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REVIEW

Phytotherapy as a Complementary Medicine for Multiple Sclerosis

Multipl Sklerozda Tamamlayıcı Tedavi Olarak Fitoterapi

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ABSTRACT

Multiple sclerosis (MS) is the most common cause of neurologic disability in adults worldwide. Two main issues have caused MS patients to face several problems. One issue is that the definite cause of MS has not yet been determined and the other issue is the lack of a definite treatment for this disease. The people with MS, therefore, seek out complementary and alternative medications to manage the symptoms of this disease. Meanwhile, medicinal plants have been demonstrated to have possible positive pharmacological effects in treating MS in different models. The reliable articles indexed in the databases *Web of Science*, *Scopus*, *PubMed Central*, *PubMed*, *Scientific Information Database*, and *Institute for Scientific Information* were retrieved and analyzed to conduct this review. Medicinal plants and plant compounds caused decreases in the neurologic deficits due to MS. Clinical evidence has demonstrated the clinical potential of *Cannabis sativa* extract, cannabinoids, *Ginkgo biloba*, beta-phytosterol, and *Lippia citriodora* extract to improve MS symptoms. These plants and compounds can also improve spasticity, muscle spasm, neuropathic pain, and urinary tract complications in at least some of these patients. Nanocurcumins and *Punica granatum* L. peel extract have exhibited positive effects in animal models and can decrease neurologic deficits by reducing inflammation. Medicinal plants and their compounds can serve as new sources of MS drugs because they can improve MS symptoms.

Key words: Multiple sclerosis, phytotherapy, medicinal plants

ÖZ

Multipl skleroz (MS), dünya çapında yetişkinlerde en sık görülen nörolojik problemdir. MS hastalarının pek çok sorunla karşı karşıya kalmasına neden olan iki ana sorun bulunmaktadır. İlk sorun, MS'in kesin nedeninin henüz belirlenmemiş olmasıdır. Diğer problem ise bu hastalık için kesin bir tedavinin olmayışıdır. Bu nedenle, MS'li hastalar, bu hastalığın semptomlarını giderebilmek için tamamlayıcı ve alternatif tedavi arayışındadırlar. Aynı zamanda, tıbbi bitkilerin, MS'in farklı modellerde tedavisinde olası olumlu farmakolojik etkilere sahip olduğu gösterilmiştir. Bu derlemenin hazırlanmasında, *Web of Science*, *Scopus*, *PubMed Central*, *PubMed*, *Scientific Information Database* ve *Institute for Scientific Information* gibi veri tabanlarında indekslenen güvenilir makalelere başvurulmuş ve değerlendirilmiştir. Tıbbi bitkiler ve bitkisel bileşikler, MS kaynaklı nörolojik problemlerin azalmasını sağlamıştır. Klinik çalışmalar, MS semptomlarını iyileştirmek için *Cannabis sativa* ekstresi, kannabinoidler, *Ginkgo biloba*, beta-fitosterol ve *Lippia citriodora* ekstresinin klinik potansiyelini ortaya koymuştur. Bu bitkiler ve bileşikler, bu hastaların en azından bazılarında spastisite, kas spazmı, nöropatik ağrı ve idrar yolu komplikasyonlarını iyileştirebilmektedir. Nanokurkuminler ve *Punica granatum* L. kabuğu ekstresi, hayvan modelleri üzerinde olumlu etkiler göstermiş ve inflamasyonu azaltarak nörolojik bozuklukları azaltmıştır. Tıbbi bitkiler ve bunların bileşikleri, MS semptomlarını iyileştirebildikleri için yeni MS ilaç kaynakları olarak kullanılabilir.

