Complementary Therapies in Medicine 45 (2019) 275–279

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Combination therapy with interferon beta-1a and sesame oil in multiple sclerosis

Fardin Faraji[a], Mahya Hashemi[b], Atefeh Ghiasabadi[b], Sadaf Davoudian[b], Afsoon Talaie[c], Ali Ganji[b], Ghasem Mosayebi[b,d,*]

[a] Department of Neurology, School of Medicine, Arak University of Medical Sciences, Arak, Iran
[b] Molecular and Medicine Research Center, Arak University of Medical Sciences, Arak, Iran
[c] Department of Health, Islamic Azad University, Arak Branch, Arak, Iran
[d] Traditional and Complementary Medicine Research Center, Arak University of Medical Sciences, Arak, Iran

ARTICLE INFO

Keywords:
Cytokine
Interferon beta-1a
Multiple sclerosis
Nitric oxide
Sesame oil

ABSTRACT

Objectives: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system. Several effector mechanisms are involved in the immunopathology of MS and a variety of medications such as beta interferons are applied to treat the disease. This study was conducted to evaluate the anti-inflammatory and immunomodulatory effects of sesame oil in combination with interferon beta-1a in MS treatment.

Methods: Ninety-three MS patients were enrolled in the study. The patients were randomly divided into two groups. The control group (n = 39) received 30 μg/week of interferon beta-1a intra-muscularly. The sesame oil-treated group (n = 54) received interferon beta-1a the same as the control group with the addition of 0.5 ml/kg/day of oral sesame oil for 6 months.

Results: After the 6-month study period, the interleukin (IL)-10 concentration in the sesame oil-treated group was significantly greater than that of the control group (p = 0.04). The concentrations of interferon-γ (IFN-γ), nitric oxide (NO), and tumor necrosis factor-α (TNF-α) in the sesame oil group after treatment were significantly less than those of the control group (p = 0.029, p = 0.0001, and p = 0.01, respectively). Lymphocyte proliferation in the sesame oil-treated group was significantly lower at the end of the study than at the beginning (p = 0.001).

Conclusion: Sesame oil, through a decrease in IFN-γ secretion and anti-inflammatory and anti-oxidant activities, may have beneficial effects for MS patients.

1. Introduction

Multiple sclerosis (MS), a chronic inflammatory demyelinating disease of the central nervous system, may be mediated by type 1 helper T Cells (Th1) and Th17 immune responses.[1,2] Studies have shown that effector mechanisms, including dysregulation of the immune responses and free radicals, are involved in the pathogenesis of MS.[3,4]

Interferon-beta (IFN-β) is a standard treatment for MS, but some MS patients have minimal responses to IFN-β therapy.[5,6] Therefore, stem cell therapy, immunosuppressive drugs, and IFN-β combined with other immunomodulatory or anti-inflammatory agents may be more effective in treatment of MS than IFN-β alone.[7–10]

Sesame seeds (*Sesamum indicum*, Linn, Pedaliaceae) as a traditional health food have been used to treat some inflammatory disorders. Some studies showed that the lignans present in sesame oil including sesaminol, sesamolin, P1, pinoresinol, and sesamin have antioxidant and anti-inflammatory properties.[11–14] In addition, sesame oil consumption reduces blood glucose and has beneficial effects on lipid peroxidation and antioxidant levels in streptozotocin-induced diabetic rats.[15] Sesame oil has anti-inflammatory effects; also, it has been suggested that sesame oil or its constituents induce growth arrest and apoptosis of cancer cells. In one study, sesame oil, a vegetable oil enriched with n-6 polyunsaturated fatty acids, attenuated the growth and metastasis of EL4 lymphoma.[16] Furthermore, Miyahara and colleagues showed that sesamolin from sesame seeds induces apoptosis in molt-4 lymphoid cells.[17]

In a previous study, we showed that intraperitoneally injection of sesame oil reduced the clinical symptoms of experimental autoimmune encephalomyelitis (EAE) and increased total antioxidant capacity in the serum of C57BL/6 mice with EAE.[18] Another study showed that oral

* Corresponding author at: Molecular and Medicine Research Center, Arak University of Medical Sciences, P.O. box: 38481-7-6941 Arak, Iran.
E-mail address: ghasemmosayebi@arakmu.ac.ir (G. Mosayebi).

https://doi.org/10.1016/j.ctim.2019.04.010
Received 13 March 2019; Received in revised form 17 April 2019; Accepted 18 April 2019
Available online 23 April 2019

sesame oil therapy protected C57BL/6 mice from developing EAE by reducing IFN-γ secretion.[19] However, the use of sesame oil in the treatment of MS has not been studied. In this clinical trial study, we investigated the effect of IFN-beta-1a both with and without sesame oil on immunological and neurological variables in relapsing-remitting MS (RRMS) patients.

