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Gut–brain connection in multiple sclerosis

Oś jelitowo-mózgowa w stwardnieniu rozsianym

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Abstract

Introduction and objective: The link between gut microbiota and multiple sclerosis has gained significant research interest in recent years. Multiple sclerosis, an autoimmune disease characterised by chronic inflammation and demyelination in the central nervous system, remains a complex condition with a multifactorial aetiology. Recent evidence suggests that alterations in gut microbiota composition, known as dysbiosis, may influence multiple sclerosis pathogenesis and progression. This paper aims to review the current state of knowledge regarding the gut–brain connection in multiple sclerosis, exploring how gut microbiota may affect disease mechanisms and potential therapeutic approaches. **Summary of the state of knowledge:** The gut–brain axis plays a crucial role in maintaining homeostasis. In multiple sclerosis, dysbiosis has been observed, with specific microbial profiles differing between patients and healthy controls. Gut microbiota can modulate immune responses, potentially influencing multiple sclerosis progression through pathways involving cytokine production and T-cell differentiation. Therapeutic interventions such as dietary modifications, probiotics, and faecal microbiota transplantation have shown promise in preliminary studies, indicating their potential to modulate gut microbiota and improve patient outcomes. **Summary:** Understanding the gut–brain axis in multiple sclerosis offers promising possibilities for new therapeutic strategies. Interventions targeting gut microbiota, such as probiotics, dietary changes, and faecal microbiota transplantation, show potential for modifying disease

progression and enhancing treatment outcomes. However, current methodologies for assessing gut microbiota have limitations, requiring improved techniques for accurate analysis. Continued investigation into the gut–brain connection could lead to more effective and targeted treatments, ultimately improving the quality of life for multiple sclerosis patients.

Keywords: probiotics, diet, dysbiosis, gut microbiota, multiple sclerosis

Streszczenie

Wprowadzenie i cel: W ostatnich latach istotnie wzrosła liczba badań analizujących związek między mikrobiotą jelitową a stwardnieniem rozsianym. Stwardnienie rozsiane, choroba autoimmunologiczna charakteryzująca się przewlekłym stanem zapalnym oraz demielinizacją w ośrodkowym układzie nerwowym, pozostaje złożonym schorzeniem o wieloczynnikowej etiologii. Najnowsze badania sugerują, że zmiany w składzie mikrobioty jelitowej, określane jako dysbioza, mogą wpływać na patogenezę i postęp stwardnienia rozsianego. Celem niniejszego artykułu jest przegląd aktualnego stanu wiedzy na temat osi jelitowo-mózgowej w kontekście stwardnienia rozsianego, z uwzględnieniem wpływu mikrobioty jelitowej na mechanizmy choroby oraz potencjalne podejścia terapeutyczne. **Skrócony opis stanu wiedzy:** Oś jelitowo-mózgowa odgrywa kluczową rolę w utrzymaniu homeostazy organizmu. W przypadku stwardnienia rozsianego obserwuje się dysbiozę, przy czym specyficzne profile mikrobiologiczne pacjentów i zdrowych osób kontrolnych różnią się. Mikrobiota jelitowa może modulować odpowiedzi immunologiczne, potencjalnie wpływając na postęp choroby poprzez takie mechanizmy, jak produkcja cytokin i różnicowanie komórek T. Wstępne badania wykazały obiecujące wyniki w zakresie interwencji terapeutycznych, takich jak modyfikacje diety, probiotyki oraz przeszczep mikrobioty kałowej, sugerując ich potencjał w modulowaniu mikrobioty jelitowej i poprawie wyników leczenia pacjentów. **Podsumowanie:** Zrozumienie osi jelitowo-mózgowej w stwardnieniu rozsianym stwarza obiecujące możliwości dla rozwoju nowych strategii terapeutycznych. Interwencje ukierunkowane na mikrobiotę jelitową, takie jak probiotyki, zmiany w diecie czy przeszczep mikrobioty kałowej, mogą mieć wpływ na modyfikację postępu choroby i poprawę wyników leczenia. Niemniej jednak obecne metody oceny mikrobioty jelitowej mają swoje ograniczenia i konieczny jest rozwój dokładniejszych technik analizy. Dalsze badania nad połączeniem jelitowo-mózgowym mogą prowadzić do skuteczniejszych i bardziej ukierunkowanych terapii, a tym samym poprawić jakość życia pacjentów ze stwardnieniem rozsianym.

