Physical Activity and Hormones (J Physic Act Horm)
Vol. 6 Autumn 2025

# The effect of endurance training and curcumin supplement on oxidative stress and memory in Alzheimer's disease

**Seyedeh Fatemeh Hosseini Kolgoo**[1]
Department of Physical Education and Sport Sciences, Ra.C., Islamic Azad University, Rasht, Iran

**Alireza Elmieh**[2]*
Department of Physical Education and Sport Sciences, Ra.C., Islamic Azad University, Rasht, Iran

**Shahram Gholamrezaei Dadsar**[3]
Department of Physical Education and Sport Sciences, Ra.C., Islamic Azad University, Rasht, Iran

**Mohammad Reza Fadaei Chafy**[4]
Department of Physical Education and Sport Sciences, Ra.C., Islamic Azad University, Rasht, Iran

## ABSTRACT

**Introduction:** Alzheimer's disease (AD) is the leading cause of dementia worldwide. One of its main pathophysiological mechanisms involves neuronal damage induced by oxidative stress. The present study aimed to investigate the effects of endurance training and curcumin supplementation on oxidative stress and memory function in a rat model of AD.

**Material & Methods:** In this experimental study, forty rats were randomly divided into six groups: healthy control, sham, AD control, exercise, curcumin, and exercise + curcumin. The experimental groups underwent eight weeks of endurance training and/or received curcumin injections. Memory performance, glutathione peroxidase (GPX) activity, and malondialdehyde (MDA) levels were assessed. Data were analyzed using two-way ANOVA and independent t-tests.

**Results:** Both exercise and curcumin significantly improved memory performance ($p=0.006$ and $p=0.008$), decreased MDA levels ($p<0.001$), and increased GPX activity ($p=0.01$ and $p<0.001$) compared with the AD control group.

**Conclusion:** These findings suggest that curcumin supplementation and endurance exercise can mitigate oxidative stress and cognitive decline in Alzheimer's disease rat models.

**Keywords:** Alzheimer's disease, oxidative stress, endurance training, curcumin.

***Correspondence:** elmieh@iaurasht.ac.ir
**Received:** Oct 2025; **Revised:** Nov 2025; **Accepted:** Dec 2025.
**DOI:** https://doi.org/10.71878/jpah.2025.1229538

## 1. Introduction

Alzheimer's disease (AD) is a progressive, age-associated neurodegenerative condition and represents the most prevalent cause of dementia among older adults (1). Globally, approximately fifty million people are affected by AD, and its prevalence continues to rise (2). Following an extended prodromal period, the disease manifests clinically through profound memory deficits, progressive cognitive decline, and gradual changes in personality and behavior (3). Existing therapeutic interventions primarily offer symptomatic relief rather than disease modification or cure, largely due to the complex and incompletely elucidated pathophysiological mechanisms of AD. Characteristically, the disorder is defined by two major neuropathological features: extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles formed by hyper phosphorylated tau protein (pTau) (4, 5).

The accumulation of β-amyloid (Aβ) polymers triggers both oxidative stress and neuroinflammatory responses. Moreover, Aβ plaques can interfere with acetylcholine (ACh) signaling, thereby impairing synaptic transmission; dysfunction within the cholinergic system is consequently associated with memory deficits. In addition, Aβ deposition activates inflammatory cascades that promote the production of reactive oxygen species (ROS), further exacerbating neuronal damage (6, 7).

The progressive accumulation of reactive oxygen species (ROS) results in persistent oxidative stress, a characteristic physiological alteration observed during the early stages of Alzheimer's disease (AD). This oxidative imbalance disrupts the metabolism of biomacromolecules, compromises mitochondrial efficiency and energy homeostasis, and impairs synaptic function, collectively contributing to cognitive deterioration (8). Furthermore, oxidative stress facilitates neuronal degeneration in AD by enhancing iron and lipid peroxidation, protein oxidation, and the expression of oxidative stress markers commonly detected within senile plaques (9). Oxidative stress emerges when the generation of free radicals surpasses antioxidant defense capacity, thereby weakening cellular antioxidant systems and promoting neuronal injury (10, 11),

Notably, the brain possesses inherently low concentrations of endogenous antioxidants, rendering it particularly vulnerable to oxidative damage (12).

According to the Lancet Commission on Dementia Prevention, Intervention, and Care, several potentially modifiable risk factors—such as hypertension, smoking, obesity, depression, physical inactivity, diabetes, and limited social engagement—collectively account for approximately 40% of the global dementia burden. Regular physical activity during midlife, and potentially extending into later adulthood, appears to confer protective effects against dementia, likely by mitigating obesity, diabetes, and cardiovascular risks (13). Exercise may also influence neurobiological mechanisms by reducing glutamine levels or enhancing hippocampal neurogenesis (14).

However, cessation of exercise in some individuals may reflect prodromal dementia, suggesting that physical inactivity could represent both a potential cause and a consequence of cognitive decline. This relationship may be particularly significant among individuals with coexisting cardiovascular comorbidities. Furthermore, as with other health outcomes, the protective benefits of exercise likely depend on its consistency and continuation into the period of highest dementia risk (15).

Given the current absence of effective therapeutic options for Alzheimer's disease (AD), increasing attention has been directed toward innovative preventive approaches involving dietary modification, supplementation with vitamins and minerals, and the utilization of bioactive natural compounds. Recently, natural phytochemicals have gained prominence as promising alternative therapeutic agents for AD management (16).

Polyphenols, a broad class of plant-derived compounds characterized by multiple phenolic structural units, play a crucial role in plant defense mechanisms against pathogens and various environmental stressors. In humans and animals, polyphenols exert neuroprotective effects by modulating numerous intracellular signaling pathways involved in neuronal maintenance and survival (17). Additionally, these compounds are known for their potent antioxidant properties, including the scavenging of free radicals and the chelation of metal ions, thereby contributing to the regulation of key protein degradation pathways (18, 19). Among the various polyphenolic compounds, curcumin is one of the most extensively studied.

