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Review

Advancements in Multiple Sclerosis Research: From Pathogenesis to Novel Therapeutic Strategies

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Abstract

This comprehensive review explores the intricate landscape of multiple sclerosi (MS), a complex autoimmune disease affecting millions worldwide. Beginning with a analysis of its etiology, including genetic predisposition, environmental factors, an immune dysregulation, the article delves into the pathophysiological mechanism underlying MS, highlighting inflammation, neurodegeneration, and gliosis as centra features. Clinical presentations and diagnostic considerations are discussed, emphasizin the diverse neurological symptoms and objective findings encountered in MS patients The review further examines current management strategies, focusing on disease modifying drugs and emerging therapies such as botanical extracts, probiotics, and nove immunomodulatory agents. Insights from preclinical studies investigating the therapeuti potential of natural compounds like Hypericum perforatum, Panax ginseng, Nigell sativa, and ginger are presented alongside discussions on bee venom and blueberries a potential adjunctive treatments. Finally, the article explores ongoing clinical trial evaluating innovative therapeutic approaches targeting immune dysregulation in MS Through a multidimensional lens, this review offers valuable insights into th complexities of MS pathogenesis and the evolving landscape of therapeutic interventions

Keywords: Multiple sclerosis, Autoimmune disease, gliosis, Nigella sativa, Hypericum perforatum, Panax ginseng.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, demyelinating, and inflammatory autoimmune disease of the central nervous system (CNS). Approximately 2.5 million individuals worldwide suffer from MS[1]. The etiology of MS is still unknown, but the causative factors may be related to genetics or the environment. Patients with MS are categorized into four various clinical presentations; the relapsing-remitting MS (RRMS), primary-progressive MS

(PPMS), secondary-progressive MS (SPMS), and progressive-relapsing MS (PRMS)[2,3] Inflammation, neurodegeneration, and gliosis are hallmarks of MS. Perivascular lymphocytic infiltrate and macrophages destroy the myelin sheaths that pathologically wrap neurons[4,5]. The most common features of MS are motor, sensory, and cognitive deficits[6]. Although the exact pathogenesis of cognitive impairment in MS is not fully understood, advanced MRI techniques attributed it to several elements, including white matter lesions, grey matter atrophy, and altered connectivity of grey matter structures such as the hippocampus and cerebral cortex[7]. MS affects different regions of the brain, such as the hippocampus, corpus callosum (CC), cortex, white and gray matters, and striatum. Immune response in CNS is compartmentalized into three parts microglia cells, astrocytes, and immune-independent processes that drive axonal dysfunction. The pathological process of MS involves multifocal inflammation, reactive gliosis, oligodendrocytes depletion, demyelination, and degeneration of axon[8]. MS subtype can further be categorized based on 'activity' and 'progression', with 'activity' defined as ongoing inflammation (e.g., new relapses, new gadolinium-enhancing [GdE] lesions and/or new/enlarging T2 lesions) and 'progression' determined via disability accumulation[9]. This is important because inflammatory activity and disability accumulation can occur in both relapsing and progressive MS and recognizing this balance can help guide treatment initiation and sequencing[10].

ETIOLOGY

MS development is influenced by various risk factors, including age, sex, race, genetics, geographical location, and certain infections like herpes simplex, chlamydia, and rabies[11,12]. The development of MS likely arises from a complex interaction involving genetics, diet, and environmental factors[13]. The main cause of MS is an autoimmune assault on the central nervous system (CNS) triggered by hyperactive immunity. While various pathways have been suggested, one prominent theory, known as the "outside-in" mechanism, implicates CD4+ proinflammatory T cells[14]. Scientists speculate that an unidentified antigen triggers the activation of both Th1 and Th17 T-helper cells, initiating adhesion to the CNS endothelium, breaching the blood-brain barrier (BBB), and subsequently provoking an immune response through cross-reactivity. Conversely, the "inside-out" theory suggests that inherent dysfunction within the CNS leads to inflammation-mediated tissue damage. The influence of environmental factors, such as latitudinal variations across different countries, has been extensively investigated[15]. Vitamin D deficiency has been suggested as a potential reason for the increased susceptibility observed in populations residing at higher latitudes[16]. There is a notable likelihood of individuals developing the disease if they have relatives with MS, with the estimated heritability ranging between 35% and 75%[17,18].