Słowa kluczowe: probiotyki, dieta, dysbioza, mikrobiota jelitowa, stwardnienie rozsiane

INTRODUCTION AND PURPOSE

Multiple sclerosis (MS) is an autoimmune disorder marked by chronic inflammation, demyelination, neuronal degradation, and gliosis within the central nervous system (CNS). Primarily affecting young adults, MS shows a higher prevalence among females and individuals of Northern European descent. The disease is characterised by an unpredictable clinical course and symptomatology, which significantly complicate its diagnosis and therapeutic management (Tafti et al., 2024).

The pathophysiology of MS is complex, involving an immune-mediated attack on CNS myelin. This results in interrupted electrical impulses along the nerves, leading to the varied symptoms observed in MS, such as fatigue, motor and sensory disturbances, visual impairment, and cognitive dysfunction. This disruption is primarily caused by autoreactive T cells, which are thought to be activated by environmental factors like viral infections, vitamin D deficiency, and smoking. These autoreactive T cells cross the blood–brain barrier (BBB), triggering inflammation and further myelin damage through cytokine production and activation of other immune cells (Ghasemi et al., 2017).

Despite advancements in research, the exact aetiology of MS remains only partially understood, though it is believed to be multifactorial, involving genetic predisposition and environmental triggers (Dobson and Giovannoni, 2019). Recently, an increasing role in MS susceptibility and progression has been attributed to the gut microbiota.

The gut microbiota is a diverse community of microorganisms inhabiting the gastrointestinal tract, impacting overall health. This complex ecosystem is essential for various physiological functions, including digestion, immune responses, and metabolic processes. By fermenting dietary fibres, the gut microbiota produces short-chain fatty acids (SCFAs) that are crucial for maintaining the integrity of the gut barrier, enhancing nutrient absorption, and providing protection against pathogens (Hills et al., 2019). Moreover, these microorganisms play a key role in modulating the immune system, thereby influencing host health during both normal conditions and disease states. Maintaining a balanced gut microbiota is essential for overall health and physiological well-being (Al Bander et al., 2020). Recent studies have increasingly recognised the critical role of gut microbiota in the pathogenesis of autoimmune diseases, emphasising that alterations in its composition and function are often linked to such conditions (De Luca and Shoenfeld, 2019).

The connection between gut dysbiosis and MS is increasingly supported by scientific research, which highlights differences in gut microbiota composition between MS patients and healthy individuals. Studies have found that certain bacteria species are more prevalent in MS patients, while others are reduced. These observations suggest that the specific microbial profiles in individuals with MS could be linked to the disease's mechanisms (Ordoñez-Rodriguez et al., 2023).

Understanding the significance of the gut microbiota in MS may impact the management and therapeutic approaches to the disease. Innovative research has explored interventions

such as dietary modifications, probiotics, and even faecal microbiota transplantation as methods to alter the gut environment in MS patients. These approaches have demonstrated promising results in preliminary studies, showing potential for not only alleviating symptoms but also possibly influencing the long-term course of the disease (Bronzini et al., 2023). Therefore, further investigation into the role of the gut microbiota in MS could revolutionise its treatment. Harnessing the therapeutic potential of the gut microbiome may lead to more effective and targeted treatments that could significantly improve the quality of life for MS patients (Altieri et al., 2023).

GUT MICROBIOTA AND IMMUNE SYSTEM INTERACTION

Gut microbiome in health and disease

The gut microbiome, comprised of trillions of microorganisms, including bacteria, viruses, fungi, and archaea, inhabits the human gastrointestinal tract. The major types are *Firmicutes* (consisting mainly of Gram-positive clostridia) and *Bacteroidetes* (consisting mainly of Gram-negative bacteria). This diverse community constitutes over 50% of the body's cells and plays a critical role in metabolism, nutrition, immune function, and disease prevention (Sidhu and van der Poorten, 2017). Despite variability in its composition, which can be influenced by factors such as diet, lifestyle, and medical treatments, the gut microbiome is essential for maintaining digestive health by breaking down complex polysaccharides that human enzymes cannot process, synthesising vitamins, and producing SCFAs, which provide energy to gut cells, support nutrient absorption, and influence metabolic functions (Cresci and Bawden, 2015).

