Anti-Fatigue and Hypnotic Effects of a Traditional Herbal Extract on Multiple Sclerosis Patients: A double blind randomized clinical trial

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Abstract

Objectives: Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder of the central nervous system. The aim of this study was to investigate the effects of a Persian herbal medicine treatment including Crocus sativus, Hypericum perforatum, Cinnamon verum, and Vitis vinifera on fatigue and sleep disorders in MS patients.

Methods: In this controlled, double-blinded, clinical trial, 52 patients with MS suffering from fatigue or sleep disorders were randomly divided into two groups (herbal remedy or the placebo). Fatigue symptoms were quantified by means of Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS). The Insomnia Severity Scale (ISI) and Pittsburgh Sleep Quality Index (PSQI) were used to assess sleep difficulties.

Results: There was a significant reduction in FSS and MFIS scores in both groups, but the mean change rate in FSS and MFIS scores in the drug group was significantly higher compared to the placebo group. In both the drug and placebo groups, ISI and PSQI scores decreased significantly after four weeks, but the change rate in ISI and PSQI scores in the drug group was significantly more than the placebo group (p=0.00).

Conclusion: The present study suggests that herbal extract treatment may improve sleep disorder and fatigue symptoms in MS patients. Further investigations are needed to know the exact mechanism of actions.

Key words: Persian medicine, multiple sclerosis, fatigue, sleeps disorder, herbal extract

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disorder of the central nervous system with physical and psychiatric comorbidities that affect the quality of life in these patients [1-3]. Several studies have suggested that psychiatric disorders, such as sleep disorders, are noted to occur more frequently in MS patients than in the general population, and that there is a significant correlation between sleep disturbances and fatigue [4, 5]. Several types of sleep disorders including insomnia, nocturnal movement disorders, sleep-disordered breathing and restless legs syndrome have been reported in patients with MS, which may affect their daily functions [4]. It is by noting the high prevalence of sleep disorders in MS patients, which amounts to almost 50% of them, and their role in exacerbating other symptoms of the disease, that the treatment of sleep disorders gains immediate importance [6].

Fatigue is one of the most common problems in MS patients; 67% of patients experienced fatigue as the most disabling symptom. The symptoms of fatigue may be acute and intermittent or chronic and persistent [5, 7, 8]. A number of different factors may affect fatigue in MS patients, including heat, pain, depression, stress and sleep disorders [9]. Although fatigue is reported by approximately 75% to 90% of patients with MS, there is still some difficulty and complexity in its management [10].

Various management strategies (pharmacological agents, exercise and behavioural therapy) have been used for its treatment, but the outcomes are not promising [10, 9]. For this reason, there has been special interest emerging to identify other management strategies to overcome fatigue and sleep disorders in MS patients, such as herbal medicine [11, 12]. It is believed that herbal medicine has fewer side effects in comparison to pharmacological agents, and they can be used as an alternative therapy to increase the effect of prescription medications [13].

To find new herbal compounds with hypnotic and anti-fatigue properties, the herbal plants were selected on the basis of Persian medicine for the treatment of sleep disorders and fatigue. Various herbal compounds have been used for treating different neuropsychiatric disorders in Persian traditional medicine. In this study a Persian compound medicine was made and evaluated, that is derived from the book of Makhzan al-Advieh (storehouse of medicaments), written by Aghili Khorasani, the Persian physician in the 18th century; under the title of Anis-al-Nafs (C). This formulary includes the medicinal plants itemised below.

A spice derived from dried stigma of Saffron (Crocus sativus L.; family of Iridaceae), has traditionally been used as a sedative and hypnotic agent to prevent insomnia [14]. The main bioactive metabolites of saffron spice are crocins, picrocrocin and safranal, which have anti-inflammatory, antioxidant and radical scavenging properties [15]. Hosseinzadeh and Nouraei (2009) investigated the anxiolytic and hypnotic effects of saffron aqueous extract in mice. Their results showed that saffron, at a dose of 0.56 g/kg, significantly improved sleep in mice, a hypnotic effect mostly attributed to safranal [16]. Also, St John's wort (Hypericum perforatum L.) is another plant from the Hypericaceae family that has been used in traditional medicine as an antidepressant for the treatment of mild to moderate depression [17]. Another observation was the beneficial effect of St John's wort treatment on psychiatric and neurological disorders such as Alzheimer's disease (AL), Parkinson's disease (PD) and experimental allergic encephalomyelitis (EAE), an animal model of MS [17, 18]. Hyperforin is one of the main bioactive constituents of St John's wort that exerts anti-inflammatory, antioxidant and antibacterial action, along with antidepressant effects [19]. Current investigations show the probable role of anti-inflammatory and antioxidant properties to control pain, fatigue, sleep disturbance, and depression [20, 21].