PATHOPHYSIOLOGY

Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by lesions scattered throughout the CNS. These lesions primarily consist of areas of demyelination and inflammation, typically seen in white matter on magnetic resonance imaging (MRI). While grey matter and cortical lesions are also common in pathological tissue, they may not be easily detected with current imaging techniques[19]. Following the initial inflammatory phase, MS lesions can transition to a chronic state, which may involve processes such as remyelination, resolution of inflammation without repair, or a persistent state of inflammation and myelin degeneration[20]. Early research highlighted the involvement of T cells in the development of inflammation and demyelination in MS. More recent studies, along with the efficacy of B-cell–depleting treatments like ocrelizumab, also indicate a likely pathogenic role of B cells, potentially through their interaction with T cells. Inflammation and neurodegeneration are observed to varying extents in individuals with MS at the onset of the disease and can evolve within an individual over time[21].

RISK FACTORS

Vitamin D Deficiency

Vitamin D's role in stimulating lymphocytes and modulating growth and immune responses, it appears to significantly contribute to the development of MS[22]. Furthermore, there is an increase in the activity of both the innate immune system and adaptive immune responses. Vitamin D has been shown to decrease the production of proinflammatory cytokines mediated by Th1 cells. In numerous trials, the administration of vitamin D has significantly influenced the levels of interleukin-10 (IL-10) and interleukin-17 (IL-17)[23]. The incidence of MS is higher in populations residing further away from the equator. Near the equator, MS prevalence is nearly absent, but it increases to 50 cases per 1,000,000 individuals living at approximately 45 degrees north or south. The regional disparity in MS prevalence is likely influenced by insufficient levels of vitamin D among MS patients[24,25].

Genetics and Family History

Evidence suggests that certain individuals inherit a susceptibility to MS. However, this genetic predisposition is not determined by a single MS-specific gene[26,27]. Genetic investigations have revealed an association among individuals who are first, second, and third-degree relatives[28].

Injury

Extensive research has explored severe injuries as potential triggers for MS by directly harming the brain or spinal cord. Traumatic events elevate the permeability of the blood-brain barrier (BBB), allowing Th1 cells to penetrate into the central nervous system (CNS). This serves as the initial trigger for the inflammatory cascade, culminating in the destruction of myelin and the development of MS lesions[29].

CLINICAL PRESENTATION

Typical symptoms of MS encompass a range of clinical presentations. These include unilateral optic neuritis, marked by blurred vision and pain, partial myelitis resulting in impaired sensation, weakness, and/or ataxia in the limbs and torso, focal sensory disturbances like limb paresthesias or chest discomfort, and brainstem syndromes such as intranuclear ophthalmoplegia, vertigo, hearing loss, and facial sensory issues. Objective findings on neurological examinations may include an afferent pupillary defect, sensory deficits, motor weakness, ataxia, and gait disturbances, often accompanied by hyperreflexia. In MS, a clinical attack or relapse is characterized by symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS. These symptoms typically emerge abruptly or gradually, last for at least 24 hours, and may or may not fully resolve, occurring in the absence of fever or infection[30].

MANAGEMENT AND TREATMENT

Present treatment approaches primarily target managing acute episodes, easing symptoms, and reducing disease activity. The mainstay of MS therapy involves the use of disease-modifying drugs such as dimethyl fumarate, interferon-beta, natalizumab, and fingolimod (Table 1). Prompt initiation of treatment is crucial upon MS diagnosis. Short-term aims include minimizing MRI lesion activity, while long-term objectives focus on preventing the progression to secondary progressive MS. Following medication commencement, ensuring patient adherence and monitoring for drug-related adverse effects are paramount considerations[31].

Table 1: Current Pharmacological Treatments for Multiple Sclerosis

Sl.No	Drug	Mechanism of Action	Administration	Side Effects	Drug Interaction
1	Ocrelizumab	Anti-CD20 mAb	IV infusion every six months	Infusion reactions, nasopharyngitis, headache, oral herpes, colitis, hypogammaglobulinemia, neutropenia, and increased cancer risk	Smallpox vaccine. Typhoid vaccine. Influenza vaccine.
2	Mitoxantrone	DNA intercalator	IV infusion every month or three months	cardiomyopathy, hepatotoxicity, promyelocytic leukemia	Valspodar. Typhoid vaccine. Influenza vaccine.
3	Fingolimod	Sphingosine-1 phosphate inhibitor	Oral, once daily	Bradycardia, atrioventricular conduction block, macular edema, elevated liver enzyme levels, and mild hypertension	Aripiprazole. Esmolol. Sulpiride.
4	Dimethyl fumarate	Nuclear factor (erythroid derived 2)-like two pathway inhibitor	Oral, twice daily	Flushing, diarrhea, nausea, upper abdominal pain, decreased lymphocyte counts, and elevated liver aminotransferase.	Diroximel fumarate.

