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REVIEW

The Effect of the Mediterranean Diet on Gut Microbiota and Its Impact on Neurodegenerative Diseases: A Narrative Review

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Abstract: Due to their complex etiology and the intricacy of brain systems, neurodegenerative diseases (NDs), which progressively deteriorate neural tissue, remain difficult to treat. The gut-brain axis emphasizes the host–gut microbiota (GM) interaction and offers a new perspective on these diseases. In Alzheimer's disease (AD), there is a hypothesis of the migration of amyloid-β oligomers from the gut to the brain may affect neuroinflammation. Also, in Parkinson's disease (PD), GM in the gastrointestinal mucosal layer may misfold and accumulate α-synuclein, leading to its transfer to the brain. Multiple Sclerosis (MS) is affected by GM that influences immune responses toward inflammation through modulation of T-helper cell polarization, T-regulatory (T-reg) cell function, and B-cell activity. Furthermore, neuromyelitis optica spectrum disorder (NMOSD) is linked to antibodies that target the astrocyte-expressed water channel protein aquaporin-4 (AQP4) and may be related to GM and needs more research. Diet is a major factor that could modulate GM composition. The Mediterranean Diet (MD) is anti-inflammatory, antioxidant, and gut-modulating due to its high vegetable, fruit, whole grain, and olive oil intake. It boosts beneficial GM and their byproducts, which suppresses inflammation and may slowing progression and improve PD, AD, MS, and NMOSD, influencing disease progression and symptoms. This review aims to investigate the interaction between GM composition and the MD and how they jointly influence neurodegenerative diseases such as AD, PD, MS, and NMOSD.

Keywords: alzheimer disease, parkinson disease, multiple sclerosis, neuro myelitis optica spectrum disease, gut microbiota, Mediterranean diet

Introduction

Neurodegenerative disorders (NDs) are characterized by the progressive loss of neural tissue, which represents a hallmark of central nervous system (CNS) dysfunction. These conditions arise primarily from abnormal neuronal activity and the inability of neurons to undergo self-repair following significant damage. Such impaired cellular responses eventually lead to neuronal degeneration and, ultimately, cell death.[1] Despite significant advances in medical science over recent decades, no definitive cure is currently available for these disorders. The existing therapeutic approaches mainly aim to slow disease progression rather than achieve complete recovery, largely due to the unclear pathophysiology and the inherent complexity of the brain. Recent evidence has revealed that the gut microbiota (GM) can communicate with the brain known as the gut–brain axis (GBA). Key mediators of this bidirectional communication include resident bacterial communities in the gut and their metabolic byproducts, such as short-chain fatty acids (SCFAs), hormone production (serotonin, dopamine and etc)., and vitamin synthesis (K, thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9), and cobalamin (B12)), which influence brain function through immune and inflammatory signaling pathways, autonomic neural circuits, and the hypothalamic–pituitary–adrenal (HPA) axis.[2–4]

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The composition of the GM is generally classified as either "eubiosis" or "dysbiosis," which are broad terms that describe the overall state of the GM as either good or bad for health. Susceptibility to various chronic conditions such as autoimmune disorders, insulin resistance, chronic inflammatory diseases, atopic disorders, and NDs is thought to be closely associated with dysbiosis within GM. Several factors play critical roles in shaping this eubiosis or dysbiosis balance, including age, alcohol consumption, physical activity, stress levels, sleep patterns, circadian rhythm, and dietary habits. Notably, a variety of plant-based diets are thought to offer the best conditions for preserving eubiosis.[5,6] The Mediterranean diet (MD) is the most beneficial dietary pattern.[7] Many of its distinctive components exhibit functional properties that contribute to overall well-being and health. The United Nations Educational, Scientific and Cultural Organization (UNESCO) has recognized the MD, a traditional dietary pattern common to the Mediterranean Sea region, as an element of cultural heritage shaped by social behaviors and environmental responsibility.[8] In most populations, adherence to the MD has been associated with a reduced incidence of chronic diseases and NDs. Moreover, strong adherence to this dietary pattern has been linked to lower rates of disease occurrence and mortality.[9,10]

This review study aimed to assess the hypothesis that the MD may affect four NDs, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, and neuromyelitis optica spectrum disease, by evaluating its potential role in modifying GM composition and mitigating disease progression. To systematically analyze the existing literature, a comprehensive search was conducted across major scientific databases (PubMed, Medline, EMBASE, Scopus, and Google Scholar) for relevant studies published over the past two decades, using combinations of keywords such as "Mediterranean diet AND gut microbiota," "Mediterranean diet AND neurodegenerative disease," "Mediterranean diet AND Alzheimer's disease," "Mediterranean diet AND Parkinson's disease," "Mediterranean diet AND multiple sclerosis," and "Mediterranean diet AND neuromyelitis optica." While numerous studies have individually explored the impact of MD on GM or on neurodegenerative disorders, there is currently no comprehensive synthesis directly linking MD-induced GM modulation to the pathogenesis and progression of these four major neurodegenerative disorders. This review seeks to fill this gap by integrating evidence from both fields to provide a clearer understanding of the potential GBA mechanisms through which the MD could influence neurodegeneration.

Mediterranean Diet

Mediterranean Diet Composition

The MD, which was initially described by Ancel Keys, is high in oils from vegetables and low in saturated fatty acids, as was the case in Greece and Southern Italy in the 1960s.[11] The MD's dietary dimension is defined by a substantial consumption of fresh vegetables and fruits, legumes, seeds, whole grain cereals, and nuts, alongside regular use of olive oil. It includes moderate intake of milk, cheese, yogurt, potatoes, eggs, fish, poultry, and red wine, while limiting red meat and saturated fats.[12] Studies have shown that this diet effectively prevents metabolic syndrome, cardiovascular disease, cancer, and neurological disorders.[13] These health benefits are linked to the presence of antioxidants including carotene, ascorbic acid, and tocopherol as well as the action of flavonoids such polyphenols and anthocyanins. Because MD is high in fiber, antioxidants, and polyunsaturated omega-3 fatty acids (ω3-PUFA), it may have a preventive effect on the neurodegenerative process. Numerous nutrients have been demonstrated to positively impact the development of NDs. Caffeine, some probiotic bacteria, polyphenols, olive oil, curcumin, vitamins B6 and B12, folic acid, unsaturated fatty acids, lecithin, quercetin, plant-based proteins, glycolipids, and glutathione are some of these. On the other hand, a diet high in branched-chain amino acids (BCAAs) and saturated fatty acids, which together show anti-inflammatory, antioxidant, and GM-modulating qualities in preclinical research, speeds up the onset of these disorders.[14,15]

