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Effects of weight training and melilotus officinalis extract on alzheimer's disease-related genes

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Abstract

Background: Recently, the role of sports training and medicinal plants in the expression of genes has been considered to prevent the progression of diseases. The purpose of this research was to investigate the role of weight training and oleander extract on interferon regulatory factor 8 (IRF8) and cathepsin S (CTSS) gene expression in the soleus muscle of Alzheimer's disease (AD) model mice.

Methods: Fifty-five male Wistar rats were randomly divided into 5 groups: healthy control group, AD control group, AD resistance training group, AD group with the supplement of *Melilotus officinalis,* and AD resistance training group + *Melilotus officinalis* supplement. Trimethyltin-induced AD was induced. In the resistance training protocol, a weight was attached to the tail of the rats, and they had to lift this weight on a ladder with 26 steps. *Melilotus officinalis* was injected intraperitoneally as a supplement for 6 weeks with a dose of 300 mmol/kg. Seventy-two hours after the last training session, the rats were anesthetized, and the hippocampal tissue was immediately extracted, frozen, and analyzed. A two-way analysis of variance was used to estimate the differences between groups in control and experimental AD mice.

Results: There was a significant increase in the expression level of interferon-regulating factor 8 and cathepsin S genes in the AD group compared to the control group. The results of Bonferroni's post-hoc test showed that in the AD group + resistance training + *Melilotus officinalis*, a significant decrease was observed compared to the AD group ($P \leq 0.05$).

Conclusion: Resistance training and the *Melilotus officinalis* extract with antioxidant mechanisms can affect CTSS and IRF8 gene expression.

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Keywords

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Article Type: Original Article

Highlights

- Herbs and physical activity may affect performance and general health. The protocol of resistance training and the consumption of *Melilotus officinalis* on rats with Alzheimer's disease induction controlled CTSS and IRF-8 neuro-inflammatory response.
- The regulation and differentiation of amyloid cells and the response to stimuli decreased the expression of these genes in the subjects and stopped or reduced the damage.

Introduction

The use of herbal supplements may be effective in improving the performance of athletes and helping them return to their basic state, especially if the exercises are heavy and cause muscle pains and sports injuries. Herbal supplements play a role in stimulating muscle growth, increasing fat metabolism, increasing resistance and strength, reducing oxidative stress, creating energy balance, and ultimately, promoting health. Antifatigue effects and excretion of metabolites have also been mentioned. Although sports activities produce free radicals, reactive oxygen species, and other metabolites, the final result of exercise is health, increased physical and movement fitness, increased range of motion of joints, and improved strength of bones. Therefore, the use of herbal supplements (due to fewer side effects and greater accessibility) along with exercise protocols can be effective in synergizing the health benefits of these two key factors (1).

Myeloid dendritic cells play an important role in maintaining homeostasis inducing and controlling neuroinflammatory responses in the CTSS, and IRF-8 plays an important role in regulating commitment and differentiation during myeloid cell maturation and response to stimuli. The expression of IRF-8 is increased in the brain of a rodent model of Alzheimer's disease (AD), and in the context of accelerated aging and AD, IRF-8 is a biomarker with the highest correlation coefficient. Here, we aimed to extend our IRF8 epigenetic findings and evaluate the IRF-8 protein expression in myeloid cells about cognition and CTSS injury and inflammation (2).