Plant Products used in treatment of MS

Hypericum perforatum

St. John's Wort, scientifically known as Hypericum perforatum L., belongs to the Hypericaceae family and is recognized as a flowering plant. While native to Europe and Asia, it has now become widespread across the globe[32]. Additionally, there are accounts of the therapeutic benefits of this plant and its derivative, hyperforin, in addressing psychiatric and neurological conditions like Alzheimer's and Parkinson's disease[33].

Research Findings in Animal Models and Human Trials: It was documented that administering the hydroalcoholic extract of H. perforatum or hyperforin orally to EAE mice reduced EAE-induced behavioral

impairments, potentially by influencing immune system activity. Similarly, oral intake of MS14, an herbal-marine medication comprising 90% Penaeus latisculatus (king prawn), 5% Apium graveolens (Umbelliferae), and 5% H. perforatum, was found to alleviate motor disability and mitigate CNS inflammation in rats with EAE. While numerous clinical trials have explored the therapeutic potential of H. perforatum, most have focused on depression and anxiety treatment. However, we found no relevant studies concerning MS patients. There is one clinical trial that evaluated the impact of MS14 on MS patients, suggesting potential improvement in lower limb mobility without significant adverse effects on vital signs or various biochemical and physiological parameters[34].

Panax Ginseng and Ginsan

Ginsan, an acidic polysaccharide, is derived from the roots of Panax ginseng, a medicinal herb belonging to the Araliaceae family. With a history spanning over 2000 years in oriental medicine, P. ginseng has been traditionally employed for treating various degenerative conditions. It is renowned for enhancing physical vitality, stamina, and combating aging effects[35].

Research Findings in Animal Models and Human Trials: Hwang et al. investigated the impact of administering ginsan at a dose of 200mg/day before symptoms onset in mice with EAE. They observed that ginsan administration reduced the behavioral symptoms of EAE and suppressed the proliferation of self-reactive T cells as well as the production of inflammatory cytokines. Similarly, Bowie et al. found that treating mice with an aqueous ginseng extract (150mg/kg) during the acute phase of EAE led to a reduction in the severity of behavioral and pathological symptoms. Recently, it was shown that oral administration of Korean red ginseng extract (at doses of 20 and 100mg/kg) mitigated behavioral symptoms, weight loss, spinal demyelination, and glial activation in EAE-afflicted rats[36]. Clinical trials exploring the therapeutic potential of ginseng or ginsan in MS treatment are limited but mainly focus on managing fatigue associated with MS. These trials suggest that ginseng might alleviate fatigue and have a notable positive impact on the quality of life for MS patients[37].

Nigella sativa

Black cumin, scientifically known as Nigella sativa and belonging to the botanical family Ranunculaceae, has a historical presence in Middle Eastern folk medicine, where its seeds have been utilized as a remedy for a range of ailments. Recent research has highlighted the neuroprotective, antioxidant, and anti-inflammatory properties associated with black cumin. Thymoquinone, identified as the principal bioactive compound in these seeds, plays a significant role in these observed effects[39].

Research Findings in Animal Models and Human Trials: Administering N. sativa seeds orally, either two weeks before inducing EAE or after the initial onset of EAE symptoms, resulted in reduced behavioral impairments, suppressed inflammation, and improved remyelination. However, there have been no clinical trials conducted on patients with MS to date[40,41].

Sesame oil

Sesame seed, belonging to the Sesamum indicum species within the Pedaliaceae family, holds a longstanding reputation as a staple food in various Asian nations, prized for its nutritional benefits and culinary versatility. Sesame oil, extracted from these seeds, has garnered attention for its potential health-promoting properties. Notably, sesame oil exhibits a remarkable ability to inhibit lipid peroxidation, a process linked to oxidative stress and cellular damage. Moreover, research suggests that sesame oil serves as a potent inhibitor of proinflammatory mediators, which play a central role in the development and progression of various chronic diseases. These findings underscore the therapeutic potential of sesame oil as a natural remedy for combating oxidative stress and inflammation, contributing to its widespread use in traditional medicine and culinary practices across diverse cultures[42].

Research Findings in Animal Models and Human Trials: A research group conducted two separate studies investigating the effects of sesame oil administration on mice with EAE, a model for multiple sclerosis[43,44]. One study explored the impact of oral administration, while the other examined the effects of intraperitoneal administration. Results from both studies demonstrated promising outcomes, showing a decrease in behavioral deficits and an improvement in immune system function following sesame oil treatment. Despite these encouraging findings, clinical trials evaluating the therapeutic potential of sesame oil in various health conditions, such as hypertension, diabetes mellitus, allergy, and inflammation, have been conducted. However, it's noteworthy that no clinical trial has yet been conducted specifically on patients with multiple sclerosis. This underscores the need for further research to explore the potential benefits of sesame oil in managing MS and its associated symptoms.