Anahtar kelimeler: Multipl skleroz, fitoterapi, tıbbi bitkiler

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory, central nervous system (CNS)-demyelinating disease that is characterized by autoimmune presentations. In MS, the immune system is stimulated for unknown reasons and specific lymphocytes against myelin are activated.[1] The entry of these cells into the brain plays a role in the immunopathology of MS and the exacerbation of the inflammatory responses in the brain. MS is 2-3 times more prevalent in women than in men and often occurs in the age range of 20 to 40 years.[1] The most important symptoms of MS include motor paralysis, sensory degeneration, visual impairment, and cognitive impairment. No definite treatment for MS has yet been offered and certain drugs are available only to improve disease symptoms and slow down its progression.[2]

Although people with MS have life spans similar to those of others, they experience major changes due to changes in the quality of their lives.[3] The treatments of choice for MS include conventional treatments such as beta-interferon and complementary and alternative therapies. Alternative therapies

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are increasingly being welcome day by day such that one out of every three people is projected to use these treatments during his/her lifespan for common diseases such as back pain, headache, anxiety, and depression.[4] The use of complementary and alternative medicine to treat chronic diseases such as Parkinson disease, epilepsy, and cancer has raised the potential of these therapies to treat MS. Although the conventional treatment for MS can help to decrease the frequencies of relapses and the severity of the disease and also slow down its progression,[5] it is only partly effective to treat symptoms and improve functioning and quality of life. Patients, therefore, often seek out various other ways to treat MS.

Alternative medicine or complementary medicine refers to different approaches to treat or prevent diseases whose protocols or efficacies are different from those of conventional or biological approaches. These approaches include exercise, meditation, medical nutrition therapy and phytotherapy, energy therapy and relaxation, acupuncture, and pressure medicine.[6]

Recent studies have shown promising results regarding the effects of medicinal plants to treat or prevent different diseases including Alzheimer disease,[7,8] stroke,[9,10] depression,[11,12] and drug abuse.[13]

In the study by Giveon et al.[14] with 150 physicians, 68% of the physicians reported that 15% of their patients used complementary medicine and 40% conjectured that 10% of patients used medicinal plants in treating diseases.

Pathogenesis of MS

In MS, acute inflammation, which is accompanied by demyelination, acts as a strong stimulus to mobilize the oligodendrocyte precursor cells. Suppressing inflammatory responses can lead to defective repair. Perhaps one reason for the impairment of remyelination in patients is that they are treated with anti-inflammatory drugs such as corticosteroids. When inflammation is suppressed, remyelination remains incomplete and demyelination becomes chronic.[1]

The etiology of MS is still unknown and it is argued that a combination of genetics and environmental factors may lead to the onset of MS. Genetically, MS is most associated with the human leukocyte antigen located on chromosome 6.[15]

MS is an autoimmune disease of the CNS. The most important protein components of the myelin that target the immune system include myelin basic protein, myelin-associated glycoprotein, protein proteolipid protein, and myelin oligodendrocyte glycoprotein.[16]

The roles of different components of the immune system in the occurrence of MS have been studied. The resident microglia and macrophages of the CNS are involved in exerting phagocytotic activities, donating antigen, and producing cytokines. The macrophages and microglia contribute to demyelinating nerves and phagocytosing myelin by producing inflammatory cytokines and myeloperoxidase.[17]

The number of mast cells in the CNS is low in normal conditions but increases in the platelets and inflammatory lesions in MS. Regulated on activation, normal T cell expressed and secreted is a potential absorbent of the mast cells that increases in the cerebrospinal fluid (CSF) of MS patients. Mast cell proteases such as tryptase and chymase activate matrix metalloproteinases (MMPs) and mast cells can produce MMP9 and MMP2. The MMPs can contribute to degenerating tissues such as the blood–brain barrier (BBB).[16]

The number of dendritic cells that act as antigen-donating cells is very low in the CNS in normal conditions but increases in the peripheral blood and CSF in patients with MS.[17]

