REVIEW

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The Efficacy of Some Herbal Therapies Preferred by Turkish MS Patients

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Abstract

Multiple sclerosis (MS), that is the most common non-traumatic cause of disability among young adults, is a chronic, progressive, inflammatory and neurodegenerative disease of the central nervous system. Despite recent remarkable advances in treatment, there is no cure for MS. Many unmet needs of persons with MS encourages them to use complementary and alternative medicines, especially herbal medicines, as a promising therapeutic option. Here, potential benefits and mechanisms of action of some herbal medicines preferred by Turkish MS patients are reviewed.

Keywords: Herbal therapy, medicinal plants, multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic, progressive, inflammatory and neurodegenerative disease of the brain and spinal cord characterized by myelin destruction and axonal loss. MS has a complex immunopathogenesis. It is presumed that, in MS, breakdown of peripheral tolerance mechanisms - through the defective/decreased T-regulatory (Treg) and B-regulatory lymphocytes, and less anti-inflammatory myeloid cells - changes the immune milieu towards a pro-inflammatory one which causes activation of previously dormant naive T cells, myeloid cells and B-cells via molecular mimicry, novel autoantigen presentation, CNS-sequestered antigens that leak to deep cervical lymph nodes or bystander activation (1,2). Naive T-cells differentiate into either pro-inflammatory effector T cell subsets including T helper (Th) 1 and Th 17 or anti-inflammatory Th 2 phenotype; depending on the cytokine environment which is modified by local antigen presenting cells and other immune cells.3,4 Th1 and Th17 are key players in MS immunopathogenesis. Th1 cells (driven by interferon-γ (IFNγ), interleukin (IL) 12, IL18) secretes IL2, tumor necrosis factor- α (TNFα) and IFNγ, and activates macrophages, natural killer cells, B cells and cytotoxic CD8+ Tcells. Th17 cells, differentiation induced by tissue growth factor-β (TGFβ), IL1, and IL6; secretes IL17 A-F, IL21, and IL22 and promotes the recruitment of other immune cells in inflammatory region (3,4). Activated T cells and inflammatory myeloid cells pass the blood-brain barrier (BBB), and infiltrates brain and spinal cord. Once in central nervous system, infiltrating myeloid cells release various pro-inflammatory cytokines, TNFα, IL1, IL6, and IL8, macrophage inflammatory protein 2, CXC-chemokines, which amplifies Th17 responses cause activation of resident microglia, effector T cell subsets' reactivation

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by myelin antigen, clonal expansion of T-effector cells and release of more inflammatory mediators which ultimately initiates an inflammatory cascade ending up with myelin, axon and oligodendrocyte destruction (1-4). The underlying chronic inflammation affects neurons and axons through a series of events such as oxidative stress, mitochondrial energy failure, ionic dyshomeostasis, and compromised protective and regenerative mechanisms eventually leading to neurodegeneration (1,2). This ongoing chronic inflammation and neurodegeneration increases the burden of disease over time and expose patients to a variety of neurological symptoms that are reflected in many aspects of their lives as increased disability. Relentless progressive course of the disease urge sufferers to use many complementary and alternative methods to relieve or control the symptoms due to MS.

Complementary and alternative medicine (CAM) use has gaining an increasing interest all over the world with a prevalence ranging from 9.8% to 76% (5). Studies have shown that individuals' preference for using CAM is affected by different factors. The most common causes are benefit expectation, dissatisfaction with conventional therapies, safety of CAM, easy access, affordability, internal health locus of control, and tradition (5). The methods and approaches the CAM umbrella covers are variable, including herbal therapy among many. Herbal therapy includes a range of pharmacologically active compounds and is employed for the treatment of a various diseases including MS. Research shows that more than one third of MS patients use at least one CAM at least once to improve the health and manage symptoms of MS; being more prevalent among women, those who have higher education and report worse health status (6,7). Homeopathy and diets are reported as the most common, and a perceived benefit reported by more than half (7). Though herbal therapy is practiced traditionally in Türkiye, its specific use by MS patients are reported in a few studies. In those, the ratio of herbal medicine use was between 10-49 %, and patients' knowledge about CAM was scarce in some (8,13). No relation has been reported between CAM use and socio-demographic features such as age, gender, education level, and disease related features such as disease duration, disability level and quality of life measures (8-10). Most commonly reported agents were capers, ginger, garlic, cumin seeds, primrose, flaxseed, St. John's wort, ginseng and turmeric (10-13).

The mechanisms of action of herbal therapy mainly depends on the bioactivities of the secondary metabolites. These often interact with major targets in cells, including enzymes, receptors, ion channels and pumps, or cytoskeletal elements (mostly tubulin or microtubules) and modulate these targets via alkaloids, phenolic compounds (e.g. flavonoids), terpenoids (e.g. saponins), polysaccharides or other secondary metabolites (14). Quite a lot of these plant-derived metabolites, either in original forms or synthetic derivatives, are used in medicine with established practices (14). Regarding MS, clinical and experimental studies have documented the beneficial effects of some herbal regimens on BBB permeability, inflammatory cell infiltration of the CNS, and T-cell polarization involved in MS pathogenesis; and some have been shown to have antiinflammatory and neuroprotective effects. Besides, many is used to relieve MS related symptoms such as fatigue, depression, cognitive impairment, spasticity, neuropathic pain, and urinary tract complications. In this review, different herbal medicines preferred by Turkish MS patients are reviewed in terms of their possible positive pharmacological effects.

Capers: Caper, a perennial shrub from the family of Capparaceae L, is typical of the Mediterranean flora known for its edible, brine flower buds and fruits and also for its therapeutic properties in various human ailments. The preferences for use in folk medicine are listed as antibacterial, antifungal, hepatoprotective, anthelmintic, antidiabetic, anti-inflammatory, anti-oxidant, anti-cancer, and antihyperlipidemic effects which have been ascribed to the phenolic acids, phytosterols, flavonoids, alkaloids, natural sugars, vitamins, and organic acids in content (15,16). The most widely studied *Capparis* species for their therapeutic and nutritional properties are Capparis ovata, *Capparis spinosa*, and *Capparis decidua*. Among these, *Capparis ovata* is the one whose impact was specifically evaluated in the experimental allergic encephalomyelitis models of multiple sclerosis. Caper is one of the most commonly used herb among MS patients. Though there is no human trial evaluating its efficacy on MS disease progress, in several experimental studies *Capparis ovata* has been found to inhibit and/or ameliorate experimental allergic encephalomyelitis (EAE) effectively in murine MS model and has been suggested as a new immune-regulatory and anti-inflammatory agent (17,18). Different studies report the effectiveness of Capparis ovata to inhibit the expression of pro-inflammatory and inflammatory genes, which are essential key players in MS pathophysiology, at a significant level including TNFα, IL6, IL17, glial fibrillary acidic protein, NFκβ (nuclear factor kappa-light-chain-enhancer of activated B cells), CC-chemokine ligand 5, CXC-chemokine 9,10, and tyrosine-protein phosphatase

nonreceptor type 11 and hypoxia-inducible factor-1 and also to enhance the up-regulation of the myelin basic protein and myelin-associated glycoprotein expression (16-19).