Alzheimer's disease is a devastating brain disease with progressive cognitive impairment and memory loss. Functional disorders of mitochondria, the release of free radicals, damage to neurons and the cholinergic system, and inflammatory damage are other pathophysiological features of AD (3). A regulatory pathway in the function of brain amyloid cells is the interferon-8 regulatory factor and cathepsin S gene, which encode proteins and develop the disease. The key gene for lysosomal cysteine is a regulatory gene that encodes interferon-8. The immune system plays a very important role in the process of AD and probably reduces the activity of the genes of the interferon-8 regulatory factor system (3). One way to treat AD is the use of medicinal plants. *Melilotus officinalis* contains coumarin, flavonoid kaempferol, quercetin glycoside, terpene, saponin, and volatile oil with anti-inflammatory, antioxidant, and neuroprotective effects that may contribute to brain health by preventing the accumulation of tau protein (4). It has been reported that physical activity reduces the destruction of the nervous and immune systems in AD patients (5). Intensifying physical activity and increasing cerebral blood flow are effective on the hippocampus and neurogenesis (6). Recent studies have shown that vigorous exercise, even for just 20 minutes, can increase long-term memory by 10% (7). Breijyeh et al. (2020) investigated the effect of resistance training and saffron extract on the plasma levels of interleukin 17 and 18 in AD rats using trimethyl tin chloride; they concluded that exercise and saffron extract do not affect inflammatory factors in rats with AD (8). Moreover, the period of exercise intervention (frequency and intensity of exercises) can be a possible cause of the lack of effectiveness of exercise on the mentioned variables (9). Herbal medicines have the potential to be effective against AD. There is considerable evidence of the effects of plants on processes related to pathological fibrillogenesis. Several herbal compounds effectively protect the aggregation of amyloid peptides, preformed fibrils, and neuronal cells against cytotoxic peptides. Besides, herbal medicines can be useful preventive agents for AD and inhibit the accumulation of Aβ42 and Aβ40 in laboratory conditions (10).

A course of resistance training increased BDNF gene expression and TrkB receptor in AD rats (11). Besides, polyphenols, *Melilotus officinalis* extract, and *Anchusa* extract are effective on oxidative, antidiabetic, and inflammatory pathways in animal models (12). Some reports show that the elderly enjoy more mental health and well-being by participating in resistance sports (13). Considering the importance of improving lifestyle, diet, prevention, and treatment of diseases, the purpose of this study was to investigate the role of strength training and the consumption of *Melilotus officinalis* extract on the expression of interferon regulatory factor 8 and cathepsin S genes in the soleus muscle of AD rat model.

Methods

Ethical statement

This research was approved by the Biomedical Ethics Committee of Islamic Azad University, Varamin Pishva branch. Efforts were made to prevent any unnecessary activities for the animals.

Animal Housing and Induction

The statistical population was male Wistar rats (220±10 g weight and 10 weeks age), 55 of which were prepared as a statistical sample from the Pasteur Institute of Iran and transferred to the laboratory (3). They were divided into 5 groups: healthy control group, AD group, AD resistance training group, AD group + *Melilotus officinalis*, and AD + *Melilotus officinalis* + resistance training group. The rats were kept for 2 weeks under new conditions with a cycle of 12 hours of light, 12 hours of darkness, and free access to water and special food. The animals were carried and kept by skilled people. Place, cage ventilation, food and water, sound, temperature, light, and humidity were under control. There were no laboratory tools and materials in the rats' training room. Their ventilation and water consumption were controlled, no shocks were used during the training, and the rats were made to move only by the touch of the expert technician's hand.

Plant Materials and Extraction

The *Melilotus officinalis* plant was procured from the Marvdasht Agricultural Jihad Center (Iran). In this study, first, 500 g of dry powder from the *Melilotus officinalis* plant was mixed with 1.5 L of 80% ethanol and placed at room temperature for 4 days. The dose used was 300 mg/kg.

Induction of Alzheimer's Disease

Alzheimer's disease was induced in 44 rats by intraperitoneal injection of a single dose of 10 mg/kg trimethyltin chloride (TMT; Sigma-Aldrich, USA) (14) (Figure 1). Fourteen days later, memory and learning tests were performed on them, and several mice were compared with the control group by the shuttle box and Y maze test (15). For familiarization of the animals with the training protocol, the rats performed weight-bearing exercises for 5 days and each training session for 5 minutes using a ladder with a height of 1 m. After this period, the training protocol was carried out for 6 weeks (Figure 2). The main exercises were done for 8 weeks, 3 sessions a week. The mice had resistance training in the first to fourth week with 30%, and in the fifth to eighth week with 10% of the body weight. The Morris water maze test was used for memory and spatial learning 4 weeks after exercise induction. The movements and behavior of the animals were tracked and recorded by Auto Vision 7 software (Calgary, Canada) and a camera installed on top of the tank. In this way, the swimming path of the mouse was recorded in each training, the time it took the animal to find the Plexiglas platform (hidden platform) and the time it spent in the quarter of the target circle was measured, and the adjustment steps were measured as well.

