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The effect of endurance, resistance and concurrent exercise with oral consumption hawthorn extract in some inflammatory biomarkers in induced Alzheimer's male rats

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ABSTRACT

Introduction: endurance and resistance exercise and the consumption of hawthorn alone and in combination have an effect on Alzheimer's disease.This study was conducted with the aim of the effect of hawthorn consumption and exercise on the inflammatory indices of Alzheimer's rats by trimethyltin chloride (TMT).

Materials and methods: rats were randomly divided into 9 healthy control and Alzheimer's groups with interventions (control, endurance training, resistance training, combined training, hawthorn, endurance training + hawthorn, resistance training + hawthorn, combined training hawthorn). Then Alzheimer's disease developed. performed resistance , combined ,endurance exercises every week (12 weeks). Finally, blood was taken from the inferior vena and the inflammatory variables CRP, IL-6 ,TNF-α were measured by ELISA method. The Shapiro-Wilk test was used to check the normal distribution of the data, and the one-way analysis of variance (ANOVA) was used to check the mean difference between the groups (Tukey's test). $P < 0.05$ were considered statistically significant.

Results: results showed that the induction of Alzheimer's disease induced by TMT caused a significant increase in the levels of TNF α, IL 6, CRP in the Alzheimer's control group compared to the healthy control. And 12 weeks of combined training with and without hawthorn had a significant decrease in the level of these variables compared to Alzheimer's control.

Conclusion: As a result, endurance and resistance sports along with the consumption of hawthorn lead to the reduction of some inflammatory factors in Alzheimer's rats.

key words: Alzheimer Disease , Hawthorn , IL-6 , TNF-α , CRP

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Introduction

The organometallic compound trimethyltin chloride (TMT) is known to exert neurotoxicity in the cerebral cortex [1].TMT can induce oxidative stress in a variety of tissues such as liver, brain and kidney which Oxidative stress is a major inducer of inflammation [2].Also ,The results of the Different studies showed that after the injection of TMT, neurodegeneration similar to that seen in neurodegenerative diseases such as Alzheimer's occurred [3].

Alzheimer's disease (AD) is a severe, chronic and progressive neurodegenerative disease associated with memory and cognition impairment [4].

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patients with AD, the oxidative stress and inflammation in the affected brain was noted to be increasing at a rapid rate [4, 5]. which the evidence shows systemic inflammation plays a fundamental role in AD [6].So that the increase in the levels of inflammatory biomarkers, including interleukin 6 (IL 6), tumor necrosis factor (TNF α) and C-reactive protein (CRP) have been observed in the elderly with Alzheimer's disease [7, 8].TNF α and IL 6 of inflammatory cytokines and CRP is an acute phase protein which are produced during acute inflammation [9-11].

Since inflammation plays a significant role in AD, anti-inflammatory strategies may have preventive or therapeutic benefits in AD. One of these strategies is regular physical activity [12].evidence indicates that Exercise induces an anti-inflammatory environment in peripheral organs and increases expression of anti-inflammatory molecules within the brain [12]. Also, moderate physical exercises reduce inflammation by regulating the secretion of interleukin and TNF α [13]. On the other hand, exercise training increases antioxidant enzyme activities and removes oxidative stress [14, 15]. but which type of exercise is more effective is not yet clear.

However The results of the Different studies showed that, acute and high intensity exercise may cause muscle injury and induce inflammation [16].Also, muscle exercise can sometimes increase the production of reactive oxygen species (ROS) and lead to oxidative stress in numerous tissues, including blood and skeletal muscles [15]. that To solve this problem, it is better to exercise along with the consumption of some supplements, including medicinal plants such as hawthorn. Hawthorn belongs to the Crataegus genus of the Rosaceae family and is an important medicinal plant [17]. hawthorn fruit is a potent inhibitor of , TNF α, , and IL 6 gene expression [18].that Recent reports have shown hawthorn fruit exhibits anti oxidant, and anti-inflammation and hypolipidemic activities [17, 18]. also Hawthorn extract reducing oxidative stress in the brain [19].The beneficial effects of exercise training and Hawthorn are remarkable in that they have an almost diametrically opposed effect to the pattern of structural and functional deficits [19].