2. Patients and method

2.1. Study design and subjects

This study was a 6-month parallel-group, randomized controlled trial performed in patients with MS. The study was performed in keeping with the Helsinki declaration on research with human subjects, and the protocol approved by the local ethics committee (Ref. Number: AUM Sec-88-69-1). All patients gave their written informed consent and randomly assigned to maintain balance across multiple stratification variables. The stratification variables were age group (and age range of 18–65 years), sex, and baseline Expanded Disability Status Scale (EDSS) (EDSS scale ranges from 0 to 5 in 0.5 unit increments). The patients were randomized independently into two groups; i.e., treatment and control patients (Fig. 1). The control group (n = 39) received IFN-β-1a (Cinnovex™, Fraunhofer Institute, Germany) as standard protocol. The sesame oil-treated patient group (n = 54) received both IFN-β-1a plus 0.5 ml/kg/day of sesame oil orally for six months. The sesame oil was obtained from Iranian white sesame seeds.[20] Neurological and immunological examinations were performed at the beginning and the end of the study

Patients were diagnosed with relapsing MS by the revised 2010 McDonald criteria.[21] Inclusion criteria were Expanded Disability Status Scale (EDSS) score of 0.5–5, at least two clinically documented relapses in the previous three years (at least one within the 12 months prior to randomization).[22] Scoring is based on an examination by a neurologist. Exclusion criteria were progressive MS, drug abuse, and pregnancy.

2.2. Proliferation assay and cytokine detection

Details of proliferation and cytokine assays have been described before.[23] Briefly, peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll-Isopaque (Lymphoprep, Nyegaard, Oslo, Norway). The cells (1×10^6 cells/mL) were cultured in RPMI-1640 containing 10% FBS (Gibco Life Technologies, Inc., Gaithersburg, MD). Lymphocyte proliferation was determined by MTT assay. For cytokine detection, 1×10^6 PBMCs/mL were incubated in cell culture and stimulated with 1 μg/mL of Phytohemagglutinin (PHA) for 72 h. The supernatants were collected and interferon gamma (IFN-γ), interleukin (IL)-10, IL-17,

