Review

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Obesity Control and Supplementary Nutraceuticals as Co-Factors of Brain Plasticity in Multiple Sclerosis Populations

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Abstract: Multiple sclerosis (MS) is an immune-mediated disease characterized by inflammation, demyelination, and neurodegeneration within the central nervous system. Brain plasticity, the brain's ability to adapt its structure and function, plays a crucial role in mitigating MS's impact. This paper explores the potential benefits of lifestyle changes and nutraceuticals on brain plasticity in MS population. Lifestyle modifications, including physical activity and dietary adjustments, can enhance brain plasticity by upregulating neurotrophic factors, promoting synaptogenesis, and reducing oxidative stress. Nutraceuticals, such as vitamin D, omega-3 fatty acids, and antioxidants like alpha-lipoic acid, have shown promise in supporting brain health through anti-inflammatory and neuroprotective mechanisms. Regular physical activity has been linked to increased levels of brain-derived neurotrophic factor and improved cognitive function. Dietary interventions, including caloric restriction and the intake of polyphenols, can also positively influence brain plasticity. Integrating these lifestyle changes and nutraceuticals into the management of MS could provide a complementary approach to traditional therapies, potentially improving neurological outcomes and enhancing the quality of life for MS population.

Keywords: multiple sclerosis; neurodegeneration; neurorehabilitation; nutraceuticals; obesity

Introduction

Multiple sclerosis (MS) is the most common form of immune-mediated pathology affecting the central nervous system (CNS) [1]. It is characterized by neuronal degeneration caused by inflammation, which, together with demyelination and axonal degeneration, represents the basis of the pathogenic mechanisms but also of the clinical manifestations [2]. The characteristic of the lesions detected in population with MS is represented by multifocal areas of demyelination that produce the destruction of oligodendrocytes in the affected areas and the appearance of glial scars. Axonal injury that appears later in the course of the disease is another pathological change characteristic of MS [3]. The symptomatology of this pathology is varied and is most frequently manifested by visual disturbances (especially changes in the visual field/visual acuity, the appearance of scotomas), paresthesia, urinary incontinence, intestinal incontinence, focal weakness, or cognitive dysfunctions.

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These symptoms are more common in young adults and are characterized by acute relapses, varying both in intensity and manifestation depending on the location of the lesions [4].

Regarding the immunopathology of MS, it has been observed that cellular immunology is dominated by altered interactions between T and B cells and myeloid cells. Additionally, a series of alleles of the major histocompatibility complex, especially from class I and II, seem to be involved in increasing the susceptibility to MS. In addition to these immunological changes and interactions, antibodies directed against myelin oligodendrocyte glycoprotein, a protein that is part of the myelin structure, have been discovered [3]. Molecular mimicry is another immunological mechanism. This mimicry occurs secondary to either bacterial or viral infection, which can trigger a cross antigenic response between viral antigens and myelin components [3].

In conclusion, immunopathology of MS involves complex interactions between B and T lymphocytes, playing crucial roles in disease initiation and progression. Here's a summary of their involvement:

1. T lymphocytes: CD4+ T cells, particularly Th1 and Th17 subtypes, are traditionally considered key players in MS pathogenesis. CD8+ T cells are also implicated, with evidence of clonal expansion in MS lesions. Regulatory T cells (Tregs) may have a protective role in MS [1–4].
2. B lymphocytes: B cells contribute through multiple mechanisms: antigen presentation, cytokine secretion, and antibody production. Ectopic B cell follicles in the meninges are associated with more severe cortical pathology in progressive MS [1–4].
3. B cells act as antigen-presenting cells to activate T cells. T-B cell interactions in secondary lymphoid organs and the CNS drive disease progression [1–4].
4. Therapeutic implications: The success of anti-CD20 therapies highlights the importance of B cells in MS pathogenesis. Treatments targeting both B and T cells show promise in modulating disease activity [1–4].

This complex interplay between B and T lymphocytes underscores the multifaceted nature of MS immunopathology, suggesting that targeting both cell types may be necessary for effective treatment strategies [1–4].

MS can be categorized into different stages depending on its progression. About 65% of cases are relapsing-remitting MS (RRMS), marked by neurological symptoms that worsen over days to weeks and last 24-48 hours. Primary progressive MS (PPMS), representing 15% of cases, involves gradual deterioration without relapses. Secondary progressive MS (SPMS) follows RRMS and is characterized by steady neurological decline. MS with progressive relapses features ongoing relapses with progressive deterioration, while an isolated clinical syndrome represents a single CNS inflammatory demyelination episode. Fulminant MS, the most severe form, rapidly leads to functional impairment, whereas the benign form is mild with infrequent relapses [1,3,5].

The most common clinical pattern is RRMS, where in most cases relapses are followed by periods of partial or complete recovery, often without treatment. However, in the case of partial recovery, residual symptomatology contributes to progressive deterioration leading to general disability [1,3,5]. The McDonald criteria are the most widely accepted diagnostic guidelines for MS, focusing on key aspects such as Dissemination in Space (DIS) and Time (DIT). DIS involves lesions in different areas of the central nervous system (CNS), while DIT refers to the development of new lesions over time. Revisions in 2010 and 2017 emphasized the use of MRI to demonstrate these criteria, enabling earlier diagnosis. Additionally, the 2017 revision reintroduced cerebrospinal fluid (CSF) analysis, particularly highlighting the presence of oligoclonal bands (OCBs). These criteria are mainly applied to populations presenting with a typical clinically isolated syndrome (CIS), ensuring that alternative diagnoses are carefully excluded.

The goals of long-term treatment are to reduce the risk of developing permanent disability and to reduce the rates of relapse [7].

Risk Factors for Development and Progression of MS

The exact cause of the development of MS is unknown, but several studies have highlighted some risk factors that could increase the susceptibility to the development of this pathology [10].

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Some studies showed that populations diagnosed with an autoimmune pathology such as type 1 diabetes mellitus present a double risk to develop MS compared to the population without the disease [8–10].

Genetic susceptibility is an important risk factor. After numerous studies conducted on this topic, more than two hundred polymorphisms involved and associated with multiple sclerosis were discovered. Although the mechanism by which these polymorphisms increase the risk of disease onset is unclear, it has been found that they are present in the regulatory regions of the genes involved in immunological functions, thus being associated with other autoimmune pathologies [11–13].

Several external risk factors have been identified that may influence the likelihood of developing MS, including viral infections, geographical factors, sunlight exposure, variations in vitamin D3 levels, smoking, obesity, and vaccination status [14,15]. Research suggests that viral infections, particularly the Epstein-Barr virus (EBV), may act as infectious stimuli for the immune system, potentially triggering an exaggerated immune response that could lead to the onset of MS, although the role of other viruses in this process has not been entirely ruled out [16,17]. Sunlight exposure, which either directly through ultraviolet radiation or indirectly by raising serum levels of vitamin D3, is believed to offer some protection against the development of MS, thereby linking it to geographical factors such as latitude, altitude, and geographical area [18]. Additionally, tobacco use, known for increasing the risk of numerous chronic diseases with significant morbidity and mortality, is also associated with a higher risk of MS. While nicotine itself may not be directly harmful, the byproducts of combustion are thought to be responsible, potentially due to the increased oxidative stress observed in smokers, although the exact mechanism remains unclear [19,20].

Acknowledging risk factors in MS is important for several reasons:

1. *Prevention and early intervention*: Understanding modifiable risk factors allows for potential prevention strategies and early interventions. For example, addressing vitamin D deficiency, smoking cessation, and maintaining a healthy weight can potentially reduce MS risk [18,20].
2. *Improved population counseling*: Knowledge of risk factors enables healthcare professionals to provide better guidance to population and those at high risk, such as relatives of individuals with MS [1–6].
3. *Personalized care*: Recognizing individual risk profiles can help in tailoring management approaches and potentially slowing disease progression [3,5].
4. *Research direction*: Identifying risk factors guides future research efforts, helping to elucidate MS pathogenesis and develop new therapeutic strategies [12].
5. *Gene-environment interactions:* Understanding how environmental factors interact with genetic predisposition can provide insights into disease mechanisms [11–13].
6. *Public health strategies:* Knowledge of population-level risk factors can inform public health policies and interventions [19,20].
7. *Prognostic information*: Some risk factors may also influence disease course, providing valuable prognostic information [11–20].

By acknowledging and addressing these risk factors, we can potentially reduce MS incidence, improve population outcomes, and advance our understanding of this complex disease.

