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Effect of MS14® on physical activity of multiple sclerosis patients: A randomized triple-blind placebo-controlled clinical trial

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ABSTRACT

Introduction: Multiple Sclerosis (MS) is a neurological disorder with an increasing global prevalence and severe complications. MS14® is a Persian-medicine-derived natural product with herbal and marine origin which has shown beneficial effects in the management of MS complications. In this study, its effect on physical activity of MS patients was investigated.

Methods: A triple-blind placebo-controlled clinical trial was conducted. Participants used either MS14 capsule or placebo 3 times a day for 3 weeks. At baseline and end of the study, physical activity indices were assessed using international physical activity questionnaire (IPAQ). Secondary outcome measures were Fatigue Severity Scale (FSS), timed 10 m walk, Ashworth scale, and Timed Get up and Go.

Results: A total number of 80 MS patients completed the study. At the end of study, improvement of general physical activity (p-value=0.047) and Timed 10 m walk index (p-value=0.003) in the MS14 group was significant when compared to placebo. No serious adverse effects were observed in this study.

Conclusion: Considering the improvement of some physical activity indices, MS14® is seems to be a safe natural product which could be considered as a supplementary treatment in MS patients. Future larger trials are suggested to further evaluate its efficacy.

1. Introduction

Multiple sclerosis is a relapsing-remitting and progressive disorder with a rising global prevalence that affects the central nervous system (Walton et al., 2020). It is the most common cause of disability among youth, especially women which mostly involves the people in the age range of 20 to 40 years (Aminoff et al., 2015; Fauci et al., 2018).

Although some theories such as genetic susceptibility, environmental factors, and abnormally enhanced immunological and inflammatory response have been established for explaining MS pathophysiology, the etiology is still unknown. No fully effective treatment has been found for this debilitating neurological disease. Medical care and pharmacological therapies which are received by patients are not consistently effective enough, in most cases, to prevent secondary progression and unfortunately, newer and older immunotherapies have adverse effects especially with long term usage (Miltenburger and Kobelt, 2002).

On the other hand, some MS related complications such as loss of walking ability as a result of multiple factors including cerebellar ataxia, spasticity, pain and muscular spasm, and a general decline in functional capacity, have a serious negative influence on patients' quality of life.

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Nonetheless, there are limited pharmacological options to effectively manage many of these complications (Monaca-Charley et al., 2003; Patti et al., 2004).

In recent years, an increasing trend has been observed in the use of natural products for the treatment of various diseases. Complementary and Alternative Medicine (CAM) is appealing to many communities and seems to be effective in the management of a vast range of diseases (Daneshfard et al., 2019). In the case of MS, the prevalence of CAM use is increasing with many patients reporting a beneficial effect on their disease (Harirchian et al., 2014; Ranjbar et al., 2021).

Persian Medicine (PM), with a very rich literature and outstanding scholars, is one of the old and comprehensive traditional systems of medicines since the ancient times (Nimrouzi et al., 2019). It is mainly based on preventive health measures and various therapeutic interventions (Nozad et al., 2016). Recent studies have shown the potential benefits of introducing new natural remedies to MS patients (Farzaei et al., 2017; Pahan, 2015; Sumowski et al., 2017).

MS14® is a natural product with herbal and marine origin containing main ingredients of *Penaeus latisculatus* (90%), *Apium graveolense* L. (5%), and *Hypericum perforatum* L (5%). Its safety and efficacy have been previously assessed. A study revealed that MS14 induces reactional hyperplastic changes in immune system organs especially lymph nodes (Sedaghat et al., 2010). In animal studies, MS14 has been found to decrease the IgM mediated cellular immunological response, significantly decrease IL-β and macrophage-secreted TNF as well as increase IL5 and IL10 secreted from TH2 cells (Sedaghat et al., 2010; Yaraee et al., 2011). Studies employing experimental autoimmune encephalomyelitis (EAE) models have also reported prevention of brain tissue destruction after using MS14 in addition to down regulation of Lipocaline2 (LCN2) expression, the transporter protein which is thought to have an important role in MS pathogenesis (Ebrahimi-Kalan et al., 2014; Roya et al., 2010; Tafreshi et al., 2008). Moreover, this natural product improves EAE clinical symptoms by decreasing the IL6 expression and suppressing proliferative responses of T cells (Kalan et al., 2014).

