

Review Article

doi:10.34172/ajpr.2020.07



Supplement Therapy in Multiple Sclerosis: A Pharmacological View

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Abstract

Natural products, herbal medicines, and supplements have received more attention of the scientific and pharmaceutical community. Supplemental and alternative medicines include dietary supplements, herbs, vitamins, minerals, and special diets. It has been found that some complementary and alternative medicines (CAMs) are safe and effective but the important point is that less is known about many of them. Medicines used in multiple sclerosis (MS) are not completely effective and various side effects have been detected. There is an increasing trend in the use of supplementary and alternative medicines in treating MS because of fewer side effects, more comfort, and more preventative effects. It has been indicated that up to 70%-80% of people with MS have tested herbal products or bioactive compounds for treating their disease. The present study aimed to investigate the use of natural products, herbal remedies, and supplements to treat MS to confirm or rule out the effectiveness or ineffectiveness of these supplementary medicines.

Keywords: Multiple sclerosis, Supplements, Herbal medicines, Natural products

Received 3 March 2020, Accepted: 17 April 2020, ePublished: 23 June 2020

Introduction

Multiple sclerosis (MS), a severely debilitating disorder, is identified by progressive demyelination and axonal damage in the central nervous system (CNS). Although the underlying causes of the disease are unknown, it is accepted in general that MS starts when autoreactive T-cells penetrate the CNS to attack the nervous system (1). Several types of MS have been recognized, the most common of which is characterized by waxing and waning of signs and symptoms to produce a "relapsing-remitting" clinical presentation. "Relapsing-remitting MS" affects 85% of MS patients (2). About 30% of these patients experience "secondary progressive MS" within a decade (3), a type with less inflammation and more neurodegeneration. "Primary progressive MS" is a distinct type of MS which is not obviously correlated with relapses and shows neurodegeneration without inflammatory change. The late-stage sequelae from advanced MS include permanent disability and death (4). Although the etiology of this autoimmune disorder is intricate, it has been suggested that both genetic susceptibility and non-genetic triggers have a role (5).

Medicines used in MS are not completely functional and various side effects are reported by patients. Nowadays,

complementary and alternative medicines (CAMs) are used increasingly and patients tend to use this kind of treatment. Having a healthy lifestyle and using CAM treatment can eliminate some of the symptoms and improve the quality of life in these patients. Many patients use CAM therapies to decrease their symptoms (6). This study attempted to investigate the use of herbal remedies and supplements in MS treatment to confirm or rule out the effectiveness or ineffectiveness of these supplementary medicines.

Herbal and Supplement Products for the Treatment of Multiple Sclerosis

Using herbal products and supplements in patients with MS is a new area for the research (7). Herbal bioactive compounds like flavonoids, lipoic acid, vitamin C, and so on are the most efficient therapies in relapsing and progressive forms of MS because of the neuroprotective and anti-inflammatory properties (8). Moreover, it should be noted that polyphenols, terpenes, alkaloids, anthocyanidin glycosides, plant amines, volatile oils, and so on play a noticeable role in the treatment of MS (9). Several studies investigated the role of minerals, vitamins, and other related supplements in symptomatic and



disease-modifying treatments in MS patients (10). However, inadequate findings are available to make recommendations regarding their effectiveness and safety for all patients (11). The commonly used vitamin and mineral supplements with antioxidant effects include vitamin D, C, and E and selenium (12).

Various herbal medicines have been studied in the treatment of MS, which are reported as follow:

Borage seed oil (*Borago officinalis*)

Borage seed oil has a gamma linoleic acid content of 25% which can be regarded as a TNF- α suppressor. In addition, borage seed oil can elevate prostaglandin E (PGE) levels, which leads to an increase in cyclic adenosine monophosphate (cAMP). The point is that cAMP augmentation clarifies anti-inflammatory effects in MS treatment (13).

Blackcurrant (*Ribes nigrum*)

The reduction of proinflammatory mediators including tumor necrosis factor-alpha (TNF- α) and Interleukin-1 β (IL-1 β) in peripheral blood monocytes and anti-inflammatory effects are induced by Blackcurrant seed oil in MS (14).

Bilberry (*Vaccinium myrtillus*)

The mechanism of bilberry in inflammatory diseases such as MS is through decreasing high-sensitivity C-reactive protein (hs-CRP), IL-12, IL-6, and Lipopolysaccharide concentrations. The anti-inflammatory effect of bilberry extract is exerted by anthocyanins. In addition, anthocyanins can improve visual impairment in MS patients (15).

