimmune Disorders (Multiple Sclerosis): A New Approach

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Abstract

The autoimmune disorders are distinguished by inflammatory processes mediated by the immune system, causing damage to target organs and leading to substantial morbidity and mortality. They affect the central and peripheral nervous systems, including the brain, spinal cord, peripheral nerves, and skeletal muscle. The gut-brain axis (GBA) helps in regulating the CNS function and the immune system via gut microbiota. The living microorganism probiotics have shown beneficial health effects when administered appropriately. They showed promising results in autoimmune disorders, like multiple sclerosis (MS) or neuromyelitis Optica (NMO), by regulating the immune system via modulating immune activity and decreasing inflammation. Yet, their actual clinical effectiveness is often limited due to their transit through the digestive system, which reduces their viability. The emergence of nanotechnology introduces a novel avenue for probiotic encapsulation and the enhancement of their effectiveness. The encapsulated probiotics in nanocarriers are released gradually in the intestine, improving absorption and colonization in the gut, enhancing gut-brain communication. Engineered probiotics could be a more precise approach to deliver therapeutics as they offer site-specific delivery and high accuracy compared to traditional drug delivery methods. In this review, we summarize the role of probiotics in the management of autoimmune CNS conditions, specifically, MS.

Keywords

Multiple sclerosis, Probiotics, Precision probiotics, Nanoparticles

Article History

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List of Abbreviations

Encephalomyelitis	EAE
Central Nervous System	CNS
Peripheral nervous system	PNS
Multiple Sclerosis	MS
Neuromyelitis Optica	NMO
Blood-Brain Barrier	BBB
Gut-brain axis	GBA
Colony forming Units	CFU

1. Introduction

The importance of the human gut microbiome in maintaining health and well-being is evident, as a growing body of evidence underscores that dysbiosis can contribute to the development of various diseases [1]. The gut microbiota influences various facets of brain development and function, impacting the maturation and polarization of microglia and astrocytes, the formation and permeability of the blood-brain barrier (BBB), neurogenesis, and myelination [2]. The term "gut-brain axis" (GBA) encompasses the complex interactions involving the intestinal microflora and is interconnected to the nervous and immune systems, establishing a communication link between brain activity and gut function [2-4]. The disruptions in GBA have surfaced in individuals diagnosed with autoimmune CNS disorders, indicating a potential involvement in the pathogenesis of the disease [5].

Autoimmune disorders are distinguished by inflammatory processes mediated by the immune system, causing damage to target organs and leading to substantial morbidity and mortality [6]. They target the nervous system and can impact different components, encompassing the brain and spinal cord (central nervous system, CNS), peripheral nerves, neuromuscular junction, and skeletal muscle (peripheral nervous system, PNS). These encompass demyelinating disorders of the CNS, e.g., multiple sclerosis, neuromyelitis optica, autoimmune encephalitis, CNS vasculitis, Opsoclonus-Myoclonus-Ataxia syndrome, Susac syndrome, Bechet disease, chronic inflammatory demyelinating polyneuropathy (CIDP), etc., [7,8].

Probiotics are live microorganisms that, when administered appropriately, trigger beneficial health responses within the host by reducing gut acidity, eradicating harmful bacteria, and generating short-chain fatty acids (SCFA) [9]. In recent decades, probiotics, e.g., *Bifidobacteria, Lactobacilli, and Saccharomyces,* have captured the attention of medical communities that serve as medicine for treating various diseases [10]. There are three types of Probiotics: bacteria-enriched foods, capsules with bacteria, and yeast. Foods like cheese, yogurt, snacks, ice cream, breakfast cereals, nutrition bars, and infant formulas often contain added probiotics. There is a market for probiotics in the form of lyophilized pills. The effective dose of viable probiotic bacteria ranges from 10^6–10^8 CFU/g colony-forming units (CFU) per gram or exceeds 10^8–10^{10} CFU/d per-day. Probiotics are obtained from bacteria, yeast, and fungi, among which most are found in gram-positive bacteria, as depicted in Figure 2. Among all the micro-organisms, *Bifidobacteria, Lactobacillus, and Lactococcus* species are generally regarded as safe (GRAS) and could be used for health purposes [11].

Extensive clinical trials have evidenced the capacity of probiotics to enhance outcomes in conditions related to the immune system and viral infections [12]. The consumption of probiotics enjoys broad support from the medical community, particularly among physicians specializing in gastroenterology [13]. Currently, probiotic-infused foods account for approximately 70% of the functional food market. Notably, the global probiotics market, valued at $4.62 billion in 2019, is anticipated to achieve a valuation of $7.59 billion by 2026 [12]. Probiotics have shown promise in regulating immune responses, potentially reducing inflammation, and modulating immune cell activity associated with autoimmune conditions, such as MS and NMO [14]. The viability of probiotics can be compromised by the harsh conditions of the digestive tract during the in vivo transportation process, posing a significant challenge. To address this issue, probiotic nanotechnology emerges as a valuable solution [15].

The emergence of nanotechnology introduces a novel avenue for probiotic encapsulation and the increment of their effectiveness [15,16]. The investigation into nanonization strategies for probiotics and the application of nanoprobiotics in delivering encapsulated bacteria is underway. The primary method employed for probiotic encapsulation involves using nanoparticles, specifically selenium and gold particles [11]. Nanofibers are emerging as novel techniques for probiotic delivery due to their greater porosity and surface area, thus protecting the bioactivity of encapsulating probiotics [15].

