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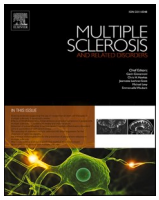

Original article

The effect of saffron and corrective exercises on depression and quality of life in women with multiple sclerosis: A randomized controlled clinical trial

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ABSTRACT

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system which causes various complications such as reduced ability to do daily activities, depression and early death of patients. The present study aimed to compare the effect of saffron and corrective exercises on depression and quality of life in women with MS. This randomized controlled clinical trial was conducted on 80 MS women for 12 weeks. Participants were selected through convenience sampling and allocated into four study groups (three intervention groups and one control group) using the stratified block randomization. The Expanded Disability Status Scale, Beck Depression Inventory and The Multiple Sclerosis Impact Scale were used to collect data at the start of the study and also at the end of the sixth and the twelfth weeks. At the end of the twelfth week, the depression mean scores in all experimental groups (saffron group, corrective exercises group, corrective exercises + saffron group) were significantly different compared to the control group ($P < 0.05$), and this difference in corrective exercises + saffron group was more than the others. Also, at the end of the twelfth week, the mean scores of the quality of life (both physical and mental dimensions) in all experimental groups were significantly different from the control group ($P < 0.05$). The saffron group in physical dimension and the corrective exercises + saffron group in psychological dimension showed a significant difference with other groups. Although each of the corrective exercises program and saffron consumption alone were effective in reducing depression and enhancing the quality of life in MS patients, the consequences will be more beneficial in case these two interventions are used together. Therefore, it is necessary to encourage MS patients to consume saffron supplement along with doing physical activities in caring and rehabilitation programs.

1. Introduction

Multiple sclerosis (MS) is a degenerative disease that destroys the neurons' myelin in the central nervous system (Hauser and Cree, 2020). This disease causes many complications such as numbness, weakness and paralysis of limbs, dizziness, fatigue, weight loss and decreased muscles' power (Kraft, 1999), impaired balance (Noon et al., 2019), physical disability, cognitive defects, reduced quality of life (Yang et al., 2022), depression, and early death of patients (Kraft, 1999). The global prevalence of MS is estimated to be 5–300 per 100,000 people and its distribution ratio in women is approximately three times more than that of in men (McGinley et al., 2021). According to the statistics of the Iranian MS Association, there are about 30,000–40,000 people with MS in the country (Heidari et al., 2023; Mohaghegh et al., 2021). The evidence shows that MS has a significant impact on people's quality of life in different dimensions (Heidari et al., 2023; Mohammad et al., 2014). In particular, the severity and duration of the disease along with increased anxiety and depression are related to the quality of life of these patients (Noon et al., 2019). Pittock showed that the quality of life in people with MS is lower than that of healthy people in the dimensions of

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physical function, vitality and general health (Pittock et al., 2004). In addition, the quality of life in MS patients is worse in those who have more fatigue and disability (Mostert and Kesselring, 2002). Since the lack of proper caring program makes the life conditions of MS patients become more unfavorable, taking practical actions regarding the quality of life of these patients is necessary (Mohaghegh et al., 2021).

MS disease has a negative impact on skeletal muscle fibers, muscle strength and muscle mass of the lower limbs (Dettmers et al., 2009). Thus, choosing an active lifestyle such as doing endurance and balance exercises is recommended for MS patients (Heine, 2015). This is because proper physical activity or exercise enhances physical function and leads to the treatment and reduction of fatigue (Dettmers et al., 2009).

Moreover, the prevalence of depression in MS patients is high. About 48% of MS patients experience symptoms of anxiety, stress and depression in the first year after diagnosis (Mitchell et al., 2005). In Ghaffari 's study, the prevalence of depression in MS patients was reported to be 50–60 % (Ghafari et al., 2008). MS patients experience a high level of anxiety and depression because they are worried about the effect of the disease and its severity on their physical, social, family, and daily activities at home or at work (Mitchell et al., 2005). Potagas et al. conducted a study on 120 MS patients in Norway. In their study, 31.4 % of the patients reported symptoms of depression and 19.3 % of them had symptoms of anxiety, which indicated that the levels of depression and anxiety in these patients were almost twice and three times, respectively, higher than that of healthy population (Potagas et al., 2008). Disability and depression in MS patients have a significant relationship with the decrease in their quality of life (Mostert and Kesselring, 2002) and the increase in their dependence (Mobaraki et al., 2013). The effect of depression on the quality of life in MS patients is determined by the disturbance in social functioning, suicidal thoughts and disease recurrence (Ghafari et al., 2008). According to the studies, doing exercise in the early stages of MS is effective in compensating and correcting the symptoms of the disease and may delay the disease (Riemenschneider et al., 2018). This is due to the fact that exercise makes depressed people happy, energetic and self-confident, and also enhances their inner satisfaction and feeling of achieving success (Armstrong et al., 1983). Also, endurance exercise can be effective on MS by increasing balance (Amiri et al., 2019; Ritonga, 2014).