On the other hand, new evidence suggests that cinnamon, the brown bark of the cinnamon tree (Cinnamomum verum J. Presl; from the family of Lauraceae), may be used to control EAE via different mechanisms. Cinnamaldehyde is the main constituent of cinnamon, which is converted into cinnamic acid by oxidation. Cinnamic acid is then β-oxidized to benzoate in the liver and is made available as sodium salt (sodium benzoate). Several studies have shown the beneficial effects of cinnamon and its metabolite, sodium benzoate, in treating different neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and MS [22, 20, 21]. The grape (Vitis vinifera L.; from the family of Vitaceae) is a fruit with neuroprotective properties, due to its bioactive components in the seed and skin [23, 24]. Polyphenols from grape seeds, especially proanthocyanidins, have antioxidant and anti-fatigue functions. Shan et al. (2010) showed that grape seed proanthocyanidin extract (GSPE) increased the liver and muscle glycogen reserve, delayed the occurrence of fatigue and improved the exercise capacity in mice [25]. In a study by Edwards et al, the administration of pure anthocyanidins derived from grape seed, bilberry and cranberry, improved sleep quality and fatigue in patients with fibromyalgia disorders [26]. Xie et al showed that GSPE has an anti-fatigue effect through increasing hemoglobin and hepatic glycogen and decreasing blood lactic acid concentration in mice [27]. Resveratrol is another polyphenolic compound in red grapes which has antioxidant, anti-inflammatory and neuroprotective effects [28]. Several studies have demonstrated its potential use in the treatment of inflammatory and autoimmune diseases including MS [29]. Resveratrol maintains the blood brain barrier integrity and can promote remyelination in animal models of MS [30, 31]. Wu et al studied the effect of resveratrol on physical fatigue and exercise performance in mice. They found that resveratrol treatment decreased serum lactate and ammonia levels and increased glucose levels in a dose-dependent manner [32].

The present study was undertaken to test the anti-fatigue and hypnotic effects of Persian herbal medicine (including C.sativus, H.perforatum, C.verum, and V.vinifera) in MS patients, using a double blind, randomized, placebo controlled trial design.

Material and Methods

Study design and ethical issues

This study was a one-month parallel group, placebo controlled trial undertaken from March 2017 to October 2017 in Sina Hospital in Tabriz, Iran. The trial was approved by the Ethics Committee of Tabriz Medical University (TBZMED.REC.1394.884) and registered in Iranian Clinical Trial Registry (IRCT2016012916369N3). Also, written informed consent was obtained from each patient before enrolment.

Drug and Placebo

The plants of St John's wort (Voucher No. PMP-389) and cinnamon (Voucher No. PMP-913) and also grape syrup were purchased from a traditional herbal store (Attari) in Tehran and their identification and quality control were done in the Herbarium Center of School of Pharmacy, TUMS. Also, the standard saffron (Saharkhiz Co.) was used in the study.

Each 10 milliliter of the herbal extract contained the extracts of 64 mg saffron, 357 mg cinnamon and 857 mg St John's wort which was supplied via maceration, Soxhlet, and Clevenger (for both aqueous extract and essential oil), respectively in 4.3 ml grape syrup. The rest of 10 ml had about 2g sugar and also distilled water. The placebo was simple syrup and 0.71 ml grape syrup and 0.1% St John's wort essential oil to reach a similar color and smell to the drug. The herbal extract and placebo were prepared in the Department of traditional pharmacy, School of traditional medicine, Tehran University of Medical Sciences.

Standardization of drug based on total flavonoid and total phenol

Standardization of the drug was performed with a spectrophotometric method. In this method total poly phenol and total flavonoid were measured based on equivalent of gallic acid and rutin, respectively. Folin-Ciocalteu's reagent (for total polyphenol content) and AlCl3 solution (for total flavonoid content) were used and absorbance was determined at λmax = 765 nm and 415 nm, respectively [33].

Inclusion and exclusion criteria

All patients who enrolled in the trial were aged between 18 and 50 years, and had confirmed MS disease according to McDonalds et al.'s criteria, by a neurologist [34]. A stable disability level of 6 or less on the Krutzke's extended disability status scale (EDSS) made the patient eligible for enrolment in the trial [35]. Other inclusion criteria included: no disease attack during the previous month, no history of other autoimmune disease, the presence of fatigue symptoms quantified by means of Fatigue Severity Scale (FSS) and the presence of sleep disorders according to Insomnia Severity Index (ISI). Patients had to have regular contact with a responsible caregiver. They were excluded from the trial if they had evidence of dementia or psychosis, cardiovascular disease, diabetes, severe depression, clinically significant major infections or pregnancy and breastfeeding status. In addition, any other herbal medications or natural antioxidants affecting fatigue and sleep disorders were not allowed during the trial. The use of other disease modifying therapies for MS was permitted. Participants were instructed to avoid changing their routine physical activity and eating habits during the trial.

Randomization, blinding and Intervention

Twenty-six patients with fatigue symptoms and 26 patients with sleep disorder were randomly allocated to either the placebo or the drug groups. A permuted block randomization using a computer-generated random allocation was used with fixed block size, using one-to-one allocation. The patients and caregivers were unaware of the treatment groups and type of medications and blinding was performed by pharmacists in the study. Each patient in both groups received 10 milliliters of the drug or placebo two times a day for 1 month.

Outcomes

Fatigue is defined as the lack of physical and mental energy or feeling of tiredness, perceived by the individual or caregiver, that interferes with usual and desired activities of daily life [7]. The symptoms of fatigue were evaluated using the following self-administered measures of it:

1) Fatigue Severity Scale (FSS; consists of 9 items with a score range of 1 to 7, with lower scores indicating less fatigue) and,
2) Modified Fatigue Impact Scale (MFIS; consists of 21 items with a score range of 0 to 84, with lower scores indicating less fatigue). FSS has been shown to have a high degree of sensitivity and consistency of changes in clinical trials, and has been found to be reliable and valid in MS [7, 36]. The Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI) were used to assess sleep difficulty. ISI consists of 7 questions, graded on a scale of 0 to 4, that assess the impact of insomnia on adults' quality of life. A cumulative score ≥ 15 reflects clinically significant insomnia [37]. PSQI consists of seven components that assess sleep difficulty and provide a global score of sleep on a scale of 0 to 21 (with higher scores indicating more sleep complaints) [38]. Patients completed the questionnaires at baseline and at the end of the 4th week.