Ginger: Ginger (*Zingiber officinale* Roscoe) is a perennial herbaceous plant from the Zingiberaceae family, cultivated in sub-tropical regions and often ingested as a spice or dietary supplement and in folk medicine (20-22). It contains more than 400 different compounds and rich from terpenes, phenolic compounds, polysaccharides, lipids, organic acids, and raw fibers (20-22). Ginger is often considered a panacea due to its numerous effects including anti-pyretic, anti-inflammatory, antihyperglycaemic, antiapoptotic, anti-tumour, antioxidant, anti-diabetic, anti-clotting and analgesic properties. Health benefits are ascribed to its active phytoconstituents such as gingerols, shogaols, zingerone, paradols beside other phenolic compounds and flavonoids. In particular, gingerol has been reported to have anti-oxidative, anti-inflammatory, immune-modulatory and neuroprotective effects (20-22). The anti-inflammatory effect of ginger, either in the form of pure active ingredient or as an extract, has been studied in experimental MS models and have been found to effectively ameliorate the clinical and pathological disease severity (23,24). It has been shown to exhibit its effects chiefly via Th1, Th17, and B cell response down-regulation, chemokines and chemokine receptors expression down-regulation, and Treg response up-regulation (22-24). Besides, it modulates Th2-, Th9-, Th22 cell-related responses along with modulation of the pro-inflammatory and anti-inflammatory cytokines production, toll like receptor-related signaling and adhesion molecules expression (22,25). The immunomodulatory properties along with anti-oxidative features poses the ginger to be considered to have a therapeutic potential for the management of MS.

Garlic: Garlic (*Allium sativum L*) belongs to the lily family, and is recognized for anti-microbial, anti-neoplastic, anti-diabetes, anti-atherosclerosis, hepatoprotective and anti-inflammatory effects which are attributed to its organosulfur compounds. Among these are 'allicin, alliin, diallyl sulfide, diallyl di- and trisulfide, E/Z-ajoene, and S-allyl-cysteine (SAC)' (26). SAC has been shown to ameliorate clinical signs and severity of the EAE along with attenuation of inflammatory cell infiltration, axonal demyelination, and axonal loss in lumbar spinal cord (27). The anti-inflammatory effects of garlic is suggested to occur by reduced activation of microglia and astrocytes, decreased expression of IL1β, NFκB, Toll-like receptor-4, nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase 1 in microglial cells and increased number of Treg cells (28,29). In addition, it has also been found to be a potent reactive-oxygen scavenger with its enhancing and regulatory effects on the antioxidant enzymes (28).

Black Cumin: *Nigella sativa* Linn is an annual indigenous herbaceous plant from the Ranunculaceae family and known as black seed or black cumin (30). Seed and oil of N. sativa have a long history of folkloric usage and regarded as a valuable traditional remedy to treat all ailments except to prevent from death (31). Black cumin seeds are rich from various chemical components including fixed and essential oil, alkaloids, carvacrol, proteins, saponin, terpenoids, quinones (such as thymoquinone, nigellone, and thymohydroquinone), minerals and vitamins (30). Beneficial effects attributed to N. sativa are mainly due to quinone ingredients of which thymoquinone is the major and most abundant bioactive component (31,32). Among many, some of the reported biological properties of N. sativa are antimicrobial, antioxidant, anti-inflammatory, anticancer, antidiabetic, cardio-protective and neuroprotective properties (31,32). In experimental studies N. sativa oil and extracts has been postulated to modulate cellular and humoral immune responses (32). The mechanisms underlying the immunomodulatory effects of thymoquinone results from its inhibitory effect on NFκβ, mitogen-activated protein kinase (MAPK) and janus kinase (JAK)/signal transduction and activator of transcription (STAT) signaling pathways (33). By this way, thymoquinone inhibits NFκβ-mediated neuroinflammation and production of inflammatory mediators (NO, PGE2, TNF-a, and IL1b) (33-35). It also attenuates neuroinflammation by decreasing a set of cytokines including IL1, IL6, IL12, monocyte chemoattractant protein 1 and 5, granulocyte colony-stimulating factor, and CXCL10/IFN-γ' induced protein 10 in microglia cells in rats (36). In EAE, protective treatment with N. sativa has been shown to reduce days of relapses significantly, ameliorate the clinical manifestations and decrease the severity of the disease (37-39).

Evening primrose: Evening primrose (*Oenothera biennis L*) is a wild medicinal plant from the Onagraceae family. *Oenothera biennis L* is the most commonly and best-studied species in the Oenothera L family which originated from Central America and now naturalized worldwide (40-41). Evening primrose have been preferred for treating a wide variety of ailments including premenstrual syndrome, asthma, eczema, inflammation, arthritis, metabolic disorders, headaches and eruptions of the skin (42). Evening primrose oil, extracted from its seeds, is rich from

omega-6 essential fatty acids (FA); 70-74% of its components are linoleic acid and about 8-10% γ-linolenic acid along with other fatty acids (palmitic, oleic, & stearic acids) and campesterol and β-sitosterol steroids (41). Linoleic acid and γ-linolenic acid are precursors of anti-inflammatory eicosanoids, major components of myelin and the neuronal cell membrane and contributes to the fluidity and flexibility of cell membranes. Evening primrose oil supplementation increases the plasma levels of γ-linolenic acid and its metabolite dihomo-γ-linolenic acid which lead to production of anti-inflammatory eicosanoids (41,43). Besides, 15-hydroxyeicosatrienoic acid, metabolized from dihomo-γ-linolenic acid inhibits the conversion of arachidonic acid to leukotriene A4, hence prevents the pro-inflammatory action of leukotrienes (41,43). Moreover, γ-linolenic acid has been reported to suppress inflammation mediators such as IL1, IL6, TNFα by inhibiting NFκβ activation (44).

In hemp seed oil/evening primrose oil treated C57BL/6 mice with EAE, Rezapour-Firouzi et al have shown a significant increase in the expression of IL10 and mTOR complex 2 (RICTOR) genes along with a remarkably reduced cell infiltration and promoted remyelination (45). Moreover, evening primrose/hemp seed oil administration prevented the development of EAE and the attenuated the severity of the disease in EAE induced models (45). Evening primrose/hemp seed oil treatment significantly inhibited the expression of the regulatory-associated protein of mammalian target of rapamycin (RAPTOR), interferon-gamma, IL17, signal transducer and activator of transcription factors (STAT3) genes and promoted the expression of regulatory-associated companion of mammalian target of rapamycin (RICTOR), forkhead box P3 (FoxP3) and IL10 genes (46).

