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The Effects of *Glycyrrhiza glabra* L. extract use with aerobic training on inflammatory factors and cognitive state in elderly with mild cognitive impairment

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ABSTRACT

Introduction: This study was aimed to investigate the effect of a 12-week aerobic training protocol and treatment with *Glycyrrhiza glabra* extract on serum interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) levels and cognitive state in the elderly with mild cognitive impairment (MCI).

Methods: Forty people who attained scores 21-25 on the Mini–Mental State Examination (MMSE) were selected by purposive and convenience sampling and randomly assigned to four groups of 10 each: training, *G. glabra*-treated, training+*G. glabra*-treated, and placebo. All interventions were conducted within 12 weeks. Aerobic training protocol consisted of an 8-minute running at an intensity of 75%-85% maximum heart rate in the first session. One minute was added to the duration of running per two sessions so that after 12 weeks, the duration of running in two last sessions was 26 minutes. *G. glabra* extract was orally administered in 200 mg/kg body weight capsules per day.

Results: IL-1β and TNF-α levels significantly decreased in training and *G. glabra*-treated groups but their decrease were more marked in training+*G. glabra*-treated group ($P<0.05$). Cognitive state in three intervention groups significantly improved compared to placebo group, and this improvement was more marked in training+*G. glabra*-treated group ($P<0.05$).

Conclusion: Consumption of *G. glabra* extract with aerobic training for 12 weeks can slow down or stop the progression of MCI in the elderly through improving their cognitive states probably via decreasing inflammatory factors.

Implication for health policy/practice/research/medical education:
The elderly people with mild cognitive impairment (MCI) should make attempt to improve their cognitive states to prevent intensification of this impairment through decreasing inflammatory factors via doing aerobic exercise and consuming *Glycyrrhiza glabra*.

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Introduction

The population aged over 60 years in Iran will reach around 10 million in 2020 and over 26 million in 2050 that will be 23% of the total population (1). Cognitive impairment represents one of the common disorders in the elderly such that around 35% of them present with it at different severities. Alzheimer disease is the progressive stage of this disorder (2). In cognitive impairment, attention, memory, language, orientation, actions, executive performance, judgement, and problem-solving are impaired mostly due to brain memory loss (3). The normal functioning of the various brain systems is responsible for cognitive function, and cognitive impairments arise as the age increases and the elements involved in these systems develop. In

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addition, different inflammatory processes and cytokines contribute fundamentally to the pathogenesis of Alzheimer disease (4). The expression of most cytokines in normal tissues is normal but in neurodegenerative diseases, their expression increases. For example, the expression of the pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α) increases in neurodegenerative diseases (5,6). In this regard, it has been reported that the immunity profile of patients with mild cognitive impairment (MCI) undergoes certain variations (7).

It is essential to take into account the interventions to prevent Alzheimer disease through slowing down or even inversing the progression of MCI; and measuring inflammatory factors following such intervention can lead to better explaining the observed effects. Consumption of medicinal plants is one of such interventions that have attracted attention (8,9). Among these plants, licorice, botanically referred to as *Glycyrrhiza glabra* L., is a perennial plant from family Fabaceae which is considered important worldwide due to pharmaceutical and nutritional compounds in its root and rhizome, and therefore has attracted the attention of pharmaceutical, food, and even tobacco industries (10). *G. glabra* root has several compounds such as different sugars, flavonoids, sterols, amino acids, gum, starch, essential oils, and saponins. The most important saponin (pentacyclic triterpene) of *G. glabra* is glycyrrhizic acid or glycyrrhizin that is made up of a glucuronic acid unit and a glycerotinic acid molecule (aglycone) (10). The presence of hypolipidemic compounds and flavonoids in *G. glabra* has been reported to be associated with its potent antioxidant activity (11). In addition, this plant has been reported to exert anti-inflammatory effect (12).

However, to the best of our knowledge, no study has yet been conducted on the effects of this plant on MCI in the elderly. On the other hand, exercise training, as an inexpensive therapeutic approach, can have optimal effects on cognitive function, which can be due to decreased inflammatory factors because cross-sectional investigations have demonstrated that active people have better cognitive function compared to inactive ones (13). Training has also been reported to induce anti-inflammatory effect (14).

