CHAPTER

25

The Role of Natural Products in the Prevention and Treatment of Multiple Sclerosis

A. Shamsizadeh[1], *A. Roohbakhsh*[2], *F. Ayoobi*[1], *A. Moghaddamahmadi*[1]

[1]Rafsanjan University of Medical Sciences, Rafsanjan, Iran; [2]Mashhad University of Medical Sciences, Mashhad, Iran

OUTLINE

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INTRODUCTION

The existing multiple sclerosis (MS) drugs aim to stop relapses and/or slow the progression of the disease. Different classes of medications including immunosuppressive, antiinflammatory, and immunomodulatory drugs have been used successfully for this purpose. However, long-term use of these drugs is usually concomitant with various adverse drug reactions that reduce the patients' compliance.[1] Furthermore, the high price of MS drugs may affect the quality of life of the affected patients. The use of herbal-based medicines for the treatment of various diseases has risen substantially. Herbal medicine as an alternative or complementary treatment of MS may be used to increase the efficacy of the current MS treatments or reduce the side effects of drugs. For example, it has been reported that an Oriental herbal medicine, *Erhuang*, improves clinical symptoms and neurological signs, and decreases the rate of relapse in animals and patients with MS.[2] By employing animal models of MS, such as experimental autoimmune encephalomyelitis (EAE), our knowledge about the effects of herbs or their compounds in the treatment of this disease has increased substantially over the past decade. The similarities between EAE and MS have made it a good and valid model for the investigation of new drugs either from laboratories or from nature.[3] In this chapter, we will review the latest findings concerning the effects of herbs and some natural products in the treatment of MS in animals and humans. This is an effort to collect and summarize the effects of the compounds of natural origin in the treatment of MS. Some of these compounds have presented good and satisfactory results in basic experimental studies. However, more studies are needed to evaluate the effects of these compounds or products before clinical use.

ACHILLEA MILLEFOLIUM

Achillea millefolium (yarrow) belongs to the Asteraceae family. In traditional medicine, yarrow has long been used as a treatment for several disorders such as wounds, infectious diseases, pain, and gastrointestinal complaints. In addition, it is reported that yarrow has anxiolytic-like and antiinflammatory properties in the nervous system.[4] Interestingly, it has no adverse effects on memory in normal mice.[5]

Animal and Clinical Studies

A recent study showed that oral administration of aqueous extract of *A. millefolium* attenuated disease severity, inflammatory responses, and demyelinating lesions in mice with EAE.[6] A few clinical studies evaluated the therapeutic effects of *A. millefolium* in different diseases. These disorders include dysmenorrhea, cancer, and chronic kidney disease. An ongoing clinical trial that assesses the effect of *A. millefolium* aqueous extract on patients with MS was designed by the authors of this chapter.

ANDROGRAPHOLIDE

Andrographolide is a bicyclic diterpenoid lactone derived from the extracts of *Andrographis paniculata*, a plant originating from Southeast Asian countries that has been used as an official medicinal herb in China. This herb has antiinflammatory and immune-modulating properties.[7]

Animal and Clinical Studies

It was reported that treatment with andrographolide reduced the behavioral deficits in mice with EAE by inhibiting T-cell and antibody responses directed to myelin.[8]

There are several clinical trials that demonstrate the positive effects of *A. paniculata* on infectious diseases, hypertriglyceridemia, and autoimmune disorders such as ulcerative colitis and rheumatoid arthritis. Two clinical trial studies are ongoing to determine the efficacy of andrographolide in patients with MS.[9]

APIGENIN

Apigenin, a natural flavonoid, is commonly found in various plants, fruits, vegetables, herbs, and spices. Apigenin is produced mainly from parsley and dried

flowers of chamomile. The antioxidant, antiinflammatory and anticarcinogenic effects of apigenin have been studied well. It is effective in the treatment of asthma, insomnia, Parkinson disease, neuralgia, and shingles.[10]

Animal and Clinical Studies

Oral and intraperitoneal administration of apigenin reduced the progression and relapse in two mouse models of MS through modulating the immune system.[11]

Despite the proven antioxidant and antiinflammatory effects of apigenin, there is no clinical trial report on patients with MS.

