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Effect of grape seed on quality of life in multiple sclerosis patients

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Objective Multiple sclerosis (MS) is an inflammatory disease in which the myelin sheaths of the neural cells in the brain and the spinal cord are damaged. This injury affects the ability of parts of the nervous system that are responsible for communication and cause many physical and mental signs and symptoms. The grape seed which is scientifically called *Vitis vinifera* is the native plant in southern Europe and western Asia and its extract has strong antioxidants, anti-inflammatory and neuron and nervous system protection properties. Therefore, it is considered to control the free radicals and inflammation that contribute to the development and progression of MS.
Methods The effect of grape seed extract on the fatigue control in patients was investigated as a double-blinded design. About 66 patients, all treated with interferon, were randomly divided into two groups. The first group received placebo for the first month and the second group had grape seed capsules for 1 month. Fatigue was calculated based on multiple sclerosis quality of life-54 before and after the study. The results were analyzed by *t*-test to compare the mean in both groups and also the pair *t*-test was applied to compare the fatigue test score before and after the treatment in the groups.
Results The results showed that the use of grape seed capsules significantly altered the physical and mental activity of patients with MS.
Conclusion The existing MS drugs reduce the number of relapses, severity of disease and prevent disease progression. They have less effect on symptoms and improving performance and the quality of life along with side effects. Due to the absence of significant side effects of grape seed and its proper effect, it can be used to improve fatigue and physical and mental activity in patients.
Keywords grape seed, multiple sclerosis, fatigue, quality of life

Introduction

Multiple sclerosis (MS) is a relatively common disease. It is a chronic progressive disease of the nervous system that usually occurs in the third and fourth decades of life.[1] There is a clear difference in MS emergence between different populations and ethnic groups. The highest known prevalence (250 per 100,000 people) is common in the north of Scotland and more than 2 million people worldwide suffer from MS.[2]

Two pathological processes occur in MS. The first process is inflammation during which the body performs an autoimmune attack against the myelin sheaths of the neural fibers in the white matter of the central nervous system. These areas that have lost myelin are seen as plaque or lesions that the recovery of inflammation also improves the disease. The second process is neurodegenerative in which the nerve axon in the white matter of the brain is degraded which is irreversible in some cases. The collected data show that oxidative stress plays an important role in the development of MS. Active oxygen species produce oxidative stress. Their excessive production in the body causes various damages including loss of myelin and damage to axons and consequently MS. Oxidative stress causes more damage in CNS cells with weak antioxidant defense. Anti-oxidant therapy can theoretically and practically prevent the spread of tissue damage and increase tissue survival.[3] Over the past two decades the effectiveness of several immune system regulating and suppressing therapies have been proven to effective in controlling MS. Most of these drugs affect the inflammatory phase of the disease, and reduce the number of relapse attacks and disability compared with the placebo.[4] The phenolic compounds in the grape (seed and pulp) have a strong free radical inhibitory activity.[5]

Fatigue is one of the most common and debilitating symptom of multiple sclerosis the main cause of which is still unknown. However, it is believed that the destruction of neurons is the central cause of fatigue and the reduction of physical activity as an environmental factor of fatigue. However, treatments are usually ineffective due to the complex nature of fatigue in patients with multiple sclerosis. Fatigue treatment methods cannot be fully effective either pharmaceutically (amantadine, pamulin, modafinil) or non-pharmaceutically in patients with multiple sclerosis.[6]

The grape seed with the scientific name *Vitis vinifera* is a native plant of southern Europe and western Asia. Grape seed and skin contain many active compounds, including flavonoids, polyphenols, anthocyanins and proanthocyanidins, and acetylbene compounds like resveratrol.[7,8] Various studies show that grape seed extract has anti-oxidant, anti-inflammatory and antimicrobial activity effects as well as cardiovascular and liver protective effects and protection of the neurons and the nervous system.[9] The evidence show that proanthocyanidins in the grape seed can suppress immunosuppression caused by ultraviolet radiation which is a risk factor for skin cancer and induce interleukin-12 and stimulates the T-cytotoxic cells and DNA reconstruction.[10] The grape seed extract reduces the free radicals produced by lipid peroxidation in the central nervous system in old rats and hypoxic ischemic brain injury in neonatal rats.[11,12]