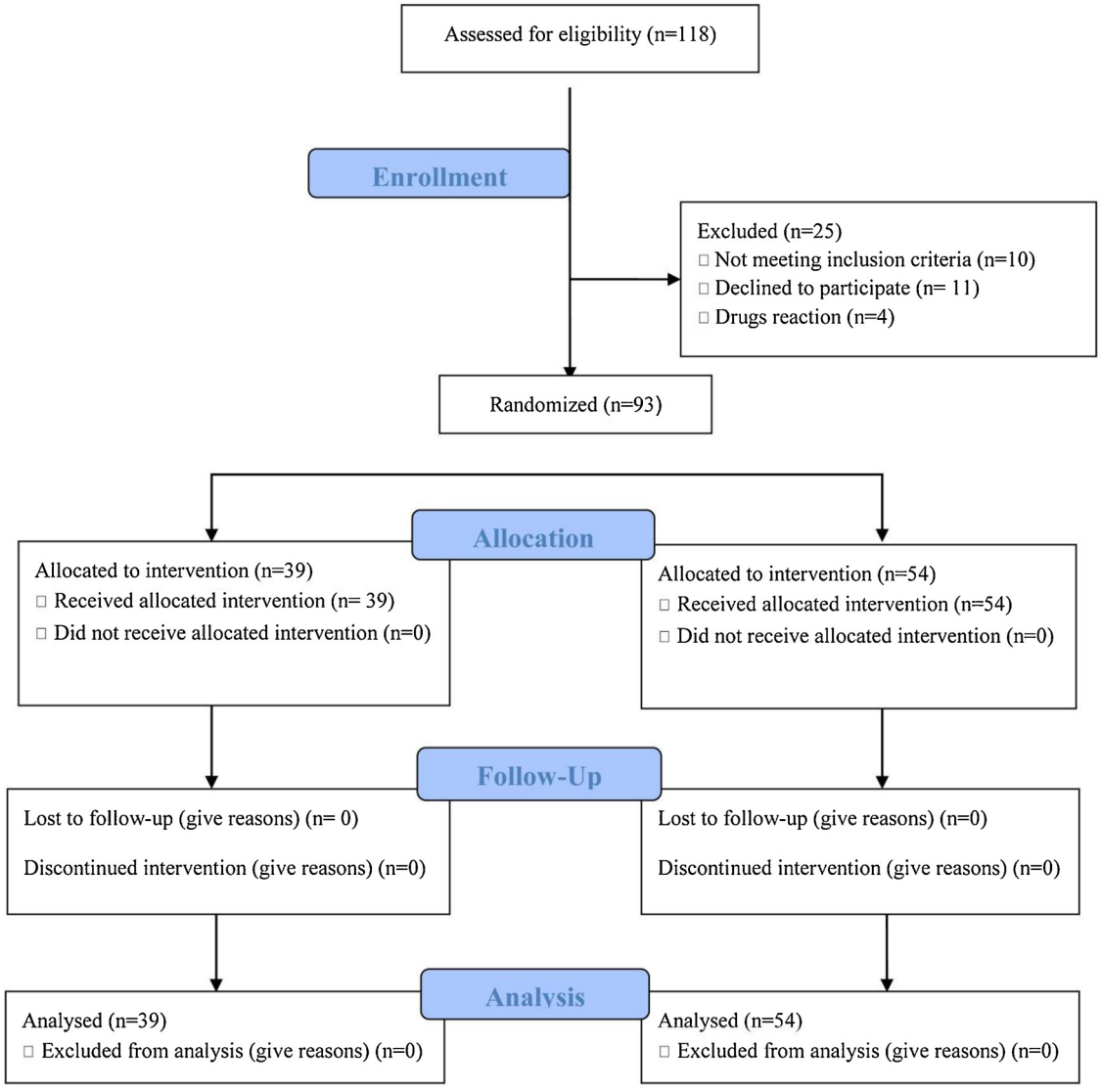

Fig. 1. CONSORT flow diagram of the study.

and tumor necrosis factor (TNF)-α were quantified by ELISA (R&D and eBiosiences) according to the manufacturer's protocol. The sensitivity of IFN-γ, IL-10, IL-17, and TNF-α were 8.0, 0.3, 1.1, and 1.5 ρg/mL, respectively.

2.3. Serum nitric oxide level

Nitric oxide (NO) was assayed based on the Griess reaction. The serum samples were mixed Griess reagent (v/v) at room temperature for 10 min. Absorbance was measured on an ELISA plate reader (Stat Fax 2100, Awareness Technology, Inc., USA) at 550 nm. The nitrite concentration was determined by a standard curve of 0.1 M sodium nitrite prepared in serial dilution with distilled water.

2.4. Statistical analysis

SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Data were presented as means ± SEMs. For clinical scores, significance between groups was examined by the Mann-Whitney *U* test. After normality evaluation, all other statistical comparisons between groups were examined using one-way multiple range ANOVA for multiple comparisons. P values less than 0.05 were considered statistically significant. Sample size was estimated by Stata/SE 12 software and Log-rank test.

3. Results

3.1. Clinical outcomes

Of 118 patients who completed the informed consent form, 93 entered the extension study. During the extension, 25 patients excluded for not meeting inclusion criteria (n = 10), declining to participate (n = 11), and drugs reaction (n = 4), (Fig. 1). No statistically significant difference was found between the control and treatment groups for age or disease duration (Table 1). After 6-month, the EDSS value between the control and treatment groups remained insignificant; however, it was reduced in the treatment group (Fig. 2).

3.2. Cytokine assay

The IFN-γ concentration after sesame oil treatment (239 ± 83ρg/mL) was significantly lower than before the treatment (420 ± 150 ρg/mL, p = 0.029, Fig. 3A). The same was true for TNF-α (p = 0.01, Fig. 3B). In contrast, the IL-10 concentration was significantly greater after treatment than before (p = 0.04, Fig. 3C). The IL-17 concentrations were not significantly different before and after sesame oil treatment (Fig. 3D). No significant difference was found between the cytokine concentrations at baseline and the end of the study in the patient control group (Fig. 3A–D).