Curcumin (Cur), a principal bioactive constituent of turmeric (20). Curcumin possesses a wide range of pharmacological properties, including anti-inflammatory (21), anti-oxidant (22) and neuroprotective effects (23). It has been demonstrated to ameliorate spatial memory impairment in experimental models (24).

The antioxidant capacity of curcumin in vivo may, at least in part, be mediated through the activation of antioxidant enzymes such as glutathione peroxidase (GPX) (25).

Although substantial progress has been made in understanding curcumin's biological activities, the specific molecular mechanisms underlying its effects on neuronal cells exposed to oxidative stress remain incompletely understood. Also, the combined effects of natural antioxidants and lifestyle interventions remain unclear. Therefore, the present study investigates the effect of the eighth week of endurance training with curcumin consumption on the levels of malondialdehyde and glutathione peroxide in the hippocampal tissue and memory of Alzheimer's rats with osteoarthritis.

## 2. Methodology

### 2.1. Materials and methods

This was an experimental study with post-test design and control group. Current study conducted based on ethical principles of Helsinki Declaration.

### 2.2. Participants

A total of 40 male Wistar rats (age 32 weeks, weight 250-300 grams) were supplied from the Animal Breeding and Reproduction Laboratory of Islamic Azad University, Marvdasht Branch and transferred to Animal Exercise Physiology Laboratory. During the study, samples were housed in 12-hour light-dark cycle, temperature of 22-24˚C and relative humidity of 55-60%. They lived in washable polycarbonate cages and sterilized wood shavings were used to absorb the moisture and urine on the floor of the cages with water and food access ad libitum. Before the beginning of the study, samples lived in these standard circumstances for one week to familiarize with the environment. After induction of OA and AD, the samples were randomly assigned to healthy control group (n=7), patient control group (AD control, n=7), Sham group (n=7), curcumin group (CUR, n=7), exercise group (EXE, n=6) and curcumin + exercise group (CUR+EXE, n=6).

### 2.3. Measurements

**Spatial Memory Evaluation:** Twenty-four hours after the last training session, spatial memory of samples was evaluated using Y maze test. During the evaluation, all necessary arrangements that could affect behavior (i.e., minimal external noise and movement, moderate lightning, eliminating olfactory clues, same experimenter for all samples, etc.) were controlled by the researchers. The Y maze had three identical opaque wood arms (46 cm length, 15 cm width and 15 cm height) which formed a Y shape (120˚ apart), label as A, B and C for convenience. To perform this test, the rat was placed at the end of one arm facing the center and allowed to explore all areas of the maze for 8 minutes. Then the sequence and number of arm entry was observed and recorded. Arm entry was counted when the animal's hind limbs are completely inside the arm. Alternation behaviors were considered successful when consecutive (serial) entries into all arms were in overlapping sets of 3 (i.e., ABC, BCA, CAB, etc.). The following formula was used to calculate the Alternation:

*(Number of Alternations / (Total Arm Entries – 2)) × 100 (32)*

**Histopathological Evaluation:** Forty-eight hours after the last training session histopathological tests were performed. After 12-hour fasting rats were anesthetized with Ketamine and Xylazine. Then the brain was extracted during a craniotomy and the hippocampus tissue was separated and instantly freeze in liquid nitrogen to preserve the tissue for further evaluations. The hippocampus tissue then embedded in paraffin for fixation. After fixation, paraffin blocks were cut into 5 µm thickness and stained with Hematoxylin and Eosin (H&E). The stained slides were examined under a bright field light microscope (Olympus-BH2, Japan) at magnification of X40, and the number of cell density per unit area (NA) of the hippocampus was calculated. The physical dissector method was used for quantitative analysis of neurons. We calculated the number of neurons in a 10,000 µm2 frame, then the mean scores of neurons NA in subdivisions of hippocampus were calculated according to the following formula: $NA=\sum Q/\sum P \times AH$ (NA is the cell density, ΣQ is the total number of counted particles in the sections, ΣP is the number of samples taken in a sample, A is the area of the sampling frame, and H is the distance between two consecutive slices or the thickness of each slice).

**Measurement of MDA levels in Hippocampal Tissue:** Hippocampal tissues were rapidly dissected on ice and immediately homogenized in cold phosphate-buffered saline (PBS; pH 7.4) containing protease inhibitors at a ratio of approximately 100 mg of tissue per 1 mL of PBS buffer. Homogenization was performed on ice using Navand Salamat homogenizer (Iran, Reg No. 16010). The homogenates were centrifuged at 5,000 × g for 20 minutes at 4 °C, and the supernatants were collected for biochemical analysis. Malondialdehyde levels were determined using ZellBio GmbH Malondialdehyde / Thiobarbituric Acid reactive substances (TBARS) assay kit (Germany, Cat No. ZB-MDA-96A). In this assay, MDA present in the tissue homogenate reacts with thiobarbituric acid under acidic and high-temperature conditions to form a pink chromogen. The optical density (OD) of the resulting complex was measured at 532 nm using Microplate reader (BMG LABTECH FLUOstar Omega). All samples were assayed in duplicate, and the mean OD value was used to calculate MDA concentration based on a standard curve.

**Measurement of GPx activity in Hippocampal Tissue:** Hippocampal tissues were rapidly dissected on ice and immediately homogenized in cold phosphate-buffered saline (PBS; pH 7.4) containing protease. Homogenization was performed on ice using Navand Salamat homogenizer (Iran, Reg No. 16010). The homogenates were centrifuged at 12,000 × g for 15 minutes at 4 °C, and the resulting supernatants were collected for biochemical analysis. GPx activity was measured using a Kiazist GPx assay kit (Iran, Reg No. KGPX96). This assay is based on the reduction of hydrogen peroxide by GPx using reduced glutathione (GSH), followed by the regeneration of GSH by glutathione reductase with concomitant oxidation of NADPH to $NADP^+$. Samples incubated in room temperature for 15 minutes and then analyzed using a Microplate reader (BMG LABTECH

FLUOstar Omega). Absorbance was recorded at 340 nm at 1-minute intervals over a 5-minute period. The decrease in absorbance corresponding to NADPH consumption was monitored, and GPx activity was calculated using formula 1 during the linear phase of absorbance decline.