This review emphasizes the importance of probiotics in addressing autoimmune disorders that affect the CNS. It highlights the progress made in utilizing nanotechnology for the targeted delivery of probiotics to the CNS.

2. Methodology

2.1 Search Engine

All the data and the literature for the current manuscript are gathered from an online database, i.e., Google Scholar, PubMed, Science Direct, Springer, and Medline Plus up to June 2025. The keywords used for searching the data were “Probiotics, “Probiotics in autoimmune CNS disorders, “mechanism of probiotics in autoimmune CNS disorders, “probiotics in multiple sclerosis, “multiple sclerosis; “engineered probiotic, “probiotic nano-formulations,” etc.

2.2 Study Design

In the current study, the literature search was divided into two sections: one was the inclusion criteria, and the other was the exclusion criteria. The inclusion criteria were based on the following (i) Information (ii) Key search, (iii)

Formulation aspect of probiotics, (iv) Probiotics study including clinical trials (v) study based on autoimmune disorders, (vi) Engineered probiotics. The exclusion criteria include (i) Abstract only, (ii) Poster only, (iii) Editorial studies.

2.3 Data Extraction

The articles were carefully collected and reviewed, and relevant articles were extracted based on the manuscript's needs. Based on the manuscript titles, probiotics, autoimmune disorders, multiple sclerosis, probiotics in multiple sclerosis, precision probiotics, and probiotics mechanism, 60 articles were extracted. The selected articles from the study were reviewed carefully, and further 50 articles were taken for final review.

2.4 Results

Based on the relevance to the review topic, a total of 145 articles were initially selected by screening keywords, titles, and abstracts. Following a detailed review using predefined inclusion and exclusion criteria, 50 articles were finalized for data extraction. The remaining 95 articles were excluded after thorough evaluation as they did not meet the criteria for this review. As illustrated in Figure 1, these 145 articles were sourced from various databases. After careful assessment, only those studies that specifically focused on clinical trials involving probiotics, probiotics in autoimmune CNS disorders, probiotics in multiple sclerosis, probiotics nano-formulations, and precision and engineered probiotics were retained. Articles that did not meet these specific criteria were excluded.

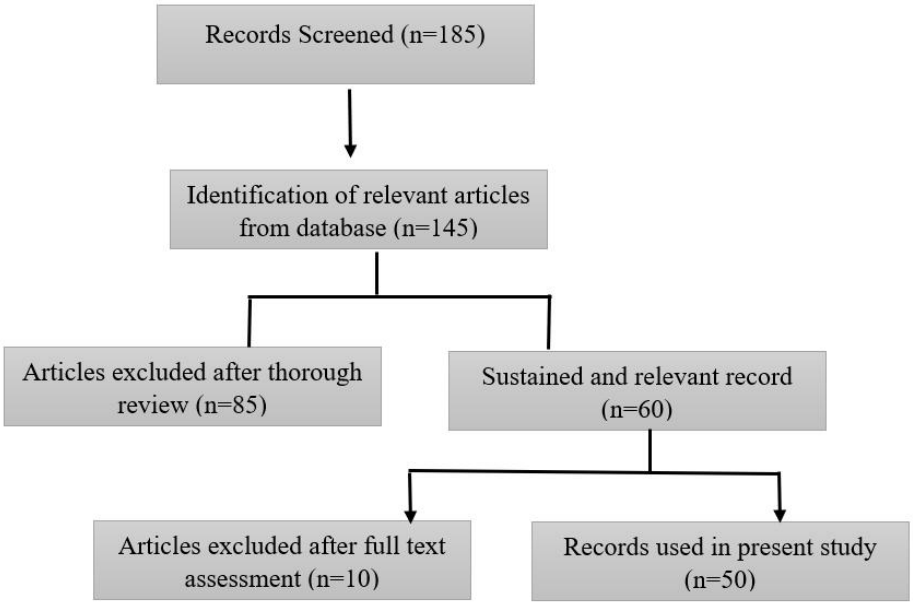

Figure 1. Methodology (Prisma chart) for data selection from different sources.

3. Probiotics in Autoimmune CNS Disorders (MS)

At present, the treatment options for MS primarily consist of corticosteroids, immunosuppressive, and immunomodulatory medications. Consequently, scientists and pharmaceutical firms globally are in pursuit of novel therapies and medications to combat MS. There is considerable focus on exploring the therapeutic benefits and inhibitory properties of probiotics across various neurological disorders like MS [5]. Probiotics serve as a supplementary treatment for autoimmune disorders. Additionally, animal studies indicate that probiotics can enhance CNS symptoms. In an open-labeled, randomized, two-center cross-over trial, the supplementation of probiotics in relapsing-remitting MS patients modestly improved bowel symptoms during 6 weeks, but showed no clinical benefits. The data could be used to gain mechanistic insights into dietary supplements in MS pathophysiology [17]. Figure 2 shows that probiotics can be obtained from different sources, like bacteria and fungi, e.g., *Bacillus, Streptococcus,* can be obtained from bacteria, whereas *Saccharomyces* species from fungi. Different types of bacterial and fungal probiotic sources are summarized in Figure 2.