3.3. Lymphocyte proliferation

The stimulation indexes (SIs) at baseline of the treated patient and control groups were not significantly different; however, after treatment, the SI of the treated group was significantly less than that of the controls (p = 0.001, Fig. 4).

Table 1
Demographic characteristics of multiple sclerosis patients.

	Treatment group (n = 54)	Control group (n = 39)
Male/Female	9/45	9/30
Age(years)[mean(SD)]	36(12)	32(16)
Range(years)	18-60	18-60
Duration of disease(years) [mean(SD)]	3(1.9)	3(2.3)

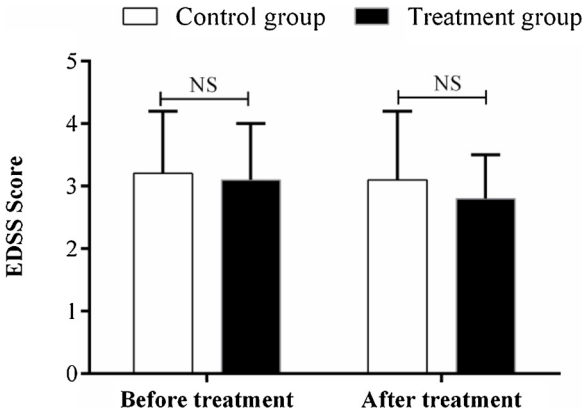

Fig. 2. Effect of IFN-β-1a and sesame oil treatment on Expanded Disability Status Scale (EDSS) in MS patients. Columns represent EDSS scores of sesame oil-treated (treatment group) and untreated (control group) MS patients at baseline (before) and at the end (after) of the six-month study. Data were presented as means ± SDs. NS; non-significant, *; p < 0.05, **; p < 0.01, ***, p < .0.001 − 0.0001.

3.4. Nitric oxide concentration

Similar to lymphocyte proliferation, the NO concentrations at baseline were not significantly different between the treatment and control groups. After the treatment, the NO concentration was significantly lower in the treatment group than in the controls (p = 0.0001, Fig. 5).

4. Discussion

Multiple sclerosis is an autoimmune disease, in which immune cells including dendritic cells, monocytes, Th1 cells, Th17 cells, and B-cells are involved in its immunopathology.[24] Higher levels of IL-17, IFN-γ, and TNF-α, and nitric oxide are found in the serum of MS patients than in healthy individuals.[25,26] However, immunomodulation by regulatory T cells (Treg cells) or a shift of the immune response to Th2 may reduce MS symptoms.

In our clinical trial, EDSS scores were not significantly affected by sesame oil treatment; however, it was reduced in the treatment group. Perhaps the reason for the insignificance EDSS results was for duration of 6 months of the study and in a longer period we can see a change in this index.

Nitric oxide and the inflammatory cytokines IFN-γ and TNF-α were significantly lesser in PBMCs from the sesame oil-treated group than in those from both the treatment group at baseline and the control group at the end of the six-month study. The mechanism by which sesame oil exerts its beneficial effects is not yet known. Reductions in inflammatory cytokines and NO can be attributed to the presence of anti-inflammatory agents in sesame oil that could show anti-inflammatory effect. In this respect, some studies showed that sesame oil has potent anti-inflammatory and antioxidant effects.[14,27] Sesame oil consumption reduced blood glucose and enhanced lipid peroxidation and antioxidant levels in streptozotocin-treated diabetic rats and ameliorated insulin resistance in KK-Ay mice.[15,28]

Sesame oil may inhibit IFN-γ production via apoptosis or inhibition of inflammatory cell proliferation. Interferon-γ is the key Th1 cytokine and plays a major pathogenic role in MS, either through activation of other immune cells or by activating apoptosis of oligodendrocyte.[29] Interferon-γ administration can potentially reverse the defects seen in MS patients.[30]

The pro-inflammatory cytokine TNF-α has been identified in astrocytes and microglial cells of the CNS and has been shown to be

