Research in Pharmaceutical Sciences, December 2025; 20(6): 815-823
Received: 09-01-2024
Peer Reviewed: 07-04-2024
Revised: 03-11-2024
Accepted: 13-11-2024
Published: 15-11-2025

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Original Article

The effectiveness of garlic (*Allium sativum*) extract in improving fatigue and quality of life in patients with multiple sclerosis (MS): a randomized single-blind placebo-controlled clinical trial

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Abstract

Background and purpose: Multiple sclerosis (MS) is a degenerative disease of the central nervous system. Fatigue is one of the most common and disabling symptoms of MS. Garlic is a plant whose anti-fatigue effects have been shown. The present study aimed to investigate the potential effectiveness of garlic on fatigue and quality of life in MS patients.
Experimental approach: In a randomized, single-blind, placebo-controlled clinical trial, adult MS patients were randomly divided into two groups: of drug (garlic) group and a placebo. The drug group received 400-mg tablets of garlic extract (equivalent to 1,200 µg of allicin) twice a day for 4 weeks, while the patients in the placebo group received placebo tablets at the same frequency and duration. Before and after the intervention, scores on a 36-item survey form (SF-36) and fatigue severity scale (FSS) questionnaires were recorded for all patients and compared between the groups.
Findings/Results: Garlic consumption was significantly associated with an increase in energy/fatigue, pain, general health, and physical health subscales scores at the end of the intervention compared to the placebo group. The scores of FSS were significantly reduced in both groups; however, the change in the drug group was remarkably higher than in the placebo group.
Conclusion and implications: Garlic extract promotes fatigue and improves the quality of life in MS patients. Therefore, garlic can be considered a potential remedy to overcome fatigue and improve the quality of life in these patients.

Keywords: Allicin; Clinical trial; Fatigue; Garlic; Multiple sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is a degenerative disease of the central nervous system, and the most disabling disease in young people (1,2). Fatigue is one of the most common and disabling symptoms of MS, which disrupts the patient's work, social activities, and daily functions (3). Eighty percent of MS patients complain of fatigue, and it has been reported that fatigue is the first and most bothersome symptom of one-third to one-half of the patients (4).

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Access this article online	
	Website: http://rps.mui.ac.ir
	DOI: 10.4103/RPS.RPS_7_24

MS-related fatigue is also associated with an increase in comorbidities (*e.g.,* mental disorders), falling, and the use of medical services and the related costs (5). Previous definitions of fatigue as a clinical complication in MS include feeling very tired, lack of energy, or feeling weak; difficulty in the beginning or prolongation of voluntary actions; and feeling physically tired (6).

MS-related fatigue and weakness can be caused by primary mechanisms such as the release of inflammatory cytokines, including interleukin (IL)-17, IL-1β, and interferon-γ (IFN-γ), hormonal disorders, oxidative stress, and axonal depletion, or by secondary mechanisms such as sleep disorders, restless leg syndrome, or irregular breathing during sleep (1,7).

Treatment of MS-induced fatigue is challenging and includes medications, rehabilitation, and cognitive-behavioral therapy, with drug therapy being the least effective measure (5).

Therefore, due to the adverse effect of MS-related fatigue on the patient's quality of life and activities, as well as the lack of effective treatment for it, it is necessary to find effective and inexpensive therapy to improve this complication. Some herbs have been studied and used to relieve MS fatigue (2,8,9). Garlic (*Allium sativum*) is one of the most well-known medicinal plants of the Liliaceae family, which has been shown to have anti-fatigue effects in some studies (10-12). In a study, aged garlic extract relieved physical fatigue in rats subjected to repeated endurance exercise on a mechanical treadmill (10). In another animal study, garlic prolonged the running time on a treadmill and enhanced the speed of recovery of rectal temperature after immersion in cool water. It was suggested that this effect was due to enhanced peripheral circulation and improvement of nutrition (11). The positive effects of garlic on physical performance and learning behavior were shown in another study (12). In an *in vitro* study in 2016, garlic was shown to inhibit IL-17 gene expression by T-helper cells (13). This cytokine has been implicated in the pathogenesis of several inflammatory and autoimmune diseases, including MS, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and cancer, and has been considered in studies as a therapeutic target in autoimmune diseases (13). Furthermore, the neuroprotective and analgesic effects of garlic are also significant, which can improve the symptoms of MS (14).

