



**Review Article**

**COMPLEMENTARY AND ALTERNATIVE MEDICINE USE IN MULTIPLE SCLEROSIS**

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**Abstract:** Multiple sclerosis (MS) is a chronic, disabling, recurrent demyelination of the central nervous system (CNS). MS could influence different region in the brain and spinal cord and according to the domain of them which is affected could cause different symptoms such as motor, sensory, or visual impairment; fatigue; bowel, bladder, and sexual dysfunction, cognitive impairment, and depression. MS patients also face with reducing quality of life. Drugs that is used in MS are not fully efficient and patient are almost suffer from many symptoms and adverse effects. Today use of complementary and alternative medicine (CAM) is increasing. People are more likely to use this type of treatment. Using appropriate life style and CAM therapy can subside some of symptoms and could elevate quality of life in these patients. Many people with MS explore CAM therapies for their symptoms. This review is aimed to introduce CAM therapies that could be used in MS patients.

**Key words:** multiple sclerosis, complementary and alternative medicine, CAM therapy

**INTRODUCTION**

**1. Multiple sclerosis**

Multiple sclerosis (also known as Disseminated sclerosis, encephalomyelitis disseminate) was introduced by Charcot and Vulpain in 1866 for first time.(1) MS is a chronic, disabling, incurable recurrent demyelination of the central nervous system that about 2.5 million people in the world are involved (2-4).

MS is an inflammatory disease of the central nervous system. The inflammation causes damage called plaques or lesions that are located primarily in the CNS white matter. At the site of inflammatory lesion, the myelin sheath is destroyed in the process of demyelination. When myelin is lost, transmission of signals through nerves are slowed or blocked. In some cases, the myelin sheaths around axons after reducing inflammation can be rebuilt. This process is called remyelination that is done by Oligodendrocytes. If there are not enough Oligodendrocytes at the lesion site, remyelination will not occur or will be done partially. Therefore, nerves will be done their function in an abnormal pathway and the axons continue to remain for long periods without damage. The lost myelin sheath can be replaced by scar tissue where it is called MS; multiple means many and sclerosis means that scar formation(1).

When the axons are damaged, they will not completely lose its previous function. As the disease progresses, oligodendrocytes, and ultimately axons are destroyed, leading to a worsening of the symptoms. There is strong evidence that the destruction caused by the immune system, which indicates that MS is an autoimmune disease (1).

**1.2. The prevalence of MS**

The prevalence of MS in the Northern Hemisphere is more than the Southern Hemisphere(3). Probably more than two million men and women in the world have affected with MS and mainly they experience the first symptoms between the ages of 20 and 40 years. Women are two times more likely to develop the disease.(5) Iran is located in a low risk area for MS (6). Prevalence of MS in Iran in different region is vary from 5.3 to 74.28 per 100,000 (7).

**1.3. Pathology**

MS is affected neurons; brain and spinal cord's cells that carry information create thought and perception and allow the brain to control body. Around these neurons is a fatty acid layer that is known as myelin sheath. Myelin sheath help neurons to transfer signals. MS cause gradual demolition of myelin and transection of axon in brain and spinal cord. According to the area of demyelination in brain and spinal cord symptoms of MS will be appear (3, 8).

Pathologically MS is known by appearance of demyelinated areas and perivascular T cell inflammation in white matter of CNS. Although some axon may be not affected with this pathological process (3, 8).

Severity of demyelination is determined with preservation or destruction of oligodendrocytes. It is indicated that in the early stage of disease more oligodendrocytes are preserved in plaque lesion. Thus, some degree of remyelination is still possible. In other patient that oligodendrocytes are destructed completely remyelination possibility is very low (3, 8).

**1.4. Causes**

Today, the prevailing theory is that MS is caused by the immune system attacks the nervous system thus commonly

known as an autoimmune disease(3, 9). There are also more trivial theory says that MS is not an autoimmune disease but is a metabolic neurodegenerative disorder. Although the main cause of MS is still unknown(3, 10).

Although the exact mechanism of this disease is unknown, but there is considerable evidence that the autoimmune nature of this disease. It has been observed that Immunoglobulin G levels in the cerebrospinal fluid of MS patients increases; it is thought that IgG is produced in the CNS. Using Immunofluorescent and Immunoperoxidase techniques were observed that IgG in the white matter of normal appearing brain as well as in MS plaques tissue have been detected. According to the features previously observed autoimmune IgG extracted from the brains of MS patients has the Anti-MBP activity (4).

In MS, immune dysfunction can be detected locally in the CNS and cerebral spinal fluid, as well as systemically in peripheral circulation. Autoimmune nature of MS has long been suspected. It is known that patients with MS have inflammation and demyelination in their CNS and oligoclonal bands in their cerebrospinal fluid (3).

### 1.5. MS symptoms

Mainly, every function that completely or partially controlled by the CNS could be lose. According to the CNS domains, which may be affected, and how badly it is damaged, the type and severity of symptoms widely varies (1).

RRMS Type mainly started with sensory disturbance, unilateral optic neuritis, diplopia (inter nuclear ophthalmoplegia), Lhermitt's signs (limbs and trunk paresthesia associated with the curvature of the neck), limb weakness, clumsiness, gait ataxia, and neurological bladder and bowel dysfunction. Many patients suffer from fatigue that is worsen in the afternoon and it is associated with increased physiological body temperature. Some patients have recurrent stereotypical phenomena (sudden pain or paresthesia, trigeminal neuralgia, episodic clumsiness or dysarthria and tonic limb posturing), which is very common in MS (1). Cognitive impairment in MS patients leads them to spend more time for their tasks (11).

### 1.6. Type of MS

There are three types of MS that is identified.

