



Treadmill running and *Levisticum Officinale* extract protect against LPS-induced memory deficits by modulating neurogenesis, neuroinflammation and oxidative stress

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Abstract

Neuroinflammation plays an essential role in the pathogenesis of Alzheimer's disease. The preventive effect of physical exercise on attenuating neuroinflammation has not been completely defined. *Levisticum officinale* is known as a medicinal plant with antioxidant and anti-inflammatory properties. The current study was designed to investigate the neuroprotective impacts of treadmill running and *Levisticum officinale* on lipopolysaccharide (LPS)-induced learning and memory impairments and neuroinflammation in rats. Male Wistar rats ran on a treadmill and/or were pretreated with *Levisticum officinale* extract at a dose of 100 mg/kg for a week. Then, rats received intraperitoneal injection of LPS at a dose of 1 mg/kg. Treadmill running and/or treatment of extract lasted three more weeks. Behavioral, molecular, biochemical and immunohistochemical assessments were carried out after the end of the experiment. LPS administration resulted in spatial learning and memory impairments along with increased mRNA expression of interleukin-6 and malondialdehyde levels, as well as decreased superoxide dismutase activity and neurogenesis in the hippocampus. Moreover, treadmill running for four weeks, alone and in combination with *Levisticum officinale* extract attenuated spatial learning and memory deficits, decreased the mRNA expression of interleukin-6 and malondialdehyde levels, and enhanced superoxide dismutase activity and neurogenesis in the hippocampus. In conclusion, the advantageous effects of running exercise and *Levisticum officinale* extract on LPS-induced memory impairments are possibly due to the antioxidant and anti-inflammatory activity and enhancing neurogenesis.

Keywords Treadmill exercise · *Levisticum officinale* · Lipopolysaccharide · Neuroinflammation · Oxidative stress · Neurogenesis

Introduction

Alzheimer's disease (AD) is identified by degeneration of cholinergic neurons in the basal forebrain and clinical manifestations of memory impairment and dementia (Donev 2017). AD devotes up to 70% of dementia cases (WHO,

2021). Histopathological characteristics of AD are the accumulation of A β plaques outside neurons and neurofibrillary tangles within neurons that eventually causes synaptic dysfunction and neuronal loss (Murphy and LeVine 2010). Chronic inflammatory processes by activation of microglia and production of proinflammatory mediators and free radicals contribute to synaptic impairment and neuronal death in AD. Excessive amounts of proinflammatory mediators, including interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and tumor necrosis factor- α (TNF- α) have been reported in the brain of patients with AD (Veerhuis 2011). Neuroinflammation also suppresses hippocampal neurogenesis and causes cognitive decline in AD (Ryan and Nolan 2016; Sung et al. 2020). Moreover, most studies have confirmed an increase in lipid peroxidation markers such as malondialdehyde in

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the brain of AD patients, particularly in the hippocampus and temporal cortex (Castellani et al. 2011).

Lipopolysaccharide (LPS) is a potent endotoxin derived from cell wall of Gram-negative bacteria. Evidence indicates that LPS administration induces learning and memory deficits in experimental animals and imitates AD in pathology and memory deficits (Zakaria et al. 2017). Systemic or central administration of LPS, results in neuroinflammation by activating nuclear factor- κ B (NF- κ B) and inducing the release of proinflammatory mediators such as IL-6, IL-1 β and TNF α (Zhao et al. 2019; Bossu et al. 2012). Moreover, the elevation of these cytokines induces the expression of amyloid precursor protein (APP) and amyloidogenesis (Lee et al. 2008). Inflammatory responses induced by LPS also produce excessive amounts of free radicals and peroxides in the central nervous system (Ali et al. 2016). Systemic LPS also reduces neurogenesis and expression of BDNF in the hippocampus and deteriorates spatial memory (Valero et al. 2014; Amraie et al. 2020).