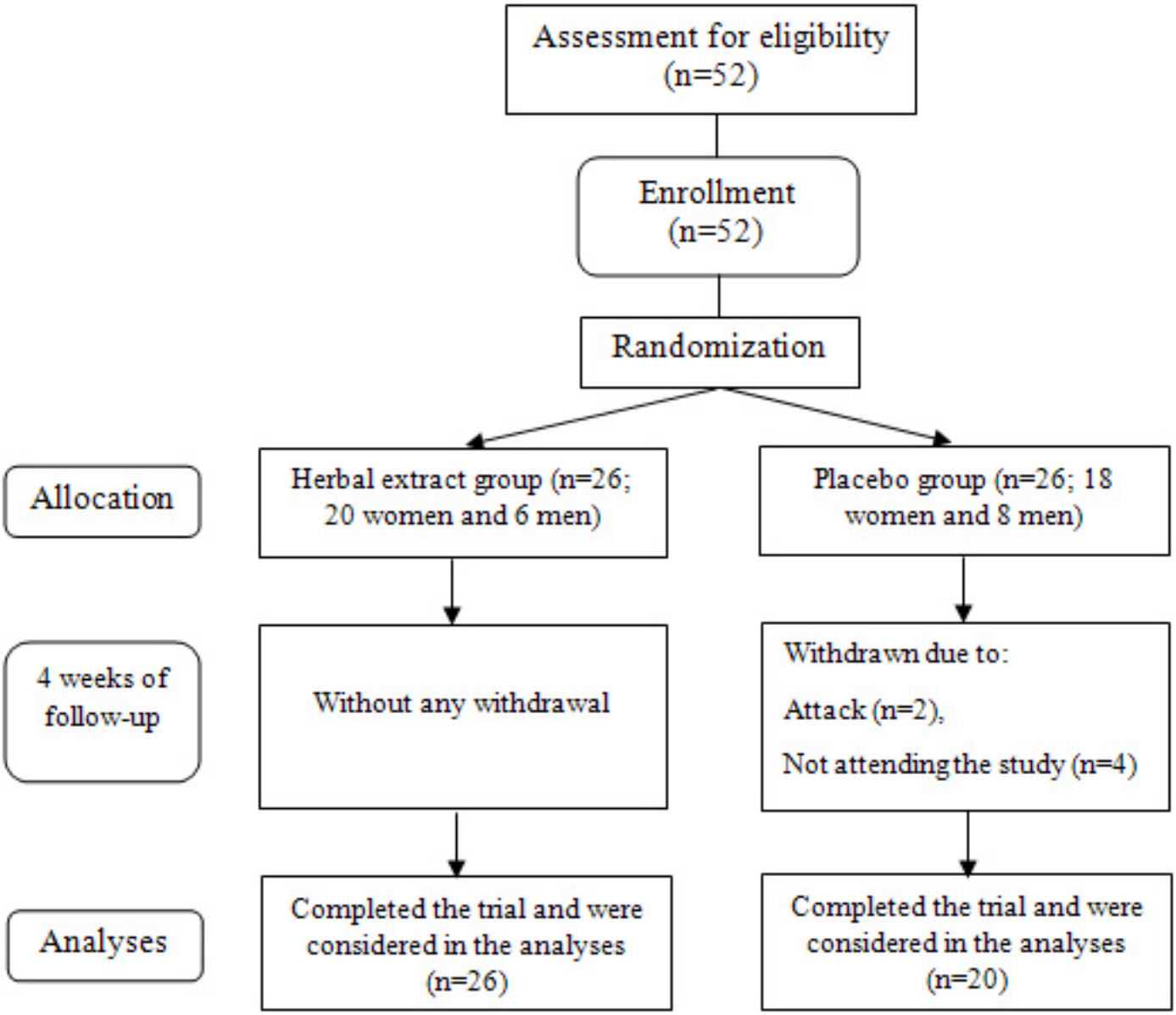
Statistical analyses

Values are expressed as mean ± standard deviation (SD). Comparisons between groups (drug and placebo) were performed using the independent t test. Within-group differences (before and after intervention) were determined by Paired-sample t tests. Statistical comparisons were made between mean scores for the placebo and those for the herbal extract using repeated-measures analysis of variance (ANOVA). This ANOVA model included terms of time effect and interaction of time and treatment, within the main effect (herbal extract vs. placebo). $p < 0.05$ was considered to be statistically significant. Results were statistically analyzed using SPSS, version 16 (SPSS Inc., Chicago, IL, USA).

Results

The experiments showed that the compound drug contains total phenol and total flavonoid equal to 346 ± 6 mg gallic acid equivalent/100 ml and 297 ± 2 mg rutin equivalent/100 ml, respectively.

Figure 1. Flow diagram of the patients



Six patients in the herbal extract group were excluded from the trial, due to the occurrence of disease attack (n=2) and unwillingness to continue the trial (n=4). There was not any exclusion case in the placebo group. Finally, a total of 46 participants [the drug group (n=20) and the placebo group (n=26)] completed the study (Figure 1). The mean (± SD) of baseline age was 36.8 ± 7.4 years and 35 ± 9 years in the herbal extract and placebo group, respectively. There were no significant differences between the two groups in terms of their marital status and gender (Table 1). Also, at baseline, there were no significant differences in FSS, MFIS, ISI and PSQI scores between the herbal extract and placebo groups.