The gut microbiome also serves as a critical component of the body's primary defence mechanism against pathogenic microorganisms. It achieves this by strengthening the gut barrier, producing antimicrobial compounds, and outcompeting harmful pathogens. Moreover, it is integral to the development and training of the immune system, promoting a balanced immune response. It helps in the maturation of immune cells and the production of substances that modulate immune responses, thereby contributing to the body's overall immunity and infection resistance. The microbiome's ability to communicate with distant organs through metabolic pathways further underscores its vital role in health and disease management (Fan and Pedersen, 2021).

A "healthy" gut microbiota is characterised by stability, resilience, and a symbiotic relationship with the host, typically showing high taxonomic diversity and microbial gene richness. However, the composition of the gut microbiota varies significantly among individuals and changes throughout life due to factors such as age, diet, and environmental influences, including medication use. There are also differences in microbiota across different sections of the gastrointestinal tract, influenced by local environmental conditions like transit time and bile concentration (Rinninella et al., 2019).

In contrast, microbiota dysbiosis is implicated in the development and progression of various diseases. In neurological conditions such as Alzheimer's, Parkinson's, and MS, an altered gut microbiota influences neuroinflammation via the gut–brain axis. Imbalances in gut microbes can lead to increased permeability of the gut barrier, creating a condition commonly known as "leaky gut", which results in systemic inflammation and ultimately neuroinflammation, contributing to the progression of these diseases (Sorboni et al., 2022).

Gut–brain axis

The gut–brain axis is a bidirectional communication network between the CNS and the gastrointestinal tract, facilitated by four main pathways: neurologic, metabolic, endocrine, and immune. This axis enables the brain to influence gastrointestinal functions and vice versa, with the gut microbiota playing a crucial role in this interaction. Gut microbes are involved in producing neurotransmitters and other bioactive molecules that impact both gut and brain functions (Osadchiy et al., 2019).

The neurologic pathway of the gut–brain axis involves the vagus nerve, the enteric nervous system, and neurotransmitter activities within the gastrointestinal tract. This pathway directly produces neurotransmitters such as GABA, serotonin, and acetylcholine, affecting local nerve activity and producing active catecholamines. Although the vagus nerve does not directly interact with the gut microbiota, it can detect microbial signals through bacterial metabolites or be affected by changes in gut cells like enteroendocrine and enterochromaffin cells (Bonaz et al., 2018). These interactions involve metabolites such as SCFAs, which bind to free fatty acid receptors and influence gut functions such as motility and inflammation. Other receptors on vagal nerve fibres respond to serotonin and various gut peptides, further facilitating communication pathways (Fülling et al., 2019). Additionally, the autonomic nervous system regulates immune responses in the gut, modulating the activity of macrophages and mast cells in response to bacteria. Furthermore, the gut microbiome is crucial for maintaining the normal function of intrinsic primary afferent neurons in the gut (Appleton, 2018).

The metabolic pathway involves SCFAs such as butyrate, propionate, and acetate, produced by bacterial fermentation of dietary fibres in the colon. SCFAs impact gut, systemic, and brain health by entering circulation and crossing the BBB, where they enhance BBB integrity. Additionally, SCFAs contribute to the maturation of microglia, and modulate neurotransmitters and neurotrophic factors, impacting neurological functions (Erny et al., 2015). They also affect intracellular potassium levels and regulate enzymes critical for the synthesis of key neurotransmitters such as serotonin, dopamine, adrenaline, and noradrenaline (Rutsch et al., 2020).