According to our information, no study has been conducted on the simultaneous effect of three types of endurance, resistance, and combined exercise along with the consumption of hawthorn extract on inflammatory factors in Alzheimer's male rats. Therefore, in the present study we aimed to find the effect of endurance, resistance and combined exercise with the consumption of hawthorn extract on some inflammatory factors in Alzheimer's male rats.

Methods and Materials

Animals

sixty three male Wistar rats (4–5weeks old, initial weight 200±20 g) were used for this study. All animal were housed in standard cages under temperature, humidity and light controlled conditions (20_ 24 °C, 45_55% humidity, 12 h light/12 h dark cycle, respectively). The animals had ad libitum access to food and water. Animal experimental procedures were in accordance with institutional guidelines and approved by the ethical committee of laboratory animals Care at Bu-Ali Sina University (BASU), Hamedan, Iran.

Ethical considerations

The steps of the current research were carried out based on the guidelines of the National Research Council for the care and use of laboratory animals. And the effort was to eliminate any unnecessary stress to the animals. The protocol of this study has been approved by the research ethics committee of Bu-Ali Sina University of Hamadan with the code IR.BASU.REC.1400.050.

Experimental protocol

All animals were familiarized with the atmosphere of animal exercise physiology laboratory for 1 week. At the end of this period, rat were prepared for induction of Alzheimer's disease with the drug trimethyltin chloride (TMT). The organometallic compound trimethyltin chloride (TMT) is known to exert neurotoxicity in the cerebral cortex And hippocampus and induce learning and memory impairments Similar to those of AD in animal models [1]. In order to induce Alzheimer's disease in male field rats, 8 mg/kg of TMT (Sigma Aldrich, St. Louis, Missouri, United States) was injected intraperitoneally with 1 mg/kg of freshly

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dissolved normal saline buffer. After a week, the behavioral signs of Alzheimer's were observed in the rats. These Behavioral symptoms include: aggression and hyperactivity , muscle tremors, increased body temperature, nausea, convulsions, twisting of the tail, self-gassing. Then they were randomly divided into 9 groups of 7 each. healthy control group (H), Alzheimer's diseased control (A), Alzheimer's diseased with swimming endurance exercise (E), Alzheimer's diseased with hawthorn consumption (Ha), Alzheimer's diseased with swimming endurance exercise and hawthorn consumption (E+Ha) Alzheimer's disease with resistance training (R), Alzheimer's disease with resistance training and hawthorn (R+Ha), Alzheimer's disease with combined exercise (E+R), Alzheimer's disease with combined exercise and hawthorn (E+R+ Ha).

Preparation steps of hawthorn feed

Consumed plant material Normal animal feed was purchased from Behparvar Animal Feed Company (Tehran, Iran). Hawthorn was purchased from a local market in Isfahan City (Iran) and approved by the Department of Agriculture at Bu Ali Sina University in Hamadan. After scientific approval, the dried Hawthorn fruit was ground with a special spice grinder and the resulting powder was mixed (with a weight ratio of 6.25%) with standard rat food, to the extent that the ingredients was turned into completely homogeneous. The resulting dough was poured into a funnel and cut into pellets after drying, they were given to the Hawthorn food groups.

Swimming training protocol

Swimming training was performed in a swimming pool (50x50x80 cm) (for each rat) filled with tap water warmed (approximately 25-30°C) by an electric heater, and a pump was used to continuously make waves in order to prevent the rats from floating. The rats (3+5) were exposed to forced swim test; the swimming program included two phases: adaptation and training. In the first week (adaptation), the rats swim 10 min per day for 5 days (in 1 week). The training period began from the beginning of the second-week, and the swimming duration was progressively increased from 15 min to approximately 60 min per day (up to the twelfth week); from the tenth to the twelfth week, two 1-hr sessions were conducted every day. This protocol was performed and maintained up to the end of the training program on Saturdays, Sunday, Mondays, Wednesday, and Thursdays, while Tuesday and Friday was without any swimming activity for the experimental rats. The rats were exposed to a swimming test from 08.30 am to 14.00 pm (Table1).

