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Research Article

The effect of 12 weeks aerobic training on TNF-α levels in the hippocampus and prefrontal cortex, and depression in rats with Alzheimer's disease

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Abstract

Background: Exercise training plays an important role in combating Alzheimer's disease. Present study aimed to investigate the effect of 12 weeks aerobic training on the levels of tumor necrosis factor alpha (TNF-α) in the hippocampus and prefrontal cortex, and also depression in rats with Alzheimer's disease.

Materials and Methods: The 40 Wistar rats were divided into four equal groups including saline (S), saline +training (ST), training +STZ (AT) and STZ (A). Alzheimer's was induced by injection of 3 mg/kg streptozotocin (STZ) into the ventricles of brain. The aerobic training program (each session lasted 30 minutes with 10-12 meters per minute speed) performed for 12 weeks and five sessions per week on a treadmill. The 48 hours after last training session, brain tissue (hippocampal and prefrontal cortex areas) was removed and TNF-α levels were measured by ELISA method. Data were evaluated using the statistical method of analysis of variance at a significant level ($P < 0.05$).

Results: TNF-α levels in the hippocampus were significantly higher in group A compared to S ($p= 0.010$), ST ($p= 0.014$) and AT ($p= 0.041$) groups. Moreover, no significant change was observed for TNF-α levels in prefrontal cortex in different groups ($p= 0.276$). In addition, a significant increase in inactivity duration (FST) was observed in group A compared to other groups ($p < 0.05$) and also a significant decrease in sucrose preference (SPT) was observed in group A compared to other groups. ($p<0.05$).

Conclusion: The present study findings indicated that, the positive effects of aerobic training in rats with Alzheimer's disease are exerted partly by modulating the levels of inflammatory factors such as TNF-α in the brain especially the hippocampus.

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1. Introduction

Dementia is a very common syndrome in people over 65 years of age, characterized by a gradual decrease in memory and other mental abilities, and Alzheimer's is the most common type of dementia, which affects 62% of patients with dementia (1) . It was reported that 46.8 million people worldwide had dementia in 2015, which is estimated to reach 131.5 million by 2050 (2). Alzheimer's is a progressive neurodegenerative disease characterized by the accumulation of extra-neuronal stores of beta-amyloid (Aβ) fibrils and the intra-neuronal accumulation of hyperphosphorylated tau protein. It leads to the activation of glial cells and then a neuroinflammatory response involving oxygen reactive mediators and inflammatory cytokines such as IL-6, IL-1β, and tumor necrosis factor (TNF-α) (3). In addition, Aβ has been reported to stimulate inflammation (4). In fact, among the effective factors in the development of Alzheimer's disease are systemic inflammation and increased levels of inflammatory mediators such as levels of cytokines IL-6 and tumor necrosis factor alpha (TNF-α) centrally and peripherally. (5). Cytokines are small peptides, hormone-like, and messengers produced by cells activated by inflammatory elements (6). Based on in vivo activity, cytokines are divided into proinflammatory, anti-inflammatory, mitogenic (regulating cell growth and proliferation), hematopoietic, and chemotactic (chemokines) (7). It should be noted that some studies have generally divided cytokines into two categories, proinflammatory and anti-inflammatory. Inflammation is thought of as a tissue response to injury, pathogen attack, or irritants that is characterized by increased blood flow, redness, swelling, and pain. Inflammation is divided into two types: acute and chronic inflammation.

Short-term or acute inflammation is a protective attempt by the organism to eliminate the stimuli of injury or to initiate the healing process. Nevertheless, long-term or chronic inflammation leads to several inflammatory disorders and chronic diseases. The process of inflammation is very complex and is usually precisely regulated: in such a way that one mediator initiates and maintains the inflammation, and another mediator eliminates the inflammation. In the case of chronic inflammation, an imbalance between the two regulators occurs, which leads to cell damage and leads to different types of chronic diseases (8). Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that can have direct effects on vascular endothelial cells to stimulate chemotactic agents, other cytokines, cell adhesion molecules, and facilitate leukocyte infiltration. These can play a role in the inflammatory process (9). TNF-α is produced by a variety of immune and non-immune cells, including lymphocytes, mast cells, endothelial cells, fibroblasts, and adipocytes, and is involved in regulating various physiological processes such as cell proliferation. Differentiation and apoptosis are involved in various inflammatory processes as well as in a variety of pathological conditions such as chronic inflammation and the onset of acute phase reactions by increasing inflammatory signaling and stimulating cell death, especially necrosis and apoptosis of tumor cells. Disruption of TNF-α production and secretion leads to the spread of diabetes, tumorigenesis, cardiovascular disease, rheumatoid arthritis, and inflammatory bowel disease (10).