BEE VENOM

The venom of the honey bee (*Apis mellifera*) has different types of light and heavy chain peptides. It also consists of various proteins such as apamin, melittin, adolpin, and phospholipase A2. Bee venom has antiinflammatory and antinociceptive effects on inflammatory reactions.[12]

Animal and Clinical Studies

Injection of bee venom to rats with EAE improved the pathological changes and the glutamate level and increased the brain level of γ-aminobutyric acid. However, researchers did not report the effect of the bee venom on behavioral deficits following EAE.[13] In a recent study, exposure of phospholipase A2, from bee venom and other venoms, to isolated myelin produced a deleterious effect on this structure.[14]

Two clinical trial studies evaluated the effect of the bee venom on patients with MS. The results showed that the bee venom did not reduce the disease severity or disability or fatigue or quality of life of patients with MS.[15,16]

BERBERINE

Berberine is an isoquinoline alkaloid. It is isolated from various herbs including *Hydrastis canadensis* (goldenseal), *Cortex phellodendri* (Huang bai), and *Rhizoma coptidis* (Huanglian). It has a wide range of pharmacological properties and is considered to have antiinflammatory and neuroprotective effects.[17]

Animal and Clinical Studies

It was reported that oral administration of berberine in mice with EAE improved behavioral deficits, pathological parameters, and attenuated the permeability of blood–brain barrier.[18–20] Moreover, oral administration of berberine in the experimental autoimmune neuritis model in rats ameliorated experimental autoimmune neuritis. Accordingly, it also may have therapeutic effects for other autoimmune diseases in the peripheral nervous system.[21]

There has been no clinical trial for the effects of berberine on patients with MS. However, over 90 clinical trials have been published for this compound so far. Most of these studies focused on its antidyslipidemic effect.

β-ELEMENE

β-Elemene is the main constituent of *Rhizoma zedoariae* and *Pterodon emarginatus* as Chinese and Brazilian medicinal herbs, respectively. This compound has antiinflammatory and antitumor properties and is able to pass the blood–brain barrier.[22]

Animal and Clinical Studies

Zhang et al. reported that β-elemene ameliorated motor disability and reduced the optic nerve inflammation in mice with EAE. Furthermore, it was revealed that part of the effects of β-elemene on EAE is mediated through inhibition of differentiation and development of Th17 cells–mediated inflammation.[22,23] In addition, a recent study demonstrated that oral administration of essential oil from *P. emarginatus* decreased the neurological signs and demyelination in mice with EAE.[24]

A few clinical trials have evaluated the beneficial effect of β-elemene on lung cancer. However, no clinical trial has been performed to evaluate its effects on MS, so far.

BLUEBERRIES

Blueberries are flavonoid-rich fruits and have been suggested to limit neurodegeneration associated with neurodegenerative diseases. They are able to prevent age- and neural-damage-related cognitive function loss.[25]

Animal and Clinical Studies

In an interesting study, Xin et al. fed EAE mice with a diet containing 1% whole, freeze-dried Tifblue blueberries (*Vaccinium ashei*). They reported that blueberry-fed EAE mice had lower motor disability scores as well as greater myelin preservation in the lumbar spinal cord.[26]

There are clinical trials on diseases other than MS, showing memory enhancing, antioxidant, and antiinflammatory properties for blueberry, but none have been specifically studied in patients with MS.

CASTANOSPERMINE

Castanospermine is a compound derived from the Australian rainforest plant, *Castanospermum australe*. This compound inhibits glucosidases I and II, which are crucial in posttranslational processing of the complex N-linked oligosaccharides within the endoplasmic reticulum. It was reported that castanospermine can modulate some immunopathologies including transplantation rejection and arthritis.[27]

Animal and Clinical Studies

It was reported that castanospermine prevented behavioral deficits of EAE and inhibited inflammatory infiltrates of the central nervous system (CNS).[28,29] No clinical study has been performed on patients with MS so far.