Certain subgroups of natural killer (NK) cells contribute to regulating the immune system in MS. It has been reported that NK cells in patients with relapse-remitting MS express greater amounts of Fas (CD95) and also secrete the cytokines of T helper 2 (Th2) cells such as interleukin 5 (IL-5) and IL-13. In the immune system, the Th cells are classified into different subgroups depending on the pattern of the produced cytokines, including Th2, Th1, Th17, Th9, and Th22. The other subgroup of T cells, known as regulatory T cells (Tregs), are also essential to maintain self-tolerance.[18]

Th1 lymphocytes produce certain cytokines such as IL-2 tumor necrosis factor (TNF)-α, TNF-δ, and granulocyte-macrophage colony-stimulating factor (GM-CSF) and play important roles in increasing delayed sensitivity and defense against intracellular pathogens. The differentiation of Th1 cells from naïve T cells depends on interferon (IFN) and IL-12 that express the T-bet factor, which is indeed the specific patterning factor of Th1 cells, by activating the signal transducers STAT-1 and then STAT-4. The T-bet factor leads to production of Th1 cytokines, especially IFN-δ, and therefore strengthens the differentiation of Th cells via developing a positive feedback ring. Meanwhile, the T-bet factor also leads to suppression of differentiation of other Th cell subgroups. IFN-δ is the most important cytokine of Th1 cells and leads to an increase in toll-like receptor expression, induction of immunoglobulin production, increase in phagocytosis, major histocompatibility complex classes I and II molecules, and alienation as well as activation of macrophages.[19]

Th17 cells produce a variety of cytokines, such as IL-17a, IL-17F, IL-6, IL-9, IL-21, IL-22, IL-23, TNF-α, GM-CSF, and IL-26. However, IL-17A is a specific cytokine of these cells. In humans, the effects of IL-17 in demyelinating nerve cells in MS patients have been demonstrated, and MS exacerbation is associated with an increase in the number of Th17 cells in the patients' blood. During the development of experimental autoimmune encephalomyelitis (EAE), Th17 cell infiltration occurs in the brain before the onset of clinical symptoms, while a significant Th1 cell infiltration occurs after the development of EAE.[20] The purpose of this article is to review the findings of the studies with animal models as well as clinical trials on the effects of medicinal plants and their compounds on MS (Table 1).

DISCUSSION

The use of medicinal plants has long been on the rise and the evidence indicates that this trend will predictably persist. The use of medicinal plants is more common in patients at risk