Resistance training protocol

The rats in the resistance exercising groups (Groups 6 and 7) were trained five days a week for 12 weeks. A weight was attached to their tails; that they had to lift this weight while climbing up a 26-step 1-meter-long ladder (with angle of 85 degrees to the ground). In order to adaptation, the rats were climbed up the ladder for three sessions without loading. The rats in the resistance groups were precisely weighed every week. The initial weight was 40% of a rat's body weight, which was gradually increased up to 150% of the rat's body weight in the following 12 weeks (10% each week). Each training session consisted of three sets of four repetitions, with a break of 30 to 60 seconds between each to repetitions and 120 to 150 seconds between each to sets. This protocol was performed on Saturdays, Sunday, Mondays, Wednesday, and Thursdays, while Tuesday and Friday was without any resistance activity for the experimental rats. The rats were exposed to resistance training from 08.30 am to 14.00 pm (Table 2).

Combined training protocol

The combined training program consisted of 12 weeks, five days per week so that the rats in the combined training groups (Groups 8 and 9) performed swimming training three days per week (Saturday, Monday, and Thursday according to the swimming training protocol) resistance training was performed two days per week (Sunday and Wednesday according to the resistance training protocol).

Blood sampling

One day after the end of the training and supplementation protocol, the rats were anesthetized by sodium pentobarbital (50 mg/kg

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body weight). To measure the serum levels of inflammatory parameters, blood was collected from the inferior vena cava of rat, and the serum was separated by centrifugation. The sera were poured into a microtube and kept at minus 20 degrees Celsius until the end of the work. Research variables were measured by ELISA method.

Statistical analysis

The statistical analyses were performed using the SPSS 22.0 software (SPSS, IBM, Chicago, Illinois, United States). The Shapiro-Wilk test was used for the normality of the data distribution. One-way analysis of variance test (ANOVA) (Tukey's post-hoc test if needed) was used to check the difference in means**.**

Results

In our study, systemic inflammation was increased following the induction of Alzheimer's disease by TMT. Statistical analysis showed that there was a significant difference between the groups in the serum levels of CRP (P=0.000, F=20.641), IL 6 (P=0.000, F=161.322) and TNF α (P=0.000,F=26.834) Alzheimer's and healthy rats in different group. That After 12 weeks of endurance, resistance, combined exercises and oral consumption of hawthorn alone and in combination, we saw significant changes in the levels of CRP, IL-6 and TNFα in the serum of Alzheimer's rats.

In the two-by-two comparison of groups based on Tukey's post hoc test The results showed that the induction of Alzheimer's caused an increase in the levels of TNF α (P=0.000), CRP (P=0.000) and IL 6 (P=0.000) in the serum of Alzheimer's control group rats (A) compared to the healthy control (H).

So that, 12 weeks of combined endurance and resistance training along with oral consumption of hawthorn caused a significant decrease in TNF-α level in groups E+ R+ Ha (p=0.000), R +Ha (p=0.023), E+ Ha (p=0.000), E+ R (P=0.002) compared to the Alzheimer's control group. Our E+R+Ha group has decreased more than other groups. In addition, no significant difference was observed compared to the Alzheimer's control group E(p=0.411), R (p=0.999), Ha (p=0.831).(Fig 1)

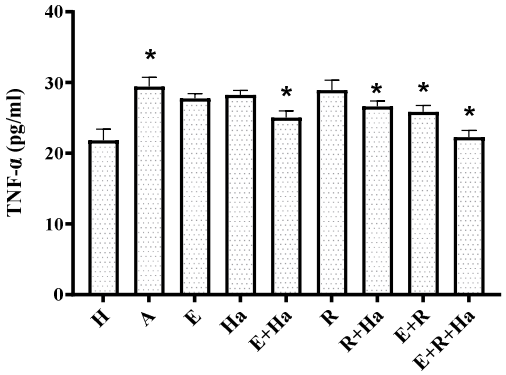

Fig 1: Comparison of mean and standard deviation TNF-α of serum level of field rats in different groups. * (Means a significant difference compared to the Alzheimer's control group)

Also, 12 weeks of combined endurance and resistance training alone and along with oral consumption of hawthorn caused a significant decrease in IL-6 levels in groups E+R+Ha (p=0.000), R+Ha (p=0.000). E+Ha(p=0.000), E+R(P=0.000), R(P=0.001), E(P=0.009) compared to Alzheimer's control group. But the E+R+Ha group has decreased more than the other groups. In addition, no significant difference was observed in the Ha group (p=0.613) compared to the Alzheimer's control group. (Fig 2)

