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Original Article

The Effects of Combination of Hydro Alcoholic Extracts of *Nigella Sativa* and *Linum Usitatissimum* on General Health, Fatigue and Its Contributing Factors in Relapsing-Remitting Multiple Sclerosis; a Pilot Randomized Double-blind Placebo-Controlled Clinical Trial

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Abstract

Introduction: Fatigue is one of the most common and debilitating symptoms experienced by multiple sclerosis (MS) patients. This study aimed to evaluate the effects of combination of hydroalcoholic extracts of *Nigella sativa* and *Linum Usitatissimum* on general health, fatigue and its contributing factors in patients with relapsing-remitting MS (RRMS).

Methods: In this parallel-group, randomized, double-blind, placebo-controlled pilot clinical trial, patients diagnosed with RRMS based on the 2017 McDonald criteria, with Expanded Disability Status Scale (EDSS)<4.5, and experiencing fatigue were enrolled. Participants were randomly assigned to receive the either the herbal supplement (n=25) or placebo (n=25). Capsules were administered twice daily over a period of three months. Fatigue and its contributing factors were assessed using the Comprehensive Fatigue Assessment Battery for Multiple Sclerosis (CFAB-MS) at baseline and at the end of the interventions.

Result: A total of 35 patients completed the trial, 17 in the intervention group and 18 in the placebo group. Based on the visual analogue scale (VAS) for general health, the intervention group showed a statistically significant improvement in nutritional status (p-value:0.009). However, no significant differences were observed between the groups in terms of physical, mental, and social fatigue, pain, sleep disturbances, stress, mood, anxiety and worry, nutrition, environmental interactions, or fatigue management indices (*P*-values>0.05).

Conclusion: Based on this preliminary research, three months of supplementation with a combination of hydroalcoholic extracts of *N. sativa* and *L. Usitatissimum* did not produce a significant improvement in fatigue and its associated factors among patients with RRMS.

Introduction

Multiple sclerosis (MS) is a leading cause of neurological disability in young adults. [1] It is an inflammatory disease of the central nervous system (CNS) characterized by demyelination and axons degeneration in the brain and spinal cord. Although MS most commonly affects individuals between 20 and 40 years of age, it can develop at any stage of life. [2] The majority of patients experience relapsing-remitting MS (RRMS), which is marked by episodes of neurological dysfunction followed by periods of remission. [3]

Fatigue is one of the most prevalent and disabling

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symptoms of MS, affects up to 90% patients. [4,5] MS-related fatigue can be categorized as primary, resulting directly from the disease process and CNS inflammation, or secondary, caused by factors such as sleep disturbances, mood disorders, and medication side effects. [6,7] A large cross-sectional study involving 1,142 patients found no correlation between disease-modifying therapies (DMTs) and fatigue reduction, suggesting that fatigue may arise from mechanisms beyond immune dysregulation. [8,9] Currently, available treatments for fatigue in MS, such as pemoline, methylphenidate, amantadine, and modafinil have shown improvements in clinical trials; however, the effectiveness of these agents is yet to be established. Several studies suggest these agents may not outperform placebo and often lead to undesirable side effects, [10] highlighting the need for safer and more effective therapeutic alternatives. [6,11,12]

Herbal therapy has long history of use in managing a variety of conditions, including neurological disorders like MS. [13-15] *Linum usitatissimum*, also known as common flax or linseed (flaxseed) is one of the richest plant sources of alpha-linolenic acid (omega-3) and linoleic acid (omega-6). [16] It exhibits anti-inflammatory, antioxidant, neuroprotective properties, [17,18] and has demonstrated anti-fatigue effects in clinical studies. [19] Additionally, its potential to alleviate depressive symptoms, [20,21] suggests a possible role in addressing fatigue, a symptom often linked to mood disturbances in MS. *Nigella sativa* (black cumin), a member of the Ranunculaceae family, also possesses anti-inflammatory, antioxidant, and neuroprotective effects. [22-24] In silico evidence suggests potential involvement of active components of *N. sativa* in MS treatment. [25] Experimental evidence shows that *N. sativa* oil and its major active constituent, thymoquinone, can inhibit pro-inflammatory mediators. [26,27] Animal models have further demonstrated its ability to reduce inflammation and promote remyelination in the CNS. [24] Given its anti-fatigue properties, [28,29] efficacy in inflammatory conditions, [30] and positive effects on fatigue such as sleep disturbances, [31] stress, anxiety, [32] and depression, [33,34] *N. sativa* appears to be a promising candidate for fatigue management in MS.

