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Effects of spirulina (Arthrospira) platensis supplementation on inflammation, physical and mental quality of life, and anthropometric measures in patients with relapsing-remitting multiple sclerosis (RRMS): a triple-blinded, randomized, placebo-controlled trial

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Abstract

Background Multiple sclerosis (MS) is a chronic neuroinflammatory disorder marked by demyelination and axonal damage, where oxidative stress and cytokine-mediated inflammation are key pathological factors. Spirulina, a microalga rich in phycocyanin, phenolic compounds, and omega-3 fatty acids, exhibits potent antioxidant and anti-inflammatory properties, potentially targeting these pathways. This study investigated spirulina's impact on inflammatory biomarkers and quality of life in relapsing-remitting MS (RRMS) patients.

Methods A triple-blind, placebo-controlled trial randomized 80 RRMS patients (EDSS 0–6) to receive 1 g/day spirulina ($n=40$) or placebo ($n=40$) for 12 weeks. Sixteen participants (20%) withdrew. Primary analysis followed the intention-to-treat (ITT) principle ($N=80$) using baseline-observation-carried-forward for missing data. Serum IL-1β and IL-6 (primary outcomes) were measured by ELISA. Quality of life (MSQoL-54) and anthropometric measures were secondary outcomes.

Results A linear mixed-effects model revealed that spirulina supplementation significantly reduced serum IL-1β (Estimate = -1.07 ± 0.14, $p<0.001$) and IL-6 levels (Estimate = -2.66 ± 0.26, $p<0.001$) compared to placebo. Significant improvements were also observed in health perception (Estimate = -0.49 ± 0.12, $p<0.001$), physical function (-0.37 ± 0.11, $p<0.001$), role limitation–physical (-0.36 ± 0.16, $p=0.030$), energy (-0.64 ± 0.15, $p<0.001$), and sexual function (-1.31 ± 0.29, $p<0.001$). No significant effects were found for emotional wellbeing, health distress, social function, cognitive function, sexual satisfaction, overall quality of life, or total mental health. Anthropometric analysis showed a significant weight reduction in the spirulina group versus placebo (-2.85 ± 1.13 kg, $p=0.015$), while

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BMI reduction was borderline significant (−0.78 ± 0.41, $p = 0.060$). No significant changes were observed in waist circumference, waist-to-hip ratio, energy intake, or physical activity.

Conclusion Spirulina supplementation significantly reduced pro-inflammatory markers and improved multiple physical and cognitive quality of life domains in patients with RRMS. Spirulina shows promise as a safe adjunct therapy in MS management, but larger trials with longer follow-up are warranted to confirm these findings and explore its clinical utility alongside DMTs.

Trial registration The trial is registered with the Iranian Registry of Clinical Trials (ID IRCT2024124060794N1), with registration completed on 4 February 2024. Informed consent will be secured from each participant or their legal guardian.

Keywords Multiple sclerosis (MS), Clinical outcomes, Quality of life, Inflammatory factors, Spirulina platensis (RA), Interleukin

Background

Multiple sclerosis (MS), a debilitating autoimmune disorder, affects over 2.8 million people worldwide, causing significant physical and cognitive impairments [1, 2]. The clinical presentation of MS varies, with the most common subtype being relapsing-remitting MS (RRMS), affecting about 85% of cases initially [3]. Over time, many patients transition to secondary progressive MS (SPMS), where symptoms steadily worsen without clear relapses or remissions. Other forms, such as primary progressive MS (PPMS), involve continuous neurological decline from onset, representing a smaller but more challenging group to treat [4, 5]. Globally, MS prevalence varies by latitude and environmental factors, with higher rates in Europe and North America. In Iran, it has risen to 89 per 100,000 over the past two decades, with urban centers like Tehran and Isfahan exceeding 100 per 100,000, and Mashhad reporting 78 per 100,000, driven by urbanization, improved diagnostics, and risk factors such as vitamin D deficiency, particularly among women [6–11].

At the core of MS pathology lies inflammation and oxidative stress, initiated by autoreactive T and B lymphocytes breaching the blood-brain barrier (BBB) to trigger a CNS immune response amplified by microglial activation [12]. Pro-inflammatory cytokines such as TNF-α, IL-6, and IFN-γ, alongside reactive oxygen species (ROS), drive demyelination and axonal injury, accelerating neurodegeneration and reducing quality of life [13]. Animal models, such as experimental autoimmune encephalomyelitis (EAE), further demonstrate these mechanisms and highlight potential neuroprotective interventions [14].

MS severely impairs quality of life through chronic fatigue, cognitive decline, sexual dysfunction, and mobility limitations, contributing to emotional distress [15]. Although disease-modifying therapies (DMTs) reduce relapse rates, their limited effect on oxidative stress and long-term neurodegeneration—for example, natalizumab reduces relapses but fails to mitigate ROS, unlike fingolimod's partial antioxidant effects—highlights a therapeutic gap [16]. Moreover, DMT efficacy varies across patients, with women and those with higher disability often showing suboptimal responses, underscoring the need for complementary approaches [17].

Among these, spirulina, a blue-green microalgae rich in phycocyanin, polyphenols, vitamins, and fatty acids, offers potent anti-inflammatory and neuroprotective effects [18].

Phycocyanin inhibits NF-κB signaling, reducing pro-inflammatory cytokines (IL-1, IL-6) while promoting IL-10, countering MS's core drivers of inflammation and oxidative stress, as evidenced in EAE models [19]. Unlike other supplements like coenzyme Q10, which showed limited efficacy in MS, spirulina's multi-target profile may alleviate fatigue and disability, making it a promising candidate [20]. Despite this potential, its clinical efficacy in MS remains understudied due to limited randomized trials, prompting this investigation into its role as an adjunctive therapy for RRMS.

