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The effect of aerobic training along with black pepper extract consumption on memory disorders markers in rats with Alzheimer's disease

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Abstract

Introduction: The aim of the present study was to investigate the combined effect of eight weeks of aerobic exercise and black pepper extract consumption on memory disorders markers in rats with Alzheimer's disease (AD).

Methods: 30 male Sprague-Dawley rats with AD were randomly divided into AD, sham, black pepper, aerobic training, and training + black pepper groups. AD induced by injection of 10 mg/kg trimethyltin chloride (n=6). Six rats were also placed in the healthy control group. Aerobic training was performed on a treadmill for eight weeks, three sessions per week, at a speed of 10 to 24 meters per minute. Black pepper was administered daily at a dose of 100 mg/kg via intraperitoneal injection. 48 hours after the last training session, hippocampal GABA-RA and Aβ gene expression were measured and the results were analyzed with one-way and two-way analysis of variance tests.

Results: In the AD group, GABA-RA gene expression was significantly lower, and Aβ gene expression was significantly higher than in the healthy control group (P=0.001). GABA-RA gene expression was significantly higher in the aerobic training + black pepper group than the black pepper, training and AD groups. Aβ gene expression was significantly lower in the training + black pepper group than the black pepper, aerobic training and AD groups. (P=0.001).

Conclusions: Generally, it seems that aerobic exercise along with black pepper consumption have a synergistic effect in improving memory disorders markers in the AD model. Generalizing these results to the human population requires further studies

Key Words: Aerobic exercise, Black pepper, Memory disorders, Alzheimer's disease, Amyloid β.

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1. Introduction

Alzheimer's disease (AD) is the sixth leading cause of death and one of the main causes of dementia in the world (1). AD is the most common age-related neurodegenerative disease, in which dementia and neuronal loss occur, especially in the brains of elderly individuals (2). In AD, brain regions related to memory and learning, including the hippocampus, forebrain base, and cerebral cortex, are most commonly affected. In this disease, plaques of amyloid beta (Aβ) peptides and hyperphosphorylated tau protein form (3). Increased Aβ deposition is known to be an early event in the pathogenesis of AD, leading to the loss of neurons and synapses (3). Increased Aβ deposition is known to be an early event in the pathogenesis of AD, leading to the loss of neurons and synapses (3). Aβ peptides are known to be key molecules in the pathogenesis of AD. Their deposition in the brain as senile plaques and increased inflammation activate a chain of events that leads to the onset of AD (4). In addition to memory impairment, Aβ deposition also causes depression in these patients (4).

On the other hand, the neurotransmitter gamma-aminobutyric acid (GABA) is the most important inhibitory chemical mediator in the mammalian central nervous system, affecting the activity of other chemical mediators, and defects in GABA synthesis are associated with neurological disorders such as anxiety and depression (5). The involvement of synaptic and GABA systems in the development and progression of AD is well established (6). The mechanisms of the relationship between depression and AD and dementia are still not fully understood, but evidence suggests that Aβ accumulation and dysfunction of GABA-A receptors (GABA-RA) play a pivotal role in the pathogenesis of AD, including depression, behavioral disorders, and cognitive deficits (7).

Regular exercise is known to be a neuroprotective agent that positively regulates neurotrophins and has beneficial effects on cognition, brain volume, and neural network activity (8). These effects have been observed in controlled studies in cognitively healthy older adults and adults with memory impairment (8). Although it has been suggested that reducing brain Aβ levels and increasing GABA levels reduce the risk of depression, cognitive impairment, and dementia (9, 10), the effects of different types of exercise on brain and blood Aβ and GABA levels are not well understood. Results of studies on changes in amyloid burden and factors affecting Aβ clearance after exercise are inconsistent, with reports of reductions (11, 12) and no changes (13). Liu et al. (2024) reported increased hippocampal GABA-RA gene expression and reduced depression-related behaviors in AD mice after a period of aerobic exercise including running and swimming (10). Kang and Cho (2014) also reported a reduction in Aβ in Alzheimer's mice after a 6-week exercise protocol (running on a treadmill at a speed of 20 m/min), but these results were not confirmed by Brown et al. (2019) (13).

Black pepper is a widely used spice that contains volatile essential oils and alkaloids such as piperidine, piperine, and chavicine. The pungency of black pepper is due to the presence of piperine. In addition to its culinary uses, pepper also has important medicinal and preservative properties. Based on cellular, animal, and human studies, piperine has been shown to have immunomodulatory, antioxidant, and anticarcinogenic properties (14) and can affect the central nervous system and has antidepressant, anticonvulsant, and anti-ischemic effects (15). There are limited studies on the effects of black pepper consumption on AD complications, but recently it has been shown that piperine in black pepper reduces cognitive impairment in Alzheimer's disease mice by increasing GABA and decreasing Aβ (16). Do et al. (2013) also showed that piperine can enhance memory, reduce stress, and play a role in preventing AD (17).