1. relapse-remitting multiple sclerosis (RRMS)
2. primary progressive multiple sclerosis (PPMS)
3. secondary progressive multiple sclerosis (SPMS)

MS can be in many forms, with new symptoms that are occurred in separate relapse or slowly over time. Clinically, most patients with MS from relapsing - remitting type of the disease, which is depends on final phase of disease. After that, the most common type of disease is neurodegenerative phase that is called secondary- progressive MS. Currently there is no cure for MS. Various treatments can slow the appearance of new symptoms, although they have their own side effects of treatment (3).

### 1.7. Treatment of MS

Currently there is no cure for MS. However, treatments for slowing the disease process or treatment of MS symptoms are available. Medications to modify the disease process are called disease-modifying therapy. 4 classes of drugs have been approved for remission phase of multiple sclerosis: 1-

interferon beta, 2- Glatiramr acetate, 3-mitoxantrone (a chemotherapy agent), fingolimod(1, 12, 13).Interferon beta-1b (betaseron<sup>®</sup>) and interferon beta- 1a (Avonex<sup>®</sup>) to reduce the number and severity of relapses were successfully used. Glatiramr acetate is an alternative drug for Interferon beta in RRMS (3).

For relapse phase of MS, Corticosteroids are the choice treatment for exacerbations.

## 2. Complementary and alternative medicine (CAM)

National Institute of Health (NIH) published a classification for alternative therapies (14, 15) in five categories.

1. Biologically based therapies
2. Alternative medical system
3. Mind-body intervention
4. Manipulative and body-based methods
5. Energy therapies

CAM studies on MS are very limited. A study in California and Massachusetts shows that 60% of MS patients use CAM for treatment and each individuals use two or three different form of CAM. Another study in British Columbia was shown that 67% of MS patients are use CAM (15).

### 2.1 Biologically based therapies

Biologically based therapy includes herb, diet and bee venom therapies (14, 15).

#### 2.1.1. Herb

Using herbs can be classified as herbal medicine, food, and spices.

##### 2.1.1.1. Herbal medicine

###### 2.1.1.1.1. St John's Wort:

MS patients usually affected with depression. In United State, this herb is the most popular medicinal herb. Many Clinical trials indicate its anti-depression activity e.g. A study in Germany showed that St John's Wort affects depression more than fluoxetine (15).

###### 2.1.1.1.2. Valerian

The root of valerian traditionally used for insomnia. Several clinical confirm this effect. Valerian affects through GABA-ergic system like benzodiazepines. Although it may increase MS fatigue (15).

###### 2.1.1.1.3. *Ginkgo biloba*

*Ginkgo biloba* (G.b) is a popular medicinal plant mainly because of its effect on dementia. Ginkgolides are the chemical ingredient of G.b has anti-oxidant properties and inhibits the effect of Platelet Activating Factor (PAF). According to the effect of PAF in inflammation, it is suggested that G.b could be useful in MS. One clinical study shows that G.b decrease the exacerbation in MS patients (15).

###### 2.1.1.1.4. Evening primrose

Evening primrose contains linoleic acid,  $\gamma$ -linoleic acid, and vitamin E.  $\gamma$ -linoleic acid is the presource of prostaglandin E. At the first time because of  $\gamma$ -linoleic acid content of evening primrose clinically used in MS (16-19).

###### 2.1.1.1.5. Ginseng

Ginseng, the most widely used herb in traditional Chinese medicine is known for anti-aging and tonic effects. It is considered as an adaptogenic herb, effective in increasing body resistance to stress, trauma, and fatigue by modulating immune function. Furthermore, a clinical trial shows that it

improves memory, learning performance and motor activity. it could also protect against neurodegenerative process (20).

#### 2.1.1.1.6. *Salvia officinalis*

*Salvia* is one of Mediterranean herbal medicine with anti-oxidant and anti-inflammatory activity could improve cognitive function and modulate mood. In a clinical trial essential oil of *Salvia* enhanced the memory of young people (20).

#### 2.1.1.1.7. Marijuana

Several Clinical studies investigated that smoking marijuana or orally administrated cannabinoids could improve some MS-related symptoms include spasticity, pain, tremor, and depression. In animal model it also improved tremor (15).

### 2.1.1.2. Spices

#### 2.1.1.2.1. Turmeric

Turmeric rhizome (*Curcuma Longa*) is one of medicinal herb routinely uses as spice. Curcumin is its main bioactive ingredient. Turmeric traditionally is used in dyspepsia, wounds, jaundice, and arthritis and eye infection. On the other hand, curcuminoids have anti-oxidant, anti-inflammatory, antiviral, anti-proliferative and anti-apoptotic activity. Curcumin could also suppress exacerbation in neurodegenerative disease (20).

#### 2.1.1.2.2. Cinnamon

Cinnamon, the bark of Cinnamon tree is widely uses as flavor in food industries. It has anti-inflammatory and anti-oxidant effect (21-29). It has characteristic astringent, stimulant, carminative, used in the treatment of rheumatism, colic, diarrhea, and nausea, and vomiting. Moreover it has immune modulatory effect (27, 29). Sodium benzoate, one of cinnamon metabolites, which is commonly used as food additive and a Food and Drug Administration-approved nontoxic drug for urea cycle disorders, shows treating in relapse remitting Experimental Allergic Encephalomyelitis (EAE) animal model of MS (29, 30).

#### 2.1.1.2.3. Saffron

Daily oral administration of saffron significantly reduced clinical symptoms in EAE mice model. Onset of disease also delayed in comparison of control group (31). It can also affect depression (32, 33).

