

## Current Approaches for the Management of Multiple Sclerosis – A Review

Lakhwinder Singh<sup>1</sup>, Sabina Yasmin<sup>1</sup>, Rajiv Sharma<sup>1</sup>

<sup>1</sup>University Institute of Pharma Sciences, Chandigarh University, Mohali.

### **ABSTRACT**

Multiple sclerosis (MS) is an autoimmune, neuroinflammatory disease which interferes with the central nervous system and damages the myelin sheath and axons. It is mediated by auto-reactive lymphocytes that cross the blood-brain barrier, cause inflammation, demyelination, and axonal loss, disturbing the communications between the neurons. The exact cause of MS is not known, but it is reported that it may be due to genetic, environmental factors, and viral infections (Epstein-Barr virus). There are various approaches for the management of Multiple Sclerosis, like disease-modifying agents, which are mainly used. Some of the monoclonal antibodies (Ocrelizumab) are approved recently for the management of MS. Due to various unwanted side effects with conventional medicines, people are eager to use cost-effective medicines with no or less side effects; therefore, herbal medicines are the best choice for them. They work by different pharmacological actions like reduce oxidative stress, anti-inflammatory, antioxidant effects, and others. Mainly used herbal plants like Ginkgo biloba, Salvia officinalis, and Nigella sativa.

**Keywords:** Multiple sclerosis, autoimmune, DMTs, Herbal plants

### **INTRODUCTION**

Multiple sclerosis is a chronic and progressive autoimmune, inflammatory, neurological disease of the CNS. It destroys the myelin sheath and axons to varying degrees [1]. It is characterized by inflammation, selective demyelination, and gliosis. It targets the Central Nervous System and is mediated by auto-reactive lymphocytes that cross the blood-brain barrier. These lymphocytes enter the CNS and cause local inflammation, resulting in demyelination and axonal loss; by damaging the protective covering of the nerve axons (myelin sheath), cause communication problems between your brain and rest of your body [2]. According to the World Health Organization, Multiple Sclerosis affects approximately 2.8 million people worldwide, and Multiple Sclerosis affects people aged between 20-50 years old, and it is investigated that females are more prone to Multiple Sclerosis than males [3]. The Multiple Sclerosis characteristic features are common vision loss, pain, fatigue, and impaired coordination, low personal activity-related self-effectiveness, limitation of self-regulatory concepts, socio-demographic factors restrictions, decline employment state, and decrease educational level [4]. People with Multiple Sclerosis may also develop; muscle stiffness or spasm, paralysis

typically in the legs, problems with bladder, bowel, sexual functions, mental changes depression epilepsy. The cause is unknown, but it appears to involve a combination of genetic factors and non-genetic factors such as environmental factors, virus, Metabolism that together result in a self-sustaining autoimmune disorder that leads to recurrent immune system attacks on the central nervous system[5]. All the Multiple Sclerosis treatments try to attempt to improve the neuronal function following Multiple Sclerosis occurs and stop any progression of the disease. The use of Multiple Sclerosis treatments in the early stage of Multiple Sclerosis can induce adverse side effects and can be ineffective at all. The treatments with good results are observed in teenager women where Multiple Sclerosis appears early with relapsing type with few neurons damaged. Multiple Sclerosis decreases life with an average 5–10 years than other healthy ones. There are many treatments and diagnostic procedures of Multiple Sclerosis are in the process of development [3].

Neurologists agree that patients may be grouped into four major categories based on the course of disease

Table 1: The categories of Multiple Sclerosis [6].

<b>Types</b>	<b>Clinical features</b>
Relapsing/Remitting Multiple Sclerosis (RRMS)	Relapses followed by incomplete remissions, during relapses, symptoms can get more severe
Secondary Progressive Multiple Sclerosis (SPMS)	Gradual progression of symptoms and disability over time following a period of RRMS
Primary Progressive Multiple Sclerosis (PPMS)	Gradual, progression of symptoms from initial presentation
Progressive Relapsing Multiple Sclerosis (PRMS)	Gradual symptoms progression over time accompanied by acute attacks of undesired effects

## **CAUSES**

The exact cause of the multiple sclerosis is unknown but some of the investigations shows that it may be due to the genetic and environmental factors some other cause are such as viral infections. Most of the studies suggest that multiple sclerosis is immune-genetic viral disease with Epstein Barr Virus[7].

Risk factors are age (most of the time between 20-50 years old), sex (females are more prone to multiple sclerosis than males), family history (genetic susceptibility), certain viral infections like EBV, vitamin D deficiency[8].