Emerging trials suggest spirulina improves MS-related level energy, mobility, and cognition, with preclinical evidence of reduced oxidative stress and enhanced antioxidant activity [21]. We hypothesize that 12-week spirulina supplementation reduces serum IL-6 by ≥ 30% and improves MSQoL-54 physical health subscale scores by ≥ 15 points compared to placebo, addressing an unmet need for therapies that mitigate inflammation and enhance physical function in RRMS. Therefore, this study aimed to investigate the efficacy of 12-week spirulina supplementation on serum inflammatory biomarkers (IL-1β, IL-6) and multiple domains of quality of life, including physical, mental, and cognitive function, as assessed by the MSQoL-54, in patients with RRMS compared to placebo.

Methods

Study design

This was a parallel-group, triple-blind, randomized, placebo-controlled clinical trial (RCT).

was conducted over a 12-week period to evaluate the effects of Spirulina supplementation in patients with

relapsing-remitting multiple sclerosis (Fig. 1). The study was conducted at the Isfahan Neurology Hospital, Affiliated with Isfahan University of Medical Sciences, Isfahan, Iran. The trial protocol is reported under the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Ethics

The study protocol was approved by the Medical Ethics Committee at the Isfahan University of Medical Sciences (Registration No. IR.MUI.PHANUT.REC.1402.070). The trial was registered at the Iranian Registry of Clinical Trials (Registration No. IRCT2024124060794N1) before participant enrollment. The study was conducted under the principles of the Declaration of Helsinki. Written informed consent, including consent for the use of biological samples for research purposes, was obtained from all participants before any study procedures commenced.

Study participants and eligibility criteria

Participants were recruited from patients diagnosed with RRMS attending the Isfahan Neurology Hospital. Potential participants were informed about the trial, and eligibility screening was performed. Inclusion criteria were: confirmed RRMS diagnosis based on the 2017 revised McDonald criteria [22], age between 18 and 50 years, Body Mass Index (BMI) between 18.5 and 30 kg/m ^{2}, Expanded Disability Status Scale (EDSS) score between 0 and 6, stable disease-modifying therapy (DMT) regimen for at least three months before enrollment, and no intake of dietary supplements (except prescribed Vitamin D) for at least three months.

Exclusion criteria were: pregnancy or lactation, current hospitalization, acute liver or biliary diseases, acute pancreatic disorders, severe viral infections, presence of other autoimmune diseases known to affect Th1/Th2 balance (e.g., systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease), chronic kidney or cardiovascular diseases, BMI < 18.5 kg/m ^{2} or ≥ 30 kg/m ^{2}, substance dependence, use of anticoagulant medications, or use of multivitamins or other supplements that could interfere with the study outcomes.

Participants were withdrawn from the study if they experienced severe adverse reactions deemed related to the intervention, became pregnant, or expressed unwillingness to continue participation. Participants were also excluded if they developed an unwillingness to continue, became pregnant during the trial, or experienced severe adverse reactions attributed to the intervention.

Sample size calculation

The required sample size was calculated using G*Power software (version 3.1.9.7) [23, 24]. Based on detecting a

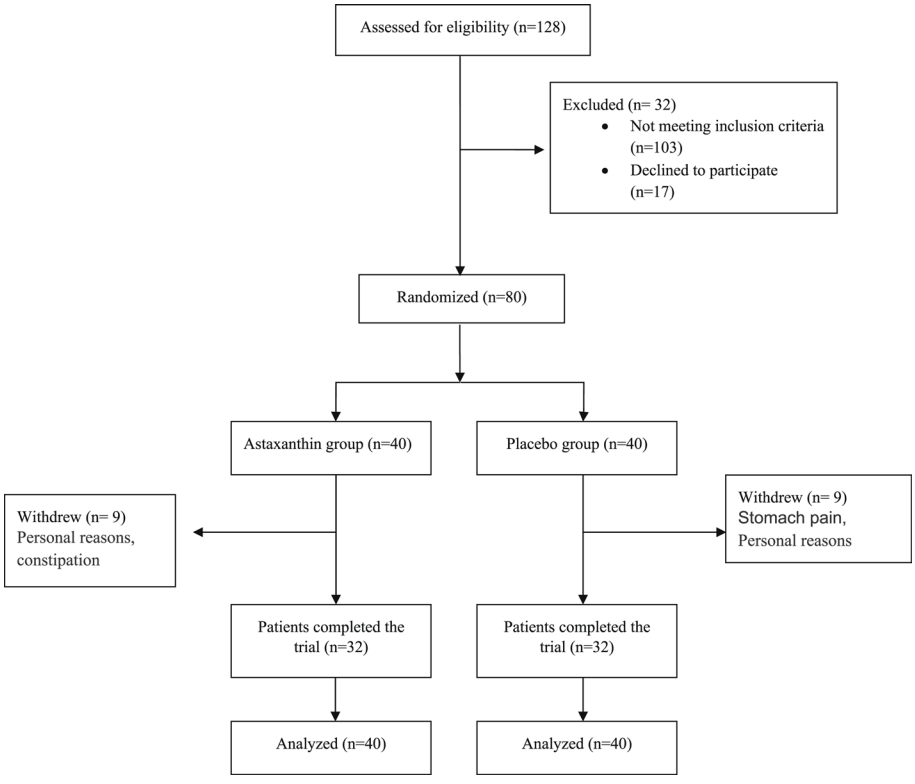

Fig. 1 Study flow diagram of study recruitment

clinically relevant difference in the primary outcome, serum IL-6 levels. assuming an effect size (Cohen's d) of 0.7 derived from prior studies on spirulina's anti-inflammatory effects [25, 26]., a two-tailed alpha of 0.05, and 80% power (1-β), a minimum of 32 participants per group (total $N = 64$) completing the study were estimated to be needed. To account for an anticipated attrition rate of approximately 20%, we aimed to recruit a total of 80 participants (40 per group).

Random allocation and blinding

Eligible participants were randomly assigned in a 1:1 ratio to either the Spirulina (SP) or placebo group. Randomization was performed by an independent statistician using computer-generated random numbers via SPSS v24 with permuted blocks of size 4 to ensure balanced allocation between groups. Participants were stratified based on sex (male/female) before randomization. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes prepared by the statistician. These envelopes were opened sequentially by a research coordinator only after a participant was confirmed eligible and had provided consent.