Cannabis (*Cannabis sativa* L)

Several reports on the usefulness of cannabis in treating MS have been published. Consumption of cannabis can lead to various effects, including treatment of spasticity, improvement of tremor, reduction of depression, relief of pain, and recovery of anxiety. Both lipophilic nature and central depressant effects of cannabinoids lead to thoughts that their mechanism of action occurs via membrane disruption, similar to general anesthetics. The first cannabinoid receptor (CB1), a G-protein coupled receptor, inhibits adenylate cyclase and regulates Ca²⁺ and K⁺ channels. The receptor may also interact with other pathways, such as inositol phospholipid pathway. CNS (particularly basal ganglia, hippocampus, and cerebellum) is the main area for CB1 receptors. The inhibition of neurotransmitter release is the overall effect of CB1 receptor activation in the CNS (7).

Cat's Claw (*Uncaria tomentosa*)

The anti-inflammatory effect of the bark of this plant is the same as dexamethasone. Furthermore, this plant can reduce IL-4 level, while dexamethasone does not have this

property. It should be noted that Cat's Claw extract can decrease PGE-2 production (16).

Devil's Claw (*Harpagophytum procumbens*)

The root extract of Devil's Claw inhibits inflammatory cytokine (IL-6, IL-1 β , and TNF- α , and PGE-2), prevents arachidonic acid metabolism, and induces eicosanoid biosynthesis, leading to COX-2 inhibition and inflammation reduction (17).

Dog Rose (*Rosa canina*)

The anti-inflammatory action of the rosehip seeds is induced by inhibition of PGE-1 which leads to the down-regulatory effect on COX-1, COX-2, and leukotriene B4 (LTB 4) (18).

Evening Primrose oil (*Oenothera biennis*)

This oil contains sterols such as β -sitosterol and campesterol, which have an effect on the modulators such as nitric oxide (NO), IL-1 β , TNF- α , and thromboxane B2 (TXB2), leading to the suppression of the COX-2 genome, and anti-inflammatory outcome (19).

Ginger (*Zingiber officinalis*)

In several investigations, it has been indicated that Ginger has immunomodulatory, anti-inflammatory, and anti-oxidative characteristics. Inflammation can be decreased in MS patients by Ginger via reducing the production of TNF- α and hs-CRP. Moreover, the inhibition of cyclooxygenase and lipoxygenase pathways in synovial fluid is a mechanism that leads to analgesic effects (20).

Indian Frankincense (*Boswellia serrata*)

The mechanism of Indian Frankincense is through the reduction of erythrocyte sedimentation rate and plasma levels of leukotriene C4, NO, and malondialdehyde. In addition, the reduction of inflammatory cytokines such as TNF- α , IL-1 β , IL-6, IFN- γ , and PGE2 can be mentioned (21, 22).

Olive oil (*Olea europaea*)

Olive oil exerts its effect through modulation and decrease of pro-inflammatory cytokines, TXB2, and leukotriene B4, leading to the reduction of inflammation in MS patients. Moreover, the reduction of lipid and protein oxidation and elevation of glutathione peroxidase can protect against oxidative damage (23).

Rosemary (*Rosmarinus officinalis*)

The level of inflammatory mediators such as TNF- α and IL-1 β can be reduced by rosemary extract (24). Additionally, according to an open-label trial, the use of rosemary extract reduced hs-CRP (an indicator of the presence of inflammation), indicating that rosemary is involved in reducing inflammation (25).

ussian olive or Oleaster (*Elaeagnus angustifolia*)

In a randomized clinical trial, a significant decrease in TNF- α and IL-10 level was observed after using Oleaster. The anti-inflammatory properties of this fruit extract can be explained by inhibition of COX-1 and COX-2 (26).

Saffron

The therapeutic effects of saffron components, like safranal, crocin, and crocetin seem to include anticarcinogenic, antioxidant, and immunomodulating properties (27).

Sage (*Salvia officinalis*)

Carnosol and carnosic acid are two important components in chloroform extract of *Salvia* leaves. It has been shown that these phenolic diterpenes have anti-inflammatory effects (28) and can inhibit the production of PGE through the inhibition of microsomal PGE 2 synthase-1 (29, 30).

The Stinging Nettle (*Urtica dioica*)

The activation of NF- κ B (31) and reduction of PGD2 production can explain the anti-inflammatory effects of *Urtica Dioica* leaves extract. Moreover, Stinging Nettle used simultaneously with nonsteroidal anti-inflammatory drugs induces an excellent synergistic effect, with a remarkable reduction in CRP level (32).

