

## The Gut-Brain Axis in Multiple Sclerosis: A Systematic Review of Microbiome Modulation and Neurological Outcomes.

S. Murugesan<sup>1</sup>, T. Arunprakash<sup>2</sup>, P.S. Yogitha<sup>3</sup>, M R Suchitra<sup>4\*</sup>

<sup>1</sup>Professor, Department of neurology, Mahatma Gandhi medical college and research institute, Sri Balaji Vidyapeeth (deemed to be university), Pondicherry, India. drsmneuro99@gmail.com. <https://orcid.org/0000-0002-8373-7731>

<sup>2</sup>Associate Professor, Department of neurology, Mahatma Gandhi medical college and research institute, Sri Balaji Vidyapeeth (deemed to be university), Pondicherry, India. drarunt@gmail.com. <https://orcid.org/0000-0001-9161-0389>

<sup>3</sup>Research scholar, Department of chemistry and biosciences, SASTRA(SRC) Kumbakonam, India. yogithapsy@gmail.com-  
<https://orcid.org/0009-0000-5525-9405>

<sup>4\*</sup>Assistant Professor, Department of chemistry and biosciences, SASTRA(SRC) Kumbakonam, India. dietviji@yahoo.com <https://orcid.org/0000-0001-6055-7589>

Correspondence to

M.R.Suchitra, dietviji@yahoo.com, <https://orcid.org/0000-0001-6055-7589>

### KEYWORDS

membrane technology, gut microbiome, multiple sclerosis

### ABSTRACT:

**Background:** The disease multiple sclerosis (MS) is an autoimmune chronic disorder that afflicts the central nervous system with demyelination and is associated with a variety of neurological symptoms. Increasing research interest is focused on the gut-brain axis, which constitutes a communication network between the gastrointestinal tract and the central nervous system, especially regarding the modulation of immune responses and the influence on neurological health.

**Objective:** The current systematic review looks to establish whether alterations in the human microbiome due to dietary change, probiotics, and prebiotics relate to neurological effects in patients with multiple sclerosis via the gut-brain axis.

**Methods:** The inclusion criteria will be original research articles that include randomized controlled trials, cohort studies, case-control studies, and observational studies on human subjects with all types of MS. The studies should report neurological outcomes such as symptoms, disease progression, and biomarkers of neuroinflammation. Articles published within the last ten years will be included, while animal studies, non-pertinent neurological disorders, and those lacking relevant methodologies will be excluded.

**Results:** The review synthesized the effects of microbiome modulation on immune responses, focusing on cytokine production and inflammatory cell activation. Preliminary findings suggest that dysbiosis exacerbates neuroinflammation and contributes to disease progression. Therapies targeting the gut microbiome, such as probiotics, prebiotics, and fecal microbiota transplantation, show potential for improving clinical outcomes, although results remain variable. The variability of individual microbiota, lack of robust clinical trials specifically for MS, and concerns regarding safety and efficacy of these interventions present significant challenges. Membrane technology enhances the study of the gut-brain axis in multiple sclerosis (MS) by enabling the isolation of gut-derived biomolecules, which influence immune responses and neuroinflammation. This integration offers insights into microbial signatures and potential therapeutic interventions, paving the way for innovative treatments targeting gut health to improve MS outcomes. Understanding the interplay between gut microbiota and MS is essential for developing innovative therapeutic strategies. This review aims to provide insights into the GBA's role in MS, paving the way for future research and clinical applications.

## **Introduction:**

Multiple sclerosis is a chronic autoimmune disorder characterized by demyelination of neurons within the central nervous system, leading to a wide range of neurological manifestations, including dysfunction in motor coordination, cognitive processes, and generalized fatigue<sup>1</sup>. Despite substantial advances in therapeutic strategies, the underlying mechanisms of the disease remain unknown, and investigations into novel pathways that may play a role in disease progression or symptomatology continue. One such pathway is the gut-brain axis, a bidirectional communication network linking the gastrointestinal tract and the CNS, mediated by neural, hormonal, and immunological mechanisms<sup>2</sup>.

