



The Effect of Jollab Beverage on Fatigue and Happiness in Patients with Multiple Sclerosis: A Triple-Blind Randomized Clinical Trial

Zahra Gholami¹, Shahin Heidari^{2,3}, Mahboobeh Raeiszadeh⁴, Alimohammad Madahian^{5,6},
Fatemeh Ayoobi⁷, Alireza Vakilian^{5,8}, Zahra Jamali⁸, Tabandeh Sadeghi^{8,9*}

¹Student Research Committee, School of Nursing and Midwifery, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

²Department of Fundamental Nursing, School of Nursing and Midwifery, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

³Geriatric Care Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

⁴Herbal and Traditional Medicines Research Center, Kerman University of Medical Sciences, Kerman, Iran

⁵Department of Internal Medicine, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

⁶Physiology-Pharmacology Research Center, Research Institute on Basic Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

⁷Occupational Safety and Health Research Center, NICICO, World Safety Organization and Rafsanjan University of Medical Sciences, Rafsanjan, Iran

⁸Non-Communicable Diseases Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

⁹Department of Pediatric Nursing, School of Nursing and Midwifery, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Received: 2 Jun 2024

Revised: 26 Oct 2024

Accepted: 16 Dec 2024

Abstract

Multiple sclerosis (MS) causes different physical and mental symptoms. Fatigue and decrease of happiness are the common problems in MS patients. This study aimed to determine the effect of Jollab beverage on fatigue and happiness in MS patients. In this triple-blind clinical trial, 70 MS patients visiting the MS Association in an urban area of Iran were randomly assigned to the two groups by minimization method. The intervention group consumed Jollab beverage, including a combination of saffron (*Crocus sativus* L.), rose water (*Rosa x damascena* Herrm.) and brown sugar (*Saccharum officinarum* L.), three times a day orally, 15 mL each time for four weeks. The control group consumed placebo similar to the intervention group. Fatigue and happiness of the patients were evaluated before and after the intervention using Oxford happiness questionnaire and fatigue severity scale. Data were analyzed using SPSS software. Based on the results, there was no statistically significant difference between two groups in the mean score of fatigue and happiness before the intervention. But, after the intervention, the mean score of fatigue was lower in the intervention (34.66 ± 7.72) vs. control group (39.12 ± 9.22) CI: 0.26, 8.64, $p=0.03$). However, the mean score of happiness after the intervention was not statistically significant between the intervention (39.21 ± 17.46) and control (45.12 ± 14.30) groups (CI: -1.93, 13.75, $p=0.13$). According to the results, the use of Jollab beverage can reduce the fatigue of MS patients. Therefore, use of this beverage can be recommended to the patients by neurologists and MS associations.

Keywords: Multiple Sclerosis; Fatigue; Happiness; Medicinal plants; Jollab; Persian medicine

doi <http://doi.org/10.18502/tim.v10i1.18231>

Citation: Gholami Z, Heidari S, Raeiszadeh M, Madahian A, Ayoobi F, Vakilian A, et al. **The Effect of Jollab Beverage on Fatigue and Happiness in Patients with Multiple Sclerosis: A Triple-Blind Randomized Clinical Trial.** Trad Integr Med 2025;10(1): 30-37. <http://doi.org/10.18502/tim.v10i1.18231>

*Corresponding Author: Tabandeh Sadeghi

Non-Communicable Diseases Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Email Address: t.sadeghi@rums.ac.ir, t.b_sadeghi@yahoo.com

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Introduction

Multiple sclerosis (MS) is one of the most common neuroinflammatory diseases affecting young adults [1]. MS is characterized by inflammation, myelin destruction, and scarring [2]. Approximately, 2.5 million people in the world and 350 thousand people in the United States are suffering from MS [1]. The prevalence of the disease in Iran is about 15 to 30 people per hundred thousand people and every year 5000 new MS patients are identified [3].

