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Original Article

Effects of aerobic training and combination of resveratrol and fisetin on brain neurogenesis signaling pathways in Alzheimer's mice

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Abstract

Background and aims: Alzheimer's disease (AD) is a brain disorder that slowly destroys memory through the destruction of neurons by activating BDNF/VEGF/FGF7 signaling. The purpose of this study was to investigate the effects of aerobic training and combination of resveratrol and fisetin on brain neurogenesis signaling pathways in Alzheimer's mice.

Methods: In this experimental study, twenty-five C57BL/6J AD mice were randomized into 5 groups, including control, AD, AD+AT, AD+RSV+Fis, and AD+AT+RSV+Fis. The mice of the AD groups became AD by injecting amyloid-beta (Aβ1)-42 into the hippocampus. The AT protocol was five days per week for eight weeks before and after AD induction. RSV and Fis with concentrations of 25 mg/kg and 20 mg/kg were used, respectively. One-way analysis of variance was utilized to compare different groups, and Tukey's post hoc test was employed at $P \leq 0.05$.

Results: AD induction caused a significant decrease in the expression of *BDNF/VEGF/FGF7* genes in hippocampal ($P=0.001$). AT and consumption of RSV+Fis significantly increased BDNF ($P=0.001$), VEGF ($P=0.001$), and FGF ($P=0.001$) in hippocampal.

Conclusion: It seems that AT and RSV+Fis, both alone and simultaneously, can help increase brain neurogenesis in elderly people with AD by increasing the expression of *BDNF*, *VEGF*, and *FGF7* genes in the brain tissue.

Keywords: Aerobic training, Resveratrol, Fisetin, BDNF, VEGF, FGF7

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Introduction

Aging is associated with molecular, cellular, structural, and functional changes in the brain. Neurons may respond adaptively to these changes or lead to neurological disorders such as Alzheimer's (AD) and Parkinson's disease (1). With increasing age, the number of brain cells decreases significantly, and cerebral blood flow decreases by about 20% (2). In addition, research reported that AD is associated with the accumulation of amyloid beta (Aβ) outside the cell, and that of the spindles of neuronal fibers, and the increase in the amount of the hyperphosphorylated tau protein in different parts of the central nervous system, such as the brain cortex, hippocampus, hypothalamus, and other parts of the brain (3). In other words, the accumulation of amyloid plaques in the nerve coils of hippocampal neurons with the increase of inflammatory factors, as well as inflammatory and pro-inflammatory cytokines, causes the violation of cholinergic function and changes in neurotrophins such as brain-derived neurotrophic factor (BDNF) (4). Studies show that the expression of the *BDNF* gene in the hippocampus and cerebral cortex causes plasticity of neurons, neurogenesis, improvement of the function of synapses in the transmission of chemical mediators, and an enhancement in memory and learning (5). The results of previous studies demonstrated that the level of BDNF in elderly patients with AD is reduced by 33% (6). However, the researchers have linked the mechanism of the reduction of these neurotrophins to the increase of Aβ and its binding to the promoters of tyrosine kinase B receptor gene expression (7). Further, brain neurogenesis decreases in old age and causes a progressive decline in cognitive function (8). Furthermore, aging leads to several changes in the vascular system that are involved in the age-related destruction of the brain. At the macroscopic level, the decrease in vascular density in the old brain leads to a decrease in blood flow and oxygen to the brain tissues, which may even be caused by pathological factors and becomes worse (9). The research results revealed that the vascular endothelial growth factor (VEGF) is lower in the microscopic vessels of the brain of old mice compared to young mice (10). VEGF mediates both angiogenesis and neurogenesis and can support nerve cells independently of its essential role in the growth of blood vessels (11). Neurogenesis occurs in the vicinity of growing blood vessels, and VEGF plays an essential role in the regulation and proliferation of neural progenitor cells, survival, migration, axon/dendrite patterning, and synaptic function (12). Moreover, previous studies have shown that fibroblast growth factor (FGF7) is necessary for the