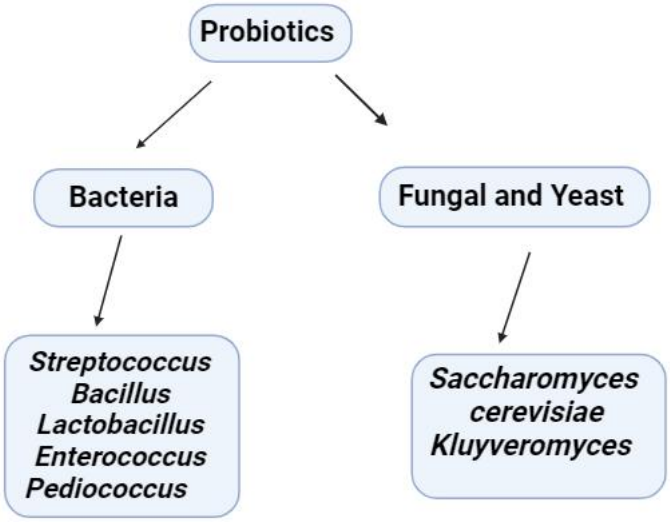

Figure 2. Sources and types of probiotics.

3.1 Probiotics Mechanism in Autoimmune CNS Disorders

Recent data strongly indicate a connection between gastrointestinal and CNS disorders. Probiotics influence immune function by activating signaling pathways that increase the production of anti-inflammatory cytokines and growth factors. They facilitate the differentiation of T-regulatory cells (Tregs) and engage with GBA through endocrine regulation and neurological functions (Figure 3) [11,18]. There is a pressing need for a more comprehensive understanding of the protective role played by probiotics in unveiling innovative mechanisms employed to stimulate regulatory T cells, offering potential avenues for treating systemic autoimmunity [19].

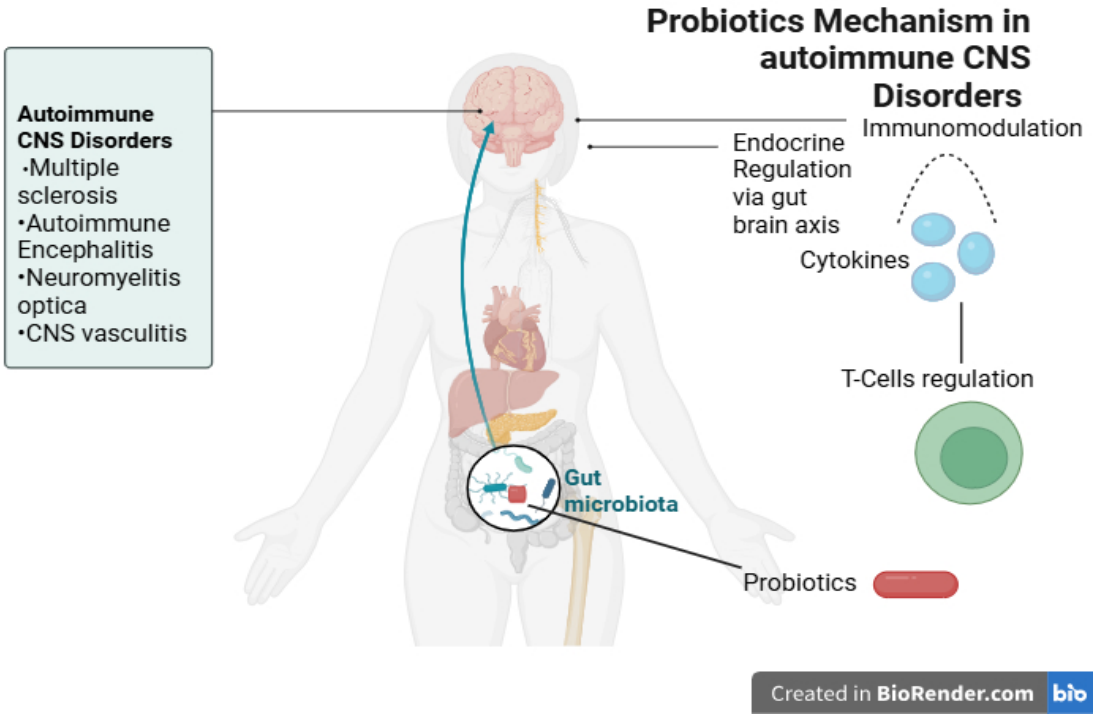

Figure 3. Probiotics in autoimmune CNS disorders.

3.2 Multiple Sclerosis (MS)

MS is a neurodegenerating autoimmune and inflammatory disorder causing demyelination and affecting about 2.5 million people worldwide [14,20,21]. MS predominantly impacts people in their 20s and 30s and stands as the foremost cause of neurological impairment among young adults [22]. Given the significant role of the gut microbiota in immune function and the emerging concept of the gut-brain axis, researchers have hypothesized that probiotics could benefit autoimmune diseases like MS [23]. Research into the effects of probiotics on MS is still in its early stages, and findings have been mixed. Some studies suggest that probiotics may reduce the frequency and severity of MS relapses, improve

quality of life, and modulate inflammation and neurological function biomarkers. However, other studies have found minimal to no significant effects [24]. Numerous investigations using animal models of MS have indicated that certain constituents of the gut's natural microbiota can either worsen or mitigate neuroinflammation.

Preclinical investigations have demonstrated that consuming probiotics lowers the occurrence and intensity of MS. Moreover, it has been observed to delay the progression of MS in 15 studies, enhance motor function in 3 studies, and bring about positive changes in immune and inflammatory markers in 20 studies. Additionally, alterations in intestinal microbiome compositions related to MS were observed in 4 studies [25]. The above research concludes that consuming probiotics in MS patients may be beneficial, as it delays disease progression and improves motor function. However, more research needs to be conducted to support the use of probiotics in MS patients.