L. usitatissimum and *N. sativa* may offer a beneficial approach to alleviating fatigue in MS. To the best of our knowledge, no prior studies have evaluated the effects of *L. usitatissimum* in MS, and the evidence on *N. sativa* is limited to animal research and a clinical trial involving 31 patients, which reported no significant effectiveness on tremor or quality of life. [23,24,35-37] This pilot randomized controlled trial aimed to evaluate the effects of combination of hydroalcoholic extracts from *N. sativa* and *L. usitatissimum* on general health, fatigue and its contributing factors in patients with RRMS.

Method

Trial Design and Settings

This study was a parallel-group, double-blind, randomized, placebo-controlled pilot clinical trial conducted to evaluate the effects of a combination of hydroalcoholic extracts from *N. sativa* and *L. usitatissimum* on general health, fatigue and its contributing factors in patients with RRMS. The trial was carried out at Imam Reza Hospital, affiliated to Tabriz University of Medical Sciences. The study period was from January to September 2023. This study adhered to the CONSORT statement with an allocation ratio of 1:1. Ethical approval was obtained from the Ethics Committee of Tabriz University of Medical Sciences and the protocol for this trial was registered before participant enrolment in the Iranian Registry of Clinical Trials (IRCT20140617018126N6, Registration date: November 1, 2022). Because no prior comparable clinical trials were available, an evidence-based estimation of effect size for a formal sample size calculation was not feasible.

Participants and Interventions

Eligible participants were:

- Adult (> 18 years-old) patients with RRMS according to the 2017 MacDonald criteria [38]
- Self-reported fatigue
- Expanded Disability Status Scale (EDSS) < 4.5
- Informed consent
- Exclusion criteria included:
- MS relapse or active infection within the last four months
- Receipt of corticosteroid pulse therapy in the last four months.
- Drug abuse or regular alcohol consumption
- Pregnancy
- Use of sedatives or antidepressants
- Presence of pulmonary disease, anemia, uremia, or discopathy
- Lack of consent to participate
- Presence of significant concomitant conditions

Demographic information, medical history, and medication usage were documented prior to randomization. Participants were randomly assigned to either intervention (n = 25) or placebo (n = 25) groups. The intervention group received soft gel capsules combination of hydroalcoholic extracts: 0.75 mL *N. sativa* and 0.75 mL *L. usitatissimum* hydroalcoholic extracts (total volume 1.5 mL per capsule) in addition to routine MS treatment. The placebo group received soft gels containing inert additives, in addition to their routine treatment. Both preparations were manufactured by Sinanoandish Company. Capsules were provided in closed containers. Randomization and group allocation were performed by a researcher not involved in clinical assessments or data collection. Adherence to the intervention was monitored through capsule counts at follow-up visits and participant self-report. Participants were instructed to maintain their prescribed MS medications throughout the study period. Adverse events were recorded if spontaneously reported by participants; no formal adverse event monitoring system was implemented.

Outcome Measures

The primary outcome, fatigue and its contributing factors, was assessed using the Comprehensive Fatigue Assessment

Battery for Multiple Sclerosis (CFAB-MS). The CFAB-MS is a validated instrument that evaluates fatigue across 13 domains through 133 questions, including personal information (7 items), medical information (5 items), general health based on Visual Analogue Scale (VAS-based 9 items), fatigue characteristics (29 items), pain (7 items), sleep (14 items), stress (10 items), mood (7 items), stress and worry (7 items), nutrition (8 items), mobility (7 items), environment (8 items), and history of fatigue management (15 items). Unlike other fatigue assessment scales that primarily assess severity, CFAB-MS offers a comprehensive evaluation of factors that influence fatigue. The tool has demonstrated acceptable validity ($P < 0.05$) and moderate to high reliability (Cronbach's alpha: 0.20–0.75). This study utilized the Persian version of CFAB-MS which has been validated through comparisons with other established instruments, including the Modified Fatigue Impact Scale (MFIS), Hospital Anxiety Depression Scale (HADS), Short-Form McGill Pain Questionnaire (SF-MPQ), and Pittsburg Sleep Quality Index (PSQI). [39,40]

