



Major aspects of gut microbiota, probiotics and immunomodulation in patients with multiple sclerosis: a systematic review

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Abstract

Introduction: Multiple sclerosis (MS) is an autoimmune neurodegenerative disease that affects young adults. The etiology of MS is complex, involving various environmental and genetic factors. The gut microbiota plays a central role in the gut-brain axis (GBA). Modulation of the gut microbiota through probiotics and nutrients is considered a fundamental aspect in the treatment of MS. **Objective:** This study aimed to present the nutritional importance of probiotics and nutrients in immunomodulation in patients with multiple sclerosis. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was carried out from March to May 2025 in the Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 154 articles were found. A total of 39 articles were fully evaluated and 14 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 31 studies with a high risk of bias and 24 studies that did not meet

GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with $X^2=89.5\%>50\%$. It was concluded that interference in the composition of the gut microbiota of patients with multiple sclerosis allows the development of diagnostic tools and personalized adjuvant therapy. Diets rich in fruits, yogurt, and vegetables can reduce the risk of onset and progression of MS. Furthermore, the Mediterranean diet and the ketogenic diet have shown the potential to reduce inflammation, supporting neuroprotection. Tregs can potentially decrease the migratory capacity of effector cells to the central nervous system. These results suggest that Tregs can be used as a therapeutic opportunity. Oral administration of butyrate, propionate, and acetate, individually or in combination, led to an increase in the number of Treg cells in the colon. Also, all-trans retinoic acid (atRA), a bioactive form of vitamin A, stimulates Treg cells in the human gut. Probiotics, together with gut microbiota, have been increasingly proposed for the stimulation of Treg cells.

Keywords: Gut microbiota. Probiotics. Immunomodulation. Multiple sclerosis.

Introduction

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease that affects young adults. The etiology of MS is complex and involves a variety of environmental and genetic factors. The gut microbiota plays a central role in the gut-brain axis. Modulating the gut microbiota through probiotics and nutrients is considered a fundamental aspect of MS treatment. This therapeutic approach operates through several mechanisms, including strengthening intestinal epithelial integrity, increasing host resistance to pathogenic microorganisms, and facilitating mucosal immunomodulatory processes [1-3].

In this context, regulatory T cells (Tregs) are capable of suppressing autoreactive immune cells, which drive MS pathology. However, Tregs are functionally impaired in people with MS. It has recently been reported that Tregs also have regenerative capacity. Therefore, experts agree that Treg cell therapy has the potential to improve the disease. However, to perform their local anti-inflammatory and regenerative functions in the brain, they must first migrate across the blood-brain barrier [4].

Also, immunomodulation and regenerative processes for the control and treatment of multiple sclerosis progression, regulatory T cells (Tregs) correspond to a minority subpopulation of T cells that have the ability to induce suppression of effector T cells. Tregs are, in fact, fundamental cells in preventing autoimmunity [4,5].

The introduction of Bifidobacterium, one of the most commonly used probiotics, not only colonizes the gut but also alters the entire microbiota landscape. This treatment was found to activate the anti-CTLA-4 antibody, a checkpoint inhibitor that often causes autoimmunity in humans undergoing cancer treatment. This effect is due to the effect of this probiotic treatment on CD4+ regulatory cells, whose metabolic and immunosuppressive functions are altered. These CD4+ regulatory T cells are known to be a key mechanism in controlling autoreactivity in the immune system in humans [6-8].

The most attractive inhibitors in both scientific research and clinical applications include cytotoxic lymphocyte-associated T molecule (CTLA-4), programmed cell death receptor-1 (PD-1), and programmed cell death ligand-1 (PD-L1) [9-12], but with low success. Thus, new strategies, such as the action of probiotics on the activation and regulation of Tregs, are urgently needed to improve host responses and outcomes of immune checkpoint inhibition therapy [5].

Although many new immune control molecules and pathways have been explored to increase the

efficacy of existing immune checkpoint blockade therapy, they may result in an increase in the incidence and severity of immune-related adverse events [13]. However, emerging evidence supports that the efficacy of immune checkpoint blockade therapy strongly correlates with the basal gut microbiota of recipients [14-16]. Interestingly, dysbiotic gut microbiota has been implicated in ineffective multiple sclerosis therapies [17,18], while "healthy" gut microbiota often leads to beneficial immunotherapy outcomes [19,20].