formation of inhibitory synapses in the hippocampus (13). Researchers believe that, in addition to exercise, a proper diet and natural antioxidants modulate immune system function, reduce inflammation, and increase neurogenesis in patients with nervous system disorders (14). Resveratrol (RSV) is a strong polyphenol and biologically active substance in some seeds, vegetables, and fruits, especially berries and red grapes, which increases the lifespan of cells (15). RSV was noticed due to its anti-aging effects through sirtuin deacetylase-1 (16). Fisetin (Fis) is also a natural flavonoid that is found in various vegetables and fruits such as apples, cucumbers, strawberries, persimmons, grapes, and onions (17). It has antioxidant, anti-inflammatory, neurotrophic, and anti-cancer effects against cognitive and neurological disorders such as AD (18). Little is known about the simultaneous effects of RSV and Fis supplementation with aerobic training (AT) on the hippocampal neurogenesis signaling pathway and learning in AD induction in mice. Therefore, the present study examined the effect of AT, RSV, and Fis supplementation on brain neurogenesis signaling pathways in aged AD mice.

Materials and Methods

Subjects

For this experimental study, C57BL/6J mice (8 weeks old) were purchased from the Isfahan Embryo Center and were kept under supervision and control in the laboratory for one week. During this study, the animals were kept under standard conditions, including a room temperature of 20–22 ˚C, a 12-hour light-dark cycle, 55% relative humidity, and free access to food and water. Aβ1-42 oligomer was purchased from Sigma-Aldrich Company. C57 mice were anesthetized by the intraperitoneal administration of sodium pentobarbital 0.2% (50 mg/kg) and then placed in a stereotaxic apparatus (Stoelting, Wood Dale, IL, USA). Aβ1-42 oligomer with 50 µM or 1 mM sterile 0.9% saline (1 µL per side, at 0.2 µL/minute) was injected into the bilateral dentate gyrus area of the hippocampus dorsal to a C57-Mouseinjected (15). Decreased expression of *BDNF*, *VEGF*, and *FGF7* genes in the hippocampal tissue was utilized to evaluate AD. It should be noted that the random allocation method used blocks. The animals split the experiment into smaller sub-experiments (blocks), and treatments were randomized to experimental units within each block. Finally, the rats were randomly divided into 5 groups, including control, AD, AD + AT, AD + RSV + Fis, and AD + AT + RSV + Fis. It is noteworthy that the randomization was conducted via GraphPad online software (https://www.graphpad.com/).

Preparation of Resveratrol and Fisetin

RSV and Fis compounds were purchased from Sigma-Aldrich Company (USA). The safe dose used for each compound was determined based on previous data (RSV with a concentration of 25 mg/kg and Fis with a concentration of 20 mg/kg). RSV and Fis were given orally to mice (16-19).

Aerobic Training Protocol

The total training period was 8 weeks, and training was performed 5 days a week in the familiarization, overload, and stabilization stages. In the familiarization stage (the first week), the mice walked on the treadmill every day for 10–15 minutes at a speed of 10 m/minute. In the overload phase (the second to fourth week), the intensity and duration of the activity were gradually increased during 3 weeks until reaching the final amount of 60 minutes with a speed of 27 m/min. This intensity is equivalent to 75%–80% of the maximum oxygen consumption with 6.7 mL of oxygen per 100 g of mouse weight per minute (13).

Dissection and Sampling

A combination of 50 mg/mL of ketamine and 20 mg/mL of the xylazine solution was used to anesthetize the rats 48 hours after the last training session and 12 hours of fasting. First, laboratory specialists performed pain tests to diagnose anesthesia. Once complete anesthesia was assured, the animals' brains were opened, and the harvested brain tissue was immediately placed in nitrogen. To measure BDNF/VEGF/FGF variables, the brain tissue was maintained at -80 ˚C.

Real-Time Polymerase Chain Reaction Method for Brain Tissue Molecular Analysis

RNA was extracted from the brain hippocampus tissue using TRizol reagent and according to the manufacturer's protocol (Yekta Tehiz Azma). A wavelength ratio of 260/280 was considered for measuring the amount of RNA and the quality of the obtained RNA. Moreover, electrophoresis was used on agarose gel, and the 28S and 16S bands were observed accordingly. Then, cDNA synthesis was performed according to the protocol of the BIOFACT kit. The target gene sequence was obtained from the National Center for Biotechnology Information site, and the nucleotide sequence of the forward primer and the nucleotide sequence of the reverse primer complementary to *BDNF*, *VEGF*, and *FGF7* genes were designed through Oligo7 and Beacon designer software. Finally, real-time PCR was performed by the SYBR Green kit and Corbett rotor gene 6000 machines. The *B2M* gene was utilized as a housekeeping gene in this research. Gene expression analysis was performed using the 2-ΔΔCT method (Table 1).