Formula 1. GPX activity calculation

$$GPX\ Activity\ = \frac{\Delta A340/min}{0.00216\ \mu M^{-1}} \times \frac{110}{sample\ volume\ (\mu L)} \times sample\ dilution\ factor$$

### 2.4. Intervention

**Alzheimer's disease Induction:** For the induction of Alzheimer's disease, after 12-hour fasting, single dose of 10mg/kg trimethyltin chloride (TMT) was injected intraperitoneal (TMT was supplied by Sigma-Aldrich Corporation, USA). After 14 days, the samples were accessed based on clinical symptoms including aggression, tail twitching, periorbital hemorrhage and Y maze memory and learning test and compared with healthy group to insure the AD induction (26).

**Knee Osteoarthritis Induction:** For inducing knee osteoarthritis, we used meniscus transection method. Samples were anesthetized using diethyl ether inhalation. Left knee of samples were immobilized, shaved and sterilized and 0.03 mg/kg buprenorphine was injected locally to alleviate pain. We made a 1 cm incision in the skin and soft tissue of the medial part of left hind limbs along the tibio-femoral junction. After a complete exposure, we severed the medial meniscus. In Sham group the medial collateral ligament (MCL) was only touched and no injury were made to MCL or medial meniscus. Soft tissue was closed with 4-0 vicryle sutures and skin was closed. The sutures were removed after one week when the skin was healed. Samples were placed in different cages o spend post-surgical recovery. Previous studies revealed that osteoarthritis would appear on histological evaluations after 3 weeks. We postponed the training 4 weeks after the surgery (27-29).

**Endurance Training Protocol:** At first, the samples ran on a rodent treadmill without slope for 8 minutes with 8 m/min speed for 7 days to familiarize with treadmill. The endurance training protocol was as followed: At the beginning of each session, animals warmed up with a 5-minute run (speed 8-10 m/min), followed by a 15-minute run with 10 m/min speed during first week. The speed and duration were gradually increased (table 1). Finally they cooled down with a 5-minute run (speed 8-10 m/min) at the end of each training session (26).

***Table 1.*** *Endurance training Protocol*

| week | Exercise duration (minutes) | Speed (m/min) |
|---|---|---|
| **1** | 15 | 10 |
| **2** | 20 | 12 |
| **3** | 25 | 14 |
| **4** | 30 | 16 |
| **5** | 35 | 18 |
| **6** | 40 | 20 |
| **7** | 45 | 22 |
| **8** | 48 | 24 |

**Curcumin Administration:** The Curcumin was supplied from by Sigma-Aldrich Corporation, USA (Industrial Code C-1386). According to previous study the optimal curcumin dose for ameliorating beta amyloid in rodents with AD was 100 mg/kg/day (30, 31). So, we solved 500 mg/kg curcumin in 6 ml of corn oil and injected 0.3 cc (30 international units) intraperitonealy every day.

### 2.5. Statistical Methods

The data was analyzed using SPSS 26.0 software (SPSS Statistics/IBM Corp, Chicago, IL, USA). The results are presented as mean ± SD. The normal distribution was assessed using Shapiro-Wilk test. To analyze data, two-way analysis of variance (ANOVA) test followed by independent T test (post hoc) was performed. The value of p=0.05 was considered statistically significant.

## 3. Results

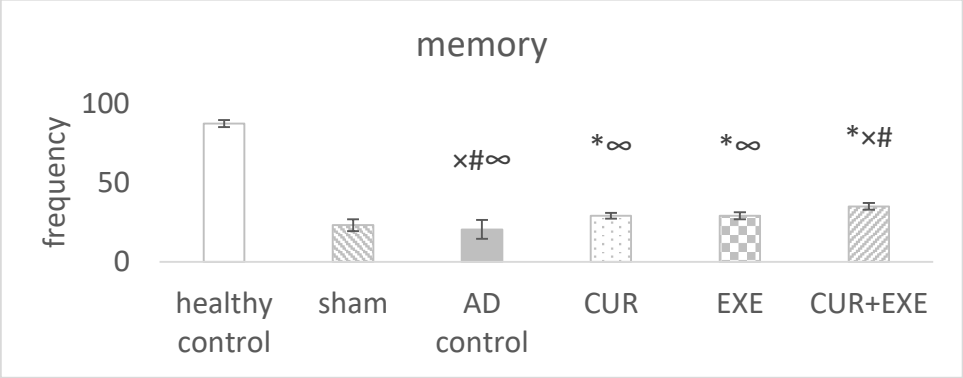
Spatial memory, MDA and GPX activity were measured in all experimental groups. The mean and standard deviation (mean ± SD) values in control, Sham, AD control, CUR, EXE and CUR+EXE groups are presented in table 2.

***Table 2.*** *Spatial memory, MDA and GPX levels of the rats in experimental groups*

| variable | control | Sham | AD control | CUR | EXE | CUR+EXE |
|---|---|---|---|---|---|---|
| **Memory (alternation)** | 87.285±2.138 | 23.142±3.716 | 20.428±5.968 | 29.00±1.825 | 29.166±2.228 | 35.00±2.097 |
| **MDA (µmol)** | 7.361±1.003 | 17.124±1.455 | 18.160±1.333 | 13.791±1.671 | 14.954±0.713 | 10.542±1.405 |
| **GPX (U/mg)** | 165.536±29.658 | 108.430±16.506 | 103.090±2.189 | 137.699±1.449 | 131.504±18.725 | 152.993±19.799 |

**Memory:** For evaluating the effects of exercise and curcumin on memory in AD rats, we conducted two-way analysis of variance (ANOVA). Leven's test indicated that the assumption of homogeneity of variances was violated ($p<0.001$); therefore, Robust test of equality of means were applied. The results demonstrated that exercise significantly increased memory compared to the AD control group ($p<0.001$). Similarly, curcumin administration produced significant elevation in memory ($p<0.001$). The combination of exercise and curcumin also resulted in a significant enhancement of memory (p=00.8).