Table 1. Basic characteristics of study subjects

Variable	Herbal extract group (n=26)	Placebo group (n=20)
Mean age (years)	36.8 ± 7.4	35 ± 9
Mean disease duration (years)	7.1 ± 5.8	12 ± 5.6
Gender [*n* (percent)]		
Male	6 (23.1 %)*	4 (20%)*
Female	20 (76.9 %)*	16 (80%)*
Marital status [*n* (percent)]		
Married	22 (84.6 %)*	4 (20%)*
Single	4 (15.4 %)*	16 (80%)*

Values are mean ± standard deviation.
* Values are number (%).

After intervention, as shown in Table 2, there was a significant reduction in FSS and MFIS scores in both groups, but in regard to Table 3, the mean change rate in FSS (-19.8 ± 11.8 vs. -4.6 ± 5.9, p=0.00) and MFIS scores (19.7 ± 12.8 vs. -3.5 ± 5.2, p=0.00) in the drug group was significantly higher compared to the placebo group. ISI and PSQI scores decreased significantly after four weeks in the drug group (9.7 ± 7.5, p =0.00 and 8.8 ± 7.0, p =0.00) and the placebo group (2.3 ± 2.8, p =0.00 and 1.2±1.5, p =0.00), but the change rate in ISI (- 9.7 ± 7.5 vs. - 2.3 ± 2.8, p =0.00) and PSQI scores (- 8.8 ± 7.0 vs. - 1.2 ± 1.5, p =0.00) in the drug group was significantly higher than the placebo group. Repeated measures of ANOVA with ISI and PSQI scores demonstrated significant reduction in both the drug and the placebo groups (Tables 2 and 3, Figure 2).

Table 2. Comparison of scores on FSS, MFIS, ISI and PSQI between herbal extract and placebo group

	Herbal extract group (n=26)			Placebo group (n=20)		
	baseline	endpoint	p*	baseline	endpoint	p*
FSS score	49.9 ± 9.4	30 ± 12.3	0.000	47.1 ± 9.9	42.5 ± 13	0.000
MFIS score	51.2 ± 17.8	31.4 ± 17	0.000	42.5 ± 10.5	39 ± 12.2	0.005
ISI score	18.8 ± 3.4	9.15 ± 7.0	0.000	19.4 ± 2.9	17.1 ± 4.7	0.005
PSQI score	15.9 ± 4.1	7.0 ± 6.0	0.000	16.7 ± 2.3	15.4 ± 3.1	0.000

Values are means ± standard deviation. *Indicates within-group differences (paired-sample *t* test).

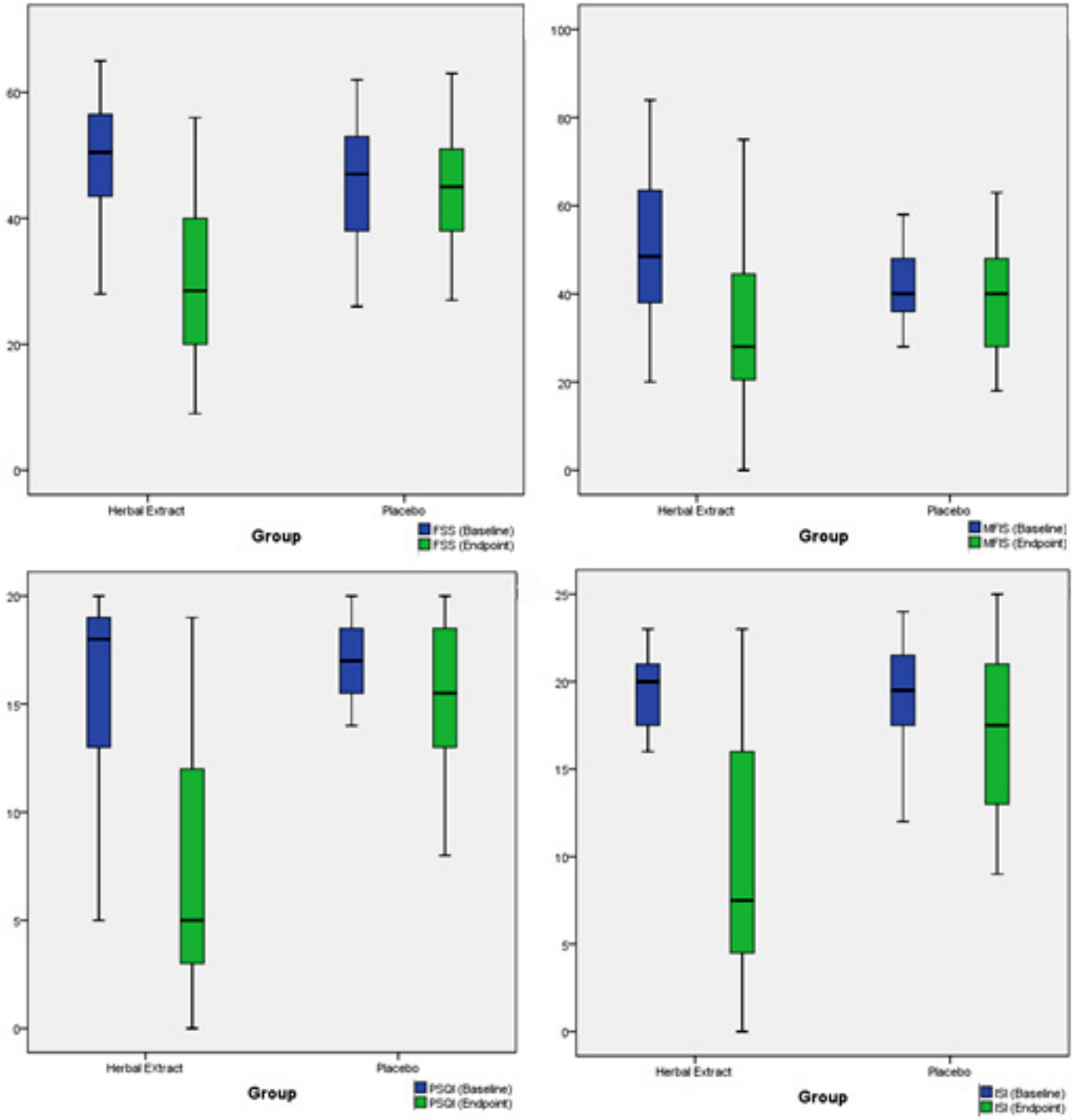
Table 3. Comparison of the mean difference of variables at baseline and endpoint of study between two groups