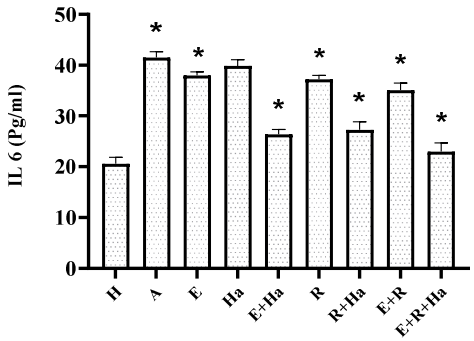

Fig 2: Comparison of mean and standard deviation IL-6 of serum level of field rats in different groups. * (Means a significant difference compared to the Alzheimer's control group).

And finally, 12 weeks of combined endurance and resistance training alone and along with oral consumption of hawthorn caused a significant decrease in CRP levels in groups E+R+Ha(p=0.000), R(P=0.000), E (P=0.000) R+Ha(p=0.001), E+Ha(p=0.000), E+R(P=0.000), Ha(p=0.020) to Proportion of Alzheimer's control

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group. But the E+R+Ha group has decreased more than the other groups. (Fig 3)

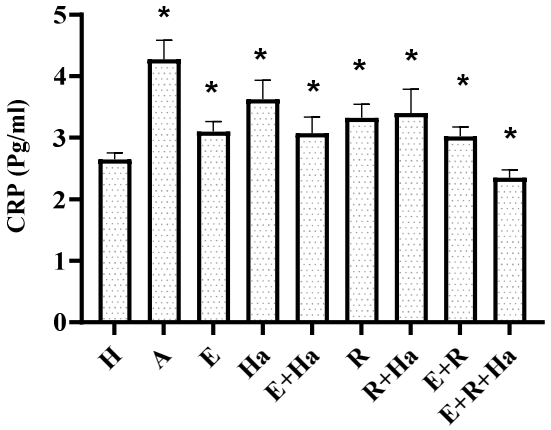

Fig 3: Comparison of mean and standard deviation CRP of serum level of field rats in different groups.
* (Means a significant difference compared to the Alzheimer's control group).

Discussion

Alzheimer's disease (AD) is a neurodegenerative disorder. that chronic inflammation has an important role in the onset and progression of of this disease. Mediators involved in the initiation of systemic inflammatory responses include inflammatory cytokines such as CRP, IL 6 and TNF-α [8, 20]. which research has shown regular exercise is considered as a kind of natural protector against chronic inflammatory diseases by releasing anti-inflammatory cytokines into the circulation [21].Although exercise may initiate a series of inflammatory cascades [21].To solve this problem, we use supplements along with exercise. For this reason, in this research, to relieve inflammation we used hawthorn extract along with exercise.

In this study, the effects of combined endurance and resistance exercise along with hawthorn extract on some inflammatory factors (IL 6 and TNF α and CRP) in Alzheimer's rats have been investigated. Our results showed that the induction of Alzheimer's disease caused by TMT increased the levels of TNF- α and IL-6 and CRP in the serum of rats in the Alzheimer's control group compared to healthy controls. And 12 weeks of combined training with hawthorn caused a significant decrease in the levels of these variables compared to other groups. The reduction of these variables in the E+R+Ha group was not different from the healthy control group. TNF- α It is mainly produced by monocytes/macrophages [22].In chronic systemic inflammation, there is usually a two- to three-fold increase in the systemic concentrations of α TNF, IL6, and CRP [23]. Evidence shows that exercise with anti-inflammatory effects reduces TNFα [24].

IL-6 It is generally classified as a pro-inflammatory cytokine because it is secreted by T cells and macrophages, activates the immune system and leads to inflammation [8]. Regarding aerobic exercise, our results were consistent with Nicklas et al who showed that regular aerobic exercise is effective in reducing IL-6 levels [25]. One of the main effects of IL 6 is stimulating the production of CRP [9]. CRP It is an acute phase protein that is produced in the liver and is released into the bloodstream during an inflammatory period [9]. Another recent meta-analysis on elderly people showed that exercise intervention reduces CRP levels [26].

Evidence shows that Alzheimer's disease is associated with increased systemic inflammation that Both acute and chronic systemic inflammation is characterized by the systemic production of C reactive protein (CRP) from the liver and the proinflammatory cytokine tumor necrosis factor α (TNF α) from macrophages and IL-6 [20, 27].