Brain Plasticity

Brain plasticity refers to the brain's ability to change its structure and function in response to experiences, learning, and environmental stimuli [21]. It is a fundamental process that allows the brain to adapt, learn, and recover from injuries or diseases [22]. Plasticity can occur at the cellular and molecular levels, leading to changes in neuronal properties, synaptic connections, and neural networks [23]. Research has shown that brain plasticity is present throughout the lifespan, although the efficiency of plasticity may decline with age [24]. Genetic factors also play a role in brain plasticity, with heritability estimates suggesting that genetic variations contribute to interindividual variability in plasticity [25].

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The mechanisms of brain plasticity refer to the processes by which the brain can reorganize and modify its neural connections in response to numerous factors such as experience, learning, injury, and disease. These mechanisms include the following (Figure 1):

1. Brain plasticity involves modifications in the *strength and number of connections* between neurons, known as synapses. This can occur through processes such as long-term potentiation and long-term depression, which are activity-dependent changes in synaptic transmission.
2. Plasticity can also involve the creation of *new synapses* between neurons. This process, known as synaptogenesis, allows for the establishment of new connections and the rewiring of neural circuits.
3. Plasticity can lead to alterations in the *structure and function* of individual neurons. This can include changes in dendritic branching, axonal sprouting, and the generation of new neurons through neurogenesis.
4. Plasticity can be influenced by changes in the levels and activity of various *neurotransmitters and neuromodulators*. These substances can affect synaptic transmission and neuronal excitability, thereby influencing the plasticity of neural circuits.
5. Plasticity mechanisms rely on *complex signaling cascades* within neurons. These pathways involve the activation of specific genes and the production of proteins that regulate synaptic plasticity and neuronal connectivity [26–28].

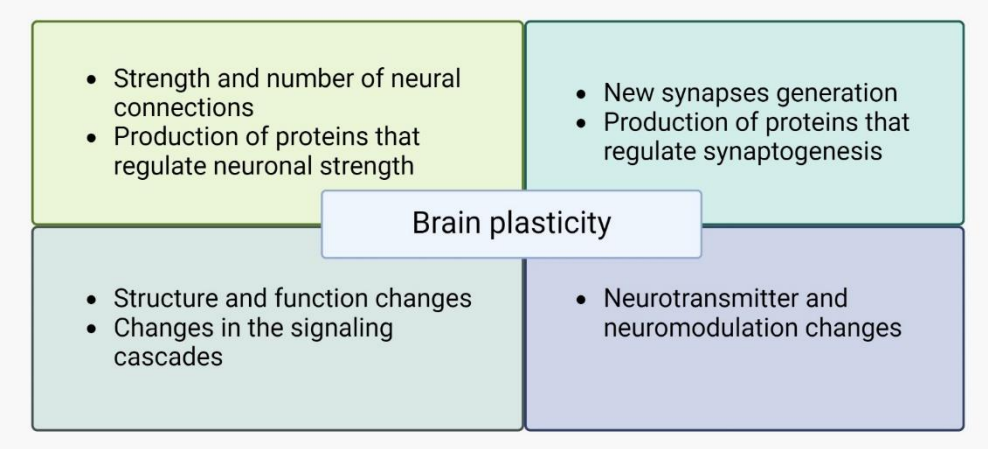

Figure 1. Mechanisms involved in brain plasticity.

Brain plasticity has important implications in various contexts, including neurodevelopmental disorders, addiction, stroke recovery, and neurodegenerative diseases [22,29,30].

Physical activity has a significant impact on brain plasticity, which refers to the brain's ability to reorganize and modify its neural connections. Several studies have shown that physical activity can enhance brain plasticity and promote various neuroadaptive processes.

One study found that voluntary exercise in rats increased both precursor and mature forms of brain-derived neurotrophic factor (BDNF) in the hippocampus, a region important for learning and memory [31]. BDNF is a neurotrophic factor that plays a crucial role in synaptic plasticity and neuronal survival. Exercise also increased the activity of tissue-type plasminogen activator (tPA), an enzyme involved in the cleavage of proBDNF into mature BDNF. Blocking tPA activity reduced the exercise-induced effects on BDNF and its downstream signaling pathways [31].

Regular physical activity has also been shown to enhance brain plasticity in humans. Studies have demonstrated that aerobic exercise, anaerobic exercise, and resistance exercise can positively influence brain plasticity and cognitive function [32]. These exercise modalities can lead to changes in the expression of neurotrophic factors, such as BDNF, lactate, and vascular endothelial growth factor, which promote neurogenesis and synaptic plasticity [32].

Furthermore, physical activity can reduce short interval intracortical inhibition, a measure of cortical inhibition, and create a more optimal environment for plasticity [33]. Exercise-induced reductions in SICI may contribute to enhanced neuroplasticity and improved motor learning [33].

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Overall, physical activity has been shown to promote brain plasticity through various mechanisms, including the upregulation of neurotrophic factors, modulation of synaptic activity, and reduction of cortical inhibition. These findings highlight the importance of regular physical activity for maintaining and enhancing brain health and function [31–36].

There is limited information available specifically addressing the adverse effects of MS medications on brain plasticity. However, some studies suggest that certain medications used to treat MS may have a positive impact on brain plasticity by reducing inflammation and promoting recovery. One study found that treatment with interferon beta-1a, a commonly used MS medication, improved cortical function and cognitive deficits in newly diagnosed MS populations with gadolinium-enhancing lesions [37]. Another study showed that reduction of inflammation with interferon beta was associated with the restoration of brain plasticity in MS populations, as evidenced by improvements in task performance and synaptic plasticity [38].

It is important to note that the studies mentioned above focused on the positive effects of MS medications on brain plasticity, rather than adverse effects. Adverse effects of MS medications can vary depending on the specific medication and individual risk factors. It is recommended to consult with a healthcare professional for a comprehensive understanding of the potential adverse effects of specific MS medications on brain plasticity.

Overall, while there is limited research specifically addressing adverse effects, current evidence suggests that some MS medications may have a positive impact on brain plasticity by reducing inflammation and promoting recovery. Further research is needed to fully understand the relationship between MS medications and brain plasticity.

Different diets can have an impact on brain plasticity, which refers to the brain's ability to change and adapt in response to experiences and environmental factors. Several studies have investigated the effects of various dietary interventions on brain plasticity markers and cognitive function.

Caloric restriction and intermittent fasting have been shown to enhance brain plasticity in animal studies. These dietary interventions have been associated with increased expression of neurotrophic factors, synaptic function, and adult neurogenesis in the hippocampus, a brain region important for learning and memory [39]. However, more research is needed to understand the mechanisms underlying these effects and to determine their translatability to humans.

Dietary supplementation with polyphenols and polyunsaturated fatty acids (PUFA) has also been found to impact brain plasticity. For example, docosahexaenoic acid (DHA), an omega-3 fatty acid found in fatty fish, has been shown to influence protein levels related to metabolic homeostasis and synaptic plasticity in the hypothalamus and hippocampus of rats [40]. Additionally, DHA supplementation has been associated with improved spatial memory ability in mice [41].

Furthermore, the consumption of dark chocolate, which contains flavonoids and other bioactive compounds, has been shown to have positive effects on brain functions. In a rat study, different dietary patterns of dark chocolate were found to reverse the harmful effects of chronic isolation stress on synaptic potency, plasticity, learning, and memory in the hippocampus [42].

Overall, these studies suggest that different diets can modulate brain plasticity markers and cognitive function. However, more research is needed to fully understand the specific mechanisms and to determine the optimal dietary interventions for promoting brain health and function in humans.

Neurodegeneration in MS

Neurodegeneration in MS is a key factor in disease progression and disability. Several mechanisms have been proposed to contribute to neurodegeneration in MS, as shown in the following image (Figure 2).