In a clinical study on 100 relapsing-remitting MS patients, the effects of evening primrose/hemp seed oil and olive oil were evaluated. At the end of the study, patients on the evening primrose/hemp seed oil group has been reported to show significantly better disability scores and reduced relapse rate compared to olive oil group (47). In another study on 52 MS patients, evening primrose oil consumption for 3 months along with their immunomodulator drugs for their disease provided better outcomes involving cognitive function, pain, fatigue, and overall life satisfaction compared to placebo (48).

Flaxseed: Flaxseed, *Linum usitatissimum*, whose Latin name means very useful, is one of the oldest crops grown widely all over the world (49). It has been reported to have potential health imparting benefits at reducing the risk of some disease including cardiovascular diseases, cancer, arthritis, menopausal symptoms and osteoporosis with its antitumoral, antioxidant, and anti-inflammatory effects (49-51). Flaxseed is the richest plant source of polyunsaturated fatty acids (PUFA); linoleic acid (omega-6) and α-linolenic acid (omega-3,) with a ratio of approximately 0.3:1, which are dietary essential fatty acids that cannot be synthesized by humans (49,52). It also contains monounsaturated FAs and at a much lesser amount saturated FAs. Omega-3 PUFAs (docosahexaenoic acid, eicosapentaenoic acid and alpha-linolenic acid) exhibits anti-inflammatory properties. Besides, it is also a good reservoir of lignans, phytoestrogens, phenolic compounds, dietary and protein fiber, minerals, and vitamins (A, C, and E) (49). Flaxseed shows direct antiatherogenic, anti-inflammatory and immunomodulatory effects through leukocyte adhesion inhibition, the proinflammatory eicosanoids production decrease, and cellular migration and proliferation inhibition with abundant omega-3 it contains (53). Although results of two recent meta-analysis are controversial, flaxseed supplementation has been reported to modulate the levels of some circulating inflammatory biomarkers including C-reactive protein, IL6, TNFα, NFκβ, macrophage marker mac-3, vascular cell adhesion protein 1, E-selectin, and intercellular adhesion molecule 1(53-55).

Data from a large international MS cohort suggest a significant association for omega 3 supplementation with flaxseed, showing reduced relapse rate and reduced likelihood of worsening relapse rate (56). However, a recent Cochrane analysis, evaluating the efficacy of PUFAs and monounsaturated fatty acids, states the uncertainty of evidence in terms of disability worsening, relapse rate, or overall health status in persons with MS (57).

St. John's wort: St. John's wort (*Hypericum perforatum L.*) is a perennial herb from the family Hypericaceae (58). Traditionally, it has been used orally and topically for the treatment of several human ailments, including burns, wounds, hemorroids, diarrhea, and ulcers and depression (58). St. John's wort contains naphthodianthrones (hypericin, pseudohypericin, protohypericin, protopseudohypericin, and cyclopseudohypericin), flavonoids (rutin, hyperoside, quercetin, quercitrin and luteolin), acylphloroglucinols (hyperforin and adhyperforin), proanthocyanidins, procyanidines, several amino acids, and tannins (59). St. John's wort preparations are widely investigated for their antidepressant activity but also for their antioxidant, anxiolytic, anticancer, and anti-inflammatory activities (58,59). Hyperforin

Table 1 Summary of he effects of herbal medicines used in multiple sclerosis and EAE models

Plant		Compound	Study group	Effect	Reference
Caper	*Capparis ovata* *Capparis spinosa*	β-sitosterol	EAE Human PBMC	↓ TNFα, IL-6, NF-κB, CCL5, CXCL9, CXCL10, HIF1A gene expression ↓ IL-17 & ↑ IL-4 gene expression	17-19 16
Ginger	*Zingiber officinale*	Gingerol	EAE	↓ Clinical disease score, ↓ inflammatory cell infiltration in CNS ↓ Th1, Th17 & B cell-related response ↑Treg cell response, TGF-β expression ↓ IL-17, IL-27, IL-33 TNF-α, CCL20, CCL22, CCR6, CCR4 expression	20-25
Garlic	*Allium sativum L*	S-allyl-cysteine	EAE	↓ Clinical disease score, ↓ inflammatory cell infiltration in CNS ↓ IL1β, NFκB, TLR-4, Nrf2 & heme oxygenase 1 in microglial cells ↑ Treg cell frequency	27 -29
Black Cumin	*Nigella sativa*	Thymoquinone	EAE	↓ Clinical disease score, ↓ inflammatory cell infiltration in CNS ↓ Reactive astrocytes number, ↑ remyelination ↓ NF-κB, MAPK, JAK/STAT signaling pathway ↓NO, PGE2, TNFα, IL1, IL6, IL12	32-39
Evening primrose	*Oenothera biennis L*	Linoleic acid, γ-linolenic acid	EAE Human	↑ IL10, RICTOR, FoxP3 gene expression ↓ IL1, IL6, IL17,TNFα IF-γ, NFκβ, RAPTOR, STAT3 expression ↓ Cell infiltration, ↑ remyelination ↓ Relapse rate, disability Better quality of life	44-46 47, 48
Flaxseed	*Linum usitatissimum*	Linoleic acid, α-linolenic acid	Acute inflammation Human	↓ NFκβ, reactive oxygen species ↓ cRP, IL6, VCAM-1, no effect on TNFα, E-selectin, ICAM-1 ↓ hs-CRP & TNFα; no effect on IL6 & cRP ↓ Relapse rate & disability No evidence of certain effects on disability & relapse rate	51 54 55 56 57
St. John's wort	*Hypericum perforatum L.*	Hyperforin	EAE	↓ Clinical disease score, ↓ inflammatory cell infitration in CNS ↓ Th1 & Th17 cells differentiation ↑ Th2 and Treg cell differentiation	60,61
Ginseng	*Panax ginseng C.A. Meyer*	Ginsenosides	EAE Human	↓ BBB permeability ↓ IL1, IL6, NFκβ; ↑ IGF-1, TGFβ, and VEGF-1 ↓ Th1 & Th17 cells; ↑ Treg cells Effect on fatigue: controversial results	64-67 68,69
Turmeric	*Curcuma longa*	Curcumin	EAE Human	↓ Clinical severity of EAE ↓ Astrocytes proliferation, ↑ myelinogenesis, oligodendrocyte activity ↓ IL1, IL6, IL17, IL21, IL23, NF-kB, TNF-α , IFN-γ, STAT3, RORγt ↑ IL4, IL10, FOXP3 & TGF-β ↑ Treg cells ↑ FoxP3, TGF-β, IL-10 expression	70-75 76-78

is the major lipophilic constituent responsible for the anti-depressant and anti-inflammatory activities of *H. perforatum* (58,59).