CHRYSIN AND CAFFEIC ACID

It has been reported that honey and propolis have high levels of the flavonoids chrysin and caffeic acid. They are neuroprotective, improve cognitive decline, and are effective in neurodegenerative diseases such as Alzheimer and Parkinson diseases.[30,31]

Animal and Clinical Studies

Treatment of EAE rats with caffeic acid inhibited reactive oxygen species production induced by EAE and ameliorated behavioral deficits in rats.[32] Also, Zhang et al. reported that oral administration of chrysin for 3 days before the induction of EAE alleviated the behavioral deficits and suppressed dendritic and Th1 cells.[33]

There is no clinical trial for chrysin and caffeic acid in patients with MS. However, caffeic acid was effective in the treatment of cancer in previous clinical studies.

CURCUMIN

Curcumin is a natural polyphenolic phytochemical isolated from the rhizome of the *Curcuma longa*.[34] Traditionally, curcumin has been used for coloring and flavoring food products, treatment of inflammatory diseases, and wound healing.

Animal and Clinical Studies

There are studies reporting that treatment with curcumin reduced behavioral disability scores and decreased inflammatory reactions through the immune system in mice and rats with EAE.[35–37]

Up to 144 clinical studies have been conducted on potential therapeutic effects of curcumin, so far. Most of them focused on cancer prevention and treatment. One clinical trial is going on to determine the efficacy of curcumin in patients with MS,[9] but no results are available as of this writing.

EPIGALLOCATECHIN-3-GALLATE

Epicatechin-3-gallate is the most biologically active and most abundant catechin in green tea (accounting for 50–80% of the total tea catechins). Green tea or epicatechin-3-gallate can quench several different reactive oxygen species, and its health benefits have been partially attributed to its antioxidant properties.[38]

Animal and Clinical Studies

Feeding with a diet (30 days before induction of EAE) supplemented with epicatechin-3-gallate attenuated motor disability and pathological features (leukocyte infiltration and demyelination) in mice with EAE. Interestingly, dietary supplementation of epicatechin-3-gallate after EAE induction also effectively ameliorated motor disability.[39] Epicatechin-3-gallate treatment improved animals' recovery from EAE and protected them for long term.[40]

The results of a clinical trial showed that administration of epicatechin-3-gallate to patients with MS (over a 12-week period) improved muscle metabolism during moderate exercise. The improvement was greater in women than in men.[41] Five clinical trials are under progress to determine the efficacy of epicatechin-3-gallate in patients with MS.[9]

ERHUANGFANG

Erhuangfang (Bu Shen Yi Sui) is a Chinese remedy mainly composed of Shengdi (Radix Rehmanniae), leech (the dried body of *Whitmania pigra*), Zhe Bei Mu (Bulbus Fritillariae), scorpion (the dried body of *Buthus martensii*), and He Shou Wu (Radix Polygoni Multiflori).

Animal and Clinical Studies

Administration of erhuangfang decreased behavioral deficits and diminished inflammatory reaction and demyelination in CNS of animals with EAE.[42,43]

In 2012, Zhou and Fan, in a 1-year retrospective study, indicated that erhuangfang effectively reduced relapse rate in patients with MS.[44] After that, it was approved by the Beijing Food and Drug Administration as a hospital preparation (No. 10003). In 2015, in a 2-year, prospective,

randomized study, they showed that erhuangfang significantly reduced relapse rate and prevented progression of MS. Again, the researchers suggested this product as an effective therapy for relapsing MS.[45]

GENISTEIN

Genistein is a common form of phytoestrogens that are found in a variety of plants, especially in soy. Phytoestrogens are a group of plant substances that have a chemical structure similar to estrogen, exerting estrogenic and antiestrogenic effects.[46]

Animal and Clinical Studies

Administration of genistein ameliorated the behavioral deficits and modulated pro- and antiinflammatory cytokines in mice with EAE.[47] Lately, it was demonstrated that oral administration of 300 mg/kg genistein reduced EAE severity if started in early phases of the disease.[48]

There are many clinical trials for genistein in metabolic syndrome, prostate disorders, osteoporosis, and breast cancer. Up to the present, no clinical study has been performed on patients with MS.