Because MCI is one of the common problems in the elderly and represents the onset of a course that leads to Alzheimer disease and death, and no definite treatment has yet been suggested for Alzheimer disease, it is essential to use preventive interventions that slow down, stop, or even inverse the course of MCI. Besides that, the use of medicinal plants is particularly important because they are natural and lead to comparatively fewer side effects (9). Because the roles of exercise and physical activity in improving cognitive functions (13) and inflammatory factors (14) have been confirmed, it is recommended to investigate the combined effects of training and plants on cognitive functions. However, as far as we searched, no study has yet been conducted on the combined effect of aerobic training and *G. glabra* extract on the inflammatory factors and the cognitive states in the elderly with MCI. The aim of the current study was to investigate the effect of a 12-week aerobic training protocol and treatment with *Glycyrrhiza glabra* extract on the serum IL-1β and TNF-α levels and cognitive states in the elderly with MCI.

Materials and Methods

This semi-experimental study with pretest-posttest design was conducted on four groups. Eighty-seven people aged 60-70 years volunteered to participate in the study after advertising our study among different elderly populations living in Shiraz County. Then, the Mini–Mental State Examination (MMSE) was administered to volunteers. The MMSE, developed by Folstein et al in 1975, consists of 11 subscales: Orientation to time and place, registration, attention and calculation, memory, language, executive skills, reading, writing, and doing fine works (15). The subjects that do not have any problems in these subscales are given the score 30; the scores <20 represent in-depth cognitive disabilities and the scores 20-25 represent partial cognitive damage. The reliability (Cronbach alpha) of the MMSE has been reported 0.87 with sensitivity and specificity of 90% and 84%, respectively (16). Forty volunteers who attained the MMSE scores 21-25, with the average age 68.125 ± 3.708 years, the average height 174.55 ± 6.118 cm, the average weight 78.15 ± 5.176 kg, and the average body mass index (BMI) of 25.666 ± 0.599 kg/m^2 were enrolled in the study and randomly assigned to four groups of 10 each: Training, *G. glabra*-treated, training + *G. glabra*-treated, and placebo.

Inclusion criteria were being male, being over 60 years, attending at least 90% of intervention sessions, being examined by a physician for confirming general health to do aerobic training, attaining the MMSE scores 21-25 and the scores <10 on the Geriatric Depression Scale, and not being under pharmacotherapy for cognitive impairment. Exclusion criteria were not attending over 10% of intervention sessions, being dependent to do daily routines, suffering from other physical or psychiatric illnesses, taking medicines, not providing consent to participate in the study, and being under treatment for cognitive impairment. All interventions were conducted within 12 weeks. Aerobic training protocol consisted of 8-minute running at an intensity of 75-85% maximum heart rate in the first session. One minute was added to the duration of running per two sessions so that after 12 weeks, the duration of running in two last sessions was 26 minutes. *G. glabra* extract was orally administered in 200 mg/kg body weight capsules per day.

The final 5 minutes of each session was specified to cool-down. Five milliliters of arm venous blood was taken 24 hours before and 48 hours after interventions after 12-

hour fasting. To isolate serum, blood samples were left to clot and then centrifuged at 2000 rpm for 10 minutes. The resulting samples were stored at -20°C till measurement of the variables of interest. Serum IL-1β and TNF-α levels were measured with the sensitivity of 8 and 2 pg/mL, respectively, using a kit (Dialcone, France). Cognitive states were measured using the MMSE. Data were described by average and standard deviation. Inter- and intra-subject mixed analysis of variance (ANOVA) was used to investigate inter- and intra-group changes.

In addition, independent one-way ANOVA and Tukey tests were used to compare the changes in the variables among the groups. To investigate the association between the changes in the variables, Pearson correlation coefficient was used to investigate the association between the changes in the variables. The level of significance (P) was considered ≤0.05. Data analysis was conducted in SPSS 16.