Mestre and colleagues explored how *Vivomixx* impacts gut health as well as central and peripheral immune reactions in a mouse model of primary progressive MS. There was a noticeable enhancement in the motor function of mice infected with Theiler's virus; within the CNS, *Vivomixx* diminished microglial activation, astrocyte proliferation, and the infiltration of leukocytes. The probiotic limited the secretion of IL-17 by Th17-skewed CD4+ T-cells isolated from the mesenteric lymph nodes of mice infected with Theiler's virus. Our findings further support the beneficial impact of orally administered probiotics, which could serve as a supplementary treatment alongside existing therapies for MS [26]. The research highlights the role of probiotics as an adjunctive therapy in MS. The use of probiotics may offer a cost-effective and low-risk strategy in MS treatment via restoring microbial imbalance.

Consonni and associates' experimental work on experimental autoimmune myasthenia gravis (EAMG) and experimental autoimmune encephalomyelitis (EAE) in the Lewis rat model contributes valuable insights into the potential therapeutic applications of probiotics in autoimmune diseases. Results revealed that probiotics-induced immunomodulatory effects are significant and can influence the immune system in a way that may be beneficial for managing autoimmune conditions. The results show that treatment with *lactobacilli* and *bifidobacteria* can modulate the disease symptoms in EAMG and EAE models [27]. This study revealed that probiotics could be potentially used in autoimmune disorders as they improved the immunity and strengthened the immune system.

Asghari and colleagues demonstrated that a four-month regimen of *Saccharomyces boulardii* supplementation can significantly impact patients with MS. The research findings indicated a notable decrease in the levels of high-sensitivity C-reactive protein (hs-CRP) and an enhancement in total antioxidant capacity (TAC) serum levels among the subjects, in contrast to those who received a placebo. These results underline the potential of *Saccharomyces boulardii* as a supportive treatment option for mitigating clinical symptoms, inflammation, and oxidative stress in MS patients. Additionally, the probiotics' capacity to ameliorate mental health, fatigue, quality of life, and pain underscores its significant role in the comprehensive management of neuropsychological symptoms associated with MS [28]. This study highlights the potential of probiotics in MS patients as they reduce inflammation and oxidative stress, and improve mental well-being, thus improving overall quality of life.

In a study involving 9 MS patients and 13 healthy individuals, participants were given a probiotic blend containing strains of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* twice a day for two months. The administration of this probiotic formulation led to a notable increase in the population of gut microbiota such as *Lactobacillus*, which are often found in reduced numbers in individuals with MS. Conversely, the study observed a reduction in the populations of Akkermansia and Blautia, microorganisms linked to the gut dysbiosis characteristic of MS. Further insights were gained through predictive metagenomic analysis, which highlighted a decrease in the representation of certain Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. These pathways, related to methane metabolism among others, are typically altered in the gut microbiome of MS patients, suggesting a positive shift in gut microbiota functionality post-probiotic intervention. Moreover, the probiotic-induced enrichment of *Lactobacillus* and *Bifidobacterium* was correlated with a reduced expression of the MS risk allele HLA-DPB1 among the healthy control participants. This study highlights the potential of targeted probiotic therapy to modulate gut microbiota, improve immune responses, and possibly influence genetic risk factors associated with MS, marking a significant step toward understanding and managing the condition through gut microbiome interventions [29]. This research underscores how carefully selected probiotics can reshape the gut microbiome in ways that may benefit people with MS. The link between microbial changes and reduced expression of a known MS risk gene suggests that gut health could play a meaningful role in both managing symptoms and possibly influencing disease risk. Table 1 summarizes the role of probiotics in the management of MS by concluding the data from various research, preclinical, and clinical trials.

A meta-analysis by Tabatabaeizadeh and Tafazoli suggested that supplementation of probiotics improved the inflammatory and oxidative status in MS patients suffering with depression. The results from the study concluded the potential of probiotics as therapeutics in MS patients with depression symptoms and in alleviating inflammation. However, the study warrants more research to assess the relationship between MS, depression, and gut microbiome [30].

Table 1. Probiotics for the management of MS.