To ensure triple blinding, the SP and placebo capsules were identical in appearance (size, color, smell) and packaged in identically labeled containers coded as "A" and "B" by a third-party pharmacist not involved in participant recruitment or assessment. Participants, investigators (including clinicians and research staff interacting with participants), and outcome assessors remained blinded to the treatment allocation throughout the study period and data collection phase. The allocation code was kept confidential and was only revealed after the final database lock and completion of the primary statistical analysis.

Intervention and Follow-up

Participants in the Spirulina group ($n = 40$) received 1 g/day of SP (Espiro-Bushehr, Iran) administered as two 500 mg capsules. The detailed chemical composition of the Spirulina platensis used in this study, sourced from Espiro-Bushehr, Iran, has been previously reported [27]. The dosage and timing were based on prior studies [28]. Participants in the placebo group ($n = 40$) received two identical-appearing capsules containing maltodextrin (produced by Espiro-Bushehr, Iran). Participants were instructed to take one capsule after breakfast and one capsule in the evening for 12 consecutive weeks. Both SP and placebo capsules were identical in color, weight, shape, and size.

Participant adherence was monitored by counting returned unused capsules at follow-up visits scheduled at week 6 and week 12. Adherence was calculated as [(total capsules dispensed - capsules returned)/total capsules expected to be taken] × 100. Participants were also contacted biweekly via telephone by a research assistant (blinded to allocation) to monitor for any potential adverse events, changes in concomitant medications, or significant changes in health status. Participants were instructed to maintain their usual dietary habits and physical activity levels throughout the 12-week intervention period and to continue their prescribed DMT regimen without changes unless medically indicated. Primary assessments were conducted at baseline (Week 0) and the end of the intervention (Week 12).

Outcome assessments

Primary outcomes

The primary outcomes were the changes in serum levels of Interleukin-1β (IL-1β) and Interleukin-6 (IL-6) from baseline to week 12.

Secondary outcomes

Secondary outcomes included changes in quality of life measured by the MSQoL-54, and changes in anthropometric measures (Weight, BMI, Waist Circumference (WC), Waist-to-Hip Ratio (WHR)).

Demographic and anthropometric assessments

Baseline demographic information (age, gender, education level, employment status) and clinical characteristics (disease duration, EDSS score, DMT type) were collected using a structured questionnaire. Anthropometric measurements were performed by trained personnel at baseline and week 12. Height was measured to the nearest 0.5 cm using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg using a calibrated digital scale, with participants wearing light clothing and no shoes. BMI was calculated as weight (kg)/height (m^2). WC was measured to the nearest 0.1 cm using a non-elastic tape measure at the midpoint between the lower costal margin and the iliac crest. Hip circumference (HC) was measured at the widest point over the buttocks. WHR was calculated as WC (cm)/HC (cm). These anthropometric indices are widely accepted as valid indicators of physical status in patients with multiple sclerosis and provide objective measures for tracking intervention-related changes [29].

Dietary intake

Dietary intake was assessed at baseline and week 12 using three-day food records (two weekdays and one weekend day). Participants received detailed instructions on how to record all food and beverages consumed. Total energy and macronutrient intake were estimated using Nutritionist IV software (First Databank, San Bruno, CA), adapted for Iranian foods [30].

Physical activity

Physical activity levels were assessed at baseline and week 12 using the short form of the validated International Physical Activity Questionnaire (IPAQ-SF 8) [31].

Total physical activity was expressed as Metabolic Equivalent of Task minutes per week (MET-min/week).

ELISA assay of IL-1 and IL-6

Fasting venous blood samples were collected between 7:30 – 8:30 a.m. and centrifuged at 3000 rpm for 10 min to separate serum. Serum aliquots were stored at −80 °C until analysis. IL-1β and IL-6 levels were measured using ELISA kits (LDN, Germany) with intra-assay CV)8%) and inter-assay CV (11%), following the manufacturer's protocol. Absorbance was read at 450 nm.

Quality of life assessment (MSQoL-54)

Quality of life was evaluated using the validated Persian version of the Multiple Sclerosis Quality of Life-54 (MSQoL-54) questionnaire (28) at baseline and week 12. This 54-item instrument assesses 12 subscales related to physical and mental health, aggregated into a Physical Health Composite (PHC) score and a Mental Health Composite (MHC) score. The instrument also provides scores for individual subscales, including physical function, role limitation-physical, bodily pain, energy, emotional well-being, role limitation-emotional, social function, cognitive function, health perception, sexual function, health distress, and overall quality of life. This tool is considered appropriate for assessing quality of life in individuals with MS, as it combines both generic and disease-specific components and has been widely validated as a reliable and standardized instrument [32, 33]. Calculation of composite scores involved weighting individual subscale scores according to established algorithms studies [34]. Higher scores generally indicate better quality of life or functioning.

Data management

All data collection forms were checked for completeness and accuracy by the research coordinator. Data were double-entered into SPSS software (version 24.0; SPSS Inc., Chicago, IL, USA) by two independent research assistants to minimize entry errors. Each participant was assigned a unique identification code to ensure confidentiality. The final dataset was provided to the study statistician for analysis.

Safety evaluations

Safety and tolerability were monitored throughout the trial. Participants were asked about any adverse events during the biweekly phone calls and at the final study visit using open-ended questions. All reported adverse events, regardless of perceived causality, were recorded, assessed for severity, and potential relationship to the study intervention by the study physician.

Statistical analysis

The primary analysis was conducted based on the intention-to-treat (ITT) principle, including all 80 randomized participants (Spirulina: $n = 40$, Placebo: $n = 40$) in their original assigned groups. Missing data for primary and secondary outcomes at week 12 were handled using the Baseline Observation Carried Forward (BOCF) method. Descriptive statistics (mean ± SD or median [IQR] for continuous variables; frequency (percentage) for categorical variables) were used to summarize baseline characteristics. Baseline comparability between groups was assessed using independent samples t-tests or Mann-Whitney U tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Normality of data distribution and residuals was checked using Shapiro-Wilk test and Q-Q plot.