Results

Descriptive data, the results of inter- and intra-subject mixed ANOVA and Tukey test, and Pearson correlation coefficients are shown in Tables 1-4, respectively.

There were significant differences in the changes in weight, BMI, cognitive state, IL-1β and TNF-α levels among the four groups over time ($P=0.001$). Weight and BMI in training+*G. glabra*-treated group and training group significantly decreased compared to *G. glabra*-treated group and control group ($P<0.05$). There were not any significant differences in the changes in weight and BMI between training group and training+*G. glabra*-treated group ($P>0.05$) as well as between *G. glabra*-treated group and control group ($P>0.05$).

Cognitive state improved in the three intervention groups significantly compared to control group ($P<0.05$). Improvement of cognitive state was significantly more marked in training+*G. glabra*-treated group than training group and *G. glabra*-treated group ($P<0.05$), but the changes in the cognitive state in training group and *G. glabra*-treated group were not significantly different ($P>0.05$). The levels of IL-1β and TNF-α in the three intervention groups significantly decreased compared

Table 1. The mean (standard deviation) values of variables before and after interventions

Variables	Groups	Before	After
Weight (kg)	Training +*G. glabra*-treated	77.70 ± 4.547	75.30 ± 4.398
	Training	77.50 ± 3.628	75.60 ± 3.835
	G. glabra-treated	77 ± 5.537	76.90 ± 5.762
	Placebo	80.40 ± 6.619	80.40 ± 6.397
BMI (kg/m^2)	Training +*G. glabra*-treated	25.664 ± 0.432	24.877 ± 0.725
	Training	25.748 ± 0.429	25.116 ± 0.585
	G. glabra-treated	25.348 ± 0.775	25.306 ± 0.623
	Placebo	25.907 ± 0.631	25.935 ± 0.808
Cognitive State (MMSE)	Training +*G. glabra*-treated	22.20 ± 1.549	25.20 ± 1.316
	Training	22.70 ± 1.636	24.40 ± 1.429
	G. glabra-treated	22.50 ± 1.354	24.10 ± 0.994
	Placebo	24.30 ± 0.948	24.20 ± 0.632
TNF-α (pg/ mL)	Training +*G. glabra*-treated	8.516 ± 1.204	5.926 ± 0.691
	Training	7.863 ± 1.341	6.723 ± 0.930
	G. glabra-treated	9.224 ± 1.285	8.114 ± 1.268
	Placebo	7.572 ± 1.612	7.897 ± 1.466
IL-1β (pg/mL)	Training +*G. glabra*-treated	3.561 ± 0.453	2.270 ± 0.295
	Training	3.344 ± 0.770	2.778 ± 0.432
	G. glabra-treated	3.598 ± 0.712	3.023 ± 0.620
	Placebo	3.345 ± 0.721	3.514 ± 0.635

Table 2. The results of inter- and intra-subject mixed ANOVA regarding the comparison of variables among 4 groups

Variables	*F* value	*P* value	Effect size
Weight	8.76	0.001 *	0.42
BMI	8.59	0.001 *	0.41
Cognitive State	21.24	0.001 *	0.64
TNF-α	11.33	0.001 *	0.49
IL-1β	10.96	0.001 *	0.48

*Significant at 0.05.

Table 3. The results of Tukey test regarding the points of significant difference

Pair wise comparison	Weight	BMI	Cognitive State	TNF-α	IL-1β
Training+*G. glabra*-treated/training	0.83	0.86	0.010 *	0.031 *	0.035 *
Training+*G. glabra*-treated/*G. glabra*-treated	0.002 *	0.003 *	0.005 *	0.027 *	0.038 *
Training+*G. glabra*-treated/placebo	0.001 *	0.001 *	0.001 *	0.001 *	0.001 *
Training/*G. glabra*-treated	0.021 *	0.026 *	0.99	1	1
Training/placebo	0.013 *	0.011 *	0.001 *	0.029 *	0.032 *
G. glabra-treated/placebo	0.99	0.98	0.001 *	0.033 *	0.029 *

*Significant at 0.05.