Randomization and blinding

Participants were randomized using a computer-generated block randomization sequence with a fixed block size of six, generated using Random Allocation Software. An independent researcher who was not involved in participant recruitment, clinical assessments, data collection, or statistical analysis generated the allocation sequence and prepared sealed, opaque, sequentially numbered envelopes containing the group assignments. Eligible participants were enrolled by the study investigators, while assignment to the intervention or placebo group was performed according to the pre-generated allocation sequence by the independent researcher. Corresponding white boxes containing either placebo or active soft gels were labeled with matching participant numbers. Only the packaging staff were aware of the allocation. The soft gels were identical in size, shape, color, and odor to maintain blinding. Both participants and study personnel remained blinded to group assignments throughout the study.

Data Collection and Statistical Methods

Data were collected at the baseline and after the intervention using clinical assessments and standardized questionnaires. Given the pilot nature of this study, statistical analyses were considered exploratory and were primarily intended to estimate effect sizes and assess feasibility outcomes to inform a future definitive trial. A per-protocol analysis was conducted using SPSS version 23 for macOS. Statistical tests were selected based on data type and distribution which was assessed using the Shapiro-Wilk test. The independent t-test was used for normally distributed continuous variables, while the Mann-Whitney U-test was used for non-parametric alternative. Chi-square or Fisher's exact tests were applied for categorical variables. In addition, effect sizes for between-group comparisons were calculated as $r = Z/\sqrt{N}$ based on the Mann–Whitney test statistics or Cohen's d (and its 95% confidence intervals) based on the independent sample t test statistics. Intragroup comparisons were made using the Wilcoxon signed-rank test or paired sample t-test. All statistical tests were two-tailed, with a significance level of P-value < 0.05 and 95% CI reported.

Results

Demographic and Clinical Characteristics of Participants

A total of 67 patients were initially assessed for eligibility and 50 were randomized into two the groups. By the end of the trial, 15 participants were lost to follow-up due to failure to return for the post-intervention evaluation at the three-months mark. The final analysis included 35 patients, with 17 in the intervention group and 18 in the placebo group (Figure 1). Baseline characteristics were compared between participants who completed the study and those who withdrew. No significant differences were observed, suggesting that attrition was unlikely to have substantially biased the findings. The mean age of participants was 34.11 ± 9.10 years-old, and the majority (85.7%) were females. There were no statistically significant differences between the groups in terms of age (P-value = 0.245) or sex distribution (P-value = 0.658). Occupational status was similar across both groups, with housekeeping being the most commonly reported occupation (60% overall; 58.8% in the intervention group, and 61.1% in the placebo group; P-value = 0.777). Likewise, no significant difference was found between the groups in terms of disease duration (P-value = 0.660) or DMT (P-value = 0.387). The sociodemographic and clinical characteristics of the participants are summarized in Table 1.

The effects of intervention on general summary of health

At an exploratory level, visual Analogue Scale (VAS) assessments for subjective fatigue, pain, depression, stress, anxiety and worry, sleep disturbances, and waking disability did not show significant differences either between two groups or within groups over the course of the study (all P-values > 0.05). However, the nutrition VAS scores demonstrated a statistically significant improvement in the intervention group (P-value = 0.008). Furthermore, the change in nutrition VAS score from baseline to the end of the study showed a significantly greater improvement in the intervention group compared to the placebo group (P-value = 0.009) (Table 2). Given that multiple subjective outcomes were assessed and pilot nature of this study, these findings should be interpreted cautiously and as exploratory.

The effects of intervention on fatigue and its contributing factors

Scores for physical, Mental, and Social Fatigue index improved in both the intervention and placebo groups; however, these improvements did not differ significantly between the groups. Additionally, no statistically significant difference was observed between the groups in other CFAB-MS domains, including sleep duration, pain, sleep quality, stress, mood, anxiety and worry, nutrition,