In EAE models St. John's wort extract and hyperforin has been shown to reduce the incidence and severity of the disease, through decreasing the inflammatory cell infiltration (60,61). Furthermore, it inhibits Th1 and Th17 cells differentiation and promotes Th2 and Treg cell differentiation through regulation of their transcription factors Foxp3, T-bet, ROR-γt and GATA3 (60).

Ginseng: Ginseng, called the king of all herbs, is a deciduous perennial plant from the Panax genus and

belongs to the Araliaceae family (62,63). The plant is indigenous to the East Asia and consists of about 20 species or variants among which '*Panax ginseng C.A*. Meyer (Asian or Korean ginseng), *Panax quinquefolius L* (American ginseng) and *Panax notoginseng*' (Sanchi ginseng) are the most widely used ones as traditional remedy for thousands of years (62,63). The major bioactive compounds of the genus Panax are ginsenosides or ginseng saponins and gintonins (63). Ginsenosides have been reported to show their effect by interaction with membrane ion channels, cell membranes, and extra-/intracellular receptors, thus promoting alterations at the transcriptional level with resultant immune-regulatory, anti-oxidant, anti-cancer and anti-inflammatory, anti-nociceptive, anti-apoptotic and neuroprotective effects (62-64). Neuroprotective effects are proposed to be via cholinergic recovery, regulation of brain-derived neurotrophic factor, and activation of the Akt/mTOR signal pathway in addition to the main mechanisms described above (64).

In EAE models ginseng has been shown to ameliorate the clinical severity of disease through BBB permeability, negative regulation of pro-inflammatory cytokine expressions (TNFα, IL1β, and IL6), Th1 and Th17 cells suppression, Treg cells upregulation, the p38 MAPK/ NFκβ signaling pathway downregulation, and growth factors (IGF-1, TGFβ, and VEGF-1) expression enhancement (65,66). Besides, ginseng and its non-saponin fraction has also been reported to enhance innate immunity and attenuate cytokine production via Toll-like receptor (TLR)4/myeloid differentiation primary response 88 (MyD88)/nuclear factor (NF)-κB signaling pathway inhibition. All these studies suggest that P. ginseng and related materials (extract, fraction, components, etc.) might have a potential and be a good candidate for multi-targeted approaches in the treatment of MS (67). However, in two double-blind, placebo-controlled clinical trials comparing the effect of ginseng on fatigue in multiple sclerosis patients controversial results has been reported though both state its use as safe (68,69).

Turmeric: Recognized as 'spice of life' or 'golden spice' turmeric (*Curcuma longa* Linn) contains curcumin as the main active component which can easily pass through all cell membranes and BBB due to its lipophilic properties (70). Curcumin has a plethora of broad therapeutic potential with anti-oxidant and anti-inflammatory and neuroprotective properties and have been assessed in many neurodegenerative diseases (70,71). Curcumin's anti-inflammatory activity is due to the modulation of inflammatory responses through down-regulation of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) activities, inhibition of NFκβ pathway, inhibition of TNFα, IL1, IL2, IL6, IL8, and IL12, MCP, and migration inhibitory protein production; activation of adenosine monophosphate (AMP)-activated protein kinase/silent mating type information regulation 2 homolog 1 (AMPK/SIRT1) axis,and down-regulation of the Janus kinase 2 /signal transducers and activators of transcription 3 (JAK2/STAT3) signaling pathway (70-73). Treatment with curcumin has been shown to reduce the clinical severity of EAE significantly and also ameliorate neuroinflammation by down-regulating Th17 production, inhibiting Th1 differentiation and increasing Th2 polarization (70-76). Curcumin has been shown to reduce the inflammatory cells infiltration and demyelination (70-72,74). Besides, reduced astrocytes proliferation, improved myelogenesis due to enhanced repair mechanisms, and activity and differentiation of oligodendrocytes have also been reported with curcumin treatment (71,72). These ameliorative effects of curcumin is mainly via changed cytokines expression profile in favor of anti-inflammatory mediators. The decrease of the pro-inflammatory gene expression of NFκβ, IL1, IL17, IFNγ, TNFα, MCP-1 RAR-related orphan receptor gamma (RORγt), and STAT3, and a robust increase of the anti-inflammatory gene expression IL4, IL10, FoxP3 and TGFβ have been convincingly reported (70-72,75).

In two placebocontrolled studies MS patients who were on interferonβ-1a treatment were supplemented with curcumin for 6 months. It has been shown that curcumin treatment resulted in significant decrease in the proportion of Th17 cells and expression level of RORγt and IL-17; and also an increased expression of FoxP3, TGF-β, and IL-10 as well as restoration of Treg cells frequency and function (76,77). In another study the effect of curcumin as an add-on therapy on new/ enlarging T2 lesions in relapsing remitting MS patients under treatment with subcutaneous interferon-β failed to reveal any beneficial effect in comparison to placebo group. However, the authors also note that the study drop-out rate was higher than expected and therefore no definite conclusion can be drown (78).

In these clinical and in-vitro and in-vivo trials curcumin's outstanding anti-inflammatory and neuroprotective effects has been shown convincingly and has been suggested as a promising nutraceutical agent with a therapeutic potential in the management of MS, however in demand of more clinical trials (74).

Aloysia citrodora (Lemon verbena), *Andrographis paniculata* (creat or green chiretta), *Boswellia papyrifera* (Sudanese frankincense), *Camellia*

sinensis (Green Tea), *Ginkgo biloba*, *Ruta graveolens* (common rue or herb-of-grace), and *Vaccinium spp*. (Cranberry) and Cannabis sativa are other herbal plants tried to relieve symptoms of MS (42). Among these, only extracts of Cannabis sativa L has been developed by the pharmaceutical industry and was approved as a legal therapeutic option in MS-related spasticity, neuropathic pain, and urinary symptoms in some countries. In numerous studies cannabinoids, bioactive constituent of cannabis-cannabidiol and tetrahydrocannabinol, have been shown to reduce cytokine production, induce apoptosis, inhibit cell proliferation and enhance T regulatory cell function (78-80). In a recent meta-analysis covering 3161 MS patients, results favored cannabinoid use for spasticity, pain and bladder dysfunction but with limited efficacy (81). In Türkiye cannabis use is illegal and under strict legal regulations.