Vitamins, carotenoids, polyphenols, and ω3-PUFA possess anti-inflammatory characteristics that also influence the condition of cell membranes.[16] Olive oil has a wealth of polyphenols and possesses anti-inflammatory and antioxidant characteristics.[17] Astaxanthin and quercetin are plant pigments with potent antioxidant and anti-inflammatory characteristics due to their capacity to neutralize free radicals, mitigate oxidative stress, regulate immunological responses and neuroprotection.[18] Polyphenolic [19] and phenolic acids [20] in nuts augment antioxidant activity and possess barrier protection and GM modulation potential.[21] Plant-based proteins,[22] including legumes, nuts, and seeds, enhance anti-inflammatory butyrate-producing bacteria while diminishing pro-inflammatory bacteria.[23] Glycolipids extracted from tilapia heads mitigate inflammation and modulate the GM by enhancing beneficial bacterial populations.[24] Conversely, proteins originating from animals, especially those found in processed and red meats, are linked to heightened inflammation and worsening of IBD symptoms; in contrast, plant-based proteins possess anti-inflammatory characteristics that may alleviate disease activity.[25,26] Diverse native starches from sources including potatoes and peas, in addition to polysaccharides from *Lycium barbarum* fruits, have demonstrated effectiveness in reducing histological damage and disease progression in colitis-modeling mice. These chemicals also promote GM balance by suppressing bacteria that are harmful.[27] Berry fruits, such as cranberries, are abundant in phenolic bioactive compounds that may support human health.[28,29] Moreover, cranberries, one of the most significant sources of flavonoids with potent anti-inflammatory and antioxidant properties, have been observed to mitigate alterations in GM composition and functioning caused by an animal-based diet in healthy individuals.[30,31] The research has demonstrated that dietary interventions can control mitochondrial ROS generation, detoxification, and oxidative damage repair. Scientists are interested in the bioactive chemicals indicated above because of their potential for neuroprotection, antioxidant and anti-inflammatory actions, and mitochondrial homeostasis to resist neuroinflammatory illnesses associated with mitochondrial dysfunction. The MD is one of the best dietary patterns for reducing the incidence of neurological problems, according to these preliminary research.[14]

Mediterranean Diet and Gut Microbiota

Growing attention is being shown in the connection between diet and GM. Since the GM may support a number of health advantages.[32,33] The GI tract serves as a significant interface between the host and its surrounding environment, while the GM comprises a sophisticated ecological community. As previously emphasized, the GM serves numerous advantageous roles for the host, including the preservation of the intestinal epithelium's integrity, the defense against infections, the production and uptake of dietary nutrients and their by products, and the control of the host's immunological response.[34]

The GM composition is determined at birth and undergoes evolution until adulthood, at which point it stabilizes.[35] The consumption of antibiotics, infections, and many environmental and stress variables can influence and vary the makeup of GM.[36] Alterations in the makeup of this intricate ecosystem have been linked to the emergence of many GI, metabolic, and NDs.[37] Recently, the impact of GM on CNS function, commonly known as the GBA (Figure 1), has garnered considerable attention, with modifications in the GM related to NDs such as MS, AD, and PD.[38]

Numerous factors influence the GM, with nutrition being a significant lifestyle factor affecting the GM. The Western diet, marked by elevated intake of animal-derived proteins, fosters the proliferation of bacteria that contain LPS while diminishing the prevalence of bacteria that produce SCFAs, potentially resulting in systemic inflammation and impairment of the blood-brain barrier (BBB).[39–41] In contrast, studies have shown that gram-positive GMs produce SCFAs (acetate, butyrate, and propionate) primarily through the fermentation of dietary fibers and complex carbohydrates, whereas bacterial metabolism of amino acids leads to the generation of branched-chain fatty acids (BCFAs). These metabolites exert distinct immunomodulatory effects. Polyamines derived from these processes further reduced inflammation by inhibiting the release of IL-1, IL-6, and TNF-α. Additionally, Maintaining intestinal function and microbial balance requires a sufficient protein intake.[42]

The physiological effects on host health are shaped by a combination of direct host–GM interactions and indirect microbial processes. For instance, the fermentation of complex carbohydrates (eg, fiber) and plant-based foods—hallmarks of the MD that cause GM eubiosis and promote the production of microbe-associated anti-inflammatory mediators such as SCFAs.[43] Conversely, diets heavy in sugar and fat cause dysbiosis in the GM, which in turn causes inflammation, endotoxemia, gut barrier and BBB permeabilization, and systemic low-grade inflammation and may lead to CNS autoimmunity. CNS inflammation is initiated and/or exacerbated by chronic systemic inflammation.[44,45]

MD contains a high concentration of complex and insoluble fiber relative to a conventional Western diet. A substantial consumption of dietary fiber is recognized for its beneficial effect on GM, characterized by a diminished presence of Firmicutes and an elevated abundance of Bacteroidetes, resulting in increased amounts of SCFAs, especially butyrate, in the GI tract. These SCFAs influence cellular function and have been shown to provide protection against a range of intestinal, inflammatory, allergy, NDs and promote Foxp3+ Treg cell development.[46–50] SCFAs can interact and activate immune cell and G protein-coupled receptors (GPR), including GPR41, GPR43, and GPR109,[51] facilitating enhancements in intestinal

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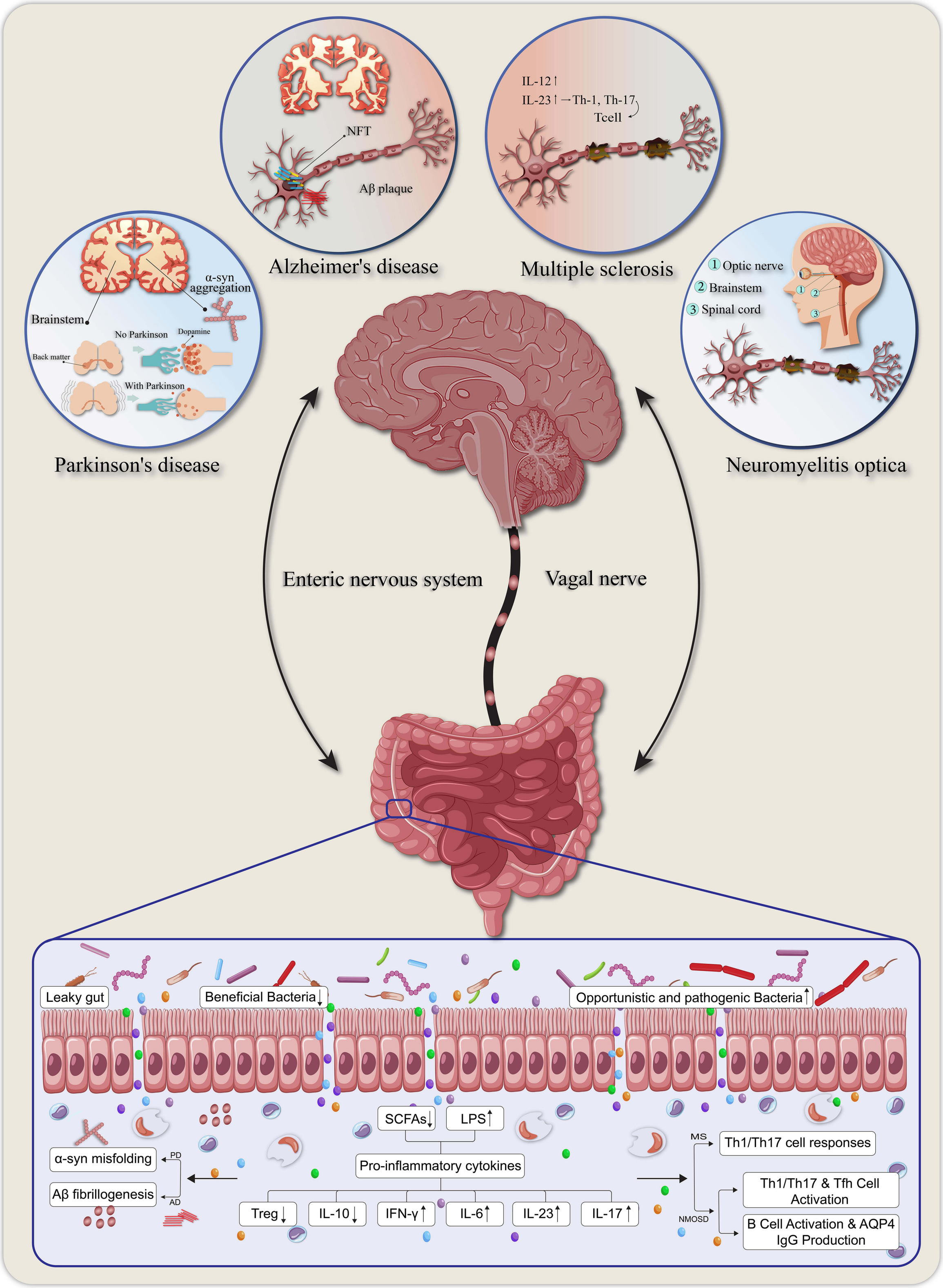