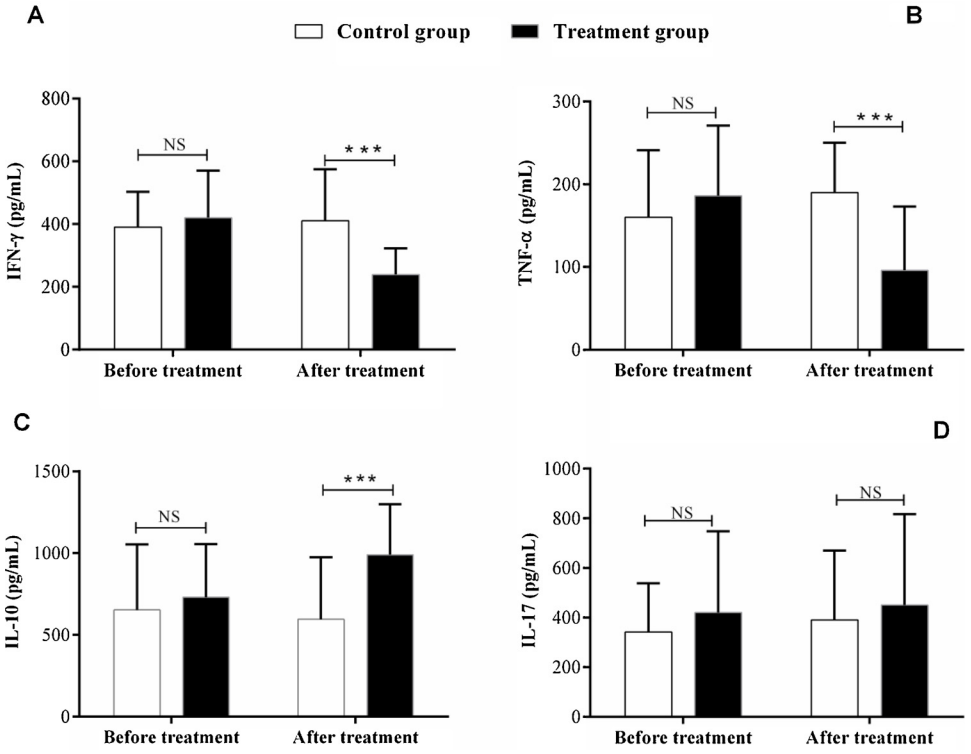

Fig. 3. Effect of IFN-β-1a and sesame oil treatment on IFN-γ (A), TNF-α (B), IL-10 (C), and IL-17 (D) concentrations in supernatants of PBMCs from MS patients cultured in triplicate in the presence of 1 μg/mL PHA after 72 h (baseline) and after 6 months of treatment. The control group received IFN-β-1a only, the treatment group received both IFN-β-1a and sesame oil. Data were presented as means ± SDs. NS; non-significant, *; $p < 0.05$, **; $p < 0.01$, ***, $p < .0.001 - 0.0001$.

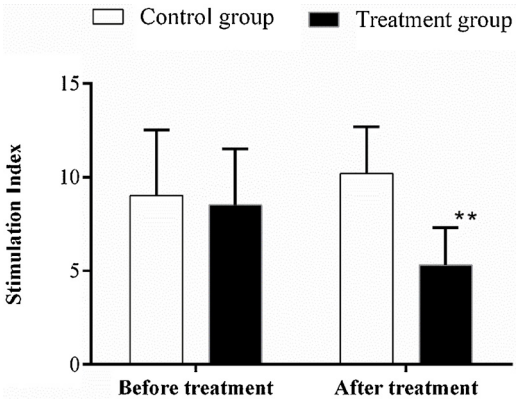

Fig. 4. Effect of IFN-β-1a and IFN-β-1a plus sesame oil on cell proliferation. Peripheral blood mononuclear cells from sesame oil-treated and untreated (control) MS patients at baseline and after 6 months of treatment were cultured in triplicate in the presence of 1 μg/mL PHA. After 72 h, proliferation was assessed by MTT assays. Proliferation is referred to as the stimulation Index. Data were presented as means ± SDs. NS; non-significant, *; $p < 0.05$, **; $p < 0.01$, ***, $p < .0.001 - 0.0001$.