#### 2.1.1.2.4. Black seed

*Nigella Sativa* is a traditional medicinal plant with different properties such as diuretic, antihypertensive liver tonic, digestive, antidiarrheal, appetite stimulant, analgesic and antibacterial. Thymoquinone is one of the *Nigella* active substances with immunomodulatory and immune therapeutic potential. Studies show that Thymoquinone inhibits oxidative stress that is leading to improve EAE. A clinical study confirms its effect on MS associated muscle spasticity (34-36).

### 2.1.1.3. Herbal food

#### 2.1.1.3.1. Cranberry

MS patients often suffer from bladder problem and urinary infection. One study shows that 20-day use of 12 oz. cranberry with 1000mg ascorbic acid could acidify urine better than orange juice and ascorbic acid, so it could be helpful in treating urine infections and inhibits some bacteria(37, 38).

#### 2.1.1.4. Other herbs

##### 2.1.1.4.1. Potentially useful

- Herbs that are rich in  $\gamma$ -linoleic acid such as flax seed and Rapeseed because of intervention in fatty acid metabolism

and lymphocyte function are also could be useful in MS treatment (39-41).

- Herbs, fruits and berries that are rich in flavonoids such as blueberry could be helpful (3).

##### 2.1.1.4.2. Potentially harmful

- Some plant such as *Echinacea*, *Asteragalus*, and *Spirulina* because of their immune stimulating properties should be avoided in progressive systemic immune disease such as MS (19, 42-44).

- Since, fatigue is one of the most common symptoms in MS; MS patients prefer to use herbal energy enhancer. However, it should be considered that some plant such as tea, coffee, and guarana because of caffeine and Cola, *Citrus aurantium*, and Ephedra because of CNS stimulating properties could be harmful for MS patients and might worsen the symptoms (19, 45, 46).

### 2.1.2. Diet and nutritional supplements

#### 2.1.2.1. Vitamins and minerals

The advantage of vitamins and minerals as supplements are not clearly understood (15).

##### 2.1.2.1.1. Antioxidant vitamins

Anti-oxidant vitamins including vit A, C and E and seems to be useful in MS because of battling free radicals may be useful in preventing myelin injury and damage (15).

Non-vitamin anti-oxidant supplements such as  $\alpha$ -lipoic acid, Co Q10, grape seed extract, oligomeric proanthocyanidine (OPC) and pycnogenol are more expensive than vitamins and their efficacy in MS patients and safety are not known (15).

##### 2.1.2.1.2. Vitamin D and Calcium

The MS prevalence in areas with low vitamin D intake is very high.(47) Vitamin D deficiency is associated with increased progression of MS (48). Vitamin D level in the body is influenced by two factors vitamin D intake through food such as milk, eggs, fish, and vegetables and the amount of sun exposure, because cholesterol, which is made in the skin, converts to cholecalciferol or D<sub>3</sub>, the active form of vitamin D by UV B irradiation. Vitamin D resulting from each route will be transported to the liver to be hydroxylated(49). In cytoplasm, calcitriol links to intracellular receptors then passes through the nuclear membrane. The hormone-receptor complex binds to DNA and regulates the expression of several genes including IL1, IL2, and TNF $\alpha$ , which reduces inflammatory reactions. Therefore, D<sub>3</sub> is known to be an immune regulator and anti-inflammatory. Some studies show that administration of vitamin D<sub>3</sub> in EAE mice and rat model, may modulate severity of disease (2, 47). It could also reduce the complications associated with the disease including muscle weakness and bone fragility (15, 47, 49, 50).

##### 2.1.2.1.3. Vitamin B<sub>12</sub>

Vitamin B<sub>12</sub> deficiency may cause damage to spinal cord and optic nerve. MS patients with B<sub>12</sub> deficiency may benefit from it's supplements. (15)

##### 2.1.2.2. Antioxidant and polyunsaturated fatty acids

Inflammatory conditions and lack of antioxidant defense mechanisms increase ROS, which can damage lipids, proteins, and nucleic acids. This damage leads to mitochondrial dysfunctions and induce cell death. Low levels of antioxidants, such as tocopherol, carotene, retinol, ascorbic acid, and inhibition of antioxidant enzymes in patient with MS causes oxidative stress leading to cell damage or death. Supplementation of antioxidants may be useful in MS(51).

Risk of developing MS with high levels of saturated fatty acids in the diet is increased. Many studies introduce omega-3 as immune system regulators with reducing the levels of inflammatory cytokines like TNF $\alpha$ , IL1, IL2, and vascular cell adhesion molecule (VCAM1). The beneficial effects of omega-3 in inflammatory diseases such as rheumatoid arthritis and MS have been observed. A study reported that administration of omega-3 for 3 months could reduce level of inflammatory cytokine. In addition, omega-3 fatty acids may reduce the level of Matrix metalloproteinase (MMP). MMP are zinc-dependent endopeptidase that plays an important role in the migration of inflammatory cells in the CNS fluid, which breaks down blood-brain barrier. Studies show that MS patients has higher level of MMP compared with normal individuals. Chemical compounds of *Yarrow* extract can have beneficial effects in preventing or treating neurodegenerative disease (52).

#### 2.1.2.2.1. Linoleic acid

Studies on relationship between MS prevalence and dietary fatty acid have shown the effectiveness of linoleic acid in MS. It is suggested that linoleic acid has role in regulation of cell-mediated immunity. Prostaglandin derivatives of linoleic acid show immune suppressive effect (53).

#### 2.1.2.2.2. $\alpha$ -linoleic acid derivatives

Eicosapentenoic (EPA) and Docosahexaenoic (DHA) are effective in symptoms of MS patients. EPA and DHA are  $\alpha$ -linoleic acid derivatives and they are found in fish oil (53).

