The effects of aerobic exercise with lavender essence use on cognitive state and serum brain-derived neurotrophic factor levels in elderly with mild cognitive impairment

Mohammad-Ali Kohanpour[1], Maghsoud Peeri[2*], Mohammad-Ali Azarbayjani[2]

[1]PhD Candidate, Department of Exercise Physiology, Islamic Azad University, Central Tehran Branch, Iran
[2]Professor, Department of Exercise Physiology, Islamic Azad University, Central Tehran Branch, Iran

A B S T R A C T

Introduction: The aim of this study was to investigate the effects of 12-week aerobic exercise and lavender essence on cognitive states and brain-derived neurotrophic factor (BDNF) levels of elderly with mild cognitive impairment (MCI).
Methods: In this clinical study, 40 elderly whose scores for mini–mental state examination (MMSE) ranged 21 to 25 were purposively selected by simple sampling. They were randomly divided into 4 equal groups: aerobic exercise, lavender extract, aerobic-lavender. and placebo. They underwent their respective treatments for 12 weeks. The aerobic exercise consisted of 8-minute running session with intensity of 75%-85% HRR Max for the first session. One minute was added to the running span after each 2 sessions. Accordingly, the running span reached 26 minutes at the end of the 12-week exercise period. To conduct treatment with lavender, 2 drops of lavender essence were administered twice a day. Before and after the treatments, cognitive state was measured and blood samples collected to measure BDNF.
Results: BDNF levels of the exercise and exercise + lavender groups increased significantly compared to those of the other 2 groups ($P < 0.05$). In addition, the cognitive states of the 3 intervention groups increased significantly compared to that of the placebo group ($P < 0.05$).
Conclusion: Combination of 12-week aerobic exercise and lavender may decelerate or probably halt the progressive process of the impairment via improving the cognitive state in elderly with MCI.

Introduction

The population of over 60-year-old people of Iran will reach around 10 million up to 2020 and even will exceed 26 million (23% of the whole population) up to 2050 (1). Cognitive impairment is one of the common difficulties of the elderly such that around 35% of the elderly people suffer from various levels of cognitive impairment. Alzheimer disease is the progressive stage of cognitive impairment (2). Paying attention, recalling, orientation, actions, executive function, judgment, and problem solving become difficult due to cognitive impairment. Memory loss is the main cause of cognitive impairment

(3). The normal functions of different systems of the brain are required for accurate cognitive performance. Cognitive impairments occur due to aging and depletion of the contributing factors in those systems. Hence, some interventions for progressive deceleration or even reverse of cognitive impairment seem essential.
Using herbs is one of the interventions that has attracted the attention of researchers in the recent years (4). Lavender is a shrub-like perennial plant with a height of about one meter and rectangular-shaped stalks that gradually become woody toward the lower part of the stem. This plant has pointed leaves that are placed on

*Corresponding author: Maghsoud Peeri, Faculty of Physical Education and Exercise Sciences, Central Tehran Branch of Islamic Azad University, Iran Zamin Blvd., Shahrak-E Gharb, Tehran, Iran. Tel: (+98) 912 112 44 34,
Email: m.peeri@iauctb.ac.ir