Recent studies have highlighted the role of the gut microbiome, which consists of trillions of microorganisms residing in the intestinal lumen and thus modulates immune responses and influences neuroinflammatory processes<sup>3</sup>. The ability of microbiota to generate metabolites and signalling molecules has profound implications for the health and disease of the CNS, especially concerning autoimmunity disorders such as MS. Dysbiosis, or disruption in the normal balance of the gut microbiome, has been linked to higher systemic inflammation, which may play a role in the pathogenesis of neurodegenerative diseases<sup>4</sup>.

This systematic review will examine the association between microbiome modulation and neurological outcomes in MS patients through the gut-brain axis. Through a synthesis of existing literature, we hope to clarify how changes in gut microbiota may influence neuroinflammatory processes, symptom profiles, and disease progression. We will review interventions, including dietary changes, probiotics, and prebiotics, that target microbiome composition and their potential effects on clinical outcomes in MS patients.

Understanding the interplay between the gut microbiome and MS is critical for developing innovative therapeutic strategies that could enhance patient outcomes. This review examines the current body of evidence, providing insight into the mechanisms underlying the gut-brain axis and its relevance to multiple sclerosis, paving the way for future research and clinical applications in this field.

## **Methodology:**

Original research articles will be used in this systematic review, including randomized controlled trials, cohort studies, case-control studies, and observational studies investigating the relationship between modulation of the microbiome and neurological outcomes for multiple sclerosis (MS). Review articles will be incorporated when they provide essential background or overview information summarizing original research relevant to the topic. Human subjects with all types of MS—relapsing-remitting, primary progressive, and secondary progressive—are included in the population of interest, as are studies that provide controls of healthy subjects for comparative purposes. Interventions will be considered that modulate the gut microbiome specifically, such as probiotics, prebiotics, dietary interventions, and faecal microbiota transplantation. Research that looks at natural variations in the composition of the gut microbiome as predictors of neurological outcomes is also included. Studies eligible for inclusion must document neurological outcomes, including symptoms (such as fatigue, cognitive impairment, and motor function), disease progression, and biomarkers of neuroinflammation, as well as those documenting changes in gut microbiome composition or diversity. Only peer-reviewed articles published within the last 10 years and written in English will be considered, with additional languages included based on available resources. PRIMA flow chart – figure 1

## **Exclusion Criteria**

Exclusion criteria will include several key elements to ensure the integrity of the review. Studies on animals or preclinical research that do not provide direct evidence applicable to human MS will be excluded, as well as case reports, opinion pieces, or commentaries without original data. The studies involving people with neurological disorders other than MS will not

be included, especially if the populations have comorbid conditions that may confound the results. Additionally, studies that do not directly assess gut microbiome modulation—such as those focusing solely on pharmacological treatments unrelated to gut health—will be excluded. Research that fails to report relevant neurological outcomes or microbiome assessments, or lacks clear methodologies for assessing gut microbiota or neurological measures, will also be disregarded. Finally, studies with a high risk of bias or methodological flaws will be evaluated using standard quality appraisal tools, such as the Cochrane Risk of Bias Tool, ensuring a high standard of evidence in this review.

PICO Framework:

Population: Human participants with all types of multiple sclerosis (MS), including relapsing-remitting, primary progressive, and secondary progressive, alongside healthy controls for comparison.