The gut microbiota influences nutrient availability, which directly affects peptide secretion by enteroendocrine cells. This includes peptides like galanin and ghrelin, which play significant roles in modulating stress and metabolic re-

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sponses via the hypothalamic–pituitary–adrenal (HPA) axis. Galanin can stimulate the release of corticotropin-releasing factor (CRF) and adrenocorticotropic hormone (ACTH), enhancing glucocorticoid secretion from the adrenal cortex and directly triggering the release of cortisol and norepinephrine. Ghrelin also promotes ACTH and cortisol release, influencing the HPA response to stress and metabolic changes (Carabotti et al., 2015).

The immune pathway involves the release of cytokines and other mediators, such as interferon-gamma, during dysbiosis. In some conditions, dysregulated microbiota trigger immune responses that increase gut permeability, activate pain pathways, and disrupt the enteric nervous system (Koloski et al., 2012).

Immune system modulation by gut microbiota

Immunomodulation is the process of adjusting the immune system's activity, either by suppressing or stimulating its function, to achieve a therapeutic effect in treating various diseases (Strzelec et al., 2023). Recent studies have shown that the gut microbiota significantly influences immune system responses through various mechanisms (Geva-Zatorsky et al., 2017).

The immune surveillance of the gut involves the recognition of various microbial components through receptors such as Toll-like receptors (TLRs) and nucleotide binding oligomerisation domain proteins (NODs). Activation of these receptors can lead to either tolerance and healthy inflammatory on or proinflammatory responses, depending on the cellular context (Sanderson and Walker, 2007).

Despite the physical segregation of bacteria by the mucin layer, the gut microbiota plays crucial roles in immune development, homeostasis, and tolerance. Commensal colonisation induces the expression of antimicrobial peptides and contributes to the balance of T-effector cell function. Additionally, the microbiota influences regulatory T (Treg) cell activity and the production of anti-inflammatory cytokines (Izcue et al., 2006).

Numerous microbe-host interactions modulate immune homeostasis, including the regulation of NF-κB activity, cytokine production, and T cell differentiation. These interactions collectively support immune surveillance and tolerance in the gut, highlighting the extensive cooperation between the microbiota and the host immune system (Peterson et al., 2015).

CURRENT RESEARCH ON GUT MICROBIOTA AND MS

Triggering and exacerbation of MS pathology

Fully understanding the importance of the connection between the gut microbiome and MS requires a comprehension of the condition's pathogenesis. MS involves localised inflammation in the CNS, where T cells become autoreactive due to unknown antigens presented by MHC class II molecules. These T cells spread into lymphatic tissues and circulation, breaking down the BBB. In the CNS, they attack myelin, leading to proinflammatory Th1 cells and anti-inflammatory Th2 cells. Th2 cells release cytokines that target macrophages and microglial cells. Autoreactive T cells also trigger B-cell antibody production, forming myelin autoantibodies and initiating the complement cascade, which further damages myelin (Haki et al., 2024). The microbiota in MS patients can induce Th1 cell differentiation and reduce Treg numbers, while decreased microbiota in MS patients stimulate anti-inflammatory IL-10-expressing T cells and $FoxP3^+$ Tregs. Gut microbiota modulate the balance of Th17 and Treg cells, with specific species influencing these mechanisms. Additionally, $CD8^+$ T cells and B cells contribute to MS pathogenesis through cytotoxic processes and antibody production (Cheng et al., 2019).

Furthermore, gut bacteria generate reactive oxygen species (ROS) either directly or indirectly through metabolites like SCFAs and formyl-peptides. Excessive ROS production, often due to pathogenic bacteria, disrupts cellular signalling and exacerbates inflammation in MS patients (de Vos et al., 2022).

