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Evaluation of the synergistic effects of resistance training and saffron supplementation on reducing amyloid beta accumulation and improving cognitive function in a rat Alzheimer's model

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ABSTRACT

Introduction: Alzheimer's disease is a major challenge for the scientific and medical community. This progressive disease is associated with weakening brain function and leads to disorders in thinking and memory, while no specific and definitive treatment has been provided for it so far. So far, many studies have been conducted to find solutions to improve the condition and reduce the effects of this disease. This article investigates the combined effect of resistance training and saffron extract consumption on spatial memory and the amount of amyloid beta accumulation in the hippocampal tissue of animal models of Alzheimer's disease.

Material & Methods: In this experimental study, 32 adult male Alzheimer's rats were randomly divided into four groups including control, resistance training, combination of resistance training and extract, and extract alone. To create an Alzheimer's model, amyloid beta 42-1 was injected into the hippocampus. The resistance training program was performed for 12 weeks with 5 weekly sessions. The radial maze test was used to measure spatial memory. The amount of amyloid beta protein was calculated using the ELISA technique and data analysis was performed using one-way analysis of variance.

Results: The findings indicate that after 12 weeks of resistance training with saffron extract, spatial memory performance in the intervention groups was significantly improved compared to the control group ($P < 0.05$). In addition, the amount of amyloid beta accumulation in the groups that received resistance training, resistance training with saffron extract, and saffron extract alone was significantly reduced compared to the control group ($P < 0.05$).

Conclusion: It seems that the combination of resistance training with saffron extract can improve spatial memory performance and reduce amyloid beta accumulation in the hippocampal tissue of male mice with Alzheimer's disease.

Keywords: Resistance Training, Saffron, Alzheimer's, Spatial Memory, Amyloid Beta.

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1. Introduction

Alzheimer's disease is a progressive and chronic disorder of the nervous system that causes the destruction of nerve cells and leads to a severe decline in memory function and cognitive abilities. This disease is considered one of the main causes of dementia and is mainly observed among the elderly [1]. This disease is accompanied by the gradual destruction of brain cells and a decrease in cognitive function. Its clinical features include a decline in cognitive functions, impairment in daily activities, and changes in the individual's behavior. Various factors play a role in the occurrence of Alzheimer's, including oxidative stress, the accumulation of extracellular amyloid beta plaques (Ab), the formation of intracellular nerve fiber tangles (NFT), neurotoxicity, genetic mutations, neuro inflammation and the process of apoptosis [2].

Two main factors affecting the development of this disease have been widely studied and investigated. The first factor is the accumulation of amyloid beta peptides and the second factor is the accumulation of phosphorylated tau proteins. It seems that the reduction of both factors is essential for successful treatment. Animal models, particularly Alzheimer's disease rats, are valuable tools for testing new therapeutic approaches, with the hope that the results of such studies will be extrapolated to humans [3]. Amyloid beta is a protein composed of 36 to 43 peptides and is the main component of the amyloid plaques seen in the brains of Alzheimer's disease patients. These peptides are produced by the degradation of the amyloid beta precursor protein (APP) by the enzymes beta-secretase 1 and gamma-secretase. The aggregation of amyloid beta results in the formation of soluble oligomers that have flexible structures and appear in a variety of shapes. It is now believed that some misfolded oligomers (called seeds or microbeads) can induce the misfiling of other amyloid-beta molecules. This process, through a chain reaction, shows a mechanism similar to prion infections. Such oligomers have strong toxic effects on nerve cells [4]. On the other hand, the tau protein also plays an important role in Alzheimer's disease, forming misfolded oligomers similar to prions. Evidence suggests that misfolded amyloid beta can even lead to misfiling and misfiling of tau, and this complex interaction between the two proteins plays a key role in the progression of the disease [5]. Amyloid beta is the main component of amyloid plaques, which are seen as extracellular deposits in the brains of people with Alzheimer's disease. It can also cause deposits in the blood vessels of the brain during cerebral amyloid antipathy. Amyloid plaques are composed of a tangle of organized strands called "amyloid fibrils." This type of protein folding is seen in other peptides such as prions, which are responsible for the development of protein misfiling diseases [6].