Turmeric (*Curcuma longa*)

Curcumin can inhibit inflammatory proteins and cytokines. The inhibition of the differentiation of Th17 cells is noticed in a study on chronic inflammatory diseases. The importance of Th17 cells in CNS infection in patients with MS and experimental autoimmune Myasthenia gravis has been demonstrated (33).

Figure 1 summarizes the effects of some of the medicinal plants in the treatment of MS.

List of the Vitamins and Supplements Used for the Treatment of Multiple Sclerosis

Vitamin B12: This vitamin is known as cobalamin and has important structural and functional roles in the CNS, and its deficiency leads to anemia, axonal degeneration, and death (34). Based on this information, fixing the deficiency of this vitamin can be effective in improving the quality of life in MS patients (33). The nature of this disease that is associated with megaloblastic and pernicious anemia along with reduced serum levels of vitamin B12 in patients with MS treated with interferon and Copaxone[®] is considered in numerous studies. Moreover, the role of this vitamin in myelin repair should be noticed (34).

Vitamin D: Vitamin D can suppress the function of antigen-presenting cells which leads to a reduction in the penetration of inflammation in the CNS. The mechanism that seems to affect vitamin D nutrition in MS involves the paracrine or autocrine action of 25-hydroxyvitamin D by enzyme 1 α -hydroxylase in peripheral tissues which play a role in the function of the immune and nervous system.

Optimum serum concentrations of 25-hydroxyvitamin D throughout the year may be beneficial for patients with MS, both for the removal of immune cells from disease activity as well as the reduction of disease-related complications, including increased bone turnover, fracture and muscle weakness (35).

Vitamins E and C: It has been observed that antioxidant deficiency can increase the risk of developing MS in MS patients. Indeed, antioxidants such as vitamin E (alpha-tocopherol) and vitamin C (ascorbic acid) in the MS animal models reduced the clinical symptoms of the disease. Antioxidants have the ability to reduce the symptoms of the disease by targeting specific pathogens and supporting recovery in MS (36). It should be noted that cell damage can be reduced by reducing harmful free radicals. The immune system in the nervous system can be attacked and damaged by free radicals (37).

Zinc: Numerous functions in the immune system including peripheral T-cell count, cytotoxic T-cell activity, T-helper cell function, NK-cell activity, and macrophage and neutrophil functions are influenced by zinc (Zn) deficiency (38). Zn is predominantly found in presynaptic vesicles in neurons. It is clear that effective Zn homeostasis in the brain is important (39). Increasing Zn can lead to the expression of the high-affinity receptors for IL-2, which are important for the proliferation and differentiation of CD4+ and CD8+ lymphocytes to effector cells (40).

CoQ10: CoQ10 has different mechanisms for anti-inflammatory activity in MS. Among these mechanisms, the immunomodulatory properties of CoQ10 are more prominent. CoAQ10 can reduce the production of certain inflammatory mediators such as IL-6. Moreover, it can elevate antioxidant enzyme activity and diminish oxidative stress in patients with relapsing-remitting MS (41).

Polyunsaturated fatty acids: A specific deficiency of linoleic acid in the serum of MS patients has been detected by biochemical studies (42).

Omega 3, 6: The findings of a study indicated that Omega 3 and 6 have anti-inflammatory effects by reducing T-cell proliferation (43).

L-Carnitine: L-Carnitine is a natural metabolic drug that acts as a carrier molecule for long-chain fatty acids in mitochondria and generates energy. L-carnitine deficiency is associated with the accumulation of acyl CoA esters and disorders of intermediary metabolism (44). L-carnitine is reported to be effective in reducing fatigue in MS patients. It is one of the amino acid derivatives that plays an important role in the metabolism of lipids and is a key factor in mitochondrial energy production (45); therefore, it can improve fatigue in MS patients (46). Table 1 represents the effects of some supplements and medicinal plants in MS treatment.

Conclusion

Supplement therapy is regarded as a way to improve the symptoms of the disease with fewer complications for