Gut dysbiosis in MS

There is a close link between gut dysbiosis and MS. Current research suggests that gut bacteria may predispose individuals to neurodegenerative diseases like MS. Studies across different populations have shown significant changes in gut microbiota composition in MS patients compared to controls, although some controversies remain regarding specific bacterial differences (Torres-Chávez et al., 2023). Research on this connection began with studies on experimental autoimmune encephalomyelitis (EAE). These studies, using germ-free (GF) mice and antibiotic treatments, revealed that the microbiota significantly influences both pro- and anti-inflammatory immune responses in the CNS (Ochoa-Repáraz et al., 2009). Studies using EAE models treated with specific antibiotics or GF mice colonised by certain bacteria confirmed that microbial signals influence inflammation in extra-intestinal tissues. When gut microbiota from MS patients was used in experiments, it triggered immune changes that could exacerbate EAE. MS patients exhibited a distinctive microbial imbalance, characterised by a decrease in the *Firmicutes* phylum, *Akkermansia* and *Dorea* (which can metabolise mucin and induce pro-inflammatory cytokines) and an increase in the *Bacteroidetes* phylum, with lower abundance of certain genera such as *Prevotella*, *Parabacteroides*, and *Bacteroides* (which can induce Tregs), both of which are known for producing SCFAs that possess immunoregulatory properties (Shahi et al., 2017) (Tab. 1).

THERAPEUTIC IMPLICATIONS OF MODULATING GUT MICROBIOTA

Current treatment strategies for MS predominantly involve disease-modifying therapies aimed at reducing relapse

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frequency and delaying disease progression. However, despite this progress, many existing therapies come with significant side effects and are often ineffective for certain subsets of patients (Selmaj et al., 2024).
The relationship between gut microbiota and MS can help understand how manipulating the gut microbiota could provide new therapeutic possibilities, potentially providing complementary or alternative solutions to existing drug treatments. In this regard, targeted interventions involving diet, probiotics, prebiotics, and faecal microbiota transplants are under active investigation for their potential to reshape the gut–immune axis.

Diet

Diet significantly influences the composition of the gut microbiome, which in turn affects immune responses and can potentially modulate disease activity in MS.
A study exploring the dietary habits of a large international cohort of people with MS found significant associations between healthy dietary practices – particularly a high intake of fruit, vegetables, and healthy fats, and avoidance of meat and dairy – and improved health-related quality of life (HRQOL) and reduced disability. Although the impact on MS relapse rates and disease activity was less conclusive, the findings support the potential benefits of dietary modifications in managing MS symptoms and overall health outcomes (Hadgkiss et al., 2015).

High-fibre diet

Carbohydrate fermentation by the gut microbiota serves as an energy source for the colon and plays a fundamental role in digestive processes. Dominant bacteria break down complex polysaccharides into simpler forms for other bacteria to ferment, producing SCFAs and gases. These byproducts provide about 10% of daily human energy. SCFAs like butyrate, propionate, and acetate regulate intestinal and immune functions, influencing oral tolerance, inflammation resolution, and systemic inflammation, including in adipose tissue (Marchesi et al., 2016).
A high-vegetable/low-protein (HV/LP) diet is associated with a higher abundance of *Lachnospiraceae* in the gut microbiota, known for producing butyrate, a compound that supports Treg cell activity and anti-inflammatory cytokine production. Patients on an HV/LP diet experienced a significant reduction in the Expanded Disability Status Scale (EDSS) score and relapse rate over 12 months (Saresella et al., 2017).

Ketogenic diet and fasting

Recent research highlights the potential benefits of the ketogenic diet in managing MS due to its role in myelin sheath repair and modulation of neuroinflammation. Clinical studies have shown that the ketogenic diet improves satiety, body composition, and metabolic parameters in MS patients, potentially decreasing inflammation and enhancing overall quality of life (Dyńka et al., 2022).
A series of studies demonstrated that dietary interventions, such as ketogenic and intermittent fasting diets, significantly improve colonic function and alleviate symptoms in MS and EAE by positively influencing the gut microbiome. These diets were found to restore microbial concentrations to healthy levels, reduce inflammation, demyelination, and axonal damage, and enhance the presence of beneficial bacterial families. The resulting changes in the gut microbiome were associated with reduced leptin levels, enhanced metabolic pathways related to ketone production and glutathione metabolism, and improved antioxidative capacities (Cignarella et al., 2018; Swidsinski et al., 2017).