#### 2.1.2.2.3. Flavonoids

Flavonoids are colored antioxidants that are found in plants. These substances are responsible for the color of fruits and vegetables. Epidemiological studies show that fruits and vegetables rich in flavonoids can be used as anti-virus and anti-allergic and anti-inflammatory anti-tumor (54).

Luteolin, regulator of the immune system can be effective in neurodegenerative diseases like multiple sclerosis with inhibiting inflammatory responses found in leaves of artichoke, rosemary, thyme, and chamomile (54).

Quercetin is another flavonoid which exists in onion, apple and *Ginkgo biloba* (54).

#### 2.1.2.2.4. Special diet

Low fat diet (intake of saturated fat less than 20g/day, avoiding of whole milk, cheese, margarine and other source of hydrogenated oil, encouraging eating fish three or more per week and vegetable with high polyunsaturated fat, using cod liver oil supplement 5g/day) could reduce severity of disease and frequency of exacerbation episode of MS. Mortality rate and serious disability in MS patients who eat saturated fat more than 20 g/day were more (19, 55).

### 2.1.3. Venom therapy

Venom therapy involves the use of Bee venom, snake venom and sea anemone venom.

#### 2.1.3.1. Bee venom

Although *Apis mellifera* or Bee's sting can cause pain but it's venom containing peptide, enzyme, and amines(56) can inhibit migration of leukocytes and decrease the amount of TNF- $\alpha$  leading to anti-inflammatory effects (56, 57). Melittin one of it's components known as anti-inflammatory, Adolapin another component may play a role in analgesia by inhibition of cyclooxygenase (58). Bee venom also can decrease the symptoms of EAE in rat (57). In Bee venom therapy, Patients may be at risk of allergic reactions. nine patients with MS were treated with Bee venom, no serious allergic reaction were

seen however 4 patients showed some neurological symptoms that needs further study(59).

Although new informations about the efficacy of the venom therapy in the treatment of MS is achieved, but further clinical trials studies are needed.

#### 2.1.3.2. Snake venom

Snake venom contains various compounds such as polypeptides, protein, and phospholipase. Venom of Malayan pit viper (*Calloselasma rhodostoma*) is called Ancord has an anticoagulant polypeptide. It also can delay inflammatory demyelination in animal models.

In inflammatory conditions, fibrin is deposited. Since brain is permeable in multiple sclerosis to protein, deposition of fibrins lead to damage to axons and inflammatory demyelination. Therefore, fibrin exhaustion by venom of snakes can inhibit inflammatory reaction.

Overall, there is no clinical trial for the efficacy of snake venom therapy and studies are usually limited to experimental models (56).

#### 2.1.3.3. Sea anemone venom

*Stichodactyla helianthus* is a Sea anemone, which can produce peptide and protein as venom. In EAE models, Voltage-gated potassium channels (Kv channels) are expressed. Venom of *Stichodactyla helianthus* can block these channels. In addition, by blocking of Kv channels (especially KV1.3) production of cytokine and proliferation of T-cell reduces. So venom of sea anemone may plays a role as immunosuppressive and be useful in MS.(56)

### 2.2. Alternative medical system

The six most used CAM therapies in MS include Reflexology, Massage, Yoga, relaxation, meditation, aromatherapy, and acupuncture (60).

#### 2.2.1. Homeopathy

Homeopathy is a treatment system which its basic principle is "let like be treated by like". This means that individual who had an illness or a condition could be treated with a medicine that produce similar symptoms when a healthy individual use. Homeopathic are given in a highly dilute form, so they are nontoxic it uses very wide range of natural substances.(61)

Some homeopathic treatment is used frequently in MS symptoms. For example for bladder symptoms and urinary retention, *Causticum* could be helped. Bowel dysfunction mainly constipation may be affected by *Opium*, *Alumina*, *Nux Vomica* and Sulphurare. Daily use of Phosphorus have been reported helpful for optic neuritis, combination with *Hypericum* made it more effective. *Gelsemium* for Double vision *Cuprum Metallicum*, *Cuprum Arsenicum*, *Nux Vomica*, and *Ignatia*, for cramp and spasm and *Secale* for Sensory symptoms has been reported effect in MS patients (61).

#### 2.2.2. Aromatherapy

Aromatherapy is use of essential oil to improve health and well-being. In pain management, it has been commonly used. Aromatherapy in MS patients could affect in some symptomatic relief such as helping in sleep, relaxation, mobility of joints and muscle and improvement in feeling of well-being (62).

#### 2.2.3. Acupuncture

Acupuncture is a frequently used method in neurological condition such as spasticity, stroke, and fibromyalgia. Studies shows that acupuncture could be helpful for treat MS associated fatigue. Acupuncture could release some neurohormones and opioids that affect disease process and

these substances also could slow or even reverse progression of MS (63).

#### 2.2.3.1. Chinese scalp puncture

Chinese scalp puncture is a combination between Chinese needling method and western medical knowledge of the cerebral cortex and has been shown that could be a very effective technique for treating MS and other CNS disorders. In this technique different area in the brain such as motor area, sensory area, foot motor and sensory area, balance area, hearing and dizziness area and tremor area were stimulated for MS patients. After treatment, patients were able to stand and walk without any problem. Patients have more energy and their urine problem and dizziness were solved. This technique not only relieves symptoms but also increases quality of life and slow or reverse the progression of physical disability. It is also reduce the number of relapses and help patients to remain in remission (64).

#### 2.2.3.2. Neural therapy

Neural therapy is a modified form of acupuncture that is investigated by Gibson for the amelioration symptoms of MS. This treatment is cheap and effective for MS and for patients with ambulatory problem is very useful. It is suggested that this treatment restores the conduction capacity in intact demyelinated axons. However this treatment is almost new (53).