Figure 1 When dysbiosis occurs in the gut, the intestinal epithelium becomes permeable, allowing certain bacteria and their harmful metabolites to cross the intestinal barrier. This process triggers the inflammatory system, leading to the activation of inflammatory cytokines. These cytokines enter the bloodstream and, upon reaching the brain, contribute to the progression of neurodegenerative diseases. Furthermore, in the case of dysbiosis, beta-amyloids can form in the gut and migrate to the brain, exacerbating AD. In PD, misfolding of alpha-synuclein proteins begins in the gut and their transfer to the brain accelerates the disease progression. Lastly, in MS and NMO, dysbiosis inhibits Treg cells and activates certain T cell subsets, ultimately leading to the destruction of neuronal myelin.

barrier function, anti-inflammatory responses, and antioxidant activity.[52] Omega-3 polyunsaturated fatty acids, primarily derived from fish oil, are recognized for their ability to attenuate inflammatory responses through GPR120 activation.[51]

The variety and makeup of GM are greatly influenced by both macronutrients (protein, fiber, and fatty acids) and micronutrients (vitamins and minerals). The advantages of high-fiber diets (ie, MD) have been shown in both short-term and long-term dietary treatments, which reduce systemic inflammation and promote longevity. Rural communities have a more diverse GM, which is associated with their high fiber intake and increased the ability of GM to ferment fiber; individuals that eat a lot of whole grains and total carbohydrates have also been shown to have similar health benefits. In contrast, diets like the Western diet are linked to higher levels of inflammation and the potential loss of certain bacterial species [53,54] (Figure 2).

A class of bioactive phytochemicals known as dietary polyphenols is primarily found in a variety of fruits, vegetables, seeds, herbs, and beverages (including wine, beer, fruit juice, coffee, tea, and chocolate) as well as, to a lesser degree, dry legumes and cereal. Polyphenols may help prevent a number of diseases, such as diabetes, heart disease, obesity, and NDs, according to numerous research. The GM influences the stability of dietary polyphenols through a number of multi-enzymatic reactions, including as deglycosylation, sulfation, glucuronidation, C ring breakage of the benzo-γ-pyrone system, dehydroxylation, decarboxylation, and hydrogenation. By altering the GM, polyphenol ingestion may help the host by encouraging the growth of beneficial bacteria and/or limiting the formation of dangerous bacteria.[55] The GM's composition was altered by the administration of meals or extracts rich in polyphenols in addition to pure polyphenols. After being exposed to green tea polyphenol extracts for eighteen weeks, dogs showed reduced levels of Bacteroidetes and Fusobacteria and increased levels of Firmicutes.[56] The administration of polyphenols may change the production of SCFAs by changing the composition and, hence, the function of the GM. The in vitro fermentation of rutin, quercetin, caffeic acid, and chlorogenic acid significantly increased the synthesis of propionate and butyrate. Rutin produced the greatest propionate and butyrate during the fermentation of caffeic acid.[55]

Dietary fiber and polyphenols work in concert to modify microbial diversity, boost the production of SCFAs, and improve gut barrier integrity in the GM, all of which promote immunological and metabolic balance.[57] Unabsorbed polyphenols interact with the GM in the colon, aid in the production of microbial metabolites including phenolic acids and SCFAs, and fortify mucosal and immunological barriers. These microbial interactions and immunomodulatory actions, such as NF-κB inhibition and regulation of innate and adaptive immune cells, are essential to comprehending their systemic efficacy.[58] However, GM may cause acute or long-term changes in tryptophan levels by depletion, supplementation, or molecular modification, which may affect brain function and change the peripheral and central levels of tryptophan metabolites. The metabolic cascades for tryptophan metabolism and tryptophan metabolite synthesis, which are intimately linked to the GBA, are significantly influenced by microbial regulation.[59] Furthermore, the liver produces Trimethylamine n-oxide (TMAO) from trimethylamine (TMA), which is created by GM fermentation of choline-rich substances like betaine, phosphatidylcholine, and L-carnitine, which are primarily found in meat and eggs. *Clostridium* species, *Eubacterium* species, and *Escherichia coli* are the primary bacteria that produce TMA. The hepatic enzyme FMO3, whose expression exhibits sexual dimorphism and is higher in females, mostly converts ingested TMA to TMAO.[60] TMAO, a byproduct of the GM, is derived from phosphatidylcholine. There is evidence linking TMAO to the pathophysiology of a number of NDs. On the one hand, TMAO levels are elevated by age-related cognitive decline. But TMAO also induces mitochondrial failure, glial cell polarization, oxidative stress, and neuroinflammation in the brain.[61] Red meat consumption is associated with cognitive impairment, and patients with cognitive dysfunction had higher TMAO levels.[62] In addition to their conventional role in lipid metabolism, bile acids are neuro-modulatory substances in the gut-liver-brain axis. Their synthesis and conversion into secondary bile acids require the GM.[63] GM tightly controls tryptophan metabolism, which influences immunological response and serotonergic pathways. Under healthy settings, microbial activity produces serotonin and indole derivatives, which are neuroprotective and anti-inflammatory. Dysbiosis exacerbates this shift by increasing the synthesis of pro-inflammatory kynurenine derivatives while decreasing the synthesis of beneficial indole molecules. This imbalance affects both microglial activation and chronic neuroinflammation. Interventions that modify dietary consumption or microbial makeup to restore tryptophan metabolism may have neuroprotective benefits.[64]