By knowledge, no study has been conducted on the simultaneous effect of exercise and black pepper on factors affecting cognitive impairment in AD samples, and the neuroprotective properties of piperine, the main alkaloid extracted from black pepper, have been recently investigated, and its mechanism of action is still not well understood (18). Therefore, the present study aimed to investigate the combined effect of eight weeks of aerobic exercise and black pepper extract consumption on some markers of cognitive impairment in AD rats.

2. Methods

2.1. The animals

In this experimental and fundamental study, 36 male Sprague-Dawley rats, 4 to 6 months old and weighing approximately 230-250 grams, were purchased from the Pasteur Institute and transferred to the Animal Laboratory of Pishtazan Higher Education, Shiraz. In order to familiarize the samples with the laboratory environment, they were placed in standard conditions (temperature 22 ± 3°C, humidity 40 to 60%, proper ventilation, 12-hour light and dark cycle, and free access to food and water) for one week. Animal maintenance was carried out under the supervision and approval of the Research Department of Zand Institute of Higher Education, Shiraz, with the ethical code IR.IAU.SHIRAZ.REC.1404.250 and in accordance with the Helsinki Declaration.

2.2. AD induction and animal grouping

Furthermore, 30 rats were induced with AD after 12 hours of fasting using a single intraperitoneal injection of 10 mg/kg trimethyltin chloride (TMT) manufactured by Sigma-Aldrich, USA (19). Two weeks after TMT injection, in order to confirm the induction of AD, in addition to observing clinical signs including aggression, tail twitching, and periorbital hemorrhage, the patient rats were evaluated for memory and learning using the Y-maze test and compared with the healthy control group. After confirming the induction of AD, 30 rats were randomly divided into groups (1) AD, (2) sham, (3) black pepper, (4) training, and (5) aerobic training + black pepper. Six rats were also considered as the healthy group without any intervention.

2.3. Exercise protocol

First, the samples were familiarized with the treadmill for one week. During this time, they ran on the treadmill without incline for 8 minutes every day at a speed of 8 m/min and became familiar with the training environment. After this stage, the main training protocol was implemented for 8 weeks and 3 sessions per week. In this protocol, the rats first worked at a speed of 8 to 10 m/min for 5 minutes to warm up. Then, the main exercises were performed and at the end of each training session, a cool-down period of 5 minutes at a speed of 8 to 10 m/min was considered (20). To stimulate the samples to move, tactile stimulation or mild vibration was used.

Table 1. Aerobic training protocol

	Time (min)	Speed (m/min)
Familiarization	8	8
Warm-up	5	8-10
Week 1	15	10
Week 2	20	12
Week 3	25	14
Week 4	30	16
Week 5	35	18
Week 6	40	20
Week 7	45	22
Week 8	48	24
Cool-down	5	8-10

2.4. Nutritional intervention

300 grams of black pepper approved by the Agricultural Jihad of Marvdasht city were prepared. Subsequently, this amount of black pepper was converted into powder and then mixed with half a liter of 98% ethanol. The resulting solution was kept in the environment for 4 days. On the fourth day, the liquid part of this solution was separated and transferred to the distillation and extraction machine after passing through filter paper. The ethanol extract of black pepper was extracted with care and appropriate concentration and then this extract was placed on a rotary to obtain its powder. Given the number of samples in the supplement and exercise + supplement groups, 400 mg of this extract was mixed with 6 cc of normal saline and 30 international units of ethanolic black pepper extract were injected into each rat. Thus, each rat was injected with 100 mg/kg of ethanolic black pepper extract (21).

2.5. Tissue collection and gene expression measurement

In order to investigate the effect of independent variables on possible changes in dependent variables according to a predetermined schedule, 48 hours after the last training session, all samples were anesthetized by intraperitoneal injection of a combination of ketamine (70 mg/kg) and xylazine (3 mg/kg). Then, hippocampal tissue was removed and immediately frozen at -80°C for subsequent measurements. To measure the expression of GABA-RA and Aβ genes, hippocampal tissue was first incubated in a frozen state. Then, a homogenous solution was obtained from the tissue. For RNA extraction, a special kit manufactured by ROSH, Germany, with the economic code R.41444A was used. To assess the quality of RNA, it was evaluated using a spectrophotometer at a wavelength of 420 to 510 nm, and after confirming the purity of RNA, the samples were used for cDNA synthesis. At this stage, cDNA was synthesized using the Kiazyst Company kit protocol made in Iran with the economic code (K1296). Then, the designed primers were tested using the NCBI site, and after confirming the efficiency of the primers, these primers were mixed with cDNA and placed in a qReal Time PCR device made in Italy called Step One to be expressed in different cycles. As soon as the expression threshold was reached, the device stopped and gene expression values were measured relative to an internal control gene. The formula $2^{-\Delta\Delta CT}$ was used to quantify the data.