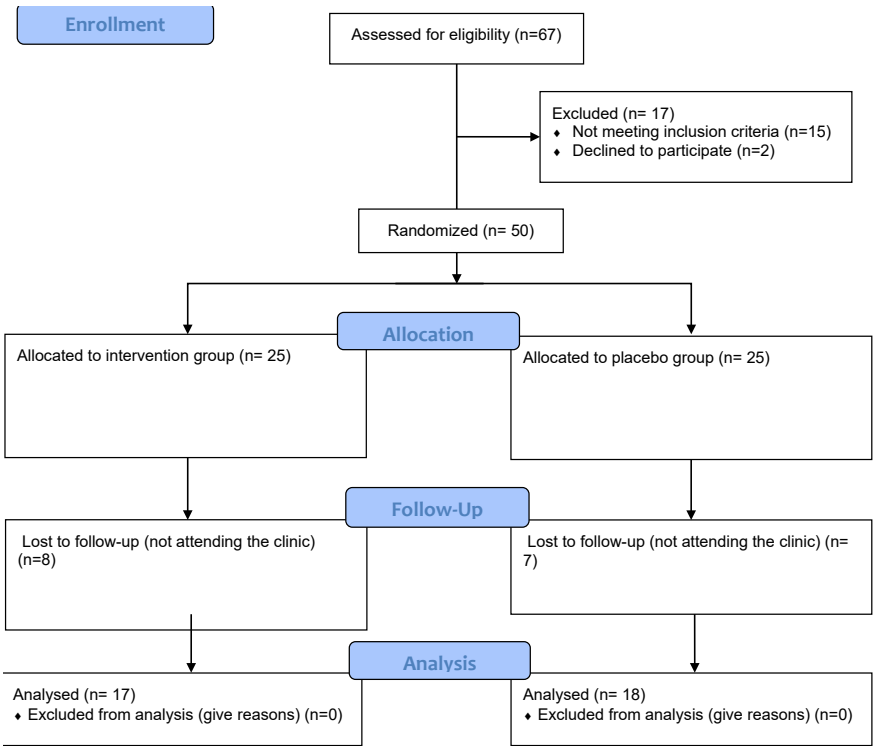


Figure 1. CONSORT 2010 flow diagram of participant recruitment and allocation

mobility, environment, or fatigue management both before and after the intervention (all *P*-values > 0.05) (Table 3). Given the exploratory nature of the study, these findings are reported descriptively, and within-group changes are not interpreted as indicators of treatment efficacy.

Discussion

This study investigated the effects of a combination of hydroalcoholic extracts from *N. sativa* and *L. usitatissimum* on fatigue and its contributing factors (including both primary and secondary fatigue) in patients with RRMS with EDSS < 4.5. The intervention group exhibited a statistically significant improvement in subjective nutrition assessment; however, there were no significant improvements in fatigue levels or related factors such as mood, stress, anxiety, pain, mobility, environmental influences, or fatigue management. The findings did not provide clinically meaningful insights into the potential therapeutic implications of combination of these herbal extracts in MS management. The findings should be interpreted as exploratory and hypothesis-generating given the pilot nature of the study.

Alternative therapies, particularly supplementation with herbs, are being increasingly explored for managing MS-related fatigue. [10,41-44] Despite growing popularity, evidence supporting their efficacy and safety remains limited and inconsistent. [45,46] Additionally, herbal interventions may exhibit placebo effects, [47] although such effects were not evident in our trial. The widespread belief in the safety of herbal supplements is not always justified, as some compounds may pose toxicological risks. [48-50] Therefore, rigorously designed clinical trials are essential to support evidence-based recommendations in this area. Given these limitations, new research indicates that herbal therapies may help alleviate MS fatigue. [51,52] For example, Broch et al. and Toosy et al. note an increasing interest in non-pharmacological treatments that complement holistic MS management approaches. [8,53] Some studies suggest that herbs such as lavender and *ginkgo biloba* may provide benefits, with these natural remedies having less side effects and perhaps reducing symptoms without the hazards associated with synthetic medications. [54,55] Emerging research has also shown that certain herbal therapies may alleviate fatigue in MS. For instance, *Andrographis paniculata*, showed a 44% improvement in fatigue over 12 months, [56] and *Ginkgo biloba* demonstrated short-term benefits. [55] *Ginseng* was also reported to significantly improve physical fatigue after three months, [57,58] while EGCG (epigallocatechin-3-gallate), from green tea improved muscle metabolism and energy use. [59] Conversely, other natural products, including cannabis and omega-3/omega-6 fatty acids, have not shown significant improvements in MS-related fatigue. [60-62] The present study examined the combination of *N. sativa* (black cumin) and *L. usitatissimum* (flaxseed), both of which possess bioactive compounds with known anti-inflammatory and antioxidant properties, mechanisms potentially relevant to MS fatigue. Despite promising preclinical data, at an exploratory level, three months of supplementation did not produce significant improvements in fatigue or its contributing factors when compared with placebo. The only notable effect was an improvement in the subjective nutritional status of participants, possibly attributable to the nutritional and metabolic properties of the extracts used. This suggests a potential secondary benefit worth further exploration. The lack of significant results may stem from limitations such as suboptimal dosage, inadequate intervention duration, or insufficient sample size.