To assess the effects of the intervention on changes in primary and secondary outcomes—including levels of inflammatory cytokines (IL-1β and IL-6), domain scores of the Multiple Sclerosis Quality of Life-54 (MSQoL-54) instrument, and anthropometric indices—linear mixed-effects models (LMMs) were employed. This statistical approach, which incorporates baseline values as covariates, allows for the analysis of longitudinal changes over time and effectively handles missing data through maximum likelihood estimation [35]. Effect sizes for significant between-group differences were calculated using Cohen's d (interpreted as small ≈ 0.2, medium ≈ 0.5, large ≈ 0.8) respectively [36]. Within-group changes from baseline to week 12 were assessed using paired t-tests or Wilcoxon signed-rank tests.

A per-protocol (PP) analysis, including only participants who completed the 12-week intervention with ≥ 80% adherence ($n = 64$), was conducted as a sensitivity analysis. Further sensitivity analyses included all two-sided statistical tests, and a P-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 24.

Results

Participant's characteristics

A total of 128 patients were assessed for eligibility. After excluding 48 participants, mostly due to declining to participate, 80 patients were randomized to the Spirulina ($n = 40$) and placebo ($n = 40$) groups. Sixty-four patients completed the 12-week study (32 patients in the Spirulina group and 32 patients in the placebo group). Eight participants were lost to follow-up from the Spirulina group: personal reasons ($n = 5$), stomach pain ($n = 2$), and constipation ($n = 1$). Eight participants were lost to follow-up from the placebo group: personal reasons ($n = 3$),

Table 1 General characteristics of study subjects

Variable	Spirulina ($n=40$)	Placebo ($n=40$)	P^a
Age (years)	42.96 ± 7.05	43.87 ± 6.07	0.598
Gender (Female/Male), n	27/13	26/14	0.877
Education, n (%)			0.866
Below Diploma	5 (12.5%)	6 (15.0%)	
Diploma	15 (37.5%)	16 (40.0%)	
University	20 (50.0%)	18 (45.0%)	
Occupation, n (%)			0.953
Homemaker	7 (17.5%)	9 (22.5%)	
Employee	16 (40.0%)	15 (37.5%)	
Self-employed	15 (37.5%)	16 (40.0%)	
DMT type, n (%)			
Interferon-beta-1a	10 (25.0%)	9 (22.5%)	0.765
Glatiramer acetate	9 (22.5%)	7 (17.5%)	0.740
Natalizumab	4 (10.0%)	5 (12.5%)	0.690
Cyclophosphamide	2 (5.0%)	1 (2.5%)	0.554
Other DMTs	15 (37.5%)	18 (45.0%)	0.610

Data presented as mean ± SD or n (%). P^a-values derived from an independent samples t-test for continuous variables and χ^2 test for categorical variables, comparing Spirulina vs. Placebo groups

Abbreviations: *DMT*, disease-modifying therapy; *SD*, standard deviation

stomach cramp ($n=2$), and constipation ($n=3$) (Fig. 1). Normality of continuous variables was assessed by Q–Q plot and the Shapiro–Wilk test, and homogeneity of variances was evaluated using Levene's test; no significant departures from normality or influential outliers were observed. Patients' compliance with the intervention, assessed among completers, was high in both groups. All 80 randomized patients were included in the final analysis using the Intention to Treat (ITT) principle, with missing data handled by the Baseline Observation Carried Forward (BOCF) method. Baseline characteristics of the ITT population were comparable between the two groups (Table 1).

Anthropometric and anthropometric parameters

Anthropometric measurements revealed a significant reduction in body weight in the Spirulina group compared to the placebo group at the end of the intervention (Estimate = −2.85 ± 1.13, $p=0.015$, 95% CI: −5.23 to −0.48), as assessed by a linear mixed-effects model adjusted for baseline values. A borderline significant reduction in BMI was also observed in the Spirulina group relative to placebo (Estimate = −0.78 ± 0.41, $p=0.060$, 95% CI: −1.53 to 0.02) using the same statistical approach. No significant between-group differences were found for other anthropometric variables, including waist circumference and waist-to-hip ratio, or for lifestyle factors such as energy intake and physical activity ($p>0.05$) (Table 2).

Quality of life assessment (psychological, physical, sexual, and pro-inflammatory cytokines: IL-1β and IL-6 levels

A linear mixed-effects model revealed significant Time × Group interactions for several outcomes. IL-1β levels

Table 2 The effects of spirulina supplementation on anthropometrics, energy intake, and physical activity levels

Variable	Comparison SPl: $n=32$ PLb: $n=32$	Estimate ± SE	t-value	*p*-value	95% CI
BMI	Between-group after intervention	−0.78 ± 0.41	−1.91	0.060	[−1.53, 0.02]
	Within-group (Plb)	−0.71 ± 0.42	−1.71	0.094	[−1.56, 0.14]
	Within-group (Spl)	−0.73 ± 0.36	−2.01	0.050	[−1.45, −0.01]
Weight	Between-group after intervention	−2.85 ± 1.13	−2.52	0.015	[−5.23, −0.48]
	Within-group (Plb)	−1.75 ± 1.04	−1.68	0.098	[−3.91, 0.42]
	Within-group (Spl)	−2.06 ± 0.90	−2.29	0.025	[−3.91, −0.21]
WC	Between-group after intervention	2.25 ± 1.73	1.30	0.201	[−1.23, 5.73]
	Within-group (Plb)	−1.22 ± 0.92	−1.32	0.192	[−3.45, 1.01]
	Within-group (Spl)	−1.13 ± 0.86	−1.32	0.192	[−2.91, 0.64]
WHR	Between-group after intervention	0.01 ± 0.06	0.20	0.838	[−0.11, 0.13]
	Within-group (Plb)	−0.04 ± 0.03	−1.19	0.238	[−0.09, 0.02]
	Within-group (Spl)	−0.04 ± 0.02	−1.68	0.094	[−0.08, 0.01]
Energy Intake	Between-group after intervention	37.63 ± 46.60	0.81	0.420	[−45.26, 120.53]
	Within-group (Plb)	34.00 ± 26.35	1.29	0.200	[−19.40, 87.40]
	Within-group (Spl)	27.68 ± 19.04	1.45	0.150	[−12.03, 67.38]
Physical Activity (IPAQ-SF)	Between-group after intervention	120 ± 240	0.50	0.620	[−180, 420]
	Within-group (Plb)	150 ± 145	1.04	0.300	[−80, 380]
	Within-group (Spl)	100 ± 120	0.83	0.410	[−100, 300]