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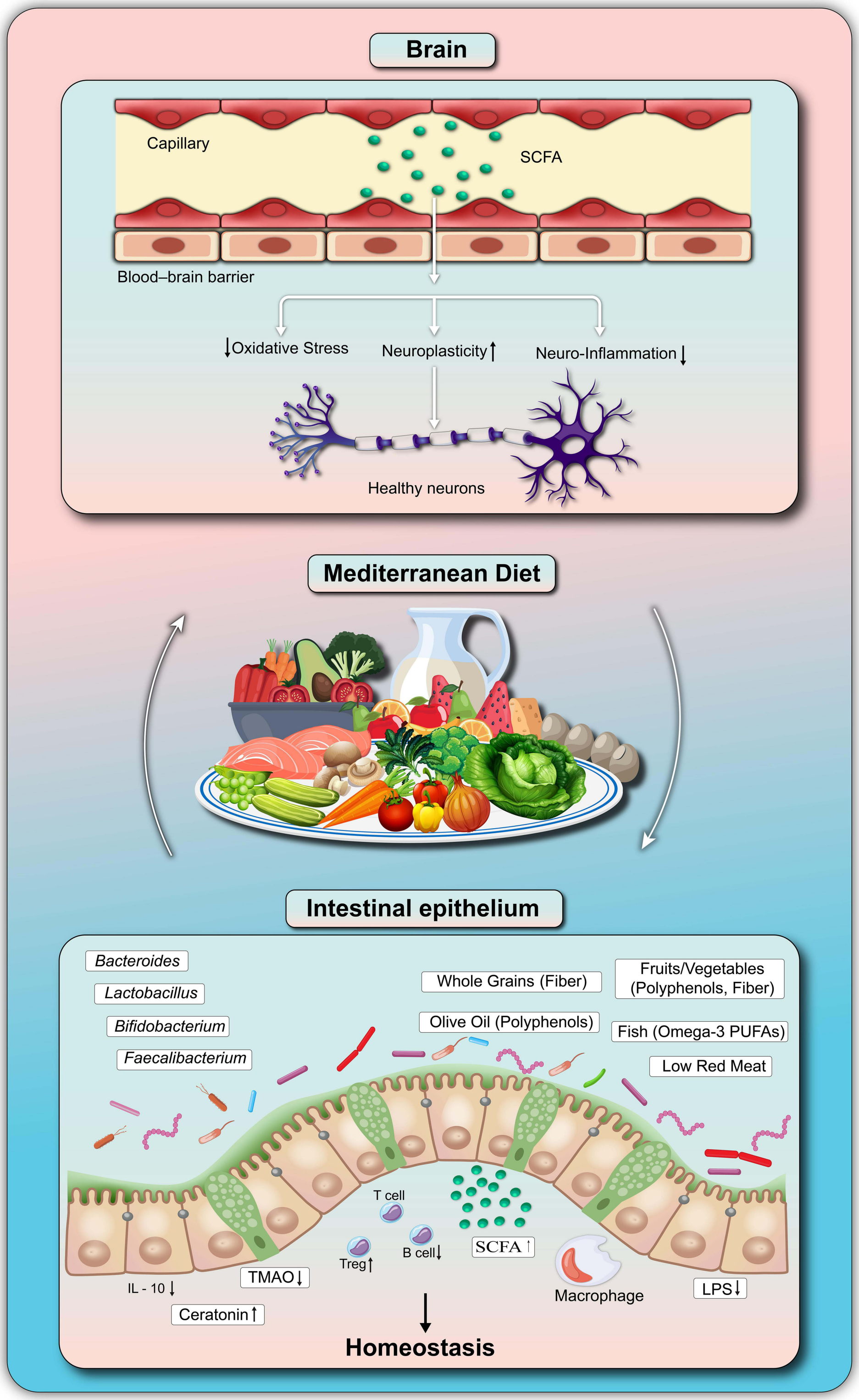

Figure 2 Adherence to a Mediterranean diet modulates the gut microbiome, resulting in the production of beneficial metabolites. One such metabolite is short-chain fatty acid (SCFA), which is capable of crossing the blood-brain barrier and provides neuroprotective effects.

But in NDs like Alzheimer's, a metabolic shift away from the serotonergic pathway diminishes these protective advantages, potentially accelerating emotional dysregulation and cognitive deterioration. In contrast, the neurotoxic branch of the kynurenine pathway breaks down tryptophan into metabolites such quinolinic acid and 3-hydroxykynurenine. Quinolinic acid, a potent N-methyl-D-aspartate receptor (NMDAR) agonist, induces excitotoxicity through oxidative stress, excessive calcium influx, and eventually neuronal cell death.[64] Quinolinic acid accumulation not only has direct neurotoxic effects but also promotes glial activation and pro-inflammatory cytokine production, which feeds the cycle of growing brain damage.[63] Based on these complex mechanisms and the effects of dietary micronutrients on the GM and GBA, it can be argued that nutrition might probably affect the GM and, consequently, the signaling pathways of NDs.

Neurological Disorders and Mediterranean Diet

Alzheimer's Disease

A majority (60–70%) of dementia patients are caused by Alzheimer's disease (AD), making it the predominant cause.[65] It is defined through progressive accumulation of amyloid β (Aβ) plaques and neurofibrillary tangles. These aberrant protein aggregates induce cognitive decline, memory loss, and behavioral alterations by disrupting neuronal transmission.[66] Despite extensive research endeavors to elucidate the pathophysiology of the disease, the causal linkages among the many biological processes implicated in AD remain inadequately comprehended. The absence of clarity presents considerable obstacles in formulating successful therapies, underscoring the need for a thorough and multifaceted strategy to address the condition.[67]

Gut Microbiota in AD Patients

The multifactorial characteristics of AD and current research hypothesized that GM plays a role in the etiology of AD.[68] Multiple studies undertaken in the last decade have shown a significant association between GM and the initiation and progression of AD.[67,69] Research demonstrated that the development of AD may start in the GI tract and then advance to the brain. A1-42 oligomers were administered to mice's intestinal walls, and the progression of amyloids from the colon to the brain was monitored over the span of one year. The scientists determined that AD and neuroinflammation are possibly considerably influenced by the cross of A oligomers from the GI tract to the brain.[70] The elevated numbers of various Gram-negative bacteria (*Escherichia coli, Salmonella* spp., *Helicobacter pylori, Klebsiella* spp., and *Citrobacter* spp.) in the GI tract, together with reports of bacterial-derived components or bacterial DNA detected in the brain or cerebrospinal fluid of AD patients, have led to the hypothesis about the pathophysiology and role of these microbial communities in NDs.[71]

It was discovered that LPS, an essential part of Gram-negative bacteria like *E. coli, Salmonella* species, and *H. pylori*, is crucial for the extracellular aggregation of amyloid fibers.[72] LPS may contribute to the beta-amyloid fibrillogenesis, resulting in the analytical deficit seen within in vitro circumstances.[73] Concurrently, several GM strains produce a significant quantity of functional amyloid-like proteins. Chapman's group discovered that extracellular fibers known as "curli," produced by *E. coli* and other GM, may have physicochemical and structural properties similar to amyloids.[74] Scientific investigation indicates that *Staphylococcus, Streptococcus, Salmonella, Klebsiella, Citrobacter, Mycobacteria*, and *Bacillus* species are capable of forming extracellular amyloids [75] (Figure 1). Additionally, SCFAs, tryptophan-derived metabolites, and GM bile acids are among the most well-researched substances that have been linked to the pathogenesis of AD.[63] Nevertheless, further clinical trials and human research are required in this field.

Mediterranean Diet in AD Patients

Evidence has increased about the crucial role of the MD in avoiding cognitive decline and mitigating the risk of AD.[76–78] A meta-analysis determined that strict adherence to the MD correlates with a 17% and 40% reduction in the risk of Mild Cognitive Impairment (MCI) and AD, respectively.[79] A comprehensive meta-analysis based on findings from 15 distinct dietary cohort investigations indicated that the MD markedly enhanced cognitive function in older individuals.[80] The MD was found to be beneficial for both AD incidence and cognitive decline, as demonstrated by a decline in a cognitive function test score.[14]