the stems in a bilateral manner. Volatile oil, flavonoids, tannins, coumarins, potassium, and calcium are the most prominent pharmaceutical components of lavender. Lavender is used in pharmaceutical products due to its medicinal properties including tranquilizing, anti-neuralgia, anti-depression, and anti-anxiety activities in the traditional medicine. In addition, its extract can serve as an anti-inflammatory one with inhibitory effects against acetylcholinesterase (AChE) to treat Alzheimer disease (5). However, no research has yet investigated the effects of lavender on elderly with mild cognitive impairment (MCI). Besides that, exercise (as an inexpensive therapeutic approach) can cause optimal effects on cognitive performance through neurotrophic factors (NTFs). Juncture studies have shown that active persons exhibit superior cognitive performance over their inactive peers (6). It has been suggested that use of antioxidants increases the effect of exercise. Measurement of the relevant post-intervention indices of neurological and cognitive states can help understand the effects of exercise and herbal supplements better. Accordingly, brain-derived neurotrophic factor (BDNF(is expressed as a secreted protein, consisting of 247 amino acid and with molecular weight of 27.8 kDa, that plays a role in neurological development, neuronal differentiation, synaptic plasticity, and cell death and exerts its effects inside the cells through 2 protein receptors, i.e. tyrosine kinase and low-affinity nerve growth factor receptor (LNGFR). BDNF has been reported to distribute in different brain regions especially hippocampus, which is responsible for learning and memory (7). To the best of our knowledge, no study has yet been conducted on the effects of lavender on BDNF levels; however, Kim et al reported that treadmill exercise would enhance cognitive performance through increasing the expression of the BDNF and tyrosine kinase B (8). In addition, Cho and Roh found that BDNF levels would significantly increase after aerobic exercise (9). In contrast, Schega et al study demonstrated that 4-week aerobic exercise would lead to enhancement of physical and cognitive performances without any significant increase in BDNF levels (10). Because MCI is one of the common problems of the elderly and is considered to lead ultimately to Alzheimer disease and death, and no definite treatment has yet been offered for Alzheimer disease, it seems essential to conduct preventative interventions that can decelerate, stop, or even reverse the progression of MCI. In addition, it is particularly important to use medicinal plants because of being natural and causing no or few side effects (4). Exercise and physical activity were reported to have definitely confirmed effects in improving cognitive function and neurological system (6).

Since no research has investigated the combination effects of aerobic exercise and lavender essence on cognitive state and BDNF levels in elderly with MCI, this study was conducted to investigate the effects of 12-week aerobic exercise and lavender essence on cognitive states and BDNF levels of elderly with MCI.

Materials and Methods

This clinical study was conducted with pretest and post-test on 4 groups of the elderly people. After we informed the societies of the elders of Shiraz about the purposes of the current study, 61 men aged 60-70 years volunteered to participate in this study. Then, the cognitive states of the participants were examined by using the mini–mental state examination (MMSE). The MMSE was developed by Folstein et al in 1975 and consists of 11 domains, including orientations to time and place, registration, attention and calculation, recall, language, ability to follow simple command, reading, writing, and ability to do delicate complex commands (11). The total score for the MMSE is 30 that represents absence of any problem in the above mentioned domains. Scores under 20 indicate severe (scores ≤9) and moderate (scores 10-19) cognitive impairment and scores 20-25 represent MCI. The consistency coefficient of the MMSE has been reported 0.87 by Cronbach α coefficient. In addition, its sensitivity and specificity were derived 90% and 84%, respectively (12). Forty people whose scores ranged from 21 to 25 were selected as the subjects. The participants' mean age was 67.85 ± 3.89 years, mean height 174.6 ± 6.007 cm, mean weight 78.30 ± 5.18 kg, and mean body mass index (BMI) 25.69 ± 0.54 kg/m². They were randomly divided into 4 groups: aerobic exercise, lavender, aerobic exercise + lavender, and placebo. The inclusion criteria were being male and over 60 years old, having sufficient general health to conduct aerobic exercise according to examinations conducted by a physician, attending at least 90% of the intervention sessions, attaining scores 21-25 for the MMSE, attaining scores under 10 for the Geriatric Depression Scale (GDS), and not being under treatment for cognitive impairments; the exclusion criteria were not attending more than 10% of the intervention sessions, being dependent on others in daily activities, suffering from other physical or mental illnesses, taking medication, being under treatment for cognitive impairments, and withdrawing from continuing participation in the study. The length of the interventions was determined to be 12 weeks. To prepare lavender essence, newly sprouted branches and flowers of this plant were used. The essence collection was conducted by distillation in Barij Essence Pharmaceutical Co. (Kashan, Iran). The essence was administered at daily dose of 2 drops twice a day. The placebo was made by pharmacist at a concentration of 1/10 000 such that it did not possess any therapeutic effect. The 12-week aerobic exercise consisted of 3 weekly sessions. The first exercise session included 8-minute warm-up and 8-minute running with intensity of 75%-85% of HRR Max, and 5-minute cool down. After each 2 successive sessions, one minute was added to the very later session. Therefore, the running span reached 26 minutes at the end of the 12-week exercise period. Five milliliters blood samples were taken from the brachial vein of the subjects (as they were fasted for 12 hours) both 24 hours before and 48 hours after the interventions. In addition, the cognitive states of the subjects were examined by