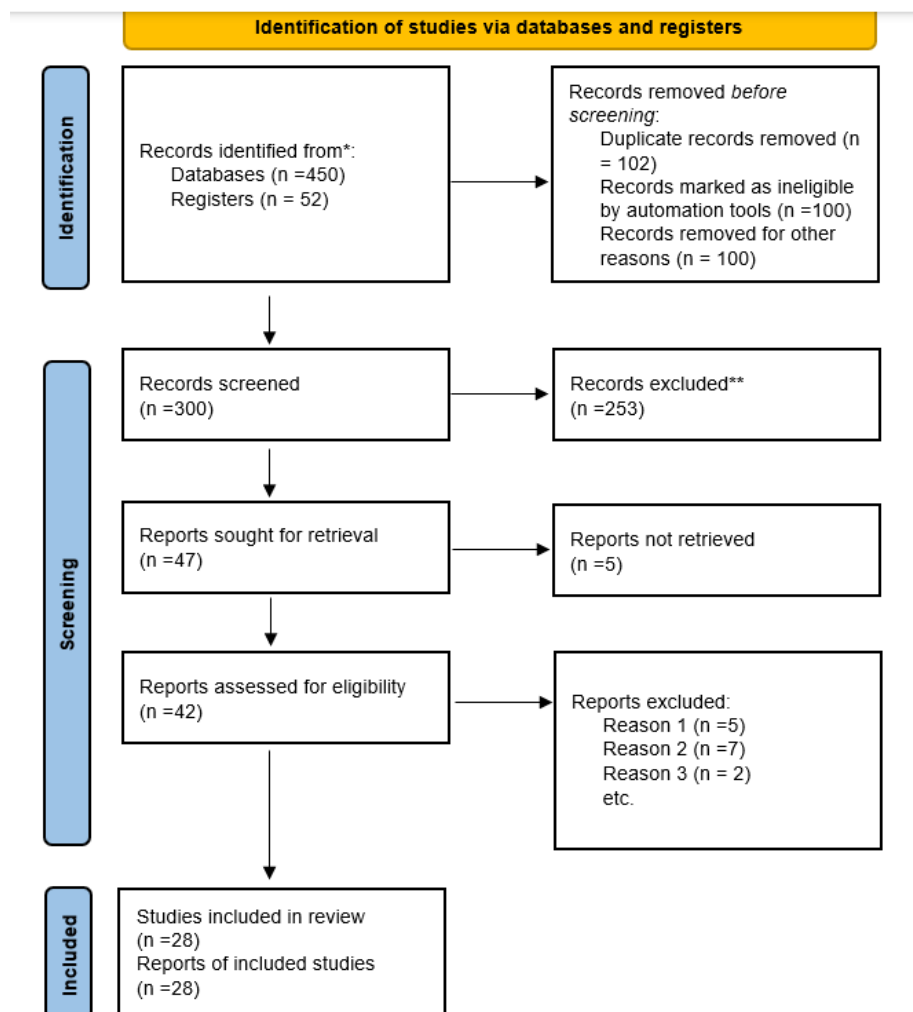
Intervention: Modulation of the gut microbiome through probiotics, prebiotics, dietary interventions, or faecal microbiota transplantation.

Comparison: Neurological outcomes in MS patients compared to healthy controls or baseline assessments.

Outcomes: Improvements in neurological symptoms (fatigue, cognitive impairment, motor function), disease progression, and biomarkers of neuroinflammation.

Prospero registration – application – 643777

**Figure 1 with PRISMA flow chart**



## **Review and summary of trials**

### **Role of the Gut Microbiome in MS**

The gut-brain axis (GBA) is an example of a bidirectional communication network that bridges the gastrointestinal system and the CNS, thus playing an important role in immune response modulation as well as influencing neurological health<sup>5</sup>. One mechanism by which the gut microbiome modulates neurological outcomes is through modulating immune responses, particularly the differentiation and activation of T-cells. This means that the balance between pro-inflammatory and anti-inflammatory responses is affected by the interaction of the gut microbiota with the immune system, and this aspect is particularly important for patients with MS, a condition characterized by autoimmunity and neuroinflammation<sup>6</sup>. Dysbiosis, or the alteration of the gut microbial composition, results in the exacerbation of disease conditions through the modulation of immune responses into a pro-inflammatory phenotype. On the other hand, a healthy and diverse microbiome may promote regulatory T-cell (Treg) differentiation, which can help mitigate inflammation and autoimmune responses<sup>7</sup>.