To assess AD induction, memory was compared between control group and others using independent T test and the results show a significant decline in every groups in comparison to healthy control group ($p<0.001$). Memory was significantly higher in EXE, CUR and CUR+EXE groups in comparison to Sham group (p=0.005, p=0.003 and $p<0.001$; respectively) and AD control group (p=0.006, p=0.008 and $p<0.001$, respectively) .There was no significant difference in memory between CUR and EXE group. But the memory was higher in CUR+EXE group in comparison to EXE ($p<0.001$) and CUR group ($p<0.001$) (figure 1).

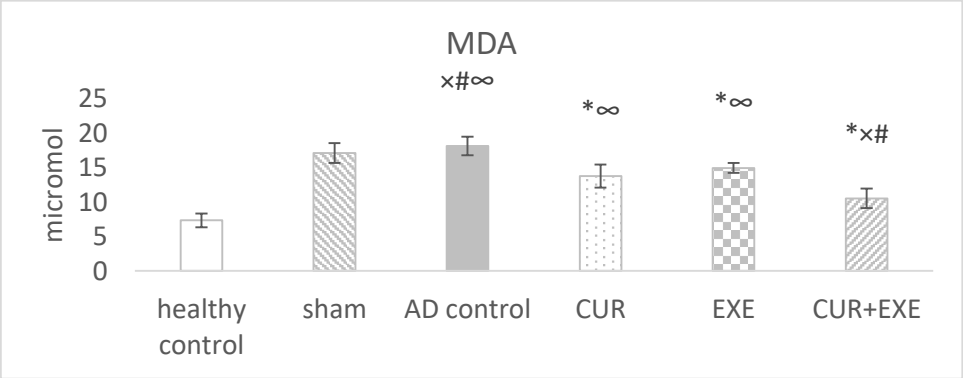



* Significant difference compared to AD control ($p<0.05$), × significant difference compared to CUR control ($p<0.05$), # significant difference compared to EXE control ($p<0.05$), ∞ significant difference compared to CUR+EXE control ($p<0.001$)

***Figure 1.*** Memory in the research groups

**Malondialdehyde:** A two-way ANOVA was performed to examine the effects of curcumin and exercise on MDA levels in hippocampus of AD rats. Due to the violation of homogeneity of variances according to Leven's test ($P<0.001$), Robust tests were applied. The results showed that both exercise ($p<0.001$) and curcumin ($p<0.001$) significantly decreased MDA levels compared to AD control group. The combination of exercise and curcumin also produced a significant decrease in MDA levels (p=0.012). These findings indicate that both treatments separately and in combination, effectively decrease ROS in the AD rat models.

MDA level was significantly higher in every group compared to healthy control group ($p<0.001$) and significantly lower in CUR, EXE and CUR+EXE groups compared to AD control ($p<0.001$) and Sham groups (p=0.002, p=007 and p<00.1; respectively). MDA level was significantly lower in CUR+EXE compared to CUR and EXE group ($p<0.001$) (synergistic effect) and there was no significant difference between CUR and EXE group (figure 2).

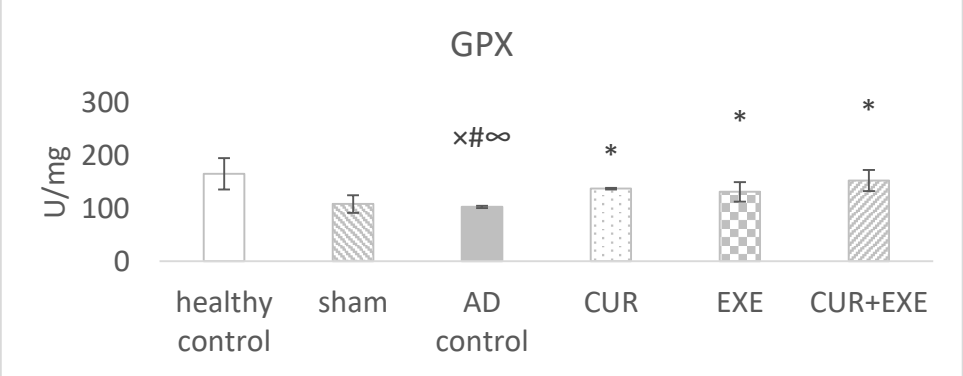



* Significant difference compared to AD control ($p<0.001$), × significant difference compared to CUR control ($p<0.05$), # significant difference compared to EXE control ($p<0.001$), ∞ significant difference compared to CUR+EXE control ($p<0.05$)

***Figure 2.*** MDA level in hippocampal tissue in the research groups

**Glutathione Peroxidase:** A two-way ANOVA was used to examine the effects of exercise and curcumin on GPX activity in AD rats. Because the assumption of homogeneity of variances was violated according to Leven's test (p=0.003), Robust tests were employed. The results revealed that neither exercise (p=0.09) nor curcumin (p=0.08) had significant effects on GPX activity compared with the AD control rats. Also, the combined intervention of exercise and curcumin did not produce a significant enhancement in GPX activity (p=0.51).

The results of independent T test revealed no significant difference in GPX activity between healthy control group and CUR+EXE group but GPX activity were significantly ameliorated in Sham (p<0.001), AD control (p<0.001), EXE (p=0.03) and Cur (p=0.02) groups in comparison to healthy control group. GPX activity were significantly increased in EXE, CUR and CUR+EXE group in comparison to Sham (p=0.03, p<0.001 and p<0.001; respectively) and AD control group (p=0.01, p<0.001 and p<0.001 respectively). There was also a synergic effect between EXE and CUR compared to EXE. There were no significant difference between GPX activity in EXE, CUR and CUR+EXE groups (figure 3).