Statistical Methods

After collecting the data, the Shapiro-Wilk test was employed to check the normality of the data distribution. Finally, the statistical analysis was conducted by one-way analysis of variance (ANOVA) with Tukey's post hoc test for between-group comparisons. All analyses were performed at the level of $P \leq 0.05$ using SPSS software, version 21.

Results

BDNF/*VEGF*/*FGF* gene expression is shown in Figures 1, 2, and 3. The ANOVA results indicated a significant difference in *BDNF* ($P=0.0001$), *VEGF* ($P=0.0001$), and *FGF* ($P=0.0001$) genes in rat brain tissues in different study groups. The means and standard deviations of BDNF/VEGF/FGF variables are provided in Table 2.

Tukey's test results showed that *BDNF*/*VEGF*/*FGF* gene expression in the AD group significantly decreased compared to other groups ($P=0.001$). The expression of the *BDNF*/*VEGF*/*FGF* gene in AD + RSV + Fis had a significant increase in comparison to AD. In addition, there was a significant increase in the expression of the *BDNF*/*VEGF*/*FGF* gene in AD + AT compared to AD + RSV + Fis. Further, the expression of the *BDNF*/*VEGF*/*FGF* gene in AD + AT + + RSV + Fis had a significant increase compared to AD + AT.

Discussion

AD is a progressive neurodegenerative disease characterized by neuronal loss and extracellular senile platelets, leading to memory deficits. AD is associated with a consistent pathological cascade, beginning with the accumulation of Aβ. This study investigated the effect of AT + RSV + Fis supplementation on brain neurogenesis signaling pathways in AD mice. The results demonstrated that the expression of *BDNF* and *VEGF* genes plays an important role in neurogenesis and cognitive disorders in AD mice. The expression of BDNF, VEGF, and FGF-

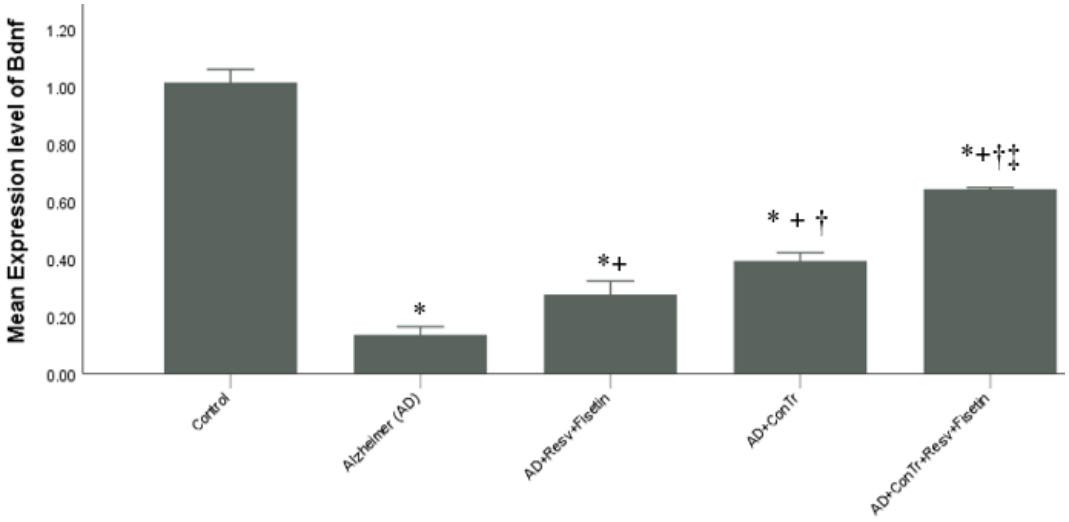

Figure 1. Changes in the Levels of *BDNF* Gene Expression in Different Research Groups. *Note*. AD: Alzheimer's disease; RSV: Resveratrol; Fis: Fisetin; AT: Aerobic training; BDNF: Brain-derived neurotrophic factor. The obtained values are displayed as means and standard deviations. Statistically significant differences between the mean values ($P<0.05$). *It indicates a significant difference between the experimental groups and the control group ($P<0.001$). †It demonstrates a significant difference between the experimental groups and AD ($P<0.001$). ‡It implies a significant difference between the experimental groups and the AD + RSV + Fis group ($P<0.001$). ‡It represents a significant difference between the experimental groups and the AD + AT group ($P<0.001$).