Data are presented as Estimate ± standard error (SE). The distributions of variables were assessed using the Shapiro-Wilk test and were found to be normal. the-value represents the ratio of the estimated effect to its standard error, indicating the strength and direction of the association. *P*-values were obtained from linear mixed-effects models, comparing end-of-trial values between groups while adjusting for the respective baseline values. a $P<0.05$ was considered statistically significant

Abbreviations: *WC*, waist circumference; *WHR*, waist-to-hip ratio; *MET*, metabolic equivalent of task. *Plb*, placebo, *SPL*, Spirulina

significantly decreased in the spirulina group (Estimate= −1.07, SE = 0.14, $p < .001$), with no significant change in the placebo group ($p = .512$), indicating a potential anti-inflammatory effect. Similarly, IL-6 levels declined significantly in the spirulina group (Estimate = −2.66, SE= 0.26, $p < .001$), while no significant change was observed in the placebo group ($p = .467$).

Significant between-group differences were also observed for Health Perception (Estimate =−0.49, SE = 0.12, $p < .001$), Physical Function (Estimate = −0.37, SE = 0.11,$p < .001$), Role Limitation–Physical (Estimate = −0.36, SE = 0.16, $p = .030$), Energy (Estimate = −0.64, SE = 0.15, $p < .001$, and Sexual Function (Estimate= −1.31, SE = 0.29, $p < .001$), indicating that spirulina supplementation led to improvements in these domains.

In contrast, no significant Time × Group interactions were found for Emotional Wellbeing, Health Distress, Social Function, Cognitive Function, Sexual Satisfaction, Overall Quality of Life, or Total Mental Health, suggesting no statistically significant effects of spirulina on these domains over the intervention period (Table 3).

Effect size calculations (Cohen's d, Table 4) demonstrated significant within-group improvements in the Spirulina group for overall physical health (d = 1.17, $P< 0.01$), physical function (d = 0.64, $P < 0.01$), role limitations due to physical problems (d = 0.52, $P < 0.01$), sexual function (d = 0.72, $P < 0.01$), as well as significant reductions in pro-inflammatory cytokines IL-1β (d= 1.00, $P < 0.01$) and IL-6 (d = 0.96, $P < 0.01$), and body weight (d = 0.85, $P < 0.01$). Between-group comparisons confirmed significantly greater improvements in the Spirulina group for these outcomes, with effect sizes ranging from d = 0.54 to 1.28 (all $P < 0.05$). Non-significant changes were observed in bodily pain, sexual satisfaction, and several cognitive and social measures.

Adverse effects

The spirulina supplement was generally well-tolerated. The rate of discontinuation due to reported adverse events did not differ significantly between the spirulina group (3 out of 40 participants, 7.5%) and the placebo group (5 out of 40 participants, 12.5%) (Fisher's Exact Test, $P = 0.72$). Adverse events leading to withdrawal consisted primarily of mild gastrointestinal symptoms, namely stomach pain or cramp (reported by 2 participants in each group) and constipation (reported by 1 participant in the spirulina group and 3 in the placebo group). Participants were withdrawn from the study if they experienced severe adverse reactions deemed related to the intervention, became pregnant, or expressed unwillingness to continue participation.

Discussion

This randomized controlled trial demonstrated that spirulina supplementation in patients with multiple sclerosis resulted in: 1) significant improvements in overall physical health status, 2) enhanced physical functioning, 3) reduced role limitations due to physical problems, 4) increased energy levels, 5) improved sexual function, 6) significant reductions in pro-inflammatory cytokines, particularly IL-1β and IL-6, and 7) a notable decrease in body weight. However, no statistically significant differences were observed in general health perception, cognitive function, body pain, social functioning, sexual satisfaction and mental health status.

Given the 40–60% prevalence of cognitive impairment in MS, the lack of significant improvement in cognitive function following spirulina supplementation in our study might be due to the relatively short intervention period or the complex multifactorial nature of cognitive deficits in MS. Cognitive improvements often require longer durations or combination therapies to manifest. Additionally, biological and psychosocial factors such as neuroplasticity and stress reduction through trial participation may influence cognitive outcomes, potentially masking subtle effects of the intervention [37]. Although a recent randomized controlled trial on older adults reported positive effects of spirulina extract on memory performance, this effect was not observed in our study conducted on patients with multiple sclerosis, possibly due to differences in population characteristics, intervention duration, or disease pathology [38].

Despite spirulina's anti-inflammatory effects, it did not significantly reduce bodily pain in our MS patients, contrasting with preclinical evidence [39–41]. This discrepancy likely reflects the multifactorial nature of MS-related pain, involving neuropathic mechanisms and central sensitization, which may not respond to anti-inflammatory interventions alone. While animal models support spirulina's analgesic properties [42],clinical findings highlight the challenge of translating these effects to complex human conditions. Although MS-specific trials are limited, one study in progressive MS showed that anti-inflammatory diets may alleviate pain [43]. The lack of correlation between reduced inflammation and pain relief suggests that persistent neuropathic processes, such as glial activation and sodium channel dysregulation, may sustain pain independently of peripheral inflammation [44]. underscoring the need for multimodal approaches to pain management in MS.