While the mechanisms via which the MD provides neuroprotective advantages are not fully elucidated, numerous studies have suggested possible paths. The MD intensely increases the growth of bacteria that break down fiber and produce SCFA, including *Bacteroides, Bifidobacteria, Prevotella*, and *Eubacterium eligens*, and reduces the prevalence of *Ruminococcus gnavus* as a pro-inflammatory bacterium, leading to elevated levels of advantageous SCFAs and diminished levels of toxic metabolites.[81–83] These metabolites, as well as biologically active substances and botanical compounds, can traverse the intestinal barrier, enter the bloodstream, and even penetrate the BBB to reach the brain.[84] Furthermore, as AD progresses, these compounds have been shown to increase synaptic plasticity and reduce the accumulation of tau and Aβ in the brain.[85] The nutritional intervention improved individual memory and cerebral blood flow, as researchers found.[86] MD causes significant changes in the GM community and metabolites, according to another study conducted on an animal model of AD. Most significantly, MD encouraged the *Lactobacillus* population to proliferate, which raised the amount of lactate produced by the bacteria increased serum levels of metabolites originating from genetically modified organisms and nutrition, indicating their impact on the brain. Crucially, these alterations in serum metabolites caused modifications in the hippocampus's neuroinflammatory-associated pathway profiles and elevated certain receptors with neuroprotective properties. Furthermore, these metabolites showed a strong positive correlation with neurobehavioral outcomes, gut-brain integrity, and inflammatory markers [87] (Table 1). But in AD, the formation of neurotoxic metabolites like quinolinic acid—a strong NMDAR agonist that causes excitotoxicity and neuronal damage—is favored by a change in metabolic flux toward the kynurenine pathway. This change is made worse by dysbiosis, which increases the production of pro-inflammatory kynurenine derivatives while reducing the production of advantageous indole molecules. Chronic neuroinflammation and microglial activation are both influenced by this imbalance. Neuroprotective advantages may result from interventions that alter dietary intake or microbiota composition to restore tryptophan metabolism.[64] Anthocyanins, flavonoids, and phenolic acids are some of the MD's constituents may regulate the neuronal Nrf2 pathway. Alzheimer's disease etiology was influenced by Nrf2. Through the phosphorylation of Fyn, the protein GSK-3, a Chinese medication that stimulates aberrant tau protein phosphorylation, encourages the destruction of Nrf2 as part of the proteasomal activity in AD. Moreover, tau hyperphosphorylation brought on by GSK-3 activation in AD may have an impact on mitochondrial function. Neurofibrillary tangles (NFT), which are thought to be a characteristic indication of AD, may then develop as a result of an accumulation of tau pathogenic forms. Cranberry fruit extracts' anthocyanin component reduced prostaglandin synthesis by blocking COX, which in turn lowered inflammatory processes. Additionally, anthocyanins may precede the formation of amyloid plaques or neurofibrillary tangles by increasing the activation of the FKBP52 protein, affinity for phosphorylated tau protein and inhibits its aggregation. Autophagy is a crucial mechanism for removing misfolded proteins or damaged organelles.[14]

n-3 PUFAs exhibit a multifaceted capacity to mitigate pathological alterations characteristic of AD. Through modulation of neuronal membrane properties and glial reactivity, n-3 PUFAs counteract the effects of pro-inflammatory n-6 derivatives, facilitating the clearance of amyloid-β aggregates and attenuating tau protein hyperphosphorylation. Furthermore, these fatty acids inhibit the nuclear factor-kappa-B signaling cascade, leading to a marked reduction in the secretion of proinflammatory cytokines.[95] Preclinical and clinical studies further suggest that n-3 PUFA supplementation can alleviate neuroinflammation, support synaptic function, and diminish amyloid-β aggregation, thereby mitigating early neuropathological alterations and contributing to improved memory and cognitive outcomes in AD.[96]

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopamine-producing neurons in the substantia nigra, which leads to impaired motor function.[97] Motor symptoms such as tremors, bradykinesia, rigidity, and postural instability are induced via this deficiency of dopamine.[98] Non-motor symptoms, such as cognitive deterioration and emotional disturbances, are also associated with PD. Lewy bodies, aggregates of the protein alpha-synuclein, are the hallmark of PD. Despite the association of inherited variables and environmental chemical exposure with PD, its precise origin remains unidentified.[66]

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Table 1 Gut Microbiome Alterations with Mediterranean Diet in PD, AD, MS Diseases

Author's Name	Country	Type of Disease	Design	Case (N, Age)	Control (N, Age)	Gender (Male/Female)	Intervention	Duration of Intervention	Main Findings	Ref
Rusch et al, (2021)	USA	PD	Case control (Pilot Study)	8 71.4 ± 2.6	8	Case (63.8%/ 36.2%)	MD*	5 weeks	↓ Desulfovibrionaceae, Clostridium bolteae, Ruminococous, Blautia, Dorea, Lachnospiraceae ↑ Proteobacteria	[88]
Kwon (2024)	USA	PD	Cohort	85 51-90	-	Case (67%/33%)	MD	9.7 years	↑ *Butyricicoccus, Coprococcus 1, Hydrogenoanaerobacterium, Negativibacillus, Romboutsia, Ruminococcaceae NK4A214 group, and Ruminococcaceae*	[89]
Nagpal et al (2019)	USA	AD (mild cognitive impairment)	Pilot study	11 64.6 ± 6.4 yr	6 64.6 ± 6.4 yr		MMKD* or AHAD*	6 weeks	↑*Enterobacteriaceae, Akkermansia, Slackia, Christensenellaceae and Erysipelotriaceae*, ↓ *Bifidobacterium* and *Lachnobacterium* reduces on MMKD ↑ *AHAD increases Mollicutes Ctinobacteria*,family Bifidobacteiaceae, and genus Bifidobacterium were significantly reduced among the MCI* group after MMKD compared to CN*participants	[90]
Mateo et al (2024)	Spain	AD	Case/control	25	25	Case (mean 70.6) Control (mean 73)	–	–	Dysbiosis observed in Spanish AD patients is characterized by reductions richness and alpha-diversity were significantly lower in the AD group compared to the HC. alterations in GM composition, may be linked to adherence to the MD and cognitive and functionality symptoms.	[91]

(*Continued*)

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Table 1 (Continued).

Author's Name	Country	Type of Disease	Design	Case (N, Age)	Control (N, Age)	Gender (Male/Female)	Intervention	Duration of Intervention	Main Findings	Ref
Mirza et al (2024)	Canada	Pediatric-onset MS	Case/control	27	32	–	-	-	More abundant in the MS participants relative to the HC: *Methanobrevibacter, Eggerthella* sp. and *Lactococcus* sp., P < 0.019. lower abundance in the MS participants relative to HC: *Clostridiales vadin BB60* group and *Ruminococcaceae NK4A214* group sp. (P < 0.025). Findings suggest that the potential interaction between diet and the gut microbiota is relevant in MS	[92]
Nitzan et al (2023)	Israel	MS	Case/control	57	43	(29.8%/70.2%-case) (41.9%/58.1%-cont)	-	-	Two taxa enriched in MS group correlated negatively with MD, namely, the *Peptostreptococcaceae* family (p = 0.035) and the *Romboutsia* genus (p = 0.018) belonging to the same family, while two taxa reduced in MS, the genus *Ruminococcaceae* UCG-013 (p = 0.036) and the species *Bifidobacterium Animalis* (p = 0.015), correlated positively with MD	[93]
Saresella et al (2017)	Italy	MS	Pilot study	10 (western diet) 10 (high vegetable/ low protein)	HV/LP* (7 females and 3 males) WD (8 females and 2 males;)	-	WD Hv/lp	12 months	Lachnospiraceae family was significantly more prevalent; IL-17-producing T CD4+ lymphocytes (p = 0.04) and PD-1 expressing T CD4+ lymphocytes (p = 0.0004) were significantly decreased; and PD-L1 expressing monocytes (p = 0.009) were significantly increased. In the HV/LP diet group, positive correlations between Lachnospiraceae and both CD14+/ IL-10+ and CD14+/TGFβ+monocytes (p = 0.05, p = 0.04, respectively), between Lachnospiraceae and CD4+/CD25+/ FoxP3+ T lymphocytes (p = 0.02) were observed.	[94]

Abbreviations: *MD, Mediterranean diet; MCI, Mild cognitive impairment; CN, Cognitively normal; HV/LP, High vegetable/ Low protein; MMKD, Modified Mediterranean-Ketogenic Diet; AHAD, American Heart Association Diet; ↑, increase; ↓, decrease.