GINGER

Ginger is the rhizome of *Zingiber officinale*, commonly used as a spice or food supplement. In Iranian traditional medicine, ginger is used for the treatment of memory deficit and digestive diseases.[49] Recent research has reported potent antiinflammatory effects for ginger and its derivatives.

Animal and Clinical Studies

Administration of hydroalcoholic extract of ginger reduced the behavioral deficits and modulated the immune functions in mice with EAE[50]; no clinical study has been performed on patients with MS.

HESPERIDIN

Hesperidin is a natural flavonoid that is abundant in citrus species such as lemon and orange. Various biological properties have been reported for hesperidin including anticancer, antiviral, and antiinflammatory activities.[51]

Animal and Clinical Studies

Recently, Ciftci et al. treated EAE mice with hesperidin. They reported that hesperidin prevented the oxidative stress and decreased behavioral deficits in these animals.[52]

The therapeutic effects of hesperidin in diseases other than MS have been evaluated extensively in clinical studies. However, there is no clinical trial on patients with MS.

HUPERZINE A

Huperzine A is a sesquiterpene alkaloid extracted from *Huperzia serrata* (club moss), a plant that is native to India and Southeast Asia. It has potential antiinflammatory properties with anticholinesterase effects. Huperzine A has been used for the treatment of certain neurodegenerative diseases such as Alzheimer disease.[53]

Animal and Clinical Studies

Wang et al. reported that administration of 0.2 mg/kg of huperzine A ameliorated EAE by suppressing autoimmune responses, inflammatory reactions, and by subsequent demyelination and axonal injury in the spinal cord.[54,55]

There are a few clinical trials for Huperzine A, and most of them were performed on patients with Alzheimer disease. Results indicated that huperzine A improved both cognitive functions and the quality of life.[56] However, there is no clinical trial on MS yet.

HYPERICUM PERFORATUM

Hypericum perforatum (St. John's wort) is a member of the Hypericaceae family. It has been used in folk remedies for the treatment of depression. Moreover, there are reports about the therapeutic effect of this plant and its derivative (hyperforin) in psychiatric and neurological disorders such as Alzheimer and Parkinson disease.[57]

Animal and Clinical Studies

It was reported that oral treatment of the EAE mice with hydroalcoholic extract of *H. perforatum* or with hyperforin attenuated EAE-induced behavioral deficits possibly via modulation of immune system function.[58] In line with these results, it was revealed that oral administration of MS14, an Iranian herbal-marine medicine that contained 90% *Penaeus latisculatus* (king prawn), 5% *Apium graveolens* (Umbelliferae), and 5% *H. perforatum*, decreased the motor disability and attenuated the inflammation in the CNS of the rats with EAE.[59–61]

There are many clinical trials for *H. perforatum*. Most of them are focused on the treatment of depression and anxiety. However, we did not find any relevant study on

patients with MS. There is one clinical trial study that investigated the effect of MS14 on patients with MS. The results demonstrated that MS14 may improve patients' mobility (lower limb) without serious adverse effects on vital signs and biochemical, hematological, liver, and kidney function tests.[62]

LIPOIC ACID

Lipoic acid is a natural antioxidant that exists in many foods. The main sources of the lipoic acid are liver, kidney, heart, spinach, broccoli, and yeast extract. It may be used as a dietary supplement. Studies showed that lipoic acid is effective in ischemia-reperfusion injury, diabetes, and neurodegeneration.[63]