Figure 1. Demonstration of subcutaneous injection of trimethyl tin in rats

Figure 2. Demonstration of weight-bearing exercises by rats

Sampling, tissue evaluation, and cDNA preparation

After 48 h of the last training session and 12 hours of fasting, the rats were anesthetized using ketamine (50 mg/kg) and Xylazine (15 mg/kg). Then, the upper part of the animal's skull was shaved, and the skull tissue was cut with a cutter and scissors. Separation of brain and hippocampus tissues was performed by experts. After sampling, the hippocampus was washed, weighed, and transferred to special microtubes to preserve the tissue. Besides, 3 tissues from each group were transferred to an 18% formalin solution for pathology evaluation and cell counting. First, a thin slice of the tissue was prepared and placed in a sterile envelope. Then, xylose was added and centrifuged. After adding cold ethanol, the solution was centrifuged and affected by protease and proteinase k. Their concentration was measured by a NanoDrop device at a wavelength of 260 to 280, and cNA synthesis was prepared according to the protocol in the fermentation kit (K1621). The expression of regulatory factor interferon 8, cathepsin S, and TBP was evaluated by real-time polymerase chain reaction (PCR) based on the standard method. After the amplification of cDNA by the reverse transcription method, a real-time PCR test was performed on the tissue samples, and the natural sample was used as a reference sample to compare the changes in the treatment samples. The changes in the treatment samples of the TBP gene were also used as an internal control. The measurement of expression by real-time PCR reaction was carried out relatively based on the standard method. The relative quantification in real-time PCR was done by measuring the increase in fluorescence radiation due to the binding of cybergyrin dye using an ABI-7500 device. Real-time PCR reaction components were determined in the final volume of 20 µL and the final concentration of the materials.

Primer preparation of Interferon Regulatory Factor 8 and Cathepsin S Genes

Primer design was performed using Primer3 software and the National Center for Biotechnology Information (NCBI) blast website, and then it was purchased from Metabion, Germany (Table 1).

The thermal program of the reaction had four stages: initial PCR-RT, annealing, binding, and extension. The melting curve diagram for IRF8, CTSS, and internal control gene TBP was drawn separately by the real-time PCR device (ABI 7500) to evaluate the specificity of primers and fluorescence dye (SYBR green) and to ensure the amplification of specific products and the absence of nonspecific products in the PCR product.

Real-time PCR was performed according to the protocol of RealQ Plus 2x Master Mix Green (Ampliqon Inc.) in Applied Biosystems StepOne™ Instrument (ABI, Step One, USA). The real-time PCR conditions were set to 10 minutes at 94 °C, followed by 40 cycles of 15 seconds at 94 °C, 60 seconds at 60 °C, and extension steps. After each real-time PCR run, gel electrophoresis and melting curve analysis were carried out to confirm the specific amplification of targets. The amplification signals of different samples were normalized to TBP Ct (cycle threshold), and then, the delta-delta CT (2-ΔΔCT) method was applied to compare the mRNA levels of the test versus the control, which was represented as fold change in the data analysis.

Table1. Preparation of the primers of the studied genes

Genes	**Primer Sequences**	**Sizes (bp)**
Interferon regulatory factor 8	Forward: 5'- GAACCGGTGGCAGGATGT -3'	175
	Reverse: 5'- GCGTCCACTTCCTGGTTGTA -3'	
Cathepsin S	Forward: 5'- GATGACCCCTCCTGTACCGA -3'	108
	Reverse: 5'- GTGAAGGCCCCAACTGTTTTT -3'	
TBP	Forward: 5'- GCGGGGTCATGAAATCCAGT-3'	147
	Reverse: 5'- AGTGATGTGGGGACAAAACGA -3'	

Statistical analysis

The mean ± standard error of the mean (SEM) was used to compare research data via descriptive statistics. Two-way analysis of variance (ANOVA) was used to compare the difference between the averages of the experimental groups and the control group, and Tukey's post-hoc test was used in the case of significance (P≤0.05).