In addition to the above, TNF-α has been reported to be involved in the pathogenesis of Alzheimer's disease, and increased levels have been observed in the brain tissue of elderly people with Alzheimer's disease (11). In contrast, the results of studies have shown that reducing the expression of inflammatory cytokines including IL-6, IL-1β and TNF-α in the brain tissue of Alzheimer's rats is associated with improved learning and memory. Shows the placement of inflammatory pathways in the recovery of Alzheimer's samples (12). In human samples, inhibition of the TNF-α signaling pathway also reduces the risk of Alzheimer's disease in the elderly (13). Exercise is one of the strategies that has been shown to reduce inflammation and modulate levels of inflammatory mediators such as IL-6 and TNF-α, and therefore, exercise is considered as an anti-inflammatory agent. (14). In addition to the anti-inflammatory effects of exercise, its role in the prevention and improvement of Alzheimer's risk factors has been reported, and exercise can delay the onset of Alzheimer's symptoms (15). Despite the positive effects of exercise, including its anti-inflammatory effects, changes in levels of inflammatory factors such as TNF-α in response to exercise in Alzheimer's samples have not been studied. Depressive behavior and cytokine measurement of tumor necrosis factor alpha (TNF-α) in the hippocampus and peripheral cortex of Alzheimer's patients.

2. Materials and Methods

The present study was experimental and basic and the statistical population of the present study consisted of Wistar rats in the age range of 90-80 days, of which 40 Wistar rats were purchased as a statistical sample from the Pasteur Institute and sent to the storage room. The animals were moved. Rats were randomly divided into 10 female mice in saline (S), saline + training (ST), training + STZ (AT) and STZ (A): Group 1 (S): Animals Do not exercise and receive saline, Group II (ST): Animals exercise and receive saline, Group 3 (AT): Animals exercise and receive STZ, and Group 4 Animals do not exercise and receive STZ. After the rats were transferred to the laboratory environment, they adapted to the new laboratory environment for one week. For this purpose, mice in groups of four in an environment with a temperature of 22 ± 1.4 ° C, humidity of 55% and a light cycle of darkness of 12:12 hours in special cages made of polycarbonate with dimensions of 47 × 27 × 20 cm were kept. Mice in different groups had free access to standard mouse food during the study, which was placed every two days in the cage net that was available to the mice. Water was also available to mice indefinitely in 500 ml bottles for rodents. The contents of the water bottles were changed daily and made available to the mice again. In addition, the rat lice were replaced every other day. In all stages of the research, the ethical and professional principles of working with animals were observed and the mice were moved and trained by only two people. Items such as painless killing, as well as prevention of surgical pain and sampling of animals were observed.

Exercise protocol

Aerobic exercise in the present study included 12 weeks of treadmill running, which began after one week of getting acquainted with the treadmill. In each session, first warm up for 5 minutes (with an intensity of 5 meters per minute), then the main part of the training program and finally 5 minutes of cooling (with an intensity of 5 meters per minute). The duration of the exercise program from the first week to 12 was the same and 30 minutes per session. The intensity of aerobic exercise in the first 6 weeks was equal to 10 meters per minute and in the last 6 weeks was 12 meters per minute. complete aerobic exercise program is shown in Table 1.