2.8. Statistical analysis

In the present study, mean and standard deviation were used for data analysis in the descriptive statistics section. In order to examine the normality of data distribution, Shapiro-Wilk test was used. One-way analysis of variance test was used to examine the difference between groups and if significant, Tukey's post hoc test was used. Two-way analysis of variance test was used to examine the main effects of exercise, supplementation and interaction between these two and if significant, Bonferroni post hoc test was used.

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All data were analyzed with SPSS software version 22 and at a significance level of 0.05.

3. Results

The results of one-way analysis of variance showed that there was a significant difference in the expression levels of GABA-RA gene in the hippocampal tissue of rats in different research groups (P=0.001 and F=178.93). The results of Tukey's post hoc test showed that the expression levels of GABA-RA gene in the AD group (P=0.001) and sham group (P=0.001) were significantly lower than the healthy control group, but no significant difference was observed between the sham group and the AD (P=0.99). The expression of GABA-RA gene in the black pepper (P=0.001), aerobic training (P=0.001) and training + black pepper (P=0.001) groups was significantly higher than the AD group, but no significant difference was observed between the aerobic training and black pepper groups (P=0.89). However, GABA-RA gene expression in the training + black pepper group was significantly higher than the aerobic training (P=0.001) and black pepper (P=0.001) groups. The interaction effect of training and supplementation was examined using a two-way ANOVA test. The results of this test showed that the training factor (P=0.001, F=200.76, and effect size 0.90) and black pepper (P=0.001, F=164.73, and effect size 0.89) had a significant effect on increasing GABA-RA levels in the hippocampal tissue of rats with AD; however, the interaction of training and black pepper on GABA-RA was not significant (P=0.19, F=1.78, and effect size 0.08; Figure 1).

The results of one-way analysis of variance showed that there was a significant difference in the expression levels of Aβ gene in the hippocampal tissue of rats in different research groups (P=0.001 and F=375.41). The results of Tukey's post hoc test showed that the expression levels of Aβ gene in the AD group (P=0.001) and sham (P=0.001) were significantly higher than the healthy control group, but no significant difference was observed between the sham and AD groups (P=0.99). The expression of Aβ gene in the black pepper (P=0.001), aerobic training (P=0.001) and training + black pepper (P=0.001) groups was significantly lower than the AD group, but no significant difference was observed between the aerobic training and black pepper groups (P=0.58). However, Aβ gene expression in the training + black pepper group was significantly higher than the aerobic training (P=0.001) and black pepper (P=0.001) groups. The interaction effect of training and supplementation was examined using a two-way ANOVA test. The results of this test showed that the training factor (P=0.001, F=10.553, and effect size 0.96) and black pepper (P=0.001, F=13.418, and effect size 0.95) had a significant effect on reducing Aβ levels in the hippocampal tissue of rats with AD. Training and black pepper also had an interactive effect on reducing Aβ (P=0.005, F=9.84, and effect size 0.33; Figure 2).