In addition, the gut microbiota is involved in the production of various metabolites, such as short-chain fatty acids (SCFAs) including butyrate, propionate, and acetate. These metabolites play critical roles in gut health and exert neuroprotective effects that might benefit patients with MS<sup>8</sup>. SCFAs are generated by gut bacteria through the fermentation of dietary fibres and have been shown to maintain the integrity of the BBB, decrease neuroinflammation, and promote neuronal health. SCFAs, by supporting the BBB, inhibit the infiltration of inflammatory cells into the CNS and thus protect against neurodegenerative processes typical of MS<sup>9</sup>. In addition, these metabolites may regulate neurotransmitter production and influence behaviour, which could potentially reduce the anxiety and depression that often accompany MS patients.

The interactions between the gut microbiome and the blood-brain barrier are important for maintaining CNS homeostasis. The gut microbiota contributes to the regulation of tight junctions within the BBB, which are crucial for preventing the passage of harmful substances from the bloodstream into the brain. Such disruption of these interactions leads to increased BBB permeability, thus facilitating neuroinflammatory processes detrimental in conditions like MS<sup>10</sup>. With such an understanding of these interactions, the gut microbiome could be targeted as a therapeutic avenue for modulating the immune system, enhancing neuroprotection, and ultimately improving neurological outcomes in MS patients. Such an integrated approach may open avenues for innovative treatments aimed at taking advantage of the gut-brain axis to improve the health of MS-affected patients<sup>11</sup>.

### **Dysbiosis and neuroinflammation:**

Recent studies have focused attention on dysbiosis, the imbalance of gut microbiota, as a potential contributor to the pathophysiology of multiple sclerosis, an autoimmune disorder characterized by neuroinflammation and demyelination in the central nervous system. The gut microbiome is crucial in modulating the immune response, and alterations in its composition may significantly affect the way the immune system responds to antigens, thus potentially worsening autoimmune conditions such as MS<sup>12</sup>.

A healthy gut microbiota keeps immune homeostasis in place by supporting beneficial regulatory T-cells (Tregs) and maintaining a homeostatic balance between pro-inflammatory and anti-inflammatory responses<sup>13</sup>. Through this mechanism, dysbiosis can drive the development of more pro-inflammatory responses. Populations of anti-inflammatory-benefiting bacteria might decrease, while pathogenic or pro-inflammatory microbes might increase in number. For instance, lower levels of some beneficial bacteria, like *Lactobacillus* and *Bifidobacterium*, have been implicated with increased intestinal permeability, also referred to as a "leaky gut"<sup>14</sup>. That means larger molecules, toxins, and antigens can translocate across the intestinal wall into the bloodstream, thus creating systemic inflammation that might stimulate autoimmune reactions targeting the myelin sheath in the CNS.

In addition, dysbiosis can modulate the maturation and activation of immune cells. Studies have found that certain commensal microbiota can even influence the lineage commitment of resting T-cells into different subset types, such as Th1 and Th17, both of which are involved in MS pathogenesis<sup>15</sup>. Increased activation of these proinflammatory T-cell subtypes leads to the infiltration of immune cells within the CNS and thus sustains neuroinflammation and further tissue damage. In particular, Th17 cells have been shown to produce cytokines like IL-17 and IL-6 that can further aggravate neural inflammation and disrupt the integrity of the blood-brain barrier (BBB)<sup>16</sup>.

In addition to immune modulation, dysbiosis also results in altered production of microbial metabolites, which can have downstream effects on inflammation and immune responses<sup>17</sup>. Short-chain fatty acids, the end products of the fermentation of dietary fibres by beneficial gut bacteria, are fundamental regulators of immune function. SCFAs augment Treg differentiation and contribute to preserving epithelial barrier integrity. However, excessive proliferation of pathobionts in the dysbiotic microbiome results in reduced SCFA production, thereby negating these protective effects while amplifying inflammation<sup>18</sup>.

### **Microbiota-related treatment and faecal transplantation schedules:**

Recent years have witnessed the exploration of microbiome-targeted therapies in the management of multiple sclerosis, with researchers working to understand how modulation of gut microbiota influences disease progression and symptomatology. Promising insights are being generated by clinical studies investigating probiotics, prebiotics, and faecal microbiota transplantation (FMT) as potential therapeutic interventions for MS patients.

