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

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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 β1 in rats. Hemp seed as a therapeutic herb to treat multiple sclerosis is believed to increase AMPK, suppress NF-κB, 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 neurodegenerative, 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 thymoquinone (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)

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-y (IFN-y) 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: diinosine monophosphate-activated protein kinase, NF-Κb: 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 β1 (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 (reactive 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-kB. 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

<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tavakkoli A et al 2020 (25)</td>
<td>- Upregulation of the Nrf2/HO-1 pathway</td>
</tr>
<tr>
<td></td>
<td>- Antioxidant effects</td>
</tr>
<tr>
<td>Gali-Muhtasib H et al 2006 (26)</td>
<td>- Improved natural killer cell health</td>
</tr>
<tr>
<td>Fahmy HM et al 2014 (27) Noor NA et al 2015 (28)</td>
<td>- Ameliorated the clinical signs of EAE</td>
</tr>
<tr>
<td></td>
<td>- Suppressed inflammation</td>
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<td></td>
<td>- Enhanced remyelination in the cerebellum</td>
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<tr>
<td></td>
<td>- Reduced the expression of TGF β1 (Transforming growth factor) in CNS (central nervous system)</td>
</tr>
<tr>
<td>Mohamed A et al 2009 (29)</td>
<td>- Decreases ROS production and levels of NO and MDA in the brain and medulla spinalis tissue</td>
</tr>
<tr>
<td>Mohamed A et al 2005 (30)</td>
<td>- Increase the red blood cell glutathione, infiltration of mononuclear cells, and counter perivascular cuffing within the brain and neural structure</td>
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<tr>
<td></td>
<td>- Inhibited the activation of NF-kappaB</td>
</tr>
<tr>
<td>Maroon J et al 2018 (31)</td>
<td>- Anti-inflammatory, oligo-protective, and neuroprotective compounds that target the ECS</td>
</tr>
<tr>
<td>Luo Q et al 2019 (32)</td>
<td>- Grossamide, a representative lignanamide in hemp seed, could inhibit neuroinflammation in neurodegenerative diseases like MS</td>
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<tr>
<td>Wang S et al 2019 (18)</td>
<td>- CLG increased AMPK expression</td>
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<tr>
<td></td>
<td>- Suppressed the NF-κB signaling pathway</td>
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<tr>
<td></td>
<td>- Decreased pro-inflammatory cytokine levels.</td>
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<tr>
<td></td>
<td>- Stimulated the Nrf-2 signaling pathway</td>
</tr>
<tr>
<td></td>
<td>- AMPK was also involved in the anti-inflammatory effect of CLG</td>
</tr>
<tr>
<td>Zhou Y et al 2018 (33)</td>
<td>- Rich in phenylpropionamides dosan, which has effective anti-neuroinflammatory activity</td>
</tr>
<tr>
<td>Rezapour-Firouzi S et al 2013 (6)</td>
<td>- 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.</td>
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</table>

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) antioxidant and anti-inflammatory responses in activated microglia are increased by hydrolysis by alcalase and flavourzyme, obtaining HPHs (Hemp protein hydrolysate) [34]. Grossamide, a representative lignanamide in hemp seed, inhibited the NF-κB 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, Coumaroy Laminobutanol Glucopyranoside (CLG), which is believed to increase dinosine monophosphate-activated protein kinase (AMPK) expression, suppress the nuclear factor-kappa B (NF-κB) signaling pathway by inhibiting the phosphorylation of IkBα and NF-κB 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 β1 in rats. Hemp seed as a medicinal herb to treat multiple sclerosis is believed to increase AMPK, suppress NF-κB, 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

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