the MMSE. In order to isolate the blood serum, after coagulation, the samples were centrifuged at 2000 rpm for 10 minutes. The isolated serum samples were stored at -20°C until later use. The serum level of BDNF was gauged by Human BDNF PicoKine™ ELISA kit (Boster Biological Technology, China). Data were described by mean and standard deviation (SD). In order to compare variations in the variables, mixed analysis of variance (ANOVA) (within-subject and inter-subject) was conducted with Bonferroni post hoc correction at significance level of 0.05. Data analysis was conducted by SPSS 16.

Results
The results of descriptive statistics, mixed ANOVA (intra-subject and inter-subject), and Bonferroni post-hoc test are shown in Tables 1-3, respectively.
Statistically significant differences in weight variation, BMI, BDNF, and cognitive state were observed among the 4 groups ($P=0.001$). Differences in weight, BMI, and BDNF were significant between the exercise group and the lavender and placebo groups ($P<0.05$). In addition, differences in weight, BMI, and BDNF were significant between the exercise + lavender group and the lavender and placebo groups ($P<0.05$). In addition, differences in weight, BMI, and BDNF were not statistically significant between the exercise group and the exercise + lavender group ($P>0.05$). In addition, the differences in weight, BMI, and BDNF were not statistically significant between

the lavender group and the placebo group ($P>0.05$). All differences in cognitive states between exercise + lavender and placebo groups, exercise and placebo groups, and lavender and placebo groups were statistically significant ($P=0.001$, 0.001, and 0.004, respectively). However, there were not any significant differences in cognitive state among the 3 intervention groups ($P>0.05$).

Discussion
In the current study, 12-week aerobic exercise, either alone or combined with lavender essence, led to significant increase in cognitive state and serum BDNF level in elderly with MCI. In addition, lavender essence usage led to significant enhancement of cognitive state. Although lavender use increased BDNF levels, such increment was not statistically significant. No significant difference was observed in cognitive state among the 3 intervention groups; however, variations in the BDNF levels of the 2 exercise groups were significantly higher than the corresponding changes in other 2 groups. Although adding lavender essence to aerobic exercise increased cognitive state score and BDNF level to some extent, these enhancements were not statistically significant. Perhaps, a longer-term intervention may lead to a significant interaction effect between the 2 interventions. As far as we searched, we found no study on the effect of lavender on cognitive state and serum BDNF levels. Lavender may help improve the cognitive state through other mechanisms.

Table 1. The mean (standard deviation) value of variables before and after intervention

Variables	Group	Before	After
Weight (kg)	Training + lavender	78.70±5.59	75.90±5.95
	Training	75.60±3.83	77.50±3.62
	Lavender	76.60±4.37	76.60±3.94
	Placebo	80.40±6.61	80.40±6.39
BMI (kg/m²)	Training + lavender	25.50±0.44	24.58±0.48
	Training	25.74±0.42	25.11±0.58
	Lavender	25.62±0.62	25.63±0.50
	Placebo	25.90±0.63	25.93±0.80
BDNF (pg/mL)	Training + lavender	108.82±32.88	179.81±62.69
	Training	110.25±28.61	192.84±59.51
	Lavender	118.22±30.68	138.15±29.62
	Placebo	110.75±26.07	111.09±24.19
Cognitive state (MMSE)	Training + lavender	22.50±1.35	24.90±0.87
	Training	22.70±1.63	24.40±1.42
	Lavender	22.80±1.75	24.30±1.05
	Placebo	24.30±0.94	24.20±0.63

Abbreviations: BMI, Body mass index; BDNF, Brain-derived neutrophic factor; MMSE, mini–mental state examination.