Variable	Herbal extract	placebo	P*
FSS	- 19.8 ± 11.8	- 4.6 ± 5.9	0.000
MFIS	- 19.7 ± 12.8	- 3.5 ± 5.2	0.000
ISI	- 9.7 ± 7.5	- 2.3 ± 2.8	0.000
MSQI	- 8.8 ± 7.0	- 1.2 ± 1.5	0.000

Values are means ± standard deviation.
*Indicates between-group differences (Independent *t* test).

Furthermore, there were no side effects reported by the patients using drug and placebo in both groups.

Figure 2. Changes in the ISI, PSQI, FSS and MFIS scores after an 8-week period of intervention. ISI, insomnia severity scale; PSQI, Pittsburgh sleep quality index; FSS, fatigue severity scale; MFIS, modified fatigue impact scale



Discussion

The main purpose of this study was to investigate the effects of a Persian herbal remedy on fatigue and sleep disorder in patients with MS. Our study showed that this herbal extract treatment for four weeks in MS patients resulted in improved fatigue status, a significant decrease in FSS scores and MFIS scores. We found that this Persian medicine treatment reduced sleep disorder complications with decreased ISI and PSQI scores in the intervention group. All changes in fatigue and sleep disorder scores were significant, even after adjustments were made for age, marital status and disease duration. To the best of our knowledge, this study is the first of its kind to examine the anti-fatigue and hypnotic effects of a combination of several herbal extracts in MS patients.

MS is associated with several comorbid disorders, such as fatigue and sleep disorders, with detrimental impacts on overall health and quality of life in the patients [4, 8]. Due to the high prevalence of fatigue and sleep disorders in MS patients and its potential role in exacerbating other MS symptoms, the treatment of these complications are important [9, 6]. Fatigue treatment is a difficult and complex task and in most cases combined approaches are recommended [9]. Currently, there is an increasing interest in using complementary and alternative medicine (CAM) to overcome MS symptoms and improve quality of life among MS patients. Herbal medicine is among the most common CAM therapies being used by MS patients [11, 12]. In this regard, we examined the effect of a combination of several herbal extracts which have been used in Persian medicine in the treatment of fatigue and sleep disorders. Previous studies have reported the effects of every single one of these herbal extracts on fatigue and sleep disorders in other clinical conditions, but the combined effects of these extracts in MS patients have not been assessed. In our study, a combination of these herbal extracts significantly reduced fatigue and sleep disorders in MS patients. These anti-fatigue and hypnotic effects could be attributed to bioactive components in each of these herbal extracts and to their synergistic effects.

There are several modifiable factors that contribute to sleep problems in MS patients, including fatigue, depression, leg cramps, pain and nocturia. Among these, depression has the highest association with sleep disorders in MS patients [6]. Sleep disorders are associated with increased levels of systemic inflammation [39]. Experimental sleep deprivation studies have reported increased levels of circulating proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α [40]. Elevated levels of IL-6 and TNF-α were also observed in MS patients [8]. The results from animal studies have demonstrated that proinflammatory cytokines signal the CNS to initiate a series of behavioral changes such as fatigue, sleep disturbances and depressive-like symptoms [41]. Depression has a strong relationship with fatigue and a reduction in fatigue severity was observed after the treatment of depression [42].

C.sativus (saffron) has traditionally been used throughout the world for its therapeutic effects. These include anticonvulsant, antispasmodic, anxiolytic, hypnotic, sedative and relaxant effects [15, 14]. Safranal is one of the bioactive compounds found in saffron which has been shown to increase sleeping time, dose dependently [14]. In recent years, the potential neuroprotective role of crocin, the other bioactive compound in saffron, in chronic neuroinflammatory diseases such as AD, PD and MS, has been the subject of some research [15]. In a study by Ghazavi et al., the effects of ethanol extract of saffron in the treatment of EAE mice were evaluated. They noted that saffron significantly reduced the clinical symptoms in EAE mice, inhibited leukocyte infiltration to CNS and increased total antioxidant capacity production [43]. The anti-inflammatory effects of saffron and its bioactive components have been studied in different models of inflammation. Saffron may enhance antioxidant enzymes involved in the scavenging of reactive oxygen species (ROS) which are key mediators of oxidative stress and inflammatory response [44]. A study by Tamaddonfard et al. showed that anti-inflammatory and antinociceptive effects of crocin and safranal may also be mediated by the inhibition of cyclooxygenase [45]. St John's wort (H.perforatum) is another herbal extract in our study that has been used to treat insomnia and depression in traditional medicine [46]. Sharpley et al. studied the effect of two doses (0.9 and 1.8 mg) of St John's wort on the sleep polysomnogram of 12 healthy elderly volunteers using a cross-over placebo-controlled design. The results showed that both doses of St John's wort significantly induced an increase in deep sleep and the latency to rapid eye movement (REM) sleep [47]. The mechanisms by which conventional antidepressant drugs increase REM sleep are attributed to their ability to potentiate serotonin and noradrenaline neurotransmission. St John's wort's ability to modify some aspects of serotonin and noradrenaline function have been shown in animal studies [47]. Chronic treatment with St John's wort may also upregulate post-synaptic serotonin and serotonin receptors [46]. Further studies are needed to investigate the exact mechanisms of action of St John's wort in modulation of sleep.