Gut Microbiota in PD Patients

A Recent study indicates a possible connection between PD and the GI system. Current findings demonstrate α-synuclein accumulation might initiate in the submucosal neurons of the GI tract, perhaps happening as much as eight years before the manifestation of motor symptoms.[99,100] Research indicates that pathogenic microorganisms in the GM may misfold and accumulate α-synuclein under certain circumstances. This misfolding later reaches the brain via a network of continuous projection neurons, hence promoting the development of PD.[101]

GM may stimulate the immune system via a compromised gut barrier, leading to a systemic inflammatory response that subsequently disrupts the BBB, fosters neuroinflammation, and ultimately causes neural injury and degeneration.[102] Bacterial pathobionts may induce intestinal inflammation, which might contribute to the onset of α-syn misfolding.[103] Systemic or vagal routes, in conjunction with microglia in the intestinal wall, may enable the transmission of aggregated α-synuclein to the brain, therefore activating microglia. The activation of microglia may intensify pre-existing brain inflammation and facilitate further aggregation.[104] Furthermore, α-synuclein facilitates the misfolded aggregation of itself, resulting in the degeneration of midbrain neurons that release dopamine [105] (Figure 1).

Mediterranean Diet in PD Patients

As no therapeutic interventions are available to halt the advancement of PD, preventive measures may be implemented to mitigate risk factors and decrease the likelihood of disease onset. In this context, nutrition may serve as a part of the environment that can either facilitate or inhibit the progression of PD, similar to other pathological diseases.[34]

MD is considered to serve a preventive function and reduce the likelihood of PD development.[106] The MD encourages the growth of good bacteria such as *Bifidobacteria, Prevotella, Lactobacillus, Bacteroides*, and *Eubacterium eligens* while diminishing pathogenic bacteria including *Escherichia, Shigella*, and *Clostridium*. The outcome is an elevation in SCFAs and bioactive molecules capable of traversing the BBB.[107] It is hypothesized that unsaturated fatty acids and fiber diminish the likelihood of metabolic endotoxemia, specifically a two-to-three-fold elevation in LPS.[108] Significantly, endotoxins can induce tau in AD and α-synuclein in PD patients [109] (Figure 2).

MD is thought to have an anti-inflammatory effect, which could lower the chance of acquiring PD. This dietary regimen is associated with the promotion of a healthy GM metabolism and the induction of intestinal gluconeogenesis, and also the enhancement of brain-derived neurotrophic factor (BDNF) production. These mechanisms contribute to improved synaptic plasticity and cognitive function, in addition to the secretion of glucagon-like peptide 1 (GLP-1), which mitigates neuroinflammation by inhibiting the NLRP3 inflammasome.[110,111] Additionally, prior studies have shown that SCFA concentrations are higher while TMAO levels are lower. TMAO is a metabolite derived from GM that is considered a biomarker for advanced PD when present in elevated levels.[16]

However, the relationship between TMAO and PD is inconsistent across studies. While some clinical reports associated higher peripheral TMAO with PD severity and progression, other studies most notably Chung et al in a cohort of drug-naive early PD patients found lower plasma TMAO in PD versus controls and linked lower TMAO to faster longitudinal increases in levodopa-equivalent dose. These discrepant findings may reflect differences in disease stage, medication status (drug-naive vs chronic therapy), sample type (plasma vs stool), diet, comorbidities, geographic or cohort differences, and analytical methods. Accordingly, TMAO cannot yet be unambiguously considered a marker of advanced PD, and further longitudinal and mechanistic studies are needed to clarify its role.[112] Clinical trial results have indicated that adherence to MD is associated with improvements in cognitive functions, including attention, memory, and executive functioning, among patients with PD [39] (Table 1). As discussed in AD, flavonoids, anthocyanins, and phenolic acids may regulate the Nrf2 pathway in neurons. Nrf2's role in the etiology of AD and PD. Increased dopamine release in PD may affect mitochondrial function, which raises ROS levels that impact Nrf2 activity and the body's reaction to oxidative damage. Furthermore, the decrease in Parkin and PINK expression levels found in PD may affect the mitochondrial system's ability to operate by generating depolarization, fragmentation, a respiratory deficit, and a decrease in ATP. These alterations will affect synapse function and exacerbate the neurodegeneration and cognitive decline associated with PD.[14]

Multiple Sclerosis

Among early-onset chronic conditions, Multiple Sclerosis (MS) shows predominant prevalence with significant disability metrics. Together with the disease's socioeconomic effects, the incidence of MS is rising globally. Even while the specific cause of MS and the mechanisms behind this rise are yet unknown, intricate gene–environment interactions most certainly play a significant part.[113] Two pathological hallmarks of MS are 1) inflammation with demyelination and 2) neurodegeneration and gliosis, or proliferation of astrocytes. Only the CNS sustains tissue damage in MS, leaving the peripheral nervous system unaffected.[114] The pathological hallmark of MS is inflammatory lesions around the veins, leading to demyelinating plaques. MHC class I-limited CD8+ T-cells predominate among the T-lymphocytes found in inflammatory infiltrates; B-cells and plasma cells are also present, albeit in significantly smaller quantities. Inflammation leads to demyelination and damage to oligodendrocytes. Early in the disease, axons are largely unharmed, but as the condition worsens, irreversible axonal damage occurs.[115–117]

Dendritic cells (as antigen-presenting cells), that which exhibit an active phenotype in MS patients, seem to be the source of immune dysregulation. Memory T cells are differentiated into pro-inflammatory T helper 1 (Th1) and Th17 lymphocytes by dendritic cells that cross the BBB. Demyelination and axonal loss are caused by oxygen and nitric oxide radicals and also other pro-inflammatory cytokines, which are produced when macrophage and microglial activation is induced. CD8+ T cells and memory B cells in the CNS are two additional recognized mediators of MS pathogenesis.[118]

Gut Microbiota in MS Patients

Both environmental and genetic variables play a role in the development of MS. One of the environmental risk factors associated with the onset of MS is the composition of commensal GM. According to recent research, dysbiosis functions as a pathogenic environmental factor and contributes to several autoimmune diseases. It shapes both innate and adaptive immune responses toward the inflammatory profiles found in many illnesses, including MS.[119–121] By acting as the locus where various disease-related risk factor, including T-helper-cell polarization, T-reg-cell function, and B-cell activity converge, GM specifically influences the course of MS.[122,123]

Several gut bacterial strains with potential probiotic effects, such as *Lactobacillus, Bifidobacterium, Bacteroides coprophilus*, and *Faecalibacterium prausnitzii*, are known SCFAs producer and have been reported to be reduced in MS patients.[124–126] Lower amounts of *Bacteroides*, a beneficial bacterium that promotes Interleukin 10 (IL-10), are typically found in patients with MS. According to published research, *F. prausnitzii* is a marker of a healthy GM and is diminished in MS patients.[127,128] By producing SCFAs and promoting tight junction protein expression levels in epithelial cells, Lachnospiraceae contributes to the decrease of mucosal permeability.[129] Several pieces of evidence indicate that the GM influences immunological function, which in turn contributes to MS. One feature that has been found to remain constant across the MS clinical stages is intestinal dysbiosis.[130]

Although most butyrate is locally metabolized by colonocytes as an energy source, several mechanisms allow it to influence neuronal function. SCFAs can modulate CNS neuroinflammation and cross the BBB via specific transporters on endothelial cells. In particular, butyrate has potent immunomodulatory properties, regulating inflammatory processes by maintaining the balance between Th17 cells and pro-/anti-inflammatory cytokine levels. Additionally, butyrate acts as an inhibitor of histone deacetylase (HDAC), which can enhance the expression of neurotrophic factors such as BDNF that support neuronal survival, growth, and synaptic plasticity. Moreover, by strengthening intestinal barrier integrity, reducing systemic inflammation, and modulating vagal afferent signaling, butyrate indirectly contributes to improved neuronal function through the gut–brain axis.[33] Gut dysbiosis may disrupt the balance between pro-inflammatory long-chain fatty acids and anti-inflammatory SCFAs, thereby promoting disease progression.[131,132] Indeed, a recent study reported lower serum levels of propionic acid in MS patients, and supplementation with this metabolite delayed disease onset in experimental autoimmune encephalomyelitis (EAE), an animal model of MS, by inducing regulatory T cells through modulation of the GM.[133] SCFAs also act on intestinal epithelial cells to increase the secretion of β-defensins and regenerating islet-derived III (REGIII) proteins, which lower IL-1 and IL-6 expression while increasing IL-10, thereby suppressing intestinal infection, promoting Treg differentiation, and shifting immune responses toward an anti-inflammatory state by boosting Treg cell counts and suppressing Th1/Th17 cell responses [131] (Figure 2).