According to the results of a past clinical istudy, MS14 may improve MS patients' quality of life (Naseri et al., 2009). Regarding its safety, MS14 does not induce any significant histopathological changes on main organs based on toxicological assessments (Naseri et al., 2007; Sedaghat et al., 2010).

In line with our previous investigations on MS14, this study was conducted to evaluate the effect of MS14 on the physical activity of MS patients.

2. Material and method

2.1. Study design

This study was a randomized triple-blind placebo-controlled clinical trial with 1:1 allocation ratio. It was conducted in Shahed University with the cooperation of Herbal Medicine Research Center. All clinical assessments were performed in Iranian Center of Neurological Research in Tehran University of Medical Sciences.

2.2. Ethical considerations

This study was approved in ethical committee of Shahed University with dedicated code of shahed.REC.1386.6. All of the participants signed the written informed consent before the enrollment. In addition, the study was registered in the Iranian clinical trial registry (ID: IRCT20161203031205N3).

2.3. Drug information

MS14® has herbal and marine ingredients including 90% king prawn (*Penaeus latisculatus*), 5% celery (*Apium graveolense* L.), and 5% St John's wort (*Hypericum perforatum* L) (Yaraee et al., 2011). It contains inorganic salts or complexes in addition to trace elements such as strontium (Sr), bromine (Br), zinc (Zn), nickel (Ni), titanium (Ti), and vanadium (V) (Naseri et al., 2009). MS14® is formulated according to PM literature which has been patented by invention and patent registration office of Islamic Republic of Iran (NO: 29350) and classified as equivalent to food (Naseri et al., 2022). The therapeutic dose of this natural product has been determined to be 50 mg/kg daily with maximum dose of 2500 mg/kg (Ahmadi et al., 2010).

2.4. Inclusion and exclusion criteria

Multiple sclerosis patients whom had been diagnosed based on the McDonald criteria were included in this study. Age of 18 years and older, difficulty walking, spasticity degree more than 2 (Ashworth score>2), Expanded Disability Status Scale (EDSS)≤6, not experiencing relapse of MS in last 6 months prior to study, and ability to walk more than 5 m with or without help were additional inclusion criteria.

Patients with cardiovascular diseases, active definite infection, major cognitive disorder or psychotic disease and major depression were excluded from the study. Patients whose condition relapsed during the study period were also excluded from further analysis. Pre-existing advanced lower limb movement disorders (such as fixed tendon contractures) and any significant abnormality in complete blood count, liver and/or kidney function tests in the beginning of the study were other exclusion criteria.

2.5. Intervention

Participants in the intervention group received MS14 capsules (500 mg) three times a day for 3 weeks. Participants in the control group received placebo caplets containing starch powder with the same properties in terms of color and shape and with same order. All of the capsules were coded; thus, the physicians, patients and their family, and also the statistician were unaware of the allocations.

2.6. Outcome measures

Participants were examined regarding their vital signs and nervous system at the beginning and at the end of the third week of the trial. International physical activity questionnaire (IPAQ) was used as the primary outcome measure of the study. Moreover, Fatigue Severity Scale (FSS), timed 10 m walk, Ashworth scale, and Timed Get up and Go were assessed as the secondary outcome measures. Assessments were done at the beginning and end of the third week of the study. Participants were also asked for any possible adverse effects.

2.7. Statistical analysis

Statistical analysis was carried out using the R programing language (version 4.0.4 for MacOS). Quantitative and qualitative variables were described using mean (standard deviation) and frequency (percent), respectively. The paired t-test was applied to compare the change in values in each group, separately, and independent t-test as well as Fisher's exact test to analysis the differences at the baseline, follow up and baseline-follow up difference values between two groups. P values <0.05 was considered as statistically significantly different.