The evidence has proven the role of nutrition in maintaining the health of MS patients (Duke, Bogenschutz-Godwin, DuCellier, & Duke). The recent projects on medicinal plants for the treatment of MS can open new horizons for researchers (Duke et al., 2002). Medicinal plants used in the prevention or treatment of MS are herbs which have a sedative action and are beneficial for enhancing the memory and stimulating blood flow. These plants such as Boswellia carteri, Frankincense, Coffea arabica, Saffron, Caffeine, Ginkgo biloba, and Cannabis sativa are effective in the treatment of MS (Huang, 1998). Out of many herbs, Saffron has been especially known for its soothing properties. Weekly consumption of one tablespoon of saffron can help treat MS. The healing substance of saffron is called crocin which protects the brain cells and prevents damage to the cells creating a protective layer of fat for myelin. In MS disease, this protective insulation is lost due to brain cell edema. However, consumption of crocin can reduce this cell swelling to a great extent in MS patients (Jana and Shekhawat, 2010). Saffron is a cooking spice in Middle Eastern countries and is used in traditional Iranian medicine to relieve stomach pain, reduce pain caused by kidney stones and treat depression. Saffron may exert its antidepressant effect by increasing the level of certain chemicals such as "serotonin" in the brain (Siddiqui et al., 2022). It is recommended to use saffron in food and tea for relaxation. In addition, saffron increases concentration and is effective in preventing Alzheimer's and Parkinson's disease, and also treating nerve pain and insomnia (Avgerinos et al., 2020; Siddiqui et al., 2022). Since the simultaneous effect of physical activity and saffron consumption on reducing depression and improving the quality of life of MS patients has not been studied in Iran, this study aimed to investigate the effect of corrective exercises and saffron on depression and quality of life in women with MS during a 12-week period.

2. Methods

2.1. Research design, environment, and sample

The present study was a randomized controlled clinical trial conducted during a 10-month period from June 2020 to April 2021. The study population included all women with MS, about 460 individuals, engaged in the association of MS in Khorramabad city. In order to receive healthcare services, these women referred to the neurology clinic of Shahid Rahimi Hospital that was affiliated to MS association. According to Table B. 12 offered by Kutner et al., the sample size in each group calculated to be 20 people, considering $r = 4$, $\Delta/\sigma \approx 1.25$, $\alpha = 0.05$, $1\text{-}\beta = 0.9$ (Kutner et al., 2005). To be more precise, the standard deviation of Beck depression score was considered to be the same for all studied groups and σ was estimated to be 10.5 through R/6 (63–0/6). Δ was the maximum difference between depression mean scores in studied groups which was estimated to be 13.8 based on a pilot study (5 participants per each group). According to these calculations, Δ/σ was accounted for 1.31 and this figure was something near 1.25 in Table B. 12 by Kutner et al.

80 women with MS in the age group of 25–45 years, with mild and moderate levels of disability (EDSS $\leq$ 4), mild and moderate scores of depression and quality of life, and were willing to participate in the research entered the study through convenience sampling and completed the informed consent. After entering the study, the samples were divided into four groups (three intervention groups and one control group) using stratified block randomization. In each block with size of 4, the order of allocating patients to four groups was determined using a random number table. Due the nature of the study, we did not consider blinding for our patients especially those groups that underwent corrective exercises. The blinding was only considered for researchers assessing the depression and quality of life of the patients and also the biostatistician. The studied groups were offered as letters A, B, C and D, and the evaluator or decoder was outside the research team.

2.2. Measurements

The data collection tool in this research included three questionnaires. The Expanded Disability Status Scale (EDSS) is the most wildly used scale in MS patients and is a very effective method of reflecting disability (Kurtzke, 1955). EDSS scores range between 0 and 10 in 0.5 step intervals with 0 being no disability, and 10 being death due to MS (Collins et al., 2016). The scale measures functional systems (FS) as well as ambulation. There are 8 FSs, including visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral. Patients with scores up to 5 are fully ambulatory, and at this point, the main determinant of EDSS are FSs. The ambulation condition is the main determinant in the degree of disability after score 5 (Sedat, 2018). EDSS scores could be classified as mild (0–3), moderate (3.5–5.5), and severe (6–9.5) (Gray et al., 2009; Marrie et al., 2021). In this research, the patients who were examined by the neurologist and obtained grades between 1 and 4 with mild and moderate disability were included in the study.

Beck Depression Inventory (BDI) is one of the most common tools for measuring depression and has 21 questions designed based on the symptoms of depression especially cognitive symptoms (Beck et al., 1996). Items are rated on a 4-point (0–3) scale and the total score range from 0 to 63. In this scale, getting a score of 0–13 represents minimal depression. A score between 14 and 19 indicates mild depression and requires consultation with a psychologist or psychiatrist. A score of 20–28 shows moderate depression and scores between 29 and 63 indicate severe depression. In Iranian context, test-retest reliability and Cronbach's alpha coefficient were calculated to be at 0.74 and 0.87, respectively (Kamkar et al., 2019).