Mediterranean Diet in MS Patients

In MS, the MD may improve comorbidities, GM, and the systemic inflammatory state. The MD appears to control GM, lower inflammatory markers, and contribute factors for vascular disease in relation to many autoimmune diseases. As a result, it has been proposed that the MD is linked to a low chance of developing MS.[134] Much research is currently being conducted to determine whether there is a direct correlation with nutrition and GM.[135,136] The composition of the GM can be influenced by food, which may indirectly promote the onset of autoimmune inflammatory diseases like MS.[137] It's interesting to note that a diet low in whole grains, fiber, and iron is reflected in the gene composition (metagenome) of the GM in young people with MS that started in childhood.[138] However, little is known about how nutrition and GM interact in MS patients, particularly in younger patients who are just beginning the disease.[32]

The MD may be able to change how MS develops and the symptoms that come with it, according to new research. A higher MD score among MS patients was linked to lower disease severity, disability, fatigue, and depression, according to two cross-sectional investigations and a randomized controlled pilot experiment.[139–141] Additionally, a recent study found that MRI evidence of damage to tiny arteries in the brain decreased with the degree of MD adherence.[142] The idea that the MD might help avoid chronic diseases was highly supported by the most current pooled analysis of epidemiological studies.[143] Moreover, another investigation demonstrated a strong correlation between higher intakes of iron and fiber and a decreased chance of MS with a pediatric onset.[92] Additionally, a protective association was found between MS risk and the GM variance linked with fiber and the alternative MD measure, both in terms of the overall composition and the quantity of specific taxa. According to the study's findings, a healthy diet high in fiber, like the MD, and the host's gut flora probably interact to cause MS and suggest that dietary practices could account for variations in a number of gut taxa between MS patients and healthy controls (HC). These findings also corroborate the human and animal nutrition intervention research. For instance, a lower abundance of *Eggerthella* [144] and *Methanobrevibacter* [145,146] was linked to animal diets high in fiber, such as resistant starch and cereals. In their MS cases, these genera were likewise enriched. *Eggerthella* and *Lactococcus* abundances quickly increased when consumption of carbohydrates and fiber was reduced. Similarly, in a study of ten subjects, a brief, one to three-day decrease in carbohydrate and fiber intake led to an increase in the number of *Lactococcus* and *Eggerthella*.[147,148]

Based on the findings of another study, people with MS who adhered to their doctors' orders for the MD diet more closely had less severe MS than those who did not. Furthermore, the potential positive impact of MD may be mediated by the entire dietary pattern rather than being associated with just one food type or component of this regimen.[149] Diets heavy in fat, sugar, and animal protein can boost adaptive immunity cross-reactive cells, harm the gut barrier, and cause enteric inflammation. After that, the impact on the MS course.[150–152] In this regard, according to a study [153] involving 435 MS patients, the MD may have a positive impact on the course and impairment of MS. Because MD modulates the GM and low-grade chronic systemic inflammation, it may have a favorable effect on MS long-term impairment outcomes. This is clear considering how long-term impairment is linked to secondary neurodegeneration and autoimmunity, both of which are maintained by chronic systemic inflammation.

Fifty MS patients and twenty-one HC participated in another study by Vacaras et al.[127] According to their findings, MS patients who did not receive treatment had reduced levels of *Actinobacteria, Bifidobacterium*, and *F. prauznitzii*, as well as higher levels of *Prevotella stercorea*, whereas treated patients had lower quantities of *Ruminococcus* and *Clostridium. Lachnospiraceae* and *Ruminococcus* were lower in treated MS patients than in the original sample, whereas *Enterococcus faecalis* was higher. After receiving homeopathic medication, *Eubacterium oxidoreducens* decreased. According to the study, dysbiosis may be present in MS patients. Additionally, various taxonomic alterations were implied by therapy with homeopathy, teriflunomide, or interferon beta-1a. However, they notice the rise in Firmicutes and a decline in the phyla Bacteroidetes and Actinobacteria in the microbiome profiles of their MS cohort. These alterations are unique to the typical Western diet, which is heavy in fats and sugars. Firmicutes are better at obtaining energy from food, which leads to weight gain. Conversely, a diet high in fiber and complex carbohydrates encourages the development of advantageous metabolites and Bacteroidetes. Together, these first results are promising since they imply that dietary factors may change GM and, in turn, MS susceptibility.[127,154,155] Table 1 catalogs empirical evidence documenting diet-associated GM restructuring through MD interventions.

Neuromyelitis Optica Spectrum Disease

The inflammatory demyelinating condition known as Neuromyelitis Optica Spectrum Disorder (NMOSD) is linked to antibodies that target the astrocyte-expressed water channel protein aquaporin-4 (AQP4). T cells are thought to have a key part in the pathophysiology of NMOSD, despite the fact that it is mostly regarded as a humoral autoimmune disease. The immunoglobulin G1 subclass, which is dependent on T cells, includes AQP4-specific antibodies. T cell-induced inflammation is necessary for the entry of AQP4 antibodies into the CNS. AQP4-specific T cells are more common in NMOSD patients, and they generate IL-17, which suggests that Th17 cells play a part in the pathophysiology of NMOSD. Finding environmental stimuli that could cause the development of AQP4 autoantibodies has received a lot of attention. Research on AQP4-reactive T cells in NMOSD patients showed that T cells that recognized the AQP4 T-cell epitope displayed a Th17 characteristic and cross-reacted to a comparable peptide.[156] NMOSD was long believed to be a severe atypical type of MS.[157] An abundance of neutrophils and eosinophils, as well as the deposition of complement and antibody, are characteristics of NMO lesions, which are mainly limited to the optic nerves, brainstem, and spinal cord as opposed to MS.[158] Like MS, NMOSD primarily affects young adults, especially women.[159]