Animal and Clinical Studies

The effect of lipoic acid on EAE has been evaluated in many studies. The results demonstrated that lipoic acid suppressed EAE possibly through modulation of the immune system and inflammatory responses.[64–69]

There are some clinical trials of this compound on patients with MS. First, Odinak et al. reported that administration of lipoic acid reduced relapse frequency and decreased corticosteroid consumption in patients with MS. However, the sample size was only 14. They also reported that administration of a combination of antioxidants to patients with MS was more effective than administration of lipoic acid alone.[70] Other studies revealed that consumption of 1200 mg lipoic acid per day decreased inflammatory cytokines in patients with MS.[71–75] There are even more ongoing clinical trials that aim to determine the efficacy of lipoic acid in patients with MS.[9] However, more studies with bigger sample sizes are required to make a clearer interpretation of the effects of lipoic acid on patients with MS.

LUTEOLIN

Luteolin is a common flavonoid abundantly present in several plant products, including broccoli, pepper, thyme, and celery. Studies have shown that luteolin possesses beneficial neuroprotective effects both in vitro and in vivo. It also has antioxidant and immunomodulatory properties.[76]

Animal and Clinical Studies

Hendriks and colleagues administered luteolin (50 mg/kg/day) to rats with EAE. They reported that both oral and intraperitoneal administration of luteolin suppressed behavioral deficits, prevented relapse, and reduced inflammation and axonal damage.[77] Furthermore, it was recently reported that exposure to a special mixture of palmitoylethanolamide/luteolin promoted the maturation of oligodendrocyte precursor cells that make myelin sheet around neurons.[78] Conversely, Verbeek et al. reported that oral administration of luteolin (10 mg/day) delayed the recovery of behavioral deficits rather than reducing disease severity.[79]

Some clinical trials show the effectiveness of luteolin on autism, diabetes mellitus type 2, and some kinds of cancers. However, there are no clinical trials on patients with MS.

MATRINE

Matrine and oxymatrine are two natural alkaloid components extracted from the herb Radix Sophorae flavescentes. Various pharmacological activities have been reported for matrine including antiinflammatory, antiallergic, and cardiovascular protective effects.[80]

Animal and Clinical Studies

A growing number of studies revealed that matrine (150, 200, and 250 mg/kg) reduced behavioral deficits, inflammatory cells, and blood–brain barrier leakage in rats with EAE.[81–86]

Many experimental reports demonstrated beneficial effects of this compound on EAE. In addition, matrine has long been used for the treatment of viral hepatitis, cardiac arrhythmia, and skin inflammation, without known side effects. So, it can be recommended to enter clinical trials on patients with MS.

N-ACETYLGLUCOSAMINE

N-acetylglucosamine is a simple sugar (monosaccharide derivative of glucose). This sugar is mainly derived from chitin, which is abundant in fungi. *N*-acetylglucosamine is a dietary supplement available in some countries. It has been used safely in humans by the oral route. Several biological effects have been reported for *N*-acetylglucosamine, including modulation of the immune system.[87]

Animal and Clinical Studies

Oral administration of *N*-acetylglucosamine enhanced *N*-glycosylation, suppressed inflammatory T-cell responses, and inhibited behavioral deficits in mice with EAE.[88]

No clinical trial has been performed on patients with MS.

NIGELLA SATIVA

Nigella sativa or black cumin belongs to the botanical family Ranunculaceae. The seeds of this plant have been used in Middle Eastern folk medicine as a remedy for various diseases. Recent studies reported neuroprotective, antioxidant, and antiinflammatory effects for black cumin. Thymoquinone is the major bioactive component of this seed.[89]

Animal and Clinical Studies

Oral administration of *N. sativa* seeds, 2 weeks prior to EAE induction or after the appearance of first signs of the EAE, decreased behavioral deficits, suppressed inflammation, and enhanced remyelination.[90,91] No clinical trial has been performed on patients with MS.