Probiotics	Research Outcomes	References
B. animalis, L. plantarum A7, and a combination of both in the MS experimental model. Dose: 10^9 CFU/mL	Amelioration in EAE condition by improving anti-inflammatory cytokines and cells like Interleukins (IL)-10, IL-4, T-regs, TGF-β, CD25+, CD4+, and Foxp3+ in spleen and lymph nodes. Additionally, there is an increase in T-reg (Foxp3) and Th2 (T-helper 2) (GATA3) in; the brain and spleen. A significant decrease in demyelination, inflammation, and leukocyte infiltration was found when a combination of both probiotics was used.	[31]
Probiotic Capsules	A 12-week intake of probiotics capsules enhanced the Expanded Disability Status Scale (EDSS) in MS patients compared with a placebo. A significant change in C-reactive protein, nitric oxide metabolite of plasma, and malondialdehyde was observed in comparison to placebo. A favorable effect on mental health factors, inflammatory factors, and cholesterol was observed with probiotic capsules.	[32]
Enterococcus durans (Edu) lactobacilli (Lacto-mix) strains- *L. rhamnosus*, *L. casei*, and *L. plantarum.*	A rise in inflammatory cell penetration and myelin sheath degradation among the Experimental Autoimmune Encephalomyelitis (EAE). Significantly high levels of pro-inflammatory cytokines, specifically Interleukin-17 (IL-17) and Interferon-gamma (IFN-γ), in brain and spinal cord supernatant tissues in the EAE group compared to the normal saline control group.	[33]
Lactobacillus strains, L. Paracasei DSM 13434 and L. Plantarum DSM 15312 *Group 1-L Plantarum; group2-L Paracasei; group 3- both probiotic; group 4- control*	A significant reduction in both the proportion of Th1 cells and the mean fluorescence intensity (MFI) of IFN-γ within Th1 cells (CD4+ IFN-γ+) when contrasted with the control group. A combination of probiotics showed anti-inflammatory effects and a significant reduction in CD4+ T cells and IL-17 secretions.	[34]
Bacillus Coagulans IBRC-M10791	A significant reduction in mouse-treated groups of genes, e.g., IDO-1, having a significant role in immune response and tolerance, NLRP1, NLRP3 involved in innate immune response, CYP27b1-critical for immune function, and AIM2-host defence against pathogens and in inflammatory diseases in comparison to the MS-induced mice group.	[35]
Lactobacillus casei strain T2 (IBRC-M10783) C57BL/6 mice: Group 1- normal saline; Group 2- cuprizone induced; Group 3, probiotic; Group 4- 4-week probiotic treatment; Group 5- 4-week treatment with cuprizone for 4 weeks, and Group 6-Vitamin D3 and cuprizone treated mice for 4wk.	A marked reduction in miR-155 expression in group 1 and group 2 mice. A significant decrease in IL-17 within probiotic and cuprizone-induced mice was noticed. L casei showed a significant decrease in proinflammatory cytokines and demyelinating symptoms involved in MS pathogenesis.	[36]
Streptococcus thermophilus	A marked decrease in pro-inflammatory cytokines secretion, i.e., IFN-γ and IL-1β, and a significant increment in anti-inflammatory cytokines expression, i.e., IL-5, IL-4, and IL-10. *Streptococcus thermophilus* could be beneficial in MS and other autoimmune disease treatments if consumed regularly.	[37]

4. Probiotics Nano-formulations

The promise of probiotics for treating various gastrointestinal and CNS conditions is significant. Yet, their actual clinical effectiveness is often limited due to numerous conditions, e.g., the reduced viability of probiotics when using conventional production and packaging techniques, and the lower effectiveness of probiotics due to several factors, including pH, oxygen presence, and temperature during their processing, storage, and transit through the digestive system. Therefore, for probiotics to deliver health benefits, they must withstand the acidic conditions of the stomach, remain active metabolically, and be released in sufficient quantities at the intended site [38]. The exploration of nanoformulation for a variety of nutraceuticals and probiotics has garnered attention because of the improved bioavailability it offers. Nanoformulations can change the solubility, stability, and permeability of probiotics [10,39]. Nanoformulations like nanofibers, nanobeads, and nanolayers created using the layer-by-layer technique, nanoparticles, and nanoemulsions have been developed and investigated to encapsulate probiotic bacteria [40]. The exploration of an engineering nanoformulation approach for probiotics presents a promising avenue for advancing therapeutic interventions in autoimmune CNS disorders. Our review has highlighted the potential of probiotics in modulating the GBA, thereby positively affecting the immune response and inflammation associated with autoimmune CNS conditions. Probiotic bacteria (*L. acidophilus)* nanoencapsulation using chitosan enhances bacteria's viability and survival rate in environmental conditions of the gastrointestinal tract [11]. The encapsulated probiotics in nanocarriers are released gradually in the intestine, improving absorption and colonization in the gut, enhancing gut-brain communication. Then, probiotics interact with the immune system and stimulate cytokines, T-regulatory cells, and dendritic cells, leading to reduced neuroinflammation and immune system regulation in the CNS. Thus, the released probiotics reach the CNS and relieve the oxidative stress and neuroinflammation in the brain, supporting the MS treatment. The mechanism of nanoformulations for the delivery of probiotics to the CNS is summarized in Figure 4.

Pandey and associates concentrated on the encapsulation of probiotics in nanoparticles and their survival under different conditions within the gastrointestinal tract. The studies evinced an improved viability of nanoparticles encapsulated probiotics over time compared to free probiotics [41].

Feher and associates in their laboratory and human studies examined that probiotic (Bifidobacterium longum and Lactobacillus acidophilus lysates) nanoparticles exhibit potential anti-inflammatory activities as they decrease pro-inflammatory cytokines release. The study summarized the use of nanoscale probiotics might represent a novel strategy for the prevention and management of neuroinflammation and associated neurological conditions [42].