As a corollary of this, modulation of the gut microbiota combined with the inhibition of immune checkpoints could be a promising and powerful strategy for the development of new-generation treatments [21,22]. Probiotics have attracted much attention due to their strong ability to modulate gut microbiota to promote intestinal or host health. Exogenous probiotics can directly or indirectly produce beneficial metabolites in vivo to activate and promote the immune response [23-25]. Therefore, this systematic literature review study sought to present the nutritional importance of probiotics and nutrients in immunomodulation in patients with multiple sclerosis.

Methods

Study Design

This study followed an international systematic review model, adhering to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Available at: <http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1>. Accessed on: April 7, 2025. Methodological quality standards from AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) were also followed. Available at: <https://amstar.ca/>. Accessed on: April 7, 2025.

Data Sources and Search Strategy

The literature search process was conducted from March to May 2025 using Scopus, PubMed, LILACS, EBSCO, SciELO, and Google Scholar, covering scientific articles from various periods up to the present. The following descriptors (DeCS /MeSH terms) were used: "Gut microbiota," "Probiotics," "Immunomodulation," and "Multiple sclerosis," employing the Boolean operator "AND" between MeSH terms and "OR" between historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low based on risk of bias, clarity of comparisons, precision, and consistency of analyses. Priority was

given to systematic reviews or meta-analyses of randomized clinical trials, followed by randomized clinical trials themselves. Low evidence quality was attributed to case reports, editorials, and brief communications, in accordance with the GRADE instrument. Risk of bias was assessed using the Cochrane tool via funnel plot analysis (sample size versus effect size) and Cohen's d test.

Results and Discussion

Summary of Findings

A total of 154 articles were identified and subjected to an eligibility analysis, with 14 studies ultimately selected for inclusion in the results of this systematic review. The selected studies demonstrated moderate to high quality (Figure 1), based on the level of scientific evidence associated with study designs such as meta-analyses, consensus statements, and randomized, prospective, and observational studies. Bias did not compromise the scientific foundation of the studies. According to the GRADE instrument, the majority of studies showed homogeneity in their results ($X^2 = 89.5\% > 50\%$). Based on the Cochrane risk-of-bias tool, the overall assessment identified 31 studies with a high risk of bias, while 24 studies failed to meet the criteria for GRADE and AMSTAR-2.

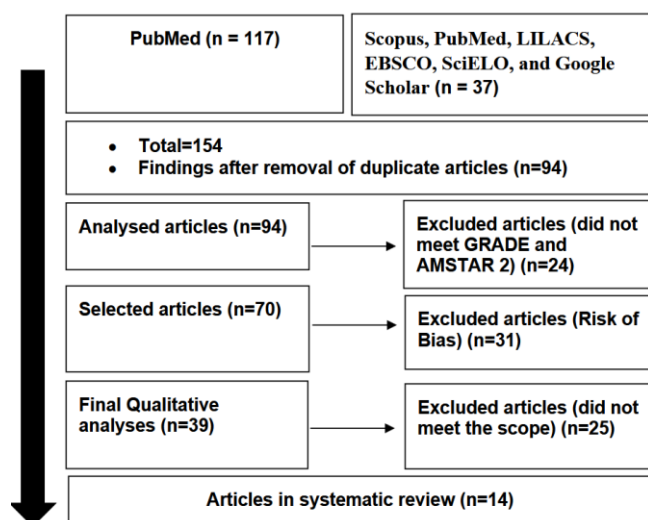


Figure 1. Flowchart showing the article selection process. Source: Own Authorship.

Figure 2 presents the results regarding the risk of bias across the studies using a funnel plot, showing the calculation of effect size (magnitude of difference) via Cohen's d. Precision (sample size) was determined indirectly as the inverse of the standard error (1/Standard Error). The plot exhibited a symmetrical pattern, suggesting no significant risk of bias among either studies with small sample sizes (lower precision), shown at the base of the plot—or studies with large sample sizes, shown at the top.

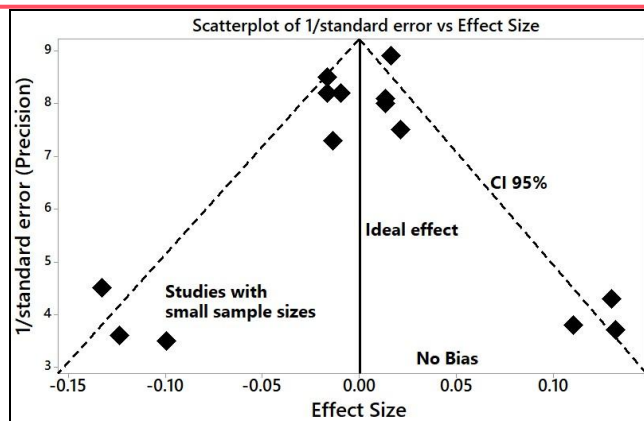


Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small-sample-size studies shown at the bottom of the plot. Studies with high confidence and strong recommendations are shown at the top of the plot (n=14 studies). Source: Own Authorship.