#### 2.3. Mind-body interventions

Mind-body intervention includes meditation such as yoga and prayer (14, 15).

##### 2.3.1. Yoga

who is used yoga mainly mentioned help mobility, improved muscle strength, help balance and general well-being (60).

Yoga is an ancient Indian, mind-body technique that is focused on meditation, mind fullness, breathing and activity or posture. Yoga exercises can improve muscle tone and reduce fatigue and spasticity. In a study on MS patients attended weekly Iyengas classes - the most common type of yoga-during 9 months significant improvement in fatigue compared with the control group observed (65).

Yoga intervention significantly improve fatigue, mobility, activity and mental function (66, 67). some forms of yoga such as Bikram yoga which is done in hot temperature are contraindicated in neurological disorder.(67)

##### 2.3.2. Spirituality

Some studies explore spirituality well-being in some neurological disorders such as multiple sclerosis. Patient planned to achieve spiritual selves through meditation and praying (68, 69). In the research in Switzerland on 150 patients with MS during 8 weeks was observed meditation can reducing the symptoms of MS like fatigue, anxiety and depression and can improve quality of life (70).

#### 2.4. Manipulative and body-based methods

Manipulative and body based methods includes massage, reflexology and chiropractic medicine(14, 15).

##### 2.4.1. Chiropractic

Many of musculoskeletal symptoms associated with MS could be managed with physical therapies. Chiropractic is one of these therapies. It has shown efficacy in treatment of chronic spinal pain so it could be used for treatment of pain in MS patients. Although Chiropractic could be one of the choice for pain management but more studies is needed to show it's efficacy in MS patient(71, 72).

##### 2.4.2. Massage

Clinical trial shows that massage in MS patients could be helpful. Patients who get massage were showed lower anxiety and less depressed mood (53). The main benefits of using massage for MS patients include reduced pain, reduced spasms, improved circulation, increased joint and limb mobility and general well-being (60).

Tai Chi is an ancient Chinese tradition exercise that is mixture of mind body therapy and exercise in form of slow rhythmic movements was originally for self-defense, today uses to improve health specially position, energy and balance. In a study on MS patients were seen depression, spasticity, walking, bladder dysfunction improve(73).

Ai-chi is combination of Tai chi and Qigong shiatsu technique is done by standing in depth water and deep breathing, and slow movements of the arms and legs. Successfully used in pain management, MS, COPD, diabetes, arthritis. In a study on 73 patients with MS during 20 weeks, Ai chi significantly could reduce pain, spasticity, and fatigue (74).

##### 2.4.3. Reflexology

Reflexology also known as zone therapy is done with pressure by thumb on specific points on the feet related to the internal body organs and glands. Reflexology could improve paresthesia, urinary symptoms, muscle strength and spasticity (53). It has been reported useful in reducing pain, stopping spasms, reducing bladder and bowel problems, improved walking and increase quality of life (60). In a study on 71 patients with MS symptoms of lack of sensation, muscle weakness and cramps after receiving 11 weeks of reflexology were improved (75).

##### 2.4.4. Aquatic exercise

Aquatic exercise is including pool therapy, hydrotherapy, and balneotherapy that are used routinely for management of pain in patients with neuralgic pain. Warm water also increases blood flow, which cause muscle relaxation(74).

#### 2.5. Energy therapies

Energy therapy include magnetic field therapy and therapeutic touch(14, 15).

Magnetic field could induce electrical field and subsequently stimulation in tissue and neuron. One study shows that repetitive stimulation has an antispastic effect on MS (53).The mechanism is still unclear.

#### 2.6. Other CAM therapies

Hyperbaric oxygen therapy is breathing oxygen at higher level than atmospheric pressure in the chamber 20 to 90 minutes each session for 4 weeks. UK Federation of MS therapy suggested as a useful, cost-effective with less side effect treatment. However, some studies showed no significant improvement.(19, 76, 77).

Art and dance therapy could be effective in emotional state of MS patients and could improve well-being of them.

MS symptoms often worsen in heat and warm environment. Cooling therapy is a method to reduce body temperature. Cool bath or shower could reduce fatigue (19).

#### 2.7. Toxic removal therapy

Toxic metals can cause neurodegenerative disease. Chelation therapy is a method for removing toxic metals by chelators such as EDTA vitamins and minerals from the body by secretion them in urine. In a study on patient with MS, is showed that level of toxic metal in urine after chelation therapies reduces (19, 78). Also chelation therapy can reduce lipid peroxidation and oxidative DNA damage (79).

Mercury, silver, copper, lead, zinc are used as amalgam for filing of teeth. Mercury vapor can be produced in mouth during chewing foods or drinking warm liquids. Removing of dental fillings can be beneficial (19, 80, 81).

#### 2.8. Hormone therapy

Higher prevalence of MS in women and late onset in men shows that testosterone level has predictive effect on MS. Studies on animal models shows that treatment with high dose of testosterone in male and female mice is effective. Supplement therapy with testosterone in men could be considered as a choice but high dose of testosterone in women has several adverse effect. Pregnancy and high dose of estradiol has protective effect. In animal models estradiol reduced severity of disease. In a clinical trial oral treatment with estradiol, reduce inflammatory lesions in brain (1, 82, 83).

#### 3. Conclusion:

CAM has different definitions and considered conventional or unconventional in different countries and it is not routinely taught in medical universities. Patients and health care professionals have problem with finding information regarding kinds and usefulness of each. In addition, MS patients have many complaints after their conventional therapies, discussing on available CAMs with their holistic nature may establish a stronger patients- physician relationship leading to elevate health and satisfaction. In addition, CAM will help patients as a friendly palliative care with low adverse effects to elevate quality of life. Any way long term large scale studies needs to show effectiveness of each CAM therapies.