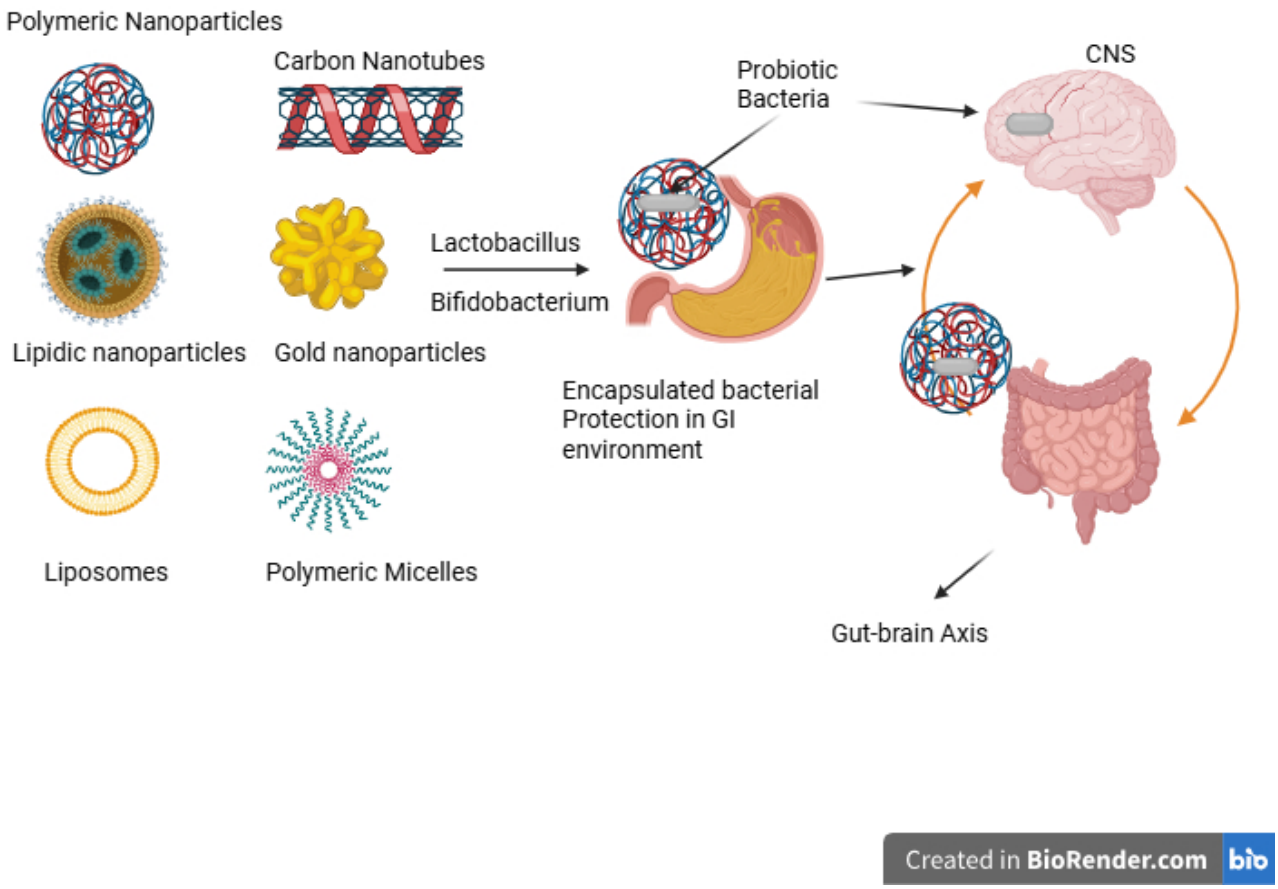

Figure 4. Mechanism of Probiotic encapsulated nano-formulation for their delivery to the brain.

5. Engineered Probiotics

Engineered probiotics refer to a new category of microorganisms created by altering the genetic makeup of existing probiotics through gene editing techniques [43]. Designer probiotics are customized to produce beneficial proteins, deliver biomaterials, eradicate infectious pathogens, and fight against cancers, infectious diseases, and metabolic disorders. Bioengineered probiotics with diverse immunogenic or antagonistic characteristics could serve as an effective means to enhance human health. These genetically modified bacteria are designed to precisely deliver medications, therapeutic proteins, or gene therapy vectors, offering a higher level of site-specific accuracy compared to traditional drug delivery methods [23,44]. Modified bacteria can target affected tissues or organs, identify unique biomarkers within the disease setting, and even induce a specific state. Additionally, a carefully constructed intracellular metabolic pathway can turn on or off specific gene expressions, produce biologically active therapeutic agents, and accurately transport medications to the targeted diseased tissues or organs. *Lactococcus* (*L. lactis*), *Salmonella (S. typhi*), and *E. coli* (*E. coli Nissle*) rank among the most extensively researched engineered microbes utilized for drug delivery [45]. The anti-inflammatory cytokine IL-10 plays a pivotal role in moderating inflammatory responses and is a focus for the development of genetically modified probiotics.

Around 100 million nerve cells connect the gastrointestinal tract to the base of the brain via the vagus nerve, enabling signals from gut microbes to affect various behavioral and physiological responses. Lactate, secreted by activated dendritic cells (DCs) and other immune cells, enhances NDUFA4L2 expression through a process driven by HIF-1α. NDUFA4L2 curtails the creation of mitochondrial reactive oxygen species, which activate XBP1-regulated transcriptional frameworks in DCs that manage pathogenic autoimmune T cells. Dendritic cells play a crucial role in preventing the formation of self-reactive, harmful T cells, making them a promising focus for the treatment of autoimmune disorders. Thus, the genetically modified probiotic that generates lactate and mitigates T-cell autoimmunity in the central nervous system through the activation of the HIF-1α/NDUFA4L2 signaling pathway in dendritic cells could be a beneficial approach in the treatment of autoimmune disorders and MS [46].

