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The efficacy of traditional formulation on quality of life and fatigue in multiple sclerosis patients: a randomized double-blind placebo-control clinical trial

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Objective According to effects that cinnamon, ajwain and Iranian borago shows in involving mechanisms in MS and MS animal model, we decided to survey the effect of traditional formulation on MS patient by clinical trial.
Methods In a double blind randomized clinical trial study, 60 patients with MS observed. They take formulation 15 cc per day, fill the MSQOL-54, and fatigue questionnaires every month. The data were analyzed with 18th version of SPSS, independent *t*-test and repeated measure tests. The *P*-value for tests was 0.05.
Results The mean quality-of-life and fatigue of patient with MS were significantly changed during 3 months.
Conclusion Most patients with MS had better quality-of-life during 3 month and get less tired. In some patient tremor and pain reduce. Because of good result and revenue of formulation, it seems to be useful for MS patient.
Keywords quality of life, fatigue, multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinated disease of central nervous system (CNS) that could be disabling and fatal. MS attack to myelinated axons in CNS and destroy it. This disease generally occurs at the age of 20–40 years. The key of pathologic mechanism of MS shows a breakdown in immunologic tolerance or a peripheral infection and following a demineralizing inflammation attack to CNS. Start of this pathologic process represents the complex interference of genetics and environment that is not understand completely. In MS, neurologic symptoms (visual, sensory and motor) occur because of neurodegenerative process. In CNS there are lesions with penetrated specific inflammatory cells and demyelinated. The cause of neurodegenerative process is unknown. One possibility is a chronic infection in CNS. Various kinds of neurotropic micro-organisms in MS are known although there is no definitive evidence for the reasons. The grade of MS is wildly different and unpredictable. In several patients MS initially diagnosis with reversible neurologic disorder episodes that is often followed by progressive neurologic attack. In 2013 almost 2.5 million patients in the world affected with MS that 50% of them, need help for walking after 15 years of disease onset. Women twice the men affected with MS, and northern Europe people are in higher risk for MS.[1–3]

Using complementary and alternative medicine (CAM), for chronic disease such as MS is an important issue for patients. CAM's methods use in addition or instead of conventional medicine. In summary, CAM is wildly described as a positive cure without major defeat and without or with low adverse effect by patients. CAM is part of varied medical system which is not considered as a conventional medicine and include mind–body practice and manipulative, traditional medicine and modern medical system. Unani medicine is a part of traditional medicine that is according to Harrison's book" Unani medicine is a western Indian medical system that is derived from Iranian medicine and initially use in Muslim country and also called hikmet".[4–6]

Moreover traditional Persian medicine (TPM), is an ancient temperament medicine with thousands years history. This kind of medicine is thought in traditional and complementary medicine and traditional pharmacy faculty in Iran. Recently use of herbal medicine as CAM in cure disease is increased.[7,8]

In TPM one categories of disorders generally called *Khaddar*, that similar point of them is sensory disorders. *Khaddar* is any kind of sensory deficiency or invalidity, which may be associated with motor symptoms. This sensory disorder is painful, like creeping sensation, having a prickly sensation or sense of ant walking on the skin. According to these definitions, it seems that *Khaddar* is similar to hypesthesia and paresthesias.[9–13]

Ajwain or *Trachyspermum ammi* belong to Apiaceae that is wildly grown in Iran, Egypt, Pakistan, Afghanistan, India and some part of Europe. This plant is known as zenyan or nankhah in medicine and pharmaceutical references of TPM. Ajwain's seeds are wildly prescribed by traditional Iranian physician's foe several disorders. Because of its various chemical constituents, this seeds have numerous pharmacologic effects. Ajwin's seed has stimulant, carminative, diuretics, analgesic, antimicrobial, antiviral, antiulcer, antihypertensive, and antitussive, and bronchodilator, antiplatelet and hepatoprotective properties.[14,15]