Table 4. Pearson correlation coefficients to examine the association between the changes in variables

Variables	Weight	BMI	Cognitive state	TNF-α	IL-1β
Weight	-	r = 0.99, *P* = 0.001 *	r = - 0.44, *P* = 0.004 *	r = 0.43, *P* = 0.005 *	r = 0.30, *P* = 0.054
BMI	r = 0.99, p = 0.001 *	-	r = - 0.44, *P* = 0.004 *	r = 0.44, *P* = 0.004 *	r = 0.31, *P* = 0.051
Cognitive state	r = - 0.44, p = 0.004 *	r = - 0.44, *P* = 0.004 *	-	r = - 0.66, *P* = 0.001 *	r = - 0.56, *P* = 0.001 *
TNF-α	r = 0.43, p = 0.005 *	r = 0.44, *P* = 0.004 *	r = - 0.66, *P* = 0.001 *	-	r = 0.52, *P* = 0.001 *
IL-1β	r = 0.30, p = 0.054	r = 0.31, *P* = 0.051	r = - 0.56, *P* = 0.001 *	r = 0.52, *P* = 0.001 *	-

*Significant at 0.05.

to control group ($P<0.05$). These levels in training+*G. glabra*-treated group significantly decreased compared to training group and *G. glabra*-treated group ($P<0.05$), but the changes in IL-1β and TNF-α levels in training group and *G. glabra*-treated group were not significantly different ($P>0.05$).

Results indicated that the changes in weight and BMI were significantly and inversely correlated with changes in cognitive state ($P<0.05$), and were significantly and directly correlated with changes in TNF-α levels ($P<0.05$). The changes in weight and BMI were not significantly associated with the changes in serum IL-1β levels ($P>0.05$). In addition, the cognitive state of the elderly improved significantly with decreasing their serum TNF-α levels ($r=-0.66$, $P=0.001$) and IL-1β serum levels ($r=-0.56$, $P=0.001$)

Discussion

After the interventions, cognitive state improved significantly and inflammatory factors (IL-1β and TNF-α) decreased significantly in training group and *G. glabra*-treated group, but the corresponding changes in training+*G. glabra*-treated group were more marked. Besides that, results indicated that in the elderly with MCI, cognitive state improved and TNF-α levels decreased with decreasing weight and BMI. The current study also demonstrated that cognitive state in these elderly improved with decreasing IL-1β and TNF-α, and this association was more marked for TNF-α. Accordingly, although such associations cannot be considered causal relationships, the significant association between the changes in cognitive state and the variations in inflammatory factors may be explained by the role that decreased inflammatory factors, following doing aerobic training and using *G. glabra* extract, play in improving the cognitive states of the elderly with MCI. Indeed, doing aerobic training and using *G. glabra* extract prevent MCI from progressing toward more advanced cognitive impairments and Alzheimer disease through preventing its progression. However, this argument should be further investigated

The effect of *G. glabra* on inflammatory factors has already been studied. Jung et al studied the effect of this plant on alcohol-induced fatty liver due to inflammation and oxidative stress in mouse model. To achieve this purpose, they treated mice with an alcohol-containing diet with and without *G. glabra* extract. Consumption of alcohol led to increase in TNF-α levels and fat accumulation, but consumption of *G. glabra* led to decrease in the levels of triglyceride and TNF-α. Taken together, the study of Jung et al that consumption of *G. glabra* resulted in improvement of kidney damage due to decreased inflammation (17).

Nakamura et al studied the effect of glycyrrhizin on the inflammatory factors macrophage inflammatory protein, TNF-α, interleukin 6 (IL-6), and interferon gamma due to fungal infection, and glycyrrhizin caused decrease in inflammation in fungal infection (18). Studying the anti-inflammatory effects of *G. glabra*, Yu et al measured IL-6, IL-1β, and TNF-α, and observed that *G. glabra* and its three bioactive compounds could be used for treating inflammation-associated disorders such as hepatic oxidative stress and hepatic inflammation (19). Li et al also reported that *G. glabra* caused decrease in the levels of lL-6, IL-1β, and TNF-α (20). The study of Yu et al showed that *G. glabra* extract caused decrease in the levels of the inflammatory factors cyclooxygenase-2 (COX-2), interleukin 1 (IL-1), lL-6, IL-1β, and TNF-α in inflammation-induced kidney damage while the expression of lL-6, IL-1β, and TNF-α decreased (19). In

addition, Yang et al reported that the consumption of *G. glabra* root led to down-regulation of the gene expression of COX-2, IL-6, and IL-1β (21).