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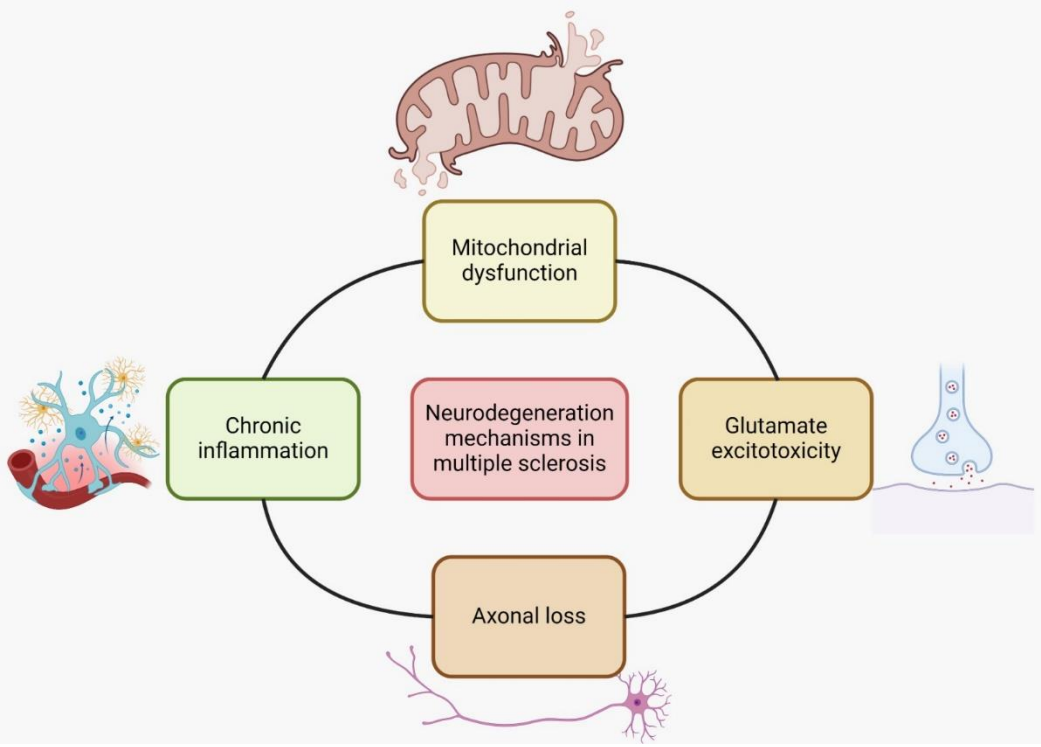

Figure 2. Proposed mechanisms of neurodegeneration in MS.

1. *Chronic inflammation* in MS leads to the activation of microglia, which releases inflammatory mediators and generates oxidative stress. This can result in damage to neurons and axons [43–45]. Neuroinflammation, characterized by the infiltration of immune cells into the central nervous system, can contribute to neurodegeneration in MS. Immune-mediated mechanisms, such as the release of inflammatory cytokines and autoantibodies, can cause neuronal damage [46].
2. *Dysfunction of mitochondria* in axons can lead to energy failure and subsequent neurodegeneration [47,48].
3. *Glutamate*, an excitatory neurotransmitter, can accumulate in the extracellular space during inflammation and demyelination in MS. Excessive glutamate can lead to *excitotoxicity*, causing damage to neurons and axons [45].
4. *Axonal loss* is a major contributor to neurodegeneration in MS. Inflammatory processes, demyelination, and oxidative stress can directly damage axons, leading to their degeneration [49,50].
5. Additional mechanisms:
   a. Altered sodium and calcium homeostasis contributes to axonal injury [44].
   b. Activated microglia release neurotoxic factors [45].
   c. Myelin debris accumulation impairs neurorepair and plasticity.
   d. Increased TNF signaling in neurons leads to programmed cell death [50].
   e. Impaired astrocytic support may contribute to axonal degeneration [49].
   f. Injury to one neuron leads to degeneration of connected neurons, a process named trans-synaptic degeneration [49,50].

Clinical and lifestyle predictors for MS progression can help identify individuals at risk for worsening disease outcomes. Younger age at onset of MS has been associated with a higher risk of disease progression [51]. Men with MS have been found to have an increased risk of disease progression compared to women [52]. Population with progressive forms of MS, such as SPMS, are more likely to experience disease progression [52]. A higher number of relapses during the disease has been associated with an increased risk of progression [52]. Higher levels of disability at baseline have been linked to a greater likelihood of disease progression [51]. Smoking has been identified as

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a lifestyle factor that is associated with subsequent disability worsening in individuals with MS [53]. Higher levels of physical activity, both premorbid and current, have been found to be associated with a reduced risk of disability progression in MS [54]. A high-quality diet, including the avoidance of meat and dairy, has been associated with better fatigue and disability trajectories in MS [55]. Lower sun exposure during childhood and adolescence has been linked to an increased risk of disease progression [51].

The most important modifiable factors which act as a risk/protective factor in MS are summarized in the following table (Table 1).

Table 1. Modifiable risk and protective factors of neurodegeneration in MS.

Risk factors	Protective factors
Smoking	Smoking cessation
Obesity	Calorie restriction Physical activity
Childhood low sun exposure	Higher sun exposure Vitamin D3 supplementation
Oxidative diet	Antioxidant supplementation Diet re-assessment

Vascular and psychiatric comorbidities have also been associated with subsequent disability worsening in individuals with MS [53].

Nutraceuticals in MS

Nutraceuticals are natural or bioactive compounds found in food or dietary supplements that have potential health benefits beyond basic nutrition. They are often used as adjunctive treatments to support overall health and well-being.

In MS, several nutraceuticals have been studied for their potential benefits. The most used nutraceuticals in MS include:

1. Vitamin D supplementation has been extensively studied in MS due to its role in immune regulation and its potential to reduce disease activity and progression [56–58].
2. Alpha lipoic acid (ALA) is an antioxidant that has shown promise in improving clinical and biological outcomes in MS, such as reducing fatigue and improving brain volume [59].
3. Ginkgo biloba has been reported to improve clinical and biological outcomes in MS, including fatigue and antioxidant capacity [59].
4. Biotin supplementation has shown potential in improving clinical outcomes in MS, such as reducing disability progression and improving walking ability [59].
5. Omega-3 fatty acids, found in fish oil, have anti-inflammatory properties and may help reduce inflammation in MS [58].

A study found no significant evidence for drug interactions between conventional MS drugs and several nutraceuticals, including ginger, cranberry, vitamin D, fatty acids, turmeric, probiotics, or glucosamine [60].

The presumed mechanisms of action of nutraceuticals in MS involve their ability to target various pathways involved in the pathogenesis of the disease (Figure 3). Some of these mechanisms are:

1. Nutraceuticals such as polyunsaturated fatty acids (PUFAs), green tea flavonoids (epigallocatechin-3-gallate), curcumin, and scorpion toxins have been found to possess anti-inflammatory properties and can *modulate the immune response* in MS. They can inhibit pro-inflammatory signaling pathways, such as NF-κB or toll-like receptors and reduce the activity of auto-aggressive immune cells. These effects may help reduce inflammation and immune-mediated damage in MS [56].
2. *Oxidative stress* is implicated in the pathogenesis of MS. Nutraceuticals like green tea, curcumin, and resveratrol have antioxidative properties and can scavenge free radicals, reducing oxidative

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damage. By reducing oxidative stress, these compounds may protect against neuronal damage and inflammation in MS [61].

3. Nutraceuticals such as flavonoids, terpenoids, and polyphenols have shown potential in promoting *neuroprotection and myelin repair* in animal models of MS. They may support the survival and function of neurons, promote remyelination, and enhance endogenous repair processes [62].
4. Epigenetic modifications play a role in MS. Some nutraceuticals, such as plant polyphenols, Ω-3 and Ω-6 polyunsaturated fatty acids, and sulfur-containing compounds, can influence gene expression through *epigenetic mechanisms*. These compounds may regulate the production of pro-inflammatory proteins and modulate immune responses in MS [63].

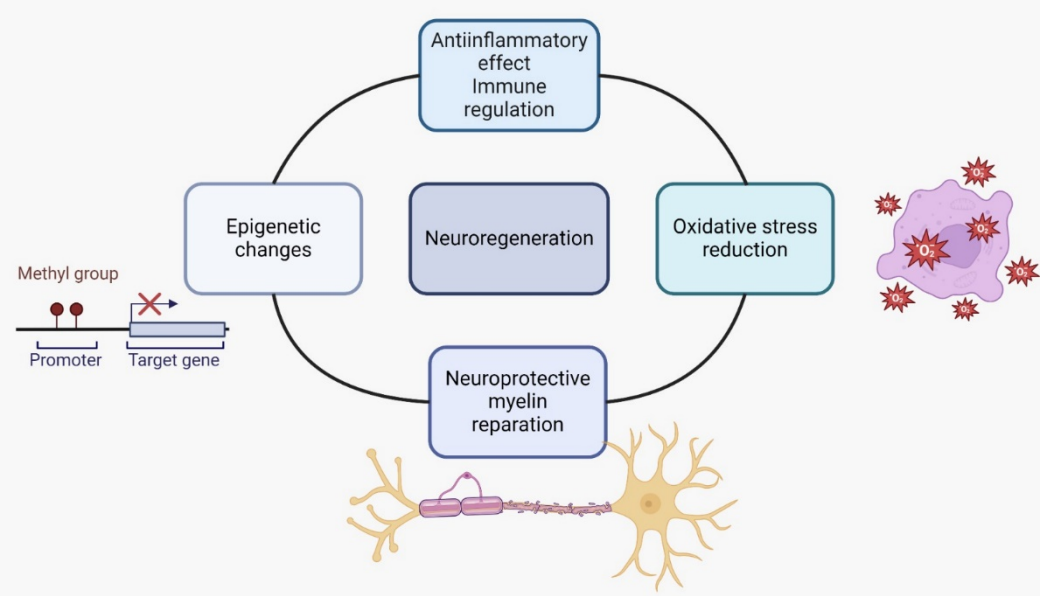

Figure 3. Proposed mechanisms of neurodegeneration-nutraceuticals interference.