The Multiple Sclerosis Impact Scale (MSIS-29) contains 29 questions. The first 20 questions measure the physical impact and the last 9 questions measure the psychological impact of MS on the patient's quality of life. The response to each question is rated based on a 5-point Likert scale. Higher scores indicate lower health condition. The maximum score in the physical dimension is 100 and the minimum is 20, and the maximum score in the mental dimension is 45 and the minimum is 9 (Hohart et al., 2001). Content and concurrent validity has been confirmed in various foreign (Rosti-Otajärvi, Hämäläinen, Wiksten, Hakkarainen, and Ruutiainen, 2017; Turpin et al., 2007) and domestic studies. In the previous study in Iran, The reliability of the questionnaire was confirmed with Cronbach's alpha as 0.72 (Karimi et al., 2022).

2.3. Procedure

At the start of the study, three questionnaires were completed by MS women referring to the neurology clinic of Shahid Rahimi Hospital which was affiliated to the MS association in Khorramabad city. 80 women who met the inclusion criteria were entered the study through convenience sampling and then divided into three intervention groups (saffron group, corrective exercises group, corrective exercises + saffron group) and one control group using stratified block randomization. After that, the patients' information was recorded and they were informed by the researchers about how to perform the interventions. The first intervention group ($N = 20$) consumed 15 mg saffron, in the shape of capsule, twice a day for 12 weeks. At the same time, they underwent sports training and corrective exercises for 3 sessions a week. Corrective exercises included stretching and strength movements that were performed at the discretion of a specialist trainer in the field of corrective movements. In order to do strength exercises, women were encouraged to perform weight-bearing exercises without using any equipment. The second intervention group ($N = 20$) underwent sports training and corrective exercises, 3 sessions a week, for 12 weeks. The third intervention group ($N = 20$) used saffron capsules with a dose of 15 mg twice a day for 12 weeks. The fourth group ($N = 20$) was considered as the control group and the samples of this group only received routine treatment and did not undergo any interventions. MS women were followed up in terms of adherence to the study protocol. With regard to the consumption of saffron, telephone calls were made with women to make sure that they consume it according to the protocol and to find out if they had any problems or complications regarding the consumption of saffron. As for corrective exercises, women were given the letters to go to Farhangian sports hall for sports training and their attendance and performance of sports program were controlled by the specialist trainer who was the third researcher in this study. To avoid sample contamination, MS women in corrective exercises group and corrective exercises + saffron group referred to sports hall on odd and even days, respectively. After the sixth week and at the end of the twelfth week, the post-test was done for all four groups and the data were analyzed after extraction. At the end of the research, the samples in the control group underwent corrective exercises according to study protocol to observe ethical issues.

2.4. Statistical analysis

The data from the pre-test and post-test were analyzed using SPSS 22.0 (IBM Corp., Armonk. NY, USA) at the significant level of 0.05. Frequency distribution table, median and interquartile range, mean and standard deviation, and linear graph were used to describe the data. Kruskal-Wallis test was used to compare the groups in terms of background variables and for multivariable modeling due to the longitudinal nature of the data, the marginal model with the identity link function, exchangeable covariance matrix and GEE method were used to estimate the parameters. Considering the significance of the interaction between the experimental group and the time factor, at each time separately, pairwise comparisons of the groups were performed with the Bonferroni test. In addition, we used intention to treat (ITT) analysis to analyze the data. In order to manage missing data and those participants who did not complete the study (loss to follow-up), we benefited from imputation method or last observation carried forward (LOCF).

2.5. Ethical considerations

The present study was approved by the ethics committee of Lorestan University of Medical Sciences (LUMS.REC.1395.209) and registered in the Iranian Clinical Trials Registry (IRCT20170514033961N4). We received a letter of introduction from Research Deputy of Lorestan University of Medical Sciences and MS Association and presented it to the research environment, explaining the research goals to MS women, obtaining informed consent, assuring the patients of the confidentiality of the information obtained from them, and providing the results of the research to the relevant authorities.

3. Results

In the present study, 80 MS women with disability grade 1–4 were studied in four experimental groups. Kruskal-Wallis test showed that there was no significant difference between the age distribution of the patients ($P = 0.946$) and the body mass index (BMI) of them ($P = 0.895$) (Table 1).

3.1. Depression

Table 2 compares the depression mean scores of the studied groups during different times. The marginal model with the identity link function and GEE showed that the interaction effect of the experimental group factor and the time factor on the depression mean scores of the patients was significant ($P < 0.001$, df = 3, $x^2 = 144.185$). In other words, the difference between experimental groups in terms of depression mean scores depends on time.

According to Bonferroni's pairwise comparison test, at the beginning of the study, there was no statistically significant difference between any pair of experimental groups regarding depression mean scores ($P > 0.05$). In the sixth week, there was a statistically significant difference between the control group and other experimental groups in terms of depression mean scores ($P < 0.05$), but no significant statistical difference was observed in other pairs of comparisons ($P > 0.05$). In the twelfth week, there was a statistically significant difference between the control group and other experimental groups in terms of depression mean scores ($P < 0.05$) and also a statistically significant difference was observed between the saffron group and the corrective exercises + saffron group ($P < 0.001$). Meanwhile, in other pairs of comparisons, no significant statistical difference was observed ($P > 0.05$) (Table 2 and Graph 1).