Exercise training is known to be beneficial for brain function. It was shown that regular physical activity postpones the occurrence of dementia and AD (Rovio et al. 2005; Zhu et al. 2022). Also, exercise promotes antioxidant defense system and protects against lipid peroxidation damage in aged individuals (Bouزيد et al. 2018). Treadmill running prevents memory impairments by increasing neurotrophic factors and reducing oxidative stress in the hippocampus of aged rats (Vanzella et al. 2017). Exercise also enhances anti-inflammatory cytokines (Lovatel et al. 2013), long-term potentiation (LTP), neurogenesis and learning in healthy and aged animals (van Praag et al. 1999; Farmer et al. 2004; van Praag et al. 2005). Although physical exercise enhances memory function in healthy and aged rats, its mechanisms of action on learning and memory performance under brain inflammation conditions are not completely clarified.

Lovage (*Levisticum officinale* Koch) is a perennial aromatic plant from the Apiaceae family found in many European and East Asian countries (Downie et al. 2001). *Levisticum officinale* has been used as a medicinal plant due to its spasmolytic and diuretic properties. Previous studies have demonstrated that *Levisticum officinale* extract possesses anti-inflammatory, antioxidant (Złotek et al. 2019; Ghaedi et al. 2019), anti-apoptotic (Mollashahee-Kohkan et al. 2019) and anticholinesterase (Zarei et al. 2013) activities. Our previous study showed that the *Levisticum officinale* extract contains flavonoids (catechin, rutin, luteolin and quercetin) and phenolic acids (rosmarinic acid, chlorogenic acid and caffeic acid) (Amraie et al. 2020; Ghaedi et al. 2019).

The aim of the current study was to examine the neuroprotective effects of treadmill exercise, alone and in combination with *Levisticum officinale* extract on spatial learning

and memory impairments and their mechanisms of action using LPS-induced brain inflammation in rats.

Materials and methods

Animals

Experiments were carried out on male Wistar rats, weighing 200–250 g (average age of 8 weeks). Animals were kept in a colony room under controlled environment (22 ± 2 °C), 12 h dark/light cycle with free access to a standard pellet diet and tap water. The maintenance and treatment of animals were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publication, 8th edition, 2011). All experimental procedures were approved by Ethics Committee for Animal Experimentation at Isfahan University of Medical Sciences (IR.MUI.MED.REC.1396.1.067).

Levisticum officinale extract

The stems and leaves of *Levisticum officinale* were collected from Bardsir in Kerman province, and graciously identified at the MIR Herbarium of the Shahid Bahonar University of Kerman. The dried powdered plant was soaked in 80% methanol for 24 h. Then, the extract was filtered, evaporated by a rotary evaporator and oven-dried at 40 °C.

Treatments

Rats were assigned to five groups (n=10), including the control, LPS, LPS + exercise, LPS + extract and LPS + exercise + extract groups. LPS from E.coli (Sigma-Aldrich Co., USA) was administered intraperitoneally at a single dose of 1 mg/kg body weight (BW). *Levisticum officinale* extract was prepared in distilled water and administered orally to rats at a dose of 100 mg/kg BW. The control and LPS groups received distilled water by gavage at the same volume as the treated groups. Treadmill running or treatment of extract was carried out one week before the LPS injection for four weeks, according to previous protocols (Hou et al. 2014). Morris water maze (MWM) was used to assess spatial learning and memory on days 18–22 after LPS administration.

Tissue collection

After the end of behavioral experiments, rats were euthanized and the hippocampus was dissected out and kept at -80 °C for biochemical and molecular assessments or placed in formaldehyde for histology.

Treadmill running

Exercise training was performed on rats using a five-lane motorized treadmill. Firstly, rats were trained on the treadmill at 5 min/day with 10 m/min speed for five days to reduce their stress. Thereafter, they ran on the treadmill at a speed of 20 m/min for 30 min once a day for four weeks. This protocol was performed one week before LPS injection for four weeks.

MWM task

MWM test was performed on post-injection days 18–22 to assess spatial learning and memory abilities. The maze was a black circular pool (150 cm diameter) filled with water (23 ± 1 °C) to a depth of 30 cm. A hidden platform (10 cm diameter) was located at a midpoint of the south-east quadrant. During acquisition training, rats were trained to reach the hidden platform within 60 s (4 trials per day \times 4 days) with 60 s intersession interval. In each trial, the rat was released at one of the four starting points to find the platform. Computer software (NeuroVision, Tajhiz Gostar Co.) calculated the escape latency and traveled distance for each animal. On day 22, a probe test was carried out to assess memory consolidation. The platform was removed and rats had permission to swim in the maze for 60 s. The time spent in the target zone was recorded (Ahmadi et al. 2017).