GM in NMOSD

Disturbances in the GM of NMOSD patients in comparison to HC have been noted in multiple academic reports. In a study, the NMOSD and HC groups' GM compositions were obviously different so that the pathogenic genera *Streptococcus* and *Flavonifractor* were more prevalent in NMOSD patients than in HC patients. Furthermore, a number of GM, such as *Faecalibacterium, Coprococcus, Lachnospiraceincertaesedis, Blautia, Prevotella, Romboutsia, Roseburia*, and *Fusicatenibacter*, were found in significantly reduced abundance in NMOSD patients than in HC. Furthermore, ROC curve analysis from a functional study indicated that GM abundance had predictive capacity to differentiate NMOSD from HC. The study provides evidence that alterations in the GM contribute to the development of NMOSD. Three metabolic pathways—"photosynthesis", "photosynthesis proteins", which are categorized as energy metabolism pathways, and "thiamine metabolism" which is linked to thiamine pyrophosphokinase deficiency disease and involves the metabolism of cofactors and vitamins—were found to be significantly downregulated in the GM of NMOSD patients. Even when many comparisons were taken into account, these differences were still substantial.[160] It has been observed that thiamine deficit increases the Th1 and Th17 cell subsets.[161] Additionally, these pathways are crucial for the persistence of GM through the metabolism of vitamin B. Remarkably, patients with AQP4-IgG sera-positive NMOSD had previously been found to have low levels of vitamin B12 in their serum,[162,163] and NMOSD patients also had lower levels of vitamin D, which may be related to the decrease in the photosynthesis proteins pathway.[164] Additionally, it was reported that an overabundance of *Streptococcus sp*. was linked to a decrease in SCFAs in NMOSD patients, which boosted CD4 (+) T cell activation to encourage inflammatory responses.[165,166]

According to another investigation, T cells from patients with NMOSD who were treated with the peptide p61-80 showed noticeably increased proliferation. A region inside the *Clostridium perfringens* adenosine triphosphate-binding cassette transporter permease, a common anaerobic Gram-positive spore-forming bacterium present in human GM, showed high resemblance to the peptide p63-76. In addition to proliferating to this homologous bacterial sequence, the T cells from NMOSD patients demonstrated cross-reactivity, corroborating the function of molecular mimicry.[167] In this sense, compared to stool samples from NMOSD patients with HC, they had noticeably greater concentrations of a number of microbial communities, including *C. perfringens*.[168] Additionally, the majority of NMOSD patients received immunotherapy, primarily rituximab, which may also have an impact on dysbiosis and the gut microbiome [168] (Figure 1). Also, another investigation on HCs and NMOSD patients showed significant differences in bacterial taxonomic levels during the acute stage of NMOSD, so that NMOSD patients had lower abundances of certain bacteria and higher species diversity. The GM distribution in NMOSD patients during remission phase was similar to that of HCs and NMOSD patients had notably diminished levels of acetate in their feces compared to HCs. When NMOSD feces were transplanted into germ-free mice, the IL-6, IL-17A, and IL-23 levels were elevated while IL-10 levels were reduced.[169]

The role of T follicular helper (Tfh) cells in NMOSD recurrence was recently examined by Cheng et al.[170] They also assessed whether serum levels of the microbiota metabolite glycoursodeoxycholic acid (GUDCA) affected serum levels of C-X-C motif ligand 13 (CXCL13) which serves as a key indicator of Tfh cell activity and their influence on B cell-mediated humoral immunity. Patients with low activity NMOSD had greater levels of GUDCA, which was favorably connected with CXCL13. The incidence of *Clostridium boltae* was considerably increased in stool samples taken from AQP4 positive individuals than in seronegative specimens, according to a study by Pandit et al [171] on 39 NMOSD patients from India who had blood and stool samples. *C. boltae* was not found in stool samples obtained from HC. Additionally, the AQP peptide p 92–104 and the *C. boltae* peptide on p 59–71 were similar. *C. boltae* may be associated with both Th17 cell activation and the synthesis of inflammatory genes relevant to B cell chemotaxis.

As well as, the biopsy of the sigmoid colon mucosa taken from patients with NMOSD often has a lower diversity of GM; *Granulicatella* sp. and *Streptococcus sp*. were nonetheless widely found in the samples.[172] Additionally, fecal butyrate levels were significantly diminished in NMOSD patients,[165] and butyrate-producing species were more prevalent in HC patients than in NMOSD patients. Notably, both the AQP4+ and AQP4− NMOSD groups had lower abundances of butyrate-producing bacteria, including the genera *Faecalibacterium, Roseburia, Ruminococcus2*, and *Coprococcus*, which have a variety of effects on host physiology, when compared to HC. In their results, GM compositions in AQP4+ patients, AQP4− patients, and HC were predominantly characterized by Proteobacteria, Bacteroidetes, and Firmicutes, respectively.[173] These results point to a possible role of the GM in this disease.

Mediterranean Diet in NMOSD Patient

Although a comprehensive analysis of a number of environmental risk factors, including certain food preferences in both sexes, as well as in women, past trauma or abortion, low levels of physical activity, and low body mass index (BMI) associated with NMOSD.[174,175] A recent study demonstrated how nutrition can control the GM's makeup in NMOSD patients. The results showed that the GM of Egyptian children who followed MD high in vegetables was more abundant in SCFAs that inhibit inflammation than the GM of American children who consumed a diet high in animal proteins, fat, and highly processed carbohydrates.[176] TNF-α, IL-16, and IL-6 can all be elevated by dysbiosis, which can lead to systemic and neuroinflammation. Moreover, a retrospective study found that pro-inflammatory diets are linked to a heightened risk of NMOSD.[177]

Oily fish include ω3PUFAs called eicosa pentaenoic acid (EPA) and docosahexaenoic acid (DHA).[178] According to an experimental study, the immune system, GM, and ω3PUFAs are important for preserving gut wall integrity.[179] Eating a lot of fish that is oily can consequently improve the GM profile and decrease the level of inflammation, which may reduce the likelihood of developing NMOSD, according to the GBA theory.[180] Previous studies found that the risk of NMOSD increased by 1.72-fold for every 10 g more of dietary sugar consumption. But aside from maltose and lactose, all types of dietary sugar raise the risk of the condition.[181] Low intake of dairy, seafood, eggs, red meat, poultry, lipids, fruits, and vegetables between the ages of 13 and 18 are among the dietary components that are suggested to be risk factors for NMOSD,[175] having the capacity to influence the metabolites of the GM. Sidhu et al [182] conducted a comprehensive analysis that looked at how plant-based diets affected the composition of the GM and how they might be used to treat inflammatory and metabolic disorders. However, much more research and clinical trials are needed in this area to better understand the exact mechanisms and the relationship between diet, GM, and this disease.

Conclusion

Due to its high fiber content and low fat and sugar content, the MD is very good for human health. Numerous diseases, particularly inflammatory and neurodegenerative ones like Alzheimer's, Parkinson's, MS, and NMOSD, can be improved in course and symptom by following this diet, which has been demonstrated to improve the human GM and to produce beneficial and anti-inflammatory microbial metabolites. In fact, various studies show that the MD, by influencing the GM (especially butyrate producers), can influence inflammation, immunity, and physiology of the host, especially in neurological diseases. It also offers a hypothesis for helpful care and slowing progression strategies for these conditions and directs future studies in this direction. Physicians can help avoid and treat a lot of ailments by incorporating this diet into the dietary regimen of patients.

Abbreviation

ND, Neurodegenerative disorders; GM, Gut microbiota; CNS, Central nervous system; GBA, Gut Brain Axis; MD, Mediterranean diet; NMDAR, N-methyl-D-aspartate receptor; AD, Alzheimer's disease; PD, Parkinson's disease; MS, Multiple sclerosis; BBB, blood–brain barrier; Th1, T helper 1; NMOSD, Neuromyelitis Optica Spectrum Disorder; SCFAs, short-chain fatty acids; REGIII, Release of -Defensins and regenerating islet-derived III; Tfh, T follicular helper; GUDCA, Glycoursodeoxycholic acid; CXCL13, C-X-C motif ligand 13; ω3-PUFA, Omega-3 fatty acids; GPR, G-protein coupled receptors; MCI, Mild Cognitive Impairment; BDNF, Brain-derived neurotrophic factor; GLP-1, Glucagon-like peptide 1; TMAO, Trimethylamine N-oxide.

Data Sharing Statement

No data was used for the research described in the article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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