The lack of significant improvement in emotional well-being in the spirulina group may reflect the complex interplay of physical, cognitive, social, and psychological factors affecting mental health in MS [45, 46], A 12-week intervention may be insufficient to impact this multifaceted domain. Although spirulina contains

Table 3 Quality of Life Assessment (Psychological, Physical, Sexual) and Pro-inflammatory Cytokines: IL-1β and IL-6 Levels

Variable	Comparison Spl: *n* = 32 Plb: *n* = 32	Estimate ± SE	95% CI	t-value	*p*-value
Total Physical	Between-group	−0.73 ± 0.09	[−0.91, −0.55]	−7.91	< 0.001
	Within-group (Plb)	0.47 ± 0.10	[0.25, 0.67]	4.48	< 0.001
	Within-group (Spl)	−0.73 ± 0.09	[−0.91, −0.55]	−7.91	< 0.001
Physical Function	Between-group	−0.37 ± 0.11	[−0.59, −0.16]	−3.43	0.001
	Within-group (Plb)	−0.28 ± 0.13	[−0.53, −0.02]	−2.19	0.032
	Within-group (Spl)	−0.37 ± 0.11	[−0.59, −0.16]	−3.43	0.001
Bodily Pain	Between-group	−0.41 ± 0.20	[−0.81, 0.01]	−2.04	0.144
	Within-group (Plb)	0.73 ± 0.23	[0.28, 1.19]	3.21	0.002
	Within-group (Spl)	−0.41 ± 0.20	[−0.81, −0.01]	−2.04	0.044
Sexual Function	Between-group	−1.31 ± 0.29	[−1.87, −0.74]	−4.56	< 0.001
	Within-group (Plb)	1.02 ± 0.30	[0.41, 1.62]	3.36	0.001
	Within-group (Spl)	−1.31 ± 0.29	[−1.87, −0.74]	−4.56	< 0.001
Sexual Satisfaction	Between-group	−1.35 ± 0.37	[−2.09, −0.62]	−3.63	< 0.001
	Within-group (Plb)	1.48 ± 0.39	[0.71, 2.25]	3.83	< 0.001
	Within-group (Spl)	−1.35 ± 0.37	[−2.09, −0.62]	−3.63	< 0.001
Energy	Between-group	−0.56 ± 0.18	[−0.92, −0.20]	−3.08	0.003
	Within-group (Plb)	0.28 ± 0.22	[−0.16, 0.71]	1.28	0.206
	Within-group (Spl)	−0.56 ± 0.18	[−0.92, −0.20]	−3.08	0.003
Total Mental	Between-group	−0.44 ± 0.13	[−0.70, −0.19]	−3.42	0.001
	Within-group (Plb)	−0.11 ± 0.10	[−0.31, 0.09]	−1.07	0.288
	Within-group (Spl)	−0.44 ± 0.13	[−0.70, −0.19]	−3.42	0.001
Health Perception	Between-group	−0.49 ± 0.12	[−0.73, −0.26]	−4.18	< 0.001
	Within-group (Plb)	0.20 ± 0.13	[−0.05, 0.45]	1.59	0.116
	Within-group (Spl)	−0.49 ± 0.12	[−0.73, −0.26]	−4.18	0.000
Emotional Wellbeing	Between-group after intervention	−0.17 ± 0.16	[−0.48, 0.14]	−1.12	0.266
	Within-group (Plb)	−0.15 ± 0.15	[−0.44, 0.14]	−1.02	0.313
	Within-group (Spl)	−0.22 ± 0.16	[−0.53, 0.09]	−1.39	0.168
Health Distress	Between-group after intervention	−0.35 ± 0.31	[−0.96, 0.26]	−1.15	0.252
	Within-group (Plb)	−0.03 ± 0.35	[−0.72, 0.66]	−0.09	0.926
	Within-group (Spl)	0.15 ± 0.31	[−0.46, 0.76]	0.47	0.638
Social Function	Between-group after intervention	−0.27 ± 0.15	[−0.56, 0.02]	−1.83	0.069
	Within-group (Plb)	0.26 ± 0.14	[−0.01, 0.53]	1.85	0.069
	Within-group (Spl)	0.13 ± 0.15	[−0.16, 0.42]	0.82	0.414
Cognitive Function	Between-group	−0.60 ± 0.24	[−1.07, −0.14]	−2.56	0.012
	Within-group (Plb)	−0.35 ± 0.25	[−0.86, 0.15]	−1.41	0.165
	Within-group (Spl)	−0.60 ± 0.24	[−1.07, −0.14]	−2.56	0.012
Overall QoL	Between-group	−0.79 ± 0.36	[−1.49, −0.09]	−2.22	0.028
	Within-group (Plb)	−0.29 ± 0.31	[−0.91, 0.33]	−0.94	0.353
	Within-group (Spl)	−0.79 ± 0.36	[−1.49, −0.09]	−2.22	0.028
IL-1β (pg/mL)	Between-group	1.07 ± 0.14	[0.80, 1.34]	7.84	0.000
	Within-group (Plb)	−0.07 ± 0.10	[−0.27, 0.14]	−0.66	0.512
	Within-group (Spl)	1.07 ± 0.14	[0.80, 1.34]	7.84	< 0.001
IL-6 (pg/mL)	Between-group	8.56 ± 1.25	[6.09, 11.03]	6.87	< 0.001
	Within-group (Plb)	−0.88 ± 1.57	[−3.99, 2.23]	−0.56	0.564
	Within-group (Spl)	7.56 ± 1.15	[5.29, 9.83]	6.55	< 0.001

Data are presented as Estimate ± standard error (SE). The distributions of variables were assessed using the Shapiro-Wilk test and were found to be normal. the-value represents the ratio of the estimated effect to its standard error, indicating the strength and direction of the association. *P*-values were obtained from linear mixed-effects models, comparing end-of-trial values between groups while adjusting for the respective baseline values. Within-group comparisons represent changes from baseline to endpoint. a $P < 0.05$ was considered statistically significant

Abbreviations: *IL-6*, interleukin *6; IL-1*, interleukin. *Plb*, placebo, *SPL*, Spirulina

Table 4 Effect size comparisons: spirulina supplementation vs. Placebo on health outcomes (Cohen's d)