3. Results

3.1. Study flow

A total number of 92 participants were randomly enrolled in the trial with 80 of them in the final analysis including 42 participants in the MS-14 group (95.2% female; mean age of 40.49±9.13 years) and 38 participants in the placebo group (86.8% female; mean age of 38.47±10.21 years). No adverse event was observed in both treatment arms (Fig. 1).

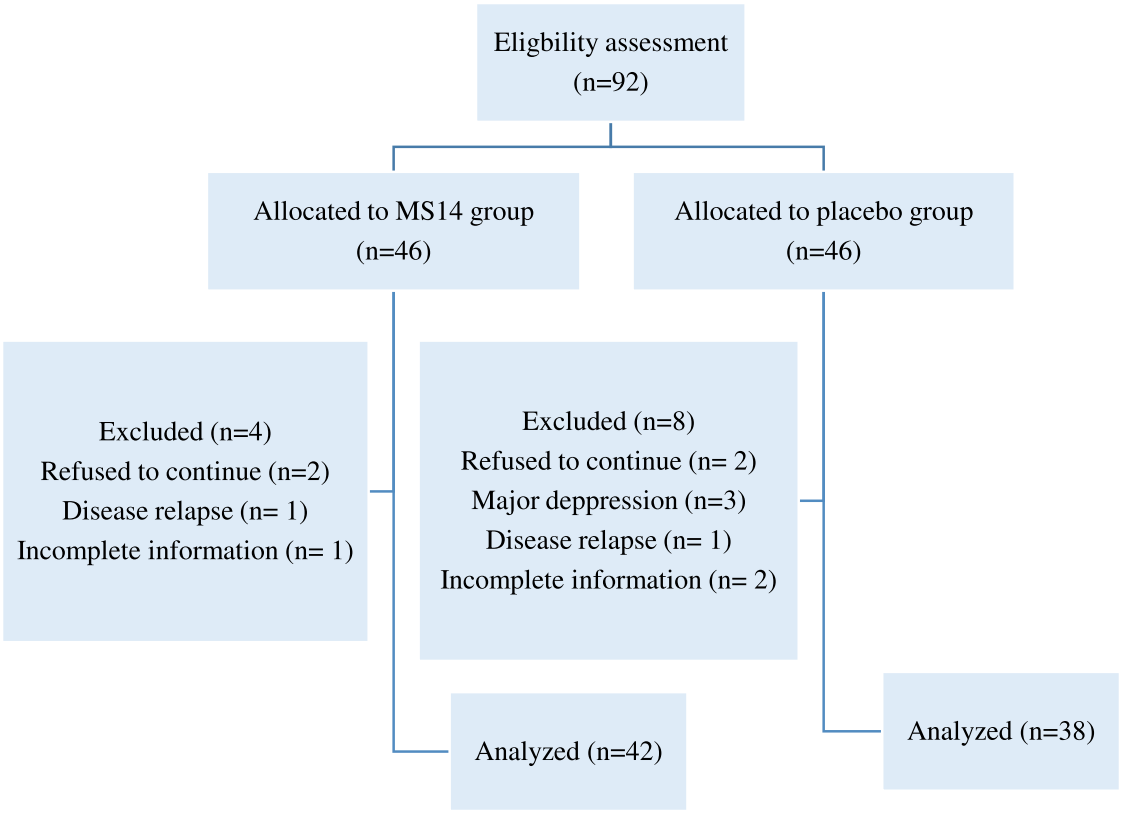

Fig. 1. CONSORT Flow diagram of the MS14 clinical trial in MS patients.

Table 1 shows the baseline demographic and laboratory data of the patients. Groups were not significantly different in any of the variables except for the aspartate aminotransferase level (P=0.026).