Mediterranean diet

The components of the Mediterranean diet (MD), such as fibre, antioxidants from fruit and vegetables, and omega-3 fatty acids from fish and nuts, are thought to play a role in modulating neuroinflammation and gut microbiota, benefiting MS patients. Higher adherence to the MD is associated with lower MS Severity Scores (MSSS) (Bronzini et al., 2024).
Studies have shown that transitioning to a MD significantly improves gut microbiota composition and reduces

	Reference	Overexpressed species in MS	Underexpressed species in MS	Main findings
1.	Ordoñez-Rodriguez et al., 2023	*Akkermansia*, *Dorea*	*Prevotella*, *Parabacteroides*	Dysbiosis in multiple sclerosis patients linked to lower levels of *Prevotella* and *Parabacteroides* and higher levels of *Akkermansia* and *Dorea*
2.	Shahi et al., 2017	*Bacteroides fragilis*	*Clostridia*, *Firmicutes*	*Bacteroides fragilis* is overrepresented in multiple sclerosis patients, while *Clostridia* levels are diminished
3.	Swidsinski et al., 2017	No specific species mentioned, general dysbiosis reported	No specific species mentioned	Multiple sclerosis patients show reduced microbial diversity
4.	Cignarella et al., 2018	*Lactobacillus reuteri*	*Clostridia*	Intermittent fasting alters gut microbiota, reduces multiple sclerosis symptoms, and shifts the microbiota toward a healthier profile
5.	Ochoa-Repáraz et al., 2009	*Bacteroidetes*, *Firmicutes*	No specific species mentioned	Commensal gut microflora can induce immune changes that exacerbate experimental autoimmune encephalomyelitis
6.	Torres-Chávez et al., 2023	*Bacteroidetes*, *Akkermansia*, *Dorea*	*Firmicutes*, *Prevotella*, *Parabacteroides*, *Bacteroides*	Dysbiosis influences pro- and anti-inflammatory responses

Tab. 1. Summary of microbiome studies in MS patients

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inflammation in MS patients. Specifically, the MD increased beneficial *Lachnospiraceae*, which produce butyrate, enhancing colonic health. This shift was linked to reduced cholesterol levels, decreased inflammatory markers, and increased anti-inflammatory monocytes and Treg cells. Additionally, a rehabilitation programme incorporating physical activity and dietary changes, with a focus on adherence to the MD, effectively modulated gut microbiota and improved metabolic markers without altering energy or macronutrient intake (Katz Sand et al., 2023; Meslier et al., 2020).

Vitamin D supplementation

Recent research suggests a link between vitamin D deficiency and an increased risk of developing MS. The CHOLINE study, the largest two-year randomised controlled trial in relapsing-remitting MS (RRMS), found that cholecalciferol (vitamin D_3) was associated with a lower relapse rate, fewer new T1 lesions, reduced magnetic resonance imaging lesion volume, and slower progression of disability (EDSS). High-dose vitamin D_3 supplementation in RRMS patients also increased anti-inflammatory IL-10^+ $CD4^+$ T cells and decreased the pro-inflammatory Th1/Th2 cell ratio, indicating a shift toward a less inflammatory profile (Camu et al., 2019; Smolders et al., 2010).

Probiotics and prebiotics

Recent research shows that specific probiotics can reduce symptoms and inflammation in autoimmune diseases like MS. Studies using various probiotic strains in animal models of MS have demonstrated significant benefits. Probiotics such as *Lactobacillus reuteri* have been shown to reduce clinical symptoms and inflammation by modulating gut and systemic inflammation. Multispecies probiotics, including combinations of *Lactobacillus* and *Bifidobacterium* strains, have positively impacted the immune response, reduced CNS inflammation, and even reversed disease symptoms (Calvo-Barreiro et al., 2020; He et al., 2019).

Studies have shown that certain prebiotics, such as pomegranate peel extract (PPE) and *Palmaria palmata* aqueous extract, can reduce inflammation, modulate gut microbiota, and provide neuroprotection. These prebiotics have demonstrated potential in alleviating symptoms and improving overall health outcomes in animal models of MS and other inflammatory conditions (Lu et al., 2020).