When expressed in *L. lactis*, heat shock proteins (specifically Mycobacterium Hsp65) function as immunomodulatory elements by acting as autoantigens and supporting the survival of regulatory T cells (Tregs), thereby protecting both Experimental Autoimmune Encephalomyelitis (EAE) and DSS-induced colitis (Gomes-Santos et al., 2017). Figure 5 reveals the mechanism of probiotics for targeting neuroinflammation that involves various microbial factors, like colonization factor antigen I (CFA/I) fimbriae or polysaccharide A (PSA), that encourage the development of immunoregulatory cell subsets. These actions adjust the balance between inflammatory and immunoregulatory cells through the inhibitory impacts on antigen-presenting cells (APCs), or by directly aiming at proinflammatory cell groups with anti-inflammatory cytokines, thereby (1) suppressing experimental inflammatory demyelination. (2) Probiotics are also noted for their ability to restore intestinal balance by adjusting the microbiota composition. (3) Additionally, designing probiotics to boost the production of other metabolites, including neurotransmitters, may influence the neurobiology of central nervous system (CNS) inflammatory diseases. (4) This overview encompasses antigen-presenting cells (APCs), regulatory B cells (Breg), colonization factor antigen I (CFA/I) of enteroxigenic Escherichia coli, short-chain fatty acids (SCFAs), central nervous system (CNS), 5-hydroxytryptamine (5-HT), interleukins (IL), interferons (IFN), natural killer T cells (NKT), polysaccharide A (PSA), and transforming growth factor (TGF) [47].

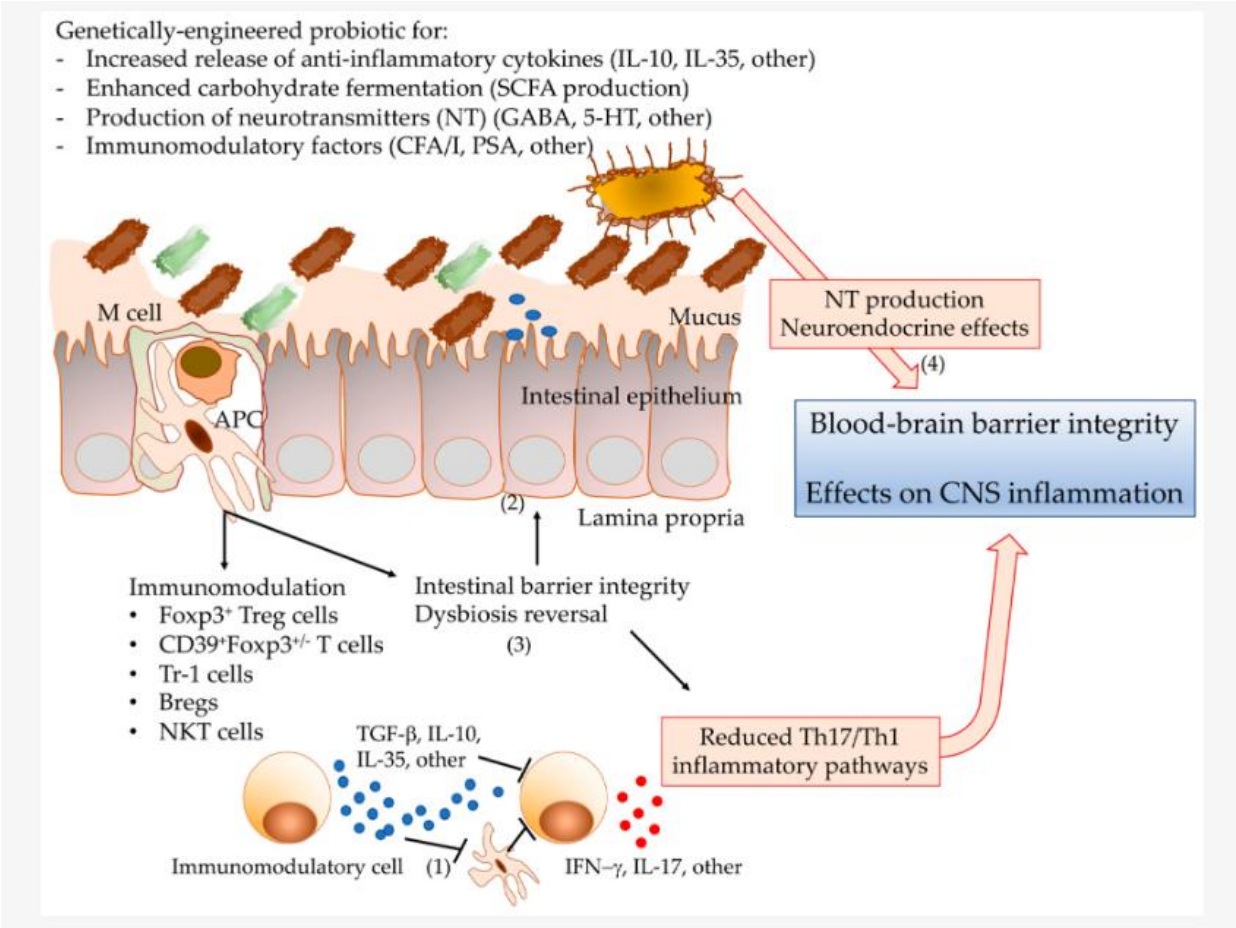

Figure 5. Potential mechanisms of probiotics for targeting neuroinflammation. (1) suppressing experimental inflammatory demyelination. (2) Probiotics are also noted for their ability to restore intestinal balance by adjusting the microbiota composition. (3) Additionally, designing probiotics to boost the production of other metabolites, including neurotransmitters, may influence the neurobiology of central nervous system (CNS) inflammatory diseases. (4) This overview encompasses antigen-presenting cells (APCs), regulatory B cells (Breg), colonization factor antigen I (CFA/I) of enterotoxigenic Escherichia coli, short-chain fatty acids (SCFAs), central nervous system (CNS), 5-hydroxytryptamine (5-HT), interleukins (IL), interferons (IFN), natural killer T cells (NKT), polysaccharide A (PSA), and transforming growth factor (TGF). Reproduced from an open-access journal under the terms of Creative Commons Attribution [47].