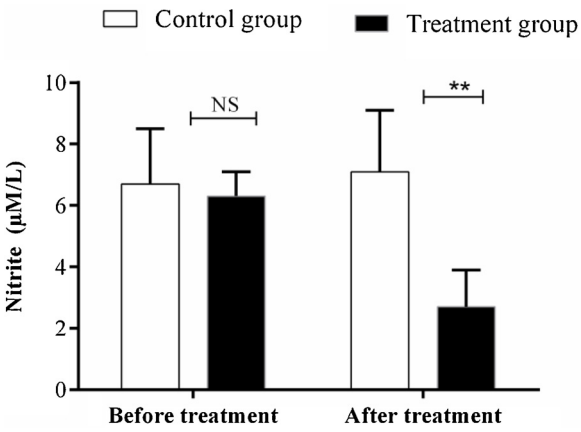

Fig. 5. Effect of IFN-β-1a and IFN-β-1a plus sesame oil on serum nitric concentrations in MS patients at baseline and after six months of treatment. Data were presented as means ± SDs. NS; non-significant, *; $p < 0.05$, **; $p < 0.01$, ***, $p < .0.001 - 0.0001$.

associated with acute and chronic brain lesions in MS patients.[31,32] Immunohistochemical studies in EAE suggested a role for TNF-α in immune-induced demyelination.[33]

Considerable evidence supports the positive role of anti-inflammatories and anti-oxidants in MS therapy. Curcumin has been shown to exert anti-inflammatory, anti-oxidant, and anti-tumor activities, which have therapeutic effects on MS.[34,35] Curcumin dramatically reduced the number of inflammatory cells and TNF-α inhibited Th17 cell differentiation and abated NO release in a dose-dependent manner.[36–38] The immunomodulatory therapies are focused on shifting the responses from Th1 to Th2 in autoreactive T cells.[39] Our results are inconsistent with previous studies that showed reductions in pro-inflammatory cytokines, including IFN-γ and TNF-α.

In agreement with recent studies, sesame oil exhibited its anti-oxidant activity through reduced nitric oxide in the treated patients. We previously reported that sesame oil increased ferric reducing anti-oxidant power (FRAP) activity in EAE mice.[19,40] In this report, we showed that NO was less in sesame oil-treated than in untreated MS patients. Therefore, sesame oil offers promise in the treatment of MS.

Interleukin-17 was not affected by the sesame oil treatment. Recent data from the EAE model suggested that IL-17 has a pivotal role in MS pathogenesis.[41] Interleukin-17-producing cells are important in demyelination initiation in the relapsing phase of MS.[42]

The regulatory T cell functions and characterization and IL-10-receptor signaling is impaired in MS[43,44]; and aMS is associated with downregulation of TGF-β and IL-10 cytokine release. [45] The immunohistochemistry and RNA studies on EAE mice central nervous system (CNS) tissues with spontaneous recovery of these mice have been correlated with the proliferation of Th2-like cells via corresponding increases in IL-10 and TGF-β.[46]

Eventually, after the treatment, the SI of PBMCs from the sesame oil-treated patients was significantly lower than that of controls. Histological examination of mice brain tissues revealed reduced leukocyte infiltration in sesame oil-treated EAE mice.[18] Sesame oil has also been shown to induce apoptosis in cancer cells.[16,17] Our previous work showed a significant reduction in disease severity and leukocyte proliferation following sesame oil treatment in EAE mice.[19]

The number of patients who tended to consume sesame oil for 6 months, and study period were the major limitations of this study. To the best of our knowledge, this paper is the first demonstration of sesame oil treatment in MS patients and provides insights into the mechanisms of sesame oil treatment in MS therapy. Sesame oil, by reducing IFN-γ secretion and inducing anti-inflammatory and anti-oxidant activities, may reduce symptoms and improve the quality of life of MS patients.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

This work was supported by the Molecular and Medicine Research Center (MMRC), Arak University of Medical Sciences.

Acknowledgments

We thank the members of the Research Committee of Arak University of Medical Sciences for their support and the MS patients who participated in this study.