In recent years, research results have shown that increased amyloid beta causes a decrease in nerve cells and memory impairment, and suppression of its expression leads to improvement in memory and an increase in the number of synaptic connections [7]. Currently, there is no definitive cure for Alzheimer's, and drug treatment strategies focus only on the signs and symptoms of the disease, which often do not lead to satisfactory results [8, 9]. On the other hand, research has shown that people with less exercise and physical activity throughout their lives are more susceptible to Alzheimer's disease and have a twofold incidence rate compared to active people [8, 10]. Exercise increases synaptic variability and improves the antioxidant system, improves signaling, plasticity, and synaptic transmission, and reduces apoptosis [11]. Meanwhile, exercise training increases memory and learning through mechanisms such as increasing BDNF levels as a mediator of synaptic effects, neural connections, and plasticity in the brain. Exercise also improves the function of nerve cells by increasing cell proliferation in the hippocampus, inhibiting apoptosis in the dentate gyrus of the hippocampus, and increasing the synaptic space in different parts of the brain. The information obtained from the research findings showed that exercise activities increase cognitive performance in people in old age, while some other researchers believe that physical activity and exercise have little effect on this performance [12]. Increasing physical activity increases brain activity, especially in the hippocampus, and as a result, reduces the secondary effects of Alzheimer's disease [13]. According to the results of the research, regular exercise is useful in preventing destructive pathways and neuroinflammation, especially in the hippocampus. It has also been shown that regular exercise has proven effects on improving cognitive function, increasing the expression of brain growth factors and neurogenesis, synaptic plasticity, reducing oxidative stress, and delaying the progression of neurodegenerative diseases, while potentially slowing the progression of Alzheimer's disease [14].

In a study conducted by Naderi et al. in 2018, it was found that six weeks of high-intensity exercise training in rats with Alzheimer's disease improved cognitive functions and reduced the accumulation of amyloid beta protein and inflammatory factors in the hippocampus. Also, Shiva Khorramshahi et al. in 1402 examined the effect of eight weeks of voluntary exercise on the amount of amyloid beta in the hippocampal tissue of male Wistar rats, and their results showed that exercise activities can reduce the level of amyloid beta accumulation [15]. On the other hand, there are medications to prevent the progression of Alzheimer's disease, which usually have limited therapeutic effects and may have many side effects.

2. Methodology

2.1. Materials and methods

This study, which was designed as a post-test experimental study, consisted of four experimental groups, which were respectively: Alzheimer's group, the control group, the Alzheimer's group under aerobic exercise, the Alzheimer's group under aerobic exercise with extract, and finally the group receiving only extract. The laboratory animals used included rats weighing about 260 to 270 grams, which were obtained from the Pasteur Institute of Iran. After being transferred to the animal center of the Vira Armanian Institute in Rasht, the animals were maintained under controlled conditions. These conditions included a light cycle of 12 hours of light and 12 hours of darkness, an ambient temperature in the range of 22 to 24 degrees Celsius, and a relative humidity between 50 and 60 percent. During the study, the animals had free access to food and water [18].

2.2. Participants

Rats in the extract group and the training group received the extract at a rate of one hundred milligrams per kilogram of body weight, once a day at 8 am for 7 days a week for 12 weeks via gavage.

2.3. Measurements

To induce Alzheimer's disease, amyloid beta 42-1 purchased from Sigma-Aldrich, USA, was used, dissolved in sterile double-distilled water, and incubated at 37°C for one week. Terpinolene was dissolved in 0.5 cc of sterile double-distilled water at a dose of 100 mg/kg and injected intraperitoneally into rats via an insulin syringe. The animals were anesthetized by intraperitoneal injection of ketamine (50 mg/kg) and xylazine (5 mg/kg), and after being placed in a stereotaxic apparatus, the hair on the head was shaved, and a sagittal incision was made, the bregma and lambda sutures were completely identified. Then, the skull was gently drilled. For amyloid beta injection, 2 microliters of amyloid beta were slowly and bilaterally injected using a Hamilton syringe through holes made in the brain with a calculated depth. To completely absorb the drug, the injection lasted for 60 seconds. It is worth noting that the needle remained in place for 2 minutes [19, 20].