Some other risk factors like climate (more in cold areas), autoimmune diseases (higher risks with thyroid diseases, type 1 DM, and IBS), smoking, stress, fatigue, physical injury.

## **PATHOPHYSIOLOGY**

Due to etiological factors activated T cells (recognise self-antigen) gain entry into the brain via disruption in the blood brain barrier and macrophages (B cells) enters into the brain from peripheral circulation, production of inflammatory cytokines and free radical species than activated B cells and T cells causes demyelination and destruction of oligodendrocytes and damage the immune system; oligodendrocytes are the cells which are responsible for myelination of axonal nerves now without oligodendrocytes there's no more myelination to the axon. Formation of plaque cause scarring and destruction of sheath it further interrupt the transmission of impulses. Demyelinated axons scattered irregularly throughout the CNS. The most frequently affected areas are the optic nerves, cerebrum, brain stem, cerebellum, and spinal cord. On early stages oligodendrocytes can heal and re-myelination of the axons occurs but over time re-myelination will stop and damage will become permanent or irreversible with loss of axons [9, 10, 11].

## **CURRENTTREATMENT**

There is currently no cure for Multiple Sclerosis. The objective of the drugs are to suppress the immune response slow disease progression, limit relapses, decrease long-term neurologic impairment, and manage symptoms while limiting adverse reactions. Disease modifying therapies discussed below are approved for RRMS. Other types of MS are typically treated with the same drugs, chemotherapy, anti-inflammatory drugs, monoclonal antibodies, immunosuppressive drugs and corticosteroids are mainly used for the management of multiple sclerosis[12].

**Table 2: The FDA approved disease modifying drugs with their mode of action, indications, route of administration and dosing frequency of the drug[13, 14, 15]**

<b>Drugs name</b>	<b>Mode of action</b>	<b>Indications</b>	<b>Route of administration and dosing frequency</b>
Ocrelizumab	Anti-CD20 mAb	First line for RMS, PPSM	IV infusion, every 6 months
Ofatumumab	Anti-CD20 mAb	First line for RMS	SC injection, every 4 weeks
Natalizumab	a4b1 integrin inhibitor	Second line for RMS	IV infusion, every 4 weeks
Alemtuzumab	Anti-CD52 mAb	First line RMS	IV infusion, once daily

Mitoxantrone	DNA intercalator	Second line for RMS and SPMS	IV infusion, every month or 3 months
Fingolimod	Sphingosine-1-phosphate inhibitor	Second line RMS	Oral, once daily
Siponimod	Sphingosine 1-phosphate receptor modulator	First line CIS, RMS, SPMS	Oral, once daily
Ozanimod	Sphingosine 1-phosphate receptor modulator	SPMS, CIS, RMS	Oral, once daily
Dimethyl fumarate and diroximel	Nuclear factor (erythroid-derived 2)-like 2 pathway inhibitor	First line for RMS	Oral, twice daily
Cladribine	Not fully known	Second line for RMS	Oral, 4-5 days over 2-week treatment courses
Teriflunomide	Dihydrorotate dehydrogenase inhibitor	First line for RMS	Oral, once daily
Glatiramer acetate	Activates T lymphocytes suppressor cells	First line for RMS	SC injection, once daily or 3 times weekly
Interferon $\beta$ -1a (avonex, rebif)	Suppress expression of inflammatory cytokines	First line RMS, CIS	IM injection, once weekly SC injection, 3 times weekly
Peginterferon $\beta$ -1 (plegridy)	Suppress expression of inflammatory cytokines	First line RMS, CIS	SC injection every 2 weeks
Interferon $\beta$ -1b (betaseron)	Suppress expression of inflammatory cytokines	First line RMS, CIS	SC injection every other day after initial dose

## Treating Progressive Multiple Sclerosis[16, 17]

Secondary Progressive Multiple Sclerosis:

Siponimod<sup>44</sup> is a selective S1P modulator that is approved for relapsing forms of Multiple Sclerosis, including active SPMS, meaning patients with secondary progressive multiple, Ocrelizumab, cladribine, and diroximel fumarate can also be used for patients with active Secondary progressive multiple sclerosis.

Primary Progressive Multiple Sclerosis:

Ocrelizumab is the only approved DMTs for the management of Primary Progressive Multiple Sclerosis. Dosing is the same as for Relapsing Multiple Sclerosis. Ocrelizumab decreases progression of clinical disability by approximately one-quarter, and improves other clinical and MRI markers of inflammatory and degenerative disease activity in this population.

Some other drugs which are used in multiple sclerosis such as Immunosuppressive agents like azathioprine, methotrexate, cyclophosphamide, other such as Corticosteroids like Methylprednisolone and physical therapy.