Vitamin D3

Vitamin D3, also known as cholecalciferol, is a form of vitamin D that is synthesized in the skin when exposed to sunlight or obtained through dietary sources. It plays a crucial role in maintaining calcium and phosphate balance in the body, which is essential for bone health. However, emerging research suggests that vitamin D3 also has important roles in brain plasticity and MS [64].

Vitamin D3 has been found to have immunomodulatory and neuroprotective effects within the central nervous system. It acts through its receptors in glial cells, such as astrocytes and microglia, to influence the production of proinflammatory cytokines and antioxidants. This modulation of neuroinflammation may help mitigate the cascade of events leading to neuronal damage. Vitamin D3 also contributes to neurogenesis and synaptic plasticity, which are important processes for brain plasticity [65].

In the context of MS, vitamin D3 has been investigated for its potential therapeutic effects. Studies have shown that vitamin D3 supplementation may reduce disease activity and demyelination in animal models of MS. Clinical studies have also suggested that vitamin D3 deficiency is associated with an increased risk of developing MS and that supplementation may have beneficial effects on disease progression and activity [66].

In a study on mice with experimental autoimmune encephalomyelitis (EAE), an animal model of MS, early intervention with the active form of vitamin D3 (1,25-dihydroxyvitamin D3) was found to control neuroinflammation and reduce inflammation, demyelination, and oxidative stress. This suggests that vitamin D3 may have potential as an adjunct therapy for MS population [64].

Vitamin D3's role in modulating neuroinflammation and its potential neuroprotective effects make it an interesting target for further research and therapeutic strategies in neurodegenerative and

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neuropsychiatric disorders. However, more clinical studies are needed to validate these findings and fully understand the mechanisms and benefits of vitamin D3 supplementation in these conditions.

In summary, vitamin D3 plays a role in brain plasticity and has been investigated for its potential therapeutic effects in multiple sclerosis. It has immunomodulatory and neuroprotective properties that may help reduce neuroinflammation and promote neurogenesis and synaptic plasticity. However, further research is needed to fully understand the benefits and mechanisms of vitamin D3 in brain health and disease.

Immunoglobulin Y

Immunoglobulin Y (IgY) is a type of immunoglobulin, or antibody, found in the blood of birds, reptiles, and amphibians. It is the avian equivalent of mammalian immunoglobulin G (IgG). IgY is produced by specialized cells called B lymphocytes in these animals and plays a crucial role in their immune defense against pathogens. One unique characteristic of IgY is that it is actively transported from the bloodstream into the egg yolk during egg formation. As a result, IgY is present in copious quantities in the egg yolk, providing passive immunity to the developing embryo or offspring. This is an evolutionary adaptation that allows birds and reptiles to pass on immune protection to their young before they have fully developed their own immune systems. IgY has gained attention in biomedical research and applications due to its potential as an alternative to mammalian antibodies, such as IgG. It offers several advantages, including ethical considerations (no need for animal bleeding as antibodies are extracted from eggs), cost-effectiveness (production from egg yolks), and potential therapeutic applications. Research on IgY has explored its use in various fields, including immunodiagnostics, immunotherapy, and antimicrobial applications. Studies have investigated its effectiveness in detecting and treating infectious diseases, as well as its potential in modulating immune responses and targeting specific pathogens [67,68].

There is limited research specifically investigating the role of IgY in MS. However, a study mentioned that IgY supplements derived from chicken egg yolk have shown potential in modulating gut microbiota and immune responses and have been effective against various infections [69]. In terms of MS, the study mentioned that clinical trials using IgY supplements in MS are limited but have shown positive outcomes, including reduced symptoms and altered immune responses [69]. However, further research is needed to understand the mechanisms of IgY's interaction with gut microbiota, determine optimal dosage, and assess long-term safety [69].

Homeopathy and Alternative Medicine

Homeopathy is a form of complementary and alternative medicine (CAM) that is sometimes used by people with MS. It is relatively cheap, and some find relief in it. While there is no definitive treatment for MS, management is largely focused on symptom relief. Conventional therapies may not be effective for everyone or may cause unacceptable side effects. As a result, some individuals with MS turn to CAM, including homeopathy, to help manage their symptoms. Homeopathy is a whole-person approach that allows for individualized treatment based on the specific symptoms and needs of the person with MS. It aims to stimulate the body's self-healing mechanisms by administering highly diluted substances that would produce similar symptoms in a healthy person. Homeopathic treatments for MS symptoms such as urinary incontinence, sexual dysfunction, cramps and spasms, tremor, and trigeminal neuralgia have shown some benefit in certain individuals [70–72]. However, it is important to note that the evidence supporting the effectiveness of homeopathy in treating MS is limited. Studies on the use of homeopathy in MS have mainly focused on individual cases or small groups of populations, making it difficult to draw definitive conclusions. Additionally, the placebo effect may play a role in the perceived benefits of homeopathic treatments [70–72].

Overall, while some individuals with MS may find relief from certain symptoms through homeopathy, more research is needed to determine its efficacy and safety in the management of MS[12,73].

Ginkgo Biloba

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Ginkgo biloba extract (GBE) is a plant extract derived from the leaves of the Ginkgo biloba tree. It has been used for centuries in traditional medicine and is now commonly consumed as a dietary supplement. The presumed effects of GBE on brain plasticity are based on its potential neuroprotective and neuroregenerative properties. GBE has been shown to have antioxidant and anti-inflammatory effects, which can help protect neurons from damage and promote their survival [74]. It has also been found to enhance cerebral blood flow and improve vascular function, which is important for delivering oxygen and nutrients to the brain [74]. In terms of brain plasticity, GBE has been studied for its effects on synaptic plasticity, which is the ability of synapses to change and adapt in response to experience. Some studies have suggested that ginkgo biloba extract can enhance synaptic plasticity by modulating neurotransmitter pathways and promoting the release of endogenous relaxing factors [74]. These effects may contribute to improved cognitive function and memory.

There is limited evidence on the specific effects of Ginkgo biloba on brain plasticity in MS. However, some studies have investigated the effects of GBE on cognitive function and neuroprotection in MS.

One study evaluated the effects of GBE on cognitive function in individuals with MS and found that treatment with GBE did not improve cognitive performance [75]. Another study investigated the effects of GBE on cognitive performance in MS and found that GBE did not show a statistically significant improvement in cognitive function, except for a trend towards improvement on the Stroop test [76].

While these studies focused on cognitive function, they did not specifically examine brain plasticity. However, GBE has been shown to have neuroprotective effects in various neurological diseases. It has been found to promote myelin generation, regulate the balance of microglia and astrocytes, and induce the generation of oligodendrocyte precursor cells, which are important for remyelination [77]. These effects may indirectly contribute to brain plasticity in MS.

Overall, the evidence on the effects of GBE on brain plasticity in MS is limited. Further research is needed to determine the specific effects of Ginkgo biloba on brain plasticity in individuals with MS.

Alpha Lipoic Acid

Alpha lipoic acid (ALA) is a natural compound with antioxidant and anti-inflammatory properties. It acts as a cofactor for mitochondrial enzymes involved in energy production and has various biological functions, including scavenging reactive oxygen species, regenerating other antioxidants, and modulating signal transduction pathways [78].

In terms of brain plasticity, ALA has been studied for its potential neuroprotective effects after brain injury. Animal studies have shown that ALA can stimulate the synthesis of glutathione, decrease cell death, promote angiogenesis, and reduce the formation of glial scars, which allows for the formation of new neural tissue [79]. These findings suggest that ALA may have a role in promoting brain repair and regeneration after injury.