Nutrological Importance of Probiotics and Nutrients in Immunomodulation in Patients with Multiple Sclerosis (MS)

MS is characterized by neurodegeneration, axonal damage, demyelination, and inflammation. Gut dysbiosis has been linked to MS and other autoimmune conditions. The gut microbiota plays a vital role in regulating immune function, influencing immune cell development, cytokine production, and intestinal barrier integrity. Research shows that diets high in saturated fat are associated with disease progression. Diets rich in fruits, yogurt, and legumes may reduce the risk of MS onset and progression. Furthermore, the Mediterranean and ketogenic diets have demonstrated potential to reduce inflammation and support neuroprotection. By restoring microbial balance, probiotics may also help mitigate the immune dysfunction observed in MS [26].

The gut-brain axis (GBA) refers to the multifactorial interactions between the gut microbiota and the nervous, immune, and endocrine systems, linking brain activity and gut functions. Alterations in the GBA have been identified in people with MS, suggesting a potential role in the disease's pathogenesis and making it a promising therapeutic target. Studies have revealed that MS patients are more likely to exhibit altered gut microbiota, altered levels of short-chain fatty acids, and increased intestinal permeability. Probiotic supplementation may improve cognitive, motor, and mental behaviors through the modulation of GBA molecular pathways [27].

MS is an autoimmune disease characterized by T-cell-mediated demyelination and neurodegeneration of the central nervous system (CNS), with a multifactorial etiology. The autoimmune view of MS is strongly

supported by the use of the experimental animal model of autoimmune encephalomyelitis, which exhibits some of the key characteristics of MS. For example, during the activation phase, antigen-presenting cells migrate to lymph nodes and present the immunodominant peptide to naive T cells via major histocompatibility complex (MHC) molecules [1-3].

In this context, class II-restricted CD4⁺ T cells secrete numerous inflammatory cytokines, such as IFN- γ , TNF- α , IL-6, and IL-17. During the effector phase, antigen-recognizing CD4⁺ T cells proliferate, cross the blood-brain barrier, and subsequently activate macrophages and microglia, leading to demyelination, oligodendrocyte death, and axonal degeneration. As the disease progresses, remyelination and oligodendrocyte regeneration become inefficient and ultimately fail, resulting in disease progression. Several drugs used to treat MS have proven effective in reducing immune responses; however, their impact on long-term disease progression, the accumulation of irreversible neurological disability, and immune system function remains unclear. The limitations of immunomodulatory pharmacological treatments stem from both the relatively non-specific inhibition of immune responses—leading to immunosuppression, and the inability to repair myelin-damaged lesions in affected tissues [3,4].

Although the relationship between nutrients, fasting, and autoimmune diseases is only just beginning to be understood, dietary treatment for MS and other autoimmune diseases holds great potential, as it can stimulate and harness the body's ability to repair and replace damaged cells without interfering with the function of normal cells and systems [2-4].

The specific mechanism by which symbionts stimulate the accumulation of Tregs is not fully understood. It is believed that *Clostridia spp.* may act synergistically to stimulate Treg induction. One proposed mechanism of action is the cooperative production of short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, through the fermentation of dietary fiber by commensals, including *Clostridium spp.* and *Bacteroides spp.*, in the colon. SCFAs are absorbed via passive diffusion and H⁺-coupled active transport—mediated by MCT1 (SLC16A1) and MCT4 (SLC16A3), two electroneutral monocarboxylate transporters, or via Na⁺-coupled electrogenic monocarboxylate transporters, SMCT1 (SLC5A8) and SMCT2 (SLC5A12) [28].

Oral administration of butyrate, propionate, and acetate, either individually or in combination, led to an increase in the number of colonic Treg cells [29]. Butyrate is known to participate in Treg differentiation

by facilitating histone H3 acetylation at the promoter region and the CNS1 and CNS3 elements of the Foxp3 gene [30]. Recognition of butyrate by G protein-coupled receptors—such as GPR43 and GPR15, expressed by colonic Treg cells, and GPR109A, expressed by DCs and macrophages [28-30], also promotes Treg differentiation. Interestingly, treatment with SCFAs increased the number of Helios⁺ Tregs, indicating that SCFAs also promote the expansion of tTregs [29].