MS causes different physical and mental symptoms [4]. Sensory disorders, lethargy, muscle cramps, vision disorders (blurred vision and diplopia), cognitive impairment, fatigue, limb tremors, balance disorders, forgetfulness, and speech disorders are among the symptoms reported for this disease [5]. Fatigue is one of the common problems in MS patients, which causes depression, pain, insomnia, and movement problems. Fatigue adversely affects many aspects of MS patients' lives from general performance to quality of life [6,7]. In addition to physical symptoms, MS patients also suffer from psychological problems such as depression, anxiety, and cognitive disorders. Depression is the most common psychiatric diagnosis in these patients [4].

Fatigue adversely affects many aspects of life, such as employment, socialization process, adaptation to illness, and other factors affecting daily life activities, and it is considered one of the main reasons for reducing the quality of life and unemployment in MS patients [8]. Papalardo and Reggio showed that 80% of MS patients suffer from fatigue and its consequences for daily activities and work, and some lose their jobs as well [9]. According to Zifko et al., 71% of MS patients who were employed were absent from work for several days, and 28% were forced to change jobs or engage in jobs with lower incomes due to extreme fatigue [10].

Treatment options for MS include conventional medical treatments and complementary or alternative medicine (CAM) therapies. According to the previous studies, 67% of MS patients use different CAM methods [11]. Currently, raw or processed medicinal plants are used in traditional and modern medicine and are economically important [12]. Jollab beverage is a well-known drink in the Persian medicine, which has been introduced as an anti-depressant and joy-enhancing agent [13]. This beverage has saffron and sweet ingredients based on rose beverage [14].

Crocus sativus L. or saffron is a small plant from the Iridaceae family [15]. Saffron has uplifting effects due to its compounds such as crocin and safranal. Safranal inhibits the reabsorption of dopamine and norepinephrine, while crocin inhibits the reabsorption of serotonin. Together, they contribute to the antidepressant and uplifting effects of saffron [16]. *Rosa x*

damascena Herrm. (Damask rose) is one of the medicinal plants that have health benefits such as improving digestive disorders, chest pain, lung disorders, stress, and depression [17,18]. *R. damascena* contains several components such as flavonoids and terpenes. Therefore, it is suggested that these compounds may be responsible for the soothing effect of *R. damascena*. Flavonoids have been shown to have anxiolytic and/or antidepressant activity in numerous studies [19]. Brown sugar is extracted from sugarcane and contains a sap called molasses. Sugars, such as brown sugar and refined sugar, are usually sequentially processed: washing, extraction, purification, crystallization, drying, and packaging. Brown sugar has higher amounts of phenolics than refined sugar. Phytochemicals play an important role in maintaining physical health. Aside from conferring sweet taste and extra energy, the phytochemicals help improve health and reduce the risk of metabolic diseases [20]. Recently, it has been reported that sugarcane molasses extracts have antioxidant, anti-inflammatory, and infection-resistant properties, as well as protective effects against DNA oxidative damage [21].

Many studies have addressed the effects of medicinal plants. Majdinasab et al., showed that the lavender plant is effective in reducing tremors in MS patients [12]. Safari et al., also found that ginseng can cause anti-inflammatory effects and reduce MS symptoms such as fatigue and myelin damage [22]. However, Kim et al., reported that American ginseng does not improve fatigue in MS patients [23]. Yusefian Babaki et al., showed that mixed Jollab (with a composition different from Jollab) is effective in improving fatigue in MS patients [24]. In line with these findings, the present study aimed to examine the effect of Jollab beverage on fatigue and happiness in MS patients.

Materials and Methods

Ethics approval and consent to participate

The protocol for this study was confirmed with the code of ethics (IR.RUMS.REC.1401.009) from the research ethics committee of Rafsanjan University of Medical Sciences. Informed consent was obtained from the participants. They were also assured that their information would be kept confidential and anonymous. They were told that their participation in the study would be voluntary. The resources were also used without any distortion and based on ethical principles. All study protocols were performed in accordance with the Declaration of Helsinki and CONSORT guidelines.