Table 3 shows the relationship between the mean differences of all intervention groups compared to the control group at different times. The results of the marginal model showed that in the sixth week of the study, the adjusted depression mean scores of the corrective exercises, saffron and corrective exercises + saffron groups were 3.899, 3.749, and 5.100 units lower, respectively, compared to the control group. In the twelfth week of the study, the adjusted depression mean scores of the corrective exercises, saffron and corrective exercises + saffron groups were 9.023, 7.223, and 10.650 units lower, respectively, compared to the control group.

3.2. Physical dimension of quality of life

In Table 4, the mean scores of the physical dimension of the studied groups were compared during different times. The marginal model with the identity link function and GEE showed that the interaction effect of the experimental group and the time factor on the mean scores of the physical dimension of the patients' quality of life is significant ($x^2 =$

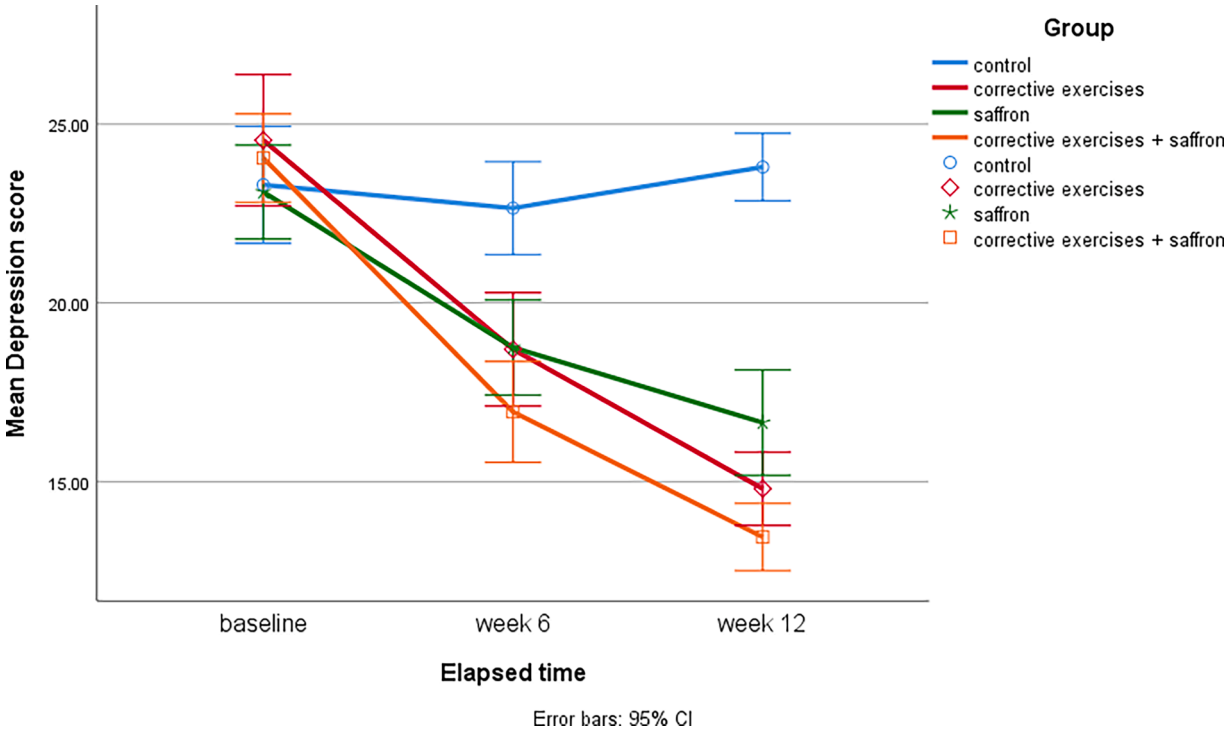
Table 1
Comparison of the studied groups in terms of background characteristics such as age and BMI.

Variable	Studied groups								Between groups P-value
	Corrective exercises + saffron		Corrective exercises		Saffron		Control		
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	
Age	36	5	37.5	12	35	10	36	6.75	0.946
BMI	25.59	2.49	25.37	3.11	25.27	2	25.14	2.42	0.895

Table 2
Comparison of the depression mean scores in studied groups during different times.

Elapsed time	Groups				P-value		
	Corrective exercises + saffron Mean* ± SD	Corrective exercises Mean*± SD	Saffron Mean* ± SD	Control Mean* ±SD	Time	Group	Time * group
Baseline	24.05 ± 2.65[a]	24.55 ± 3.93[a]	23.10 ± 2.81[a]	23.30 ± 3.50[a]	0.001>	0.001>	0.001>
Week 6	16.95 ± 3.02[b]	18.70 ± 3.39[b]	18.75 ± 2.84[b]	22.65 ± 2.78[a]			
Week 12	13.45 ± 2.01[c]	14.80 ± 2.19[b,c]	16.65 ± 3.15[b]	23.80 ± 2.02[a]			

*Unadjusted mean.
In each separate time, the groups not sharing the same superscript are significantly different at $P < 0.05$ in the test of equality for means. For example, different letters (e.g., a and b) used in the same row suggest a significant difference between the group means. However, the use of the same letters (e.g., b and b,c) shows that the difference in group means is not significant.