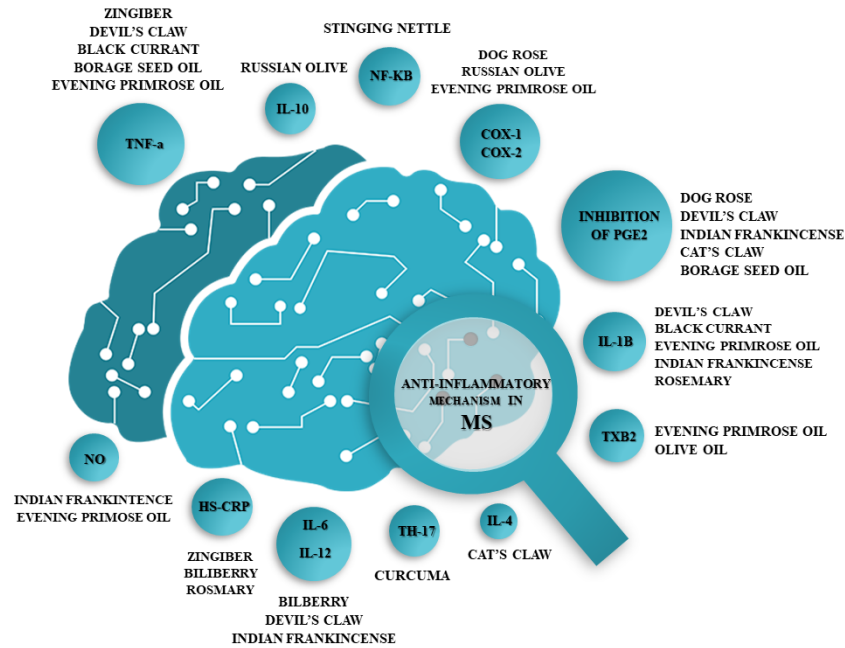


Figure 1. Effects of Some of the Medicinal Plants in the Treatment of Multiple Sclerosis

Table 1. Summary of the Studies Conducted to Determine the Effects of Some of the Supplements and Medicinal Plants in MS Treatment

Supplement	Result	Publication Year	Number of Subjects	Amount	Duration	Subjects	References
Vitamin A	Results of this study suggest that using this vitamin could have a regulatory role in the treatment of autoimmune diseases such as MS	2013	35	25000 IU/day	1 year	Human	(47)
Vitamin B12	Results of this study suggest that anemia improves with vitamin B12 and folic acid supplementation which reveals the potential role of these two vitamins in improving the quality of life of MS patients. Additionally, serum homocysteine level decreases.	2019	50	Folic acid 5mg/day + 3 doses of vitamin B12 (1 mg)	2 months	Human	(48)
Vitamin D	Results of this study indicate that 1,25-(OH)2D3 halted EAE (Experimental autoimmune encephalomyelitis) progression and maintained the EAE disease severity below stage 2 for the duration of the observations (40 days post immunization).	1996	Three groups of twelve	20 ng/day	5-8 weeks	Mice	(49)
Vitamin D	Results of this study indicate that use of vitamin D supplements could have a substantial impact on bone density, fracture risk, morbidity, and mortality in MS patients.	1994	80	Vitamin D (800 IU) and Calcium (1200 mg)	23 months	Human	(50)
Vitamin D	Results of this study indicate that supplementing with a high dose of vitamin D3 cannot reduce relapse rate.	2012	35	20000 IU/day	96 weeks	Human	(51)
Vitamin D	Lower 25(OH)D levels have been reported in MS patients compared to healthy control populations.	2008	267	-	<5 Years	Human	(52)

Vitamin D	Results of this study indicate that higher level of sun exposure rather than 25(O) D levels were associated with less depressive symptoms and levels of fatigue in MS patients.	2012	80	high-dose (average daily dose 10200 IU) or low-dose (average daily dose 200 IU)	18 months	Human	(53)
Vitamin D+Ca	Results of this study indicate that MS patients treated with Ca+D have fewer relapse events and a persistent reduction in T-cell proliferation compared to controls.	2010	49	Vitamin D 10000 IU/day, Ca 1200 mg/d	52 weeks	Human	(54)
Vitamin D	Results of this study support a protective effect of vitamin D intake on the risk of developing MS.	2004	173	400 IU/day	2 year	Human	(55)
Vitamins E and C	Results of this study indicate that the increase the level of vitamins C and E can be helpful as antioxidants in the recovery of MS.	2005	-	-	-	-	(36)
Zinc and Copper	Results of this study indicate that lower level of Zn and higher level of Cu in serum were found in the MS patients compared to the control.	2012	60	-	9 months	Human	(56)
Zinc and Copper	Based on results, low plasma levels of Zn and copper have been reported in multiple sclerosis.	1982	50	-	3 years	Human	(38)
CoQ10	Results of this study indicate that CoQ10 can decrease oxidative stress and increase antioxidant enzyme activity in patients with relapsing-remitting MS.	2014	60	200 mg/d	24 weeks	Human	(41)
Linoleate	Results of this study indicate that relapse of MS was decreased after 9-12 months.	1973	87	30 mL of a sunflower seed oil emulsion providing 6-8 g of linoleic acid	2 years	Human	(57)
Linoleic acid	Results of this study indicate that linoleic acid marginally affected the duration and severity of relapses of MS but had no effect on the overall disability.	1978	116	20 g linoleic acid daily	12-24 months	Human	(42)
Omega-3	Results of this study indicate that omega-3 fatty acid can be used as an augmentation therapy for treatment-resistant depression in MS patients	2016	39	6 g daily	3 months	Human	(58)
Omega-3	Results of this study indicate that omega-3 fatty acid has the ability to significantly decrease matrix metalloproteinase-9 levels and was well tolerated at a dose of 9.6 g/d over 3 months so can be effective in the process of MS improvement.	2009	31	9.6 g daily fish oil	6 months	Human	(59)
Omega-3 and Omega-6	Results of this study indicate that treatment with PLP10 significantly reduced annualized relapse rate and the risk of sustained disability progression without any serious adverse events.	2018	41	Omega-3 600 mg/d, omega-6 650 mg/d	30 months	Human	(43)
Acetyl L-carnitine	Results of this study indicate that acetyl L-carnitine is well tolerated by patients with MS and is more effective than amantadine in the treatment of MS-related fatigue.	2004	60	100 mg twice daily	3 months	Human	(60)