The dried stigma of the edible saffron plant, known as Qaenat saffron, was prepared. Then, the soaking method was used to prepare the aqueous extract of saffron. In this way, after pouring the dried saffron stigmas into a cylindrical glass, ten milliliters of distilled water were added to the containers for each gram of saffron stigma and it was gently mixed for 72 hours at 30°C on a rotating machine to ensure good extraction. Then, the solvent and plant mixture were separated by a filter to obtain the primary extract. The initial extract was introduced into a vacuum distillation apparatus and at a temperature of 80°C, the solvent was slowly evaporated to obtain a concentrated extract. The resulting solution was placed in a bain-marie apparatus at a temperature of 55°C for two weeks so that the extract solvent also slowly evaporated and the extract powder was left behind [21].

2.4. Intervention

2.4.1 8-arm radial maze test for memory assessment

This apparatus has 8 completely identical arms that branch radially from a smaller circular central plate with a diameter of 25 cm and its height from the ground is about 60 cm. The arm length is 50 cm, its width is 10 cm and the height of the walls is 13 cm. Due to the photophobia of rats, the cage and apparatus were dark and opaque. First, one day before training and testing, food was completely removed from the rats' reach. On the training day, rats were transferred to the laboratory and introduced to the maze. In this way, food was placed as a reward in one of the arms of the maze. To implement learning and memory processes on the first day, without measuring time, the rat was released into the central compartment of the maze. And as soon as it found the food, it was allowed to eat some of the food. The purpose of this stage was firstly to make the animal learn that there was food in one arm of the maze and secondly to remember which maze the food was in. On the second day of the test, the food was placed in the same specific arm and the rat was released into the center of the maze and allowed to search for food. The time spent finding food was measured by a stopwatch and if the rat did not find the food within 10 minutes, it was removed from the maze. In the radial maze test, the shorter the time it took to find food, the better the memory was [22].

2.4.2 Resistance training program

The exercises included 3 training sessions per week (Saturday, Monday, and Wednesday) for 8 weeks, which included 3 sessions and each session included 4 times climbing a special ladder with a height of one subway and twenty-six steps, with a distance of 4 cm between the steps and a 30-second rest period for the animals between each session. After tying a weight to the animals' tails, they were forced to climb the ladder vertically. In the first week, the amount of weight tied to the animals' tails was 50% of their body weight, and gradually from the second week, 60%, the third week, 70%, the fourth week, 80%, the fifth week, 90%, the sixth week, 100%, the seventh week, 110% and the eighth week, 120% of their body weight [23].

2.4.3 Tissue collection

48 hours after the last intervention, all rats were fasted for 8 to 10 hours and weighed before starting the tissue collection. Then, anesthesia was performed by inhalation and with chloroform. After complete anesthesia and pain testing and ensuring unconsciousness, to collect the samples, the animal's head was separated from the neck area using a special guillotine. First, the skull was split using a scalpel and the brain was carefully removed. Then, the healthy brain was divided into two halves using a scalpel (precisely) in the middle and, according to the coordinates of the hippocampus, the hippocampus was separated from the limbic system using a sinusoidal atlas. Then, hippocampal samples were collected and stored at -70°C for subsequent measurements [24]. After separation, the samples were placed in a 10% formalin solution for 24 to 72 hours (to maintain the cells and body tissue in a similar and close to the living state). The samples were then dehydrated with ethyl alcohol. After dehydration, the samples were placed in xylol so that paraffin could be used to harden and prepare the tissues for tissue casting and sectioning [25].

2.4.4 How to measure beta-amyloid by staining

First, the slides were deparaffinized and the dehydration steps were performed. Then, for 10 to 15 minutes, a 1% thioflavin solution (T1892-Sigma) was poured onto the slides in the dark. Then, the slides were washed with 80% ethanol two times, each time for three minutes, and placed in 95% ethanol for three minutes. After that, the samples were washed with distilled water, and glycerol and phosphate buffered saline solution was poured onto the samples, and they were placed on the slides for fluorescent photography with an Olympus microscope [25].

2.5. Statistical Methods

Descriptive statistics were used to describe the data and inferential statistics were used to analyze the data. The Shapiro-Wilk test was used to determine the normality of the population, and according to the results obtained, all data had a normal distribution. To compare the results of the desired experiments, a one-way analysis of variance was analyzed using SPSS version 20 software.