Graph 1. Comparison of the depression scores of the studied groups over time.

371.842, df = 3, $P < 0.001$). In other words, the difference between the experimental groups in terms of the mean scores of the physical dimension of quality of life depends on time. According to Bonferroni's pairwise comparison test, at the beginning of the study, there was no statistically significant difference between any pair of experimental groups regarding the mean scores of the physical dimension of quality of life ($P > 0.05$). In the sixth week, the control group and the saffron group still did not show a statistically significant difference with each other in terms of the mean scores of the physical dimension of quality of life ($P > 0.05$). Furthermore, the groups of corrective exercises and corrective exercises + saffron have no statistically significant difference regarding the mean scores of the physical dimension of quality of life ($P > 0.05$). In the twelfth week, there was a statistically significant difference between the control group and other experimental groups, as well as between the saffron group and other experimental groups regarding the mean scores of the physical dimension of quality of life ($P < 0.05$). However, no statistically significant difference was observed between the corrective exercises group and the corrective exercises + saffron group ($P > 0.001$) (Table 4 and Graph 2).

Table 5 gives information about the relationship between the mean differences of all intervention groups compared to the control group at different times. In the sixth week of the study, the results of the marginal model showed that the adjusted mean scores of the physical dimension of the quality of life in the saffron, corrective exercises and corrective exercises + saffron groups were 2.783, 11.115, and 11.631 units lower, respectively, compared to the control group. However, in the twelfth

Table 3
The effect of different interventions on depression scores by "time factor" using the marginal model.

Comparison type	The formula for the average difference of each experimental group compared to the control group in terms of time (t)	Baseline	Week 6	Week 12
Corrective exercises group compared to control group	*1.225 - 0.854 × t*	1.225	−3.899	−9.023
Saffron group compared to control group	*−0.275 - 0.579 × t*	−0.275	−3.749	−7.223
Corrective exercises + saffron group compared to control group	*0.450 - 0.925 × t*	0.450	−5.100	−10.650

week of the study, the adjusted mean scores of the physical dimension of the quality of life in the saffron, corrective exercises, and corrective exercises + saffron groups were 6.083, 21.567, and 22.479 units lower, respectively, compared to the control group.

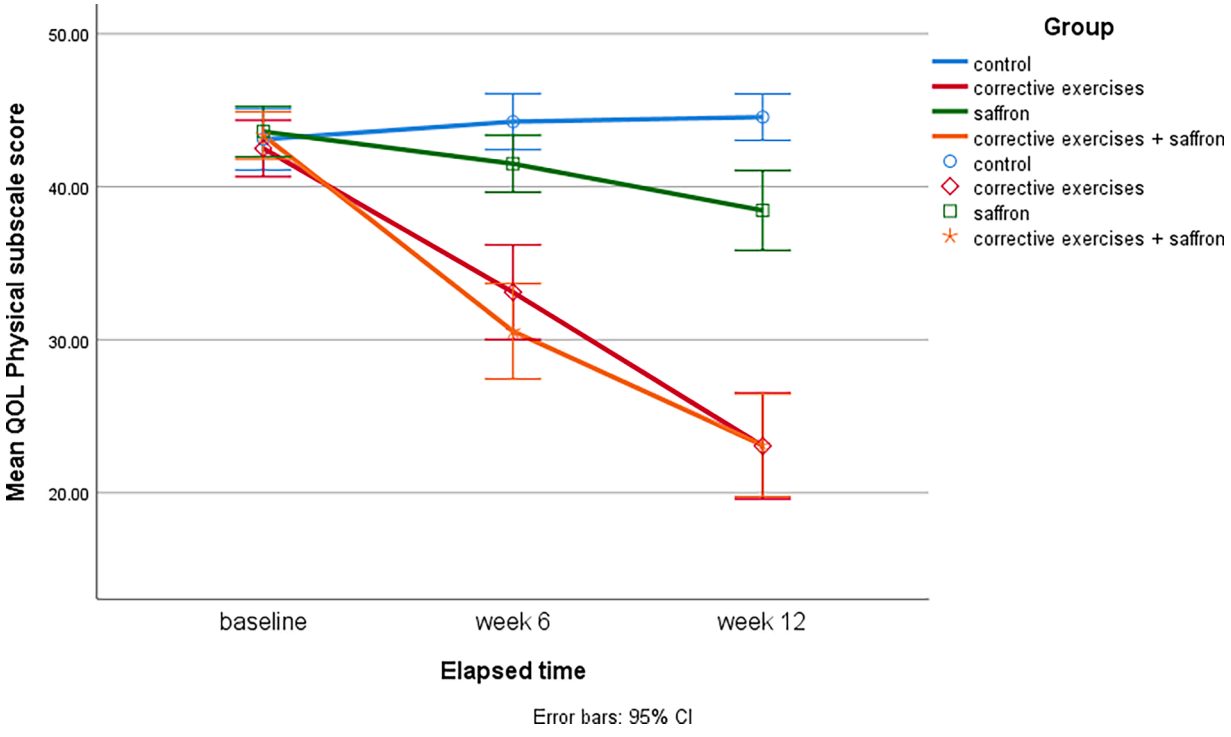
3.3. Psychological dimension of quality of life

