

Therapeutic Effects of Nigella Sativa and Cannabis Sativa Seeds On Multiple Sclerosis

Arefhosseini SR¹, Alijani S^{1*}, Simal-Gandara J^{2*}, Jazar H¹ and Firozi SR¹

¹Department of Biochemistry and Diet Therapy, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Iran

²Nutrition and Bromatology Group, Department of Analytical Chemistry and Food Science, Faculty of Food Science and Technology, University of Vigo - Ourense Campus, E-32004 Ourense, Spain

*Corresponding author:

Sepideh Alijani,

Department of Biochemistry and Diet Therapy, Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Iran, Tel: +989372552882;

E-mail: spd.aliyani@gmail.com

Jesus Simal-Gandara,

Nutrition and Bromatology Group, Department of Analytical Chemistry and Food Science, Faculty of Food Science and Technology, University of Vigo - Ourense Campus, E-32004

Ourense, Spain, E-mail: jsimal@uvigo.es

Received: 25 Feb 2021

Accepted: 12 Mar 2021

Published: 18 Mar 2021

Copyright:

©2021 Alijani S, Simal-Gandara J, et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Citation:

Alijani S, Simal-Gandara J, Therapeutic Effects of Nigella Sativa and Cannabis Sativa Seeds On Multiple Sclerosis. Clin Surg. 2021; 5(4): 1-5

Keywords:

Multiple sclerosis; Black seed (Nigella sativa); Hemp seed (Cannabis sativa L.); MS patients

1. Abstract

Multiple sclerosis remains an incurable inflammatory neurodegenerative chronic disease with various life-affecting symptoms. Nigella sativa (black seed) and hemp seed (Cannabis sativa L.) were used to treat various chronic diseases by their anti-inflammatory and neuroprotective effects. We discuss a new therapeutic way to treat multiple sclerosis to help further research approach a way to prevent and cure this disabling disease. The article review had been performed by the electronic search among published articles about the effect of Nigella sativa and hemp seed. Nigella sativa consumption by MS patients and its preventive effects can be therapeutic by suppressing inflammation, enhancing remyelination, and reducing the expression of TGF β 1 in rats. Hemp seed as a therapeutic herb to treat multiple sclerosis is believed to increase AMPK, suppress NF- κ B, inhibit the secretion of pro-inflammatory mediators in rat models, and improve the disability status scale in human models. Although many studies indicate that the therapeutic effects of these herbs on MS, the number of clinical interventional human research projects is low.

2. Introduction

Multiple sclerosis (MS) is one of the most common neurode-

generative, chronic inflammatory diseases causing disabilities in young adults worldwide. This long-lasting neurological problem affects the central nervous system by destroying the myelin sheath around nerves [1] MS is mostly unpredictable still, the environment and genetic factors could both be the highlighted risk factors [2]. MS consists of three phases: the high-risk phase, the relapsing-remitting phase, and the progressive phase. There is currently no definite treatment for MS, and cures have mainly been based on the prescription of immune-modulating and immunosuppressive agents [3]. Epidemiology of MS shows an uneven geographic distribution, but in some developed and developing countries like Japan, there has been a sharp increase in MS prevalence [4].

In recent years, evidence from prospective observational studies and clinical trials has shown that some herbal supplementations represent a promising therapeutic approach for multiple sclerosis [5]. In this review article, the efficacy of two herbal treatments, including Nigella sativa and Cannabis sativa, on MS patients' enhancement, will be assessed.

Nigella sativa (N. Sativa) annual herb of the Ranunculaceae family, also known as the Black seed with a great historical and religious background, is mostly cultivated in Southwest Asia, southern Eu-

rope, and North Africa [7]. Studies have reported that black seed contains a bioactive component called thymo quinone (TQ) that have numerous benefits like immunomodulatory, anti-inflammatory [8], hepato protective [9], diuretic [10], antihypertensive [11], hypoglycemic [12], hypo lipidemic [13], anti-microbial [14], and gastro protective [15] effects; thus it is used to treat various diseases like cancers, diabetes, and neurodegenerative diseases [5].