Iranian borago or *Echium amoenum* is belonging to Boraginaceae family that is a 2 year or perennial herb. This plant is endemic of north of Iran and Caucasus. Iranian borago is one of the important medicinal herbs in TPM. *E. amoenum* has different effect such as pain relief, anti-inflammatory, antioxidant, and analgesic, antianxiety, sedative and anticonvulsant. This plant commercially cultivated for the seed' oil which

is prepared from seed. The leaves and flower are also used as drug. They are used for fever, cough and depression. Seed's oil is used for skin disorder such as eczema, seborrhea dermatitis and neuro dermatitis. Also it is used for rheumatoid arthritis, alcoholism, obsessive compulsive disorder, pain and swelling and preventing cardiovascular disease.[16]

Cinnamon is prepared from inner bark of an ever green tree which is endemic of Sri lanka and south of India. Its scientific name is *Cinnamomum verum* or *Cinnamomum zeylanicum*. Cinnamon bark is wildly used as a spice and flavoring agent.[17,18] In addition to home uses of cinnamon, in ayurveda, cinnamon is used for respiratory digestion and women disease. Almost all part of cinnamon tree such as bark, leaves, flower, fruits and root have home and medicinal application. The essential oil which is prepared from roots bark, bark and leaves is significantly different in chemical constituents. So it is suggested that they have different pharmacologic effect. *In vitro*, *in vivo* and clinical studies all over the world demonstrated numerous beneficial effect for cinnamon, such as anti-inflammatory, antibacterial, reduce cardiovascular disease, increase cognitive function and reduce risk of colon cancer.[18]

The aim of this study is evaluate the efficacy of a traditional formulation on quality-of-life and fatigue of MS patients.

Materials and Methods

Two part of ajwain and one part of Iranian borago were soaked in water for 24 h and one part of cinnamon was soaked in water for 72 h then were distilled to yield the drug. Drug and placebo were gave to patients 15 cc per day for 3 months.

This study was a 3-month, double-blind study of parallel group of patients with multiple sclerosis and was taken in Khuzestan MS association in Iran from July 2018 to November 2018.

Sixty adult patient (20–50 years old), who were member of MS association were eligible to participate. Patient were required proved MS disease according to clinical examination and disease history, Expanded Disability Status Scale score 2–5.5,[19] had a regular drug therapy and no change in drugs for last 4 weeks. A neurologist examined all patients.

Patients with any of the following conditions were not qualified for the study: history of drug or alcohol abuse, pregnancy or lactation during the last 12 months, renal or liver failure, and steroid therapy during last 2 months, another neurologic disease except MS, cardiovascular disease, or infection and sensitivity to cinnamon.

This trial is in accordance with the Helsinki Declaration of 1975. The Ethics committee of Ahvaz Jundishapur University of Medical Sciences (ethics No. IR.AJUMS.REC.1397.063) approved the protocol. The patients authorized the testimonial and were informed that they could withdraw from the trial any time they want. A written consent was obtained from all participants. The measurements that include quality-of-life score, fatigue score, and cognition were monitored by filling standardized and validate questionnaire MSQL-54, fatigue severity score, and California Verbal Learning Test score respectively. All measures were done at baseline and monthly after the treatment started.

We used block method for randomization. The investigator provided with a randomization code for each available medication. All randomization codes were opened at the end of the study. Patients were randomized to receive drug or placebo in 1:1 ratio. Drug and placebo were not visually identified. All participants were supposed to take four capsules per day (every 6 h).

Results

Of total 60 patients, who enrolled into the trial, 30 patients were assigned to either drug or placebo group. During follow-up, nine patients were dropped out. Three for disease progression, one for moving to another city, one for drug sensitivity, and five for lack of compliance in follow-up. Finally, 51 patients completed full 3 months of study period. Basic demographic data are presented in Table 1. There were no significant differences between the two group's participants.

After 3 months follow-up of all participants, our study, demonstrate that for patient's fatigue score, the difference between two groups was not significant (*P*-value: 0.353, *f*: 1.0464), but interaction difference between drug and placebo group in four levels was significant (*P*-value <0.001, *f*: 126.393).