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) shows promise as a therapeutic approach for MS, with case reports indicating its significant impact on symptom reversal. By correcting gut microbiome dysbiosis, FMT has the potential to prevent further disease progression. Animal studies have demonstrated that FMT from healthy donors can slow the development of EAE, alleviate symptoms, enhance BBB integrity, and restore microbiota diversity. FMT also reduces the activation of microglia and astrocytes, providing protection to the BBB and preserving myelin and axons. Human studies have shown FMT to be safe, tolerable, and potentially

	Reference	Intervention	Study status	Main findings
1.	Hadgkiss et al., 2015	High-fibre diet	Clinical trial	Healthy dietary practices improve health-related quality of life and reduce disability in multiple sclerosis patients
2.	Marchesi et al., 2016	High-fibre diet (polysaccharide fermentation)	Clinical trial	Short-chain fatty acids produced by fibre fermentation regulate immune functions, influencing multiple sclerosis symptoms
3.	Saresella et al., 2017	High-vegetable/low-protein diet	Clinical trial	Reductions in relapse rate and disability over 12 months
4.	Dyńka et al., 2022	Ketogenic diet	Animal and clinical data	Reduced inflammation, improved quality of life in multiple sclerosis patients
5.	Meslier et al., 2020	Mediterranean diet	Clinical trial	Increased *Lachnospiraceae*, reduced inflammatory markers
6.	Katz Sand et al., 2023	Mediterranean diet	Clinical trial	Improved metabolic markers, gut microbiota composition in multiple sclerosis patients
7.	Bronzini et al., 2024	Mediterranean diet	Clinical trial	Modulated gut microbiota, reduced inflammation, improved MS Severity Scores
8.	Smolders et al., 2010	Vitamin D_3 supplementation	Clinical trial	High-dose vitamin D_3 shifted immune response toward a less inflammatory profile
9.	Camu et al., 2019	Vitamin D_3 supplementation	Clinical trial (phase 2)	Reduced relapse rates and magnetic resonance imaging lesions in multiple sclerosis patients
10.	Lu et al., 2020	Prebiotics (e.g. pomegranate peel)	Animal data	Reduced inflammation, modulated gut microbiota in multiple sclerosis animal models
11.	Calvo-Barreiro et al., 2020; He et al., 2019	Probiotics	Animal and clinical trials	Reduced central nervous system inflammation and multiple sclerosis symptoms
12.	Al et al., 2022; Zhanel et al., 2023	Faecal microbiota transplantation	Clinical trial (pilot)	Promising in restoring microbiota diversity and improving symptoms in multiple sclerosis patients

Tab. 2. Summary of interventions impacting MS microbiome

beneficial for MS patients by enriching MS-protective microbiota (Al et al., 2022; Zhanel et al., 2023) (Tab. 2).

CONCLUSIONS

This article has highlighted the significant connection between gut microbiota and MS, focusing on the gut–brain axis as a crucial factor in the disease's progression and potential management. Key findings suggest that dietary interventions, probiotics, prebiotics, and FMT can modulate gut microbiota, thereby influencing immune responses and potentially alleviating MS symptoms.

The significance of the gut–brain axis in MS has important implications for disease management and therapeutic development. By understanding the complex interactions between gut microbiota and the immune system, novel treatments can be designed to modulate the gut environment, potentially altering the course of the disease and improving patient outcomes.

Future research should focus on large-scale clinical trials to confirm the efficacy and safety of gut microbiota-targeted therapies. Additionally, understanding the precise mechanisms by which gut microbiota influence MS pathophysiology and developing advanced methodologies for assessing gut microbiota composition and function will be crucial for developing targeted interventions.

Clinicians should consider integrating dietary and microbiota-based strategies into comprehensive treatment plans for MS patients to enhance overall health outcomes and quality of life.

In conclusion, the gut–brain axis represents a promising frontier in MS research and treatment. By continuing to explore and validate microbiota-based therapies, we can potentially transform the management of MS and offer new hope to patients worldwide.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: GD. Collection, recording and/or compilation of data: JG, JHS, JD. Analysis and interpretation of data: JG, JHS, JD. Writing of manuscript: GD, MC, IK, MG, BS. Critical review of manuscript: AB, MO. Final approval of manuscript: GD.

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