**Symptomatic treatment [18, 19]**

Dalfampridine is a FDA approved drug which used to improve walking in people who have multiple sclerosis, it works by blocking the potassium channels on the surface of nerve fibres.

**HERBAL APPROACHES FOR THE MANAGEMENT OF MULTIPLE SCLEROSIS**

Nowadays peoples are eager to use treatment which must be cost effective and with lesser adverse effects. Herbal medicines have lesser side effects or no side effects as compared to conventional drug therapies. Upon several investigations it is reported that There are so many medicinal plants which contain different active constituents like flavonoids, alkaloids, saponins, essential oils, tannins etc; belongs to specific families like araliaceae, zingiberaceae, umbelliferae; have the potential to treat or decrease the progression of multiple sclerosis examples like Ginkgo biloba, Salvia officinalis, Cannabis spp., Crocus sativus, Vitis vinifera. These medicinal plants works by different mode of actions like anti-inflammatory effects, antioxidant effects, reduce oxidative stress, free radical scavenging activity and other mechanisms. [20, 21, 22]

**Table 3: Thelist of medicinal plants those have an potential to treat Multiple Sclerosis’s patient or decrease the progression of MS:**

Commonname	Biologicalsource Family	Activeconstituents	Pharmacological actions	References
------------	----------------------------	--------------------	----------------------------	------------

Black cumin	<i>Nigella sativa</i> Ranunculaceae	Seed oils (p-cymene, limonene), thymoquinone and flavonoids	Anti-inflammatory, antioxidant, anticholinergic property, enhance remyelation in the CNS	[30, 31]
Evening primrose	<i>Oenotherabiennis</i> Onagraceae	Fatty acids, phenolic acids, and flavonoids	Anti-inflammatory effects. Anti-asthmatic effects	[34]
Ginger	<i>Zingiberofficinale</i> Zingiberaceae	Phenolic compounds, volatile oils, sesquiterpenes(bisapolene, zingiberol)	Decrease inflammation, anti-inflammatory effects, antibacterial	[24, 25]
Ginkgo	<i>Ginkgo biloba</i> Ginkgoaceae	Flavonoids like quercetin, kaempferol and diterpene lactones like ginkgolides	It improves blood flow, reduce oxidative stress, free radicals scavenging activity, less fatigue, improve cognitive functions	[23]
Ginseng	<i>Panax ginseng</i> Araliaceae	Saponins (ginsenosides), phytosterol, carbohydrates	Neuroprotective actions, enhance immunity and CNS activity	[32, 33]
Grapes	<i>Vitisvinifera</i> Vitaceae	Tannins (catechin, epicatechin and others), flavonoids and procyanidins	Anti-inflammatory effects, antioxidant activity, improve cognitive functions	[36, 37]
Klamathweed	<i>Hypericumperforatum</i> Hypericaceae	Flavonoids like quercetin, quercitrin, and tannins, essential oils	Free radical scavenging activity, block lipid peroxidation, antioxidant activity	[28]

Marijuana	<i>Cannabis spp.</i> Cannabaceae	Cannabinoids, tetrahydrocannabinol	Reduce neuroinflammation, reduce spasticity and pain	[35]
Marijuana	<i>Cannabis spp.</i> Cannabaceae	Cannabinoids, tetrahydrocannabinol	Reduce neuroinflammation, reduce spasticity and pain	[35]
Saffron	<i>Crocus sativus</i> Iridaceae	Volatile oils, tannins, terpenes	Decrease inflammation, cytotoxic effects	[39]
Sage	<i>Salvia officinalis</i> Lamiaceae	Monoterpenes, flavonoids (apigenin), phenolic acids,	Anti-inflammatory effects, antioxidant, improve cognitive functions	[40]
Sudanese frankincense	<i>Boswellia papyrifera</i> Burseraceae	Essential oils like alpha pinene, limonene, and n- hexyl acetate	Improve visuospacial memory of MS patients	[38]
Turmeric	<i>Curcuma longa</i> zingiberaceae	Flavonoids, and other polyphenolic compounds like curcuminoid (curcumin)	Antioxidant, antimutagenic, antimicrobial, neuroprotective effects	[26, 27]
Valerian	<i>Valeriana officinalis</i> Caprifoliaceae	Alkaloids, terpenes, organic acids, flavones	Gentle sleep aid, anxiety, show their actions by binding to the GABA-A receptor	[29]

## **Conclusion**

Multiple sclerosis (MS) is an autoimmune disease that affects the central nervous system in various ways. It damages the protecting myelin coating and axons, affecting neuron connection. Females are more prone to MS than males. The exact cause of MS is unknown, but according to several reports it may be due to the genetic, environmental factors, viral infections; Epstein-Barr virus. Till now there

is no cure for MS and there are various synthetic FDA drugs, monoclonal antibodies which may be used for the management of Multiple sclerosis. But due to the undesirable side effects of the synthetic medicines people are eager to use cost effective medicines with no or less side effects therefore herbal medicines are best choice for them because herbal medicines have no adverse effects or less side effects as compared to that of conventional medicines. They work by different pharmacological actions like anti-inflammatory, antioxidant, reduce oxidative stress and others.