3. Results

To observe the weight of the subjects, weighing was performed at the time of arrival The subjects were subjected to the study. The mean and standard deviation of the weight changes of the groups during eight weeks are shown in Table 1.

Table 1. *Rat weight changes*

Variable	**Control**	**Resistance exercises**	Extract + resistance exercises	Extract
Weight of the first week of training (grams)	280/5±12/3	275±3/97	288 ± 7/8 2	**282±3/97**
The weight of the week of twelve exercises (gram	290/7±16/5	273/4±10/9	280±0/54	4.289 ± 9/9

According to the obtained results, there is a change in weight in all groups, in other words, it has increased in the control and extract groups, and the weight gain is more in the control group.

However in the aerobic exercise groups and the aerobic exercise and extract group, the weight change was associated with a decrease, and this decrease is more in the aerobic exercise group and the extract compared to the aerobic exercise group.

For investigations, an analysis of variance test was used after ensuring the natural data.

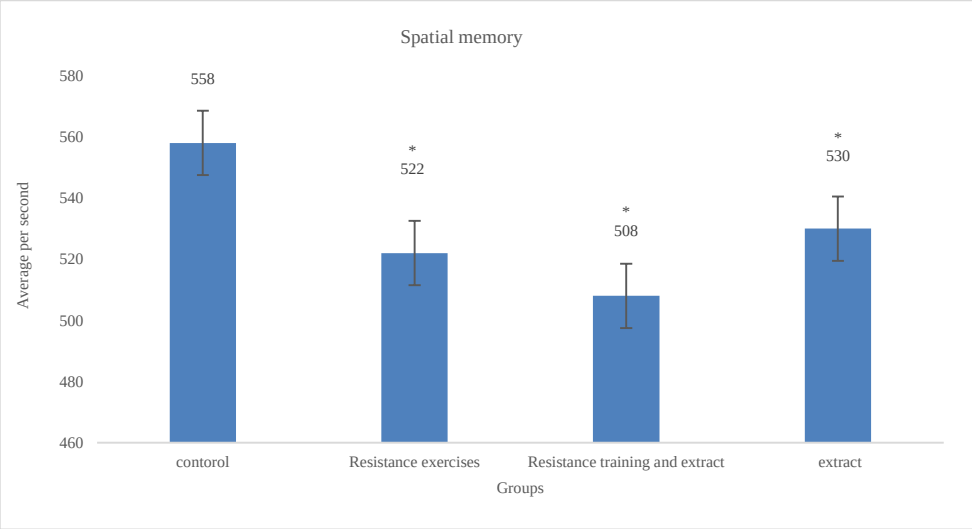
Table 2. *Results of analysis of variance*

ANOVA (Welch test results)	**Statistics**	**Degree of freedom 1**	**Degree of freedom 2**	**Meaningful**
Amyloid beta (pictogram per milligram of tissue)	0/985	7	12/97	0/002*
Spatial memory (seconds)	0/768	7	12/87	0/001*

The results of a one-way analysis of variance (Welch's test in the case of inequality of variances) showed that there was a significant difference between the research groups, and therefore, Tom Hahn's test was used to determine the difference between the groups.