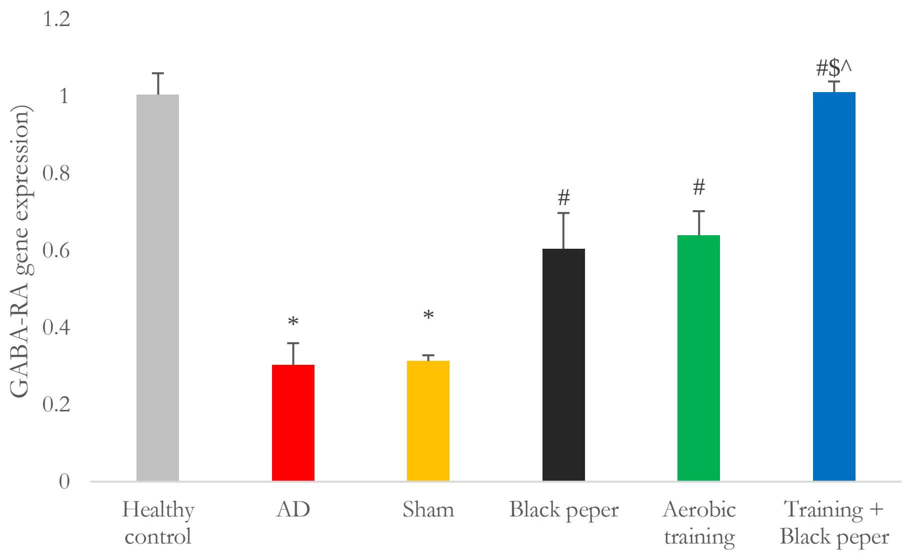

Figure 1. GABA-RA gene expression levels in the hippocampal tissue of rats in the studied groups.
* (P=0.001) significant decrease compared to the healthy control group; # (P=0.001) significant increase compared to the AD group; $ (P=0.001) significant increase compared to the black pepper group; ^ (P=0.001) significant increase compared to the aerobic training group.

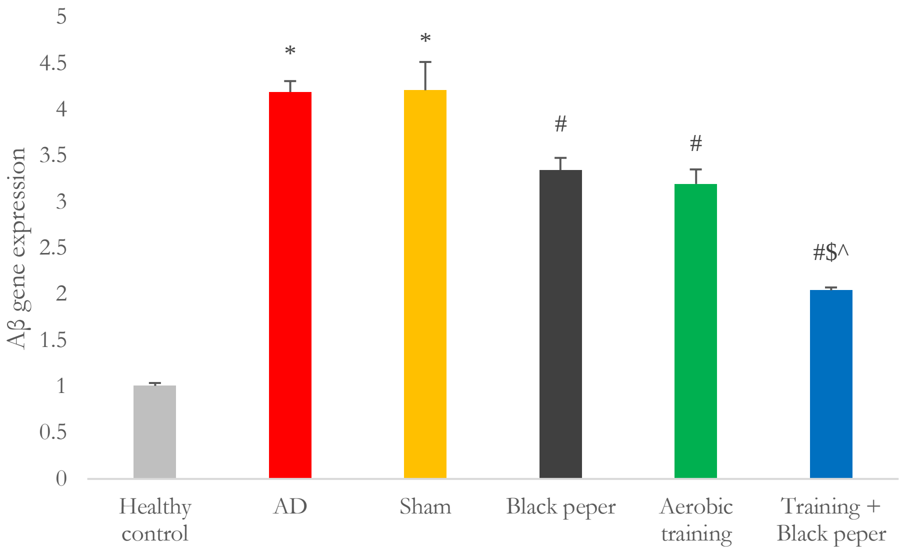

Figure 2. Aβ gene expression levels in the hippocampal tissue of rats in the studied groups
* (P=0.001) Significant increase compared to the healthy control group; # (P=0.001) Significant decrease compared to the AD group; $ (P=0.001) Significant decrease compared to the black pepper group; ^ (P=0.001) Significant decrease compared to the aerobic training group

4. Discussion

The present study aimed to investigate the effect of eight weeks of aerobic exercise and black pepper extract consumption on some markers of cognitive impairment in rats with AD. The results showed that the hippocampal GABA-RA gene expression in the AD group was significantly lower and the Aβ gene expression was significantly higher than in the healthy control group. These findings are consistent with some previous studies on the role of Aβ accumulation in cognitive and motor impairments in AD patients (3, 4). The accumulation of Aβ plaques between neurons has been shown to disrupt cellular communication and cause inflammation (22). The same researchers reported that the accumulation of Aβ and tau protein leads to inflammation, oxidative stress, and neuronal cell death, ultimately causing hippocampal and cortical atrophy (22). The findings of Rador et al. (2017) also confirm that Aβ42 oligomers cause neurotoxicity by damaging cholesterol-rich membranes (23). In this regard, Rabiei et al. (2015) described a mechanism in which Aβ42 binding to 7α-nAChRs in astrocytes leads to glutamate secretion and activation of NMDAR receptors, which ultimately leads to Ca^{2+} surge, ROS production, caspase 3 activation, and tau protein hyperphosphorylation, all of which play a role in the destruction of synapses and dendritic branches (24).

On the other hand, the decrease in GABA-RA gene expression in the AD group compared to the healthy control group is also consistent with the findings of Carlo Collar et al. (2023), who showed that inhibition of cholinergic neurons by GABA neurons can reduce acetylcholine release and disrupt the conversion of short-term to long-term memory (25). Abbas et al. (2016) also emphasized that defects in GABA signaling and excessive glutamate stimulation can lead to neurodegeneration and cognitive impairment (26). In contrast, there are some inconsistent studies. For example, Gomez et al. (2018) showed that cholinergic neurons are more active during learning (27). This discrepancy may be due to differences in animal models and the way AD is induced.