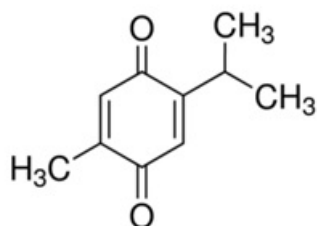


Figure 1: The chemical structure of the bioactive component of nigella seeds, Thymoquinone (TQ)

Cannabis or hemp seed is originated from China and has been mostly used to produce textile and animal food. Hemp seed also has anti-microbial, anti-inflammatory, and anti-lipogenic effects [16] due to a perfectly balanced content of omega three and omega six polyunsaturated fatty acids [17]. Hemp seed also contains a phenylpropionamide, called coumaroyl-amino butanol glucopyranoside (CLG), providing some neuroprotective effects that will be discussed in this article [18].

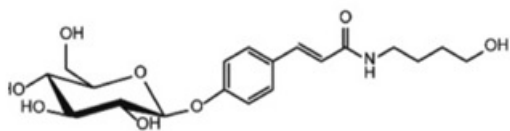


Figure 2: The chemical structure of the bioactive component of hemp seeds, Coumaroyl-amino butanol glucopyranoside (CLG)

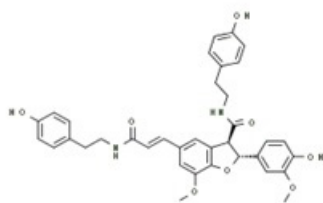


Figure 3: The chemical structure of the lignanamide in hemp seed, Grosamide

Recently, some studies have indicated the efficacy of consuming herbal treatments to improve health in MS patients. We proposed anti-inflammatory and neuroprotective effects of black seed and

hemp seed might help to improve multiple sclerosis patients' disabilities and decrease extended disability status scores. Although the researches on human are low, the interpretation of this article will promote a potential therapeutic strategy to prevent or treat multiple sclerosis.

3. Materials and Methods

An article review is performed by the electronic search for the manuscripts published among current databases and declared facts about the effect of *Nigella sativa* and hemp seed on multiple sclerosis patients. Keywords used for electronic search on PubMed and Science Direct databases are Multiple sclerosis, Black seed (*Nigella sativa*), Hemp seed (*Cannabis sativa* L).

4. Discussion

Impairment of T helpers (Th) is persuaded to be the leading risk factor for MS etiology. MS is a disorder related to the impairment of the balance status of some significant types of Th cells, including Th1 (producing interferon- γ (IFN- γ) and interleukin-12 (IL-12) and Th2 producing IL-4 and IL-10) (19, 20). Th1/Th2 balance is considered one of the risk factors in MS etiology, while the exact etiology of developing multiple sclerosis is related to genetic and environmental factors. High oxygen consumption, low antioxidant defenses, and high content of polyunsaturated fats in the brain made it particularly vulnerable to oxidative stress and damage [21, 22]. Oxidative stress neutralization might represent a therapeutic approach to provide neuroprotection in MS [22, 23]. Herbal treatments are increasingly used worldwide due to their safety and cost-efficacy. Fatty acids, antioxidants, vitamins, phytochemicals, and melatonin are micronutrients that may positively affect multiple sclerosis symptoms [24]. *N. Sativa* and *C. Sativa* L. are herbs with various therapeutic effects like neuroprotective, anti-inflammatory and anti-oxidative effects, as shown in Table 1. EAE: Experimental Autoimmune Encephalomyelitis, CNS: central nervous system ROS: reactive oxygen species MDA: malondialdehyde, ECS: endocannabinoid system, MS: Multiple sclerosis CLG: coumaroyl-amino butanol glucopyranoside, AMPK: di-nosine monophosphate-activated protein kinase, NF-Kb: nuclear factor-kappa B, Nrf-2: nuclear factor erythroid 2-related factor 2 RRMS: relapsing-remitting multiple sclerosis.