Real-time PCR

Total RNAs from rat hippocampus were extracted using Total RNA Purification Kit (GeneAll; Korea) and reverse-transcribed into cDNA as explained previously (Amraie et al. 2020). Relative quantitative real-time PCR was performed using the SYBR kit. Relative mRNA expression of IL-6 gene was determined by $2^{-\Delta\Delta CT}$ method (Livak and Schmittgen 2001). GAPDH was used as a reference gene. Primers sequences were as:

(1) IL-6, forward: CTGGTCTTCTGGAGTTCCGT, reverse: TGGTCCTTAGCCACTCCTTCT; (2) GAPDH, forward: GTCTTACCACCACGGAGAAGGC, reverse: ATGCCAGTGAGCTTCCCGTTCAGC.

Lipid peroxidation level

The malondialdehyde (MDA) level was measured in the serum and hippocampus, to estimate lipid peroxidation level. To measure serum MDA level, a mixture containing trichloroacetic acid, thiobarbituric acid, and HCL was added to samples and centrifuged at 10,000 g for 10 min. Then, the butylhydroxytoluene were added to the supernatant and the solution was placed in a boiling water bath for 15 min.

Thereafter, it was centrifuged and the absorbance of the supernatant was read at 532 nm (Kurtel et al. 1992).

To measure hippocampal MDA level, the hippocampus was homogenized in sucrose and then centrifuged at 4 °C. Later, the sodium dodecyl sulphate and thiobarbituric acid were added to the supernatant and heated in a boiling water bath for 1 h. Trichloroacetic acid was added after cooling and then the mixture was centrifuged at 1000 g for 10 min. Finally, the absorbance was read at 532 nm against the blank. MDA level was measured using an extinction coefficient of $155 \text{ m/M} - 1 \text{ cm} - 1$ (Ohkawa et al. 1979).

Catalase (CAT) and superoxide dismutase (SOD) enzymes activity

To measure antioxidant enzyme activity, the hippocampus was homogenized in phosphate buffer and centrifuged. The protein content of the supernatant was determined according to Bradford's method using bovine serum albumin as the standard (Bradford 1976). CAT enzyme activity was measured as described before (Aebi 1984). One unit enzyme activity of CAT was defined to decompose 1 μmol of H_2O_2 per min at 240 nm.

For SOD activity, the supernatant was added to the reaction solution containing potassium phosphate buffer, Na-EDTA, methionine, riboflavin and nitroblue tetrazolium. After exposure to fluorescent light for 15 min, the absorbance was read at 560 nm. One unit SOD activity was defined to inhibit the nitroblue tetrazolium photoreduction to 50% (Giannopolitis and Ries 1977).

Histology

The histological method was performed as described before (Amraie et al. 2020). Briefly, the hippocampus (3 in each group) was placed in 10% formaldehyde and embedded with paraffin to make 5 μm sections using a microtome. Thereafter, some sections were deparaffinised, dehydrated and stained with hematoxylin and eosin (H&E). Sections were studied by a light microscope (Olympus BX41, Japan).

For Ki67 immunohistochemistry, some sections were processed by dewaxing, dehydration, and microwave antigen retrieval. Sections were placed in PBS for 5 min and H_2O_2 for 10 min. Then, sections were incubated with primary monoclonal mouse anti-human Ki67 antibody (DBS, USA) for 1 h. After washing with PBS, sections were incubated with a secondary antibody conjugated to HRP (Diagnostic BioSystems, USA) for 30 min. After coloring with diaminobenzidine (DAB) (DAKO, Denmark), sections were counterstained with hematoxylin. Ki67+ cells were counted within the dentate gyrus in 5 fields in each section of the animal using Image J.