Smith and Lassmann[13] proved that nitric oxide as a potential intermediary causes the initial demyelination of microglia cells. Increased nitric oxide has a direct relationship with the incidence of autoimmune inflammatory diseases, including multiple sclerosis, rheumatoid arthritis,

insulin-dependent diabetes and inflammatory bowel disease.[14] Therefore, one of the important treatments for multiple sclerosis is to use nitric oxide synthesis inhibitor. The resveratrol in the grape seed has strong anti-inflammatory and nitric oxide inhibition effects.[15]

Regarding the key role of free radicals in the development of MS disease and the antioxidant, anti-inflammatory and immune system regulation effects of grape seed extract, its usage is considered to control fatigue in patients with multiple sclerosis.[16,17]

Materials and Methods

This study was a double-blind, randomized, single centered and placebo-controlled research.

Patient selection

At first, 100 patients with MS disease who were clinically diagnosed by McDonald Criteria and referred to the MS association in Khuzestan province were selected.[18]

Among these patients the ones who did not have relapse during the last 6 weeks included in the study and the patients who had stroke and other neurological diseases, such as depression, diabetes and other autoimmune diseases such as lupus and those with new MS attacks as well as patients who had taken corticosteroid therapy up to 6 weeks before the study or pregnant or breastfeeding were excluded.

In this study, 70 patients were selected and 30 patients were excluded (10 patients with stroke, 11 with depression and 9 had received corticosteroids) were excluded from the study.

All participants received written information about the study and after this study they were requested to sign a written consent form.

Drug preparation

In this study, red grapes were first purchased from reputable centers and seeds were separated manually, and then seeds were extracted by 70% ethanol by maceration method. Accordingly 70% ethanol solvent (1000 ml) was poured on the plant powder (100 g). It was then kept at the laboratory for 48 h and then shaken for 2 h. The extract was then filtered, concentrated with rotary evaporator and then completely dried by freeze dryer and kept in a freezer (−20°C) until the preparation of the product.[19]

The capsules were formulated and prepared by the Medicinal Plants Research center of Ahvaz Jundishapur University of Medical Sciences. After preparing the desired formulation, the prepared powder was placed into the capsule shell by manually filling machine and packed in 60 capsules and labeled with information required by patients (such as effective ingredients, usage, warnings, etc.). The placebo group used the formulation without the extract and the capsules were uniform and packed identically. Packages were encoded at the Medicinal Herbs Research Center and were not unpacked until the end of the study.

Treatment procedure

The 60 patients were randomly separated into two groups of treatment and placebo according to a balanced 1:1 randomization in which a computer-generated randomization table was applied (each group included 30 persons). The treatment group received a capsule containing 450 mg powder of grape seed extract (plus excipients 50 mg) twice a day for 1 month while placebo group received a capsule of the same size without extract (Drug preparation section).

The study was approved by the Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (registration number: IR. ajums. REC.1396.326) and it was registered in the Iranian Registry of Clinical Trials (IRCT). It is available at www.irct.ir under registration number: IRCT201708218013N1.

Measurement tools

Patients' fatigue was calculated based on Multiple Sclerosis Quality of Life-54 (MSQOL-54) before the start of the study. After a month, MSQOL-54 was measured in each group again. Then MSQOL-54 scales and physical and mental health composite score were compared in both groups.[20] Based on the rating of physical health factors, role limitation due to emotional problem, emotional well-being, energy, health perception, social function, cognitive function, health distress, sexual function and change in health the total score was calculated.