OLEANOLIC ACID, ERYTHRODIOL, AND CELASTROL

Oleanolic acid, erythrodiol, and celastrol are natural pentacyclic triterpenes, which are widely found in a variety of plants including *Tripterygium wilfordii* hook (thunder of god vine). One of the sources of oleanolic acid is the leaves and fruits of *Olea europaea* (olive tree). There are reports of antiinflammatory, antitumor, and immunomodulatory effects of these triterpenes.[92,93]

Animal and Clinical Studies

It was reported that treatment with either oleanolic acid or erythrodiol (50 mg/kg), before or at the early phase of EAE, ameliorated neurological signs. Moreover, oleanolic acid treatment decreased the levels of anti-MOG antibodies, blood–brain barrier leakage, and infiltration of inflammatory cells within the CNS.[94,95] In line with these findings, oral administration of 80 mg/kg of olive leaf extract in rats with EAE reduced behavioral deficits, cellularity of the draining lymph nodes, and production of interferon-γ and interleukin-17.[96] It was also reported that celastrol (1 mg/kg/day) ameliorated the behavioral deficits and inhibited the relapse in rats with EAE.[97]

Oleanolic acid had beneficial effects in clinical trials on chronic kidney disease, diabetes mellitus type 2, and some inflammatory conditions such as arthritis. There are about 500 registered clinical trials regarding the therapeutic effects of olive.[9] However, none of them are related to patients with MS. Similarly, no clinical trial has been performed for oleanolic acid, erythrodiol, or celastrol on patients with MS.

PANAX GINSENG AND GINSAN

Ginsan is an acidic polysaccharide. It is extracted from the roots of *Panax ginseng*. *P. ginseng* is a medicinal herb of the family Araliaceae and has traditionally been used for over 2000 years in oriental countries as a medicinal preparation for various degenerative diseases. It is used for physical strength and vigor and prevention of aging as well.[98]

Animal and Clinical Studies

Hwang et al. studied the effect of pretreatment with ginsan (200 mg/day) on behavioral and inflammatory responses of mice with EAE. They reported that ginsan reduced behavioral scores of EAE and inhibited the proliferation of autoreactive T cells and the production of inflammatory cytokines.[99] In accordance, Bowie et al. also found that treatment with an aqueous ginseng extract (150 mg/kg), during the acute phase of EAE, decreased the severity of behavioral and pathological signs of EAE.[100] Recently, it was demonstrated that oral treatment with Korean red ginseng extract (20 and 100 mg/kg) caused attenuation of behavioral signs, loss of body weight, spinal demyelination, and glial activation in rats with EAE.[101]

There are a few clinical trials regarding the treatment of MS by ginseng or ginsan. Most of them have focused on the treatment of fatigue during MS.[102] According to these studies, it has been proposed that ginseng can reduce fatigue and has a significant positive effect on the quality of life of patients with MS.[103]

PROBIOTICS

Since hundreds of years, probiotics (live microorganisms) have been consumed by humans. Many studies have demonstrated the beneficial effects of probiotic bacteria on human health. Nowadays, probiotic preparations have become more common in the prevention and treatment of diseases such as gastrointestinal and autoimmune disorders.[104]

Animal and Clinical Studies

In a study, Kobayashi et al. reported that oral administration of two common probiotics (*Lactobacillus casei* and *Bifidobacterium breve*) improved neurological symptoms in EAE.[105] In accordance, it was reported that administration of a mixture of three lactobacilli strains suppressed the progression and reversed the behavioral and histological deficits in mice with EAE. Also, it was suggested that strain-specific differences influence the effect of probiotics in EAE.[106,107] No clinical trial was reported on patients with MS.