Mean ± SD score of drug and placebo group and 95% confidence interval were shown in Table 2. Results showed that fatigue in the drug group was decreased from baseline 15.74%, 23.49% and 40.65% at the end of 1st, 2nd and 3rd month respectively. While in placebo group, fatigue was increased from baseline 15.91%, 32.15% and 43.92% respectively (Fig. 1).

Quality-of-life questionnaire is divided into two parts, physical and mental quality-of-life. For physical quality-of-life score in the cinnamon group increased more than placebo group. According to Mauchly's test, due to lack of sphericity, for comparison between levels and their interactions with drugs used Greenhouse-Geisser was used. The difference

Table 1. **Demographic data for patients participated in this study**

	Drug	Placebo	*P*-Value
Gender (m/f)	10/16	9/16	ns
Age (mean ± SD) years	46 ± 1.52	48 ± 1.78	ns
Level of education			
Under diploma	6	8	ns
Diploma	12	10	ns
Higher diploma	8	7	ns

Table 2. **Fatigue score**

		Mean ± SD	95% Confidence interval	
			Down bound	Upper bound
Drug	Baseline	3.729 ± 0.027	3.355	4.103
	1st month	3.142 ± 0.033	2.684	3.600
	2nd month	2.853 ± 0.032	2.684	3.307
	3rd month	2.213 ± 0.32	1.765	2.661
Placebo	Baseline	3.520 ± 0.028	3.121	3.919
	1st month	4.186 ± 0.035	3.658	4.635
	2nd month	4.652 ± 0.035	4.168	6.135
	3rd month	5.066 ± 0.034	4.588	5.543

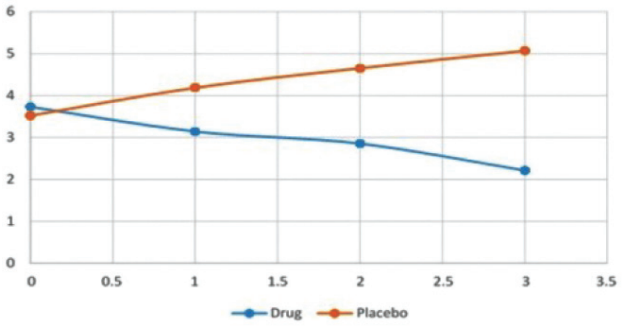

Fig. 1 **Fatigue score curve.**

Table 3. **Physical quality-of-life score**

		Mean ± SD	95% Confidence interval	
			Down bound	Upper bound
Drug	Baseline	79.280 ± 0.171	76.917	81.643
	1st month	83.480 ± 0.162	81.241	85.719
	2nd month	87.760 ± 0.161	85.563	89.984
	3rd month	90.880 ± 0.171	88.518	93.242
Placebo	Baseline	81.818 ± 0.182	79.299	84.337
	1st month	81.500 ± 0.172	79.114	83.886
	2nd month	79.636 ± 0.171	77.266	82.007
	3rd month	78.318 ± 0.182	75.800	80.836

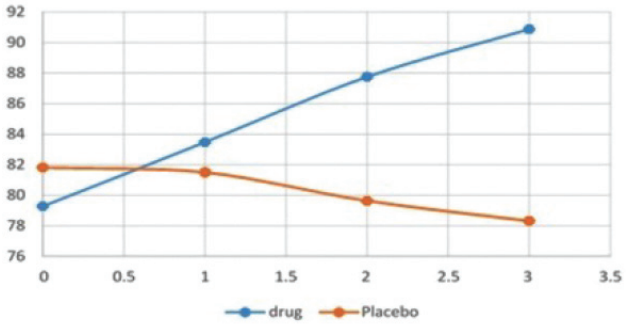

Fig. 2 **Physical quality-of-life score curve.**

between two groups was significant (Greenhouse-Geisser, *p*-value <0.001, *f*: 11630), and interaction difference between drug and placebo group in four levels was significant (*p*-value <0.001, *f*: 41.988).