Conclusion

In this article, the efficacy and mechanism of action of some herbal therapies, mainly preferred by Turkish MS patients are reviewed. A growing body of information has been gathered about the beneficial effects of herbal therapy to alleviate or suppress inflammation, oxidative stress and hence promote neuroprotection from some experimental and clinical studies. Also herbal therapy is reported to be natural, safe and reliable for the treatment of many medical conditions (42). However, the evidence is scarce to recommend their use, except a few (6). Given the complex nature of the disease and the polypharmacy the patients are on, concurrent use of herbs with MS drugs may be risky and may cause severe side effects. In conclusion, MS patients should be informed about herbal remedies and should be advised to be cautious.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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References

1. Dendrou CA, Fugger L, Friese MA. Immunopathology of Multiple Sclerosis. Nat Rev Immunol 2015 Sep 15;15(9):545-58. doi: 10.1038/nri3871.
2. Haase S, Linker RA. Inflammation in Multiple Sclerosis. Ther Adv Neurol Disord 2021;14:17562864211007687. doi: 10.1177/17562864211007687.
3. Kunkl M, Frascolla S, Amormino C, Volpe E, Tuosto L. T Helper Cells: the Modulators of Inflammation in Multiple Cclerosis Cells 2020;9(2):482. doi: 10.3390/cells9020482.
4. Ivanova EA, Orekhov AN. T Helper Lymphocyte Subsets and Plasticity in Autoimmunity and Cancer: An Overview. Biomed Res Int 2015;2015:327470. doi: 10.1155/2015/327470.
5. Tangkiatkumjai M, Boardman H, Walker DM. Potential Factors that Influence Usage of Complementary and Alternative Medicine Worldwide: A Systematic Review. BMC Complement Med Ther 2020;20(1):363. doi: 10.1186/s12906-020-03157-2.
6. Yadav V, Bever C Jr, Bowen J, Bowling A, Weinstock-Guttman B, Cameron M, Bourdette D, Gronseth GS, Narayanaswami P. Summary of Evidence-Based Guideline: Complementary and Alternative Medicine in Multiple Sclerosis: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;82(12):1083-92. doi: 10.1212/WNL.0000000000000250.
7. Pucci E, Cartechini E, Taus C, Giuliani G. Why Physicians Need to Look More Closely at the use of Complementary and Alternative Medicine by Multiple Sclerosis Patients. Eur J Neurol 2004;11(4):263-7. doi: 10.1046/j.1468-1331.2003.00758.x.
8. Gedizlioğlu M, Yumurtaş S, Trakyalı AU, Yıldırım F, Ortan P, Köşkderelioğlu A. Complementary and Alternative Therapy Use in Multiple Sclerosis: A Cross-Sectional Survey. Turk J Neurol 2015; 21(1): 13-15. Doi:10.4274/tnd.46354
9. Duru Aşiret G, Düğer Ü, Kapucu S, Tuncer Kurne A, Karabudak R. Multiple Skleroz Hastalarının Tamamlayıcı ve Alternatif Tedavi Kullanım Durumlarının Belirlenmesi. Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi 2017;6:1-6.
10. Çelik RGG, Öztürk M, Altın S, Köseoğlu M, Sariahmetoğlu H, Tütüncü M, et al. The Prevalence of Alternative-Complementary Therapies in Patients with Multiple Sclerosis. Turk J Neurol 2019; 25(3): 153-58. doi: 10.4274/tnd.2019.04207
11. Dağlı S, Ünlü MD, Demirci S. Complementary and alternative medicine use in Multiple Sclerosis. 2nd International Turkic World Congress of Multiple Sclerosis 2020 Abstract Book, pp: 31.
12. Aksoy S, Şengül Y, Karaman HIÖ. Multipl Skleroz Hastalarına Tamamlayıcı ve Alternatif Tıp Yöntemlerine Başvurunun Demografik ve Klinik Korelasyonlarının Değerlendirilmesi. 2nd International Turkic World Congress of Multiple Sclerosis 2020 Abstract Book, pp: 16-17.
13. Dayapoğlu N, Tan M. Use of Complementary and Alternative Medicine Among People with Multiple Sclerosis in Eastern Turkey. Neurology Asia 2016; 21(1): 63-71.
14. Wink M. Modes of Action of Herbal Medicines and Plant Secondary Metabolites. Medicines (Basel) 2015;2(3):251-86. doi: 10.3390/medicines2030251.
15. Gazioglu I, Semen S, Acar OO, Kolak U, Sen A, Topcu G. Triterpenoids and Steroids Isolated from Anatolian Capparis Ovata and Their Activity on the Expression of Inflammatory Cytokines. Pharm Biol 2020;58(1):925-31. doi: 10.1080/13880209.2020.1814356.
16. Moutia M, El Azhary K, Elouaddari A, Al Jahid A, Jamal Eddine J, Seghrouchni F, et al. Capparis Spinosa L. Promotes Anti-Inflammatory Response In Vitro Through the Control of Cytoki-