Cinnamon and its active metabolite in the liver, sodium benzoate, have shown neuroprotective properties in different neurodegenerative diseases including AD, PD and MS. It has been proposed that cinnamon and sodium benzoate administration in EAE may reduce inflammation in the CNS, preserve the integrity of blood brain barrier (BBB), restore myelin level and protect myelin-specific genes, improve locomotor activities and inhibit clinical symptoms [22]. Cinnamon extract treatment has been found to decrease the mRNA expression of inflammatory cytokines including IL-6, IL-1β and TNF-α and its oral administration inhibits the progression of inflammation [48]. In a study by Shokri Mashhadi et al., oral daily administration of 3 grams of cinnamon in Persian female martial athletes for 6 weeks significantly reduced muscle soreness compared to controls, with plasma levels of IL-6 significantly reduced in the cinnamon group, but the reduction was not significant compared to controls. They

noted that the dose of cinnamon was not big enough for the assessment time and number of participants in the study [48]. Also, the antioxidant effects of cinnamon in healthy subjects, through increasing total antioxidant capacity and decreasing lipid peroxidation, have been reported [49].

The syrup of V.vinifera is another compound in our herbal extract which has neuroprotective properties [23]. Its seeds and skin contain several bioactive components such as proanthocyanidins, anthocyanidins and resveratrol [23, 32]. About 70 % to 95 % of standardized proanthocyanidins found in grape seed extract and fresh grape skins contains about 50 to 100 µg/g wet weight resveratrol [32, 23]. Antioxidant, anti-inflammatory, chemopreventive, anti-cancer, anti-microbial, anti-diabetic and anti-asthmatic activities of these components have been reported in animal and human studies [23, 32]. Emerging evidence suggests that these bioactive components may also have anti-fatigue activities. A double-blind, placebo-controlled crossover study performed by Edwards et al. evaluated 40, 80 and 120 mg of anthocyanidins in patients with primary fibromyalgia for 3 months. There was a significant improvement in sleep, fatigue and general health compared to the placebo group at a dose of 80 mg [26]. In a study by Xie et al. proanthocyanidin administration to male mice for 30 days with four different doses (0, 1.7, 16.7 and 50 mg/kg body weight) resulted in a significant decrease in lactic acid concentration, an increase in hemoglobin content and hepatic glycogen content and longer performance in loaded-swimming time test compared to the control group. The author suggests that proanthocyanidin has an anti-fatigue effect [27]. Several mechanisms are involved in anti-fatigue effects of the grape seed extract 'proanthocyanidins' which include: 1) increasing liver and muscle glycogen reserves, 2) maintaining blood glucose at stable levels, 3) improving the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the liver, 4) reducing malondialdehyde (MDA) content and, 5) promoting fat utilization [25]. Wu et al. found that 3 weeks of orally administered resveratrol at three doses (25, 50 and 125 mg/kg/day) in male mice increased glucose levels and decreased serum lactate, ammonia levels and creatine kinase activity. The intervention group with a dose of 25 mg has significantly longer exhaustive swimming time than that of the control group. They concluded that resveratrol administration could be a potential agent with anti-fatigue effects [32]

Despite extensive use of herbal plants in traditional medicine for fatigue and sleep disorders, little research has been conducted in this regard. Since sleep disorders and fatigue are associated with enhanced inflammatory cytokine production, especially TNF-α and IL-6 [40, 50], the beneficial effects of our herbal extract in this study may be mediated, to some extent, through their action on reducing inflammatory cytokines. The anti-fatigue and hypnotic effects of our herbal extract observed in this study can be attributed, at least in part, to its rich content of bioactive compounds from each herbal plant in the mixture, working synergistically. Due to the complexity and diversity of bioactive compounds in this herbal extract, characterization and isolation of every compound and assessment of their activities is rather difficult. Further studies are needed to characterize different compounds of each of these herbs. In addition, the small number of patients and the short period of follow-up are other limitations of our study.

Conclusion

Eventually, it can be concluded that the mixture of herbal extracts used in this study including C.sativus, H.perforatum, C.verum, and V.vinifera, can be taken into account as a safe and effective anti-fatigue and hypnotic agent as complementary and supportive care for fatigue and sleep disorders in MS patients.

Abbreviations:
AD: Alzheimer's disease; ANOVA: Analysis of variance; BBB: Blood brain barrier; CAM Complementary and alternative medicine; CNS: Central nervous system; EAE: Experimental allergic autoimmune; EDSS: Extended disability status scale; FSS: Fatigue severity scale; GPx: Glutathione peroxidase; GSPE: Grape seed proanthocyanidin extract; IL: Interleukin; ISI: Insomnia severity scale; MDA: Malondialdehyde; MFIS: Modified fatigue impact scale; MS: Multiple sclerosis; PD: Parkinson's disease; PSQI: Pittsburgh sleep quality index; RCT: Randomized clinical trial; REM: Rapid eye movement; ROS: Reactive oxygen species; SD: Standard deviation; SOD: Superoxide dismutase; TNF: Tumor necrosis factor.