Probiotics

For centuries, probiotics, defined as live microorganisms with beneficial effects on health, have been an integral part of human consumption. Extensive research has consistently highlighted the myriad benefits associated with probiotic bacteria. In contemporary times, there has been a notable surge in the use of probiotic preparations, driven by their widespread recognition in both preventive and therapeutic approaches to health. Specifically, probiotics are increasingly being employed in the management of gastrointestinal ailments, such as irritable bowel syndrome and inflammatory bowel disease, as well as in the treatment of autoimmune disorders, where their potential to modulate immune responses holds promise. This growing utilization underscores the evolving understanding of the intricate interplay between gut microbiota and human health, propelling probiotics into the forefront of modern healthcare practices[45].

In a noteworthy study, Kobayashi et al. conducted research revealing the potential of oral administration of two widely recognized probiotics, namely Lactobacillus casei and Bifidobacterium breve, in ameliorating neurological symptoms associated with experimental autoimmune encephalomyelitis (EAE). Their findings suggested a promising avenue for utilizing probiotics as a therapeutic intervention for neurological conditions[46]. Building upon this foundation, subsequent investigations further elucidated the therapeutic potential of probiotics in EAE. One such study demonstrated that administering a mixture of three lactobacilli strains not only halted the progression but also reversed the behavioral and histological deficits observed in mice afflicted with EAE. This multifaceted approach highlighted the nuanced effects of probiotics in modulating the immune response and neuroinflammation characteristic of EAE. Moreover, emerging evidence underscored the importance of strain-specific differences in influencing the efficacy of probiotics in EAE. This nuanced understanding offers valuable insights into optimizing probiotic-based interventions for neuroinflammatory disorders[47]. Despite the promising preclinical findings, the translation of probiotic therapy into clinical practice for multiple sclerosis (MS) remains largely unexplored. To date, no clinical trials have been reported investigating the efficacy of probiotics in MS patients. However, the accumulating evidence from preclinical studies underscores the potential for further exploration of probiotic interventions as a novel therapeutic approach for MS and other autoimmune disorders. Such endeavors hold promise for advancing our understanding of the intricate interplay between gut microbiota and neurological health, paving the way for innovative strategies in MS management[48].

Ginger

Ginger, derived from the rhizome of the Zingiber officinale plant, holds a dual role as both a widely used spice and a commonly consumed dietary supplement. Its roots in Iranian traditional medicine extend to its utilization in the treatment of conditions ranging from memory deficits to various digestive disorders. In recent years, scientific investigations have shed light on the remarkable anti-inflammatory effects associated with ginger and its derivatives. These findings not only corroborate its longstanding traditional use but also open new avenues for exploring ginger as a potential therapeutic agent for addressing a broader spectrum of health issues beyond its traditional applications[49].

Research Findings in Animal Models and Human Trials: The therapeutic potential of ginger was explored through the administration of a hydroalcoholic extract, revealing promising results in mitigating behavioral deficits and modulating immune functions in mice with EAE. This study sheds light on ginger's ability to potentially alleviate symptoms and modulate immune responses associated with neuroinflammatory conditions such as EAE[50]. However, it's important to note the current gap in clinical research, as no studies have yet translated these preclinical findings into clinical trials involving patients with MS. Despite the lack of clinical evidence, the preclinical data underscores the need for further exploration of ginger's therapeutic properties in human subjects with MS, offering hope for the development of novel interventions to improve patient outcomes. Such investigations could pave the way for the integration of ginger-based therapies into mainstream treatments for MS, enhancing our arsenal of therapeutic options for this complex neurological disorder.

Bee venom

The venom secreted by the honey bee, scientifically known as Apis mellifera, boasts a complex composition characterized by a variety of peptides, including both light and heavy chain peptides. Furthermore, it contains a diverse assortment of proteins, among which apamin, melittin, adolpin, and phospholipase A2 stand out prominently. These components collectively contribute to the multifaceted pharmacological profile of bee venom. Of particular interest are its noted anti-inflammatory and antinociceptive effects, which have been extensively studied and documented. These properties endow bee venom with the ability to mitigate inflammatory reactions, offering potential therapeutic benefits in conditions characterized by inflammation and pain. While the precise mechanisms underlying these effects are still being elucidated, the multifunctional nature of bee venom constituents suggests a complex interplay with various biological pathways involved in inflammation and pain perception. Further research into the molecular mechanisms and clinical applications of bee venom could unveil novel therapeutic strategies for managing inflammatory disorders and pain-related conditions[51].