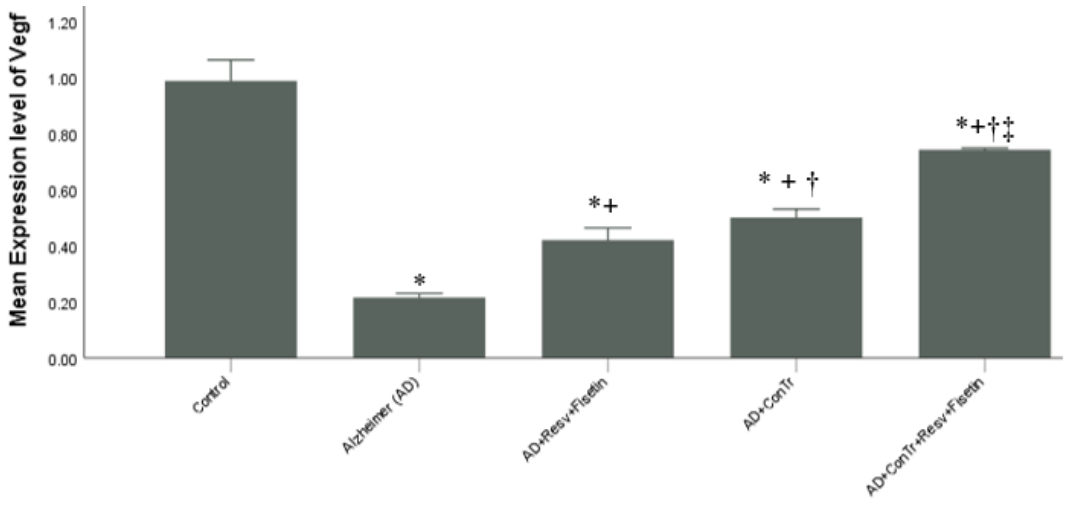

Figure 2. Changes in the Levels of *VEGF* Gene Expression in Different Research Groups. *Note*. VEGF: Vascular endothelial growth factor; AD: Alzheimer's disease; RSV: Resveratrol; Fis: Fisetin; AT: Aerobic training; VEGF: Vascular endothelial growth factor. The obtained values are demonstrated as means and standard deviations. Statistically significant differences between the mean values ($P<0.05$). *It denotes a significant difference between the experimental groups and the control group ($P<0.001$). †It indicates a significant difference between the experimental groups and AD ($P<0.001$). ‡It represents a significant difference between the experimental groups and the AD + RSV + Fis group ($P<0.001$). ‡It implies a significant difference between the experimental groups and the AD + AT group ($P<0.001$)