References

1. Lassmann H, Bruck W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. *Brain Pathol.* 2007;17(2):210–218.
2. Buhler U, Fleischer V, Luessi F, et al. Role of IL-17-producing lymphocytes in severity of multiple sclerosis upon natalizumab treatment. *Mult Scler (Houndmills, Basingstoke, England).* 2016.
3. Popescu BF, Pirko I, Lucchinetti CF. Pathology of multiple sclerosis: where do we stand? *Continuum (Mult Scler).* 2013;19(4):901–921.
4. Filippi M, Preziosa P, Rocca MA. *Multiple sclerosis. Handbook of clinical neurology.* 135. 2016; 2016:399–423.
5. Inoue M, Shinohara ML. The role of interferon-beta in the treatment of multiple sclerosis and experimental autoimmune encephalomyelitis – in the perspective of inflammasomes. *Immunology.* 2013;139(1):11–18.
6. Kieseier BC. The mechanism of action of interferon-beta in relapsing multiple sclerosis. *CNS Drugs.* 2011;25(6):491–502.
7. Freedman MS, Bar-Or A, Atkins HL, et al. The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the International MSCT Study Group. *Mult Scler.* 2010;16(4):503–510.
8. Bae DK, Park D, Lee SH, et al. Comparative effects of human neural stem cells and oligodendrocyte progenitor cells on the neurobehavioral disorders of experimental autoimmune encephalomyelitis mice. *Stem Cells Int.* 2016;2016:4079863.
9. Hovi A, Airas L. Effect of fingolimod-treatment on blood lipid profiles of multiple sclerosis patients. *J Neuroimmune pharmacol.* 2016;11(4):611–612.
10. Ghasami K, Faraji F, Fazeli M, Ghazavi A, Mosayebi G. Interferon beta-1a and atorvastatin in the treatment of multiple sclerosis. *Iran J immunol: IJI.* 2016;13(1):16–26.
11. Sankar D, Sambandam G, Rao MR, Pugalendi K. Modulation of blood pressure, lipid profiles and redox status in hypertensive patients taking different edible oils. *Clin Chim Acta.* 2005;355(1):97–104.
12. Utsunomiya T, Chavali SR, Zhong WW, Forse RA. Effects of sesamin-supplemented dietary fat emulsions on the ex vivo production of lipopolysaccharide-induced prostanoids and tumor necrosis factor α in rats. *Am J Clin Nutr.* 2000;72(3):804–808.
13. Periasamy S, Chien S-P, Chang P-C, Hsu D-Z, Liu M-Y. Sesame oil mitigates nutritional steatohepatitis via attenuation of oxidative stress and inflammation: a tale of two-hit hypothesis. *J Nutr Biochem.* 2014;25(2):232–240.
14. Narasimhulu CA, Selvarajan K, Litvinov D, Parthasarathy S. Anti-atherosclerotic and anti-inflammatory actions of sesame oil. *J Med Food.* 2015;18(1):11–20.
15. Ramesh B, Saravanan R, Pugalendi K. Influence of sesame oil on blood glucose, lipid peroxidation, and antioxidant status in streptozotocin diabetic rats. *J Med Food.* 2005;8(3):377–381.
16. Salem ML. Systemic treatment with n-6 polyunsaturated fatty acids attenuates EL4 thymoma growth and metastasis through enhancing specific and non-specific anti-tumor cytolytic activities and production of TH1 cytokines. *Int Immunopharmacol.* 2005;5(6):947–960.
17. Yoshiyukimiyahara HH, Katsuzaki H, MAI K, Komiya T. Sesamolin from sesame seed inhibits proliferation by inducing apoptosis in human lymphoid leukemia Molt 4B cells. *Int J Mol Med Adv Sci.* 2001;7:369–371.
18. Mosayebi G, Ghazavi A, Salehi H, Payani M, Khazae M. Effect of sesame oil on the inhibition of experimental autoimmune encephalomyelitis in C57BL/6 mice. *Pak J Biol Sci.* 2007;10(11):1790–1796.
19. Ghazavi A, Mosayebi G. The mechanism of sesame oil in ameliorating experimental autoimmune encephalomyelitis in C57BL/6 mice. *Phytother Res.* 2012;26(1):34–38.
20. Sadeghi N, Oveisi MR, Hajimahmoodi M, Jannat B, Mazaheri M, Mansouri S. The contents of sesamol in Iranian sesame seeds. *Iran J Pharm Res.* 2010:101–105.
21. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol.* 2011;69(2):292–302.
22. Kurtzke JF. Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS). *Neurology.* 1983;33(11) 1444-1444.