The aryl hydrocarbon receptor (AhR) is a nuclear sensor expressed by Tregs that helps them detect and respond to compounds acting as AhR ligands. Intestinal pTregs exhibit higher AhR expression than Tregs in any other tissue. Dietary tryptophan, an essential amino acid, is metabolized by IDO (indoleamine 2,3-dioxygenase) and TDO (tryptophan 2,3-dioxygenase). Kynurenine enhances the generation of Foxp3⁺ Tregs *in vitro* in the presence of TGF- β 1. *Lactobacillus spp.* can also metabolize tryptophan into various AhR ligands [31].

Another dietary metabolite that drives Treg cell development in the intestine is all-trans retinoic acid (atRA), a bioactive form of vitamin A. Dietary vitamin A—specifically retinol—is absorbed by intestinal epithelial cells via passive diffusion. Although epithelial cells are capable of synthesizing atRA from dietary vitamin A—a process regulated by commensal bacteria—the vast majority of studies to date have focused on dendritic cells, macrophages, and eosinophils as sources of atRA for iTreg induction [32].

Also, atRA has been reported to suppress the IL-6-induced conversion of Foxp3⁺ Tregs into inflammatory Th17 cells, a mechanism likely mediated by the retinoic acid receptor α . While vitamin A plays the most prominent role in Treg development, other vitamins also affect this lymphocyte population. Dietary D3 vitamin is metabolized into 1,25-dihydroxyvitamin D3, which binds to the D vitamin receptor element within the non-coding CNS region (spanning nucleotides +1714 to +2554) of the human FOXP3 gene. FR4, the receptor for B9 vitamin (folic acid), is highly expressed by Tregs and is known to promote the survival of intestinal Tregs through the upregulation of the anti-apoptotic factor BCL2 [32].

In this context, mucosal surfaces are distinct sites exposed to environmental, dietary, and microbial antigens. Particularly in the gut, the host continuously and actively adapts through complex interactions involving the microbiota, dietary compounds, immune cells, and other tissues. Tregs are essential for fine-tuning the intestinal immune response to both self and

non-self-antigens within the gut. Their importance in intestinal homeostasis is illustrated by the onset of overt inflammation resulting from deficiencies in Treg generation, function, or stability in the intestine. A substantial imbalance in Tregs was observed in intestinal tissue during pathological conditions, when a tightly regulated and balanced system becomes dysregulated, leading to chronic and unchecked immune responses [33].

Human CD4⁺ Treg cells are characterized by the expression of the forkhead box P3 (FOXP3, scurfin) transcription factor, high surface expression of CD25, and low or absent expression of CD127. Tregs express high levels of CD25 (the IL-2 receptor α -chain) due to their high dependence on interleukin-2 (IL-2) for development, maintenance, and peripheral homeostasis [4].

It has been demonstrated that Treg numbers and functions are altered in people with MS. Lower Treg numbers have been detected in peripheral blood samples from MS patients. Depending on treatment or disease status, Tregs can be identified in some, but not all, MS lesions. In contrast, an increased number of Tregs has been identified in the cerebrospinal fluid (CSF) of people with MS, although these were predominantly CD95-high cells prone to apoptosis. Tregs from people with MS are less immunosuppressive compared to those from healthy controls, thereby triggering autoreactivity and CNS inflammation [34]. A crucial factor linked to this suppressive dysfunction is the reduced expression of the FOXP3 transcription factor in Tregs. Additionally, regulatory B cells (Bregs) function similarly to Tregs, suppressing inflammatory immune responses in healthy individuals [35].

Finally, Breg dysfunction has been implicated in MS. This is characterized by reduced IL-10 production *in vitro* and a reduced number of IL-10-producing cells. Suppression of Th1 effector cells by Bregs was also found to be dysfunctional in people with MS. Consequently, Breg dysfunction likely contributes to the development or maintenance of MS [35].

Conclusion

It has been concluded that modulating the gut microbiota composition in patients with multiple sclerosis enables the development of diagnostic tools and personalized adjuvant therapies. Diets rich in fruits, yogurt, and legumes may reduce the risk of MS onset and progression. Furthermore, the Mediterranean and ketogenic diets have demonstrated the potential to reduce inflammation and support neuroprotection. Regulatory T cells (Tregs) have the potential to diminish the migratory capacity of effector

cells toward the central nervous system. These findings suggest that Tregs could represent a therapeutic opportunity. Oral administration of butyrate, propionate, and acetate—either individually or in combination—led to an increase in the number of Tregs in the colon. Additionally, all-trans retinoic acid (atRA), a bioactive form of vitamin A, stimulates Tregs in the human gut. Probiotics, in conjunction with the gut microbiota, have increasingly been proposed as a means to stimulate Tregs.

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