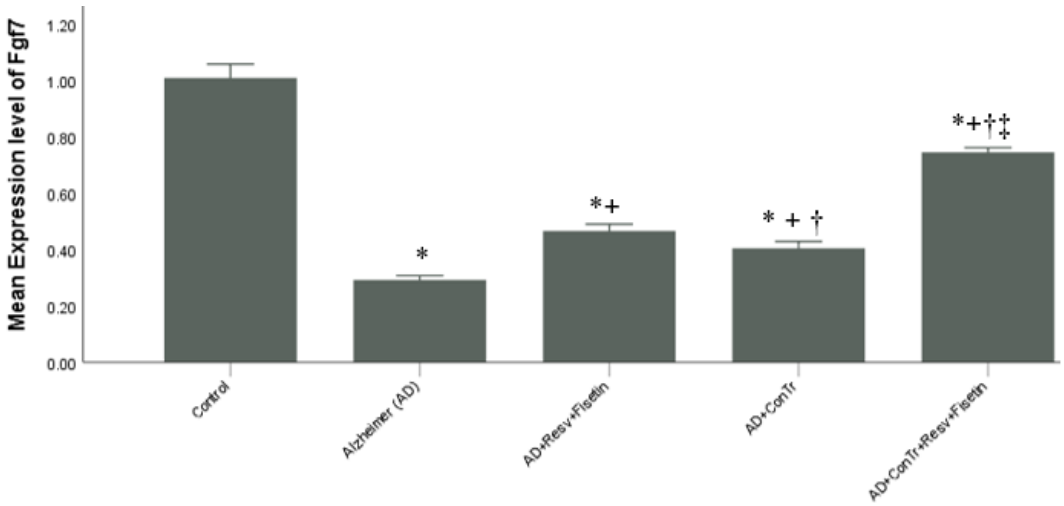

Figure 3. Changes in the Levels of *FGF7* Gene Expression in Different Research Groups. *Note*. FGF: Fibroblast growth factor; AD: Alzheimer's disease; RSV: Resveratrol; Fis: Fisetin; AT: Aerobic training. The obtained values are represented as means and standard deviations. Statistically significant differences between the mean values ($P<0.05$). *It indicates a significant difference between the experimental groups and the control group ($P<0.001$). +It demonstrates a significant difference between the experimental groups and AD ($P<0.001$). †It implies a significant difference between the experimental groups and the AD + RSV + Fis group ($P<0.001$). ‡It denotes a significant difference between the experimental groups and the AD + AT group ($P<0.001$)

Table 1. The list of primers used in this study

Genes	Primer sequences	Temperature	Size (bp)
B2m	Forward: 5′-ACAGTTCCACCCGCCTCACATT-3′ Reverse: 5′-TAGAAAGACCAGTCCTTGCTGAAG-3′	60	105
Fgf7	Forward: 5′-TGTTCTGTCGCACCCAGTGGTA-3′ Reverse: 5′-TTCCAACTGCCACGGTCCTGAT-3′	60	114
Bdnf	Forward: 5′-GGCTGACACTTTTGAGCACGTC-3′ Reverse: 5′-CTCCAAAGGCACTTGACTGCTG-3′	60	133
Vegfa	Forward: 5′-CTGCTGTAACGATGAAGCCCTG-3′ Reverse: 5′-GCTGTAGGAAGCTCATCTCTCC-3′	60	119

7 in the AD group decreased significantly compared to other groups. In addition, doing AT and taking RSV and Fis could increase the expression of BDNF, VEGF, and FGF7 compared to the AD group. A synergistic and significant effect of AT, RSV, and Fis compounds on gene expression and behavioral patterns was observed in the RSV-Fis + AT + AD group compared to other groups. Our analysis showed that the effective compounds derived from plants and the active ingredients RSV and Fis can improve cognitive disorders in AD mice. This study investigated the simultaneous effect of AT and the consumption of bioactive compounds orally (RSV with a concentration of 25 mg/kg and Fis with a concentration of 20 mg/kg) in elderly rats with AD. Synaptic abnormalities are among the main aspects of AD disease that appear as the disease progresses. A large number of studies have shown that pathological changes in neural circuits and synapses may provide a mechanistic link between tau pathology and Aβ (19). The results of the present research are in line with those of Fakhraei et al (20), Keshvari and Heidarianpour (21), Shamsipour et al (22), and Kim et al (23). Fakhraei et al evaluated the effect of 4 weeks of aerobic rehabilitation training (AT) on the expression of *BDNF* and *TGF-β1* genes in the hippocampal tissue of rats with AD caused by Aβ injection. The results revealed that aerobic exercise can counteract the harmful effects of Aβ through BDNF and TGF-β1 molecular signaling pathways (20). Kim et al found that aerobic exercise caused a significant increase in BDNF (23). BDNF is an important neuronal indicator in the hippocampus of the mammalian brain. It plays a vital role in the development and maturation of neurons through the stages of growth and regulation of synaptic transmission and plasticity in the adult brain (24). BDNF and receptor tyrosine kinase B regulate ion channel activity, neurotransmitter release, axonal guidance, and neuronal excitability. Decreased BDNF in AD patients leads to tau phosphorylation, amyloid-beta accumulation, neuroinflammation, and neuronal apoptosis (25). Neuroinflammation-induced memory impairment has been shown to activate Toll-like receptor 4/nuclear transcription factor-κB signaling and inhibit CREB/BDNF expression in AD animal models (26). Researchers believe that the angiogenic and neurogenic response to VEGF stimulation decreases with age, which may be due to the decrease in VEGF receptor activity in the brain (27). In line with the results of the present research, other researchers confirmed the increase in VEGF levels in the cortical and hippocampal parts of the brain in small middle-aged mice (11–13 months) after 6 weeks of running on a rotating wheel (28) and the increase in *VEGF* gene expression in the hippocampus of 21-month-old mice after 8 weeks of high-intensity exercise above the lactate threshold (29). The results of the research showed that AT improves learning performance and spatial memory in old animals. It seems that the exercise-induced upregulation of the VEGF/PGC1α