Cannabis- based medicinal extracts	This study suggests that patients with MS who derive symptom relief from cannabis-based medicinal extract in the first 10 weeks generally maintain that symptom relief over an extended period of treatment without any increase in dose	2006	137	11 sprays daily (equivalent to 30 mg THC and 28 mg CBD)	10 weeks	Human	(61)
Cannabis-based medicinal extracts	The results of this study suggest that Sativex® is an effective treatment for spasticity associated with MS.	2004	160	2.5-120 mg daily, in divided doses	70 days	Human	(62)
Curcumin	The results of this study indicate that overall effect of curcumin on neuroglial cells involves reduction of astrocytes proliferation, elevation of myelogenesis and elevation of activity and differentiation of oligodendrocytes.	2010	60	4, 6, and 8 g daily	3 months	Rat	(63)
Evening Primrose Oil (EPO)	The results of this study indicate that EPO consumption increases cognitive function, vitality, and life satisfaction and decreases pain and fatigue.	2018	52	1 g oral capsule containing EPO every 12 hours	3 months	Human	(64)
Ginger	The results of this study indicate that 6-shogaol or 6-paradol can have therapeutic efficacy for experimental autoimmune encephalomyelitis by reducing neuroinflammatory responses. Moreover, these two active ingredients of ginger have therapeutic potential for MS.	2018	4 mouse/ group	6-shogaol (5 mg/kg), or 6-paradol (5 mg/kg) orally daily	13 days	mice	(65)
Ginseng	Results of this study indicate that 3-month ginseng treatment can reduce fatigue and has a significant positive effect on quality of life.	2013	60	250 mg ginseng	3 months	Human	(66)
Ginseng	Results of this study indicate that American ginseng extract at a dose in common use was well tolerated but was no better than placebo in improving fatigue using validated fatigue outcome measures, the Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS) .	2011	56	100 mg, 200 mg, 400 mg/d	6 weeks	Human	(67)
Honey bee venom	Results of this study indicate that Bee venom has immune suppressive and anti-inflammatory effects in MS disease.	2012	30	2 mg/kg	20 day	Rat	(68)
Olive oil	The results of this study indicate that the utilization of fish oil and olive oil increases the fluidity of the mitochondrial membranes and decreases the catabolic activity of ATP synthase in platelets of patients with relapsing-remitting multiple sclerosis.	2017	23	1 g oleic acid daily	9 months	Human	(69)
Saffron	Results of this study indicate that use of 100 mg saffron has temporary immunomodulatory activities without any adverse effects.	2011	44	100 mg daily	6 weeks	Human	(70)
Saffron	Results of this study indicate that saffron has anti-inflammatory effects.	2012	6 mice per group	25 to 100 mg/kg/d	3 years	Mice	(71)

patients, but health care professionals face problems in finding information regarding the usefulness of supplements. The point is that there are few scientific resources to introduce the effectiveness, mechanism, and usage of natural substances for treating the disease. In addition, receiving conventional therapies induces many side effects in MS patients. Discussing the available supplement with their usage may lead to an increasing trend in the use of CAMs in MS because of fewer side effects, more comfort, and more preventive effects.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgment

The authors would like to thank Mr. Tavakoli for his contribution in preparing the figures.

Funding

There is no financial support.

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