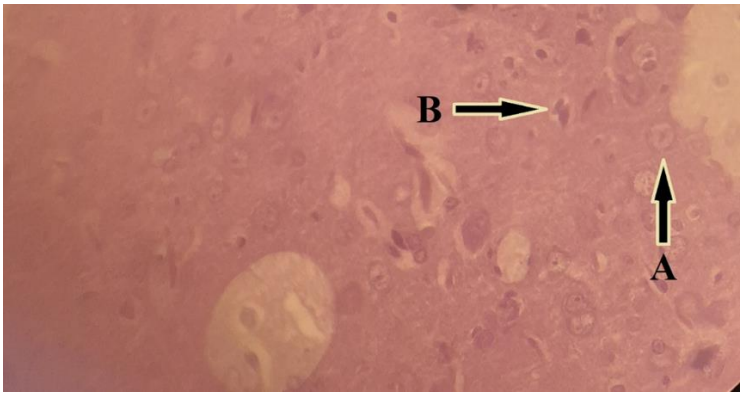

* Significant increase compared to AD control (p<0.05), × significant decrease compared to CUR control (p<0.001), # significant decrease compared to EXE control (p<0.05), ∞ significant decrease compared to CUR+EXE control (p<0.001)

***Figure 3.*** GPX activity in hippocampal tissue in the research groups

**Histopathological evaluation:** Hippocampal tissue was examined under a bright field light microscope and the healthy cell density in different groups is presented in the table 3 (figure 4).

***Table 3.*** *Cell density (healthy cell to all cell ration) in experimental groups*

| Variable | control | | Sham | | AD control | | CUR | | EXE | | CUR+EXE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sample number** | 1 | 2 | 11 | 12 | 21 | 22 | 31 | 32 | 41 | 42 | 51 | 52 |
| **CA1 area Cell Density (%)** | 0.98437 | 0.96296 | 0.85471 | 0.85542 | 0.85321 | 0.88990 | 0.89583 | 0.88888 | 0.89090 | 0.83529 | 0.93333 | 0.91836 |
| **CA3 area Cell Density (%)** | 0.93150 | 0.92941 | 0.8125 | 0.81426 | 0.83333 | 0.80701 | 0.89041 | 0.86021 | 0.875 | 0.84375 | 0.89705 | 0.90123 |




Healthy cells: The nucleus is purple and clearly visible, the cell is round and has a clear boundary. Unhealthy cells: In damaged cells, the nucleus is not visible and the cell shape has changed from round to spherical or triangular, without any clear boundary.)

***Figure 4.*** Arrows (A) indicate healthy cells and arrows (B) indicate unhealthy cells.

## 4. Discussion

The present study investigated the effects of 8 eight week endurance training and curcumin administration on oxidative stress biomarkers and memory performance in rats with experimentally induced Alzheimer's disease (AD) and knee osteoarthritis. Our findings demonstrated that both curcumin supplementation and exercise enhanced memory performance, reduced lipid peroxidation, as evidenced by lower MDA levels in Alzheimer's

disease (AD) rats with osteoarthritis (OA). The combined intervention demonstrated a synergistic effect compared to either treatments alone. Furthermore, antioxidant enzyme activity (GPX activity) was improved in treatment groups compared to AD control group, although there was no difference among the treatment modalities.

Severe oxidative damage, disruption of the cholinergic system, deposition of β-amyloid (Aβ) protein, and formation of extracellular plaques are recognized as principal contributors to memory deterioration in AD (33). The GPx activity and MDA level are commonly utilized as quantifiable indicators of oxidative injury. GPX serves as a key intracellular antioxidant enzyme that catalyzes the reduction of hydrogen peroxide by oxidizing glutathione, thereby stabilizing cell membrane integrity and preserving cellular function. In contrast, MDA is a reactive aldehyde formed as a byproduct of lipid peroxidation, reflecting oxidative damage mediated by reactive oxygen species (ROS) (34). Maintaining neural homeostasis and clearance of Aβ plaques under physiological conditions is the pivotal role of microglia, the resident immune cells of the brain (35). However, in AD, dysfunctional microglia fail to exert protective effects and instead produce exaggerated inflammatory responses that contribute to disease pathogenesis (36).

In our study, the elevated MDA levels observed in the AD control group confirmed the presence of severe oxidative stress, while curcumin treatment markedly reduced these levels. This finding is in agreement with previous reports showing that curcumin suppresses lipid peroxidation by scavenging reactive oxygen species (ROS) and inhibiting the chain reactions that damage cell membranes (37-39). The decreased GPX activity in the AD control group indicates impaired antioxidant defense in the diseased brain. Curcumin administration significantly restored GPX activity, suggesting that it either upregulates GPX gene expression or protects enzyme structure and function from oxidative damage. Previous studies have reported similar findings, showing that curcumin enhances the activity of antioxidant enzymes, including GPX (39, 40).

The impact of exercise on inflammatory processes varies according to the type, intensity, and duration of training, as well as individual and tissue-specific factors (41). Moderate, regular physical activity has been shown to induce anti-inflammatory effects, whereas high-intensity or competitive exercise may trigger pro-inflammatory responses (42). In the present study, eighth weeks of endurance training led to a significant reduction in MDA levels indicating decreased oxidative stress, along with a significant increase in GPX activity reflecting enhanced intracellular antioxidant defense. Consistent with this study, regular treadmill exercise for 12 weeks has also been shown to promote microglial polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, thereby attenuating hippocampal inflammation and oxidative damage and ultimately improving cognitive performance (43). Furthermore, five months of voluntary wheel running reduced Aβ40 and Aβ42 accumulation in the brains of AD mice (44), and a similar reduction in Aβ deposition was observed after treadmill training in 3-month-old AD mice (45). However, in contrast to these findings, a 16-week aerobic exercise intervention in AD patients failed to significantly alter cerebral Aβ levels (46).