3.2. Clinical outcomes

At the baseline, there was no significant difference between the groups for the general physical activity scores (MS14: 804.17±1127.86, placebo: 2181.03±4291.32; P = 0.060) despite moderate levels of physical activity (MS14: 566.79±892.58, placebo: 1385.13±2363.37; P = 0.047). The IPAQ indices showed an increasing and a decreasing pattern after three weeks of trial in MS14 and placebo groups, respectively. However, these was only statistically significant in MS14 group (general physical activity: P = 0.016; moderate physical activity: P = 0.041). Considering the changes of IPAQ indices after 3 weeks of trial, MS14 was statistically superior to placebo for general physical activity (MS14: 1098.61±2695.96, placebo: -283.81±3257.21; P = 0.047). However, it was not the case for moderate physical activity, although it was marginally insignificant (MS14: 674.77±1988.29, placebo: -119.3 ±1991.39; P = 0.084) (Table 2).

The two treatment arms were not statistically different at baseline for any of the secondary outcome measures. MS14 and placebo groups showed a significant within-group change for Ashworth scale (P = 0.009, <0.0001) and timed Get up and Go (P = 0.017, 0.016), respectively. Within-group changes of fatigue severity scale (P = 0.001) and timed 10 m walk (P = 0.010) were only significant for the MS14 group. Considering the difference in secondary outcome measures after 3 weeks, MS14 was statistically superior over placebo for timed 10 m walk (P = 0.003) while between groups comparisons did not reveal any significant difference for any of the other secondary outcome measures (Table 3).

A number of patients self-reported improvement in urination although this was not a primary or secondary outcome measure and hence was not statistically analyzed.

4. Discussion

In searching for a safe and efficient treatment for MS patients, this study investigated the effect of MS14 on physical activity.

Regarding the safety of this natural product, animal and human studies evaluating vital signs as well as biochemical markers and kidney function tests have not reported any adverse effects (Kalan et al., 2014). Moreover, no complaint about using MS14 was reported in the current study.

Results obtained from IPAQ indices indicated significant improvement in “moderate physical activity” and “general physical activity” in the MS14 group despite no significant change in placebo group.

In the case of secondary outcomes such as Timed 10 m walk, the MS14 group significantly improved when compared to the placebo group. Although patients who received MS14 also improved regarding Ashworth scale, Fatigue severity scale, and Timed Get up, these changes were not statistically significant in comparison to the placebo group. Such results may be due to the relatively short duration of the study period and sample size.

It should also be considered that Timed Get up and Go index usually changes slowly and is dependent on the mental and physical condition of the person when getting up. Consequently, any drug which is able to improve this index following a short duration exposure should either be very potent or have a positive effect on non-motor, for example, neuropsychiatric symptoms. Regarding fatigue severity, a dramatic effect was not expected for this natural product given its main action is directed towards the immune system.

It is also worth mentioning that many participants who used MS14 were satisfied with the improvement in the control of urination. Although this unanticipated finding was not statistically analyzed, this valuable self-report satisfaction worth further investigations considering

Table 1
Baseline demographic and laboratory data of MS patients in the experimental and control arms.