Study protocol and patient recruitment

The protocol for this randomized, triple-blind clinical trial study with a control group was registered with the

code IRCT20150713023190N12 in the Iranian Registry of Clinical Trials (IRCT). The research population consisted of MS patients visiting the MS Association in Rafsanjan, affiliated with Rafsanjan University of Medical Sciences, whose disease was confirmed by a specialist based on the results of diagnostic tests such as Magnetic Resonance Imaging (MRI). The sample size was calculated by comparing two mean formula

$$n_1 = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times (\sigma_1^2 + \frac{\sigma_2^2}{k})}{\Delta^2}, n_2 = k \times n_1$$

with an effect size ($\Delta=4$) for fatigue as well as σ_1 (SD of fatigue score in the intervention group) = 4.41, σ_2 (SD of fatigue score in the control group) = 5.5, based on previous research [25]. The significance level was set at $p < 0.05$, and the study power was assumed to be 90%. In addition, a sample size of $n = 32.57$ was determined for this study. Given the possibility of sample attrition, 35 patients were allocated to each group.

The inclusion criteria were patients with an age range of 18 to 65 years, patients diagnosed with relapsing-remitting MS (RRMS), fatigue score of 36 and above from the Fatigue Severity Scale (FSS), no other neurological diseases except MS, no allergy to herbal medicines, especially saffron and rose, absence of other diseases such as cancer, autoimmune diseases such as rheumatoid arthritis, heart disease, diabetes, and liver and kidney failure, absence of pregnancy and breastfeeding, absence of acute attack or receiving corticosteroid dose during the last month, and consent to participate in the study. The exclusion criteria were the patient's desire to withdraw from the study, pregnancy during the study period or the decision to become pregnant at the beginning of the study, drug sensitivity during the study period, an acute attack of the disease causing the patient to be hospitalized, not consuming beverage for three consecutive days or six non-consecutive days during one month, traveling or the death of the patient.

After explaining the study and obtaining written informed consent, among the patients covered by the MS Association, 90 patients were selected based on the inclusion criteria and using a random number table. However, 15 patients who did not meet the inclusion criteria and 5 patients who refused to accept the treatment were excluded from the study. Finally, 70 patients were selected and assigned to two groups using the minimization classification method based on fatigue and happiness variables. In this method, classes were first formed based on the desired variables. Then, the first participants were randomly entered into the study and placed in each of the two groups. The next participants were selected based on the sum of

indicators in two groups, and the participant was assigned to the group that had a lower sum [26].

Two participants from the intervention group (one person due to pregnancy and one person due to side effects such as hot flashes and burning legs) and two participants from the control group (both due to side effects such as severe headache and nausea) were excluded during the study. Thus, the data from 66 patients were used in data analysis (Figure 1).

Drug preparation and standardization

The Jollab beverage was prepared by a pharmacist (third author) and it consisted of rose water, saffron, brown sugar, and distilled water. Rose water was purchased from Al-Zahra Company (Kerman, Iran, health certification code 42/10947) and saffron from Saharkhiz Company (Mashhad, Iran, health certification code 50/11500). Each 100 mL of beverage consisted of 70 mL rose water, 0.1 g saffron, 62 g brown sugar, and 25 mL distilled water. The preparation was made according to Persian medicine literature with slight modifications [13,27].

Brown sugar was dissolved in rose water and distilled water under mild heat. Afterward, saffron was suspended and macerated into the beverage. After cooling the mixture at room temperature, it was packed in a dark-colored bottle. The daily dosage of Jollab beverage was adjusted to 15 mL three times a day. The