Table 1: 12-week aerobic exercise program

Exercise Training (week)	Warmup (meters per minute)	Main Exercise	Cooldown (meters per minute)	Time (minutes)
0-2	5	10	5	30
3-4	5	10	5	30
5-6	5	10	5	30
7-8	5	12	5	30
9-10	5	12	5	30
11-12	5	12	5	30

Alzheimer's induction

By the end of week 8, the rats will develop Alzheimer's by the Institute for Cognitive and Behavioral Disorders. This model is induced as follows: First, the animals were anesthetized with a combination of ketamine and xylazine (60 and 8 mg / kg, respectively). They are then placed inside a stereotaxic device for brain surgery. Then 3 mg / kg streptozotocin (STZ) was injected in 5 µl of sterile distilled water in the ventricular region of the brain: (anteroposterior: −1mm, mediolateral: ± 1.4mm and dorsoventral: -3.4).

Sucrose preference test (SPT)

On the fifth day after Alzheimer's induction, the test was performed for 48 hours. Two bottles, one with 2% sucrose solution and the other with plain water, were tested in the group cage. The amount of water consumed in the bottles was calculated immediately after the test. Dissatisfaction with sucrose bottles was considered as a depressive behavior in the studied rats and the Sucrose preference test score was calculated based on it.

Isolation of brain tissue (FST)

After completing the behavioral tests, the rats were given deep anesthesia with ketamine (50 mg / kg) and xylazine (5 mg / kg), and then perfusion was performed to remove blood from the brain, after which the animal underwent Dies. In the next step, the brain was extracted and the hippocampal and prefrontal areas were isolated.

Isolated brain samples were stored at -80 ° C until laboratory measurements. All steps of TNF-α cytokine assay were performed based on the working method in the company kit (R&D Co) using ELISA technique.

Statistical methods of data analysis

All data obtained from the present study were analyzed using SPSS software version 24. Shapiro–Wilk test was used to ensure the normal distribution of research data and one-way ANOVA test and Tukey post hoc test were used to compare differences between groups. Also, alpha was considered at the level of 0.05.

3. Results

The results of FST test as well as SPT test results are reported as mean and standard deviation in Table 2 for different groups. One-way analysis of variance test showed a significant difference between groups for FST test (p = 0.009). The results of Tukey post hoc test showed that the duration of physical inactivity in STZ group compared to STZ + training group (p = 0.022), saline (p = 0.028) and saline + training (p = 0.023) It has been significantly more. In addition, significant differences were observed between groups for SPT test (p <0.001) and Tukey post hoc test showed that FST test results in STZ group compared to STZ + training group (p = 0.021), saline (P = 0.001 and saline + exercise (p = 0.000) were significantly lower.

Table 2: FST and SPT test results

Variable	Group	Mean ± SD	P value
FST result	**saline (S)**	109.6± 18.73	0.011*
	saline +training (ST)	108.6± 25.92	
	STZ	143.1± 28.02	
	training +STZ (AT)	108.4± 28.23	
SPT result	**saline (S)**	64.1± 10.9	0.007*
	saline +training (ST)	66.2± 9.52	
	STZ	40.3± 15.57	
	training +STZ (AT)	57.2± 12.75	

Analysis of one-way analysis of variance showed that the difference between groups of TNF-α levels in the hippocampus was statistically significant (p = 0.005). The results of Tukey post hoc test to determine the location of differences between groups showed that TNF-α levels in the hippocampus in the STZ group compared with the STZ + group (p = 0.041), saline (p = 0.010) and saline + Exercise (p = 0.014) is significantly more (Chart 1).

However, no significant intergroup differences were observed for TNF-α levels in the prefrontal cortex (p = 0.276) (Chart 2).