ne Gene Expression in Human Peripheral Blood Mononuclear Cells. BMC Immunol 2016;17(1):26. doi: 10.1186/s12865-016-0164-x.
17. Ozgun-Acar O, Celik-Turgut G, Gazioglu I, Kolak U, Ozbal S, Ergur BU, et al. Capparis Ovata Treatment Suppresses Inflammatory Cytokine Expression and Ameliorates Experimental Allergic Encephalomyelitis Model of Multiple Sclerosis in C57BL/6 Mice. J Neuroimmunol 2016;298:106-16. doi: 10.1016/j.jneuroim.2016.07.010.
18. Ozgun-Acar O, Gazioglu I, Kolak U, Sen A, Topcu G. A Potential Therapeutic Role in Multiple Sclerosis for Stigmast-5,22-Dien-3b-ol Myristate Isolated from Capparis Ovata. Eurobiotech J 2017;1(3):241-46.
19. Sen A, Topcu G, Ozgun O, Kolak U, Hacibekiroglu I, Celik G, et al. Anti-Neuroinflammatory Effect of Butanolic Fraction of Capparis Ovata Water Extract Used as an Alternative and Complementary Treatment for Multiple Sclerosis. J Neuroimmunol 2014;275(1-2):172-73.
20. Choi JG, Kim SY, Jeong M, Oh MS. Pharmacotherapeutic Potential of Ginger and its Compounds in Age-Related Neurological Disorders. Pharmacol Ther 2018;182:56-69. doi: 10.1016/j.pharmthera.2017.08.010.
21. Mao QQ, Xu XY, Cao SY, Gan RY, Corke H, Beta T, et al. Bioactive Compounds and Bioactivities of Ginger (Zingiber Officinale Roscoe). Foods 2019;8(6):185. doi: 10.3390/foods8060185.
22. Jafarzadeh A, Nemati M. Therapeutic Potentials of Ginger for Treatment of Multiple Sclerosis: A Review with Emphasis on its Immunomodulatory, Anti-Inflammatory and Anti-Oxidative Properties. J Neuroimmunol 2018;324:54-75. doi: 10.1016/ j.jneuroim.2018.09.003.
23. Han JJ, Li X, Ye ZQ, Lu XY, Yang T, Tian J, et al. Treatment with 6-Gingerol Regulates Dendritic Cell Activity and Ameliorates the Severity of Experimental Autoimmune Encephalomyelitis. Mol Nutr Food Res 2019;63(18):e1801356. doi: 10.1002/mnfr.201801356
24. Jafarzadeh A, Mohammadi-Kordkhayli M, Ahangar-Parvin R, Azizi V, Khoramdel-Azad H, Shamsizadeh A, et al. Ginger Extracts Influence the Expression of IL27 and IL-33 in the Central Nervous System in Experimental Autoimmune Encephalomyelitis and Ameliorates the Clinical Symptoms of Disease. J Neuroimmunol 2014;276(1-2):80-8. doi: 10.1016/ j.jneuroim.2014.08.614.
25. Ho SC, Chang KS, Lin CC. Anti-Neuroinflammatory Capacity of Fresh Ginger is Attributed Mainly to 10-Gingerol. Food Chem 2013;141(3):3183-91. doi: 10.1016/j.foodchem.2013.06.010.
26. Shang A, Cao SY, Xu XY, Gan RY, Tang GY, Corke H, et al. Bioactive Compounds and Biological Functions of Garlic (Allium sativum L.). Foods 2019;8(7):246. doi: 10.3390/foods8070246.
27. Zeinali H, Baluchnejadmojarad T, Fallah S, Sedighi M, Moradi N, Roghani M. S-allyl Cysteine Improves Clinical and Neuropathological Features of Experimental Autoimmune Encephalomyelitis in C57BL/6 Mice. Biomed Pharmacother 2018;97:557-63. doi: 10.1016/j.biopha.2017.10.155.
28. Song H, Cui J, Mossine VV, Greenlief CM, Fritsche K, Sun GY, et al. Bioactive Components from Garlic on Brain Resiliency Against Neuroinflammation and Neurodegeneration. Exp Ther Med 2020;19(2):1554-59. doi: 10.3892/etm.2019.8389.
29. Abdullah A, Maged M, Hairul-Islam M I, Osama I A, Maha H, Manal A, et al. Activation of Aryl Hydrocarbon Receptor Signaling by a Novel Agonist Ameliorates Autoimmune Encephalomyelitis. PLoS One 2019;14(4):e0215981. doi: 10.1371/journal.pone.0215981.
30. Sıcak Y, Erdoğan Eliuz EA. Chemical Content and Biological Activity Spectrum of Nigella Sativa Seed Oil. KSU J Agric Nat 2019;22(5):928-34. doi: 10.18016/ksutarimdoga.vi.537674.
31. Dalli M, Bekkouch O, Azizi SE, Azghar A, Gseyra N, Kim B. Nigella sativa L. Phytochemistry and Pharmacological Activities: A Review (2019-2021). Biomolecules 2021;12(1):20. doi: 10.3390/biom12010020.
32. Majdalawieh AF, Fayyad MW. Immunomodulatory and Anti-Inflammatory Action of Nigella Sativa and Thymoquinone: A Comprehensive Review. Int Immunopharmacol 2015;28(1):295-304. doi: 10.1016/j.intimp.2015.06.023
33. Ali MY, Akter Z, Mei Z, Zheng M, Tania M, Khan MA. Thymoquinone in Autoimmune Diseases: Therapeutic Potential and Molecular Mechanisms. Biomed Pharmacother 2021;134:111157. doi: 10.1016/j.biopha.2020.111157
34. Wang Y, Gao H, Zhang W, Zhang W, Fang L. Thymoquinone Inhibits Lipopolysaccharide-Induced Inflammatory Mediators in BV2 Microglial Cells. Int Immunopharmacol 2015;26(1):169-173. doi: 10.1016/j.intimp.2015.03.013
35. Velagapudi R, Kumar A, Bhatia HS, El-Bakoush A, Lepiarz I, Fiebich BL, et al. Inhibition of Neuroinflammation by Thymoquinone Requires Activation of Nrf2/ARE Signalling. Int Immunopharmacol 2017;48:17-29. doi: 10.1016/j.intimp.2017.04.018
36. Taka E, Mazzio EA, Goodman CB, Redmon N, Flores-Rozas H, Reams R, et al. Anti-Inflammatory Effects of Thymoquinone in Activated BV-2 Microglial Cells. J Neuroimmunol 2015;286:5-12. doi: 10.1016/j.jneuroim.2015.06.011
37. Fahmy HM, Noor NA, Mohammed FF, Elsayed AA, Radwan NM. Nigella Sativa as an Anti-Inflammatory and Promising Remyelinating Agent in the Cortex and Hippocampus of Experimental Autoimmune Encephalomyelitis-Induced Rats. J Basic Appl Zool 2014;67(5):182-95. doi:10.1016/j.jobaz.2014.08.005.
38. Mohamed A, Afridi DM, Garani O, Tucci M. Thymoquinone Inhibits the Activation of NF-KappaB in the Brain and Spinal Cord of Experimental Autoimmune Encephalomyelitis. Biomed Sci Instrum 2005;41:388-93.
39. Noor NA, Fahmy HM, Mohammed FF, Elsayed AA, Radwan NM. Nigella Sativa Amliorates Inflammation and Demyelination in the Experimental Autoimmune Encephalomyelitis-Induced Wistar Rats. Int J Clin Exp Pathol 2015;8(6):6269-86.
40. Yüzbaşıoğlu İS. Oenothera Parodiana (Onagraceae): A New Alien Species Record for the Flora of Turkey. Biological Diversity and Conservation 2014;7(2):122-126.
41. Timoszuk M, Bielawska K, Skrzydlewska E. Evening Primrose (Oenothera Biennis) Biological Activity Dependent on Chemical Composition. Antioxidants (Basel) 2018;7(8):108. doi: 10.3390/antiox7080108.
42. Farzaei MH, Shahpiri Z, Bahramsoltani R, Nia MM, Najafi F, Rahimi R. Efficacy and Tolerability of Phytomedicines in Multiple Sclerosis Patients: A Review. CNS Drugs 2017;31(10):867-89. doi: 10.1007/s40263-017-0466-4.
43. Kapoor R, Huang YS. Gamma Linolenic Acid: An Antiinflammatory Omega-6 Fatty Acid. Curr Pharm Biotechnol 2006;7(6):531-4. doi: 10.2174/138920106779116874.
44. Cao D, Luo J, Zang W, Chen D, Xu H, Shi H, Jing X. Gamma-Linolenic Acid Suppresses NFκβ Signaling Via CD36 in the Lipopolysaccharide-Induced Inflammatory Response in Primary Goat Mammary Gland Epithelial Cells. Inflammation 2016;39(3):1225-37. doi: 10.1007/s10753-016-0358-7.
45. Rezapour-Firouzi S, Kheradmand F, Shahabi S, Tehrani AA, Mazloomi E, Mohammadzadeh A. Regulatory Effects of Hemp Seed/Evening Primrose Oil Supplement in Comparison With Rapamycin on the Expression of the Mammalian Target of Rapamycin-Complex 2 and Interleukin-10 Genes in Experimental Autoimmune Encephalomyelitis. Res Pharm Sci 2019;14(1):36-45. doi: 10.4103/1735-5362.251851.
46. Rezapour-Firouzi S, Mohammadian M, Sadeghzadeh M, Mehranfar S, Mazloomi E. The Effects of Evening Primrose/Hemp Seed Oil Compared to Rapamycin on the Gene Expression of Immunological Parameters in Experimental Autoimmune Encephalomyelitis Splenocytes. Iran J Allergy Asthma Immunol 2020;19(2):183-92. doi: 10.18502/ijaai.v19i2.2771.
47. Rezapour-Firouzi S, Arefhosseini SR, Mehdi F, Mehrangiz EM, Baradaran B, Sadeghihokmabad E, et al. Immunomodulatory and Therapeutic Effects of Hot-Nature Diet and Co-Supplemented Hemp Seed, Evening Primrose Oils Intervention in Multiple