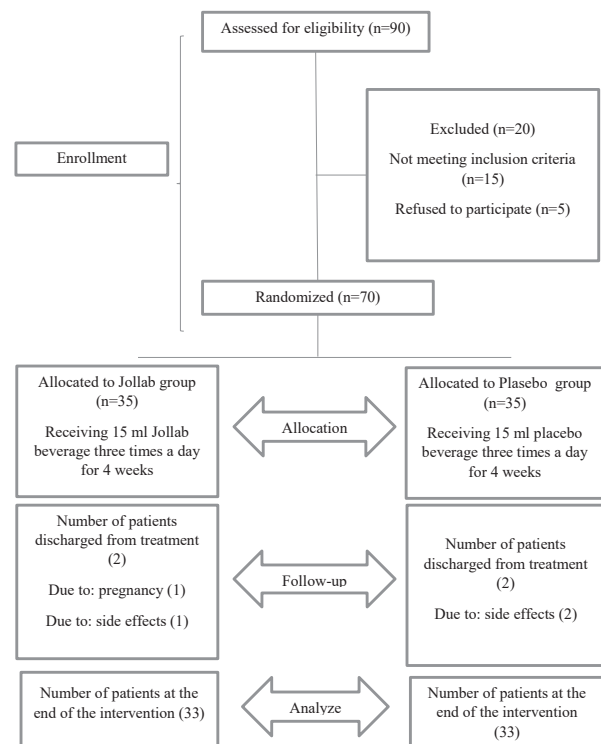


Figure 1. Flowchart: Clinical trial chart

placebo beverage consisted of 7 mL rose water, 62 g brown sugar, and 88 mL distilled water. Besides, the placebo beverage was packed in the same bottles. To standard the jollab beverage the total phenolic and flavonoid contents were determined.

Total phenolic content determination

Total phenolic content was determined by adding 100 μ L of the Jollab beverage or a standard solution of gallic acid (6-100 μ g/mL) to 500 μ L of Folin-Ciocalteu reagent (1:10 v/v diluted with distilled water) and 400 μ L aqueous solution of Na₂CO₃ (7.5% w/v). After 30 min incubation of the mixture in darkness at 25 \pm 2°C, the absorbance was measured at 765 nm [28]. The total phenolic content of the Jollab beverage was reported as mg of gallic acid equivalent/mL of Jollab beverage based on calibration curve of gallic acid ($Y = 0.0091x + 0.0537$, $R^2 = 0.998$). All experiments were performed three times and the results were reported as mean \pm SD.

Flavonoid content determination

The total flavonoids of the Jollab beverage were determined based on previously reported aluminum chloride colorimetric method and quercetin was utilized as standard [29]. After mixing 1 mL of Jollab beverage with 1 mL distilled water, 100 μ L sodium nitrite, 200 μ L AlCl₃ 10% and 1 mL of NaOH the absorbance was read at 510 nm. Quercetin solution in 80% methanol (25-200 μ g/mL) was utilized as standard to draw a calibration curve ($Y = 0.005x - 0.049$, $R^2 = 0.991$). The data were the average of triplicate test expressed as mg quercetin equivalent/mL of Jollab beverage.

The level of total phenolic content and total flavonoid

content were found to be 314.95 \pm 2.20 mg gallic acid equivalent/ mL and 329.33 \pm 1.15 quercetin equivalent mg/ mL jollab beverage, respectively.

Interventions and outcome measure

The patients took medicine or a placebo three times a day orally, 15 mL each time immediately after breakfast, lunch, and dinner for 4 weeks [13]. Each 15 mL of Jollab beverage contained 10.5 mL of rose water, 15 mg of saffron, 9.25 g brown sugar, and 3.75 mL of water, and each 15 mL placebo contained 13.5 mL of water, 1.5 mL of rose water, 25.9 g of brown sugar, and some yellow edible color enough to create a color similar to Jollab beverage [13]. The drug and placebo were in bottles A and B, and the researcher, patient, and analyst did not know whether the bottles were drugs or placebo (triple blinded). To track consumption by participants, two separate WhatsApp groups were created and the researchers and participants joined the groups. The researchers provided necessary instructions and training on how to use and store the drug and report possible side effects as well as the time of in-person delivery of the drug and placebo. They also answered the questions asked by the participants. After 4 weeks, the items in the Fatigue Severity Scale and Oxford Happiness Questionnaire were completed again by the participants in the two groups. Fatigue was measured by the Fatigue Severity Scale (FSS). This scale consists of 9 items, with 5 items (1, 2, 3, 4, and 6) measuring the quality of fatigue rather than quantity, and 3 items (5, 7, and 9) measuring physical and mental fatigue and the impact of fatigue on the respondent's social status. The remaining item compares the intensity of fatigue with other symptoms

Table 1. Comparison of the demographic characteristics of MS patients in intervention and control groups.