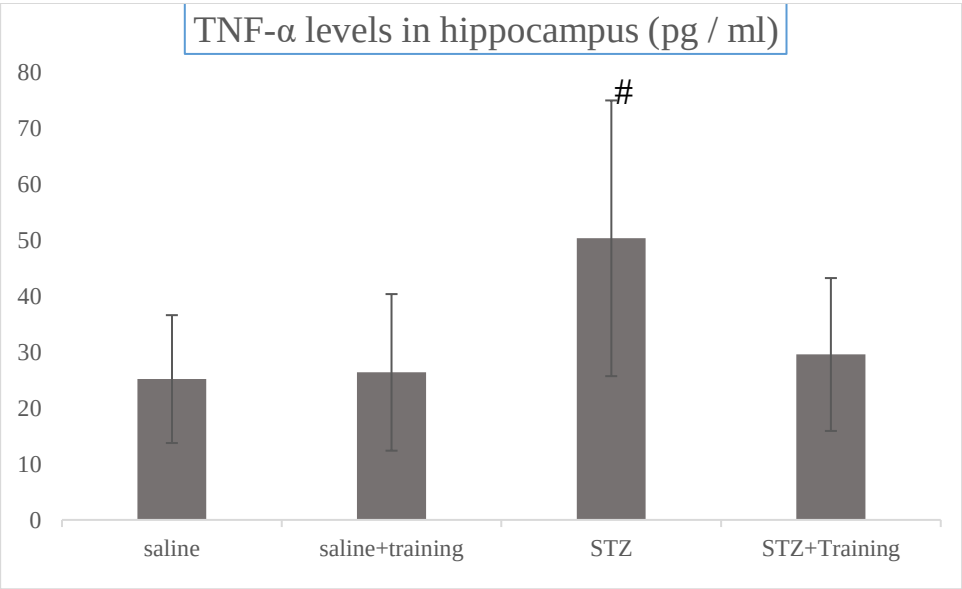

Chart 1: Changes in TNF-α levels in the hippocampus. # Signs of significant difference with groups

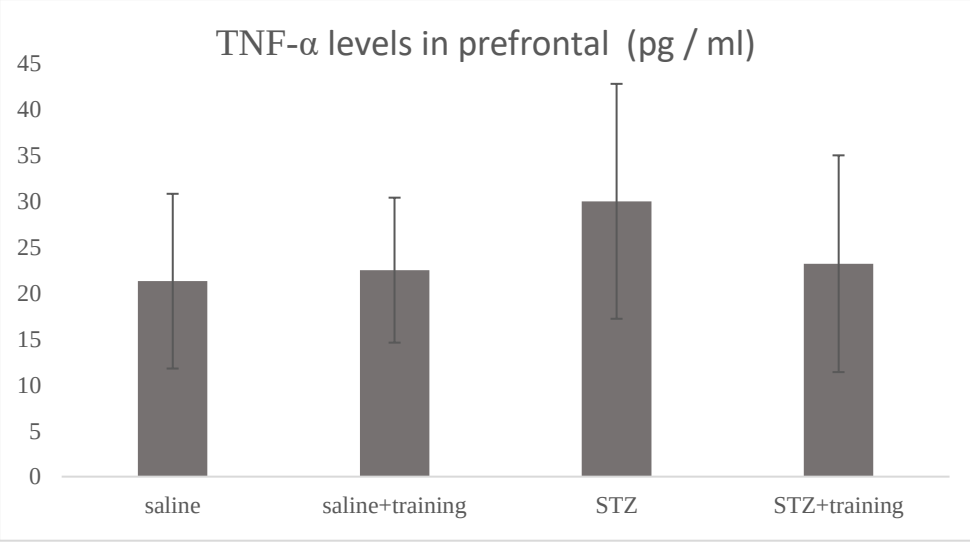

Chart 2: Changes in TNF-α levels in the prefrontal cortex

4. Discussion

The present study was performed to evaluate the effect of 12 weeks of aerobic exercise on TNF-α levels in the hippocampus and peripheral cortex and depression in rats with Alzheimer's disease. The main finding of the present study was that 12 weeks of exercise in Alzheimer's rats significantly reduced TNF-α levels in the hippocampus and TNF-α levels in the hippocampus of Alzheimer's rats compared to healthy rats. The face was more significant. In addition, the present results showed that although TNF-α levels in the prefrontal cortex were higher in rats with Alzheimer's disease than in the other groups, the differences between the groups were not significant and exercise and Alzheimer's disease had a significant effect on TNF-α levels were absent in the prefrontal cortex. These changes were associated with improved rat performance in the Depressive Behavioral Test (reduced immobility) as well as decreased sucrose preference. Studies have shown that changes in inflammatory cytokine levels can be at least partially effective in the disorders observed in the elderly, which in turn increases inflammatory cytokine levels, including TNF-α and IL1-β. Decreases in anti-inflammatory cytokines, including IL-4, have been observed in the elderly. Due to old age (16). Inflammatory mediators such as inflammatory cytokines are pronounced prominently in the vicinity of beta-amyloid stores and neurofibrillary tangles, and various types of inflammatory markers have been observed in Alzheimer's patients (17). Inflammatory cytokines such as IL-6, TNF-α and IL-1β, when produced and secreted chronically, are clearly involved in inflammatory processes near amyloid plaques, including cytotoxic effects. These cytokines can stimulate the production of beta-amyloid peptides (18).