In addition to biochemical effects, curcumin improved memory performance in the treated rats. The observed improvement may be attributed to curcumin's ability to reduce oxidative and inflammatory damage in the hippocampus, the primary brain region responsible for learning and memory. Various studies also confirmed our findings in this matter (37, 39, 40).

Epidemiological evidence indicates that regular exercise can reduce the risk of developing AD by up to 45%, suggesting a substantial protective role of physical activity in preventing dementia (47-49). Exercise also exerts favorable effects on several major risk factors for AD, including hypertension, type II diabetes, obesity, and hyperlipidemia (50). Although one study reported that moderate- to high-intensity aerobic and resistance training did not slow cognitive decline in patients with mild-to-moderate dementia, it did improve physical fitness (51). Conversely, multiple animal and clinical studies have demonstrated that exercise mitigates symptoms of neurodegenerative disorders and delays disease progression through diverse molecular and physiological mechanisms (52). The findings of this study were consistent with those of the second study but in contrast with the first, demonstrating that the exercise group exhibited significantly less memory impairment than the AD control group. Furthermore, memory performance in the combined exercise and curcumin (CUR+EXE) group was significantly improved compared to the exercise (EXE) group.

Under systemic or localized inflammatory conditions, cellular and molecular mediators transmit inflammatory signals to the central nervous system through multiple pathways. Normally, such immune responses are appropriately regulated to prevent excessive inflammation and secondary neuronal injury (53). To enhance the clinical relevance of the present study, osteoarthritis was experimentally induced in the animal model, as it represents a prevalent comorbidity among older adults and a leading cause of disability worldwide (54). Recent studies suggest that oxidative stress (OS) plays a pivotal role in maintaining cartilage homeostasis. Disruptions in redox balance can provoke intra-articular damage and trigger inflammatory processes within joint tissues, including the synovium and cartilage (55). Knee osteoarthritis was considered as a comorbid model in the present study due to its high prevalence and its characteristic association with chronic inflammation.

A major strength of the present study lies in its novel design, which simultaneously investigates Alzheimer's disease and osteoarthritis, two conditions that share common oxidative and inflammatory

mechanisms. By combining curcumin supplementation with exercise, we examined the potential impact of lifestyle modification and nutraceutical intervention on both biochemical and behavioral outcomes, thereby enhancing the reliability of our findings. Despite these strengths, certain limitations should be acknowledged. A key limitation was the absence of multi-dose validation, and potential differences between rat and human metabolism should also be taken into account. Also the effects of higher doses, long-term administration, and formulations with enhanced bioavailability should be explored to access possible adverse effects. Future studies are warranted to explore various exercise intensities and curcumin dosages, as well as the specific molecular signaling pathways underlying their effects.

## 5. Conclusion

Overall, our findings suggest that both curcumin and exercise attenuate oxidative stress and cognitive decline in AD rat models.

## 6. Acknowledgment

We are sincerely grateful to staffs at Animal Exercise Physiology Laboratory, Marvdasht, Fars, Iran, for their invaluable assistance throughout this project.