Overall, studies have demonstrated that *G. glabra* exerts anti-inflammatory effect (22-25). It has even been reported that this plant can be used for treating inflammation-associated disorders including kidney damage (19,26). Farag et al argued that *G. glabra* is a popular plant-based supplement for treating chronic inflammatory diseases that plays role in decreasing inflammation due to different active compounds including glycyrrhizin (27). Consistently, Bernela et al investigated the pharmaceutical properties of glycyrrhizic acid, a *G. glabra*-derived saponin, and demonstrated that it has anti-inflammatory properties (28). Wang et al also reported the anti-inflammatory effects of this compound (29). The antioxidant and anti-inflammatory effects of *G. glabra*-derived glycyrrhizic acid have been confirmed (29). In this regard, the anti-inflammatory effects of *G. glabra*-derived have been studied in vivo.

Results showed that this compound caused decrease in the inflammatory factors IL-6, IL-1β, and TNF-α (30). Maurya et al argued that glycerrhizic acid is the main factor for anti-inflammatory properties of *G. glabra* (31). In agreement with available evidence, Chakravarthi and Avadhani studied the effects of *G. glabra* root on memory and learning in 1-month and adult male rats. Aqueous *G. glabra* root extract was administered at 75, 150, 225, and 300 mg/kg of body weight (BW) concentrations for 6 weeks. Results showed that the treatment with this extract led to a significant improvement of memory, and in 150 and 225 mg/kg BW, significant improvement of memory and learning. Chakravarthi and Avadhani concluded that these findings are probably due to the anti-inflammatory effects of *G. glabra* (32).

Consistent with our study, Farinha et al studied the levels of TNF-α, IL-1β, and IL-23 in the women without training before and after 12-week treadmill training and without any change in diet, and observed that the aerobic training course caused significant decrease in serum TNF-α and IL-1β levels (33). However, Isanejad et al reported that 8-week endurance training led to significant increase in IL-1β and significant decrease in TNF-α (34). Knudsen and Pedersen studied the effect of training on the inflammatory factors in type 2 diabetes patients, and found that training caused significant increase in IL-6 that led to anti-inflammatory effects through inhibiting TNF-α, stimulating IL-1 receptor antagonist, and therefore restricting IL-1β signaling (14). In our study, aerobic training led to both decrease in the inflammatory factors and improvement of cognitive state. Consistently, Miller et al reported that cognitive state and physical activity were significantly and directly correlated (35), which can be due to decreased oxidative stress and inflammation, increased angiogenesis, secretion of neurotrophins and catecholamines, and neurogenesis especially in the hippocampus (36).

To date, no study has yet been conducted on the combined effects of *G. glabra* and training on inflammatory factors and cognitive state especially in the elderly with MCI, and therefore it is difficult to interpret our evidence with reference to previous findings. Altogether, according to the findings of our study, the consumption of *G. glabra* alongside aerobic training, can help decrease inflammatory factors and improve cognitive state in the elderly with MCI. However, the current study was first to investigate this issue and additional studies are needed.

Conclusion

Probably, both aerobic training and consumption of *G. glabra* extract can slow down and even stop the progression of MCI in the elderly through improving cognitive state via decreasing inflammatory factors. It seems that combining these two interventions leads to more efficient prevention of MCI progression. It is likely that decreased inflammation plays a significant role in this regard, but other mediators should be investigated in additional studies.

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Authors' contributions

MAK contributed to data collection and manuscript drafting, MP revised and copyedited the manuscript, and MAA made necessary corrections to the methodology especially data analysis. All read and confirmed the final version of the manuscript for publication.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

The study was confirmed by the Ethical Committee of the university and the ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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