## **REFERENCES**

1. Calabresi PA., "Diagnosis and management of multiple sclerosis", *Am Fam Physician* 2004;70:1935–1944.
2. Huang WJ, Chen WW, Zhang X. Multiple sclerosis: pathology, diagnosis and treatments. *Experimental and therapeutic medicine*. 2017 Jun 1;13(6):3163-6.
3. K. Mohamed Mohamed K., "Multiple sclerosis: New insights and trends", *Asian Pac J Trop Biomed* 2016; 6(5): 429–440.
4. Hauser SL, Goodwin DS. Multiple sclerosis and other demyelinating diseases. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, eds. *Harrison's Principles of Internal Medicine*, vol. II, 17th ed. New York: McGraw-Hill Medical; 2008:2611–2621.
5. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. *Ann Neurol* 2007; 61(4): 288-99.
6. S M Leary, B Porter, A J Thompson, 'Multiple sclerosis: diagnosis and the management of acute relapses' *Postgrad Med J* 2005;81:302–308. doi: 10.1136/pgmj.2004.029413.
7. J Steelman AJ. Infection as an environmental trigger of multiple sclerosis disease exacerbation. *Front Immunol* 2015; 6: 520.
8. Marvin M. Goldenberg, 'Multiple Sclerosis Review' *P&T*, march 2012; Vol. 37:175-184.
9. N. Ghasemi, Shahnaz R., Elham N., 'Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy' *Cell Journal(Yakhteh)*, Vol 19, No 1, Apr-Jun (Spring) 2017, Pages: 1-10.
10. Douglas S. Goodin, 'The pathogenesis of multiple sclerosis' *Clinical and Experimental Neuroimmunology* 6 (Suppl. 1), (2015) 2–22.
11. K. Mohamed Mohamed K., "Multiple sclerosis: New insights and trends", *Asian Pac J Trop Biomed* 2016; 6(5): 429–440.
12. Özlem TAŞKAPILIOĞLU., 'Recent Advances in the Treatment for Multiple Sclerosis; Current New Drugs Specific for Multiple Sclerosis' *Arch Neuropsychiatry* 2018;55: (Supplement 1): S15–S20.
13. Guarnera C, Bramanti P, Mazzon E. Alemtuzumab: a review of efficacy and risks in the treatment of relapsing remitting multiple sclerosis. *Ther Clin Risk Manag* 2017;13:871–879.
14. Stasiulek M, Linker RA, Hayardeny L, Bar Ilan O, Gold R. Immune parameters of patients treated with laquinimod, a novel oral therapy for the treatment of multiple sclerosis: results from a double-blind placebo-controlled study. *Immun Inflamm Dis* 2015;3:45–55.
15. M. Gholamzad, Masoumeh. E, Mehdi S Ardestani., 'A comprehensive review on the treatment approaches of multiple sclerosis: currently and in the future' Springer, 2018; *Inflammation Research* <https://doi.org/10.1007/s00011-018-1185-0>