Therefore, considering the evidence of garlic's anti-fatigue effects in various disorders, the high prevalence of fatigue in MS patients, and also the lack of ideal treatment for this complication, this study was conducted to clinically evaluate the potential effects of this plant on fatigue and quality of life in MS patients.

MATERIALS AND METHODS

Study design

This was a randomized, placebo-controlled, clinical trial conducted from October 2020 to March 2021 at the Al-Zahra and Ayatollah Kashani Hospital Clinics, both affiliated with Isfahan University of Medical Sciences (IUMS). This study was registered by the code IRCT20150721023282N15 in the Iranian Registry of Clinical Trials.

Ethical considerations

The study was approved by the ethics committee of IUMS (Ethics code: IR.MUI.RESEARCH.REC.1399.420). All included patients received their standard treatment. Informed written consent was obtained from all participants.

Patients

The patients were selected from those who were referred to the mentioned clinics. Inclusion criteria were: (1) age over 18 years; (2) diagnosis of relapsing-remitting MS (RRMS) for at least 6 months; (3) advanced disability status scale (EDSS) ≤ 6; and (5) complaint of substantial fatigue.

Patients with the following characteristics were excluded from the study: (1) use of any food and/or product containing garlic during the past week; (2) acute relapse; (3) wheelchair dependence; (4) use of psychotropic drugs (alcohol, marijuana, opioids, cocaine, dextroamphetamine) during the last month; (5) use of drugs affecting fatigue, including

modafinil, methylphenidate, and amantadine during the last month; (6) having other neurological or psychological disorders based on the history; (7) fatigue induced by other diseases including hypothyroidism, hyperthyroidism, heart failure, chronic obstructive pulmonary disease, sleep apnea, chronic renal failure, adrenal insufficiency, anemia, hematologic or non-hematologic malignancy, viral hepatitis, human immunodeficiency viruses (HIV) infection, tuberculosis, fibromyalgia, and depression (these cases were reviewed based on the patient's medical history and, if necessary, by performing relevant tests); (8) participation in rehabilitation programs such as yoga; (9) pregnancy; and (10) breastfeeding.

Interventions

Demographic and clinical information for the subjects, including age, sex, underlying disease, duration of MS, the MS drugs (disease-modifying drugs), and any antidepressant or the use of hypnotic medication, was recorded for all subjects. Patients who met the mentioned criteria were included in the study if they signed the consent form. The admitted patients were randomly and equally divided into two groups; one received the drug while the other received a placebo. For the drug group, garlic tablets (Garlet®, Amin Pharmaceutical Co., Iran) containing 400 mg of garlic extract powder (standardized based on 1,200 µg of allicin and equivalent to 2 g of fresh garlic) were administered every 12 h for 4 weeks, while for the placebo group, the placebo pills (produced by the same company) were prescribed with the same frequency and duration. Patients in both groups received their standard treatment of MS (disease-modifying therapy) according to the opinion and prescription of a neurologist. If standard treatment was changed during the intervention, the patient was excluded from the study. For randomization, the pills' containers, including an equal number of drug and placebo containers, were coded by a third person unaware of the study protocol, and upon the inclusion of each patient, a bottle was randomly selected for him/her by the prescribing physician. For blinding, the shape and size of garlic and placebo tablets were the same, and both types of tablets were packed in the same containers. The prescribing physician, the data collector, and the statistician were unaware of the contents of the containers and the type of intervention. However, due to the distinctive smell of garlic, the study could not be blinded for patients.

Evaluations and outcome variables

Before the intervention, the fatigue severity scale (FSS) questionnaire was used to determine the degree of fatigue and the short form health survey (SF-36) questionnaire to measure the quality of life were given to all patients. Following the relevant explanations, they were asked to complete them based on their symptoms and features in the last 2 weeks. The FSS questionnaire is one of the most reliable tools in fatigue assessment. This scale consists of 9 items that assess only the concept of fatigue and measure fatigue rapidly in people with MS, so that its score is perfectly proportional to the severity of the patient's fatigue (15). This questionnaire measures individuals' personal perceptions of their fatigue using a 9-item set and is used in most medical research (16). Answers of each item are scored on a seven-point scale where 1 = strongly disagree and 7 = strongly agree. This means the minimum total score possible is nine, and the highest is 63. The validity and reliability of the Persian version of this questionnaire have been reviewed and confirmed by Fereshtehnejad *et al*. (17). In this questionnaire, a higher score indicates the severity of fatigue and *vice versa*.