In Table 6, the mean scores of the psychological dimensions of the studied groups are compared during different times. The marginal model with the identity link function and GEE showed that the interaction effect of the experimental group and the time factor on the mean scores of the psychological dimension of the quality of life of patients is significant ($x^2 = 295.868$, df = 3, $P < 0.001$). In other words, the difference between the experimental groups in terms of the mean scores of the psychological dimension of the quality of life depends on time. According to Bonferroni's pairwise comparison test, at the beginning of the study, there was no statistically significant difference between any pair of experimental groups in terms of the mean scores of the psychological dimension of quality of life ($P > 0.05$). In the sixth week, the corrective exercises group and the saffron group still did not show a statistically significant difference with each other in terms of the average scores of the psychological dimension of quality of life ($P > 0.05$). Plus, the corrective exercises group + saffron showed a statistically significant difference with other groups regarding the mean scores of the psychological dimension of quality of life ($P < 0.05$). In the twelfth week, there was a statistically significant difference between all pairs of groups in terms of the mean scores of the psychological dimension of quality of life ($P < 0.05$) (Table 6 and Graph 3).

Table 4
Comparison of the mean scores of the physical dimension of the quality of life in studied groups during different times.

Elapsed time	Groups				*P*-value		
	Corrective exercises + saffron Mean* ± SD	Corrective exercises Mean* ± SD	Saffron Mean* ± SD	Control Mean* ±SD	Time	Group	Time * group
Baseline	43.35 ± 3.30[a]	42.50 ± 3.94[a]	43.60 ± 3.52[a]	43.10 ± 4.29[a]	0.001>	0.001>	0.001>
Week 6	30.55 ± 6.66[b]	33.10 ± 6.62[b]	41.50 ± 3.98[a]	44.25 ± 3.91[a]			
Week 12	23.10 ± 7.17[c]	23.05 ± 7.39[c]	38.45 ± 5.58[b]	44.55 ± 3.25[a]			

*Unadjusted mean.
In each separate time, the groups not sharing the same superscript are significantly different at $P < 0.05$ in the test of equality for means. For example, different letters (e.g., a and b) used in the same row suggest a significant difference between the group means. However, the use of the same letters (e.g., b and c) shows that the difference in group means is not significant.



Graph 2. Comparison of the scores of the physical dimension of the quality of life in studied groups over time.

Table 5
The effect of different interventions on physical dimension scores of the quality of life by "time factor" using the marginal model.

Comparison type	The formula for the average difference of each experimental group compared to the control group in terms of time (t)	Baseline	Week 6	Week 12
Corrective exercises group compared to control group	$-0.633 - 1.742 \times t$	−0.633	−11.115	−21.567
Saffron group compared to control group	$0.517 - 0.550 \times t$	0.517	−2.783	−6.083
Corrective exercises + saffron group compared to control group	$-0.783 - 1.808 \times t$	−0.783	−11.631	−22.479

Table 7 gives information about the relationship between the mean differences of all intervention groups compared to the control group at different times. The results of the marginal model showed that in the sixth week of the study, the adjusted mean scores of the psychological dimension of the quality of life of the saffron, corrective exercises, and corrective exercises + saffron groups were 2.884, 3.583, and 6.233 units lower, respectively, compared to the control group. Meanwhile, in the twelfth week of the study, the adjusted mean scores of the psychological dimension of the quality of life of the saffron, corrective exercises, and corrective exercises + saffron groups were 4.960, 7.233, and 11.483 units lower, respectively, compared to the control group.