Mean ± SD score of drug and placebo group and 95% confidence interval were shown in Table 3. Results showed that physical quality-of-life in the drug group was increased from baseline 5.29%, 10.69% and 14.63% at the end of 1st, 2nd and 3rd month respectively. While in placebo group, physical quality-of-life was decreased from baseline 0.38%, 2.66% and 12.83% respectively (Fig. 2).

For mental quality-of-life score in the cinnamon group increased more than placebo group. According to Mauchly's test, due to lack of sphericity, for comparison between levels and their interactions with drugs used Greenhouse-Geisser was used. The difference between two groups was significant (Greenhouse-Geisser, *p*-value <0.001, *f*: 14.805), and interaction difference between drug and placebo group in four levels was significant (*p*-value <0.001, *f*: 75.600).

Mean ± SD score of drug and placebo group and 95% confidence interval were shown in Table 4. Results showed that mental quality-of-life in the drug group was increased from baseline 14.37%, 31.31% and 48.88% at the end of 1st, 2nd and 3rd month respectively. While in placebo group, mental quality-of-life was decreased from baseline 2.15%, 8.77% and 16.97% respectively (Fig. 3).

For overall quality-of-life score in the cinnamon group increased more than placebo group. According to Mauchly's test, due to lack of sphericity, for comparison between levels and their interactions with drugs used Greenhouse–Geisser was used. The difference between two groups was significant (Greenhouse–Geisser, *p*-value <0.001, *f*: 20.622), and interaction difference between drug and placebo group in four levels was significant (*p*-value <0.001, *f*: 93.881).

Mean ± SD score of drug and placebo group and 95% confidence interval were shown in Table 5. Results showed that quality-of-life in the drug group was increased from

Table 4. **Mental quality-of-life score**

		Mean ± SD	95% Confidence interval	
			Down bound	Upper bound
Drug	Baseline	50.080 ± 0.312	45.751	54.409
	1st month	57.280 ± 0.257	53.721	60.839
	2nd month	65.760 ± 0.287	61.790	69.730
	3rd month	74.560 ± 0.281	70.675	78.445
Placebo	Baseline	54.909 ± 0.334	50.249	59.524
	1st month	53.727 ± 0.275	49.933	57.522
	2nd month	50.091 ± 0.306	45.859	54.323
	3rd month	45.591 ± 0.300	41.450	49.732

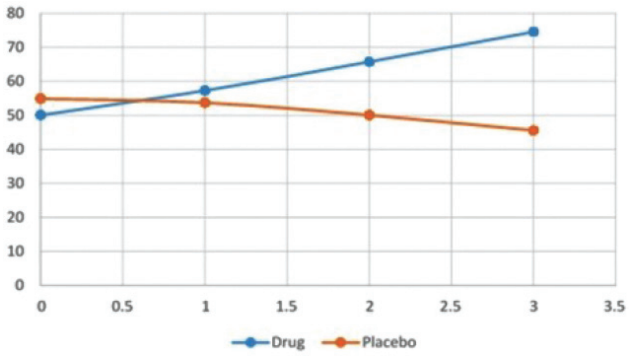

Fig. 3 **Mental quality-of-life score curve.**

Table 5. **Overall quality-of-life score**

		Mean ± SD	95% Confidence interval	
			Down bound	Upper bound
Drug	Baseline	141.76 ± 2.95	135.81	147.712
	1st month	152.68 ± 2.37	147.90	157.46
	2nd month	162.56 ± 2.45	157.63	167.48
	3rd month	173.52 ± 2.44	168.60	178.44
Placebo	Baseline	159.04 ± 3.15	152.70	165.39
	1st month	152.40 ± 2.53	147.31	147.50
	2nd month	145.81 ± 2.60	140.56	151.06
	3rd month	139.36 ± 2.60	134.122	144.60

baseline 8.81%, 18.67% and 27.89 at the end of 1st, 2nd and 3rd month respectively. While in placebo group, overall quality-of-life was decreased from baseline 1.09%, 5.12% and 9.37% respectively (Fig. 4).