Variable	MS14 (n = 42)**	Placebo (n = 38)**	P
Sex			0.248
*Male**	2 (4.8)	5 (13.2)	
*Female**	40 (95.2)	33 (86.8)	
Age (year)	40.49 ± 9.13	38.47 ± 10.21	0.358
Pulse rate	75.98 ± 6.96	75.97 ± 6.73	0.999
Respiratory rate	15.65 ± 1.21	15.50 ± 1.18	0.594
Temperature (°C)	36.38 ± 0.65	37.60 ± 0.81	0.333
Systolic blood pressure (mmHg)	111.17 ± 10.62	110.26 ± 12.02	0.722
Diastolic blood pressure (mmHg)	70.55 ± 9.91	68.73 ± 8.76	0.390
RBC count (million/mm^3)	4.59 ± 0.44	4.72 ± 0.52	0.248
WBC ×1000 count (thousands/mm^3)	6.38 ± 2.54	5.59 ± 3.12	0.251
Hemoglobin level (g/dL)	13.64 ± 1.39	17.97 ± 2.07	0.207
Hematocrit (L/L)	40.87 ± 4.10	41.24 ± 3.77	0.678
Platelet ×1000 count (per mcL)	205.36 ± 71.95	221.27 ± 49.39	0.260
BUN level (mg/dL)	26.60 ± 7.98	23.27 ± 7.76	0.064
Creatinine level (mg/dL)	1.07 ± 1.15	.89 ± 0.16	0.351
Activated U/A			1.000
*Positive**	0 (0)	0 (0)	
*Negative**	42 (100)	38 (100)	
ALT level (unit/L)	33.65 ± 38.50	25.96 ± 17.13	0.268
AST level (unit/L)	27.37 ± 19.67	20.30 ± 6.65	0.026
Triglycerides level (mg/dL)	96.60 ± 50.33	123.07 ± 74.21	0.066
Total cholesterol levels (mg/dL)	189.12 ± 33.41	185.16 ± 51.92	0.685
ESR (mm/hr)	12.32 ± 11.24	10.62 ± 7.90	0.466
CRP (mg/L)			1.000
*Positive**	0 (0)	0 (0)	
*Negative**	42 (100)	38 (100)	
Sodium level (mmol/L)	138.71 ± 2.87	140.33 ± 8.52	0.253
Calcium level (mmol/L)	8.66 ± 1.42	9.15 ± 0.47	0.064
Potassium level (mmol/L)	4.20 ± 0.52	4.23 ± 0.40	0.780

RBC: red blood cell; WBC: white blood cells; BUN: blood urea nitrogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; U/A: urine analysis; CRP: C-reactive protein.
* Frequency (percent).
** Mean ± SD.

Table 2
Intragroup and intergroup comparisons of baseline and follow-up values of IPAQ indices amongst MS patients.

	Baseline*	Follow-up*	P †	Difference*
Moderate physical activity				
MS14 (n=42)	566.79 ± 892.58	1241.56 ± 2102.53	0.041	674.77 ± 1988.29
Placebo (n=38)	1385.13 ± 2363.37	1265.79 ± 1734.07	0.714	-119.3 ± 1991.39
P †	0.047	0.956	–	0.084
General physical activity				
MS14 (n=42)	804.17 ± 1127.86	1902.78 ± 2805.77	0.016	1098.61 ± 2695.96
Placebo (n=38)	2181.03 ± 4291.32	1897.21 ± 2154.65	0.594	-283.81 ± 3257.21
P †	0.060	0.992	–	0.047

† Independent t-test.
‡ Paired t-test.
* Mean ± SD.

that most of the sexual and urinary sphincter disorders occur concurrent to the movement disorders in lower limbs.

It seems that the effect of MS14 could be attributed to its anti-inflammatory properties as it can decrease the level of cytokines like IgM, IL β, and macrophages secreted TNF; the mediators which can cause abnormal immunological responses as the main cause of this complicated disease. It can also increase the level of immunomodulatory cytokines such as IL5 and IL10. Anti-inflammatory effect of MS14 is also related to its suppressive effect on LCN2 expression, one of the most important implicated mediators in MS pathogenesis (Ebrahimi-Kalan et al., 2014; Sedaghat et al., 2010; Tafreshi et al., 2008; Yaraee et al., 2011).

Table 3
Intragroup and intergroup comparisons of baseline and post-intervention values for the secondary outcome measures amongst MS patients.