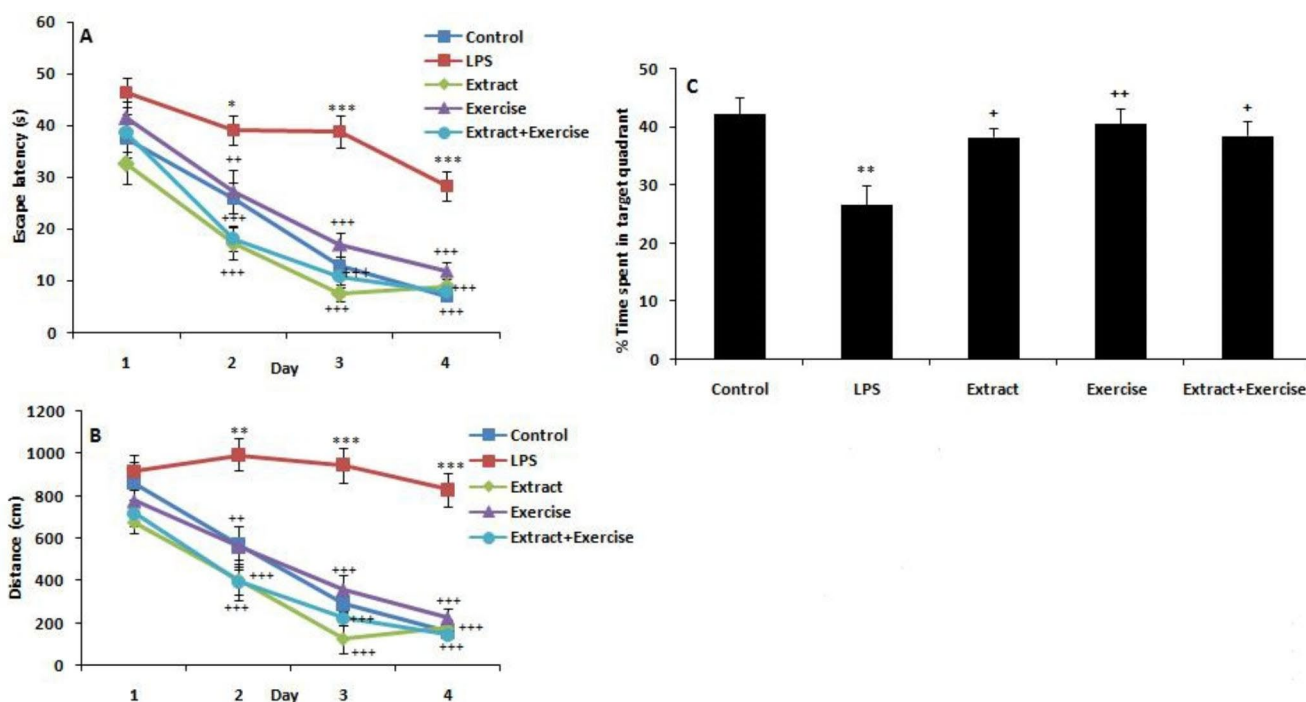


Fig. 1 Effects of exercise training and/or extract on the performance of the spatial memory acquisition phase in Morris water maze, (A) escape latency, (B) traveled distance, (C) probe trial. Data are expressed as mean \pm SEM for ten animals in each group. One-way and two-way

repeated-measures ANOVA were performed. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. control group, + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.001$ vs. LPS group

Statistical analysis

Data were presented as the mean \pm SEM and analyzed by one-way ANOVA and two-way repeated measures ANOVA followed by Tukey's *post hoc* test. $P < 0.05$ was considered significant.

Results

Effects of exercise and extract on spatial learning and memory deficits

Analysis of data by repeated-measures ANOVA indicated that the escape latency ($F(3,123) = 85.78$, $P < 0.001$, Fig. 1A) and traveled distance ($F(3,126) = 56.85$, $P < 0.001$, Fig. 1B) decreased over the four learning days in all groups, demonstrating acquisition of spatial learning (Fig. 1A and B). Statistical analysis also revealed that LPS-injected rats spent more time ($F(4,44) = 20.38$, $P < 0.001$, Fig. 1A) and distance ($F(4,44) = 28.81$, $P < 0.001$, Fig. 1B) to reach the hidden platform in comparison with the control group, indicating the impairment of spatial learning acquisition. In addition, treadmill running, treatment with the extract or both decreased the escape latency ($P < 0.001$, $P < 0.001$, $P < 0.001$)

and traveled distance ($P < 0.001$, $P < 0.001$, $P < 0.001$) as compared to the LPS group rats (Fig. 1A and B).