Table 2. The results of mixed intra-subject and inter-subject ANOVA (time interaction in group)

Variables	*F* value	*P* value	Effect Magnitude
Weight	21.88	0.001*	0.64
BMI	20.33	0.001*	0.63
BDNF	9.94	0.001*	0.45
Cognitive state	11.85	0.001*	0.49

Abbreviations: BMI, Body mass index; BDNF, Brain-derived neutrophic factor.
*Significant at 0.05.

Table 3. Results of Bonferroni post hoc test to determine location of the significant difference

Pairwise Comparison	Weight	BMI	BDNF	Cognitive state
Training + Lavender/ Training	0.24	0.36	1	0.69
Training + Lavender/ Lavender	0.001*	0.001*	0.04*	0.27
Training + Lavender/ Placebo	0.001*	0.001*	0.002*	0.001*
Training/Lavender	0.001*	0.001*	0.007*	1
Training/Placebo	0.001*	0.001*	0.001*	0.001*
Lavender/Placebo	1	1	1	0.004*

Abbreviations: BMI, Body mass index; BDNF, Brain-derived neutrophic factor.
*Significant at 0.05.

Previous studies have shown the anti-inflammatory effect of lavender, which was attributed to the inhibitory effects of lavender on AChE (5). It has been confirmed the high level of AChE activity, and therefore reduction in acetylcholine (Ach) level and neurotransmission QWL can lead to Alzheimer disease and the loss of spatial memory (13). Cho and Roh reported consistent results with those of the present study regarding the effect of exercise on cognitive state and BDNF levels (9). In addition, Zembron-Lacny et al showed that the BDNF levels of active persons were higher than those of inactive ones (14). Different intensities of exercise are a prominent parameter to explain variations in various studies (15). It has been reported that serum BDNF level does not exhibit any significant increment after low-intensity (20% below VT1) exercise; however, BDNF level increased after 30-minute high-intensity (10% above VT1) exercise (15). Exercise increases BDNF level, which leads to generating more neurons in the brain, and consequently causes improvements in learning and memory (16). The enhancement of serum BDNF level is effective on the presynaptic and postsynaptic terminals through the TrkB receptor, which leads to regulating signaling transmission pathways, e.g. mitogen-activated protein kinase 1 and MAP kinase-activated protein kinase 2, at the presynaptic and postsynaptic terminals (17). In this regard, Miller et al reported the existence of a significant correlation between cognitive state and exercise (18). This correlation can be taken into account to explain decreases in oxidative stress and inflammation, enhancement of angiogenesis, secretions of neurotrophins and catecholamines, and neurogenesis especially in hippocampus anatomy (19). To the best of our knowledge, no study has yet been conducted on the combination effect of lavender use and aerobic exercise on cognitive state and BDNF levels; it is therefore difficult to interpret the findings of the current study with reference to other studies' findings. The effects of aerobic exercise alone and lavender alone on cognitive state were significant yet without any significant difference from their combination effect on cognitive state. However, the combination of lavender and aerobic exercise caused a slightly more marked effect compared to those caused by either of them. It is therefore necessary to conduct studies with larger number of subjects and longer-term interventions. In addition, because the BDNF levels increased significantly in both groups undergoing aerobic exercise but not in the group administered with lavender alone, other mechanisms are likely to play a role in the lavender-associated improvement of the cognitive states of the elderly with MCI. To argue for BDNF role in lavender-associated variations in cognitive state more definitely, we need to perform studies with larger sample size.

Conclusion

Combination of aerobic exercise and lavender essence may decelerate or probably halt the progressive process of the impairment in elderly with MCI through improving cognitive state. Aerobic exercise may cause such changes through BDNF mediation. However, lavender extract use did not lead to any significant increase in BDNF. Therefore, other mediators are likely to be involved in the improvement of cognitive state. This issue should be addressed in future studies. This study was first to investigate the combination effect of lavender and exercise. Although the effect of aerobic exercise combined with lavender increased the effects of either alone, this increase was not significant compared to that caused by either of the interventions alone. It is therefore necessary to conduct studies with larger number of subjects and longer-term interventions.