Results

Based on the results obtained from the two-way ANOVA, the level of interferon regulatory factor 8 and cathepsin S gene expression in the AD group significantly increased compared to the control group (P<0.05). The expression level of the interferon regulatory factor 8 and cathepsin S gene increased less in the resistance training group and the AD + *Melilotus officinalis* + resistance training group (Figures 3 and 4).

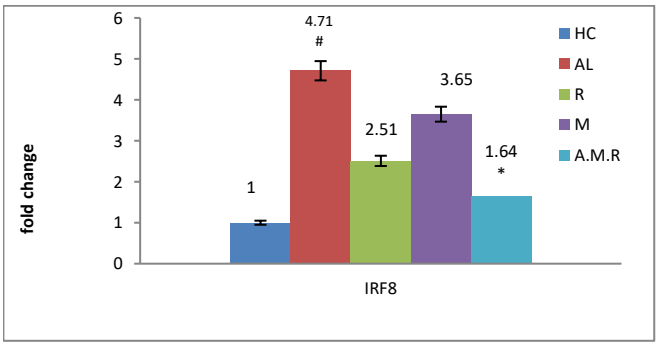

Figure 3. The difference between groups in IRF8 gene expression was determined using a two-way analysis of variance and Bonferroni's post-hoc test (P ≤ 0.05).
#: A significant increase is observed in the Alzheimer's disease group compared to other groups
*: A significant decreased in the Alzheimer's disease group + *Melilotus officinalis* + strength training compared to the Alzheimer's disease group

HC: Healthy control group, AL: Alzheimer's disease group, R: Alzheimer's disease resistance training group, M: Alzheimer's disease group + Melilotus officinalis, and AMR: Alzheimer's disease + Melilotus officinalis + resistance training group

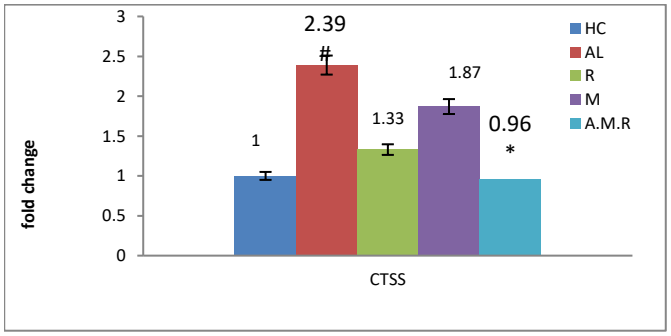

Figure 4. The difference between groups in CTSS gene expression was determined using a two-way analysis of variance and Bonferroni's post-hoc test (P ⩽ 0.05).
#: Significant increase in the Alzheimer's disease group compared to the control group
*: Significant decrease in the control group and the Alzheimer's disease + supplement + exercise group compared to the Alzheimer's disease group

HC: Healthy control group, AL: Alzheimer's disease group, R: Alzheimer's disease resistance training group, M: Alzheimer's disease group + Melilotus officinalis, and AMR: Alzheimer's disease + Melilotus officinalis + resistance training group

The expression of the RIF8 gene was significantly decreased in the AD + *Melilotus officinalis* + resistance training group compared to the AD group (P=0.020). The difference between the healthy control group with AD + *Melilotus officinalis* + resistance training was not significant. No significant difference was observed in AD+ *Melilotus officinalis* (P=1.000) and AD + resistance training groups (ŋ=0.538, P=0.018, F=4.170) (Figure 1).
The expression of the CTSS gene was significantly decreased in the AD + *Melilotus officinalis* + resistance training group compared to the AD group (P=0.000). The difference between the healthy control group with AD + *Melilotus officinalis* + resistance training was not significant. On the other hand, no significant difference was observed in AD + *Melilotus officinalis* (P=1.000) and AD + resistance training groups (ŋ=0.349, P=0.023, F=6.209) (Figure 2).