Demographic data		Intervention group	Control group	p-value
Age (years)	Mean \pm SD	39.10 \pm 66.31	41.11 \pm 93.67	* 0.51
Sex	Male (%)	3 (9.1)	3 (9.1)	*** 1
	Female (%)	30 (90.9)	30 (90.9)	
Marital status	Married (%)	28 (84.8)	26 (78.8)	** 0.52
	Single (%)	5 (15.2)	7 (21.2)	
Educational Level	Under diploma (%)	11 (33.3)	7 (21.2)	** 0/67
	Diploma (%)	13 (39.4)	16 (48.5)	
	Above diploma (%)	9 (27.3)	10 (30.3)	
Duration of the disease	Less than 5 years (%)	12 (36.4)	6 (18.2)	** 0.18
	5 to 10 years (%)	10 (30.3)	16 (48.5)	
	More than 10 years (%)	11 (33.3)	11 (33.3)	

*Mann-Whitney U

**Chi square

***Fisher

in the MS patient. Each item is scored from 1 (strongly disagree) to 7 (strongly agree). A total score equal to or higher than 36 indicates that the person is suffering from fatigue, and higher scores show the intensity of fatigue in the person. Azimian assessed the Persian version of the scale on MS patients and reported Cronbach's alpha coefficient of 0.96 and intraclass correlation coefficient (ICC) of 0.93 [30]. Happiness was also measured by the Oxford Happiness Questionnaire. The questionnaire consists of 29 items and the score range for each item is 0-3. The total score for each respondent varies from 0 to 87. The normal score on this questionnaire ranges from 40 to 42. The content validity of this questionnaire was confirmed by Hadinejad et al. (2009), and its reliability was approved with internal consistency and Cronbach's alpha coefficient ($r=0.84$) [31].

Statistical analysis

The collected data were analyzed using descriptive statistics, including mean and standard deviation, and inferential statistics, including independent and paired samples t-test, chi-square, or Fisher's test with SPSS-22 software.

Results

The demographic data indicated the majority of the participants in the two groups were women, aged 40 years, married, unemployed, with a high school diploma, and had a history of MS for more than 5 years, and were homogeneous in terms of all demographic characteristics (Table 1).

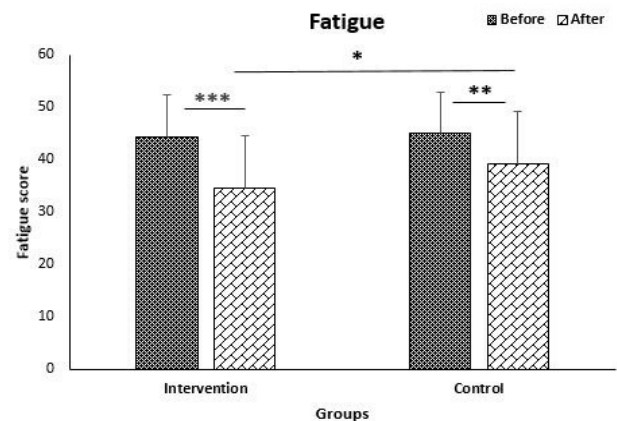
Based on the results of the Kolmogorov Smirnov test, quantitative variables had a normal distribution ($p > 0.05$), so, parametric tests were used to analyze the data. Before the intervention, the mean scores of fatigue in the intervention and control groups were 44.36 ± 8.05 and 45.03 ± 7.86 respectively and there was no significant difference between the two groups ($P = 0.73$). However, after the intervention, the mean score of fatigue in the intervention group (34.66 ± 7.72) was significantly lower than that of the control group (39.12 ± 9.22) as indicated by the independent samples t-test ($P = 0.03$). An intragroup comparison showed a statistically significant difference between the mean fatigue score before and after the intervention in both the intervention group ($P < 0.001$) and the control group ($P = 0.004$). The fatigue score decreased in both groups, but the intervention group showed more decrease in their fatigue levels (5.90 ± 10.96 vs 9.69 ± 11.16). (Table 2, Figure 2).