Statistical analysis

To describe the data, mean and standard deviation were used for quantitative variables. The *t*-test was used to compare the mean in two groups and the pair *t*-test was applied to compare the pre- and post-fatigue score between the groups and a *P*-value less than 0.05 was considered as the level of significant difference in all tests.

Results

Patient demographics

The results of the demographic data of patients who continued until the end of the trial are presented in Table 1.

Finally, 66 patients (in the placebo and treatment group) were selected. Patients were within the age range of 32.26 ± 7.12. The mean age in the treatment and placebo groups was 31.05 ± 6.25 and 33.47 ± 8.56.

Based on the patient's statements mean duration of the disease in the treatment and placebo groups was 4.05 ± 1.25 and 4.56 ± 2.12.

There was no difference between the placebo and treatment group in terms of demographic data (P <0.05).

Results of treatment efficacy

The baseline of physical and mental scores (base on MSQOL-54) of the two groups are shown in Tables 2 and 3. There was no significant difference between the two groups at baseline (P > 0.05).

Discussion

So far no definitive treatment is discovered for MS. Side effects of current commonly used drugs, such as interferon beta, glatiramer acetate, and mitoxantrone have also led researchers to seek drugs with less side effects. Although most patients are hopeful to have a natural or near normal life, their quality of life is affected by their reduced function.[20] The disease modifying therapies reduce the number of relapses, severity of disease and prevent disease progression but have less effect on symptoms and performance and quality of life

Table 1. **Demographic information of patients who completed the trial**

		Medicine (patient)	Placebo (patient)
Gender	Male	10	11
	Female	23	22
Marital status	Single	11	9
	Married	22	23
	Divorced	0	1
Education	Illiterate	1	2
	High school/ primary school	18	11
	High school diploma	0	3
	Associate's degree	2	3
	Bachelor's degree	9	7
	Master's degree	0	3
Job	Housewife	17	12
	Employee	5	8
	Unemployed	4	3
	Freelance	4	4
	Student	0	2

improvement. Therefore, finding new treatments to reduce the symptoms of the disease is very important.[21] Today, research on medicinal plants has attracted attention to identify new and safe drug molecules by screening the existing active compounds.[22] But limited plant compounds have been investigated for therapeutic purposes. Saffaron (*Crocus sativus*) is among the plants that has experimental autoimmune encephalomyelitis symptoms (experimental model of MS) in mice by inhibiting oxidative stress and leukocyte penetration into the central nervous system and thus has the potential for use in the treatment of MS.[23] Another drug for MS treatment on which many clinical trials have been done so far is Cannnabis that has a positive effect on detrusor over activity, spasticity, trembling and neuropathic pain in patients with MS.[24–26] However, it is not a good drug due to the side effects of cannabis, such as addiction, drowsiness, depression, anxiety, and decreased immune function.[26] The grape seed is a natural drug with strong anti-inflammatory and antioxidant effects and also prevents peroxidation in the central nervous system and inhibits harmful free radicals such as hydroxyl and superoxide. The grape seed has regulatory effects on the catalase, superoxide reductase and peroxidase enzymes. It reduces the inflammatory cytokines such as alpha-TNF, interferon gamma and interleukin 1 and 6 that cause the onset of inflammation in MS patients and increases anti-inflammatory cytokines such as IL-4, IL-10 and TGF-beta (transforming growth factor beta) involved in the phase of disease improvement.[27–29] Many compounds have been identified in grape seed the most important of which are proanthocyanidins, anthocyanins and resveratrol.[9]

Table 2. **Comparison of the mean of the measured physical sub-scales in the two groups. The results are expressed as mean ± SD, and $P < 0.05$ is acceptable**