SF-36 is one of the most common and comprehensive general standard tools available for assessing the quality of life, which is internationally used as a standard means for measuring the level of health (18). This questionnaire has 36 questions consisting of 8 subscales, with each subscale containing 2 to 10 items. The eight subscales of this questionnaire are: physical function (PF), role for physical health (RP), role for emotional health (RE), energy/fatigue (EF), emotional well-being (EW), social function (SF), pain (P), and general health (GH). Twenty-eight items are in ordinal type following the Likert format (for example, PF items: yes, limited a lot; yes,

limited at little; and no, not limited at all, recoded as 1, 2, and 3, respectively), seven items are in binary format (yes and no, recoded as 1 and 2, respectively), and one item, investigating the health changes over the past year is not used for evaluation of quality of life. The score of each subscale ranges from 0 to 100 (percent of the maximum sum score), while the total score ranges from 0 to 800. Also, by merging the subscales, two general subscales named "physical health" and "mental health" are obtained, with the score of each ranging from 0 to 400. The lower the score, the greater disability. This questionnaire has been translated into Persian by Montazeri *et al.*, and its validity and reliability have been reviewed and confirmed (18).

The score of these questionnaires was determined and recorded for each patient. At the end of the intervention, after the patient referred to the clinic, the questionnaires were completed again, and their scores were recorded. For the SF-36 questionnaire, the overall score as well as the score of each separate subscale was recorded. The patients' compliance was assessed and increased by reminding them through daily telephone calls or text messages. The patients were also asked to bring their drug containers for the second visit (end of the intervention), where, if at least 80% of the pills were taken, the patient was evaluated and his/her data were included in the final analysis. Finally, the mean scores of the FSS and SF-36 questionnaires were compared between the two groups.

The outcome variables in this study were the changes in the scores of the FSS and SF-36 questionnaires (overall score and scores of each subscale separately) at the end of the intervention compared to the beginning of the intervention. Furthermore, the patients were requested to report any possible side effects during the intervention.

Sample size calculation

The following equation was used to calculate the sample size. The α error was 5% and the β error was 20% and the standard deviation (δ) and the mean values (μ) were determined according to the FSS values in one of the studies related to the comparison of the two groups in the treatment of MS fatigue (19).

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times (\delta_1^2 + \delta_2^2)}{(\mu_{1-} \mu_2)^2}$$

$$n = \frac{(1.65 + 0.84)^2 \times (1.40^2 + 1.60^2)}{(3.80-4.80)^2} = 28$$

Therefore, the sample size of at least 28 patients in each group was considered.

Statistical analysis

For the statistical analysis of data, SPSS software version 24 was used. Data distribution was determined using the Kolmogorov-Smirnov test. To compare the baseline and end-of-intervention values in each group, a Paired-Samples t-test was used for normally distributed data, while the Wilcoxon Signed-Rank test was used for data with non-normal distribution. Independent-Samples t-test and Mann-Whitney U test were used to compare the initial values of the intervention between the two groups for data with normal and non-normal distributions, respectively. An ANCOVA test was used to compare the end-of-intervention values between the two groups. Chi-square test was used to compare qualitative variables between the two groups. In each case, $P < 0.05$ was considered a significant difference.

RESULTS

Patients

During the study, 98 people were evaluated, 78 of whom met the inclusion criteria and were randomly and equally divided into the two groups. During the study, 6 people in the placebo group refused to continue the study because of a lack of efficacy. Finally, 39 patients in the drug (*Allium*) group and 33 patients in the placebo group completed the study (Fig. 1). Table 1 shows the baseline demographic and clinical properties of the participants, which show no significant difference between the groups regarding these variables. As seen, in both groups, more than 80% of patients were female, the mean of MS duration was more than 60 months (5 years), and most patients were on IFN-β1a and rituximab therapy.

Table 1. Basic demographic and clinical characteristics of the patients.