Table 1. Medicinal herbs and plant compounds affecting MS

The name of plant or compound	Concentration	Study design and subjects	Properties	Reference
Cannabis sativa	Oral use of *Cannabis sativa* extract 5-25 mg daily for 10 weeks	Double-blind, placebo-controlled clinical trial	Relaxation of stiff muscles after 4, 8, and 12 weeks of treatment compared to the placebo group	21
Delta-9 THC and CBD	Oral use of THC with CBD spray at 2.5 mg/spray for 8 weeks	Clinical trial Open-label pilot study	Reducing urinary urgency, urination frequency and urine volume, urinary incontinence and night time urination frequency after treatment; Decreasing daily total body weight, reducing catheterization and urinary incontinence; Relieving pain and improving muscle stiffness and the quality of sleep	22
Cannabis sativa	Aerial parts, ethanol extract, intraperitoneal administration of ΔTHC-rich9 extract at 50 mg/kg and CBD-rich extract at 50 mg/kg	Experimental study with mouse model of autoimmune encephalomyelitis (acute and chronic phase)	Reducing neurologic deficits after administration with ΔTHC-rich9 extract	23
Cannabis sativa	Capsule containing 2.5 mg THC and 0.9 mg CBD	Clinical trial; Double-blind, randomized design placebo controlled crossover; 57 patients, administration for 14 days	Improving spasm frequency, movement	24
Sativex	Sativex used as inhaled containing 2.7 mg THC and 2.5 mg CBD/spray puff	Double-blind, placebo-controlled clinical trial	160 patients Decreasing muscle spasm	25
β-SIT	1, 4, 16, 32 μM	Clinical trial, 11 female patients and 7 controls aged 18-65 years	β-sitosterol at 4 μM causes decrease in the release of TNF-α and at 4 and 16 μM causes decrease in the release of IL-12 in the PBMCs of multiple sclerosis patients	26
Curcumin (polymerized nano-curcumin)	Intraperitoneal administration of polymerized nano-curcumin at 12.5 mg/kg	Animal model of EAE, Female Lewis rats	Decreasing neurologic deficits, demyelination, inflammation, blood–brain barrier permeability, oxidative stress; Improving remyelination Increasing the precursor of cell marker	27
Lipia citriadora (lemon verbena)	Extract at 600 mg/day PLX capsules containing 10% verbascoside w/w administered for 28 days	Clinical trial; Double-blind, placebo-controlled 30 patients	Decreasing C-reactive protein, IFN-γ levels, IL-12 levels, IL-4 and IL-10 levels	28
Capparis ovata	Butanol fraction of hydroalcoholic extract	*In vitro* study with SH-SY5Y cell line	Inhibiting the expression of the genes below in cell lines: TNF-α, NF-κB1; GFAP, CXCL10, PTPN11	29
Pomegranate peel extract	Ethanol extract, intraperitoneal administration at 100 mg/kg for 8 days	*In vitro* study with female DA rat model of EAE	Inhibiting the production of IL-17 in the GALT cell line; Decreasing the production of IL-17 in the activated T cell of an animal model of EAE	30
Ginkgo biloba	120 mg/day for 8 weeks	Open study, 30 patients; Wechsler Memory Scale Beck Depression Inventory and the MSIS-29	Improving the scores on Wechsler Memory Scale and MSIS-29	31

Table 1. Continued

The name of plant or compound	Concentration	Study design and subjects	Properties	Reference
Boswellia papyrifera	Receiving two *Boswellia papyrifera* capsules (300 g) per day for 2 months	Randomized, double-blind clinical trial with 80 patients using Brief International Cognitive Assessment for MS	Improving spatial memory; Not influencing verbal memory and information processing speed	32
Crocus sativus L.	Receiving ethanol extract (500 mg/kg) by gavage for 21 days	Experimental study with C57BL/6 mouse model of EAE	Inhibiting leukocyte infiltration into the CNS and oxidative stress	33
Pterodon emarginatus seeds	Oral use of essential oil (50 and 100 mg/kg)	Mouse model of EAE	Decreasing neurologic deficits Inhibiting immune response by Th1 cell, axonal demyelination and neuronal death; Regulating Treg response *in vitro* Activating microglia and expressing iNOS	34
Oleanolic acid	Intraperitoneal administration at 50 mg/kg for 21-24 days	C57BL/J6 mice model of EAE	Improving the symptoms of neurologic deficits Decreasing blood–brain barrier permeability; Low inflammatory cell infiltration into the CNS; Playing a molecular role in Th1/Th2 polarization Inhibiting anti-inflammatory and chemical cytokines; Stimulating its anti-inflammatory effect	35

THC: Tetrahydrocannabinol, CBD: Cannabidiol, SIT: β-sitosterol, TNF: Tumor nuclear factor, IL: Interleukin, PBMC: Peripheral blood mononuclear cell, EAE: Experimental autoimmune encephalomyelitis, IFN: Interferon, NF-κB: Nuclear factor kappa B, GFAP: Glial fibrillary acidic protein, CXCL10: C-X-C motif chemokine 10, PTPN11: Tyrosine-protein phosphatase nonreceptor type 11, GALT: Gut-associated lymphoid tissue, MSIS-29: Multiple sclerosis impact scale-29, MS: Multipl sclerosis, CNS: Central nervous system, iNOS: Inducible nitric oxide synthase

than in healthy people. Due to the lack of strong evidence to support the effectiveness of the available treatments, the use of medicinal plants continues to increase in frequency. Despite the lack of controlled studies, there is a partial yet confirmed association between the dosage and the efficacy of medicinal plants.[36]

We conducted the current review to investigate the results of studies with animals and humans regarding the effects of medicinal plants and plant compounds on treatment of MS.