N. Sativa has been used to treat degenerative diseases like Parkinson's and Alzheimer's since ancient times. The antioxidant activity of *N. Sativa* is through the improvement of both non-enzymatic (GSH and vitamin C) and enzymatic (SOD, CAT, GPX, and GST) antioxidant systems and also upregulation of the Nrf2/HO-1 pathway [25]. The seeds were found to enhance natural killer cell activity in regular volunteers by increasing the ratio of helper to suppressor T cells [26]. A study in Egypt on the EAE (Experimental Autoimmune Encephalomyelitis) model of multiple sclerosis

in 22 rats demonstrated that consumption of 2.8 g/kg *Nigella sativa* extract for four weeks ameliorated the clinical signs of EAE, suppressed inflammation, enhanced remyelination in the cerebellum, and reduced the expression of TGF β 1 (Transforming growth factor) in CNS (central nervous system) [27, 28]. Another study indicated that Thymoquinone (TQ) oil constituent extracted from *N. Sativa* due to its antioxidant effects is 90% preventive and 50% curative in CR-EAE (Chronic Relapsing Form of Experimental Autoimmune Encephalomyelitis). It also decreases ROS (reac-

tive oxygen species) production and reduces the levels of NO and MDA (malondialdehyde) in the brain and medulla spinalis tissues [29]. Another study showed that the treatment of rats with thymoquinone 1 mg/kg/day increased the red blood cell glutathione, infiltration of mononuclear cells, countered perivascular cuffing brain and neural structure and inhibits the activation of NF- κ B. These results and other clinical signs indicated the beneficial effect of thymoquinone against EAE in the rat model of MS [30].

Table 1: The main molecular mechanisms are supporting the effects of *N. Sativa* and *C. Sativa* in multiple sclerosis

| | Authors and Year | Result |
|-------------------------------|---|--|
| <i>Nigella Sativa</i> | Tavakkoli A et al 2020 (25) | - Upregulation of the Nrf2/HO-1 pathway -Antioxidant effects |
| | Gali-Muhtasib H et al 2006 (26) | -improved natural killer cell health |
| | Fahmy HM et al 2014 (27) Noor NA et al 2015 (28) | -ameliorated the clinical signs of EAE - suppressed inflammation - enhanced remyelination in the cerebellum -reduced the expression of TGF β 1(Transforming growth factor)in CNS (central nervous system) |
| | Mohamed A et al 2009 (29) | -decreases ROS production and levels of NO and MDA in the brain and medulla spinalis tissue |
| | Mohamed A et al 2005 (30) | -increase the red blood cell glutathione, infiltration of mononuclear cells, and counter perivascular cuffing within the brain and neural structure -inhibited the activation of NF-kappaB |
| <i>Cannabis Sativa</i> | Maroon J et al 2018 (31) | -anti-inflammatory, oligo-protective, and neuroprotective compounds that target the ECS |
| | Luo Q et al 2019 (32) | -Grossamide, a representative lignanamide in <i>hemp</i> seed, could inhibit neuroinflammation in neurodegenerative diseases like MS |
| | Wang S et al 2019 (18) | -CLG increased AMPK expression -suppressed the NF- κ B signaling pathway - decreased pro-inflammatory cytokine levels. -reduces the assembly of cellular reactive oxygen species -stimulated the Nrf-2 signaling pathway. -AMPK was also involved in the anti-inflammatory effect of CLG |
| | Zhou Y et al 2018 (33) | -rich in phenylpropionamidesoesan, which has effective anti-neuroinflammatory activity |
| | Rezapour-Firouzi S et al 2013 (6) | -Using hemp seed oil supplementation in the company of evening prime rose oil and hot nature diet showed immune-modulating effects with RRMS patients resulting in significant improvements in the EDSS score and the relapse rate. |

Non-drug varieties of *Cannabis sativa* L. are mostly used for their high ω -3 fatty acid-containing oil. Hemp protein (HPIs) contains a mixture of polypeptides, oligopeptides, and amino acids like Asp + Asn (11–12%) and Glu + Gln (18%), and is also rich in Arg (12–13%) [34]. Anti-inflammatory, oligo-protective, and neuroprotective compounds in hemp seed that target the ECS (endocannabinoid system) may offer therapeutic effects for MS [31].