Research Findings in Animal Models and Human Trials: In experiments conducted on rats afflicted with EAE, the injection of bee venom yielded promising results. It demonstrated efficacy in ameliorating pathological alterations, balancing glutamate levels, and enhancing the presence of γ-aminobutyric acid in the brain. However, notably absent from these findings was an assessment of the impact of bee venom on the behavioral deficits typically observed in EAE[52]. Recent investigations have delved deeper into the mechanisms underlying bee venom's effects. Specifically, exposure of isolated myelin to phospholipase A2, a component found in bee venom and other venoms, revealed detrimental consequences for this crucial neurological structure. This highlights the intricate relationship between bee venom components and their potential influence on myelin integrity, which is central to the pathology of MS and EAE[53]. Turning to clinical research, two notable clinical trials evaluated the therapeutic potential of bee venom in patients with MS. Despite initial optimism, the results from these trials failed to demonstrate significant improvements in disease severity, disability, fatigue, or overall quality of life among MS patients following bee venom treatment. This underscores the complexities inherent in translating promising preclinical findings into effective clinical interventions, emphasizing the need for further investigation and refinement in the use of bee venom as a potential therapy for MS[54,55].

Blueberries

Blueberries, renowned for their rich content of flavonoids, have garnered attention for their potential in counteracting neurodegenerative diseases. Emerging research suggests that the consumption of blueberries may offer protective effects against the progressive deterioration of neural tissues associated with such conditions. Moreover, these flavonoid-packed fruits have been implicated in the preservation of cognitive function, particularly in the context of age-related cognitive decline and neural damage. Thus, incorporating blueberries into one's diet may serve as a proactive measure to support brain health and combat the onset and progression of neurodegenerative diseases[56].

Research Findings in Animal Models and Human Trials: In an intriguing study conducted by Xin et al., mice with EAE were provided with a diet containing 1% whole, freeze-dried Tifblue blueberries (Vaccinium ashei). The results of this study unveiled compelling findings: EAE mice fed with blueberries exhibited noteworthy improvements, including lower motor disability scores and enhanced preservation of myelin in the lumbar spinal cord. These findings not only underscore the potential therapeutic benefits of blueberries in the context of neuroinflammatory conditions like EAE but also hint at their capacity to mitigate neurodegenerative processes[57]. While clinical trials investigating the effects of blueberries on various health conditions, including memory enhancement, antioxidant properties, and anti-inflammatory effects, have been conducted, none have specifically focused on patients with MS. This highlights a significant gap in our understanding of the potential benefits of blueberries in managing the complexities of MS. Further exploration through targeted clinical trials is warranted to elucidate the specific impact of blueberries on MS pathology and symptomatology, potentially opening new avenues for holistic management strategies in MS care.

Exploring Novel Therapies: Clinical Trials Investigating Drugs for Multiple Sclerosis

Inhibit T-cell receptor/peptide/MHC-II interaction

The copolymer, currently undergoing Phase I/II clinical trials, has received approval for the treatment of relapsing forms of MS in both the United States and Europe. Its mechanism of action involves blocking or competing with the binding of encephalitogenic peptides to the MHC-II molecule. This innovative therapeutic approach holds promise in modulating the immune response implicated in MS progression, offering potential benefits for patients managing this complex neurological condition.

Induction of T-cell anergy

In preclinical testing, researchers are investigating antibodies directed against B7 molecules. This experimental approach aims to induce a state of T cell anergy, wherein T cells fail to mount an immune response when encountering antigens presented by antigen-presenting cells in the absence of co-signaling. Specifically, when the T cell receptor (TCR) engages with its cognate peptide presented by major histocompatibility complex class II (MHC-II) molecules but fails to receive co-stimulatory signals through interactions with B7 molecules, T cell activation is suppressed. This strategy holds potential for modulating immune responses in conditions such as multiple sclerosis, where aberrant T cell activation contributes to disease pathology. Further research is necessary to assess the efficacy and safety of this approach in clinical settings.

Reduce T-cell trafficking across blood-brain-barrier (BBB)

In Phase I/II clinical trials, researchers are evaluating the potential of TGF-b as a therapeutic agent. This compound is being studied for its capacity to decrease the expression of adhesion molecules not only on T cells but also on vascular endothelial cells. By targeting these molecules, TGF-b may play a crucial role in modulating immune responses and dampening the inflammatory processes implicated in various diseases, including

autoimmune disorders like multiple sclerosis. This investigational approach holds promise for developing novel treatments aimed at attenuating immune-mediated tissue damage and improving patient outcomes. Further research is needed to fully elucidate the therapeutic potential and safety profile of TGF-b in clinical settings[58].