However, different types of pharmacological and non-pharmacological methods are used to reduce inflammation. Among the non-pharmacological strategies effective in reducing inflammation, exercise due to the lack of side effects has attracted a lot of attention and Is considered a strong anti-inflammatory agent (19).

In confirmation of the present findings, previous studies have also shown the neuroprotective effects of exercise in animal specimens with Alzheimer's disease. In confirmation of the present findings, Souza et al. (2013) reported that eight weeks of exercise in Swiss Alzheimer's mice injected with beta-amyloid injection resulted in decreased regulation of TNF-α levels in the hippocampus and prefrontal cortex. Decreased TNF-α levels were associated with decreased levels of other inflammatory cytokines such as IL-1β and at the same time increased levels of anti-inflammatory cytokines such as IL-10 as well as improved antioxidant capacity, which improved cytokine profile levels. Cognitive function resulted in the trained group (20). In addition, the findings of the above study in line with the present study showed that the induction of Alzheimer's disease in comparison with the healthy group leads to stimulation of inflammatory pathways (such as increased levels of TNF-α and IL-1β), which confirms Slow inflammatory pathways play a major role in the pathogenesis of Alzheimer's disease, and therefore researchers have identified exercise as an effective non-pharmacological solution to reduce the symptoms associated with Alzheimer's disease (20).

Findings similar to the present study were while the type and duration of exercise in the study of Nicole et al. (2008) was less than the present study and especially less duration of exercise compared to the present study on the positive effect of exercise even in short Duration emphasizes Alzheimer's samples (21).

Ding et al. (2006) in a study that examined the effect of 3 consecutive weeks of exercise (3 minutes daily) on Sprague Dawley rats after stroke / re-oxygenation increased TNF-α expression and its receptor (TNF-RI) Showed in the group in which the stroke was induced. Nevertheless, exercise was associated with decreased TNF-α and TNF-RI expression in both the stroke group, but no significant change was observed for them in the healthy group (22). Because TNF-α binds to TNFR1 and TNFR2 receptors and exerts its inflammatory effects by binding to its receptors (23), a decrease in TNF-α receptor levels plays a significant role in modulating activity. Inflammation has unfortunately not been studied in TNFRs in the present study. In another study on the positive effects of exercise training on brain tissue, Lane et al. (2020) reported that 12 weeks of swimming training in elderly rats stimulated the IGF1, PI3K, AKT, and AMPK pathways. SIRT1 and PGC1α suppress apoptosis and inflammation (including decreased TNF-α levels) in the hippocampus, thereby improving survival in elderly rats (24). In the present study, decreased TNF-α levels were associated with improved cognitive function and reduced depression, which is consistent with previous findings. In this regard, Sun et al. (2018) observed that tapeworm exercise in Alzheimer's rats could attenuate the destructive effects of beta-amyloid on brain tissue and improve cognitive function, which the researchers noted as positive adaptations.

In the trained group, MAPK was applied through the messenger pathway, which was also associated with decreased levels of inflammatory cytokines (TNF-α) in brain tissue (25). All of these findings underscore the fact that exercise can reduce and delay cognitive impairment as well as structural changes in brain tissue with Alzheimer's due to its anti-inflammatory effects.

Studies have shown that the reported anti-inflammatory effects of exercise are exerted through a variety of mechanisms, including the reduction of visceral fat mass, the secretion of various types of anti-inflammatory cytokines from contractile muscle (myokines). And reduced expression of Tol-like receptors (TLRs) is applied to monocytes and macrophages (with subsequent inhibition in downstream pathways such as the production of proinflammatory cytokines and the expression of MHC and co-stimulatory molecules). . In addition, based on studies in animal specimens, the anti-inflammatory effects of exercise can be attributed to other mechanisms such as inhibiting the penetration of monocytes and macrophages into adipose tissue and changing the phenotype of macrophages within adipose tissue. (14). Despite the presented findings, it seems that the effect of exercise training on changes in TNF-α levels can vary depending on the condition of the samples. In confirmation of this claim, Afzalpour et al. (2015) compared the effect of 12 weeks of moderate intensity training (with an intensity of 27 m / min) and intense intermittent training (HIIT) (2-6 3-minute intervals with a speed of 40 m). Per minute) in healthy rats showed that both types of exercise were associated with a significant increase in TNF-α and BDNF in brain tissue, which was significantly higher in the HIIT group compared to the continuous group (26) .