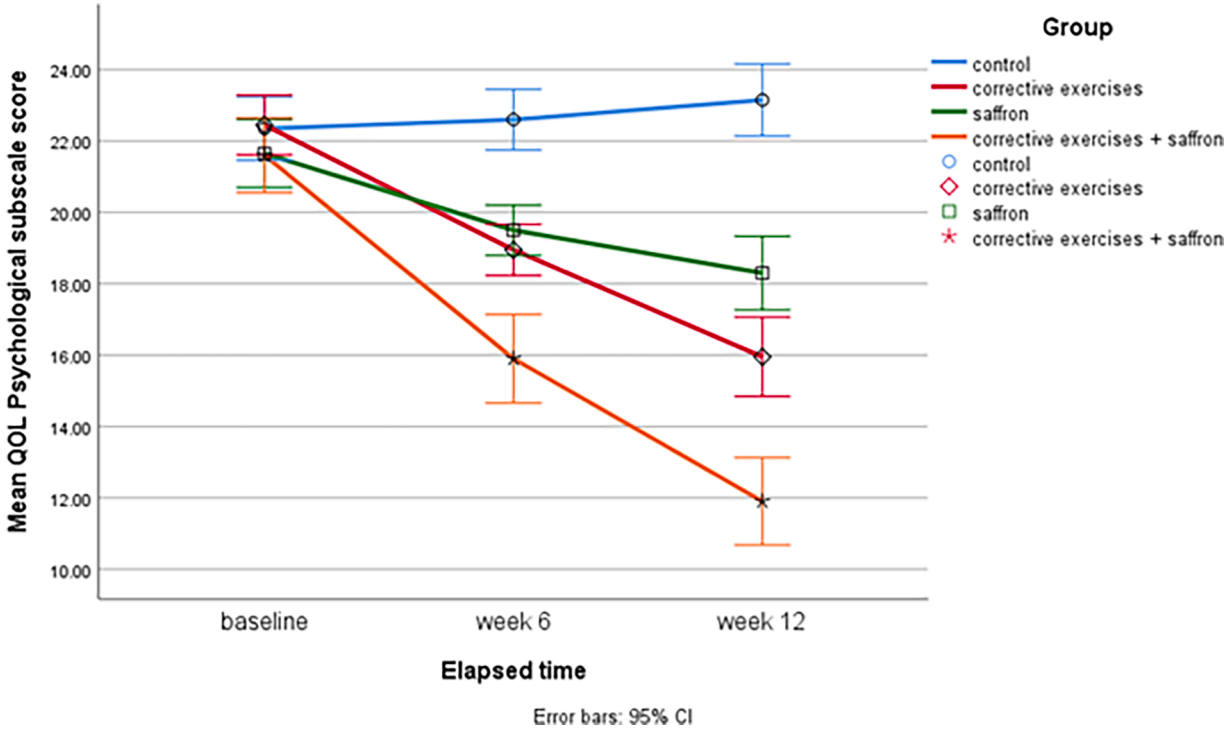
4. Discussion

Depression is common in MS patients and can be life-threatening for these people (Mobaraki et al., 2013). The results of this study showed that the consumption of saffron is effective in reducing depression and increasing the psychological aspect of the quality of life in people with MS, and the general belief that saffron is related to happiness is not just an old and superstitious belief. Several scientific researches have examined and confirmed the effect of saffron consumption in the treatment and improvement of depression (Avgerinos et al., 2020; Siddiqui et al., 2022). The results of some studies making a comparison

Table 6
Comparison of the mean scores of the psychological dimension of the quality of life in studied groups during different times.

Elapsed time	Groups				P-value		
	Corrective exercises + saffron Mean* ± SD	Corrective exercises Mean* ± SD	Saffron Mean* ± SD	Control Mean* ±SD	Time	Group	Time * group
Baseline	21.60 ± 2.23^{a}	22.45 ± 1.79^{a}	21.65 ± 2.03^{a}	22.35 ± 1.90^{a}	0.001>	0.001>	0.001>
Week 6	15.90 ± 2.65^{c}	18.95 ± 1.54^{b}	19.50 ± 1.50^{b}	22.60 ± 1.82^{a}			
Week 12	11.90 ± 2.61^{d}	15.95 ± 2.37^{c}	18.30 ± 2.20^{b}	23.15 ± 2.16^{a}			

*Unadjusted mean.
In each separate time, the groups not sharing the same superscript are significantly different at $P < 0.05$ in the test of equality for means. For example, different letters (e.g., a and b) used in the same row suggest a significant difference between the group means. However, the use of the same letters (e.g., b and bc) shows that the difference in group means is not significant.



Graph 3. Comparison of the scores of the psychological dimension of the quality of life in studied groups over time.

Table 7
The effect of different interventions on psychological dimension scores of the quality of life by "time factor" using the marginal model.

Comparison type	The formula for the average difference of each experimental group compared to the control group in terms of time (t)	Baseline	Week 6	Week 12
Corrective exercises group compared to control group	$0.067 - 0.608 \times t$	0.067	−3.583	−7.233
Saffron group compared to control group	$-0.808 - 0.346 \times t$	−0.808	−2.884	−4.960
Corrective exercises + saffron group compared to control group	$-0.983 - 0.875 \times t$	−0.983	−6.233	−11.483

between the use of saffron and common anti-depressant drugs such as SSRIs in patients, indicated a similar effect and no side effects of saffron. Therefore, saffron can be considered as an anti-depressant agent (Siddiqui et al., 2022). The anti-depressant properties of saffron are related to the neurotransmitter serotonin, which is responsible for regulating mood and sleep (Avgerinos et al., 2020). In a study by Kashani et al., to compare the effect of "saffron" with "fluoxetine" on the symptoms of mild and moderate depression; patients aged between 18 and 45 were tested for 6 weeks. Participants were given 15 mg of saffron extract or 20 mg of fluoxetine twice daily and depression symptoms were evaluated using the Hamilton scale before the study and at the end of first, third, and sixth weeks. According to the result of their study, both "saffron" and "fluoxetine" treatments showed a significant improvement in depression symptoms. Participants in the fluoxetine group experienced more headache, dry mouth, daytime drowsiness, constipation and sweating than the saffron group. However, frequencies of side effects were not significantly different between the 2 study groups. No major adverse event and no death occurred (Kashani et al., 2017). In a study by Asdaq et al., the consumption of saffron supplement for 5 days was more effective than crocin in reducing cardiac risk factors and increasing antioxidant activity. Also, performing corrective exercises regularly reduced depression and increased the mental and physical quality of life of patients with MS (Asdaq and Inamdar, 2010).