CONCLUSION

In conclusion, multiple sclerosis (MS) remains a multifaceted autoimmune disease of the central nervous system, affecting millions worldwide. Genetic predisposition, environmental factors, and immune dysregulation contribute to its pathogenesis, characterized by inflammation, neurodegeneration, and gliosis. The diverse clinical presentation necessitates comprehensive diagnostics, while current treatments primarily focus on disease-modifying drugs. Emerging research explores botanical extracts like Hypericum perforatum, Panax ginseng, and Nigella sativa, offering neuroprotective and anti-inflammatory potential. Innovative therapies targeting immune modulation, such as copolymers and antibodies, show promise in clinical trials. Collaborative efforts are crucial for advancing understanding, developing therapies, and improving patient care, aiming to enhance the quality of life for those with MS.

REFERENCES

1. Abdel-Maged AES, Gad AM, Rashed LA, Azab SS, Mohamed EA, Awad AS. Repurposing of Secukinumab as Neuroprotective in Cuprizone-Induced Multiple Sclerosis Experimental Model via Inhibition of Oxidative, Inflammatory, and Neurodegenerative Signaling. Molecular Neurobiology. 2020 Jun 8;57(8):3291–306.
2. McDonnell GV, Hawkins SA (1996) Primary progressive multiple sclerosis: a distinct syndrome? Mult Scler J 2(3):137–141
3. Thompson AJ et al (1997) Primary progressive multiple sclerosis. Brain 120(6):1085–1096
4. Noyes K, Weinstock-Guttman B. Impact of diagnosis and early treatment on the course of multiple sclerosis. Am J Manag Care. 2013 Nov;19(17 Suppl):s321-31. PMID: 24494633.
5. University of California, San Francisco MS-EPIC Team:, Cree BAC, Gourraud PA, Oksenberg JR, Bevan C, Crabtree-Hartman E, et al. Long-term evolution of multiple sclerosis disability in the treatment era. Annals of Neurology [Internet]. 2016 Oct 1;80(4):499–510.
6. Aldhahri, R.S.; Alghamdi, B.S.; Alzahrani, N.A.; Bahaidrah, K.A.; Alsufiani, H.M.; Mansouri, R.A.; Ashraf, G.M. Biochanin A Improves Memory Decline and Brain Pathology in Cuprizone-Induced Mouse Model of Multiple Sclerosis. Behav. Sci. 2022, 12, 70. https://doi.org/10.3390/bs12030070
7. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. The Lancet Neurology. 2020 Oct;19(10):860–71.
8. Stadelmann C, Wegner C, Bruck W (2011) Inflammation, demyelination, and degeneration—recent insights from MS pathology. Biochim Biophys Acta 1812(2):275–282
9. Klineova S, Lublin FD. Clinical course of multiple sclerosis. Cold Spring Harb. Perspect. Med. 8, a028928 (2018).
10. Freedman MS, Selchen D, Arnold DL et al. Treatment optimization in MS: Canadian MS working group updated recommendations. Can. J. Neurol. Sci. 40, 307–323 (2013).
11. Mulder WJM, Ochando J, Joosten LAB, Fayad ZA, Netea MG: Therapeutic targeting of trained immunity. Nat Rev Drug Discov. 2019, 18:553-66. 10.1038/s41573-019-0025-4
12. Ramagopalan SV, Dobson R, Meier UC, Giovannoni G: Multiple sclerosis: risk factors, prodromes, and potential causal pathways. Lancet Neurol. 2010, 9:727-39. 10.1016/S1474-4422(10)70094-6
13. Mahon BD, Gordon SA, Cruz J, Cosman F, Cantorna MT: Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. J Neuroimmunol. 2003, 134:128-32. 10.1016/S0165-5728(02)00396-X
14. Ntranos A, Lublin F: Diagnostic criteria, classification and treatment goals in multiple sclerosis: the chronicles of time and space. Curr Neurol Neurosci Rep. 2016, 16:90. 10.1007/s11910-016-0688-8
15. Simpson S Jr, Blizzard L, Otahal P, Van der Mei I, Taylor B: Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. J Neurol Neurosurg Psychiatry. 2011, 82:1132-41. 10.1136/jnnp.2011.240432
16. Sintzel MB, Rametta M, Reder AT: Vitamin D and multiple sclerosis: a comprehensive review . Neurol Ther. 2018, 7:59-85. 10.1007/s40120-017-0086-4
17. Willer CJ, Dyment DA, Risch NJ, Sadovnick AD, Ebers GC: Twin concordance and sibling recurrence rates in multiple sclerosis. Proc Natl Acad Sci U S A. 2003, 100:12877-82. 10.1073/pnas.1932604100
18. Dighriri IM, Aldalbahi AA, Albeladi F, Tahiri AA, Kinani EM, Almohsen RA, Alamoudi NH, Alanazi AA, Alkhamshi SJ, Althomali NA, Alrubaiei SN. An overview of the history, pathophysiology, and pharmacological interventions of multiple sclerosis. Cureus. 2023 Jan 2;15(1).