The results showed that the mean happiness score in the intervention and control groups were 36.96 ± 19.12 and 41.36 ± 12.65 before the intervention, and there was no statistically significant difference between the two groups ($p = 0.27$). The mean happiness score in the

intervention and control groups were 39.21 ± 17.46 and 45.12 ± 14.30 after the intervention, showing no statistically significant difference between the two groups. The results of the intragroup comparison indicated that happiness scores increased in both the intervention group ($p = 0.48$) and the control group ($p = 0.08$) after the intervention, but there was no significant intergroup difference (Table 3, Figure 3).

Discussion

The results of the present study indicated that the MS patients in the intervention group who consumed Jollab beverage reported a significantly lower level of fatigue after the intervention compared to their fatigue level before the intervention. There was also a significant difference between the two groups in terms of fatigue scores. Similarly, Yusofian Babaki et al., showed that mixed Jollab beverage (a combination of Jollab beverage, aqueous extract of lemongrass, lavender, and Persian echium) led to a reduction in fatigue in patients with MS [24]. In addition to the different ingredients used in the two beverages, the amount of daily



* $P < 0.05$, Intervention group vs. control group

** $P < 0.01$, Before vs. after in control group

*** $P < 0.001$, Before vs. after in intervention group

Figure 2. Comparison of fatigue score between two groups

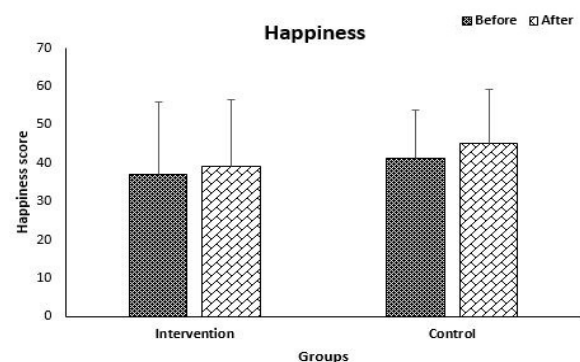


Figure 3. Comparison of happiness score between two groups

Table 2. Comparison of mean and standard deviation (SD) of the fatigue score before and after the intervention in the both groups.

Group	Intervention Group	Control Group	*p-value
Time	Mean± SD	Mean ± SD	
Before Intervention	44.36 ± 8.05	45.03 ± 7.86	0.73
After Intervention	34.66 ± 7.72	39.12 ± 9.22	0.03
** p-value	<.001	0.004	

*Independent t-test (Inter-group comparison).

**Paired t-test (Intra-group comparison).

Table 3. Comparison of the mean and standard deviation (SD) of the happiness score before and after the intervention in the both groups.

Group	Intervention group	Control group	*p-value
Time	Mean± SD	Mean ± SD	
Before Intervention	36.96 ± 12.19	41.36 ± 12.65	0.27
After Intervention	39.21 ± 17.46	45.12 ± 14.30	0.13
** p-value	0.48	0.08	

*Independent t-test (Inter-group comparison).

**Paired t-test (Intra-group comparison).

consumption was also different in the two studies. The present study showed that Jollab beverages alone can be effective in reducing fatigue.