Most studies have been conducted with *Cannabis sativa* and its compounds. *C. sativa* has been used for several pharmaceutical purposes for 4000 years, but the structure and the properties of its compounds, such as cannabinoid, have been identified only in the last few years. To date, two cannabinoid receptors, CB1 and CB2, have been cloned. Endocannabinoids are metabolized by an amino acid called fatty acid amide hydrolase and monoglyceride lipase.[37]

The endocannabinoid system is currently the therapeutic target for treating many diseases, including MS. Clinical evidence confirms the therapeutic potential of cannabinoids to treat MS symptoms.[25] Numerous studies have been conducted to investigate the effects of cannabinoids in MS treatment, suggesting that they may yield improvements in spasticity, muscle spasm, neuropathic pain, and urinary tract complications in at least some patients. These studies are not longitudinal, with treatments of over 10 to 15 weeks.[22,38,39]

It is estimated that over 80% of MS patients suffer from spasticity. Oral antispasmodics such as baclofen and benzodiazepines often fail to control these symptoms and therefore new, effective, and safe drugs are required.[40,41] Nabiximols is a cannabinoid-based oral drug that is composed of tetrahydrocannabinol (THC) and cannabidiol (CBD) at a ratio of approximately 1:1 (2.7 mg THC and 2.5 mg CBD/100 mL).[42] Several randomized clinical trials have shown the efficacy of this drug in reducing limb spasticity and pain in MS patients.[25,43-46]

Studies showed that β-sitosterol and lemon verbena reduced the secretion of IL-12 and TNF-α in the peripheral blood mononuclear cells of MS patients.[26,28] Phytosterols and lemon verbena can affect the signaling pathways in tumor cells, including the stimulation of apoptotic pathways and the sphingomyelin cycle as well as the inhibition of prostaglandin release from macrophages in the culture medium. Therefore, a possible mechanism of these can be influencing certain signaling pathways that regulate the synthesis and release of cytokines.[26,28]

Based on preliminary research on cell cultures and animal models, pilot and clinical studies suggest that curcumin may be a therapeutic agent in several inflammatory diseases associated with Th17 cells such as MS, Alzheimer disease, Parkinson disease, inflammatory bowel disease, and rheumatoid arthritis. Curcumin, as an inhibitor of nuclear factor kappa B, is effective in preventing BBB breakdown caused by Th17 cells by influencing ZO-1 expression, inhibiting myosin light chain phosphorylation, and eliminating reactive oxygen species.[47]

Cognitive changes represent a major problem among MS patients that can simultaneously be more influential than the physical disabilities due to this disease. Ginkgo treatment for

8 weeks caused a significant improvement according to the Wechsler Intelligence Test.[31]

Punica granatum peel extract exerts significant immune effects that lead to prevention or treatment of EAE or streptozotocin-induced type 1 diabetes. This extract effectively inhibits the production of IL-17 in certain lymphatic tissues and also Th17 in the immune system.[30]

Cognitive impairments represent one of the most important disorders among MS patients, with a 43-70% prevalence rate.[48] *Boswellia papyrifera* can significantly improve the spatial memory of MS patients. Two studies have separately attributed the improving effects of *B. papyrifera* and *Crocus sativus* L. to their antioxidant properties.[32,33]

CONCLUSIONS

Taken together, phytotherapy is a useful approach to decrease MS symptoms and leads to reduction of fatigue, pain, and stress in MS patients. However, physicians and neurologists are recommended to gain certain information about complementary and alternative therapies and to assess the patients' experiences by discussing this area with them.

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