**Conflict of interests:** The authors declare that they have no conflict of interest.

## *References*

1. Wu Y-Y, Kuo H-C. Functional roles and networks of non-coding RNAs in the pathogenesis of neurodegenerative diseases. Journal of Biomedical Science. 2020;27(1):49. DOI: 10.1186/s12929-020-00636-z
2. Calfio C, Gonzalez A, Singh SK, Rojo LE, Maccioni RB. The emerging role of nutraceuticals and phytochemicals in the prevention and treatment of Alzheimer's disease. Journal of Alzheimer's disease. 2020;77(1):33-51. DOI: 10.3233/JAD-200443
3. Gauthier-Umaña C, Muñoz-Cabrera J, Valderrama M, Múnera A, Nava-Mesa MO. Acute Effects of Two Different Species of Amyloid-β on Oscillatory Activity and Synaptic Plasticity in the Commissural CA3-CA1 Circuit of the Hippocampus. Neural Plasticity. 2020;2020(1):8869526. DOI: 10.1155/2020/8869526
4. Jia Z, Yuan X, Wei J-a, Guo X, Gong Y, Li J, et al. A functionalized octahedral palladium nanozyme as a radical scavenger for ameliorating Alzheimer's disease. ACS Applied Materials & Interfaces. 2021;13(42):49602-13. DOI: 10.1021/acsami.1c12206
5. Cheignon Cm, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox biology. 2018;14:450-64. DOI: 10.1016/j.redox.2017.10.014
6. Wollen KA. Alzheimer's disease: the pros and cons of pharmaceutical, nutritional, botanical, and stimulatory therapies, with a discussion of treatment strategies from the perspective of patients and practitioners. Altern Med Rev. 2010;15(3):223-44. PMID: 21155624
7. Bekdash RA. The cholinergic system, the adrenergic system and the neuropathology of Alzheimer's disease. International Journal of Molecular Sciences. 2021;22(3):1273. DOI: 10.3390/ijms22031273
8. Tönnies E, Trushina E. Oxidative stress, synaptic dysfunction, and Alzheimer's disease. Journal of Alzheimer's disease. 2017;57(4):1105-21. DOI: 10.3233/JAD-161088
9. Hernández-Zimbrón LF, Rivas-Arancibia S. Syntaxin 5 Overexpression and β-Amyloid 1–42 Accumulation in Endoplasmic Reticulum of Hippocampal Cells in Rat Brain Induced by Ozone Exposure. BioMed research international. 2016;2016(1):2125643. DOI: 10.1155/2016/2125643
10. Kancheva VD, Dettori MA, Fabbri D, Alov P, Angelova SE, Slavova-Kazakova AK, et al. Natural chain-breaking antioxidants and their synthetic analogs as modulators of oxidative stress. Antioxidants. 2021;10(4):624. DOI: 10.3390/antiox10040624
11. Peng Y, Chang X, Lang M. Iron homeostasis disorder and Alzheimer's disease. International journal of molecular sciences. 2021;22(22):12442. DOI: 10.3390/ijms222212442
12. Cassidy L, Fernandez F, Johnson JB, Naiker M, Owoola AG, Broszczak DA. Oxidative stress in alzheimer's disease: A review on emergent natural polyphenolic therapeutics. Complementary therapies in medicine. 2020;49:102294. DOI: 10.1016/j.ctim.2020.102294
13. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The lancet. 2020;396(10248):413-46. DOI: 10.1016/S0140-6736(20)30367-6
14. Chieffi S, Messina G, Villano I, Messina A, Esposito M, Monda V, et al. Exercise influence on hippocampal function: possible involvement of orexin-A. Frontiers in physiology. 2017;8:85. DOI: 10.3389/fphys.2017.00085
15. Saint-Maurice PF, Coughlan D, Kelly SP, Keadle SK, Cook MB, Carlson SA, et al. Association of leisure-time physical activity across the adult life course with all-cause and cause-specific mortality. JAMA network open. 2019;2(3):e190355-e. DOI: 10.1001/jamanetworkopen.2019.0355
16. Piccialli I, Tedeschi V, Caputo L, D'Errico S, Ciccone R, De Feo V, et al. Exploring the therapeutic potential of phytochemicals in Alzheimer's disease: Focus on polyphenols and monoterpenes. Frontiers in Pharmacology. 2022;13:876614. DOI: 10.3389/fphar.2022.876614
17. Davinelli S, Sapere N, Zella D, Bracale R, Intrieri M, Scapagnini G. Pleiotropic protective effects of phytochemicals in Alzheimer′ s disease. Oxidative Medicine and Cellular Longevity. 2012;2012(1):386527. DOI: 10.1155/2012/386527
18. Nabavi SF, Sureda A, Dehpour AR, Shirooie S, Silva AS, Devi KP, et al. Regulation of autophagy by polyphenols: Paving the road for treatment of neurodegeneration. Biotechnology advances. 2018;36(6):1768-78. DOI: 10.1016/j.biotechadv.2017.12.001
19. Singh SK, Srivastav S, Yadav AK, Srikrishna S, Perry G. Overview of Alzheimer's disease and some therapeutic approaches targeting Aβ by using several synthetic and herbal compounds. Oxidative medicine and cellular longevity. 2016;2016(1):7361613. DOI: 10.1155/2016/7361613
20. Kim H, Im YH, Ahn J, Yang J, Choi JY, Lee K-H, et al. Synthesis and in vivo characterization of 18F-labeled difluoroboron-curcumin derivative for β-amyloid plaque imaging. Scientific Reports. 2019;9(1):6747. DOI: 10.1038/s41598-019-43246-y