19. Lucchinetti CF, Popescu BF, Bunyan RF, et al. Inflammatory cortical demyelination in early multiple sclerosis. N Engl J Med. 2011;365(23):2188- 2197. doi:10.1056/NEJMoa1100648
20. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009;132(pt 5):1175-1189. doi:10.1093/brain/awp070
21. Michel L, Touil H, Pikor NB, Gommerman JL, Prat A, Bar-Or A. B cells in the multiple sclerosis central nervous system: trafficking and contribution to CNS-compartmentalized inflammation. Front Immunol. 2015;6:636. doi:10.3389/fimmu.2015. 00636
22. Ramagopalan SV, Dobson R, Meier UC, Giovannoni G: Multiple sclerosis: risk factors, prodromes, and potential causal pathways. Lancet Neurol. 2010, 9:727-39
23. Golan D, Halhal B, Glass-Marmor L, et al.: Vitamin D supplementation for patients with multiple sclerosis treated with interferon-beta: a randomized controlled trial assessing the effect on flu-like symptoms and immunomodulatory properties. BMC Neurol. 2013, 13:60. 1
24. Sadovnick AD, Ebers GC: Epidemiology of multiple sclerosis: a critical overview . Can J Neurol Sci. 1993, 20:17-29. 10.1017/s0317167100047351
25. Hayes CE, Nashold FE, Spach KM, Pedersen LB: The immunological functions of the vitamin D endocrine system. Cell Mol Biol (Noisy-le-grand). 2003, 49:277-300
26. Rodriguez M: Multiple sclerosis: basic concepts and hypothesis . Mayo Clin Proc. 1989, 64:570-6. 10.1016/s0025-6196(12)65563-3 34.
27. Miller DH, Leary SM: Primary-progressive multiple sclerosis . Lancet Neurol. 2007, 6:903-12. 10.1016/S1474- 4422(07)70243-0 35.
28. Robertson NP, Fraser M, Deans J, Clayton D, Walker N, Compston DA: Age-adjusted recurrence risks for relatives of patients with multiple sclerosis. Brain. 1996, 119:449-55.
29. Poser CM: The role of trauma in the pathogenesis of multiple sclerosis: a review . Clin Neurol Neurosurg. 1994, 96:103-10.
30. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: a review. Jama. 2021 Feb 23;325(8):765-79.
31. Krajnc N, Bsteh G, Berger T, Mares J, Hartung HP: Monoclonal antibodies in the treatment of relapsing multiple sclerosis: an overview with emphasis on pregnancy, vaccination, and risk management. Neurotherapeutics. 2022, 19:753-73.
32. Beaubrun G, Gray GE. A review of herbal medicines for psychiatric disorders. Psychiatr Serv 2000;51(9):1130-4. doi: 10.1176/appi.ps.51.9.1130
33. Kiasalari Z, Baluchnejadmojarad T, Roghani M. Hypericum perfo ratum Hydroalcoholic Extract Mitigates Motor Dysfunction and is Neuroprotective in Intrastriatal 6-Hydroxydopamine Rat Model of Parkinson's disease. Cell Mol Neurobiol 2016;36:521–30.
34. Naseri M, Ahmadi A, Gharegozli K, Nabavi M, Faghihzadeh S, Ashtarian N, Montazami F, Rezaeizadeh H. A double blind, placebo-controlled, crossover study on the effect of MS14, an herbalmarine drug, on quality of life in patients with multiple sclerosis. J Med Plant Res 2009;3:271–5.
35. Cho IH. Effects of Panax ginseng in Neurodegenerative Diseases. J Ginseng Res 2012;36:342–53.
36. Lee MJ, Jang M, Choi J, Chang BS, Kim do Y, Kim SH, Kwak YS, Oh S, Lee JH, Chang BJ, Nah SY, Cho IH. Korean Red Ginseng and Ginsenoside-Rb1/-Rg1 Alleviate Experimental Autoimmune Encephalomyelitis by suppressing Th1 and Th17 Cells and upregulating regulatory T Cells. Mol Neurobiol 2016;53:1977–2002.
37. Etemadifar M, Sayahi F, Abtahi SH, Shemshaki H, Dorooshi GA, Goodarzi M, Akbari M, Fereidan-Esfahani M. Ginseng in the treatment of fatigue in multiple sclerosis: a randomized, placebo-controlled, double-blind pilot study. Int J Neurosci 2013;123:480–6.
38. Cho YJ, Son HJ, Kim KS. A 14-week randomized, placebocontrolled, double-blind clinical trial to evaluate the efficacy and safety of ginseng polysaccharide (Y-75). J Transl Med 2014;12:283.
39. Khazdair MR. The Protective Effects of Nigella sativa and Its Constituents on Induced Neurotoxicity. J Toxicol 2015;2015:841823.
40. Noor NA, Fahmy HM, Mohammed FF, Elsayed AA, Radwan NM. Nigella sativa ameliorates inflammation and demyelination in the experimental autoimmune encephalomyelitis-induced Wistar rats. Int J Clin Exp Pathol 2015;8:6269–86.
41. Fahmy H, Noor NA, Mohammed FF, Elsayed AA, Radwan NM. Nigella sativa as an anti-inflammatory and promising remyelinating agent in the cortex and hippocampus of experimental autoimmune encephalomyelitis-induced rats. J Basic Appl Zool 2014;67:182–95.
42. Chandrasekaran VR, Hsu DZ, Liu MY. Beneficial effect of sesame oil on heavy metal toxicity. JPEN J Parenter Enteral Nutr 2014;38:179–85.
43. Ghazavi A, Mosayebi G. The mechanism of sesame oil in ameliorating experimental autoimmune encephalomyelitis in C57BL/6 mice. Phytother Res 2012;26:34–8.