Sclerosis Patients. Complement Ther Med 2013;21(5):473-80. doi: 10.1016/j.ctim.2013.06.006.
48. Majdinasab N, Namjoyan F, Taghizadeh M, Saki H. The Effect of Evening Primrose Oil on Fatigue and Quality of Life in Patients with Multiple Sclerosis. Neuropsychiatr Dis Treat 2018;14:1505-12. doi: 10.2147/NDT.S149403.
49. Goyal A, Sharma V, Upadhyay N, Gill S, Sihag M. Flax and Flaxseed Oil: An Ancient Medicine & Modern Functional Food. J Food Sci Technol 2014;51(9):1633-53. doi: 10.1007/s13197-013-1247-9.
50. Rafieian-Kopaei M, Shakiba A, Sedighi M, Bahmani M. The Analgesic and Anti-Inflammatory Activity of Linum usitatissimum in Balb/c Mice. J Evid Based Complementary Altern Med 2017;22(4):892-96. doi: 10.1177/2156587217717416.
51. Chera EI, Pop RM, Pârvu M, Soriţău O, Uifălean A, Cătoi FA, et al. Flaxseed Ethanol Extracts' Antitumor, Antioxidant, and Anti-Inflammatory Potential. Antioxidants (Basel) 2022;11(5):892. doi: 10.3390/antiox11050892.
52. Benatti P, Peluso G, Nicolai R, Calvani M. Polyunsaturated Fatty Acids: Biochemical, Nutritional and Epigenetic Properties. J Am Coll Nutr 2004;23(4):281-302. doi: 10.1080/07315724.2004.10719371.
53. Dupasquier CM, Dibrov E, Kneesh AL, Cheung PK, Lee KG, Alexander HK, et al. Dietary Flaxseed Inhibits Atherosclerosis in the LDL Receptor-Deficient Mouse in Part Through Antiproliferative and Anti-Inflammatory Actions. Am J Physiol Heart Circ Physiol 2007;293(4):H2394-402. doi: 10.1152/ajpheart.01104.2006.
54. Askarpour M, Karimi M, Hadi A, Ghaedi E, Symonds ME, Miraghajani M, et al. Effect of Flaxseed Supplementation on Markers of Inflammation and Endothelial Function: A Systematic Review and Meta-Analysis. Cytokine 2020;126:154922. doi: 10.1016/j.cyto.2019.154922.
55. Rahimlou M, Jahromi NB, Hasanyani N, Ahmadi AR. Effects of Flaxseed Interventions on Circulating Inflammatory Biomarkers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Adv Nutr 2019;10(6):1108-119. doi: 10.1093/advances/nmz048.
56. Jelinek GA, Hadgkiss EJ, Weiland TJ, Pereira NG, Marck CH, van der Meer DM. Association of Fish Consumption and Ω 3 Supplementation with Quality of life, Disability and Disease Activity in an International Cohort of People with Multiple Sclerosis. Int J Neurosci 2013;123(11):792-800. doi: 10.3109/00207454.2013.803104.
57. Parks NE, Jackson-Tarlton CS, Vacchi L, Merdad R, Johnston BC. Dietary Interventions for Multiple Sclerosis-Related Outcomes. Cochrane Database Syst Rev 2020;5(5):CD004192. doi: 10.1002/14651858.CD004192.pub4.
58. Kuo CH, Chou YC, Liao KC, Shieh CJ, Deng TS. Optimization of Light Intensity, Temperature, and Nutrients to Enhance the Bioactive Content of Hyperforin and Rutin in St. John's Wort. Molecules 2020;25(18):4256. doi: 10.3390/molecules25184256.
59. Murch SJ, Saxena PK. St. John's wort (Hypericum perforatum L.): Challenges and Strategies for Production of Chemically-Consistent Plants. Can J Plant Sci 2006;86(3): 765-71. Doi:10.4141/P05-179
60. Nosratabadi R, Rastin M, Sankian M, Haghmorad D, Mahmoudi M. Hyperforin-Loaded Gold Nanoparticle Alleviates Experimental Autoimmune Encephalomyelitis by suppressing Th1 and Th17 Cells and Upregulating Regulatory T Cells. Nanomedicine 2016;12(7):1961-71. doi: 10.1016/j.nano.2016.04.001.
61. Selek S, Esrefoglu M, Meral I, Bulut H, Caglar HG, Sonuc G, et al. Effects of Oenothera Biennis L. and Hypericum Perforatum L. Extracts on Some Central Nervous System Myelin Proteins, Brain Histopathology and Oxidative Stress in Mice with Experimental Autoimmune Encephalomyelitis. Biotech Histochem 2019;94(2):75-83. doi: 10.1080/10520295.2018.1482001.
62. Hou M, Wang R, Zhao S, Wang Z. Ginsenosides in Panax Genus and Their Biosynthesis. Acta Pharm Sin B 2021;11(7):1813-34. doi: 10.1016/j.apsb.2020.12.017
63. Ratan ZA, Haidere MF, Hong YH, Park SH, Lee JO, Lee J, et al. Pharmacological Potential of Ginseng and its Major Component Ginsenosides. J Ginseng Res 2021;45(2):199-210. doi: 10.1016/j.jgr.2020.02.004.
64. Lu J, Wang X, Wu A, Cao Y, Dai X, Liang Y, Li X. Ginsenosides in Central Nervous System Diseases: Pharmacological Actions, Mechanisms, and Therapeutics. Phytother Res 2022;36(4):1523-1544. doi: 10.1002/ptr.7395.
65. Lee MJ, Chang BJ, Oh S, Nah SY, Cho IH. Korean Red Ginseng Mitigates Spinal Demyelination in a Model of Acute Multiple Sclerosis by Downregulating p38 Mitogen-Activated Protein Kinase and Nuclear Factor-κB Signaling Pathways. J Ginseng Res 2018;42(4):436-46. doi: 10.1016/j.jgr.2017.04.013.
66. Lee MJ, Choi JH, Kwon TW, Jo HS, Ha Y, Nah SY, Cho IH. Korean Red Ginseng Extract Ameliorates Demyelination by Inhibiting Infiltration and Activation of Immune Cells in Cuprizone-Administrated Mice. J Ginseng Res 2023;47(5):672-680. doi: 10.1016/j.jgr.2023.05.001.
67. Oh J, Kwon TW, Choi JH, Kim Y, Moon SK, Nah SY, Cho IH. Ginsenoside-Re Inhibits Experimental Autoimmune Encephalomyelitis as a Mouse Model of Multiple Sclerosis by Downregulating TLR4/MyD88/NF-κB Signaling Pathways. Phytomedicine 2024;122:155065. doi: 10.1016/j.phymed.2023.155065.
68. Kim E, Cameron M, Lovera J, Schaben L, Bourdette D, Whitham R. American Ginseng does not Improve Fatigue in Multiple Sclerosis: A Single Center Randomized Double-Blind Placebo-Controlled Crossover Pilot Study. Mult Scler 2011;17(12):1523-6. doi: 10.1177/1352458511412062
69. Etemadifar M, Sayahi F, Abtahi SH, Shemshaki H, Dorooshi GA, Goodarzi M, et al. Ginseng in the Treatment of Fatigue in Multiple Sclerosis: A Randomized, Placebo-Controlled, Double-Blind Pilot Study. Int J Neurosci 2013;123(7):480-6. doi: 10.3109/00207454.2013.764499.
70. Benameur T, Giacomucci G, Panaro MA, Ruggiero M, Trotta T, Monda V, et al. New Promising Therapeutic Avenues of Curcumin in Brain Diseases. Molecules 2021;27(1):236. doi: 10.3390/molecules27010236.
71. Mohajeri M, Sadeghizadeh M, Najafi F, Javan M. Polymerized Nano-Curcumin Attenuates Neurological Symptoms in EAE Model of Multiple Sclerosis Through Down Regulation of Inflammatory and Oxidative Processes and Enhancing Neuroprotection and Myelin Repair. Neuropharmacology 2015;99:156-67. doi:10.1016/j.neuropharm.2015.07.013
72. Xie L, Li XK, Funeshima-Fuji N, Kimura H, Matsumoto Y, Isaka Y, et al. Amelioration of Experimental Autoimmune Encephalomyelitis by Curcumin Treatment Through Inhibition of IL17 Production. Int Immunopharmacol 2009;9(5):575-81. doi: 10.1016/j.intimp.2009.01.025.
73. Sadek MA, Rabie MA, El Sayed NS, Sayed HM, Kandil EA. Neuroprotective Effect of Curcumin Against Experimental Autoimmune Encephalomyelitis-Induced Cognitive and Physical Impairments in Mice: An Insight into the Role of the AMPK/SIRT1 Pathway. Inflammopharmacology 2023. doi: 10.1007/s10787-023-01399-3.
74. Mavaddatiyan L, Khezri S, Abtahi Froushani SM. Molecular Effects of Curcumin on the Experimental Autoimmune Encephalomyelitis. Vet Res Forum 2021 Winter;12(1):47-52. doi: 10.30466/vrf.2019.98789.2356.
75. Khosropour S, Shahvarooghi E, Rezaeizadeh H, Esmaeelzadeh M. Curcumin and Its Semisynthetic Derivative F-Curcumin Ameliorate the Expression of Cytokines in Autoimmune Encephalomyelitis Mouse Models of Multiple Sclerosis. Iran J Allergy Asthma Immunol 2023;22(6):575-587. doi: 10.18502/ijaai.v22i6.14646.
76. Dolati S, Ahmadi M, Rikhtegar R, Babaloo Z, Ayromlou H, Aghebati-Maleki L, et al. Changes in Th17 Cells Function After Nanocurcumin Use to Treat Multiple Sclerosis. Int Immunop-