RESVERATROL

Resveratrol is a nonflavonoid polyphenol that is found in various food sources including white *Veratrum grandiflorum* (hellebore), grapes, berries, red wine, chocolate, and peanuts. It is a plant antibiotic compound produced as a part of a plant's defense system against fungal infection. Resveratrol also has anticancer, antioxidant, and antiinflammatory properties.[108]

Animal and Clinical Studies

Oral administration of resveratrol (100 and 250 mg/kg) reduced behavioral deficits and neuronal loss and demyelination in mice with EAE. However, its effect on the immune system is controversial as some reports demonstrated little effect on inflammation in the spinal cord or optic nerves, whereas others demonstrated an antiinflammatory effect in rats with EAE.[109,110] Conversely, it was also reported that resveratrol exacerbated demyelination and inflammation and behavioral deficits of EAE.[111] The source of these discrepancies is unknown.

SESAME OIL

Sesame seed (*Sesamum indicum*, Pedaliaceae) has long been categorized as a traditional healthy food in Asian countries. Sesame oil inhibits lipid peroxidation and is a potent inhibitor of proinflammatory mediators.[112]

Animal and Clinical Studies

We found two studies from a single research group that reported both oral administration[113] and intraperitoneal administration[114] of sesame oil decreased behavioral deficits and improved immune system function in mice with EAE.

Although several clinical trials evaluated the effects of sesame oil in various disorders such as hypertension, diabetes mellitus, allergy, and inflammation, no clinical trial has been conducted on patients with MS yet.

TRIPTERYGIUM WILFORDII HOOK F

T. wilfordii Hook F is a medicinal herb. It has been used in the traditional Chinese medicine for the treatment of rheumatoid arthritis. This plant has antiinflammatory and immunosuppressive properties. The major compounds with antiinflammatory and immunosuppressive properties isolated from this plant include triptolide, 5-hydroxytriptolide, and tripchlorolide.[115–117]

Animal and Clinical Studies

It was reported that *T. wilfordii* extracts had efficacy in guinea pigs with EAE.[118] In line, Fu et al. reported that 5-hydroxytriptolide as an analog of triptolide (1 mg/kg/day) prevented EAE. It also inhibited T-cell proliferation and activation[117]. In accordance, oral administration of triptolide (100 mg/kg) exhibited both preventive and therapeutic effects in mice with EAE.[119] Similar results were obtained for tripchlorolide (40 μg/kg) as well.[116]

There are about 50 clinical trials regarding the therapeutic effect of the *T. wilfordii* Hook F on thrombocytopenia, Crohn disease, and chronic primary glomerulopathy. However, the effect of this plant on patients with MS has not been evaluated yet.

VINDEBURNOL

Vindeburnol is a semisynthetic derivative of the plant alkaloid vincamine. Vincamine is a peripheral vasodilator isolated from the plant *Vinca minor*. Vindeburnol increases activation of the locus coeruleus neurons. The primary source of noradrenaline in the brain is the neurons located in the locus coeruleus. Endogenous noradrenaline directly affects neurons and reduces neurotoxicity elicited by inflammatory or excitotoxic stimuli, both in vitro and in vivo.[120,121]

Animal and Clinical Studies

Vindeburnol (20 mg/kg) reduced behavioral deficits and the number of demyelinated regions in the cerebellum. It also improved locus coeruleus physiology and function and increased noradrenaline levels in the spinal cord.[120] There are many reports demonstrating that noradrenaline has a role in MS pathogenesis (for review please see Ref. 122). No clinical trial has been performed on patients with MS.

WHITE GRAPE JUICE

White and red grapes are well known for their health-promoting and antioxidant activities. There are many bioactive compounds in grapes including flavonoids (quercetin, catechin, epicatechin, and procyanidins) and phenolic compounds (gallic acid, resveratrol, and ellagic acids). Many studies reported that grape juices have neuroprotective, antioxidant, and antiinflammatory properties.[123]

Animal and Clinical Studies

Oral administration of white grape juice extract (20 and 40 mg/kg/day) for 1 week before EAE induction

diminished behavioral deficits, lymphocytic infiltration, and demyelination of the neurons.[124] No clinical trial has been performed on patients with MS.

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