As the first study which assessed the effects of

Table 1. The characteristics of the participants

Characteristics	Total cases (n = 35)	Intervention (n = 17)	Placebo (n = 18)	*P*-value
Age [years-old; mean (SD)]	34.11 (9.10)	35.94 (8.30)	32.39 (9.70)	0.245[a]
Sex				0.658[b]
Male	5 (14.3%)	3 (17.6%)	2 (11.1%)	
Female	30 (85.7%)	14 (82.4%)	16 (88.9%)	
Job				0.777[c]
Freelance job	3 (8.6%)	1 (5.9 %)	2 (11.1%)	
House keeping	21 (60.0%)	10 (58.8 %)	11 (61.1 %)	
Midwife	2 (5.7%)	1 (5.9 %)	1 (5.6%)	
Retired	1 (2.9%)	1 (5.9 %)	0 (0.0%)	
Student	7 (20.0%)	3 (17.6 %)	4 (22.2 %)	
Unemployed	1 (2.9%)	1 (5.9 %)	0 (0.0%)	
First sign				0.099[c]
Ataxia	2 (5.7%)	0 (0.0%)	2 (11.1%)	
Blurred vision	10 (28.6%)	5 (29.4%)	5 (27.8%)	
Diplegia	1 (2.9%)	0 (0.0%)	1 (5.6%)	
Diplopia	1 (2.9%)	0 (0.0%)	1 (5.6%)	
Muscle spasms	1 (2.9%)	0 (0.0%)	1 (5.6%)	
Optic neuritis	1 (2.9%)	0 (0.0%)	1 (5.6%)	
Paresis	6 (17.1%)	6 (35.3%)	0 (0.0%)	
Sensory	13 (37.1%)	6 (35.3%)	7 (38.9%)	
Disease duration [months; median (IQR)]	48.0 (60)	48.0 (93)	42.0 (51)	0.660[d]
MS drug				0.387[c]
Dimethyl Fumarate	14 (40.0%)	4 (23.5%)	10 (55.6%)	
Fingolimod	1 (2.9%)	0 (0.0%)	1 (5.6%)	
Glatiramer Acetate	1 (2.9%)	1 (5.9 %)	0 (0.0%)	
Interferon beta 1-a	4 (11.4%)	2 (11.8%)	2 (11.1%)	
Natalizumab	2 (5.7%)	2 (11.8%)	0 (0.0%)	
Ocrelizumab	6 (17.1%)	4 (23.5%)	2 (11.1%)	
Rituximab	5 (14.3%)	3 (17.6 %)	2 (11.1%)	
No drug	2 (5.7%)	1 (5.9 %)	1 (5.6%)	

A *P*-value of < 0.05 was considered statistically significant. Continuous variables were summarized as mean ± standard deviation when normally distributed and as median (interquartile range) when distributional assumptions were not met, based on Shapiro–Wilk test results. SD: standard deviation; IQR: interquartile range

[a] Independent samples T-test [b] Fisher's exact test [c] Chi-square test [d] Mann-Whitney U test

Table 2. The effects of combination of hydroalcoholic extracts from *N. sativa* and *L. usitatissimum* on general summary of health. Continuous variables were summarized as mean ± standard deviation when normally distributed and as median (interquartile range) when distributional assumptions were not met, based on Shapiro–Wilk test results