Variable	Within-Group SPL Cohen's d	Within-Group Plb Cohen's d	Between-Group Cohen's d	*p*-value (Between-Group)
Physical health				0.004
Overall physical health	1.17	0.47	1.28*	0.009
Physical function	0.64*	0.28	0.68*	0.041
Role limitations due to physical	0.52*	0.24	0.54*	0.078
Bodily pain	0.36*	0.29	0.39	0.004
Sexual health				
Sexual function	0.72*	0.36	0.82*	0.033
Sexual satisfaction	0.74	0.39	0.81	0.057
Cognitive/Social				
Energy	0.34*	0.16	0.60*	0.045
Total mental health	0.38	0.11	0.60*	0.068
Health perception	0.47	0.20	0.86*	0.051
Emotional wellbeing	0.22	0.15	0.20	0.272
Health distress	0.15	0.03	0.18	0.284
Social function	0.13	—	0.37	0.101
Cognitive function	0.60	0.35	0.70	0.060
Overall qoL	0.55	0.29	0.57	0.082
Biomarkers				
IL-1β (pg/mL)	1.00*	0.07	1.05*	0.016
IL-6 (pg/mL)	0.96*	0.56	1.09*	0.031
Anthropometrics				
BMI	0.44	0.40*	0.43	0.089
Weight (kg)	0.85*	0.70	0.80*	0.038
Waist Circumference (WC)	0.29	0.26	0.30	0.111
Waist-to-Hip Ratio (WHR)	0.09	0.12	0.08	0.307
Lifestyle factors				
Energy intake	0.13	0.14	0.10	0.274
Physical activity (IPAQ-SF)	0.10	0.11	0.08	0.291

Data represent Cohen's d effect sizes

Between-group comparisons (Spirulina vs. Placebo) were analyzed using linear models adjusted for baseline values. Within-group comparisons represent changes from baseline to endpoint. Significance from primary analyses: $P < 0.05$, $^{*}P < 0.01$, $^{**}P < 0.001$.

Abbreviations: *IL-6*, interleukin *6; IL-1*, interleukin. *WC*, waist circumference; *WHR*, waist-to-hip ratio; *MET*, metabolic equivalent of task *Plb*, placebo, *SPL*, Spirulina

mood-related nutrients [47], clinical evidence for its efficacy in enhancing emotional well-being in MS remains limited. Notably, physical and cognitive improvements did not translate into emotional gains, suggesting distinct underlying mechanisms. Given the established benefits of psychological interventions such as mindfulness [45], combining spirulina with such approaches may yield more pronounced effects. Interestingly, emotional well-being remained stable in the spirulina group but declined in the placebo group, indicating a possible protective role worth further investigation.

Beyond its well-established antioxidant and anti-inflammatory properties, spirulina may enhance health perception in multiple sclerosis patients through several neurobiological mechanisms. Spirulina supplementation can increase plasma tryptophan levels, a precursor of serotonin, thereby promoting central serotonergic activity, which is closely linked to improved mood, reduced anxiety, and enhanced feelings of well-being and hopefulness [48]. Moreover, spirulina has been shown to upregulate brain-derived neurotrophic factor (BDNF) expression, facilitating neuroplasticity and neuronal repair, which may contribute to better cognitive-emotional resilience and subjective health status [49, 50]. Additionally, spirulina's rich nutrient profile supports overall metabolic function and energy metabolism, potentially alleviating fatigue commonly experienced in MS, further improving patients' perceived health and quality of life [51]. Collectively, these mechanisms, alongside its antioxidant and anti-inflammatory effects, likely underlie spirulina's positive impact on health perception and quality of life in this population.

The weight-reducing mechanisms of spirulina are multifaceted, involving metabolic, inflammatory, and neurohormonal pathways. Spirulina modulates gut microbiota composition and increases satiety hormones, leading to

reduced appetite [52]. It also suppresses inflammatory pathways such as JAK/STAT3 and decreases IL-6 levels, thereby improving insulin resistance and adipose tissue inflammation. Additionally, spirulina inhibits adipogenesis regulators like PPAR-γ and activates energy expenditure pathways including AMPK, resulting in reduced fat cell formation and enhanced thermogenesis [53, 54]. Its micronutrients and phycocyanin improve mitochondrial function and energy metabolism [55]. Clinical studies have demonstrated that supplementation at doses exceeding 2 grams per day for at least 12 weeks can lead to significant reductions in body weight and fat mass, although effects on BMI and waist-to-hip ratio remain inconsistent [54].

he effectiveness of spirulina on anthropometric outcomes may be influenced by dosage, intervention duration, and individual participant characteristics [56].

Improved sexual performance without parallel changes in satisfaction scores highlights the complex, multidimensional nature of sexual health in MS. While improvements in fatigue/ energy and physical function may enhance physiological capacity, psychological aspects—such as self-esteem and relational dynamics, often require psychosocial support. Similar discrepancies between function and satisfaction have been noted in Parkinson's disease populations [57–59], suggesting the need for multidisciplinary management strategies. The divergence between physical sexual function and subjective satisfaction highlights the multidimensional nature of sexual health in MS. While spirulina improves physiological capacity, psychological and relational factors may require concurrent targeted interventions [60, 61].

The lack of significant changes in mental health, social functioning, and general health perception may reflect both the limitations of the intervention and the sensitivity of the measurement tools. Although the MSQoL-54 was employed, it may not fully capture slower-evolving psychosocial dimensions such as perceived stigma and caregiver burden—factors known to impact psychological health in MS [62, 63]. and caregiver strain is a critical determinant of psychological outcomes (65). Psychosocial benefits of nutritional interventions may take longer to emerge, particularly in the absence of adjunctive therapies like CBT or structured support. Future trials should integrate MS-specific tools like the MSQoL-54 and MSSS and evaluate multimodal interventions to address the full spectrum of MS-related challenges [64, 65]. The observed disconnect between physical/cognitive improvements and psychosocial outcomes underscores the need for comprehensive, multidimensional intervention strategies.