#### REFERENCES

- Reipert B. Multiple sclerosis: a short review of the disease and its differences between men and women. *The Journal of Men's Health & Gender*, **2004**; 1(4): 334-40.
- Ganesh A, Apel S, Metz L, Patten S. The case for vitamin D supplementation in multiple sclerosis. *Multiple Sclerosis and Related Disorders*. **2013**.
- Kostoff RN, Briggs MB, Lyons TJ. Literature-related discovery (LRD): Potential treatments for Multiple Sclerosis. *Technological Forecasting and Social Change*, **2008**; 75(2): 239-55.
- Warren KG, Catz I. Autoantibodies to myelin basic protein within multiple sclerosis central nervous system tissue. *Journal of the Neurological Sciences*, **1993**; 115(2): 169-76.
- Barten Laurie J ADR, Procacci Kendra A, Rivey Michael P. new approaches in the management of multiple sclerosis. *Dove Press*, **2010**; 4: 343-66.
- Sharafaddinzadeh N, Moghtaderi A, Majdinasab N, Dahmardeh M, Kashipazha D, Shalbafan B. The influence of ethnicity on the characteristics of multiple sclerosis: A local population study between Persians and Arabs. *Clinical neurology and neurosurgery*, **2013**; 115(8): 1271-5.
- Etemadifar M, Sajjadi S, Nasr Z, Firoozeei TS, Abtahi S-H, Akbari M, et al. Epidemiology of multiple sclerosis in Iran: A systematic review. *European neurology*, **2013**; 70(5-6): 356-63.
- Rodriguez M. Effectors of demyelination and remyelination in the CNS: implications for multiple sclerosis. *Brain Pathology*, **2007**; 17(2): 219-29.
- Holmøy T. Immunopathogenesis of multiple sclerosis: concepts and controversies. *Acta neurologica scandinavica*, **2007**; 115(s187): 39-45.
- Giovannoni G, Ebers G. Multiple sclerosis: the environment and causation. *Current opinion in neurology*, **2007**; 20(3): 261-8.
- Negahban H, Mofateh R, Arastoo AA, Mazaheri M, Yazdi MJS, Salavati M, et al. The effects of cognitive loading on balance control in patients with multiple sclerosis. *Gait & posture*, **2011**; 34(4): 479-84.
- Cohen JA, Barkhof F, Comi G, Hartung H-P, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *New England Journal of Medicine*, **2010**; 362(5): 402-15.
- Kappos L, Radue E-W, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *New England Journal of Medicine*, **2010**; 362(5): 387-401.
- National Center for Complementary and Alternative, Medicine. Available at: <http://nccam.nih.gov/nccam/fcp/classify>. Accessed September 11, 2000. In: Health NIO, editor. 2000.
- Bowling AC, Ibrahim R, Stewart TM. Alternative medicine and multiple sclerosis: an objective review from an American perspective. *International Journal of MS Care*, **2000**; 2(3): 15-28.
- Kleijnen J. Evening primrose oil. *BMJ: British Medical Journal*, **1994**; 309(6958): 824.
- Millar JH, Zilkha K, Langman M, Wright HP, Smith A, Belin J, et al. Double-blind trial of linoleate supplementation of the diet in multiple sclerosis. *British Medical Journal*, **1973**; 1(5856): 765.
- Senapati S, Banerjee S, Gangopadhyay DN. Evening primrose oil is effective in atopic dermatitis: a randomized placebo-controlled trial. *Indian Journal of Dermatology, Venereology and Leprology*, **2008**; 74(5): 447.
- Britell C, Burks JS. Alternative and complementary therapies. Multiple Sclerosis: Diagnosis, Medical Management, and Rehabilitation New York, NY: *Demos Medical Publishing*, **2000**; 491-504.
- Iriti M, Vitalini S, Fico G, Faoro F. Neuroprotective herbs and foods from different traditional medicines and diets. *Molecules*, **2010**; 15(5): 3517-55.
- Faix E, Faioxva Z, Placha L, Koppel J. Effect of Cinnamomum zeylanicum essential oil on antioxidative status in broiler chickens. *Acta Veterinaria Brno*, **2009**; 78: 411-7.
- Joshi K, Awte S, Bhatnagar P, Walunj S, Gupta R, Joshi S, et al. Cinnamomum zeylanicum extract inhibits proinflammatory cytokine TNF $\alpha$ : in vitro and in vivo studies.
- Lee HJ, Hyun EA, Yoon WJ, Kim BH, Rhee MH, Kang HK, et al. In vitro anti-inflammatory and anti-oxidative effects of Cinnamomum camphora extracts. *Journal of ethnopharmacology*, **2006**; 103(2): 208-16.
- Lin K-H, Yeh S-Y, Lin M-Y, Shih M-C, Yang K-Tu, Hwang S-Y. Major chemotypes and antioxidative activity of the leaf essential oils of Cinnamomum osmophloeum Kaneh. from a clonal orchard. *Food Chemistry*, **2007**; 105(1): 133-9.
- Noudeh GD, Sharififar F, Noodeh AD, Hassan M, Moshafi4 MAA, Behravan E, et al. Antitumor and