A general summary of health, VAS	Timing	Intervention (n = 17)	Placebo (n = 18)	Effect size[d], *P*-value
Fatigue	Baseline [b]	90.0 (28)	75.0 (25)	-0.192, 0.273
	Follow-up [b]	90.0 (35)	77.5 (34)	–0.147, 0.405
	Intragroup *P*-value [c]	0.292	0.816	-
	Score change [b]	0.00 (17.50)	0.00 (31.25)	–0.101, 0.568
Pain	Baseline [b]	35.0 (70)	17.5 (48)	-0.101, 0.568
	Follow-up [b]	45.0 (75)	20.0 (50)	–0.130, 0.463
	Intragroup *P*-value	0.665	0.777	-
	Score change [b]	0.00 (20.00)	0.00 (33.75)	–0.127, 0.463
Depression	Baseline [b]	50.0 (53)	30.0 (95)	-0.104, 0.546
	Follow-up [b]	50.0 (83)	50.0 (61)	–0.056, 0.757
	Intragroup *P*-value	0.666	0.232	-
	Score change [b]	0.00 (45.00)	7.00 (36.25)	–0.115 0.503

Table 2. Continued.

A general summary of health, VAS	Timing	Intervention (n = 17)	Placebo (n = 18)	Effect size [d], *P*-value
Stress	Baseline [b]	85.0 (35)	75.0 (20)	-0.099, 0.568
	Follow-up [b]	85.0 (80)	85.0 (33)	–0.132, 0.463
	Intragroup *P*-value	0.469	0.959	-
	Score change [a]	-9.12 (45.56)	0.56 (19.17)	0.280 (95%CI: -0.389, 0.944), 0.427
Anxiety and worry	Baseline [b]	80.0 (40)	80.0 (51)	-0.017, 0.935
	Follow-up [b]	80.0 (80)	75.0 (43)	0.757, –0.056
	Intragroup *P*-value	0.196	0.675	-
	Score change [a]	-12.06 (38.73)	-5.00 (42.77)	0.173 (95%CI: -0.493, 0.836), 0.613
Sleep Problems	Baseline [b]	60.0 (80)	62.5 (76)	-0.121, 0.483
	Follow-up [b]	10.0 (83)	47.5 (76)	–0.017, 0.935
	Intragroup *P*-value	0.115	0.208	-
	Score change [a]	-17.35 (40.62)	-7.50 (31.63)	0.272 (95%CI: -0.396, 0.936), 0.428
Poor Nutrition	Baseline [b]	50.0 (83)	42.5 (50)	-0.118, 0.503
	Follow-up [b]	5.0 (50)	45.0 (75)	–0.206, 0.232
	Intragroup *P*-value	0.008*	0.365	-
	Score change [b]	-5.00 (47.50)	0.00 (27.50)	–0.441, 0.009*
Walking disability	Baseline [b]	30.0 (83)	17.5 (50)	-0.199, 0.258
	Follow-up [b]	10.0 (88)	17.5 (50)	–0.051, 0.782
	Intragroup *P*-value	0.482	0.779	-
	Score change [b]	0.00 (7.50)	0.00 (17.50)	–0.130, 0.442

VAS: Visual Analogue Scale.
[a] Data are presented as mean (SD). *P*-value of independent samples T-test is reported
[b] Data are presented as median (IQR). *P*-value of Mann Whitney U test is reported
[c] Based on Wilcoxon signed-rank test
[d] r = Z/√N based on the Mann–Whitney U test results or Cohen's d based on the independent sample t-test
* Statistically significant

Table 3. The effects of combination of hydroalcoholic extracts from *N. sativa* and *L. usitatissimum* on fatigue and its contributing factor. Continuous variables were summarized as mean ± standard deviation when normally distributed and as median (interquartile range) when distributional assumptions were not met, based on Shapiro–Wilk test results