The results of previous studies show that both aerobic and resistance exercise training causes a decrease in TNF α, IL 6 and CRP levels, which suggests that exercise training can reduce inflammation in elderly individuals with more significant changes following aerobic exercise training [28]. Evidence also shows that The levels of the proinflammatory cytokines TNF α, and IL 6 are elevated in the cerebrospinal fluid, serum, striatum, and substantia nigra of Parkinson's disease(PD)patients that exercise has been able to reduce the pathogenesis of AD and PD in patients and animal models by reducing the expression of pro-inflammatory cytokines [16]. However, according to a study conducted on people with type 2 diabetes (T2DM), both TNF α and 6 (IL 6) and CRP cause systemic inflammation in people with T2DM But in this study, exercise could not have any significant effect on IL-6, TNF α and

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CRP because the type and intensity of their exercise were different [29].

In this way, according to previous studies, it can be said that The three possible mechanisms of exercise anti-inflammatory effects include reduction in visceral fat mass; reduction in the circulating numbers of pro inflammatory monocytes and an increase in the circulating numbers of regulatory T cells [28].

Also, inflammation causes reactive oxygen species (ROS) production and as a result oxidative stress Thus, oxidative stress is an important pathological feature in AD so antioxidants may be useful for AD treatmen [30].ROS overproduction might overload the muscle's ability to produce strength and contraction under stressful conditions, such as participating in physical activities with variable intensities of anaerobic and resistance training [31].

In previous studies Physical activity has been shown to have a positive modulatory effect on systemic inflammation by reducing pro inflammatory cytokines, increasing anti-inflammatory cytokines,and modulating reactive oxygen species (ROS) both in young and older adults [32].also Exercise reduces age related oxidative damage and chronic inflammation [33]. Based on our previous studies, endurance and resistance training with the consumption of hawthorn extract can lead to a reduction in oxidative stress due to an increase in the serum level of total antioxidant capacity and the first and second line of defense enzymes (superoxide dismutase and glutathione peroxidase) and a decrease in the serum level of malon dialdehyde in Alzheimer's experimental model(un puplish).

However, there are many evidences that show that muscle exercise increases the production of reactive oxygen species (ROS) and leads to oxidative stress in many tissues, including blood and skeletal muscles [15].But it depends on the type and intensity of exercise because long-term exercise with low intensity increases the activity of antioxidant enzymes in trained muscles and removes oxidative stress caused by contraction due to an acute period of exercise [15].It is also well documented that intense, acute exercise may induce muscle damage and inflammation, but prolonged exercise at low to moderate intensity negatively regulates the inflammatory response [16]. In our study, according to the type of exercises and their intensity, as well as the oral use of hawthorn extract, oxidative stress and inflammation caused by the induction of Alzheimer's were reduced.

Many studies have shown that hawthorn has antioxidant, anti-inflammatory ,properties [34]. Hawthorn reduces inflammation by reducing the levels of IL-6 and TNF-α which performs its anti-inflammatory activities by regulating and releasing inflammatory cytokines, including TNF α, IL-6 Also, hawthorn performs its antioxidant activity by reducing oxidative stress and increasing the activity of antioxidant enzymes [35].

Evidence shows that hawthorn fruit reduces inflammation and oxidative stress in rats with chronic heart failure [36].So, the simultaneous effect of exercise with hawthorn supplements reduces inflammation and reduces oxidative stress in Alzheimer's rats.

Conclusion

In our study, endurance and resistance exercise (combined) along with the consumption of hawthorn extract both reduced inflammation by reducing the inflammatory levels of TNF α, IL 6 and CRP and also reduced oxidative stress in Alzheimer's rats due to its antioxidant activity. that these two had a synergistic effect on the Alzheimer's rats of the E+R+Ha group.

Conflict of interest: There is no conflict of interest.

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Caption figure:

Fig 1: Comparison of mean and standard deviation TNF-α of serum level of field rats in different groups. * (Means a significant difference compared to the Alzheimer's control group).

Fig 2: Comparison of mean and standard deviation IL-6 of serum level of field rats in different groups. * (Means a significant difference compared to the Alzheimer's control group).

Fig 3: Comparison of mean and standard deviation CRP of serum level of field rats in different groups. * (Means a significant difference compared to the Alzheimer's control group).

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