The lack of correlation between improvements in physical/cognitive domains and psychosocial outcomes underscores the potential need for multifaceted interventions addressing both physical and psychological well-being in MS. However, clinical evidence on spirulina's impact on body composition is mixed. A 12-week randomized controlled trial in obese individuals reported significant reductions in body weight and BMI following spirulina supplementation compared to placebo. Additionally, a systematic review and meta-analysis of randomized controlled trials found that spirulina supplementation significantly reduced body weight and waist circumference, although effects on BMI were not significant unless the intervention lasted at least 12 weeks. These findings suggest that the efficacy of spirulina on anthropometric measures may depend on factors such as dosage, intervention duration, and participant characteristics [56].

The reductions in IL-1β and IL-6 observed in this study are mechanistically attributable to spirulina's inhibition of the NF-κB signaling pathway. Specifically, phycocyanin suppresses IKKβ activity, stabilizing IκBα and preventing NF-κB nuclear translocation, thereby reducing pro-inflammatory gene expression [66–68]. This mechanism has been validated in EAE models, where spirulina reduced CNS inflammation and demyelination [40, 69], supporting its potential as a disease-modifying adjunct. Beyond NF-κB inhibition, spirulina has been shown to modulate other inflammatory pathways, such as mTOR and NLRP3 inflammasome activation. These additional mechanisms suggest a broader anti-inflammatory role for spirulina, which could further support its therapeutic potential in MS [70]. While a formal pharmacoeconomic analysis was beyond the scope of this study, the low cost of spirulina supplementation (~ 240 annually) compared to expensive DMTs (e.g. natalizumab 240*annually*) *compared to expensive DMTs* (e.g. Natalizumab 500,000) suggests potential for favorable cost-effectiveness, warranting dedicated future investigation using metrics like QALYs [71].

Though microbiota analysis was not performed, prior studies have linked spirulina with beneficial microbial shifts, such as increases in *F.* prausnitzii and *A.* muciniphila, which enhance IL-10 production [72, 73]. Future research should explore microbiome-mediated mechanisms.

A preliminary pharmacoeconomic model supports spirulina's favorable QALY-based value[74–76, 76]. Nevertheless, full pharmacoeconomic analyses are warranted.

As the first RCT to assess spirulina's concurrent effects on cognition and metabolism in MS, this study provides foundational evidence for its integration into cost-effective care strategies [56]. Given the prevalence of metabolic comorbidities in MS, spirulina's anti-inflammatory and adiposity-modulating effects further support its role as an adjunct to immunotherapies [21, 51, 56].

Strengths and limitations

A key strength of this study lies in its multidimensional assessment using objective biomarkers and functional metrics, though limitations such as incomplete blinding should be considered when interpreting subjective outcomes. This study possesses notable strengths, including its rigorous triple-blind, randomized, placebo-controlled design, adequate sample size calculation, high medication adherence rates (overall 92.4± 3.1%), and the use of validated outcome measures (MSQoL-54, standardized anthropometrics, ELISA). A key strength is the primary analysis adhering to the intention-to-treat (ITT) principle, enhancing the external validity of the findings. The balanced baseline characteristics between the randomized groups also minimize the potential for initial confounding. Another notable methodological strength is the use of linear mixed-effects models, which allow for the evaluation of longitudinal changes over time while effectively handling missing data. This approach increases the precision and reliability of the results compared to simpler methods.Moreover, the inclusion of effect size estimations alongside mixed-effects modeling enhances the robustness and clinical interpretability of the findings.

However, certain limitations should be acknowledged. The 12-week intervention duration, while sufficient for detecting changes in inflammatory markers, might be insufficient to observe significant or sustained changes in all QoL domains, particularly mental health aspects. The single-center design may limit the generalizability of our findings to other MS populations or healthcare settings. Finally, the study did not include direct mechanistic assessments (e.g., specific oxidative stress markers or gut microbiota analysis) which could have provided further insight into spirulina's biological effects in RRMS.

Conclusion

This randomized trial demonstrates that 12-week spirulina supplementation exerts anti-inflammatory effects and improves physical health, including energy and sexual performance, and potentially mental health in patients with RRMS. Favorable metabolic changes were also observed, with predominantly mild gastrointestinal adverse events. Given its safety profile and potential cost-effectiveness, spirulina represents a promising adjunct therapy for MS management, although further large-scale studies with extended follow-up periods are warranted to establish its clinical utility and optimal implementation in treatment protocols. In particular, the observed reduction in weight suggests spirulina's potential in modulating metabolic risk factors in MS. Considering the potential of spirulina in reducing inflammation and modulating metabolic outcomes, it would be valuable for future research to explore its integration with disease-modifying therapies (DMTs). Combining spirulina with standard DMTs may enhance overall treatment efficacy, attenuate therapy-related adverse effects, and potentially target both immunological and metabolic pathways synergistically. Additionally, mechanistic studies investigating oxidative stress markers, gut microbiota alterations, and neuroprotective signaling pathways could provide deeper insights into the biological mechanisms underlying spirulina's effects. Future trials with longer durations, diverse populations, and multimodal outcome assessments including neuroimaging, cognitive batteries, and health economic modeling are essential to guide evidence-based integration of spirulina into comprehensive MS management strategies.

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Authors' contributions

Study design: SK, MK, VSN and AM. Study management: SK, MK, VSN. Study conduct SK, MK, SH and AM drafted the manuscript of the protocol, and the authors read and approved the last manuscript version. SK has primary responsibility for final content.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The protocol for this study was designed in alignment with the Declaration of Helsinki, the SPIRIT checklist, and established ethical standards for clinical research. It received approval from the Medical Ethics Committee at Isfahan University of Medical Sciences, Isfahan, Iran (ID: IR.MUI.PHANUT.REC.1402.070). Throughout the study, the research committee investigator will oversee protocol procedures and ensure any modifications are reviewed and approved by the committee. Participants will continue their standard treatment regimen during the study, which will not interfere with their usual care. The study is currently in the implementation phase.

Consent for publication

All authors have given their formal consent for publication. Additionally, patient consent has been secured to disclose non-identifiable information.

Competing interests

The authors declare no competing interests.

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