On probe trial, the percentage of time spent in the south-east quadrant decreased in the LPS group in comparison with the control group ($F(4,44) = 6.48$, $P < 0.01$, Fig. 1C). Moreover, treatment with extract ($P < 0.05$), exercise ($P < 0.01$) or both ($P < 0.05$) enhanced the percentage of time in comparison with LPS group (Fig. 1C).

Effects of exercise and extract on hippocampal IL-6 gene expression

Analysis of data showed that the mRNA level of IL-6 was enhanced ($F_{\text{value}} = 17.95$, $P < 0.001$, Fig. 2) in the hippocampus of the LPS group in comparison with the control group. Moreover, extract treatment ($P < 0.001$), exercise ($P < 0.01$) or both ($P < 0.01$) significantly reduced the mRNA level of IL-6 in comparison with the LPS group (Fig. 2).

Effects of exercise and extract on serum and hippocampal MDA level

MDA level and antioxidant enzymes activity was measured in the hippocampus to evaluate the oxidative stress status. Results revealed that the levels of MDA were enhanced in the serum ($F_{\text{value}} = 66.49$, $P < 0.001$) and hippocampus

Fig. 2 Effects of exercise training and/or extract on the relative mRNA level of IL-6 in experimental groups. Data are expressed as mean \pm SEM. *** $P < 0.001$ vs. the control group, ** $P < 0.01$, +++ $P < 0.001$ vs. LPS group

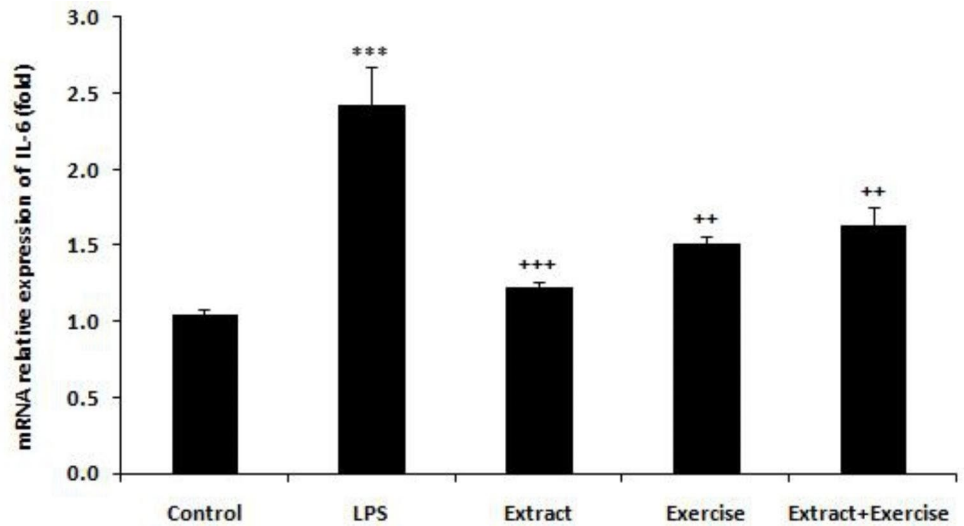
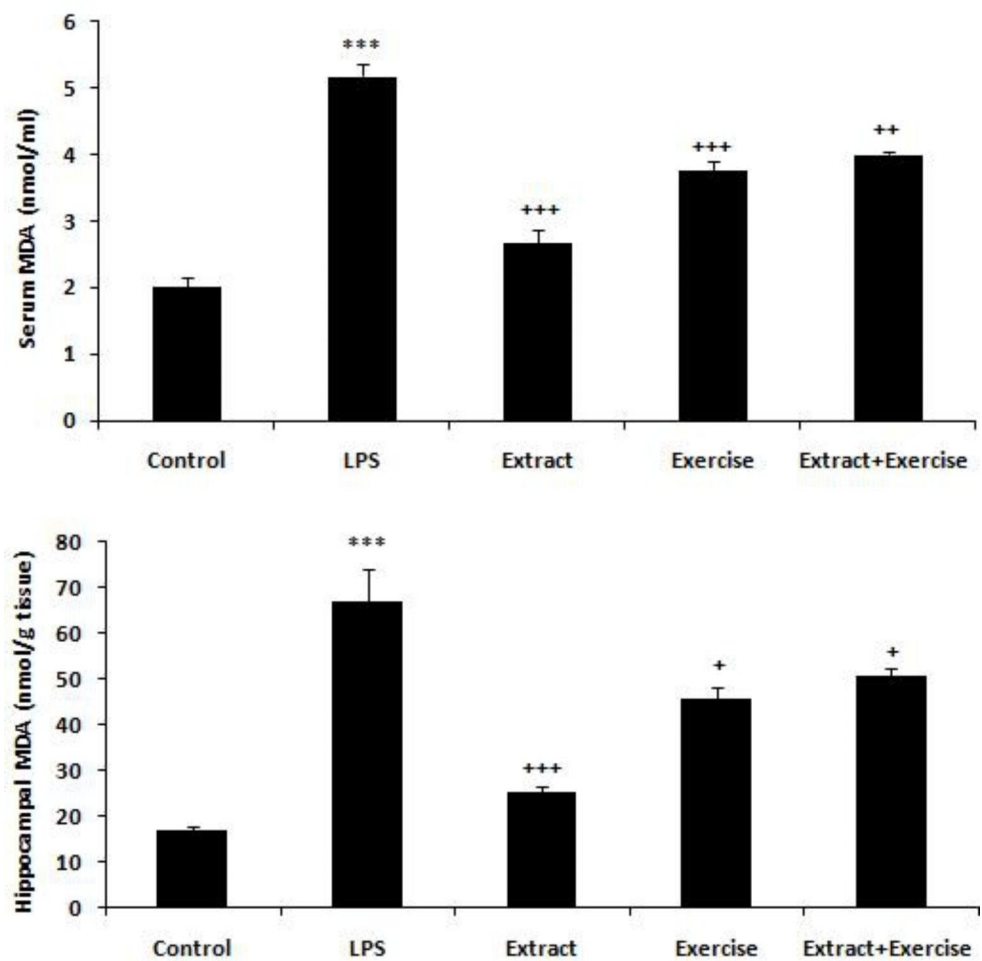