In confirmation of these findings, it has been reported that although chronic increases in TNF-α levels are involved in the pathogenesis of Alzheimer's disease (11), elevations in TNF-α levels in acute pathological conditions result in regular exercise in brain tissue. It can have neuroprotective effects and an increase in TNF-α in such a situation is associated with an increase in brain resistance to ischemia in the brain tissue of healthy rats (27). Therefore, the effect of exercise on TNF-α levels, including in brain tissue, can vary depending on the condition of the subjects. However, due to the few findings on the pathways of exercise in the brain tissue of Alzheimer's specimens and the lack of similar studies on the effect of exercise on different types of inflammatory and anti-inflammatory cytokines, the exact mechanism of effect of exercise on Brain tissue in Alzheimer's needs further investigation and will need to be addressed in future studies to identify unknown aspects of this area.

5. Conclusion

The present results showed that the positive effects of aerobic exercise in Alzheimer's rats are exerted by modulating the levels of inflammatory factors such as TNF-α in the brain (especially the hippocampus) and weakening the inflammatory pathways in Alzheimer's samples in addition to the role that ¬ Able to fight Alzheimer's and delay it, can reduce depression in Alzheimer's rats. These findings indicate the importance of exercise as an effective non-pharmacological intervention for the management and control of Alzheimer's disease, and the identification of precise mechanisms of this effect needs further investigation.

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Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: E.M., F.M., H.B.; Methodology: F.M., H.B.; Software: F.M., H.B.;Validation: E.M., F.M., H.B.; Formal analysis: F.M., H.B.; Investigation: E.M., F.M., H.B.; Resources: F.M., H.B.; Data curation: E.M., H.B.; Writing - original draft: F.M., H.B.; Writing - review & editing: E.M., F.M.; Visualization: E.M., F.M., H.B.; Supervision: E.M., F.M.; Project administration: E.M., F.M., H.B.; Funding acquisition: E.M., F.M., H.B.;

References

1. Swarbrick S, Wragg N, Ghosh S, Stolzing A. Systematic Review of miRNA as Biomarkers in Alzheimer's Disease. Mol Neurobiol. 2019 Sep;56(9):6156-6167. doi: 10.1007/s12035-019-1500-y. Epub 2019 Feb 8. PMID: 30734227; PMCID: PMC6682547.

2. Hill E, Goodwill AM, Gorelik A, Szoeke C. Diet and biomarkers of Alzheimer's disease: a systematic review and meta-analysis. Neurobiol Aging. 2019 Apr;76:45-52. doi: 10.1016/j.neurobiolaging.2018.12.008. Epub 2018 Dec 27. PMID: 30682676.

3. Mucke L. Neuroscience: Alzheimer's disease. Nature. 2009 Oct 15;461(7266):895-7. doi: 10.1038/461895a. PMID: 19829367.

4. White JA, Manelli AM, Holmberg KH, Van Eldik LJ, Ladu MJ. Differential effects of oligomeric and fibrillar amyloid-beta 1-42 on astrocyte-mediated inflammation. Neurobiol Dis. 2005 Apr;18(3):459-65. doi: 10.1016/j.nbd.2004.12.013. PMID: 15755672.

5. Holmes C. Review: systemic inflammation and Alzheimer's disease. Neuropathol Appl Neurobiol. 2013 Feb;39(1):51-68. doi: 10.1111/j.1365-2990.2012.01307. x. PMID: 23046210.

6. Borish LC, Steinke JW. 2. Cytokines and chemokines. J Allergy Clin Immunol. 2003 Feb;111(2 Suppl): S460-75. doi: 10.1067/mai.2003.108. PMID: 12592293.