Discussion

Alzheimer's disease is a progressive neurological disorder and one of the main causes of dementia (16). The results of this research showed that a significant increase in the interferon regulatory factor 8 gene was observed in the AD induction groups, which is consistent with the results of the study by Anthony et al. (17). The IRF8 (interferon regulatory factor 8) is a protein-coding gene that is related to immunodeficiency diseases and interferon-gamma signaling and cytokine signaling pathways. In the dorsal horn, reactive microglia are specific cells that express interferon regulatory factor 8 and are dramatically increased in hippocampal microglia. Thus, interferon regulatory factor 8 can activate the gene expression program and convert the microglia into a reactive phenotype. Masuda et al. (2012) have reported these results (18). Furthermore, interferon regulatory factor 8 is involved in amyloid-induced microglial activation in AD. In the presence of interferon regulatory factor 8, microglia cannot enter the junctions that lead to amyloid deposits, thus justifying this increase in AD groups. The findings of Bellenguez et al. (2022) also showed that microglia contribute to the proliferation of Aβ in healthy brain tissue and that interferon regulatory factor 8 is a critical regulator of reactive microglia (19). Of course, the experimental sample of Eriko et al. was transgenic rats, and the speed of microglial processes and their distance to damage and amyloid deposition were significantly reduced in rats. Interferon regulatory factor 8 is also expressed in immune cells, and lymphocytes and dendritic cells also play pivotal roles (20-21), but their role in the CNS is completely unknown. Treatment of IRF8-transfected microglia with a blocking antibody combination inhibits the Ctss. IRF8 is a critical transcription factor for transforming microglia into a reactive phenotype. Therefore, this transcription factor can be a therapeutic target in CNS and neuropathic disorders (18). Thus, the expression of interferon regulatory factor 8 in treated rats indicates neuropathology (22).

Changes in cathepsin S gene expression in AD groups increased significantly, which is consistent with Amini et al.'s study, but no significant cathepsin S changes were reported. Some evidence suggests that cathepsin S produces amyloid genic fragments of β-APP in the endosomal/lysosomal compartment and may play a role in the pathogenesis of AD and Down syndrome. Moreover, this gene is involved in inflammatory pathways (23) and autoimmune diseases (24).

The decrease in the expression of interferon regulatory factor 8 and cathepsin S in the group treated with the plant extract can indicate the effect of *Melilotus officinalis* on apoptosis and inflammation in the hippocampus. The anti-inflammatory and antioxidant role of plants is an important factor in reducing interferon regulatory factor 8 and cathepsin S genes. Bazazadegan et al. (2019) have reported these results (14). Of course, their sample was Sprague Dawley rats, and the changes in gene expression and the use of plant extracts did not show a significant change in the memory level among the treated groups. It seems that the plant extract may have a significant effect on the changes in the expression of genes related to AD. *Melilotus officinalis*, like many medicinal plants, has an active substance against AD and cholinesterase inhibitors, including the modification of Aβ processing and protection against apoptosis and oxidative stress. The anti-inflammatory, antioxidant, and protective effects of plants are caused by coumarin, flavonoids (kaempferol, quercetin glycosides), catechin and cinnamic acid, triterpene saponins, and volatile oil. Hu et al. (2013) and Pleşca-Manea (2002) have reported these results in their research (25-26). Plant extracts can be effective in improving microcirculation (27), reducing nitric oxide synthesis, and exerting important effects on gene expression mechanisms. Safarpour et al. (2015) also used the extract of *Melilotus officinalis* for the treatment of colitis (28). Moreover, the effects of this plant extract have been reported in AD mice treated with streptozocin (29). Herbal medicines prevent hippocampal cell damage caused by beta-amyloid peptides. Ethanol extracts from grape leaves and licorice, rose petals, and marigolds contain phenolic glycosides and flavonoid fractions and are sources of neuroprotection. This result was also confirmed by Haroutianian et al. (2016) (10).