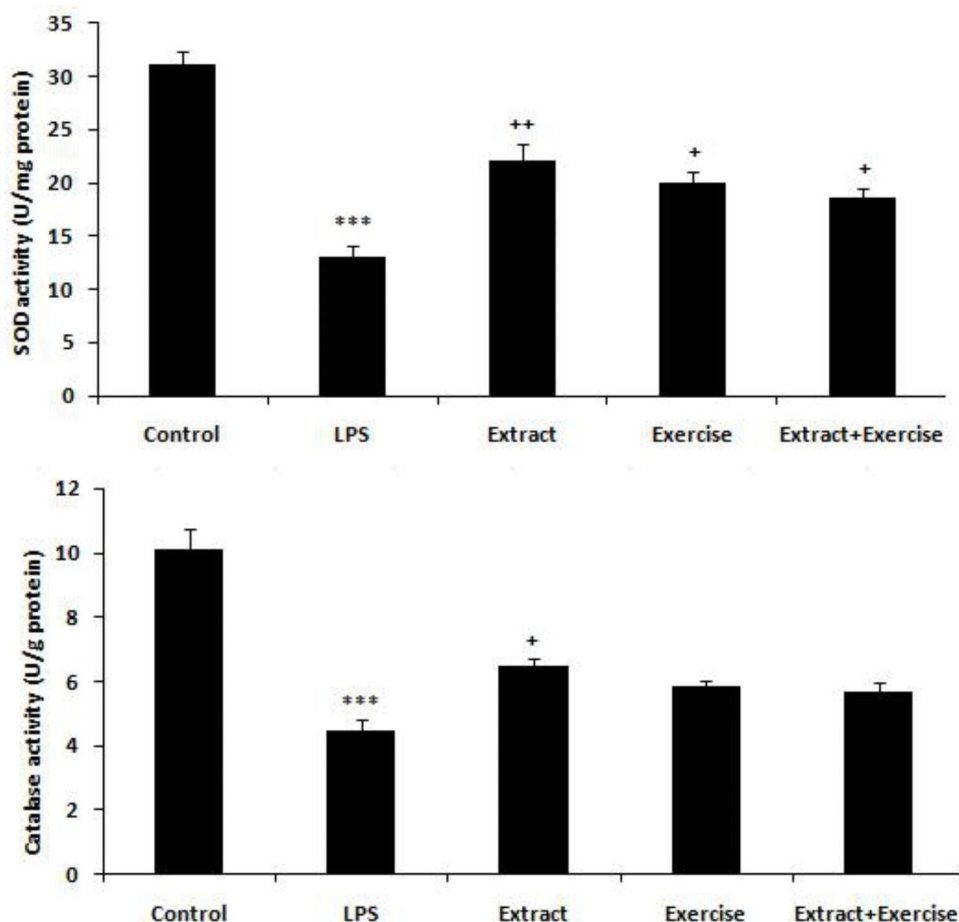
Fig. 3 Effects of exercise training and/or extract on malondialdehyde (MDA) level in the serum and hippocampus in experimental groups. Data are expressed as mean \pm SEM. *** $P < 0.001$ vs. the control group, + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.001$ vs. the LPS group