HPIs (Hemp protein isolated) antioxidative and anti-inflammatory responses in activated microglia are increased by hydrolysis by alcalase and flavourzyme, obtaining HPHs (Hemp protein hydrolysis) [34]. Grossamide, a representative lignanamide in hemp seed, inhibited the NF- κ B signaling pathway and the secretion of pro-inflammatory mediators like IL-6 and TNF- α it also decreased the level of LPS-mediated IL-6 and TNF- α mRNA. It also atten-

uated the LPS-induced expression of Toll-like receptor 4 (TLR4) and myeloid differentiation factor 88 (MyD88). To conclude, grossamide could be a candidate for inhibiting neuro inflammation in neurodegenerative diseases like MS [32].

A study on a mouse model of neuro inflammation induced by LPS (Lipopolysaccharides) found that hemp seed extracts rich in phenylpropionamides play an effective and influential role anti-neuro inflammatory role [33]. Hemp seed also provides a phenylpropionamide, Coumaroyl Laminobutanol Glucopyranoside (CLG), which is believed to increase dinosine monophosphate-activated protein kinase (AMPK) expression, suppress the nuclear factor-kappa B (NF- κ B) signaling pathway by inhibiting the phosphorylation of I κ B α and NF- κ B p65 and decrease pro-inflammatory cytokine levels during a concentration-dependent manner. CLG reduces cellular reactive oxygen species assembly and stimulates the nuclear factor erythroid 2-related factor 2 (Nrf-2) signaling pathway. AMPK is also involved in the anti-inflammatory effect of CLG [18]. However, in a study on a cellular model of Parkinson's disease, caffeoyltyramide (hemp seed extract) could not affect cell death induced by rotenone but could protect against H₂O₂ induced cell death [35]. The only human research on the effect of hemp seed on MS patients is done by Rezapour et al. They used hemp seed oil supplementation in the company of evening prime rose oil and hot nature diet. 9:1 combination of HSO (hemp seed oil) and EPO (evening primrose oil) as a dietary supplement in a daily dose of 18-21 g/day for six months showed immune-modulating effects with RRMS (relapsing-remitting multiple sclerosis) patients resulting in significant improvement in the EDSS (Expanded Disability Status Scale) score and the relapse rate [6].

5. Conclusions and Further Prospects

Sensory loss, visual disturbance, double vision, muscle weakness, ataxia, and impaired balance is now well-acknowledged to be increased in patients with multiple sclerosis. Our review focused on uncovering new treatments for reducing disabilities and decreasing the EDSS score on MS patients. According to the literature, consuming *Nigella sativa* by MS patients and its prevention effects can be therapeutic by suppressing inflammation, enhancing remyelination, and reducing the expression of TGF β 1 in rats. Hemp seed as a medicinal herb to treat multiple sclerosis is believed to increase AMPK, suppress NF- κ B, inhibit the secretion of pro-inflammatory mediators in rat models, and improve the disability status scale in human models. Although many studies indicate the therapeutic effects of these herbs on MS, the number of clinical interventional human research projects is low.