References

1. Compston A, Coles A. Multiple sclerosis. The Lancet.372(9648):1502-17. doi:10.1016/S0140-6736(08)61620-7.
2. Sanoobar M, Dehghan P, Khalili M, Azimi A, Seifar F. Coenzyme Q10 as a treatment for fatigue and depression in multiple sclerosis patients: a double blind randomized clinical trial. Nutritional neuroscience. 2016;19(3):138-43.
3. Khalili M, Eghtesadi S, Mirshafiey A, Eskandari G, Sanoobar M, Sahraian MA et al. Effect of lipoic acid consumption on oxidative stress among multiple sclerosis patients: a randomized controlled clinical trial. Nutritional neuroscience. 2014;17(1):16-20.
4. Marrie RA, Reider N, Cohen J, Trojano M, Sorensen PS, Cutter G et al. A systematic review of the incidence and prevalence of sleep disorders and seizure disorders in multiple sclerosis. Multiple Sclerosis Journal. 2015;21(3):342-9.
5. Attarian HP, Brown KM, Duntley SP, Carter JD, Cross AH. The relationship of sleep disturbances and fatigue in multiple sclerosis. Archives of neurology. 2004;61(4):525-8.
6. Bamer AM, Johnson KL, Amtmann DA, Kraft GH. Beyond fatigue: Assessing variables associated with sleep problems and use of sleep medications in multiple sclerosis. Clinical epidemiology. 2010;2:99.
7. Krupp LB, Christodoulou C. Fatigue in multiple sclerosis. Current neurology and neuroscience reports. 2001;1(3):294-8.

8. Brass SD, Li C-S, Auerbach S. The underdiagnosis of sleep disorders in patients with multiple sclerosis. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2014;10(9):1025.
9. Comi G, Leocani L, Rossi P, Colombo B. Physiopathology and treatment of fatigue in multiple sclerosis. Journal of neurology. 2001;248(3):174-9.
10. Rammohan K, Rosenberg J, Lynn D, Blumenfeld A, Pollak C, Nagaraja H. Efficacy and safety of modafinil (Provigil®) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry. 2002;72(2):179-83.
11. Ahmadi A, Habibi G, Farrokhnia M. MS14, an Iranian herbal-marine compound for the treatment of multiple sclerosis. Chinese journal of integrative medicine. 2010;16(3):270-1.
12. Namjooyan F, Ghanavati R, Majdinasab N, Jokari S, Janbozorgi M. Uses of complementary and alternative medicine in multiple sclerosis. Journal of traditional and complementary medicine. 2014;4(3):145-52.
13. Akhondzadeh S. Herbal medicines in the treatment of psychiatric and neurological disorders. Low-Cost Approaches to Promote Physical and Mental Health. 2007:119-38.
14. Andalib S, Naeini AM, Vaseghi A, Vaseghi G. Sedative and hypnotic effects of Iranian traditional medicinal herbs used for treatment of insomnia. 2011.
15. Poma A, Fontecchio G, Carlucci G, Chichiricco G. Anti-inflammatory properties of drugs from saffron crocus. Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents). 2012;11(1):37-51.
16. Hosseinzadeh H, Noraei NB. Anxiolytic and hypnotic effect of Crocus sativus aqueous extract and its constituents, crocin and safranal, in mice. Phytotherapy Research. 2009;23(6):768-74.
17. Nosratabadi R, Rastin M, Sankian M, Haghmorad D, Tabasi N, Zamani S et al. St. John's wort and its component hyperforin alleviate experimental autoimmune encephalomyelitis through expansion of regulatory T-cells. Journal of immunotoxicology. 2016;13(3):364-74.
18. Cabrelle A, Dell'Aica I, Melchiori L, Carraro S, Brunetta E, Niero R et al. Hyperforin down-regulates effector function of activated T lymphocytes and shows efficacy against Th1-triggered CNS inflammatory-demyelinating disease. Journal of leukocyte biology. 2008;83(1):212-9.
19. Lin Y, Zhang J-C, Fu J, Chen F, Wang J, Wu Z-L et al. Hyperforin attenuates brain damage induced by transient middle cerebral artery occlusion (MCAO) in rats via inhibition of TRPC6 channels degradation. Journal of Cerebral Blood Flow & Metabolism. 2013;33(2):253-62.
20. Brahmachari S, Jana A, Pahan K. Sodium benzoate, a metabolite of cinnamon and a food additive, reduces microglial and astroglial inflammatory responses. The Journal of Immunology. 2009;183(9):5917-27.
21. Pahan K. Immunomodulation of experimental allergic encephalomyelitis by cinnamon metabolite sodium benzoate. Immunopharmacology and immunotoxicology. 2011;33(4):586-93.
22. Pahan K. Prospects of cinnamon in multiple sclerosis. Journal of multiple sclerosis. 2015;2(3):1000149.
23. Waggas AM. Grape seed extract (Vitisvinifera) alleviate neurotoxicity and hepatotoxicity induced by lead acetate in male albino rats. Journal of Behavioral and Brain Science. 2012;2(02):176.
24. Sato F, Martinez NE, Shahid M, Rose JW, Carlson NG, Tsunoda I. Resveratrol exacerbates both autoimmune and viral models of multiple sclerosis. The American journal of pathology. 2013;183(5):1390-6.
25. Shan Y, Ye X-h, Xin H. Effect of the grape seed proanthocyanidin extract on the free radical and energy metabolism indicators during movement. Scientific Research and Essays. 2010;5(2):148-53.
26. Edwards A, Blackburn L, Christie S, Townsend S, David J. Food supplements in the treatment of primary fibromyalgia: a double-blind, crossover trial of anthocyanidins and placebo. Journal of nutritional & environmental medicine. 2000;10(3):189-99.
27. LIU Xie, LI Xiaoning, BAO Liuxing et al. The Antifatigue Effect of Grape Seed Extract-proanthocyanidin [J]. Practical Preventive Medicine. 2004;1:015.
28. Fonseca-Kelly Z, Nassrallah M, Uribe J, Khan RS, Dine K, Dutt M et al. Resveratrol neuroprotection in a chronic mouse model of multiple sclerosis. Frontiers in neurology. 2012;3.
29. Singh NP, Hegde VL, Hofseth LJ, Nagarkatti M, Nagarkatti P. Resveratrol (trans-3, 5, 4′-trihydroxystilbene) ameliorates experimental allergic encephalomyelitis, primarily via induction of apoptosis in T cells involving activation of aryl hydrocarbon receptor and estrogen receptor. Molecular pharmacology. 2007;72(6):1508-21.
30. Wang D, Li S-P, Fu J-S, Zhang S, Bai L, Guo L. Resveratrol defends blood-brain barrier integrity in experimental autoimmune encephalomyelitis mice. Journal of neurophysiology. 2016;116(5):2173-9.
31. Ghaiad HR, Nooh MM, El-Sawalhi MM, Shaheen AA. Resveratrol promotes remyelination in cuprizone model of multiple sclerosis: biochemical and histological study. Molecular neurobiology. 2017;54(5):3219-29.
32. Wu R-E, Huang W-C, Liao C-C, Chang Y-K, Kan N-W, Huang C-C. Resveratrol protects against physical fatigue and improves exercise performance in mice. Molecules. 2013;18(4):4689-702.
33. Hajiheydari MR, Yarmohammadi ME, Izadi P, Jafari F, Emadi F, Emaratkar E et al. Effect of Nepeta bracteata Benth. on allergic rhinitis symptoms: A randomized double-blind clinical trial. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2017;22.
34. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Annals of neurology. 2001;50(1):121-7.
35. Kurtzke JF. Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-.
36. Holtzer R, Foley F. The relationship between subjective reports of fatigue and executive control in multiple sclerosis. Journal of the neurological sciences. 2009;281(1):46-50.

37. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep medicine. 2001;2(4):297-307.
38. Moghaddam JF, Nakhaee N, Sheibani V, Garrusi B, Amirkafi A. Reliability and validity of the Persian version of the Pittsburgh Sleep Quality Index (PSQI-P). Sleep and Breathing. 2012;16(1):79-82.
39. Prather AA, Vogelzangs N, Penninx BW. Sleep duration, insomnia, and markers of systemic inflammation: results from the Netherlands Study of Depression and Anxiety (NESDA). Journal of psychiatric research. 2015;60:95-102.
40. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Archives of internal medicine. 2006;166(16):1756-62.
41. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? Journal of clinical oncology. 2011;29(26):3517-22.
42. Kos D, Kerckhofs E, Nagels G, D'hooghe M, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. Neurorehabilitation and Neural Repair. 2008;22(1):91-100.
43. Ghazavi A, Mosayebi G, Salehi H, Abtahi H. Effect of ethanol extract of saffron (Crocus sativus L.) on the inhibition of experimental autoimmune encephalomyelitis in C57bl/6 mice. Pakistan journal of biological sciences: PJBS. 2009;12(9):690-5.
44. Javadi B, Sahebkar A, Emami SA. A survey on saffron in major Islamic traditional medicine books. Iranian journal of basic medical sciences. 2013;16(1):1.
45. Tamaddonfard E, Farshid A-A, Eghdami K, Samadi F, Erfanparast A. Comparison of the effects of crocin, safranal and diclofenac on local inflammation and inflammatory pain responses induced by carrageenan in rats. Pharmacological Reports. 2013;65(5):1272-80.
46. Kim C-S, Han J-Y, Kim S-H, Hong JT, Oh K-W. Herbs for the treatment of insomnia. Biomol Ther. 2011;19:274-81.
47. Sharpley A, McGavin C, Whale R, Cowen P. Antidepressant-like effect of Hypericum perforatum (St John's wort) on the sleep polysomnogram. Psychopharmacology. 1998;139(3):286-7.
48. Mashhadi NS, Ghiasvand R, Askari G, Feizi A, Hariri M, Darvishi L et al. Influence of ginger and cinnamon intake on inflammation and muscle soreness endued by exercise in Iranian female athletes. International journal of preventive medicine. 2013;4(Suppl 1):S11.
49. Azimi P, Ghiasvand R, Feizi A, Hariri M, Abbasi B. Effects of cinnamon, cardamom, saffron, and ginger consumption on markers of glycemic control, lipid profile, oxidative stress, and inflammation in type 2 diabetes patients. The review of diabetic studies: RDS. 2014;11(3):258.
50. Heesen C, Nawrath L, Reich C, Bauer N, Schulz K, Gold S. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? Journal of Neurology, Neurosurgery & Psychiatry. 2006;77(1):34-9.