Regarding MS, ALA has shown promise in preclinical and clinical studies. In animal models of MS, ALA has been found to reduce nerve damage, inhibit the migration of inflammatory cells, and decrease the activity of matrix metalloproteinases, which are involved in the breakdown of the blood-brain barrier [80]. Clinical trials have demonstrated positive effects of ALA on cellular and physical outcomes in people with MS. However, more research is needed to determine the effectiveness of ALA as a therapy for MS, and it is not currently approved for this purpose [80].

In summary, ALA has potential roles in brain plasticity by promoting neuroprotection and repair after injury. In the context of multiple sclerosis, ALA has shown promising effects in preclinical and clinical studies, but further research is needed to establish its efficacy as a therapy for MS.

Biotin

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Biotin, also known as vitamin B7 or vitamin H, is a water-soluble vitamin that plays a crucial role in various metabolic processes in the body. It acts as a cofactor for several carboxylase enzymes involved in energy production, fatty acid synthesis, and amino acid metabolism.

In the context of MS, there is growing interest in the potential role of high-dose biotin in preventing brain neurodegeneration.

Several studies have investigated the effects of high-dose biotin (MD1003) in populations with progressive MS. These studies have shown promising results, suggesting that biotin may have a beneficial effect on disease progression and disability improvement [4,81–83]. The exact mechanisms by which biotin exerts its neuroprotective effects are not fully understood, but several hypotheses have been proposed.

1. One hypothesis is that biotin enhances energy production in demyelinated axons, which can help support their function and prevent neurodegeneration [60]. Biotin is involved in ATP production, which is essential for maintaining neuronal health and function [81].
2. Another hypothesis is that biotin promotes myelin synthesis in oligodendrocytes, the cells responsible for producing myelin, the protective covering of nerve fibers [60]. Biotin may enhance myelin production and repair, potentially slowing down disease progression [84].

It is important to note that while some studies have shown positive effects of high-dose biotin in MS, not all studies have reported significant benefits [84].

Further research is needed to fully understand the potential role of biotin in preventing brain neurodegeneration in MS and to determine the optimal dosage and treatment duration.

In summary, biotin is a vitamin that plays a role in various metabolic processes in the body. High-dose biotin has shown promise in preventing brain neurodegeneration in multiple sclerosis, potentially through its effects on energy production and myelin synthesis. However, more research is needed to confirm these findings and determine the optimal use of biotin in MS treatment.

Flavonoids

Flavonoids are a large group of plant polyphenols that are widely distributed in the human diet. They are found in various fruits, vegetables, nuts, and beverages. Flavonoids have been studied for their potential health benefits and are believed to have several presumed effects in the human body. Flavonoids can reduce free radical formation and scavenge free radicals, which can help protect cells from oxidative damage [85]. They can also increase the plasma antioxidant status and preserve the levels of antioxidants like vitamin E [85]. Flavonoids have been shown to possess anti-inflammatory effects. They can modulate intracellular signaling cascades and inhibit enzymes involved in cellular activation, leading to a reduction in inflammation [86]. Flavonoids have been associated with a lower risk of cardiovascular diseases. They have been shown to have vasodilating actions, reduce lipid peroxidation, and protect against oxidative stress, which are all beneficial for heart health [87]. Flavonoids have immunomodulatory properties and can influence immune responses. They have been reported to possess anti-allergenic and anti-viral activities [85]. Flavonoids have been studied for their pro-cognitive effects. They can interact with major signal transduction cascades in the brain and impact transcription factors involved in neuronal function [88].

It's important to note that the effects of flavonoids can vary depending on their specific chemical structure and concentration. Further research is needed to fully understand the mechanisms of action and potential health benefits of different flavonoids [89].

There is limited direct evidence on the effects of flavonoids on brain plasticity specifically in MS. However, flavonoids have been shown to have neuroprotective and neuroplasticity-promoting effects in various neurological conditions.

1. Flavonoids have been found to exert neuroprotective effects by reducing oxidative stress and inflammation, which are key factors in MS [90,91]. They have also been shown to promote synaptogenesis and neurogenesis, which are important processes for brain plasticity [90]. Additionally, flavonoids have been found to modulate signaling pathways involved in neuronal survival and synaptic plasticity [92,93].

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2. In animal models of MS, flavonoids have demonstrated positive therapeutic effects. For example, flavonoid luteolin has been shown to suppress clinical symptoms, reduce inflammation, and prevent relapse in rats with EAE [94]. A systematic review of studies on EAE and MS also reported positive outcomes for the therapeutic effect of flavonoids on these conditions [95].

While the direct effects of flavonoids on brain plasticity in MS are not well-studied, their neuroprotective and neuroplasticity-promoting properties suggest that they may have potential benefits for enhancing brain plasticity in MS. Further research is needed to explore the specific effects of flavonoids on brain plasticity in MS and to determine optimal dosages and treatment strategies [90–92,95].

Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFA) are a type of fat that is essential for human health and cannot be produced by the body, so they must be obtained through diet. PUFA can be further classified into two main groups: omega-3 (n-3) and omega-6 (n-6) fatty acids.

The presumed effects of PUFA in humans are diverse and have been extensively studied. PUFA, particularly omega-3 fatty acids, have been associated with a reduced risk of cardiovascular diseases. They can help lower blood triglyceride levels, reduce inflammation, improve blood vessel function, and prevent the formation of blood clots. Omega-3 fatty acids, especially docosahexaenoic acid (DHA), play a crucial role in brain development and function. They are important for cognitive function, memory, and mood regulation. Adequate intake of omega-3 fatty acids has been linked to a lower risk of neurodegenerative diseases and improved mental health. They also provide anti-inflammatory properties. They can help reduce chronic inflammation in the body and modulate immune responses. This can be beneficial for conditions such as rheumatoid arthritis, inflammatory bowel disease, and asthma. Some studies suggest that omega-3 fatty acids may have a protective effect against certain types of cancer, such as breast, colorectal, and prostate cancer. However, more research is needed to fully understand the relationship between PUFA and cancer prevention. PUFA can influence metabolic processes, including lipid metabolism, insulin sensitivity, and glucose regulation. They may help improve insulin resistance, reduce the risk of type 2 diabetes, and prevent fatty liver disease.

It's important to note that the effects of PUFA can vary depending on the specific type and ratio of omega-3 to omega-6 fatty acids consumed, as well as individual factors such as genetics, overall diet, and health status. Therefore, it is recommended to maintain a balanced intake of both omega-3 and omega-6 fatty acids for optimal health benefits [96–103].

The effects of PUFA on brain plasticity in MS population have been investigated in several studies. Their main effects can be concluded in:

1. A study on mice with induced CNS demyelination found that an increased n-3 PUFA status *promoted remyelination* after toxic injury to CNS oligodendrocytes. This effect may be mediated by n-3 PUFA-derived lipid metabolites [104].
2. Omega-3 PUFAs, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been shown to modulate microglial responses to myelin pathology. They can inhibit inflammation while *enhancing beneficial immune responses*, such as microglial phagocytosis. In a mouse model of MS, n-3 PUFA supplementation reduced demyelination and shifted microglial polarization towards a beneficial phenotype [105].
3. In vitro studies using oligodendroglia cells and primary oligodendrocytes have shown that supplementation with n-3 and n-6 PUFAs can promote *oligodendrocyte differentiation*. This was evidenced by increased expression of markers of oligodendroglia differentiation and enhanced myelin sheet formation [106].
4. A study on healthy older adults found that omega-3 PUFAs were associated with individual differences in *functional brain connectivity*. Specifically, they were linked to connectivity within regions supporting executive function, memory, and emotion. These regions were also found to predict general, fluid, and crystallized intelligence [107].

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It's important to note that while these studies provide insights into the potential effects of PUFA on brain plasticity in MS populations, more research is needed to fully understand the mechanisms and clinical implications. Additionally, the optimal dosage and duration of PUFA supplementation for MS populations are still being explored.

Curcumin

Curcumin is a natural compound found in turmeric, which is a spice commonly used in cooking. It has been extensively studied for its potential health benefits. Curcumin is known for its antioxidant, anti-inflammatory, and anticancer properties. It has been shown to have diverse pharmacological effects, including neuroprotective, cardioprotective, and immunomodulatory activities. Curcumin has been investigated for its potential in the prevention and treatment of various diseases, such as cancer, cardiovascular diseases, diabetes, arthritis, neurological diseases, and gastrointestinal disorders. However, curcumin's low bioavailability has been a challenge in harnessing its full therapeutic potential [108–113].