44. Mosayebi G, Ghazavi A, Salehi H, Payani MA, Khazae MR. Effect of sesame oil on the inhibition of experimental autoimmune encephalomyelitis in C57BL/6 mice. Pak J Biol Sci 2007;10:1790–6.
45. Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun 2014;38:1–12
46. Kobayashi T, Kato I, Nanno M, Shida K, Shibuya K, Matsuoka Y, Onoue M. Oral administration of probiotic bacteria, Lactobacillus casei and Bifidobacterium breve, does not exacerbate neurological symptoms in experimental autoimmune encephalomyelitis. Immunopharmacol Immunotoxicol 2010;32:116–24.
47. Lavasani S, Dzhambazov B, Nouri M, Fak F, Buske S, Molin G, Thorlacius H, Alenfall J, Jeppsson B, Westrom B. A novel probiotic mixture exerts a therapeutic effect on experimental autoimmune encephalomyelitis mediated by IL-10 producing regulatory T cells. PLoS One 2010;5:e9009.
48. Maassen CB, Claassen E. Strain-dependent effects of probiotic lactobacilli on EAE autoimmunity. *Vaccine* 2008;26: 2056-7
49. Khodaie L, Sadeghpoor O. Ginger from ancient times to the new outlook. Jundishapur J Nat Pharm Prod 2015;10:e18402.
50. Jafarzadeh A, Mohammadi-Kordkhayli M, Ahangar-Parvin R, Azizi V, Khoramdel-Azad H, Shamsizadeh A, Ayoobi A, Nemati M, Hassan Z, Moazeni S. Ginger extracts influence the expression of IL-27 and IL-33 in the central nervous system in experimental autoimmune encephalomyelitis and ameliorates the clinical symptoms of disease. J Neuroimmunol 2014;276:80–8
51. Mirshafiey A. Venom therapy in multiple sclerosis. Neuropharmacology 2007;53:353–61.
52. Karimi A, Parivar K, Nabiuni M, Haghighi S, Imani S, Afrouzi H. Effect of honey bee venom on Lewis rats with experimental allergic encephalomyelitis as regards changes of GABA and glutamate. Iran J Pharm Res 2011;7:295–300.
53. Yunes Quartino PJ, Pusterla JM, Galvan Josa VM, Fidelio GD, Oliveira RG. CNS myelin structural modification induced in vitro by phospholipases A2. Biochim Biophys Acta 2016;1858:123–9.
54. Wesselius T, Heersema DJ, Mostert JP, Heerings M, Admiraal Behloul F, Talebian A, van Buchem MA, De Keyser J. A randomized crossover study of bee sting therapy for multiple sclerosis. Neurology 2005;65:1764–8.
55. Castro HJ, Mendez-Lnocencio JI, Omidvar B, Omidvar J, Santilli J, Nielsen Jr HS, Pavot AP, Richert JR, Bellanti JA. A phase I study of the safety of honeybee venom extract as a possible treatment for patients with progressive forms of multiple sclerosis. Allergy Asthma Proc 2005;26:470–6.
56. Shukitt-Hale B. Blueberries and neuronal aging. Gerontology 2012;58:518–23.
57. Xin J, Feinstein DL, Hejna MJ, Lorens SA, McGuire SO. Beneficial effects of blueberries in experimental autoimmune encephalomyelitis. J Agric Food Chem 2012;60:574
58. Multiple Sclerosis: Current Status and Strategies for the Future [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK222385/