7. Nedoszytko B, Sokołowska-Wojdyło M, Ruckemann-Dziurdzińska K, Roszkiewicz J, Nowicki RJ. Chemokines and cytokines network in the pathogenesis of the inflammatory skin diseases: atopic dermatitis, psoriasis and skin mastocytosis. Postepy Dermatol Alergol. 2014 May;31(2):84-91. doi: 10.5114/pdia.2014.40920. Epub 2014 Apr 22. PMID: 25097473; PMCID: PMC4112246.

8. Prasad S, Sung B, Aggarwal BB. Age-associated chronic diseases require age-old medicine: role of chronic inflammation. Prev Med. 2012 May;54 Suppl (Suppl):S29-37. doi: 10.1016/j.ypmed.2011.11.011. Epub 2011 Dec 9. PMID: 22178471; PMCID: PMC3340492.

9. Huang WY, Wang J, Liu YM, Zheng QS, Li CY. Inhibitory effect of Malvidin on TNF-α-induced inflammatory response in endothelial cells. Eur J Pharmacol. 2014 Jan 15; 723:67-72. doi: 10.1016/j.ejphar.2013.11.041. Epub 2013 Dec 11. PMID: 24333549.

10. Du W, Erden O, Pang Q. TNF-α signaling in Fanconi anemia. Blood Cells Mol Dis. 2014 Jan;52(1):2-11. doi: 10.1016/j.bcmd.2013.06.005. Epub 2013 Jul 24. PMID: 23890415; PMCID: PMC3851925.

11. Ardebili SM, Yeghaneh T, Gharesouran J, Rezazadeh M, Farhoudi M, Ayromlou H, Talebi M, Ghojazadeh M. Genetic association of TNF-α-308 G/A and -863 C/A polymorphisms with late onset Alzheimer's disease in Azeri Turk population of Iran. J Res Med Sci. 2011 Aug;16(8):1006-13. PMID: 22279475; PMCID: PMC3263076.

12. Zhang YY, Fan YC, Wang M, Wang D, Li XH. Atorvastatin attenuates the production of IL-1β, IL-6, and TNF-α in the hippocampus of an amyloid β1-42-induced rat model of Alzheimer's disease. Clin Interv Aging. 2013; 8:103-10. doi: 10.2147/CIA.S40405. Epub 2013 Jan 31. PMID: 23386786; PMCID: PMC3563315.

13. Zhou M, Xu R, Kaelber DC, Gurney ME. Tumor Necrosis Factor (TNF) blocking agents are associated with lower risk for Alzheimer's disease in patients with rheumatoid arthritis and psoriasis. PLoS One. 2020 Mar 23;15(3):e0229819. doi: 10.1371/journal.pone.0229819. PMID: 32203525; PMCID: PMC7089534.

14. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011 Aug 5;11(9):607-15. doi: 10.1038/nri3041. PMID: 21818123.

15. Abraham D, Feher J, Scuderi GL, Szabo D, Dobolyi A, Cservenak M, Juhasz J, Ligeti B, Pongor S, Gomez-Cabrera MC, Vina J, Higuchi M, Suzuki K, Boldogh I, Radak Z. Exercise and probiotics attenuate the development of Alzheimer's disease in transgenic mice: Role of microbiome. Exp Gerontol. 2019 Jan; 115:122-131. doi: 10.1016/j.exger.2018.12.005. Epub 2018 Dec 6. PMID: 30529024.

16. Lovatel GA, Elsner VR, Bertoldi K, Vanzella C, Moysés Fdos S, Vizuete A, Spindler C, Cechinel LR, Netto CA, Muotri AR, Siqueira IR. Treadmill exercise induces age-related changes in aversive memory, neuroinflammatory and epigenetic processes in the rat hippocampus. Neurobiol Learn Mem. 2013 Mar; 101:94-102. doi: 10.1016/j.nlm.2013.01.007. Epub 2013 Jan 26. PMID: 23357282.

17. Bonifati DM, Kishore U. Role of complement in neurodegeneration and neuroinflammation. Mol Immunol. 2007 Feb;44(5):999-1010. doi: 10.1016/j.molimm.2006.03.007. Epub 2006 May 15. PMID: 16698083.