The findings of the present study are in line with the results of previous studies on the effect of physical activity in reducing mental problems and depression (Fossati et al., 2021; Rosenbaum et al., 2014). Corrective exercises improve basic movement patterns and reduce asymmetry and imbalance in movement (Usluer et al., 2021), which is consistent with the results of the present study. Physical exercise is beneficial for the human psyche in two ways: 1- releasing endorphins and 2- reducing the level of cortisol in the blood (Smith and Elliott, 2021). Physical exercise increases the release of endorphin in the body, which is a natural substance that reduces pain and causes pleasant feelings (Hawkes, 1992). Some other researchers came to the conclusion that physical exercise has a great effect on increasing the level of serotonin (Dunn et al., 2005). Exercise helps release more endorphin and serotonin in the body and maintain it for a long time during exercise (Aşçı, 2003). Although MS is in conflict with physical and mental health status, regular physical activity and stretching and flexibility exercises increase both physical and mental health levels (Halabchi et al., 2017). Exercise is a useful approach in MS disease, preventing the progression of the disease and removing the movement restrictions. The effect of these exercises is greater in the early stages and gives better results (Briken et al., 2014). Decreasing physical activity will decrease muscle mass and performance. The effect of sports training on improving the physical performance of patients with MS has been proven (Giesser et al., 2007). In addition, exercise improves memory and neural regeneration resulting in shape changes and better learning in MS patients (Briken et al., 2014). A study conducted by Dunn et al., showed that the public health dose (PHD) of aerobic exercise was considered to be an effective treatment for mild and moderate major depression. In their study, the mean scores of the 17-item Hamilton Rating Scale for Depression at 12 weeks showed a reduction of 47 % from baseline for the PHD condition, and 29 % for control group (Dunn et al., 2005). Their results revealed a much smaller effect size compared to the findings of our study. This might be because the two studies considered different types and amount of exercise for their studied groups. Another reason is that the control group in Dunn's study performed stretching flexibility exercise, while control group in our study did not undergo any interventions.

The effect of exercise in improving the physical condition of patients has been shown in recent studies. Therefore, sports training as a non-invasive treatment method is an effective factor in improving the ability to perform daily life activities and reducing dependence on others, which can be recommended to MS patients along with medication. However, the results of this study showed that the consumption of saffron and performing corrective exercises have an effect on reducing depression and increasing the quality of life of people with MS. The most important finding of the present study was the fact that the corrective exercises + saffron group showed relatively better and more efficient effects which is completely consistent with the study of Houshmand Moghadam et al. (Attarzade Hosseini and Gaeini, 2019). Their study showed that the interactive effect of saffron and physical activity enhances the antioxidant capacity, augments respiratory diseases, and improves blood sugar and glycemic indices. However, this review did not focus on MS patients. In fact, our research is the first study that examined the simultaneous effect of saffron consumption and performing corrective exercises on the treatment of depression and improving the quality of life in MS patients, but comparing the results with other studies is relatively possible.

4.1. Limitations

One of the limitations of this study was that the MS women were fully ambulatory and we only considered those with EDSS $\leq$ 4 and there might be the possibility of low changes in this short interval. The other two limitations were small sample size and lack of blinding for patients due to the nature of the interventions. Therefore, we suggest further studies to be carried out with different designs including larger samples and considering EDSS up to 5.5. Since the present study was conducted on women with MS, the results can only be generalized to women.

5. Conclusion

This study showed that although the program of corrective exercises and consumption of saffron is effective in reducing depression and increasing the quality of life in MS patients, the simultaneous implementation of both interventions gives more effective results. Therefore, it is expected that the simultaneous implementation of saffron and corrective exercises in an effective and complementary way and as a non-drug treatment with low complications along with other common treatments will reduce depression and increase the quality of life in patients with MS. As a result, it is recommended to pay attention to regular and suitable exercise programs for MS patients along with other care programs. Plus, considering the variety of available sports programs such as walking group, aerobics and other sports and also considering the properties of other herbal medicines such as condor and black seed; further studies are suggested to be done with regard to doing exercise and using herbal medicines to help these patients.

Author contributions

All authors contributed to manuscript writing, editing and final approval, including table design. Bahrami, Saki, Hassanpour, Ebrahimzadeh, Jafari Pour, and Jafaripour conceived the study. Bahrami, Saki, Hassanpour, Ebrahimzadeh, and Jafari Pour facilitated recruitment.

Bahrami, Saki, and Hassanpour led the data collection. Data analysis was performed by Bahrami, Saki, Hassanpour, Ebrahimzadeh, and Jafari Pour with consensus discussions with all authors. All authors reviewed the draft manuscript and provided approval to the final manuscript.

Availability of data and materials

Upon a reasonable request, the data supporting the results of this paper will be made available by the corresponding responsible author.

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Ethical approval and consent to participate

The present study was approved by the ethics committee of Lorestan University of Medical Sciences (LUMS.REC.1395.209) and registered in the Iranian Clinical Trials Registry (IRCT20170514033961N4). We received a letter of introduction from Research Deputy of Lorestan University of Medical Sciences and MS Association and presented it to the research environment, explaining the research goals to MS women, obtaining informed consent, assuring the patients of the confidentiality of the information obtained from them, and providing the results of the research to the relevant authorities.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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