Parameter	Group		*P*-value
	Allium (n = 39)	Placebo (n = 33)	
Age (mean ± SD; years)	37.58 ± 7.65	34.51 ± 8.98	0.121
Sex (n, %)			
Male	7 (17.90%)	5 (15.20%)	0.751
Female	32 (82.1%)	28 (84.80%)	
Weight (mean ± SD; kg)	69.53 ± 12.76	65.84 ± 10.23	0.119
Comorbidity (n, %)			
Diabetes mellitus	1 (2.60%)	0	0.584
Hypertension	2 (5.10%)	1 (3%)	
MS duration (mean ± SD; months)	77.53 ± 55.52	67.70 ± 54.55	0.321
MS drug (n, %)			
Interferon β1a	10 (25.60%)	12 (36.40%)	0.874
Glatiramer acetate	3 (7.70%)	1 (3.0%)	
Fingolimod	3 (7.70%)	2 (6.10%)	
Teriflunomide	4 (10.30%)	3 (9.10%)	
Dimethyl fumarate	4 (10.30%)	4 (12.10%)	
Azathioprine	2 (5.10%)	1 (3.0%)	
Rituximab	12 (30.80%)	9 (27.30%)	
Ocrelizumab	0	1 (3.0%)	
Methotrexate	1 (2.60%)	0	

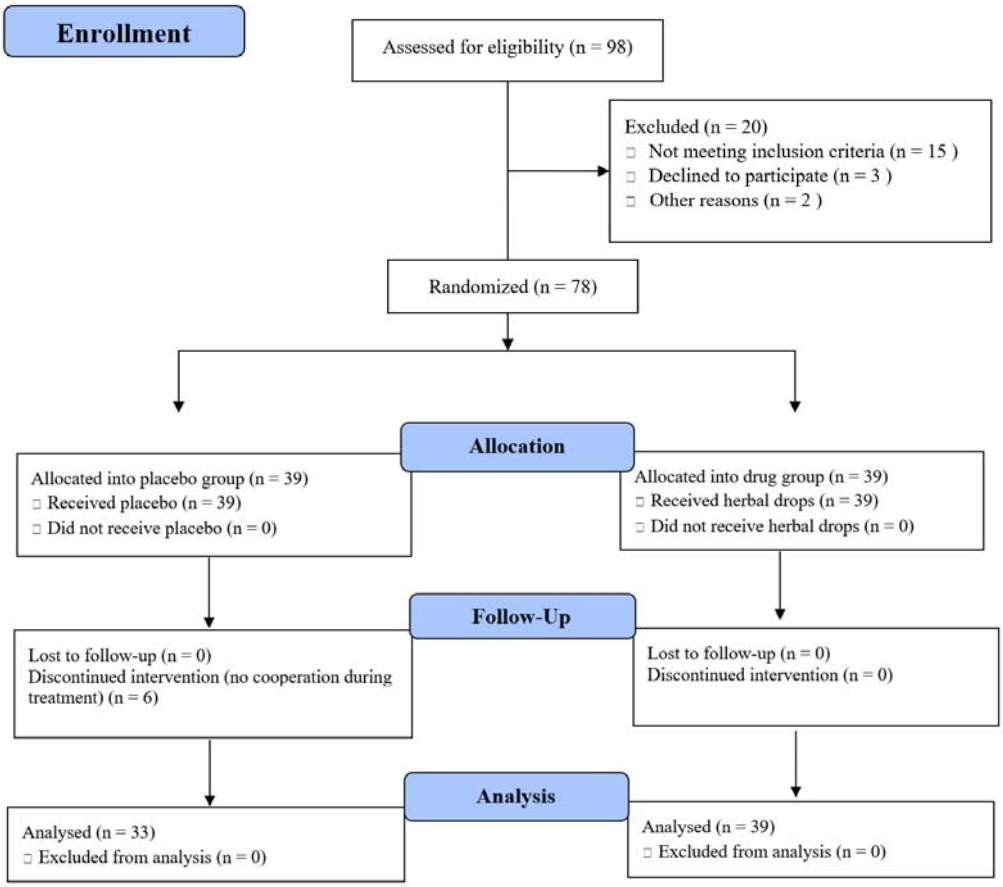

Fig. 1. Flow chart of enrollment and allocation of participants and study design

Table 2. Changes in the scores of quality of life indicators and fatigue severity during the intervention in the two groups and their comparison. The values are mean ± SD.