Table 2. Expression levels of the BDNF, VEGF, and FGF7 in different groups

Groups	BDNF	*P* value	FGF7	*P* value	VEGF	*P* value
Control	1.01 ± 0.017		1 ± 0.019		0.98 ± 0.03	
AD	0.13 ± 0.026*	< 0.000	0.29 ± 0.01*	< 0.000	0.21 ± 0.005*	< 0.000
AD + RSV + Fis	0.27 ± 0.04*	< 0.000	0.46 ± 0.023*	< 0.000	0.42 ± 0.016*	< 0.000
AD + AT	0.39 ± 0.022*	< 0.000	0.41 ± 0.019*	< 0.000	0.5 ± 0.01*	< 0.000
AD + AT + RSV + Fis	0.64 ± 0.007*	< 0.000	0.73 ± 0.015*	< 0.000	0.74 ± 0.01*	< 0.000

Note. BDNF: Brain-derived neurotrophic factor; VEGF: Vascular endothelial growth factor; FGF: Fibroblast growth factor; AD: Alzheimer's disease; RSV: Resveratrol; Fis: Fisetin; AT: Aerobic training.
* The significance of the control group with other groups.

signaling pathway in the brain is at least partially involved in this adaptation (30).

Research results revealed that in the nervous system, FGF7 plays a major role in the presynaptic organizer derived from the target of hippocampal neurons in the brain. The amount of FGF7 in dorsal root ganglion neurons was significantly decreased due to peripheral nerve damage (31). Studies have shown that the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway is highly associated with neuroprotective modulation in AD cells. The reduction of FGF7 by the negative regulation of miR107 can cause axis activation of PI3K/AKT and lead to the increase of Aβ and the progression of AD disease (32). In the present study, taking RSV and Fis, along with AT, led to an increase in FGF7 in the hippocampus of AD rats. The results demonstrated that Fis supplementation reduced aluminum-induced apoptosis and neurodegeneration in the hippocampus of adult rat brains. Based on these results, polyphenolic flavonoids such as Fis, which are extracted from natural plant sources, play an important role in the prevention of age-related neurological disorders such as AD (33). In addition, RSV, a natural polyphenol extracted from red wine, has anti-inflammatory, antioxidant, and neuroprotective functions in vitro. (34). The results of the present study confirmed that the consumption of RSV and Fis improved cognitive function and increased BDNF and VEGF in the hippocampus of elderly mice with AD (14). The limitation of this study was the control of food and calorie intake. In addition, considering the isoforms of BDNF/VEGF/FGF7 in the hippocampus and their role during exercise and the lack of measurement of different isoforms, it is recommended that other measurement methods such as the Western blot and enzyme-linked immunosorbent assay be used in future research.

Conclusion

In general, the use of RSV and Fis, along with AT, with the positive regulation of BDNF/VEGF/FGF7 in the hippocampal tissue is effective in controlling brain damage and ultimately leads to the improvement of AD; thus, it is suggested that RSV and Fis be utilized, along with AT, for AD disease.

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Authors' Contribution

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Formal Analysis: Khosro Jalali Dehkordi and Farzaneh Taghian,.
Investigation: Amir Jahanbakhsh, Khosro Jalali Dehkordi, and Farzaneh Taghian.
Methodology: Amir Jahanbakhsh and Khosro Jalali Dehkordi.
Project Administration: Khosro Jalali Dehkordi.
Software: Amir Jahanbakhsh and Khosro Jalali Dehkordi.
Supervision: Khosro Jalali Dehkordi.
Writing–original draft: Amir Jahanbakhsh and Khosro Jalali Dehkordi.
Writing–review and editing: Khosro Jalali Dehkordi and Farzaneh Taghian.

Competing Interest

The authors declare that there is no conflict of interests.

Ethical Approval

Ethical considerations in this study included obtaining permission from the Ethics Committee of Isfahan Islamic Azad University, Khorasgan Branch (No. IR.IAU.KHUISF.REC.1401.387) and obtaining written consent to participate in the study from the participants. In addition, in the current study, the ethics of working with animals were performed following the Declaration of Helsinki.

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