Sub-scores	Treatment		Placebo	
	Before	After	Before	After
Physical function	10.77 ± 1.26	12.63 ± 2.38*	10.92 ± 1.25	12.55 ± 2.48*
Health perceptions	11.01 ± 1.24	11.56 ± 1.89	10.19 ± 1.99	10.37 ± 1.01
Energy/fatigue	5.78 ± 0.5	7.63 ± +0.96*	6.23 ± 0.16	6.74 ± 0.53
Role limitations-physical	6.52 ± 0.4	8.27 ± 2.25*	7.20 ± 0.63	6.91 ± 0.68
Pain	7.63 ± 0.77	8.46 ± 0.84*	7.55 ± 0.67	7.67 ± 0.91
Sexual function	4.26 ± 0.50	4.72 ± 0.44	4.10 ± 0.62	4.24 ± 0. 94
Social function	8.08 ± 1.08	9.45 ± 1.01*	8.70 ± 0.90	9.22 ± 1.05
Health distress	4.97 ± 0.44	7.31 ± 0.94*	6.48 ± 0.10	6.68 ± 0.8
Total physical score	59.72 ± 10.34	71.05 ± 9.10*	62.53 ± 9.66	65.54 ± 10.01

Table 3. **Comparison of the mean of the measured mental sub-scales in the two groups. The results are expressed as mean ± SD, and $P < 0.05$ is acceptable**

Sub-scores	Treatment		Placebo	
	Before	After	Before	After
Health distress	6.33 ± 0.87	9.31 ± 0.74*	8.25 ± 0.94	11.48 ± 1.76
Overall quality of life	5.12 ± 0.45	6.73 ± 0.80*	6.47 ± 0.85	6.66 ± 0.92
Emotional well-being	15.73 ± 1.76	20.37 ± 2.19*	16.90 ± 1.65	17.06 ± 1.39
Role limitations-mental	13.21 ± 1.46	14.25 ± +1.93	12.99 ± 1.67	14.32 ± 1.27
Cognitive function	8.80 ± 0.95	9.55 ± 0.57	8.63 ± 0. 46	8.41 ± 0.44
Total mental score	48.73 ± 4.11	61.27 ± 6.13*	53.26 ± 5.86	55.31 ± 4.09

Resveratrol is a very valuable compound in preventing inflammatory and neurodegenerative diseases. Part of the antioxidant effects of the grape seed is associated to resveratrol in addition to the oligomeric proanthocyanidins.[30–32]

Resveratrol plays a significant role in neuronal differentiation by inhibiting SIRT1 and SIRT3 (32). Resveratrol effective mechanism is probably due to transcriptional regulation of the NF-κB proteins.[33] Resveratrol can also affect estrogen and vitamin D receptors in the brain.[34]

According to statistical tests, there is a significant difference in the total mental and physical score of patients in the grape seed group before and after intervention. There is also a significant difference between the sub scores of the grape seed group before and after intervention in each subscale. Therefore, according to these results, the positive effects of grape seed on improving the quality of life and the subscales physical function, energy/fatigue, role limitations-physical, pain, health distress, physical health composite, health distress mental, overall quality of life, emotional well-being, mental health composite, social function are proven.

According to the results in the placebo group, there is no significant difference in the total score of the patients before and after the intervention which indicates that the increase in the total score in this group has not been effective. Also, patients do not differ significantly before and after intervention in all subscales and all of these results indicate neutrality placebo on patients.

Also, the change in the total mental and physical score of the questionnaire between the grape seed and placebo groups is statistically significant before and after the intervention. Among the sub-scales of intervention the change in grape seed group sub score is not significant in physical activity, role limitations-mental and cognitive activity but the change in other sub-scores in the grape group is significant compared to the placebo.

Conclusion

This study suggests that grape seed can improve fatigue in MS patients. Due to the absence of significant side effect for grape seed and its proper effect, it can be used to improve fatigue in patients with MS. Given the fact that the questionnaire is related to the quality of life, the grape seed capsule can be added as a complementary treatment to the usual treatment of these patients to improve their quality of life.

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Conflict of Interest

None.

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