References

1. Wahls TL, Chenard CA, Snetselaar LG. Review of Two Popular Eating Plans within the Multiple Sclerosis Community: Low Saturated Fat and Modified Paleolithic. *Nutrients*. 2019; 11(2): 352.
2. Alroughani R, Boyko A. Pediatric multiple sclerosis: a review. *BMC neurology*. 2018; 18(1): 27.
3. Shaarani S, Hamid SS, Mohd Kaus NH. The Influence of Pluronic F68 and F127 Nanocarrier on Physicochemical Properties, In vitro Release, and Antiproliferative Activity of Thymoquinone Drug. *Pharmacognosy research*. 2017; 9(1): 12-20.
4. Ochi H. [Epidemiology of Multiple Sclerosis: Is Multiple Sclerosis on the Rise?]. *Brain and nerve = Shinkei kenkyu no shinpo*. 2020; 72(5): 467-84.
5. Mojaverrostami S, Bojnordi MN, Ghasemi-Kasman M, Ebrahimzadeh MA, Hamidabadi HG. A Review of Herbal Therapy in Multiple Sclerosis. *Advanced pharmaceutical bulletin*. 2018; 8(4): 575-90.
6. 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. *Complementary therapies in medicine*. 2013; 21(5): 473-80.
7. Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, et al. A review on therapeutic potential of *Nigella sativa*: A miracle herb. *Asian Pac J Trop Biomed*. 2013 ;3(5): 337-52.
8. Shaterzadeh-Yazdi H, Noorbakhsh MF, Hayati F, Samarghandian S, Farkhondeh T. Immunomodulatory and Anti-inflammatory Effects of Thymoquinone. *Cardiovascular & hematological disorders drug targets*. 2018; 18(1): 52-60.
9. Noorbakhsh MF, Hayati F, Samarghandian S, Shaterzadeh-Yazdi H, Farkhondeh T. An Overview of Hepatoprotective Effects of Thymoquinone. *Recent patents on food, nutrition & agriculture*. 2018; 9(1): 14-22.
10. Benhelima A, Kaid-Omar Z, Hemida H, Benmahdi T, Addou A. NEPHROPROTECTIVE AND DIURETIC EFFECT OF NIGELLA SATIVA L SEEDS OIL ON LITHIASIC WISTAR RATS. *African journal of traditional, complementary, and alternative medicines: AJTCAM*. 2016; 13(6): 204-14.
11. Rizka A, Setiati S, Lydia A, Dewiasty E. Effect of *Nigella sativa* Seed Extract for Hypertension in Elderly: a Double-blind, Randomized Controlled Trial. *Acta medica Indonesiana*. 2017; 49(4): 307-13.
12. Hamdan A, Haji Idrus R, Mokhtar MH. Effects of *Nigella Sativa* on Type-2 Diabetes Mellitus: A Systematic Review. *International journal of environmental research and public health*. 2019; 16(24): 4911.
13. Ibrahim RM, Hamdan NS, Mahmud R, Imam MU, Saini SM, Rashid SN, et al. A randomised controlled trial on hypolipidemic effects of *Nigella Sativa* seeds powder in menopausal women. *Journal of translational medicine*. 2014; 12: 82.
14. Forouzanfar F, Bazzaz BS, Hosseinzadeh H. Black cumin (*Nigella sativa*) and its constituent (thymoquinone): a review on anti-microbial effects. *Iranian journal of basic medical sciences*. 2014; 17(12): 929-38.
15. Rizk FH, Ibrahim MAA, Abd-Elsalam MM, Soliman NA, Abd-El-salam SM. Gastroprotective effects of montelukast and *Nigella sativa*.