21. Lee H-J, Jeong M, Na Y-G, Kim S-J, Lee H-K, Cho C-W. An EGF-and curcumin-co-encapsulated nanostructured lipid carrier accelerates chronic-wound healing in diabetic rats. Molecules. 2020;25(20):4610. DOI: 10.3390/molecules25204610
22. Theppawong A, Van de Walle T, Grootaert C, Van Hecke K, Catry N, Desmet T, et al. Synthesis of non-symmetrical nitrogen-containing curcuminoids in the pursuit of new anticancer candidates. ChemistryOpen. 2019;8(2):236-47. DOI: 10.1002/open.201800233
23. Rasouli Z, Ghavami R. Facile approach to fabricate a chemical sensor array based on nanocurcumin–metal ions aggregates: detection and identification of DNA nucleobases. ACS omega. 2020;5(31):19331-41. DOI: 10.1021/acsomega.0c00841
24. Hadizadeh-Bazaz M, Vaezi G, Hojati V. Curcumin attenuates spatial memory impairment by anti-oxidative, anti-apoptosis, and anti-inflammatory mechanism against methamphetamine neurotoxicity in male Wistar rats: Histological and biochemical changes. Neurotoxicology. 2021;84:208-17. DOI: 10.1016/j.neuro.2021.03.010
25. Rajeswari A. Curcumin protects mouse brain from oxidative stress caused by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydro pyridine. European Review for Medical and Pharmacological Sciences. 2006;10(4):157. PMID: 16910349
26. Hashemi SA, Ghadimi Z, Ghaedi H, Hashemi A. The effects of eight weeks of aerobic training with vitamin C on the expression pathway of antioxidants in the hippocampus tissue of TMT induced Alzheimer's disease rats. Brain Research. 2024;1822:148645. DOI: 10.1016/j.brainres.2023.148645
27. Lee K, Gang GG, Kang YG, Jung SS, Park H-G, Jang JH. Alleviation of osteoarthritis-induced pain and motor deficits in rats by a novel device for the intramuscular insertion of cog polydioxanone filament. Applied Sciences. 2021;11(22):10534. DOI: 10.3390/app112210534
28. McKinney JM, Pucha KA, Bernard FC, Brandon Dixon J, Doan TN, Willett NJ. Osteoarthritis early-, mid-and late-stage progression in the rat medial meniscus transection model. Journal of Orthopaedic Research®. 2025;43(1):102-16. DOI: 10.1002/jor.25976
29. Kuyinu EL, Narayanan G, Nair LS, Laurencin CT. Animal models of osteoarthritis: classification, update, and measurement of outcomes. Journal of orthopaedic surgery and research. 2016;11(1):19. DOI: 10.1186/s13018-016-0346-5
30. Ermiş M, Çiftci G. Role of curcumin on beta-amyloid protein, tau protein, and biochemical and oxidative changes in streptozotocin-induced diabetic rats. Naunyn-Schmiedeberg's Archives of Pharmacology. 2024;397(12):9833-44. DOI: 10.1007/s00210-024-03248-8
31. Khurana S, Jain S, Mediratta P, Banerjee B, Sharma K. Protective role of curcumin on colchicine-induced cognitive dysfunction and oxidative stress in rats. Human & experimental toxicology. 2012;31(7):686-97. DOI: 10.1177/0960327111433899
32. Bozorgi AD, Behboudi L, Hosseini SA, Rasoli MH. Effect of voluntary and forced training with royal jelly consumption on learning and spatial memory of rat model of alzheimer's disease. Jundishapur Journal of Chronic Disease Care. 2020;9(9). DOI: 10.5812/jjcdc.106017
33. Mushtaq A, Anwar R, Ahmad M. Lavandula stoechas (L) a very potent antioxidant attenuates dementia in scopolamine induced memory deficit mice. Frontiers in pharmacology. 2018;9:1375. DOI: 10.3389/fphar.2018.01375
34. Zou X, Feng Z, Li Y, Wang Y, Wertz K, Weber P, et al. Stimulation of GSH synthesis to prevent oxidative stress-induced apoptosis by hydroxytyrosol in human retinal pigment epithelial cells: activation of Nrf2 and JNK-p62/SQSTM1 pathways. The Journal of nutritional biochemistry. 2012;23(8):994-1006. DOI: 10.1016/j.jnutbio.2011.05.006
35. Fetler L, Amigorena S. Brain under surveillance: the microglia patrol. Science. 2005;309(5733):392-3. DOI: 10.1126/science.1114852
36. Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM. Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. Journal of Neuroscience. 2005;25(39):8843-53. DOI: 10.1523/JNEUROSCI.2868-05.2005
37. Shao S, Ye X, Su W, Wang Y. Curcumin alleviates Alzheimer's disease by inhibiting inflammatory response, oxidative stress and activating the AMPK pathway. Journal of Chemical Neuroanatomy. 2023;134:102363. DOI: 10.1016/j.jchemneu.2023.102363
38. Ruan Y, Luo H, Tang J, Ji M, Yu D, Yu Q, et al. Curcumin inhibits oxidative stress and autophagy in C17. 2 neural stem cell through ERK1/2 signaling pathways. Aging Medicine. 2024;7(5):559-70. DOI: 10.1002/agm2.12312
39. Hussain H, Ahmad S, Shah SWA, Ullah A, Rahman SU, Ahmad M, et al. Synthetic mono-carbonyl curcumin analogues attenuate oxidative stress in mouse models. Biomedicines. 2022;10(10):2597. DOI: 10.3390/biomedicines10102597
40. Xu Y, Hu R, He D, Zhou G, Wu H, Xu C, et al. Bisdemethoxycurcumin inhibits oxidative stress and antagonizes Alzheimer's disease by up-regulating SIRT1. Brain and Behavior. 2020;10(7):e01655. DOI: 10.1002/brb3.1655
41. da Luz Scheffer D, Latini A. Exercise-induced immune system response: Anti-inflammatory status on peripheral and central organs. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2020;1866(10):165823. DOI: 10.1016/j.bbadis.2020.165823
42. Pinho RA, Silva LA, Pinho CA, Scheffer DL, Souza CT, Benetti M, et al. Oxidative stress and inflammatory parameters after an Ironman race. Clinical Journal of Sport Medicine. 2010;20(4):306-11. DOI: 10.1097/JSM.0b013e3181e8d6d9
43. Zhang X, He Q, Huang T, Zhao N, Liang F, Xu B, et al. Treadmill exercise decreases Aβ deposition and counteracts cognitive decline in APP/PS1 mice, possibly via hippocampal microglia modifications. Frontiers in aging neuroscience. 2019;11:78. DOI: 10.3389/fnagi.2019.00078
44. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. Journal of Neuroscience. 2005;25(17):4217-21. DOI: 10.1523/JNEUROSCI.0496-05.2005
45. Liu H-l, Zhao G, Zhang H, Shi L-d. Long-term treadmill exercise inhibits the progression of Alzheimer's disease-like neuropathology in the hippocampus of APP/PS1 transgenic mice. Behavioural brain research. 2013;256:261-72. DOI: 10.1016/j.bbr.2013.08.031
46. Tarumi T, Rossetti H, Thomas BP, Harris T, Tseng BY, Turner M, et al. Exercise training in amnestic mild cognitive impairment: a one-year randomized controlled trial. Journal of Alzheimer's Disease. 2019;71(2):421-33. DOI: 10.3233/JAD-181175
47. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychological medicine. 2009;39(1):3-11. DOI: 10.1017/S0033291708003681
48. Yu J-T, Xu W, Tan C-C, Andrieu S, Suckling J, Evangelou E, et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(11):1201-9. DOI: 10.1136/jnnp-2019-321913
49. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. The lancet. 2017;390(10113):2673-734. DOI: 10.1016/S0140-6736(17)31363-6
50. Silva MVF, Loures CdMG, Alves LCV, De Souza LC, Borges KBG, Carvalho MdG. Alzheimer's disease: risk factors and potentially protective measures. Journal of biomedical science. 2019;26(1):33. DOI: 10.1186/s12929-019-0520-2

51. Lamb SE, Sheehan B, Atherton N, Nichols V, Collins H, Mistry D, et al. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. bmj. 2018;361. DOI: 10.1136/bmj.k1675
52. Mahalakshmi B, Maurya N, Lee S-D, Bharath Kumar V. Possible neuroprotective mechanisms of physical exercise in neurodegeneration. International journal of molecular sciences. 2020;21(16):5895. DOI: 10.3390/ijms21165895
53. Weitz TM, Town T. Microglia in Alzheimer′ s Disease: It′ s All About Context. International journal of Alzheimer's disease. 2012;2012(1):314185. DOI: 10.1155/2012/314185
54. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Annals of the rheumatic diseases. 2014;73(7):1323-30. DOI: 10.1136/annrheumdis-2013-204763
55. Mittler R. ROS are good. Trends in plant science. 2017;22(1):11-9. DOI: 10.1016/j.tplants.2016.08.002