- antibacterial activity of four fractions from *Heracleum persicum* Desf. and *Cinnamomum zeylanicum* Blume.
26. Rao YK, Fang S-H, Tzeng Y-M. Evaluation of the anti-inflammatory and anti-proliferation tumoral cells activities of *Antrodia camphorata*, *Cordyceps sinensis*, and *Cinnamomum osmophloeum* bark extracts. *Journal of Ethnopharmacology*, **2007**; 114(1): 78-85.
  27. Smerq J, Sharma M. Possible Mechanism of *Murraya koenigii* and *Cinnamomum tamala* With Reference to Antioxidants Activity.
  28. Yu YB, Dosanjh L, Lao L, Tan M, Shim BS, Luo Y. *Cinnamomum cassia* bark in two herbal formulas increases life span in *Caenorhabditis elegans* via insulin signaling and stress response pathways. *PLoS one*, **2010**; 5(2): e9339.
  29. Namjooyan F, Majdinasab N, Ghanavati R. Effect of standardized cinnamon capsules on quality of life and fatigue of Multiple Sclerosis patients referring to Khuzestan M.S society: *Ahwaz Jondi Shapour University of Medical Sciences*, **2013**.
  30. Brahmachari S, Pahan K. Sodium benzoate, a food additive and a metabolite of cinnamon, modifies T cells at multiple steps and inhibits adoptive transfer of experimental allergic encephalomyelitis. *The Journal of Immunology*, **2007**; 179(1): 275-83.
  31. 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. *Pakistan Journal of Biological Sciences*, **2009**; 12(9): 690-5.
  32. Akhondzadeh S, Tahmacebi Pour N, Noorbala AA, Amini H, FallahPour H, Jamshidi AH, et al. *Crocus sativus* L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial. *Phytotherapy Research*, 2005; 19(2): 148-51.
  33. Akhondzadeh S, Fallah-Pour H, Afkham K, Jamshidi A-H, Khalighi-Cigaroudi F. Comparison of *Crocus sativus* L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [ISRCTN45683816]. *BMC Complementary and Alternative Medicine*. **2004**; 4(1): 12.
  34. Gilani A, Jabeen Q, Khan M. A review of medicinal uses and pharmacological activities of *Nigella sativa*. *Pak, J Biol Sci*. 2004; 7: 441-51.
  35. Salem ML. Immunomodulatory and therapeutic properties of the *Nigella sativa* L. seed. *International Immunopharmacology*, **2005**; 5(13): 1749-70.
  36. 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. *Iranian Journal of Neurology*, **2013**; 12(1): 16.
  37. Schultz A. Efficacy of Cranberry Juice and Ascorbic Acid in Acidifying the Urine in Multiple Sclerosis Subjects. *Journal of Community Health Nursing*, **1984**; 1(3): 159-69.
  38. Hauser SL, Goodkin D. Multiple sclerosis and other demyelinating diseases. *Harrisons Principles of Internal Medicine*, **2001**; 2: 2452-61.
  39. Baliga M, Hilditch T. S 18. The constitution of some minor unsaturated fatty acids of rape-seed oils. *Journal of the Chemical Society (Resumed)*, **1949**; S91-S5.
  40. Bowling AC. Current complementary and alternative therapies for multiple sclerosis. *Current treatment options in neurology*, **2003**; 5(1): 55-68.
  41. Horrobin D. Multiple sclerosis: the rational basis for treatment with colchicine and evening primrose oil. *Medical hypotheses*, **1979**; 5(3): 365-78.
  42. Brinkeborn R, Shah D, Degenring F. Echinaforce® and other *Echinacea* fresh plant preparations in the treatment of the common cold: A randomized, placebo controlled, double-blind clinical trial. *Phytomedicine*. **1999**; 6(1): 1-6.
  43. Gunning K. Echinacea in the treatment and prevention of upper respiratory tract infections. *Western Journal of Medicine*, **1999**; 171(3): 198.
  44. Schwarz S, Knauth M, Schwab S, Walter-Sack I, Bonmann E, Storch-Hagenlocher B. Acute disseminated encephalomyelitis after parenteral therapy with herbal extracts: a report of two cases. *Journal of Neurology, Neurosurgery & Psychiatry*, **2000**; 69(4): 516-8.
  45. Hilton P, Hertogs K, Stanton SL. The use of desmopressin (DDAVP) for nocturia in women with multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, **1983**; 46(9): 854-5.
  46. Schwarz S, Leweling H. Multiple sclerosis and nutrition. *Multiple Sclerosis*, **2005**; 11(1): 24-32.
  47. BM VanAmerongen CD, P Lips and CH Polman. Multiple sclerosis and vitamin D: an update. *European Journal of Clinical Nutrition*, 2004.
  48. Embry AF. Vitamin D supplementation in the fight against multiple sclerosis. *Journal of Orthomolecular Medicine*, **2004**; 19(1): 27-38.
  49. Barbara L. Mark P, RD; JO Ann S. Carson, PhD, RD. Vitamin D and autoimmune disease—Implications for practice from the multiple sclerosis literature. **2006**.
  50. Embry AF. Vitamin D supplementation in the fight against Multiple Sclerosis. *Journal of Orthomolecular Medicine*, 2004.
  51. ME van Meeteren CT, CD Dijkstra and EAF van Tol. Antioxidants and polyunsaturated fatty acids in multiple sclerosis. *European Journal of Clinical Nutrition*, **2005**.
  52. L. Shinto GM, S.Baldauf-Wagner, A.Strehlowa, V.Yadav, L.Stuber, D.Bourdette. Omega-3fatty acid supplementation decreases matrix metalloproteinase-9 production in relapsing-remitting multiple sclerosis, **2009**.
  53. Huntley A, Ernst E. Complementary and alternative therapies for treating multiple sclerosis symptoms: a systematic review. *Complementary therapies in medicine*, **2000**; 8(2): 97-105.
  54. Jaiswal N. Protective effect of Flavonoids in Multiple Sclerosis. *Journal of Scientific and Innovative Research*, **2013**; 2(3): 509-11.
  55. Gaby A. Multiple Sclerosis. Global advances in health and medicine: improving healthcare outcomes worldwide, **2013**; 2(1): 50-6.
  56. Mirshafiey A. Venom therapy in multiple sclerosis. *Neuropharmacology*, 2007.
  57. Akbar Karimia FA, Kazem Parivar, Mohammad Nabuini,, Saied Haghighi SlaHA. Effect of honey bee venom on lewis rats with experimental allergic encephalomyelitis, a model for multiple sclerosis. *Iranian Journal of Pharmaceutical Research*, **2011**.