Probiotics, live microorganisms that provide health benefits when administered in adequate amounts, have been the focus of several clinical trials designed to evaluate their impact on MS. Studies have demonstrated that certain probiotic strains can improve immune regulation, thereby potentially reducing neuroinflammation<sup>19</sup>. For instance, a randomized controlled trial looked at the impact of *Lactobacillus* and *Bifidobacterium* strains on patients with MS and reported improvements in quality of life along with reduced fatigue and disability. Despite such positive outcomes, however, some studies indicate mixed results. The interpretation of effectiveness is made difficult by the variability of strains and dosages of probiotics and the characterization of participants. It calls for further research into establishing consistent benefits that cut across diverse populations of MS<sup>20</sup>.

Another area of research is on prebiotics, which are dietary fibres that enhance the growth of beneficial gut bacteria. There is some evidence from studies evaluating the effects of prebiotic supplementation on MS symptoms, suggesting that improvement in the health of the gut microbiome may promote anti-inflammatory responses<sup>21</sup>. For example, supplementation with inulin and other fermentable fibres was associated with changes in microbiome composition, which led to increased production of short-chain fatty acids (SCFAs)—metabolites that support gut health and may confer neuroprotective effects<sup>22</sup>. Although the preliminary results are promising, more robust clinical trials are required to establish the safety and efficacy of prebiotics in MS management, as the studies conducted so far are mainly focused on general immune modulation rather than MS outcomes.

FMT, a more invasive procedure, involves the transfer of stool from a healthy donor to a recipient to restore a balanced gut microbiome. Preliminary research shows that FMT may alter the dysbiotic gut microbiomes of MS patients to a healthier composition and reduce inflammatory responses. A small pilot study reported a good safety profile with some improvement in neurological function among MS patients undergoing FMT, but larger well-controlled trials are needed to define efficacy and safety parameters. The long-term consequences of FMT are not known<sup>23</sup>.

Despite the promise of these microbiome-targeted therapies, safety must be carefully evaluated. Probiotics are generally safe, but side effects have been noted, particularly in

immunocompromised patients. Probiotics may cause gastrointestinal discomfort, such as bloating or gas, and exacerbate symptoms for some patients. FMT carries risks of pathogen transmission and requires careful donor screening and procedural control<sup>24</sup>.

### **Pro-inflammatory cytokines, gut microbiome and MS**

Recent studies have shown that the interaction between gut microbiota dysbiosis and neuroinflammation in multiple sclerosis is complex and provides pathways underlying this relationship. Dysbiosis is an imbalance of the gut microbiome that causes immunological responses that can be detrimental to MS pathology<sup>25</sup>. The most significant pathway is cytokine production, where there is an increase in the secretion of pro-inflammatory cytokines, including IL-6, IL-17, and TNF- $\alpha$ . Elevated levels of these cytokines have been associated with inflammation in the CNS and are thought to play a crucial role in the activation of inflammatory cells, such as T-helper (Th) cells, macrophages, and microglia, which contribute to the pathology seen in MS<sup>26</sup>.

Specifically, expansion of Th17 cells, or a subset of CD4 + T-cells with the ability to produce IL-17, has been associated with MS disease activity<sup>27</sup>. Dysbiosis may drive this expansion through the release of microbial metabolites that influence T-cell differentiation. Additionally, the gut microbiota's role in regulating the blood-brain barrier (BBB) is of paramount importance. Such inflammatory cells infiltrate the CNS to significantly promote neuroinflammation, causing demyelination characteristic of MS. These pathways connected with this process underscore the role of the GBA in determining the neuroinflammatory profile in MS<sup>28</sup>.