Table 3. *Results of Tom Hen's post-test*

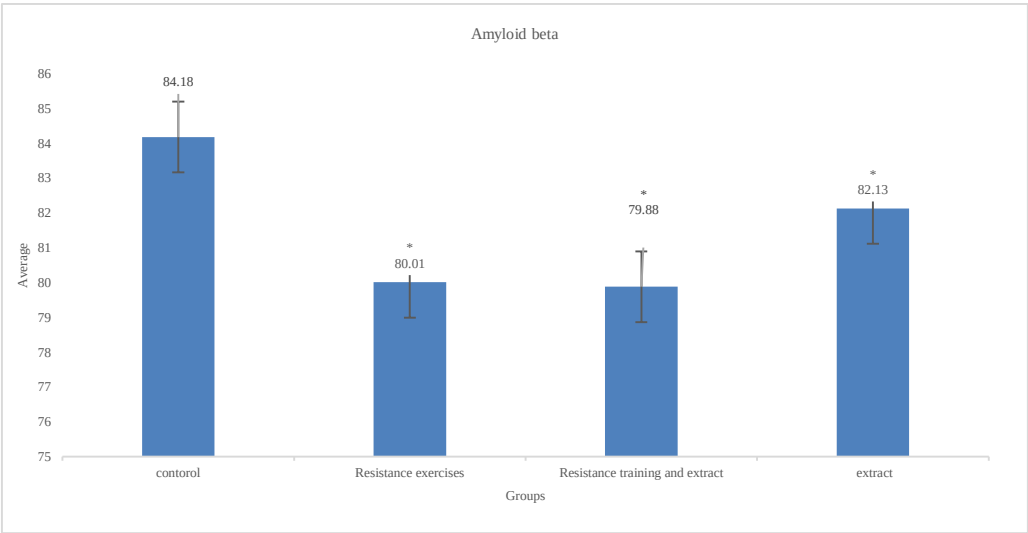
Groups		Average difference	Meaningfulness	Average difference	Meaningfulness
		Spatial memory		Amyloid beta	
Control	Resistance Exercise	0/020	0/001*	-0/208	0/002*
	Resistance Exercise and Extract	0/015	0/002*	0/114	0/001*
	Extract	0/019	0/003*	0/229	0/004*
Resistance Exercise	Resistance Exercise and Extract	-0/130	0/002*	1/750	0/003*
	Extract	-0/138	0/003*	-0/061	0/002*
Resistance Exercise and Extract	Extract	-0/022	0/002*	-0/223	0/001*



*Significant difference compared to the control group (P< 0.5)

Figure 1. *Difference in spatial memory compared to the control group in the research groups*

According to the results obtained from the present study, there is a difference in the changes in spatial memory in the studied groups between the control group with resistance training, the resistance training and extract group, and the extract group. In other words, resistance training, resistance training with extract consumption, and extract consumption improves memory. It should be noted that the effect is greater in the groups of rats that perform resistance training with extract, and this difference is greater in all groups.



** denotes a significant difference compared to the control group (P<0.05)*

Figure 2. *Ilustrates the difference in the mean amount of amyloid beta accumulation compared to the control group across the study groups*

The findings from this study indicate a significant difference in amyloid beta accumulation among the various groups when compared to the control group, particularly between the control group and the resistance

training group, as well as between the resistance training group and the extract group. In essence, resistance training appears to reduce amyloid beta accumulation in the hippocampal tissue. However, the difference between the group that engaged in resistance training and the group that participated in resistance training with saffron extract was not significant. While some differences were noted, they did not reach statistical significance. The results reveal that the reduction in amyloid beta accumulation in the hippocampal tissue of Alzheimer's rats who engaged in exercise training with saffron extract was less than that observed in all other groups.

4. Discussion

Today, the use of drugs and substances beneficial to the nervous system is an essential need. This is due to excessive mental health and optimal functioning of the nervous system in individuals. Given the increasing challenges of modern life, psychological pressures, and stresses caused by social conditions, the need for pharmacological interventions is felt. Research has shown that various drugs can help improve cognitive function and reduce complications and side effects. There is also support from others, which can play an important role in strengthening and protecting the nervous system. Considering this category and the use of drugs and medicines, it is possible to maintain the mental and physical health of individuals with great help[۲۶]. Exercise is known to be an effective way to improve blood flow in various organs. In this regard, saffron extract has been considered as a medicinal supplement. Clinical research shows that this extract has antidepressant properties and can help reduce anxiety levels and improve mental health. The results of these studies show that consuming saffron can be considered an effective treatment option for people struggling with mental and psychological problems. In general, combining exercise activities and the use of herbal extracts such as saffron can help improve the quality of life and mental health of individuals [28].

Based on the findings of this study, 8 weeks of aerobic exercise combined with saffron extract in Alzheimer's-induced rats in the control group had a longer duration and a lower frequency of exercise than the other groups. It was also found that the aerobic exercise group performed better than the group that only consumed saffron, which was better than the aerobic exercise and supplement consumption. Previous studies have suggested that energy in the brain is associated with cognitive function disorders, because brain cell functions such as energy and memory are dependent on cellular energy metabolism, and reduced available energy can disrupt the production of amyloid precursor products and tau and thus increase them in the brain [29].