23. Mosayebi G, Ghazavi A, Ghasami K, Jand Y, Kokhaei P. Therapeutic effect of vitamin D3 in multiple sclerosis patients. *Immunol Invest.* 2011;40(6):627–639.
24. Nylander A, Hafler DA. Multiple sclerosis. *J Clin Invest.* 2012;122(4):1180–1188.
25. Peiravian F, Rajaian H, Samiei A, et al. Altered serum cytokine profiles in relapse phase of relapsing-remitting multiple sclerosis. *Iran J Immunol.* 2016;13(3):186.
26. Kallaur AP, Oliveira SR, Alfieri DF, et al. Cytokine profile in patients with progressive multiple sclerosis and its association with disease progression and disability. *Mol Neurobiol.* 2016:1–11.
27. Hsu D-Z, Liu C-T, Li Y-H, Chu P-Y, Liu M-Y. Protective effect of daily sesame oil supplement on gentamicin-induced renal injury in rats. *Shock.* 2010;33(1):88–92.
28. Hong L, Yi W, Liangliang C, Juncheng H, Qin W, Xiaoxiang Z. Hypoglycaemic and hypolipidaemic activities of sesamin from sesame meal and its ability to ameliorate insulin resistance in KK-Ay mice. *J Sci Food Agric.* 2013;93(8):1833–1838.
29. Bielekova B, Martin R. Development of biomarkers in multiple sclerosis. *Brain.* 2004;127(7):1463–1478.
30. Panitch HS, Francis GS, Hooper CJ, Merigan TC, Johnson KP. Serial immunological studies in multiple sclerosis patients treated systemically with human alpha interferon. *Ann Neurol.* 1985;18(4):434–438.
31. Hirano T, Thomson A. *The cytokine handbook.* 1994; 1994.
32. Cannella B, Raine CS. The adhesion molecule and cytokine profile of multiple sclerosis lesions. *Ann Neurol.* 1995;37(4):424–435.
33. Brosnan C, Selmaj K, Raine C. Hypothesis: a role for tumor necrosis factor in immune-mediated demyelination and its relevance to multiple sclerosis. *J Neuroimmunol.* 1988;18(1):87–94.
34. Bengmark S, Mesa MD, Gil A. Plant-derived health-the effects of turmeric and curcuminoids. *Nutr Hosp.* 2009;24(3):273–281.
35. Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. *Altern Med Rev.* 2009;14(3):226–246.
36. Xie L, Li X-K, Funeshima-Fuji N, et al. Amelioration of experimental autoimmune encephalomyelitis by curcumin treatment through inhibition of IL-17 production. *Int Immunopharmacol.* 2009;9(5):575–581.
37. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int J Biochem Cell Biol.* 2009;41(1):40–59.
38. Natarajan C, Bright JJ. Curcumin inhibits experimental allergic encephalomyelitis by blocking IL-12 signaling through Janus kinase-STAT pathway in T lymphocytes. *J Immunol.* 2002;168(12):6506–6513.
39. Lopez-Diego RS, Weiner HL. Novel therapeutic strategies for multiple sclerosis—a multifaceted adversary. *Nat Rev Drug Discov.* 2008;7(11):909–925.
40. Hsu D-Z, Su S-B, Chien S-P, et al. Effect of sesame oil on oxidative-stress-associated renal injury in endotoxemic rats: involvement of nitric oxide and proinflammatory cytokines. *Shock.* 2005;24(3):276–280.
41. Ivanov II, McKenzie BS, Zhou L, et al. The orphan nuclear receptor RORγt directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell.* 2006;126(6):1121–1133.
42. McFarland HF, Martin R. Multiple sclerosis: a complicated picture of autoimmunity. *Nat Immunol.* 2007;8(9):913–919.
43. Martinez-Forero I, Garcia-Munoz R, Martinez-Pasamar S, et al. IL-10 suppressor activity and ex vivo Tr1 cell function are impaired in multiple sclerosis. *Eur J Immunol.* 2008;38(2):576–586.
44. Ebrahimi M, Ganji A, Zahedi S, Nourbakhsh P, Ghasami K, Mosayebi G. Characterization of regulatory T-cells in multiple sclerosis patients treated with interferon Beta-1a. *CNS Neurol Disord Drug Targets.* 2018;17(2):113–118.
45. Navikas V, Link H. Review: cytokines and the pathogenesis of multiple sclerosis. *J Neurosci Res.* 1996;45(4):322–333.
46. Kennedy M, Torrance D, Picha K, Mohler K. Analysis of cytokine mRNA expression in the central nervous system of mice with experimental autoimmune encephalomyelitis reveals that IL-10 mRNA expression correlates with recovery. *J Immunol.* 1992;149(7):2496–2505.