Parameter	Time	Group		*P*-value
		Allium (n = 39)	Placebo (n = 33)	
	Baseline	62.56 ± 25.90	70.15 ± 25.63	0.179[c]
SF-36 (physical function)	End	72.05 ± 25.69	72.42 ± 28.23	0.077[e]
	P-value	< 0.001[a]	0.352[a]	
	Baseline	44.87 ± 38.12	43.48 ± 38.35	0.794[c]
SF-36 (physical health)	End	69.07 ± 34.74	64.39 ± 40.03	0.606[e]
	P-value	0.001[a]	0.003[a]	
	Baseline	38.44 ± 41.56	47.46 ± 39.12	0.255[c]
SF-36 (emotional health)	End	64.10 ± 36.98	57.59 ± 38.44	0.258[e]
	P-value	0.006[a]	0.095[a]	
	Baseline	48.33 ± 18.04	51.06 ± 21.09	0.556[d]
SF-36 (energy/fatigue)	End	61.53 ± 17.25	56.06 ± 21.85	0.020[e]
	P-value	< 0.001[b]	0.054[b]	
	Baseline	52.92 ± 17.59	58.06 ± 22.34	0.279[d]
SF-36 (emotional wellbeing)	End	62.56 ± 17.99	60.87 ± 19.09	0.077[e]
	P-value	< 0.001[b]	0.247[b]	
	Baseline	53.52 ± 28.09	58.71 ± 24.89	0.414[d]
SF-36 (social function)	End	71.47 ± 20.26	69.69 ± 26.15	0.399[e]
	P-value	< 0.001[a]	0.020[a]	
	Baseline	56.15 ± 25.33	66.13 ± 29.44	0.147[c]
SF-36 (pain)	End	73.01 ± 23.10	70.30 ± 27.49	0.042[e]
	P-value	< 0.001[a]	0.611[a]	
	Baseline	53.97 ± 22.01	55.18 ± 23.97	0.824[d]
SF-36 (general health)	End	64.48 ± 19.52	57.57 ± 22.78	0.008[e]
	P-value	< 0.001[a]	0.298[b]	
	Baseline	417.80 ± 159.26	452.40 ± 165.02	0.369[d]
SF-36 (Total)	End	538.30 ± 144.25	509.22 ± 179.70	0.063[e]
	P-value	< 0.001[b]	0.010[b]	
	Baseline	217.56 ± 86.50	234.95 ± 93.53	0.416[d]
SF-36 (physical health)	End	278.62 ± 85.32	264.69 ± 100.09	0.042[e]
	P-value	< 0.001[a]	0.004[a]	
	Baseline	193.23 ± 86.06	215.30 ± 87.08	0.285[d]
SF-36 (mental health)	End	259.67 ± 73.63	244.23 ± 90.35	0.063[e]
	P-value	< 0.001[b]	0.019[b]	
	Baseline	45.46 ± 10.35	40.58 ± 12.66	0.077[d]
FSS	End	38.63 ± 8.95	38.67 ± 12.60	0.016[e]
	P-value	< 0.001[b]	0.035[b]	

SF, Social function; SF-36, 36-item short form survey; FSS, fatigue severity scale; a, Wilcoxon Signed-Rank test; b, paired-samples t-test; c, Mann-Whitney U test; d, independent samples t-test; e, ANCOVA

Outcome variables

The mean scores of the SF-36, its subscales, and FSS at the beginning and end of the intervention within each group, as well as their comparisons, are given in Table 2. As shown, the overall score of the SF-36 in both groups increased significantly at the end of the intervention; however, the comparison between the two groups did not reveal a significant difference in this regard ($P = 0.063$).

In terms of effect on SF-36 subscales, garlic consumption for 4 weeks was significantly associated with an increase in energy/fatigue (EF), pain (P), and general health (GH)

subscales scores at the end of the intervention. According to the ANCOVA test, this increase was also significant compared to the placebo group (*P*-values = 0.02, 0.042, and 0.008, respectively). Also, in terms of the effect on the two subscales of physical health and mental health, based on the results, garlic consumption significantly increased the physical health score compared to placebo ($P = 0.042$), while in the case of mental health subscale, despite the increase in the scores in both groups, there was no significant difference between the two groups ($P = 0.063$).

Regarding the effect on FSS, the score of this variable was significantly reduced in both groups. Furthermore, according to ANCOVA analysis with the control of baseline values, the rate of reduction in the drug group was significantly higher than the placebo group ($P = 0.016$).

Of note, regarding the side effects, during the study, six patients from the drug group reported gastrointestinal (GI) symptoms, including heartburn (n = 3) and abdominal pain (n = 3).