Authors' contributions

All authors contributed to the study. MAK contributed to data collection and manuscript drafting and MAA made necessary corrections to the method especially data analysis. All read and confirmed the publication of the manuscript.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct,

data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

References

1. Sharif-zadeh QR, Moudi M, Akhbari H. Health situation of elderly supported by Imam Khomeini charity. Iran Elderly Mag. 2010;5(17):52-60.
2. Sohrabi MB, Zolfaghari P, Mahdizade F, et al. Evaluation and comparison of cognitive state and depression in elderly admitted in sanitarium with elderly sited in personal home. Knowledge & Health. 2008;3 (2):27. [Persian].
3. Torpy JM, Lynm C, Glass RM. JAMA patient page. Dementia. JAMA. 2010;304(17):972.
4. Karamian R, Mohammadian A, Hassanimoghadam E, et al. Identification and comparison of the yield and composition of essential oil constituents of 4 Eucalyptus species adapted to the climatic conditions of Khorramabad. J Herbmed Pharmacol. 2015;4(1):25-28.
5. Adsersen A, Minna A, Korolainen E, et al. Screening of plants used in Danish folk medicine to treat memory dysfunction for acetylcholiesterase inhibitory activity. J Ethnopharmacol. 2006;104:418-22.
6. Hillman CH, Motl RW, Pontifex MB, et al. Physical activity and cognitive function in a cross-section of younger and older community-dwelling individuals. Health Psychol. 2006;25:678-87.
7. Kuipers SD, Bramham CR. Brainderived neurotrophic factor mechanisms and function in adult synaptic plasticity:New insights and implications for therapy. Curr Opin Drug Discov Devel. 2006;9(5):580-586.
8. Kim TW, Choi HH, Chung YR. Treadmill exercise alleviates impairment of cognitive function by enhancing hippocampal neuroplasticity in the high-fat diet-induced obese mice. J Exerc Rehabil. 2016;12(3):156-62.
9. Cho SY, Roh HT. Effects of aerobic exercise training on peripheral brain-derived neurotrophic factor and eotaxin-1 levels in obese young men. J Phys Ther Sci. 2016;28 (4):1355-8.
10. Schega L, Peter B, Brigadski T, et al. Effect of intermittent normobaric hypoxia on aerobic capacity and cognitive function in older people. J Sci Med Sport. 2016;19(11):941-945.
11. Nillson J, Parker MG, Kabir ZN. Assessing health-related quality of life among older people in Rural Bangladesh. J Trans Cult Nurs. 2004;15(4):298-307.
12. Frooghian M, Jafari Z, Shirinbaiani P, et al. Standardization of brief examination of cognitive status of elderly in Tehran. Advanced Cognitive Science Journal. 2008;10 (2):29-37.
13. Kiyofumi Yamada TN. Animal models of Alzheimer's disease and evaluation of anti-dementia drugs. Pharmacol Ther. 2000;88:93-113.
14. Zembron-Lacny A, Dziubek W, Rynkiewicz M, et al. Peripheral brain-derived neurotrophic factor is related to cardiovascular risk factors in active and inactive elderly men. Braz J Med Biol Res. 2016;49(7). pii: S0100-879X2016000700603
15. Pour-Nemati P. Investigation of effects of two resistance and endurance trainings schedules on BDNF cortisol, IGF-I, IGFBP-3 on young male rats [PhD thesis]. Tehran: University of Tehran; 2012.
16. Goekint M, De Pauw K, Roelands B, et al. Strength training does not influence serum brain-derived neurotrophic factor. Eur J Appl Physiol. 2010;110(2):285-93.
17. Molteni R, Barnard RJ, Ying Z, et al. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience. 2002;112:803-14.
18. Miller I, Vanessa T, Patrick SR, et al. measuring the impact of exercise on cognitive aging:methodological issues. Neurobiol Aging. 2012;33:622-9.
19. Adlard PA, Perreau VM, Pop V, et al. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J Neurosci. 2005;25:4217-21.