Likewise, Rezaei Ashtiani et al., showed an improvement in the fatigue score of patients with MS after consuming simple saffron beverage [32]. In addition to the difference in the duration, dosage, and herbal composition used in the two studies, the presence of the control group in the present study, unlike the aforementioned study, was one of the study strengths. On the other hand, saffron was part of the herbal composition in the present study. The high variety of different flavonoids, including anthocyanins, kaempferol, quercetin, and their glycosides, along with the large amounts of crocins, picrocrocin, safranal, and crocetin, confirms the interest of the use of whole flower of saffron as potential sources of natural antioxidants, which can be considered as active ingredients in food supplements, pharmaceutical preparations (33). The medicinal properties of saffron as an antioxidant, anti-carcinogenic, memory enhancer and neuroprotective properties has been confirmed. Antioxidant and anti-amyloidogenic activity of saffron has positive effect on cognitive function [34,35]. Majdinasab et al., also showed that evening primrose oil reduces the fatigue score and increases the quality of life in patients with MS [12]. This finding is in line with the results of the present study. However, the herbal compositions were different in the two studies.

Another variable in the present study was the sense of happiness, which increased after consuming Jollab beverage for 4 weeks, but this increase was not statistically significant. In another study, Keihan Soltani et al., examined the effect of saffron on happiness and quality of life of healthy adults, and the results did not show a significant difference in the happiness scores

between the intervention and control groups [36]. Although both studies reported similar results, the research population and the composition of the herbal medicines in the two studies were different. In the above study, only saffron was used, while in the present study, saffron was part of the composition of the herbal medicine. Bagheri et al., examined the effect of spiritual counseling on the happiness of MS patients and showed that the mean score of happiness in the group receiving spiritual counseling significantly increased after the intervention and one month after the intervention compared to the control group [37]. The type of intervention in this study was different from the intervention conducted in the present study. Thus, given the effectiveness of spiritual counseling in the sense of happiness of MS patients, both interventions (herbal Jollab beverage and spiritual counseling) can be assessed in future studies. Bolandghadr et al., also showed that yoga exercises reduce depression and anxiety scores in women with MS [4]. Since medicinal plants bring less cost to the patient and the treatment system [38], use of different interventions with medicinal plants, or their combination with sport intervention can be examined in future studies.

A significant finding in the present study was the decrease in the fatigue score in the control group. Fatigue can have many reasons and depends on mental, motor, cognitive, and respiratory disorders and conditions not related to MS [39]. Besides, fatigue can be mental [39] and because it was measured by a questionnaire, patients who also received the placebo felt that their fatigue had decreased. Thus, fatigue should be measured with more objective scales such as hours of sleep and activity, etc. in future studies.

Happiness is also a multi-factorial construct and does not depend only on internal factors as external or en-

vironmental factors including social and economic conditions, religious beliefs, social position, job satisfaction, health status, social and family environment, cultural factors, also play a role in the level of happiness [40]. As a result, it is recommended to measure happiness with additional scales. In addition, the score of happiness in the two groups increased slightly and the patients in both groups reported a low level of happiness. Thus, it can be concluded that increasing the sense of happiness in addition to pharmaceutical interventions requires multifaceted interventions such as holding counseling sessions, teaching positivity skills, conducting spiritual counseling, social support, involving patients in social activities, and also requiring the attention of officials to improve the economic situation, providing medicines, and the possibility of carefree access of patients to treatment facilities, and improving their living conditions [41]. Therefore, future studies can develop and conduct interventions based on the mentioned factors.

The present study was conducted in a small center with a small sample size of MS patients. Not measuring some variables such as Body Mass Index (BMI) was one of the other limitations, which is recommended to be considered in future studies. Moreover, no study has yet addressed the impact of Jollab beverages. This being so, further studies should be conducted in other medical centers with a larger sample size and changes in dosage.

Conclusion

The present study showed that Jollab beverages can reduce fatigue in MS patients. Since medicinal plants bring less cost to the patient and the treatment system, the use of this treatment method can be of interest to neurologists and MS associations. Future studies can address the impact of Jollab beverages with varying dosages and consumption rates on the happiness of MS patients.

Conflict of Interests

The authors declare no competing interests.

Acknowledgements

This study was extracted from a student's thesis approved by Rafsanjan University of Medical Sciences and was financially sponsored by this university. Hereby, we extend our gratitude to the authorities of the university for supporting this study. We are grateful to all of patients who participated in our study.

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