18. Belkhelfa M, Rafa H, Medjeber O, Arroul-Lammali A, Behairi N, Abada-Bendib M, Makrelouf M, Belarbi S, Masmoudi AN, Tazir M, Touil-Boukoffa C. IFN-γ and TNF-α are involved during Alzheimer disease progression and correlate with nitric oxide production: a study in Algerian patients. J Interferon Cytokine Res. 2014 Nov;34(11):839-47. doi: 10.1089/jir.2013.0085. Epub 2014 May 15. PMID: 24831467.

19. Flynn MG, McFarlin BK, Markofski MM. The Anti-Inflammatory Actions of Exercise Training. Am J Lifestyle Med. 2007 May;1(3):220-235. doi: 10.1177/1559827607300283. PMID: 25431545; PMCID: PMC4243532..

20. Souza LC, Filho CB, Goes AT, Fabbro LD, de Gomes MG, Savegnago L, Oliveira MS, Jesse CR. Neuroprotective effect of physical exercise in a mouse model of Alzheimer's disease induced by β-amyloid$_{1-40}$ peptide. Neurotox Res. 2013 Aug;24(2):148-63. doi: 10.1007/s12640-012-9373-0. Epub 2013 Jan 11. PMID: 23307759.

21. Nichol KE, Poon WW, Parachikova AI, Cribbs DH, Glabe CG, Cotman CW. Exercise alters the immune profile in Tg2576 Alzheimer mice toward a response coincident with improved cognitive performance and decreased amyloid. J Neuroinflammation. 2008 Apr 9; 5:13. doi: 10.1186/1742-2094-5-13. PMID: 18400101; PMCID: PMC2329612.

22. Ding YH, Mrizek M, Lai Q, Wu Y, Reyes R Jr, Li J, Davis WW, Ding Y. Exercise preconditioning reduces brain damage and inhibits TNF-alpha receptor expression after hypoxia/reoxygenation: an in vivo and in vitro study. Curr Neurovasc Res. 2006 Nov;3(4):263-71. doi: 10.2174/156720206778792911. PMID: 17109621.

23. Chu WM. Tumor necrosis factor. Cancer Lett. 2013 Jan 28;328(2):222-5. doi: 10.1016/j.canlet.2012.10.014. Epub 2012 Oct 22. PMID: 23085193; PMCID: PMC3732748.

24. Lin JY, Kuo WW, Baskaran R, Kuo CH, Chen YA, Chen WS, Ho TJ, Day CH, Mahalakshmi B, Huang CY. Swimming exercise stimulates IGF1/ PI3K/Akt and AMPK/SIRT1/PGC1α survival signaling to suppress apoptosis and inflammation in aging hippocampus. Aging (Albany NY). 2020 Apr 22;12(8):6852-6864. doi: 10.18632/aging.103046. Epub 2020 Apr 22. Erratum in: Aging (Albany NY). 2020 Aug 30;12(16):16663-16664. PMID: 32320382; PMCID: PMC7202519.

25. Sun LN, Qi JS, Gao R. Physical exercise reserved amyloid-beta induced brain dysfunctions by regulating hippocampal neurogenesis and inflammatory response via MAPK signaling. Brain Res. 2018 Oct 15; 1697:1-9. doi: 10.1016/j.brainres.2018.04.040. Epub 2018 May 2. PMID: 29729254.

26. Afzalpour ME, Chadorneshin HT, Foadoddini M, Eivari HA. Comparing interval and continuous exercise training regimens on neurotrophic factors in rat brain. Physiol Behav. 2015 Aug 1; 147:78-83. doi: 10.1016/j.physbeh.2015.04.012. Epub 2015 Apr 11. PMID: 25868740.

27. Guo M, Lin V, Davis W, Huang T, Carranza A, Sprague S, Reyes R, Jimenez D, Ding Y. Preischemic induction of TNF-alpha by physical exercise reduces blood-brain barrier dysfunction in stroke. J Cereb Blood Flow Metab. 2008 Aug;28(8):1422-30. doi: 10.1038/jcbfm.2008.29. Epub 2008 Apr 16. PMID: 18414498.