The results of the present study showed that in the aerobic training group, GABA-RA gene expression levels were significantly higher and Aβ gene expression was lower than in the AD group. In this regard, Liang et al. (2025) recently reported a significant reduction in Aβ in the hippocampal tissue of AD rats after four weeks of swimming training (28). Liu et al. (2024) also found that a period of aerobic training including running and swimming significantly increased hippocampal GABA-RA gene expression in AD mice (10). These studies, consistent with the present results, suggest that exercise training can improve cognitive function and reduce amyloid burden through multiple cellular and molecular mechanisms. These mechanisms include increased expression of GABA-RA and nAChR receptors, improved cerebral blood flow, increased neurogenesis, reduced reactive oxygen species (ROS), reduced tau protein phosphorylation, and modulation of the cholinergic system (29). In addition, increased catecholamine secretion due to exercise enhances memory and improves mood (30). At the cellular level, exercise training strengthens neural connections and maintains synaptic structure by increasing the expression of neurotrophic genes such as GDNF and Bcl-2, decreasing the expression of GFAP, and increasing synaptic proteins such as PSD95 and synaptophysin (31).

Among other results, it was found that with black pepper consumption, GABA-RA gene expression was significantly higher and Aβ gene expression was significantly lower than in the control group. In this regard, Du et al. (2013) showed that piperine can enhance memory, reduce stress, and play a role in the prevention of AD (17). Piperine, present in black pepper, improves memory function by increasing NGF levels and protects neurons from free radical damage. This substance can inhibit the process of inflammation and oxidative stress by reducing inflammatory cytokines such as TNF-α, IL-2, and NF-kB (32). On the other hand, by examining the neuroprotective effects of black pepper in age-related neurodegenerative disorders, it has been shown that piperine prevents the onset of AD symptoms by modulating cell survival and death signals (32). Black pepper can improve cognitive function and reduce amyloid burden through multiple molecular mechanisms, including increasing NGF, reducing inflammatory cytokines, inhibiting ROS, and modulating apoptosis pathways (33). At the cellular level, piperine prevents synapse degradation by inhibiting NF-kB and reducing chronic inflammation, and strengthens neural connections by increasing neurotrophic factors. Also, by increasing GABA-RA expression, the balance between neuronal excitation and inhibition is maintained and excessive glutamate stimulation, which leads to synaptic toxicity, is prevented (33).

Finally, the results showed that GABA-RA gene expression in the training + black pepper group was significantly higher and Aβ gene expression was lower than in the AD group. Also, in the combined training + black pepper group, GABA-RA gene expression was significantly higher and Aβ gene expression was significantly lower than in the aerobic training and black pepper groups; in such a way that aerobic training and black pepper had an interactive effect on reducing Aβ. Since, according to our knowledge, the interactive effect of exercise training and black pepper consumption on improving AD markers has not been studied so far; therefore, it is not possible to compare the results of the present study with other studies. According to these results, the effects of exercise training and active ingredients in black pepper on GABA-RA and Aβ appear to be due to a combination of reduced inflammatory factors, reduced oxidative stress markers, reduced ROS, and increased brain neurotrophins. The lack of measurement of these factors was a limitation of the present study, so it is suggested that these mechanisms be considered in future studies.

5. Conclusion

Generally, the results of the present study showed that aerobic exercise and black pepper increased GABA-RA gene expression and decreased Aβ gene expression in AD samples, and the interaction of aerobic exercise and black pepper had a synergistic effect on Aβ reduction.

6. Highlights

The results indicated the effects of aerobic training and black pepper on markers of memory impairment in animal samples with AD, which could provide a basis for a therapeutic mechanism in this group of patients. However, given that this study was of a fundamental nature, its generalization to human populations requires further studies, especially of an applied nature.

Statements

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Conflicts of Interest

There is no conflict of interest between the authors.

Authors' Contributions

The study was designed by Mehrzad Moghadasi and Zahra Mosalanezhad; Data were collected and analyzed by Mehrzad Moghadasi and Marjan Ghafari; Data interpretation and manuscript preparation were undertaken by Mehrzad Moghadasi, Marjan Ghafari and Zahra Mosalanezhad. All authors approved the final version of the paper.

Data Availability Statement

The dataset presented in the study is available on request from the corresponding author during submission or after its publication. The data are not publicly available due to privacy or ethic.

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