- va oil against corticosteroid-induced gastric damage: they are much more than antiasthmatic drugs. *Canadian journal of physiology and pharmacology*. 2017; 95(6): 714-20.
16. Jin S, Lee MY. The ameliorative effect of hemp seed hexane extracts on the *Propionibacterium acnes*-induced inflammation and lipogenesis in sebocytes. *PLoS one*. 2018; 13(8): e0202933.
 17. Citti C, Linciano P, Panseri S, Vezzalini F, Forni F, Vandelli MA, et al. Cannabinoid Profiling of Hemp Seed Oil by Liquid Chromatography Coupled to High-Resolution Mass Spectrometry. *Frontiers in plant science*. 2019; 10: 120.
 18. Wang S, Luo Q, Zhou Y, Fan P. CLG from Hemp Seed Inhibits LPS-Stimulated Neuroinflammation in BV2 Microglia by Regulating NF- κ B and Nrf-2 Pathways. *ACS omega*. 2019; 4(15): 16517-23.
 19. Fukaura H, Kent SC, Pietruszewicz MJ, Khoury SJ, Weiner HL, Hafler DA. Induction of circulating myelin basic protein and proteolipid protein-specific transforming growth factor- β 1-secreting Th3 T cells by oral administration of myelin in multiple sclerosis patients. *The Journal of clinical investigation*. 1996; 98(1): 70-7.
 20. Hafler DA, Kent SC, Pietruszewicz MJ, Khoury SJ, Weiner HL, Fukaura H. Oral administration of myelin induces antigen-specific TGF- β 1 secreting T cells in patients with multiple sclerosis. *Annals of the New York Academy of Sciences*. 1997; 835: 120-31.
 21. Cenini G, Lloret A, Cascella R. Oxidative Stress in Neurodegenerative Diseases: From a Mitochondrial Point of View. *Oxidative medicine and cellular longevity*. 2019; 2019: 2105607.
 22. Gilgun-Sherki Y, Melamed E, Offen D. The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. *Journal of neurology*. 2004; 251(3): 261-8.
 23. Gonsette RE. Oxidative stress and excitotoxicity: a therapeutic issue in multiple sclerosis? *Multiple sclerosis (Houndmills, Basingstoke, England)*. 2008; 14(1): 22-34.
 24. Tryfonos C, Mantzorou M, Fotiou D, Vrizas M, Vadikolias K, Pavlidou E, et al. Dietary Supplements on Controlling Multiple Sclerosis Symptoms and Relapses: Current Clinical Evidence and Future Perspectives. *Medicines (Basel, Switzerland)*. 2019; 6(3): 95.
 25. Tavakkoli A, Hosseinzadeh H. Chapter 21 - *Nigella sativa* L. and thymoquinone as neuroprotective antioxidants. In: Martin CR, Preedy VR, editors. *Oxidative Stress and Dietary Antioxidants in Neurological Diseases*: Academic Press; 2020. p. 325-41.
 26. Gali-Muhtasib H, El-Najjar N, Schneider-Stock R. The medicinal potential of black seed (*Nigella sativa*) and its components. In: Khan MTH, Ather A, editors. *Advances in Phytomedicine*. 2: Elsevier; 2006. p. 133-53.
 27. 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. *The Journal of Basic & Applied Zoology*. 2014; 67(5): 182-95.
 28. Noor NA, Fahmy HM, Mohammed FF, Elsayed AA, Radwan NM. *Nigella sativa* ameliorates inflammation and demyelination in the experimental autoimmune encephalomyelitis-induced Wistar rats. *International journal of clinical and experimental pathology*. 2015; 8(6): 6269-86.
 29. Mohamed A, Waris HM, Ramadan H, Quereshi M, Kalra J. Amelioration of chronic relapsing experimental autoimmune encephalomyelitis (cr-*ea*) using thymoquinone - *biomed* 2009. *Biomedical sciences instrumentation*. 2009; 45: 274-9.
 30. Mohamed A, Afridi DM, Garani O, Tucci M. Thymoquinone inhibits the activation of NF- κ B in the brain and spinal cord of experimental autoimmune encephalomyelitis. *Biomedical sciences instrumentation*. 2005; 41: 388-93.
 31. Maroon J, Bost J. Review of the neurological benefits of phytocannabinoids. *Surgical neurology international*. 2018; 9: 91.
 32. Luo Q, Yan X, Bobrovskaya L, Ji M, Yuan H, Lou H, et al. Anti-neuroinflammatory effects of grossamide from hemp seed via suppression of TLR-4-mediated NF- κ B signaling pathways in lipopolysaccharide-stimulated BV2 microglia cells. *Molecular and cellular biochemistry*. 2017; 428(1-2): 129-37.
 33. Zhou Y, Wang S, Ji J, Lou H, Fan P. Hemp (*Cannabis sativa* L.) Seed Phenylpropionamides Composition and Effects on Memory Dysfunction and Biomarkers of Neuroinflammation Induced by Lipopolysaccharide in Mice. *ACS omega*. 2018; 3(11): 15988-95.
 34. Rodriguez-Martin NM, Toscano R, Villanueva A, Pedroche J, Millan F, Montserrat-de la Paz S, et al. Neuroprotective protein hydrolysates from hemp (*Cannabis sativa* L.) seeds. *Food & function*. 2019; 10(10): 6732-9.
 35. Maiolo SA, Fan P, Bobrovskaya L. Bioactive constituents from cinnamon, hemp seed and *Polygonum cuspidatum* protect against H₂O₂ but not rotenone toxicity in a cellular model of Parkinson's disease. *Journal of traditional and complementary medicine*. 2018; 8(3): 420-7.