Sports activity changes the level of amines and endorphins and increases the levels of catecholamines, serotonin, and other neurotransmitters (30); however, improving the learning process and reducing the progression of the disease requires increasing factors like neurotrophins. Thus, another mechanism is the increase in brain-derived neurotrophic factor (BDNF) and the decrease in the level of pro-inflammatory cytokines as a result of resistance exercise, which are important predictors of AD progression. Increasing physical fitness and BDNF and reducing inflammatory cytokines also lead to positive blood circulation to improve AD. Research shows that reducing oxidative stress and increasing neurotrophins depends on the intensity, duration, and type of exercise and may be effective in reducing gene expression (31). Nevertheless, Baziar et al. (2018) showed that high-intensity resistance training increases oxidative stress, decreases neurotrophins, and increases lipoperoxide, degenerative disorders, and mitochondrial function in the direction of nerve cell disorders (32). Therefore, a suitable training program should be considered for these people. In this regard, Khodadadi et al. (2016) reported that 5 sessions of aerobic exercise per week improved spatial learning and memory in AD rats (33). Vital et al. (2012) did not observe a significant difference in the effect of weight training on the cognition of patients with AD, and their results did not demonstrate an improvement in the cognitive functions of elderly people with AD (34). As such, future studies should evaluate the effect of more intense exercise programs. Mechanisms of exercise in improving cognition include increasing cerebral blood flow, creating a greater supply of oxygen and other energy sources, changing the synthesis and use of neurotransmitters important for brain activity, and having positive interference in brain angiogenesis, synaptogenesis, and neurogenesis. Studies on elderly people have shown that weight training significantly increases cognitive functions. Of course, the human sample and the type of sports activity are factors in the difference in the results, and supplements were not used in Vital et al.'s research. Nevertheless, Lee (2020) confirmed the results of the exercise and stated that in elderly people with mild cognitive impairment, the exercise program improved cognitive functions and hand grip strength, and more studies are needed to confirm these results (35). Of course, Lee's training program included aerobic and resistance exercises.

In the pathophysiology of AD, biological mechanisms such as neuron protective effects through inhibition of acetylcholinesterase enzyme or inhibition of oxidative stress, aging, lipoprotein E4 genotype, obesity, insulin resistance, vascular factors, lipid disorders, blood pressure, and inflammatory markers are involved and can be used to justify the contradiction or confirm the results (36). In addition, AD is a vascular disorder or brain blood flow disorder, and the destruction of neurons after the accumulation of amyloid beta peptides causes damage to synaptic activity and long-term inhibition in excitatory synapses, both of which lead to impairment in the learning system and memory (37). Considering the importance of lifestyle, the increasing prevalence of AD, and its effect on memory and learning, developing a treatment strategy for this disease and finding drugs and treatment methods that can prevent the progress of this disease and increase the survival of this group of patients are important measures (38), which were considered in this research. The limitations of the research included examining the sample only at the final stage of the protocol, the small size of the sample, the frequency of changing the dose of *Melilotus officinalis*, and the intensity and duration of the training program during the protocol.

It is suggested that optional exercise programs or other supplements such as shilajit and rosebud powder be used in future research. Also, examination of other tissues such as muscles, liver, or heart can show other disorders caused by AD.

Conclusion

Weight training and *Melilotus officinalis* improved learning and memory, and these two factors together reduced the time spent in a dark house by the AD mice. Probably, *Melilotus officinalis* and exercise have increased flexibility and

antioxidant effects, increased the expression of the genes discussed in this research, and raised synaptic stimulation in the hippocampus. The high frequency in neurons and the long-term increase of synaptic potentials have probably prevented neurodegeneration in these cells. It seems that resistance training and the consumption of *Melilotus officinalis* extract can affect cognitive learning factors and reduce the destruction of the nervous system, strengthen immunity and protection, and prevent excessive destruction of the hippocampus.

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Ethical statement

The experimental research procedures were all performed according to the approval of the Research Ethics Committee of Islamic Azad University, Varamin Pishva Branch, Iran (ethical code: IR.IAU.VARAMIN.REC.1401.039). All the animals were treated and sacrificed following the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978).

Conflicts of interest

The authors declare that they have no conflict of interest.

Author contributions

All the authors participated in drafting the manuscript, and all of them reviewed the results and approved the final version of the manuscript. The authors declare that all the data were generated in-house and that no paper mill was used.

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