58. Nazaninadsat Seyed Khoei SA, Kamyar Ghabili, Nazlisadat Seyed Khoei, Omidi aY. Melittin and hyaluronidase compound derived from bee venom for the treatment of multiple sclerosis. *Iranian Journal of medical hypotheses and Ideas*, **2009**.
59. Markelov VV. Bee venom therapy and low dose naltrexone for treatment of multiple sclerosis. *Nepal Journal of Neuroscience*, **2006**; 3(71-77).
60. Esmonde L, Long AF. Complementary therapy use by persons with multiple sclerosis: Benefits and research priorities. *Complementary Therapies in Clinical Practice*, **2008**; 14(3): 176-84.
61. Whitmarsh TE. Homeopathy in multiple sclerosis. *Complementary Therapies in Nursing and Midwifery*, **2003**; 9(1): 5-9.
62. Howarth AL. Will aromatherapy be a useful treatment strategy for people with multiple sclerosis who experience pain?. *Complementary Therapies in Nursing and Midwifery*, **2002**; 8(3): 138-41.
63. McGuire C. Acupuncture in the treatment of fatigue in a patient with multiple sclerosis: Case study. *Physiotherapy*, **2003**; 89(11): 637-40.
64. Hao JJ, Cheng W, Liu M, Li H, Lü X, Sun Z. treatment of Multiple sclerosis With Chinese scalp Acupuncture. *Global Advances in Health and Medicine*, **2013**; 2(1): 8-13.
65. Hilary B. Meyer AK, Alexander C. Sones, Daniel E. Auerbach, Donna Ames, Robert T. Rubin. Yoga as an ancillary treatment for neurological and psychiatric disorders: A Review, 2012.
66. Mishra SK, Singh P, Bunch SJ, Zhang R. The therapeutic value of yoga in neurological disorders. *Annals of Indian Academy of Neurology*, **2012**; 15(4): 247.
67. Wahbeh H, Elsas S-M, Oken BS. Mind–body interventions Applications in neurology. *Neurology*, **2008**; 70(24): 2321-8.
68. Chally PS, Carlson JM. Spirituality, rehabilitation, and aging: a literature review. *Archives of physical medicine and rehabilitation*, **2004**; 85: 60-5.
69. Kim J, Heinemann AW, Bode RK, Sliwa J, King RB. Spirituality, quality of life, and functional recovery after medical rehabilitation. *Rehabilitation Psychology*, **2000**; 45(4): 365.
70. Breneman D. Meditation s effect on the physical body: scientific proof of the mind/body connection, 2011.
71. Carson EA, Swait G, Johnson IP, Cunliffe C. Chiropractic care amongst people with multiple sclerosis: A survey of MS therapy centres in the UK. *Clinical Chiropractic*, **2009**; 12(1): 23-7.
72. Dougherty P, Lawrence D. Chiropractic management of musculoskeletal pain in the multiple sclerosis patient. *Clinical Chiropractic*, **2005**; 8(2): 57-65.
73. N. Mills JA, S. CareyMorgan. Does Tai Chi/Qi Gong help patients with Multiple Sclerosis? **2000**.
74. Castro-Sánchez AM, Matarán-Peñarrocha GA, Lara-Palomo I, Saavedra-Hernández M, Arroyo-Morales M, Moreno-Lorenzo C. Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial. *Evidence-Based Complementary and Alternative Medicine*, **2011**; 2012.
75. Siev-Ner DG, L Lerner-Geva and A Achiron. Re exology treatment relieves symptoms of multiple sclerosis: a randomized controlled study, **2003**.
76. Kidd PM. Multiple sclerosis, an autoimmune inflammatory disease: prospects for its integrative management. *Alternative Medicine Review*, **2001**; 6(6).
77. Bennett MH HR. Hyperbaric oxygen therapy for multiple sclerosis, **2011**.
78. Alessandro fulgenzi sgz, Mario mauro mariani, Daniele vietti, Maria elena ferrero. A case of multiple sclerosis improvement following removal of heavy metal intoxication, **2011**.
79. Anderson AMRIH-FRSWMOKFRA. EDTA chelation therapy, without added vitamin C, decreases oxidative DNA damage and lipid peroxidation, **2009**.
80. Hal A. Huggins TEL. Cerebrospinal fluid protein changes in multiple sclerosis after dental amalgam removal. *Alternative Medicine Review*, **1998**; 3.
81. Jarmila Prochazkova IS, Hana Kucerova, Jirina Bartova & Vera DM Stejskal. The beneficial effect of amalgam replacement on health in patients with autoimmunity. *Neuroendocrinology Letters*, 2004; 25(3).
82. Haldane J. Sex Hormone Treatments for Multiple Sclerosis. *Journal of Orthomolecular Medicine*, **2012**; 27(2).
83. Sicotte NL, Liva SM, Klutch R, Pfeiffer P, Bouvier S, Odesa S, et al. Treatment of multiple sclerosis with the pregnancy hormone estriol. *Annals of neurology*, **2002**; 52(4): 421-8.