Fatigue and Contributing Factors	Timing	Intervention (n=17)	Placebo (n=18)	Effect size [d], *P*-value
Physical, Mental, and Social Fatigue index	Baseline [a]	41.59 (15.67)	42.56 (20.35)	0.053 (95%CI: -0.610, 0.716), 0.876
	Follow-up [a]	40.47 (21.33)	42.00 (23.78)	0.068 (95%CI: -0.596, 0.730), 0.843
	Intragroup *P*-value [c]	0.906	0.670	-
	Score change [a]	-1.12 (16.07)	-0.56 (14.24)	0.037 (95%CI: -0.626, 0.700), 0.913
Pain index	Baseline [a]	10.29 (5.37)	10.67 (8.40)	0.053 (95%CI: -0.611, 0.715), 0.876
	Follow-up [a]	10.88 (7.43)	11.50 (8.60)	0.077 (95%CI: -0.587, 0.739), 0.822
	Intragroup *P*-value [c]	0.641	0.997	-
	Score change [b]	-1.00 (11.50)	0.00 (5.50)	-0.003, 0.987
Sleep Duration (In hours)	Baseline [a]	6.79 (2.25)	8.17 (2.02)	0.643 (95%CI: -0.043, 1.319), 0.066
	Follow-up [b]	8.0 (1.3)	8.0 (2.3)	-0.011, 0.961
	Intragroup *P*-value [c]	0.326	0.292	-
	Score change [a]	0.65 (2.49)	-0.67 (2.25)	-0.554 (95%CI: -1.226, 0.126), 0.111
Sleep Problems index	Baseline [a]	14.41 (5.00)	14.00 (5.58)	-0.078 (95%CI: -0.740, 0.586), 0.820
	Follow-up [a]	13.47 (4.36)	12.50 (5.03)	-0.206 (95%CI: -0.869, 0.461), 0.547
	Intragroup *P*-value [c]	0.443	0.193	-
	Score change [a]	-0.94 (5.62)	-1.50 (4.38)	-0.111 (95%CI: -0.774, 0.553), 0.744

Table 3. Continued.

Fatigue and Contributing Factors	Timing	Intervention (n=17)	Placebo (n=18)	Effect size [d], *P*-value
Stress index	Baseline [a]	24.65 (6.42)	23.89 (8.39)	-0.101 (95%CI: -0.908, 0.423), 0.767
	Follow-up [a]	23.29 (8.31)	21.11 (9.52)	-0.244 (95%CI: -1.226, 0.126), 0.476
	Intragroup *P*-value [c]	0.378	0.176	-
	Score change [b]	0.00 (7.00)	0.00 (7.75)	-0.070, 0.684
Mood index	Baseline [a]	12.29 (4.00)	12.00 (5.42)	-0.061 (95%CI: -0.724, 0.602), 0.857
	Follow-up [a]	11.47 (4.91)	12.67 (4.95)	0.243 (95%CI: -0.425, 0.906), 0.478
	Intragroup *P*-value [c]	0.673	0.949	-
	Score change [b]	0.00 (5.50)	0.00 (2.50)	-0.132, 0.443
Anxiety and Worry index	Baseline [b]	9.0 (17)	13.5 (12)	-0.221, 0.195
	Follow-up [b]	11.0 (15)	10.0 (10)	-0.084, 0.636
	Intragroup *P*-value [c]	0.659	0.006*	-
	Score change [b]	-2.00 (7.50)	-3.00 (7.75)	-0.073, 0.089
Nutrition index	Baseline [a]	6.24 (3.47)	6.17 (2.73)	-0.022 (95%CI: -0.685, 0.641), 0.948
	Follow-up [a]	5.12 (3.81)	4.61 (2.70)	-0.154 (95%CI: -0.817, 0.511), 0.651
	Intragroup *P*-value [c]	0.122	0.050	-
	Score change [b]	0.00 (3.00)	-1.00 (3.25)	-0.069, 0.708
Mobility index	Baseline [b]	1.0 (6)	1.0 (1)	0.236, 0.195
	Follow-up [b]	1.0 (1)	1.0 (1)	-0.045, 0.807
	Intragroup *P*-value [c]	0.080	0.606	-
	Score change [b]	0.00 (5.00)	0.00 (0.25)	-0.229, 0.219
Environment index	Baseline [b]	1.0 (0.75)	1.0 (1.38)	-0.014, 0.935
	Follow-up [b]	1.0 (1.40)	1.0 (1.55)	-0.006, 0.987
	Intragroup *P*-value [c]	0.724	0.220	-
	Score change [a]	-0.07 (0.87)	-0.15 (0.58)	-0.107 (95%CI: -0.769, 0.557), 0.754
Fatigue management index	Baseline [b]	1.00 (4.00)	1.00 (4.00)	-0.064, 0.732
	Follow-up [b]	1.00 (3.00)	0.50 (6.00)	-0.092, 0.613
	Intragroup *P*-value [c]	0.387	0.384	-
	Score change [b]	0.00 (4.50)	0.00 (2.00)	-0.209, 0.232