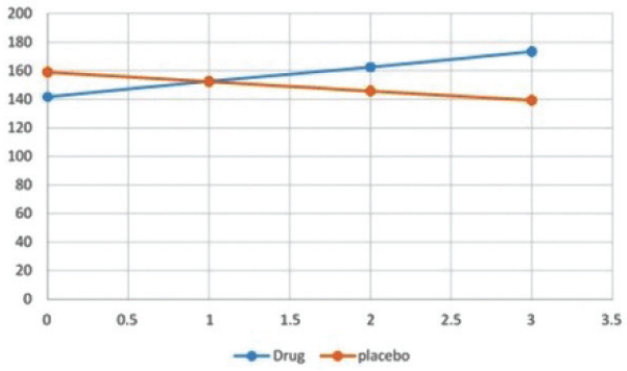

Fig. 4 **Overall quality-of-life score curve.**

Discussion

Although the etiology of MS is poorly understood, it is becoming clear that widespread inflammation, loss of regulatory T cells (Tregs), hyperactivity of autoimmune Th1 and Th17 cells, breakdown of blood–brain barrier and blood–spinal cord barrier, and loss of neuroprotective molecules in the CNS are critical for the manifestation of demyelinating pathology in MS.[20]

Sodium Benzoate (NaB) is one the direct metabolites of cinamic acid which is find in cinnamon. Human body could metabolize cinnamon to NaB. Studies showed that NaB effectively inhibited infiltration of monoulcer and demyelinated cells into spinal cord of experimental autoimmune encephalomyelitis (EAE), the animal model of MS, mice. Following NaB suppress the expression of pro-inflammatory molecules and normalized the expression of myelin in CNS. In addition, NaB showed that it could change differentiation of myelin basic protein-primed T cells from Th1 into Th2 mode. NaB increase the number of regulatory T cells and reduce the expression of various contact molecules. Thus, altogether this evidence showed that NaB in multiple steps modulate encephalitogenic T cells so it could be an important therapeutic agent in MS.[21] On the other hand, studies showed that cinnamon and its metabolite cinnamon increase neutropic factors (NF) in CNS. NaB is a FDA-approved drug against urea cycle disorder in human and increase the level of brain derived NF (BDNF) and neurotrophin-3 (NT-3) in CNS. Oral use of cinnamon increases the level of NaB and after that level of NF in CNS of mice. NaB induce activation of protein kinase A (PKA), so cAMP response elements binding (CREB) will be activated. Thus with oral use of cinnamon PKA activate and the level of phospho-CREB in mice CNS will be increased. This result shows that cinnamon and NaB has neurotropic property.[22,23] Increase and maintenance of regulatory T cells (Tregs) during inflammation process could have therapeutic effect in autoimmune disease. NaB increase Tregs and protect mice against EAE.[24,25]

Ajwain is evaluated for its anti-inflammatory effect. Both ethanolic and aqueous total extract of ajwain in animal models significantly show anti-inflammatory effect.[26] Antioxidant effect of ajwain is evaluated with hexachlorocyclohexane extract and showed that in animal model oral extract of ajwain reduce hepatotoxicity induce free radicals stress.[26,27] It is well defined that nitric oxide has an important role in inflammatory process and chronic disease such as MS. Nitric oxide toxicity increase when it react with superoxide radicals. *In vitro* studies show that aqueous and ethanolic extract of ajwain inhibited nitric oxide.[26,28] In addition ajwain seed oil is effective in neurologic pain.[27] Clinical trial shows that using ajwain product in curing neuropathy pain in MS patients was useful.[29]

In summary, we have demonstrated that this drug could improve quality-of-life and fatigue of MS patients through suggested mechanisms. Thus this drug may have therapeutic value in MS and other demyelinating conditions.

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Conflicts of Interest

None.

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