There is limited research specifically investigating the effect of curcumin on brain plasticity in MS populations. However, curcumin has been shown to have beneficial effects on brain health through various mechanisms, including its antioxidant, anti-inflammatory, and neuroprotective properties. These effects may potentially contribute to the modulation of brain plasticity in MS populations. Curcumin has been studied in animal models of MS, where it has demonstrated neuroprotective effects, reduced demyelination, and improved cognitive function. Further research is needed to determine the specific impact of curcumin on brain plasticity in MS populations [114–116].

Resveratrol

Resveratrol is a natural compound found in various plants, including grapes, berries, peanuts, and red wine. It is a polyphenol with antioxidant, anti-inflammatory, and anti-cancer properties. Resveratrol has been studied for its potential health benefits in several areas. Resveratrol may have cardioprotective effects by improving inflammatory markers, atherogenic profile, glucose metabolism, and endothelial function [117,118]. It has shown promising results in preventing or delaying the development of various types of cancer, including prostate cancer by inhibiting proliferation, promoting apoptosis, and enhancing sensitivity to radiation [119]. Also, it has been investigated for its potential in neurodegenerative diseases such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and Huntington's disease (HD). It has shown effects in in vitro models, but further research is needed [120]. Resveratrol has been associated with improved insulin sensitivity, increased energy expenditure, and a decrease in body fat [121]. It may also have anti-obesity effects by inhibiting adipogenesis and increasing lipid mobilization [122]. Also, it has been shown to reduce inflammation and oxidative stress in various tissues and organs [118]. It may also have anti-angiogenic effects [119].

It's important to note that while resveratrol has shown promising results in preclinical studies and some clinical trials, there is still a need for more research, especially in human subjects, to fully understand its effects and determine optimal doses [123,124]. Additionally, the bioavailability of resveratrol and its potential interactions with medications should be considered [122].

There is limited research specifically investigating the effects of resveratrol on brain plasticity in MS populations. In an EAE mouse model of MS, resveratrol treatment was found to improve clinical outcomes and protect against optic nerve and spinal cord degeneration [125]. Another study in cuprizone-intoxicated mice, a model of demyelination/remyelination like MS, showed that resveratrol enhanced motor coordination, reversed demyelination, and increased the expression of genes associated with active remyelination [126].

While these studies suggest potential neuroprotective effects of resveratrol in MS models, it is important to note that the effects of resveratrol on brain plasticity in human MS populations have not been extensively studied. Further research is needed to determine the specific effects of resveratrol

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on brain plasticity in MS populations and its potential as a therapeutic intervention for MS-related neurodegenerative processes [125].

Terpenoids

Terpenoids are a class of naturally occurring compounds that are derived from terpenes. They are found in various plants, animals, and microorganisms. Terpenoids have diverse biological activities and are known for their pharmacological effects on the human body.

Terpenoids have been studied for their potential therapeutic benefits in various chronic illnesses. They have been found to have anti-inflammatory, antimicrobial, antifungal, antiviral, antitumor, and antioxidant properties [127–134]. They can also act as skin penetration enhancers and have been used in the prevention and treatment of inflammatory diseases [129]. In the context of specific diseases, terpenoids have shown promise in the treatment of non-alcoholic fatty liver disease. They regulate lipid metabolism disorder, insulin resistance, oxidative stress, and inflammation, and target pathways such as AMPK, PPARs, Nrf-2, and SIRT 1 [127]. Additionally, terpenoids have been explored for their potential antiviral efficacy against SARS-CoV-2, the virus responsible for COVID-19 [15].

Furthermore, terpenoids have been investigated for their effects on psychiatric disorders. Preclinical studies have demonstrated their neuropharmacological effects and their potential as alternative therapeutic options for psychiatric disorders [131].

Two studies provide insights into the effects of terpenoids on brain plasticity in MS populations. In a study by Tomassini et al., it was found that inflammation in MS interferes with brain plasticity [135]. However, pharmacological reduction of inflammation, such as with Interferon beta treatment, can restore brain plasticity. The study used a visuomotor adaptation task and functional MRI to assess brain plasticity in MS populations. The results showed that reduced inflammation with IFN beta treatment led to a restoration of brain plasticity, suggesting that modulation of inflammation can enhance recovery-oriented strategies that rely on brain plasticity. Similarly, Shin et al. investigated the effects of terpenes on neuronal health in Drosophila AD models. They found that certain terpenes, including limonene, had neuroprotective effects against the neurotoxicity of beta amyloid 42 (Aβ42), a protein associated with AD. Limonene treatment decreased cell death, inflammation, and oxidative stress in the brains of the AD model flies. While this study was not conducted specifically in MS populations, it provides insights into the potential neuroprotective effects of terpenes on brain health [130].

These findings suggest that terpenoids, including terpenes like limonene, may have the potential to modulate brain plasticity in MS populations by reducing inflammation, promoting neuroprotection, and enhancing recovery processes. However, it is important to note that these studies were conducted in animal models and further research is needed to determine the specific effects of terpenoids on brain plasticity in MS populations.

Polyphenols

Polyphenols are a group of natural compounds found in a variety of plant-based foods, such as fruits, vegetables, nuts, seeds, whole grains, tea, coffee, and red wine. They are characterized by the presence of phenol structural units and are known for their antioxidant properties. The presumed effects of polyphenols in the human body are diverse and have been the subject of extensive research. Some of their potential benefits include:

1. Polyphenols can scavenge and neutralize harmful free radicals, *reducing oxidative stress* and protecting cells from damage [136].
2. They have been studied for their potential *lipid-lowering and atheroprotective effects*. They may help reduce oxidation of LDL cholesterol, improve endothelial function, lower blood pressure, and inhibit platelet aggregation [136,137].
3. Polyphenols possess *anti-inflammatory properties* and can help modulate the immune system by affecting the production of cytokines and other factors involved in the immune response [138,139].

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4. Polyphenols have been investigated for their potential *anti-carcinogenic effects*. They may inhibit tumor growth, induce apoptosis in cancer cells, and have anti-mutagenic properties [140].
5. Some polyphenols, such as resveratrol and epigallocatechin-3-gallate, have shown promise in protecting against neurodegenerative disorders by *reducing mitochondrial dysfunction and oxidative stress* [141].

There is evidence that the use of plant polyphenols may have beneficial effects on brain plasticity in MS. For example, grape seed extract has been shown to have neuroprotective properties and can improve brain plasticity in an EAE mouse model of MS. GSE treatment in EAE mice resulted in the correction of oxidative stress damage, restoration of antioxidant capacities, normalization of myelin protein expression, and modulation of astroglial and microglial proliferation. These effects suggest that GSE may have a positive impact on brain plasticity in MS [142].

Sulphur-Containing Compounds

Sulphur-containing compounds play important roles in the human body and have various effects. Methionine, cysteine, homocysteine, and taurine are sulfur-containing amino acids. They are essential for protein synthesis and are involved in antioxidant defense mechanisms. They contribute to the synthesis of intracellular antioxidants like glutathione, which helps protect cells from oxidative damage [143].

Glutathione and N-acetylcysteine are derivatives of sulfur-containing amino acids and act as powerful antioxidants. They help neutralize free radicals and protect cells from oxidative stress. They are also used in chelation therapy to eliminate toxic metals from the body [143]. Naturally occurring sulfur-containing ligands can act as detoxifying agents, preventing the toxic effects of heavy and transition metal ions and aiding in their elimination from the body [143]. Exposure to malodorous sulfur compounds has been associated with respiratory symptoms such as cough, respiratory infections, and nasal symptoms. Reduction in sulfur compound exposure has been shown to decrease the frequency of these symptoms [144,145]. Some sulfur compounds, such as diallyl sulfide and diallyl disulfide, have immunomodulatory effects. They can enhance white blood cell count, antibody production, and bone marrow cellularity, suggesting potential immunostimulant effects [146]. Sulphur-containing antioxidants, such as N-acetylcysteine and lipoic acid, have been shown to reduce oxidative stress induced by substances like lead. They can help protect against oxidative damage and maintain cellular health [147].

One study investigated the therapeutic effects of hydrogen sulfide (H2S) in a cuprizone-induced MS model in mice. The study found that treatment with a hydrogen sulfide donor improved locomotor coordination, reduced neuronal inflammation and demyelination, and decreased oxidative stress in the brain. These effects were associated with the downregulation of miR-146a expression and the regulation of the miR-146a/NF-κB/IL-1β axis [148].