	Baseline*	Follow-up*	P †	Difference*
Fatigue severity scale				
MS14 (n=42)	46.00 ± 11.69	40.44 ± 13.21	0.001	-5.56 ± 8.87
Placebo (n=38)	42.63 ± 11.87	39.66 ± 13.16	0.075	-2.97 ± 9.56
P †	0.239	0.806	–	0.248
Timed 10m walk				
MS14 (n=42)	25.26 ± 28.70	18.21 ± 17.81	0.010	-7.05 ± 15.58
Placebo (n=38)	22.84 ± 21.32	26.57 ± 32.16	0.117	3.73 ± 13.94
P †	0.687	0.177	–	0.003
Ashworth scale				
MS14 (n=42)	2.62 ± .92	2.12 ± 1.25	0.009	-0.50 ± 1.05
Placebo (n=38)	2.41 ± 1.02	1.76 ± .89	<0.0001	-0.65 ± 0.81
P †	0.385	0.184	–	0.521
Timed Get up and Go				
MS14 (n=42)	2.87 ± 3.10	2.28 ± 2.72	0.017	-0.60 ± 1.47
Placebo (n=38)	2.56 ± 1.99	2.16 ± 1.82	0.016	-0.40 ± 0.93
P †	0.606	0.828	–	0.496

† Independent t-test.
‡ Wilcoxon sign-rank test.
* Mean ± SD.

In addition to animal studies, there are other investigations showing the beneficial effects of the main ingredients of MS14. *Apium graveolense* L. and *Hypericum perforatum* L., two herbal components of MS14, have anti-inflammatory and anti-nociceptive effects which can play an important role in the improvement of MS symptoms (Naseri et al., 2007; Ramezani et al., 2009).

On the other hand, the beneficial role of different inorganic salts and trace elements found in MS14 such as strontium, zinc and vanadium cannot be ignored. For instance, strontium has beneficial effects on bone health; it prevents bone resorption and has anabolic activity which can maintain bone balance (Abdel-Salam, 2005). This effect may help MS patients in direct and indirect ways as their muscles weaken during the disease progression. Another trace element, vanadium, has therapeutic importance. It can enhance oxygen-affinity of hemoglobin and myoglobin so it may improve oxygen delivery to the tissues and compensate the lack of energy in MS patients (Murakami and Noda, 2000). This effect can be enhanced by the hematopoietic effect of MS14 which has been reported in a study by Eghtedardoost et al. (2012).

Generally, antioxidant, anti-inflammatory and immunomodulatory effects are suggested mechanisms of action for MS14. Although St John's wort (*Hypericum perforatum*) was only a minor constituent, we cannot exclude the possibility of a beneficial effect in some individuals. Our findings, in conjunction with previous studies, indicate that MS14 may prove to be useful as an adjunct symptomatic treatment or potentially immunodulatory agent, to current disease modifying therapies.

The main limitations of this study were relatively small sample size, in part due to financial restraints, and short duration of follow-up. We also did not have information on the proportion of patients requiring use of walking aids or on the number who were on disease modifying therapies. However, the study did have a high completion rate of 87%. There was also nonsignificant trend for lower general physical activity scores in subjects receiving MS14 when compared to placebo which may have influenced the greater degree in improvement found in those on active treatment. Although patients were randomly assigned to the MS14 and placebo arms, it is possible that subjects with lower physical activity obtain a greater response to MS14 therapy. Future larger trials are warranted to investigate the efficacy of MS14 in MS patients.

5. Conclusion

As a nutraceutical, MS14 is seems to be effective in some functional and movement disorders of MS patients. It is supposed to be helpful for patients whose physical activities and quality of life have been negatively influenced by the complications caused by their MS. MS14 could be used as a safe supplement along with other medications, including symptomatic and disease modifying therapies, for better management of MS patients. Its effectiveness should be further evaluated with larger clinical trials.

CRediT authorship contribution statement

Hossein Rezaeizadeh: Conceptualization, Methodology. **Kourosh Gharegozli:** Investigation, Software. **Seyed Masood Nabavi:** Investigation. **Vahid Shayegannejad:** Data curation, Writing – original draft. **Majid Ghaffarpoor:** Investigation. **Babak Daneshfard:** Writing – review & editing. **Dennis Cordato:** Writing – review & editing. **Mohsen Naseri:** Conceptualization, Methodology, Supervision.

Declaration of Competing Interest

The authors have declared that there is no conflict of interest.

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