DISCUSSION

In this study, garlic supplementation for 4 weeks leads to a significant increase in quality-of-life scores, including the energy/fatigue, pain, and general health subscales and overall physical health subscales, as well as a significant decrease in fatigue severity scores, compared to placebo. According to our assessment, this study is the first clinical trial to investigate the effects of garlic extract on the severity of fatigue in patients with MS. However, few studies have evaluated the effect of garlic on fatigue in other conditions or diseases. In a recent study by Moosavian *et al.* to investigate the effects of garlic supplementation, 1,000 mg equivalent to 2.5 g of fresh garlic per day for 8 weeks, on inflammatory markers, fatigue, and clinical signs of patients with active rheumatoid arthritis, this plant significantly decreased the serum levels of CRP (C-reactive protein) and tumor necrosis factor-α (TNF-α) compared to the placebo. Also, pain intensity, number of painful joints, and fatigue intensity significantly reduced in the garlic group (20). Therefore, despite the differences in the study population, the results of this study are consistent with ours in terms of the effect of garlic on fatigue severity and pain. In the study conducted by Verma *et al.,* the effect of garlic oil administration for 6 weeks on exercise tolerance in 30 patients with coronary artery disease was evaluated. The results showed an increase in tolerance as well as a decrease in the heart rate at the maximum speed (21).

Also, some animal studies have shown the effect of garlic in fatigue reduction. In a study investigating the effect of garlic on exercise-induced fatigue in mice, it was found that the plant was associated with increased tolerance to activity on the treadmill. The researchers concluded that garlic has the potential for anti-fatigue effects (22). Similar results were observed in the study of Ushijima *et al.* (11).

Probably, the anti-fatigue effect of this plant is related to the improvement of peripheral blood circulation (23), and inhibiting platelet aggregation (24). Also, the antioxidant effects of garlic include an increase in the activity of superoxide dismutase (25) and decreasing the serum level of lipid peroxide (26), can be some of its mechanisms of the anti-fatigue effect.

The most common suggested mechanism for MS-induced fatigue is immune system dysfunction resulting in neuronal injury. Inflammatory cytokines, including TNF-α, are mediators of MS, which may also contribute to fatigue (27). In a study, the TNF-α level was higher in MS patients with fatigue compared to those without fatigue (28). Garlic decreases TNF-α levels (20) and increases natural killer (NK) cell activity (29). On the other hand, the nutrients in garlic, such as iron, zinc, potassium, sulfur compounds, vitamins, amino acids, and carbohydrates, which are the metabolic requirements of all organs, may play a role in improving fatigue. In 2016, in an *in vitro* study, garlic was shown to have an inhibitory effect on IL-17 gene expression by T-helper cells (13). This cytokine has been implicated in the pathogenesis of several inflammatory and autoimmune diseases, including MS, rheumatoid arthritis, psoriasis, and inflammatory bowel disease, and has been considered a therapeutic target in autoimmune

diseases (13). In addition, considering the neuronal damage in MS, the neuroprotective effects of garlic (14) may also be involved in the observed effect.

In the present study, the pain subscale of the Quality-of-Life questionnaire in the garlic group showed a significant improvement, which indicates the analgesic effect of this plant in patients with MS. The analgesic effect of garlic has been shown in many studies. For example, in a clinical study on patients with osteoarthritis, garlic reduced knee pain severity (30). However, to evaluate the effect of garlic on pain in MS patients, it is necessary to conduct separate studies with an appropriate design using special indicators to assess the severity of pain.

The main limitations of our study were a relatively low sample size, a single-blind design (due to the distinct odor of the garlic precluding a double-blind design), and the short duration of the intervention. However, this is the first clinical study showing the positive effects of garlic on fatigue in MS patients. More studies with larger sample sizes and longer durations using other scales of fatigue assessments (*e.g.*, brief fatigue inventory and modified fatigue impact scale) are necessary to confirm our observed effects.

CONCLUSION

Using garlic extract with a dose of 800 mg daily reduced fatigue and improved the quality of life in MS patients. Therefore, garlic can be considered a potential agent to treat fatigue and improve the quality of life in these patients.

Acknowledgments

We would like to acknowledge Amin Pharmaceutical Company for providing the garlic tablets (Garlet®) used in our study.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declared no conflict of interest in this article.

Authors' contributions

R. Soltani designed the study, interpreted the results, and performed the statistical analysis. V. Shaygannejad and O. Mirmosayyeb selected the patients and interpreted the data. M. Shafiee and A. Mohsenzadeh collected the patients' data and drafted the manuscript. M. Sadeghi Dinani gave the study concept and interpreted the data.

All authors have read and approved the finalized article. Each author has fulfilled the authorship criteria and affirmed that this article represents honest and original work.

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