Another study examined the effects of sulfur dioxide exposure on synaptic plasticity in the hippocampus of rats. The study found that exposure to SO2 at different concentrations and durations resulted in the inhibition of synaptic plasticity markers and memory-related proteins in the hippocampus. The effects of SO2 on synaptic plasticity were dependent on the duration and concentration of exposure [149].

While these studies provide insights into the effects of sulfur compounds on brain plasticity in MS-related models, further research is needed to fully understand the mechanisms and potential therapeutic applications of sulfur compounds in MS.

Several dietary nutraceuticals have been tested in MS; while some have potential to aid the process of neuroregeneration, some still need research. A summary of the key current knowledge is found in Table 2.

Table 2. Summary of nutraceuticals used in MS.

Compound	Primary Function/Effect	Role in Brain Plasticity and MS	Key Findings and Studies

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Vitamin D3 (Cholecalciferol)	Maintains calcium and phosphate balance for bone health, with emerging roles in brain health.	Immunomodulatory and neuroprotective effects; promotes neurogenesis and synaptic plasticity.	May reduce disease activity and demyelination in MS; early intervention in EAE mice controlled neuroinflammation [64–66].
Immunoglobulin Y (IgY)	Avian antibody involved in immune defense; passive immunity to offspring via egg yolk.	Limited research in MS, but potential in modulating immune responses and gut microbiota.	Positive outcomes in clinical trials for MS, with reduced symptoms and altered immune responses; further research needed [67–69].
Homeopathy	CAM approach using highly diluted substances for symptom relief based on individualized treatment.	Limited evidence; potential placebo effect.	Some individuals report symptom relief; more research is required to determine efficacy in MS [12,70–73].
Ginkgo biloba extract (GBE)	Plant extract with neuroprotective and neuroregenerative properties; enhances cerebral blood flow.	Limited evidence in MS; potential effects on synaptic plasticity.	No significant cognitive improvement in MS; potential neuroprotective effects in neurological diseases [74–77].
Alpha Lipoic Acid (ALA)	Antioxidant and anti-inflammatory compound with roles in mitochondrial energy production.	Promotes neuroprotection and repair after injury; potential therapy for MS.	Preclinical and clinical studies show promising effects; more research needed to establish efficacy in MS [78–80].
Biotin (Vitamin B7)	Cofactor in metabolic processes, energy production, and fatty acid synthesis.	Potential in preventing brain neurodegeneration in MS.	High-dose biotin (MD1003) shows promise in slowing MS progression; mechanisms include enhanced energy production and myelin synthesis [4,60,81–84].
Flavonoids	Plant polyphenols with antioxidant, anti-inflammatory, and immunomodulatory properties.	Neuroprotective and neuroplasticity-promoting effects; limited direct evidence in MS.	Positive therapeutic effects in EAE models; potential benefits for brain plasticity in MS, but more research needed [85–95].
Polyunsaturated Fatty Acids (PUFA)	Essential fatty acids with anti-inflammatory properties and roles in brain function.	Modulate microglial responses; promote remyelination and oligodendrocyte differentiation.	Omega-3 PUFA supplementation reduces demyelination in MS models; associated with improved brain connectivity in humans [96–107].
Curcumin	Natural compound with antioxidant, anti-inflammatory, and neuroprotective properties.	Potential benefits for brain health and plasticity in MS, though limited research specific to MS.	Demonstrated neuroprotective effects and reduced demyelination in MS animal models; more research needed [108–116].
Resveratrol	Polyphenol with antioxidant, anti-	Limited research in MS; potential	Improved outcomes in EAE mouse models; promotes remyelination and motor

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	inflammatory, and anti-cancer properties.	neuroprotective effects.	coordination in MS-like conditions in mice [117–126].
Terpenoids	Natural compounds with diverse biological activities, including anti-inflammatory and antioxidant effects.	Studied for potential benefits in chronic illnesses, including neurological conditions.	Preclinical studies suggest neuropharmacological effects; further research needed to explore benefits in MS and brain plasticity [127–134].

Obesity

Obesity is considered both a risk for MS development and the progression of the disease [150,151]. Obesity is a medical condition characterized by excessive accumulation of body fat, which can have negative effects on health. Obesity is defined using the body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of their height in meters. A BMI of 30 or higher equals obesity. The prevalence of obesity varies across different populations and countries. In developed countries, such as the United States, Europe, and Australia, the average prevalence of obesity is estimated to be around 15-20% [152]. However, there are significant variations within and between countries.

A study conducted in the Nurses' Health Study and Nurses' Health Study II found that obesity at age 18 was associated with a more than twofold increased risk of MS [150] . Another study using Mendelian randomization analysis found that genetically BMI was associated with a 41% increased risk of MS [153]. Furthermore, a meta-analysis of observational studies reported that excess body weight during childhood and adolescence increased the risk of MS, particularly in females [154]. Another study found that obese adolescents had a higher risk of developing MS compared to non-obese individuals, even after adjusting for other factors [155,156]. Another study found that a common polymorphism in the fat-mass obesity gene, associated with obesity, was linked to being overweight/obese in MS populations [157].

In terms of disease progression, a study showed that overweight or obese MS populations had higher MRI activity and were less likely to achieve no evidence of disease activity status compared to normal-weight populations [158]. Additionally, obesity was associated with a higher risk of disability accumulation in MS populations [159].The mechanisms underlying the association between obesity and MS that were suggested are chronic inflammation, altered gut microbiota, and vitamin D deficiency [160,161].

In conclusion, obesity, particularly during adolescence and early adulthood, is associated with an increased risk of developing MS and may also impact disease progression and disability accumulation. Obesity prevention in adolescence may reduce the risk of developing MS [155,156,162,163].

Obesity has been found to have an impact on brain plasticity. A study conducted on adult volunteers with a wide range of BMI found that the effect of short-term monocular deprivation, a measure of early visual plasticity, decreased with increasing BMI. Morbidly obese individuals also showed altered binocular rivalry dynamics compared to normal-weight individuals, indicating impaired sensory processing and plasticity [164,165].

Another study investigated the plasticity of the motor cortex in obese individuals compared to those with a healthy weight. It found that obese individuals had an impaired capacity for plasticity in the motor cortex, as measured by the suppression of cortical excitability following brain stimulation. This suggests that the ability of the motor cortex to change and adapt is reduced in obesity [166].

Furthermore, obesity has been associated with alterations in synaptic plasticity in the hippocampus, a brain region involved in learning and memory. Studies have shown that obese individuals, particularly males, exhibit deficits in hippocampal synaptic plasticity, which may contribute to cognitive impairments [167].

The underlying mechanisms linking obesity and impaired brain plasticity are not fully understood. However, factors such as chronic inflammation, oxidative stress, altered gut-brain

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hormonal functionality, and insulin resistance have been proposed as potential contributors [167,168].

Obese populations with MS may experience neurodegeneration through several mechanisms, as shown in the following image (Figure 4):

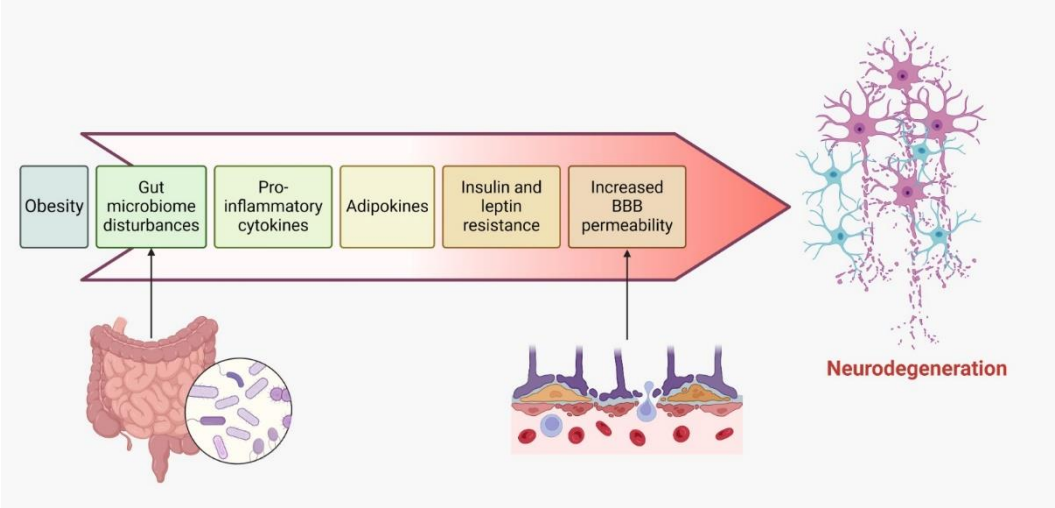

Figure 4. The cascade of mechanisms in obesity-induced neurodegeneration.