However, the GBA may also indirectly impact disease progression through comorbidities, which are very common among MS patients, including depression and anxiety. Evidence shows that dysbiosis affects neurotransmitter synthesis and signalling, especially the synthesis of serotonin and gamma-aminobutyric acid (GABA), two critical neurotransmitters involved in mood regulation<sup>29</sup>. It is indicated that microbiota alteration can therefore impact mental health outcomes. The prevalence of depression and anxiety is increased in MS patients, which might be related to immune dysregulation and neuroinflammation affecting gut health as well<sup>30</sup>.

The impact of the GBA on neuropsychological outcomes may be significant, as gut-derived pro-inflammatory cytokines may exacerbate both the physiological and psychological dimensions of MS. The inflammatory milieu in the CNS not only manifests in physical symptoms but can also contribute to mood disorders, creating a vicious cycle of worsening health conditions. According to the literature, interventions that are directed towards improving gut health—such as dietary modifications, probiotics, or prebiotics—may confer dual benefits of alleviating neuroinflammation and improving psychological well-being in MS patients.

### **Challenges:**

Modulating the gut microbiome in MS is indeed quite challenging due to a lot of limitations and hurdles encountered during the transition from research evidence into effective clinical practices. It involves intrinsic complexity and heterogeneity among gut microbiota in individuals, each unique in response to genetic influences, diet, lifestyle, and environment, which often hinders attempts to identify the universal intervention strategy for everyone. Variability in individual responses to probiotic or prebiotic treatments complicates the ability to predict outcomes, which is further exacerbated by the limited standardization of these interventions.

Another challenge is that there are limited robust, large-scale clinical trials designed for patients with MS. Most studies are either general population-based or other disease-based, making it difficult to show the safety and efficacy of the microbiome treatments in MS patients. There's also a fear of adverse reactions, such as gastrointestinal discomfort or risk of pathogen transmission via faecal microbiota transplantation.

Membrane technology is advancing our understanding of the gut-brain axis and its implications for multiple sclerosis (MS), a chronic autoimmune condition affecting the central nervous system. The gut-brain axis refers to the bidirectional communication between the gastrointestinal tract and the central nervous system, mediated by various pathways, including the immune system, neuroactive compounds, and the microbiome. Disruptions in this axis have been implicated in the pathogenesis of MS, highlighting the potential for therapeutic interventions.

Recent studies suggest that changes in gut microbiota composition may influence immune responses and inflammatory processes associated with MS. Membrane technology plays a crucial role in this research by enabling the efficient isolation and characterization of biomolecules produced by gut microbes.<sup>31</sup> For instance, techniques such as ultrafiltration and solid-phase extraction allow for the analysis of short-chain fatty acids, metabolites, and other signalling molecules that may contribute to neuroinflammation or neuroprotection.

Furthermore, membrane-based biosensors have the potential to detect specific biomarkers related to gut health and metabolic status in MS patients. This can facilitate the identification of microbial signatures linked to disease progression and treatment efficacy. By understanding how gut-derived signals affect central nervous system inflammation and myelin integrity, researchers can explore novel therapeutic strategies that target the gut microbiome to modulate MS symptoms and improve patient outcomes.

In summary, integrating membrane technology into the study of the gut-brain axis offers promising avenues for understanding and managing multiple sclerosis. It allows for a deeper exploration of the interplay between gut health and neurological function, paving the way for innovative treatments that harness the microbiome's potential to influence disease outcomes in MS.<sup>32,33</sup> As this field progresses, it may help reshape the approach to care and prevention in multiple sclerosis.

### **Conclusion:**

In conclusion, the gut-brain axis plays a crucial role in multiple sclerosis, modulating both immune responses and neurological outcomes through gut microbiota modulation. Dysbiosis contributes to neuroinflammation and the progression of MS, implicating the gut microbiome in the disease's pathophysiology. While microbiome-targeted therapies, such as probiotics, prebiotics, and faecal microbiota transplantation, show promise in improving clinical outcomes, challenges remain in standardizing interventions and ensuring safety. The overcoming of such barriers in future studies will pave the door for innovative therapeutic approaches, thereby enhancing the management and, in turn, quality of life of patients with multiple sclerosis.

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