harmacol 2018;61:74-81. doi: 10.1016/j.intimp.2018.05.018.
77. Dolati S, Babaloo Z, Ayromlou H, Ahmadi M, Rikhtegar R, Rostamzadeh D, et al. Nanocurcumin Improves Regulatory T-Cell Frequency and Function in Patients with Multiple Sclerosis. J Neuroimmunol 2019;327:15-21. doi: 10.1016/j.jneuroim.2019.01.007.
78. Petracca M, Quarantelli M, Moccia M, Vacca G, Satelliti B, D'Ambrosio G, Carotenuto A, Ragucci M, Assogna F, Capacchione A, Lanzillo R, Morra VB. Prospective Study to Evaluate Efficacy, Safety and Tolerability of Dietary Supplement of Curcumin (BCM95) in Subjects with Active Relapsing Multiple Sclerosis Treated with Subcutaneous Interferon Beta 1a 44 mcg tiw (CONTAIN): A Randomized, Controlled Trial. Mult Scler Relat Disord 2021;56:103274. doi: 10.1016/j.msard.2021.103274.
79. Jones E, Vlachou S. A Critical Review of the Role of the Cannabinoid Compounds Δ9-Tetrahydrocannabinol (Δ9-THC) and Cannabidiol (CBD) and Their Combination in Multiple Sclerosis Treatment. Molecules 2020;25:4930. doi:10.3390/molecules25214930.
80. Slaven M, Levine O. Cannabinoids for Symptoms of Multiple Sclerosis: Benefits to Patients Still Unclear. JAMA Netw Open 2018;1(6):e183484. doi: 10.1001/jamanetworkopen.2018.3484.
81. Oláh A, Szekanecz Z, Bíró T. Targeting Cannabinoid Signaling in the Immune System: “High”-ly Exciting Questions, Possibilities, and Challenges. Front Immunol 2017;8:1487. Doi:10.3389/fimmu.2017.01487.
82. Torres-Moreno MC, Papaseit E, Torrens M, Farré M. Assessment of Efficacy and Tolerability of Medicinal Cannabinoids in Patients with Multiple Sclerosis: A Systematic Review and Meta-Analysis. JAMA Netw Open 2018;1(6):e183485. doi: 10.1001/jamanetworkopen.2018.3485.