[a] Data are presented as mean (SD). *P*-value of independent samples T-test is reported
[b] Data are presented as median (IQR). *P*-value of Mann-Whitney U test is reported
[c] Based on the Wilcoxon signed-rank test
[d] r = Z/√N based on the Mann–Whitney U test results or Cohen's d based on the independent sample t-test
* Statistically significant

combination of hydroalcoholic extracts from *N. sativa* and *L. usitatissimum* in patients with RRMS, this study employed a randomized, double-blind, placebo-controlled trial design, which minimizes selection and performance bias and strengthens internal validity. Allocation concealment and blinding of both participants and investigators reduced the risk of expectation bias. Outcomes were assessed using a validated instrument in patients with RRMS and baseline and post-intervention assessments were conducted in both groups, allowing evaluation of within-group changes and robust between-group comparisons. Despite the mentioned strengths, this study had some limitations, too. First, the relatively small sample size reduced statistical power and increased the risk of Type II error. The dropout rate of (30%) may have introduced bias. Second, the intervention period may have been too short to yield measurable effects in a chronic condition like MS fatigue. Third, we did not evaluate biomarkers (e.g., inflammatory or oxidative stress markers), which could have helped elucidate underlying mechanisms of action. Finally, the single-center design and narrow inclusion criteria (e.g., EDSS < 4.5, RRMS only) limit the generalizability of the findings to the broader MS population, including those with more advanced or progressive forms of the disease. These findings highlight several avenues for future research. Larger, multi-center trials with extended intervention and follow-up periods are needed to assess the long-term impact of this herbal supplementation. Dose-response studies would help determine the optimal therapeutic range. Additionally, studies examining interactions between herbal extracts and existing MS medications would clarify potential synergistic or antagonistic effects. Incorporating biomarker analysis may also help uncover mechanism underlying observed clinical effects. Finally, evaluating outcomes across

various MS subtypes could guide personalized therapeutic approaches.

Conclusion

This pilot RCT suggested that three months of supplementation with combination of hydroalcoholic extracts of *N. sativa* and *L. usitatissimum* may not significantly improve fatigue or its contributing factors in patients with RRMS; however, the intervention may be associated with a significant subjective improvement in nutritional status. While these findings do not support the use of this herbal combination as a standalone treatment for fatigue in MS, they suggest potential secondary benefits that merit further investigation in larger, more comprehensive studies. The study provides preliminary exploratory data on the potential effects of the intervention, but definitive conclusions regarding clinical efficacy cannot be drawn.

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Authors' Contribution

Amirreza Naseri: Methodology; Formal analysis; Investigation; Resources; Data Curation; Writing - Original Draft; Visualization; Project administration; Funding acquisition; Sarvin Sanaie: Conceptualization; Methodology; Validation; Resources; Writing - Review & Editing; Supervision; Project administration; Funding acquisition; Shahriar Parvaneh: Conceptualization; Methodology; Validation; Writing - Review & Editing; Supervision; Danyal Salabat: Writing - Original Draft; Investigation; Data Curation; Visualization; Hanie Karimi: Writing - Original Draft; Investigation; Data Curation; Visualization; Anahita Najafi: Writing - Original Draft; Investigation; Data Curation; Visualization; Reza Mosaddeghi-Heris: Writing - Original Draft; Investigation; Data Curation; Visualization; Sanaz Hamedeyazdan: Methodology; Resources; Conceptualization; Investigation; Writing - Review & Editing; Mirsobhan Mousavi: Methodology; Resources; Funding acquisition; Conceptualization; Investigation; Writing - Review & Editing; Malihe Talebi: Investigation; Writing - Review & Editing; Mahnaz Talebi: Conceptualization; Methodology; Validation; Investigation; Resources; Writing - Review & Editing; Supervision; Project administration; Funding acquisition; Mostafa Araj-Khodaei: Conceptualization; Investigation; Writing - Review & Editing.

Competing Interests

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (Approval code: IR.TBZMED.REC.1401.657, Approval date: October 10, 2022). Written informed consent was obtained from all participants prior to enrollment. The trial was registered with the Iranian Registry of Clinical Trials (IRCT20140617018126N6, Registration date: November 1, 2022).

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