16. Suzi B. Claflin, Simon Broadley and Bruce V. Taylor, 'The Effect of Disease Modifying Therapies on Disability Progression in Multiple Sclerosis: A Systematic Overview of Meta-Analyses' *Front. Neurol.*, 10 January 2019 | <https://doi.org/10.3389/fneur.2018.01150>
17. Ingrid Loma and Rock Heyman, 'Multiple Sclerosis: Pathogenesis and Treatment' *Current Neuropharmacology*, 2011, Vol. 9, No. 3; 409-416.
18. Lekha Pandit, 'Multiple sclerosis: Treatment options' research gate, January 2013 DOI: 10.13140/2.1.2577.9845.
19. R. Dobson, and G. Giovannoni, 'Multiple sclerosis' *European journal of neurology*, 2019, 26: 27–40 doi:10.1111/ene.13819.
20. Sina M, , Maryam Nazm B, Maryam Ghasemi-Kasman, 'A Review of Herbal Therapy in Multiple Sclerosis' *Adv Pharm Bull*.8(4); 2018 Nov PMC6311642.
21. R Ghanavati, 'A Review of Possible Herbal Treatment in Multiple Sclerosis in Traditional Persian Medicine' *Iran J Med Sciv*.41(3 Suppl); 2016 May PMC5103523.
22. Song L, Zhou QH, Wang HL, Liao FJ, Hua L, Zhang HF. et al. Chinese herbal medicine adjunct therapy in patients with acute relapse of multiple sclerosis: A systematic review and meta-analysis. *Complement Ther Med*. 2017;31:71–81. doi: 10.1016/j.ctim.2017.02.004.
23. Susan K.Johnson, 'The Effect of *Ginkgo Biloba* on Functional Measures in Multiple Sclerosis: A Pilot Randomized Controlled Trial' Elsevier Volume 2, Issue 1, January 2006, Pages 19-24.
24. AbdollahJafarzadeh, 'Therapeutic potentials of ginger for treatment of Multiple sclerosis: A review with emphasis on its immunomodulatory, anti-inflammatory and anti-oxidative properties' *Journal of Neuroimmunology*Volume 324, 15 November 2018, Pages 54-75.
25. R Ghanavati, 'A Review of Possible Herbal Treatment in Multiple Sclerosis in Traditional Persian Medicine' *Iran J Med Sciv*.41(3 Suppl); 2016 May PMC5103523.
26. N Ghanaatian, 'Curcumin as a therapeutic candidate for multiple sclerosis: Molecular mechanisms and targets' *J Cell Physiol* 2019 Aug; 234(8):12237-12248. doi: 10.1002/jcp.27965.
27. Song L, Zhou QH, Wang HL, Liao FJ, Hua L, Zhang HF. et al. Chinese herbal medicine adjunct therapy in patients with acute relapse of multiple sclerosis: A systematic review and meta-analysis. *Complement Ther Med*. 2017;31:71–81. doi: 10.1016/j.ctim.2017.02.004.
28. Bowling AC, Ibrahim R, Stewart TM. Alternative medicine and multiple sclerosis: An objective review from an American perspective. *Int J MS Care* 2000;2:15-28.
29. R Ghanavati, 'A Review of Possible Herbal Treatment in Multiple Sclerosis in Traditional Persian Medicine' *Iran J Med Sciv*.41(3 Suppl); 2016 May PMC5103523.
30. Nematollahi M, Majdinasab N, Fakharzade L, Namjooyan F, Latifi S, Pouretzad M. The effect of *Nigella sativa* seeds on the muscle spasticity of lower limbs in patients with multiple sclerosis. *Iran J Neurol* 2013;12 Suppl 1:16.
31. Salem ML. Immunomodulatory and therapeutic properties of the *Nigella sativa* L. seed. *Int Immunopharmacol* 2005;5:1749-70.
32. Iriti M, Vitalini S, Fico G, Faoro F. Neuroprotective herbs and foods from different traditional medicines and diets. *Molecules* 2010;15:3517-55.
33. Song L, Zhou QH, Wang HL, Liao FJ, Hua L, Zhang HF. et al. Chinese herbal medicine adjunct therapy in patients with acute relapse of multiple sclerosis: A systematic review and meta-analysis. *Complement Ther Med*. 2017;31:71–81. doi: 10.1016/j.ctim.2017.02.004.

34. R Ghanavati, 'A Review of Possible Herbal Treatment in Multiple Sclerosis in Traditional Persian Medicine' *Iran J Med Sciv.*41(3 Suppl); 2016 May PMC5103523.
35. Bowling AC, Ibrahim R, Stewart TM. Alternative medicine and multiple sclerosis: An objective review from an American perspective. *Int J MS Care* 2000;2:15-28.
36. Nihitha Sanka., N. Santhipriya., R. R. Nadendla., "An updated review on Anti-Alzheimer's herbal drugs" *Journal of Drug Delivery & Therapeutics.* 2018; 8(6):360-372.
37. Hauser SL, Goodkin D. Multiple sclerosis and other demyelinating diseases. *Harrisons Princ Intern Med* 2001;2:2452-61.
38. R. Dobson, and G. Giovannoni, 'Multiple sclerosis' *European journal of neurology*, 2019, 26: 27–40 doi:10.1111/ene.13819.
39. Ghazavi A, Mosayebi G, Salehi H, Abtahi H. Effect of ethanol extract of saffron (*Crocus sativus* L.) on the inhibition of experimental autoimmune encephalomyelitis in C57bl/6 mice. *Pak J Biol Sci* 2009;12:690-5.
40. Iriti M, Vitalini S, Fico G, Faoro F. Neuroprotective herbs and foods from different traditional medicines and diets. *Molecules* 2010;15:3517-55.