6. Limitations of Probiotics for Autoimmune Disorders

Despite the promising therapeutic potential of probiotics, several limitations hinder their clinical applicability in autoimmune disorders. Firstly, the strain-specific effects of probiotics pose challenges in standardizing treatment protocols, as not all strains exert the same immunomodulatory benefits. Secondly, variations in individual microbiota composition significantly influence probiotic efficacy, making it difficult to predict therapeutic outcomes across different patient populations. Thirdly, the viability of probiotics can be compromised during processing, storage, and passage through the gastrointestinal tract, limiting their bioavailability and therapeutic action. Furthermore, long-term safety data are still limited, especially concerning immunocompromised patients, where probiotics may cause infections such as bacteraemia. Additionally, most available studies are preclinical or of small sample size, leading to insufficient evidence to support broad clinical recommendations. Regulatory frameworks and quality control for probiotic formulations also remain inconsistent, contributing to variability in effectiveness and safety.

7. Clinical Trials

Multiple clinical studies have explored the effects of probiotics on central nervous system (CNS) disorders, particularly autoimmune conditions like multiple sclerosis (MS). In a randomized clinical trial, Asghari et al. (2023) demonstrated that a four-month supplementation of Saccharomyces boulardii led to reduced high-sensitivity C-reactive protein (hs-CRP) levels and increased total antioxidant capacity (TAC) in MS patients [28]. In preclinical and clinical trials, Zangeneh et al. (2025) demonstrated that consumption of probiotics like *Prevotella*, *Lactobacillus, and Bifidobacterium* can reduce the severity of MS in the EAE animal model. Single or multiple probiotics showed a decrease in disease severity in all human trials [48]. Trager and associates conducted a 6-week cohort study in MS patients with a *Lactobacilli*-rich probiotic supplementation. The results demonstrated an increase in the regulatory immunophenotype

in people with MS after supplementation of *Lactobacilli*. The study concluded that probiotics can be used as supplements or adjunctive therapy in autoimmune disorders, such as MS [49]. The review warrants more clinical trials to evaluate the safety and efficacy of probiotics in autoimmune diseases, particularly in MS.

8. Future Aspects

The future of probiotics for autoimmune CNS disorders like MS appears bright, with advances in personalized medicine, bioengineering, and a deeper understanding of the gut-brain axis paving the way for innovative and more effective treatments. These developments promise to enhance our ability to manage such disorders, offering hope for improved quality of life for affected individuals. As probiotics become a more integral part of treating autoimmune CNS disorders, educating healthcare professionals and patients about their potential benefits, limitations, and the science behind them will be crucial. This includes understanding which strains are beneficial, how they should be administered, and what outcomes can be expected. As interest in probiotics for CNS autoimmune disorders grows, there will be an increase in clinical trials aimed at assessing their safety, efficacy, and mechanisms of action. This will necessitate the development of specific regulatory frameworks to ensure that these new types of treatments are both safe and effective for patients. Advances in genomics and microbiomics will likely enable the development of personalized probiotic treatments. By analyzing an individual's microbiome and genetic makeup, treatments could be tailored to modulate the immune system in a way that is most beneficial for their specific condition, potentially improving efficacy and reducing side effects.

An exciting frontier in this field is the use of nanoformulations of probiotics, which enhance bacterial survival through the gastrointestinal tract and improve targeted delivery to the CNS. By encapsulating probiotics in nanocarriers—such as chitosan, gold, or selenium nanoparticles—researchers aim to protect their viability and ensure sustained release at the desired site of action. This targeted delivery system could significantly boost their clinical efficacy in modulating immune responses and reducing neuroinflammation in MS. Additionally, engineered probiotics and nanoscale delivery systems may work synergistically to improve strain specificity, immune modulation, and therapeutic outcomes. As research progresses, nanoencapsulation strategies are likely to be tailored based on individual patient microbiomes and disease profiles, aligning with the principles of precision medicine.

It will be critical to conduct rigorous clinical trials to validate the efficacy and safety of these probiotic-based therapies. Furthermore, personalized medicine approaches, considering individual variations in microbiome composition and immune system functioning, may enhance the effectiveness of these interventions.

9. Conclusion

The current review underscores the potential of probiotics in autoimmune CNS disorders, specifically in MS. The study examined the role and mechanism of probiotics in preclinical and clinical trials, as well as their potential in alleviating neuroinflammation, oxidative stress, and enhanced regulatory T cell activity. Engineered probiotics take this a step further by being tailored to deliver targeted anti-inflammatory molecules, modulate specific immune pathways, or even produce neuroprotective compounds within the gut. Also, the use of nano-formulation for probiotic encapsulations to improve their efficacy and safety showed promising results in the delivery of probiotics and in alleviating the symptoms associated with MS. However, more research and clinical trials are needed to validate the efficacy or therapeutic effects of probiotics in MS and related disorders.

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