In recent decades, the effect of physical activity on improving performance and memory as a preventive solution for dementia in healthy individuals and those with dementia-related diseases such as Alzheimer's disease has been well established [30].

In a study, it was proven that 8 weeks of exercise training improved memory and spatial performance in Alzheimer's rats, stating that exercise training seems to be a non-pharmacological strategy for preventing dementia in Alzheimer's disease.

Meanwhile, saffron and its medicinal substances have a strengthening effect on animals with healthy memory but can cause a reduction in memory deterioration. Previous studies have suggested that saffron plant extract affects the processing and memory of mice and causes a significant decrease in memory [3].

There is ample evidence that degenerative diseases of the central nervous system, including Alzheimer's and Parkinson's, are caused by cellular damage caused by free radical activity, and saffron extract contains abundant carotenoids, which are potent antioxidants and can protect the central nervous system from damage [32]. Other studies have suggested that saffron extract and its nutrient crocin can improve a variety of memory disorders by different mechanisms. Further, based on evidence, both microglia and astrocytes are fed with AB. Its main role in the pathogenesis of Alzheimer's has been established. In particular, AB deposition in extracellular plaques causes synaptic dysfunction, neuronal apoptosis, and memory loss. Although the mechanism of the toxicity is unclear, the overall conclusion is that the accumulation of AB peptide in the brain induces oxidative stress and neurodegeneration. Evidence suggests that AB and its deposition in the brain with NFT formation is a key pathological feature in Alzheimer's disease.

The present study showed that the level of amyloid beta in the hippocampal tissue of rats in the resistance training and extract groups, rats in the resistance training and extract groups compared to the control group decreased and this difference was significant, but this difference was not observed in rats in the resistance training and supplement group. The resistance training and supplement group was not compared to the resistance training group, but in the resistance training and supplement group, less amyloid beta accumulation was observed.

In confirmation of these findings, Kang and Chu 2014, Liu et al. 2013 and Yaghoubi et al. 2015 stated in their results that exercise can improve performance in patients with Alzheimer's disease [3]. They stated in their results. The high volume of exercise reduces the amount of neuronal loss and reduces the amount of beta fusion in the hippocampal tissue of Alzheimer's rats [33]. In this regard, Yom et al. (2008) stated in their study that 16 weeks of exercise training significantly reduced AB in the brain of Alzheimer's mice. The results showed that the control group of Alzheimer's mice had higher levels of beta-amyloid in the hippocampal tissue than the control

group of Alzheimer's mice. In another study, Yoda et al. (2009) stated in their results that no change was observed between the groups in the amount of beta-amyloid in the hippocampal tissue after 4 months of exercise training [34]. The results of this study were not consistent with the results of the present study. Also, Ohiko et al. (2014) studied 12 weeks of exercise training on the pathology of beta-amyloid in Alzheimer's mice and, based on the findings, exercise training improves general movement and significantly identifies and reduces beta-amyloid in the hippocampal tissue [35]. The mechanisms related to changes caused by exercise in the brain are a combination of its production and clearance or destruction. Exercise training can mediate the metabolism of the precursor AAP and the AB cascade in reducing AB production. Consequently, this could affect learning and memory in trained animals. In this context, Bakker et al. (2010) suggested that increased APP breakdown may be involved. Since exercise increases the expression of gene products at both mRNA and surface levels, it induces anatomical, neurochemical, and electrophysiological changes that enhance neuronal plasticity. It may act directly or indirectly to regulate amyloid levels. One possibility is that exercise can regulate proteasome activity and thus can promote proteolytic cleavage of APP. A second possibility is that exercise directly modulates metabolic programs by increasing neuronal activity. Alternatively, cholinergic activity could be involved in the regulation of the cholinergic system by increasing exercise-induced neuronal plasticity.

Studies show that all people, especially the elderly, improve memory, performance, and performance by doing regular aerobic exercises [35]. In summary, it can be said that researchers have limitations such as abnormal saffron plant extract and the intensity and duration of aerobic.

5. Conclusion

It seems that the combination of resistance training with saffron extract can improve spatial memory performance and reduce amyloid beta accumulation in the hippocampal tissue of male mice with Alzheimer's disease.

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