1. Obesity is associated with a chronic low-grade inflammatory state, characterized by increased levels of *pro-inflammatory cytokines.* This systemic inflammation can contribute to neuroinflammation in the CNS, exacerbating neurodegeneration in MS [169,170].
2. Adipose tissue produces various *adipokines*, including leptin, resistin, and visfatin, which are dysregulated in obesity. These adipokines can cross the blood-brain barrier and activate immune cells in the CNS, promoting inflammation and demyelination in MS [4,171].
3. Obesity can lead to *increased permeability of the blood-brain barrier (BBB)*, allowing the infiltration of immune cells and inflammatory mediators into the CNS. This BBB dysfunction contributes to neuroinflammation and neurodegeneration in MS [169,172].
4. Obesity and high-calorie diets are associated with *disturbances in gut microbiota*. Emerging evidence suggests that gut dysbiosis may play a role in the development and progression of MS. Altered gut microbiota can influence immune responses and neuroinflammation, contributing to neurodegeneration in obese MS populations [161,173].
5. Obesity is characterized by *insulin and leptin resistance*, which can impair neuroprotective signaling pathways. Insulin and leptin resistance may weaken the protective effects of these molecules in the CNS, leading to increased neurodegeneration in MS [174].

Fighting against obesity is hard for all populations, and nevertheless for MS populations. Some possibilities include:

Regular exercise is crucial for weight management and overall health. The American College of Sports Medicine recommends between 150-250 minutes per week of moderate-intensity physical activity for preventing weight gain and between 225-420 minutes per week for weight loss in people with MS [175].

When designing exercise programs for individuals with MS, it is important to consider their specific needs and limitations. *Exercise programs* should exceed energy expenditure recommendations to effectively counteract weight gain [175].

1. *Behavioral weight loss interventions* have shown efficacy in achieving clinically significant weight loss in people with MS. These interventions promote calorie reduction and an increase in physical activity, leading to improvements in weight, mobility, quality of life, and fatigue levels [176,177].
2. *Bariatric surgery* may be an option for severely obese individuals with MS. Studies have shown that bariatric surgery is relatively safe and effective in achieving weight loss in populations with MS, and it may also help improve mobility [178,179].

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3. *Intermittent fasting* has shown beneficial effects on weight loss and lipid profile in people with obesity and type 2 diabetes. Although limited data is available for its effects on MS, intermittent fasting may be a safe and feasible intervention for individuals with MS [180].
4. *Tailored dietary change strategies*, nutrition education, and counseling can play a significant role in managing metabolic comorbidities in MS. Addressing barriers and facilitators to dietary changes through behavior change techniques can help individuals achieve sustainable and tailored dietary behavior changes [181].

Obesity, particularly during adolescence and early adulthood, significantly increases the risk of developing MS and worsens disease progression and disability accumulation. Studies have identified mechanisms such as chronic inflammation, altered gut microbiota, and vitamin D deficiency that link obesity with MS. Additionally, obesity impairs brain plasticity, affecting sensory processing, motor cortex adaptability, and hippocampal synaptic plasticity, which may contribute to cognitive impairments. Obesity-induced chronic inflammation, adipokine dysregulation, blood-brain barrier permeability, and insulin resistance exacerbate neurodegeneration in MS populations. Effective management strategies include regular exercise, behavioural weight loss interventions, bariatric surgery, intermittent fasting, and tailored dietary changes, which can help mitigate obesity's impact on MS progression and overall health.

Conclusions

MS presents a complex interplay of immune-mediated pathology, characterized by inflammation, demyelination, and neurodegeneration. The CNS undergoes significant changes due to the disease's progression, leading to varied symptoms and disability levels among populations [1–7]. Enhancing brain plasticity offers a promising avenue for mitigating these effects and improving population outcomes [21–23].

Brain plasticity, the capacity of the brain to reorganize its structure and function, is vital for learning, memory, and recovery from injuries. In the context of MS, promoting brain plasticity can help counteract the neurological damage caused by the disease. Several mechanisms underpin brain plasticity, including synaptic modification, neurogenesis, and the activation of complex signalling pathways that support neuronal connectivity and survival [26–28].

Physical exercise is a potent modulator of brain plasticity. Aerobic exercise, resistance training, and even simple activities like walking have been shown to enhance synaptic plasticity, neurogenesis, and cognitive functions [29,30]. The increased production of BDNF is one key mechanism through which physical activity exerts its beneficial effects. BDNF supports the survival of existing neurons and encourages the growth and differentiation of new neurons and synapses [31,32].

Diet plays a crucial role in modulating brain health. Caloric restriction and intermittent fasting have been associated with increased expression of neurotrophic factors and enhanced synaptic function [175–181]. Additionally, specific nutrients, such as omega-3 fatty acids found in fish oil, have anti-inflammatory properties that can help reduce CNS inflammation and promote brain plasticity [96–108]. Polyphenols, present in foods like dark chocolate and certain fruits, also contribute to neuroprotection and cognitive enhancement [117–119].

Obesity is a known risk factor for MS progression. Controlling body weight through diet and exercise can reduce inflammation and oxidative stress, thereby supporting brain plasticity. Nutraceuticals like ALA and resveratrol have been shown to reduce oxidative damage and support metabolic homeostasis, further aiding in the control of obesity-related impacts on brain health [150–180].

Nutraceuticals are bioactive compounds that provide health benefits beyond basic nutrition. They play a significant role in supporting brain plasticity and overall brain health in MS populations.

Vitamin D3 has immunomodulatory and neuroprotective effects. It influences the production of pro-inflammatory cytokines and antioxidants, aiding in the reduction of neuroinflammation and promoting neurogenesis and synaptic plasticity. Studies have shown that vitamin D3 supplementation can reduce disease activity and progression in MS [64–66].

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Omega-3 fatty acids, particularly DHA, have been shown to support brain plasticity by modulating synaptic function and promoting neurogenesis. They also have anti-inflammatory properties that can help mitigate CNS inflammation in MS populations [96–107].

Antioxidants like ALA and flavonoids found in green tea and dark chocolate can scavenge free radicals, reducing oxidative stress and supporting neuroprotection. These compounds have shown potential in improving clinical outcomes in MS, including reducing fatigue and supporting cognitive functions [78–80].

GBE has been reported to improve cognitive functions and reduce fatigue in MS populations. Its antioxidant capacity supports brain plasticity by protecting neurons from oxidative damage and enhancing synaptic function [74–77].

Integrating lifestyle changes and nutraceuticals into the management of MS provides a holistic approach that complements traditional pharmacological treatments. By addressing modifiable risk factors and supporting brain plasticity, populations can experience improved neurological outcomes and quality of life. Regular physical activity, a balanced diet rich in neuroprotective nutrients, and the strategic use of nutraceuticals can form a comprehensive strategy for managing MS [170–180].

Future research should focus on the long-term effects of these lifestyle modifications and nutraceuticals on brain plasticity and MS progression. Large-scale, randomized controlled trials are needed to establish definitive evidence and provide clear guidelines for clinicians. Understanding the individual variability in response to these interventions can also help tailor personalized treatment plans for MS populations.

In conclusion, the synergistic effects of lifestyle changes and nutraceuticals hold great promise for enhancing brain plasticity and improving the lives of those living with MS. By adopting these strategies, populations can take an active role in managing their condition and optimizing their neurological health.

Abbreviation list

AD = Alzheimer's disease; ALA = alpha lipoic acid; BDNF = Brain derived neurotrophic factor; CAM = Complementary and alternative medicine; CIS = Clinically isolated syndrome; CNS = Central nervous system; CSF = Cerebrospinal fluid; DHA = docosahexaenoic acid; DIS = Dissemination in Space; DIT = Dissemination in Time; EBV = Epstein-Barr virus; EAE = Experimental autoimmune encephalomyelitis; EPA = eicosapentaenoic acid; GBE = Ginkgo biloba extract; HD = Huntington's disease; MS = Multiple sclerosis; OCBs = Oligoclonal bands; PD = Parkinson's disease; PPMS = Primary progressive multiple sclerosis; PUFA = Polyunsaturated fatty acids; RRMS = Relapsing-remitting multiple sclerosis; SPMS = Secondary progressive multiple sclerosis; tPA = tissue-type plasminogen activator.

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