(F value = 32.95, $P < 0.001$, Fig. 3) in the LPS group in comparison with the control group. In addition, extract treatment ($P < 0.001$, $P < 0.001$), exercise ($P < 0.001$, $P < 0.05$) or both ($P < 0.01$, $P < 0.05$), significantly reduced the MDA level in the serum and hippocampus (Fig. 3). There was also

a significant difference between the extract group with the exercise and extract + exercise groups in the serum ($P < 0.01$, $P < 0.01$) and hippocampal MDA levels ($P < 0.05$, $P < 0.01$).

Fig. 4 Effects of exercise training and/or extract on superoxide dismutase (SOD) and catalase (CAT) activities in the hippocampus in experimental groups. Data are expressed as mean \pm SEM. *** P <0.001 vs. the control group, + P <0.05, ++ P <0.01 vs. the LPS group



Effects of exercise and extract on antioxidant enzyme activity

Data analysis showed that SOD enzyme activity (F value=32.86, P <0.001) and CAT (F value=31.16, P <0.001) significantly decreased in the hippocampus in the LPS group in comparison with the control group. Moreover, extract treatment (P <0.01), exercise training (P <0.05) or both (P <0.05) enhanced the SOD activity in the hippocampus (Fig. 4). Also, treatment with extract increased CAT enzyme activity in the hippocampus (P <0.05, Fig. 4).

Effects of exercise and extract on histopathology and cell proliferation

Histological observations demonstrated the presence of normal arrangement and density of the granule cells in the DG, and pyramidal neurons in the CA1 and CA3 areas of the hippocampus in the control group (Fig. 5 A). Moreover, we found the maximum changes including significant pyknosis (pyknotic neurons), cytoplasm vacuolization and dilated blood vessels in the DG, CA1, and CA3 areas of the hippocampus in the LPS group (Fig. 5B). In other groups, most of

the neurons were normal, and minimal presence of pyknotic neurons and other changes were detected in the different areas of the hippocampus (Fig. 5 C, D and E).

Ki67 immunohistochemistry revealed that the number of Ki67+ cells was decreased in the DG of the hippocampus in the LPS group in comparison with the control group (P <0.05, Fig. 6 A, B). Moreover, treatment with *Levisticum officinale* extract (P <0.01), exercise training (P <0.05) or both (P <0.001) enhanced the number of Ki67+ cells in comparison with the LPS group (Fig. 6 A, B). There was also a significant difference in the number of Ki67+ cells between the extract and exercise groups with the extract+exercise group (P <0.001). These findings indicated the synergistic effects of the extract and exercise training on neuronal cell proliferation in the hippocampus.

Discussion

The aim of the current study was to evaluate the neuroprotective potential of treadmill running and *Levisticum officinale* extract against LPS-induced memory deficits and find the potential mechanisms of action. Our findings

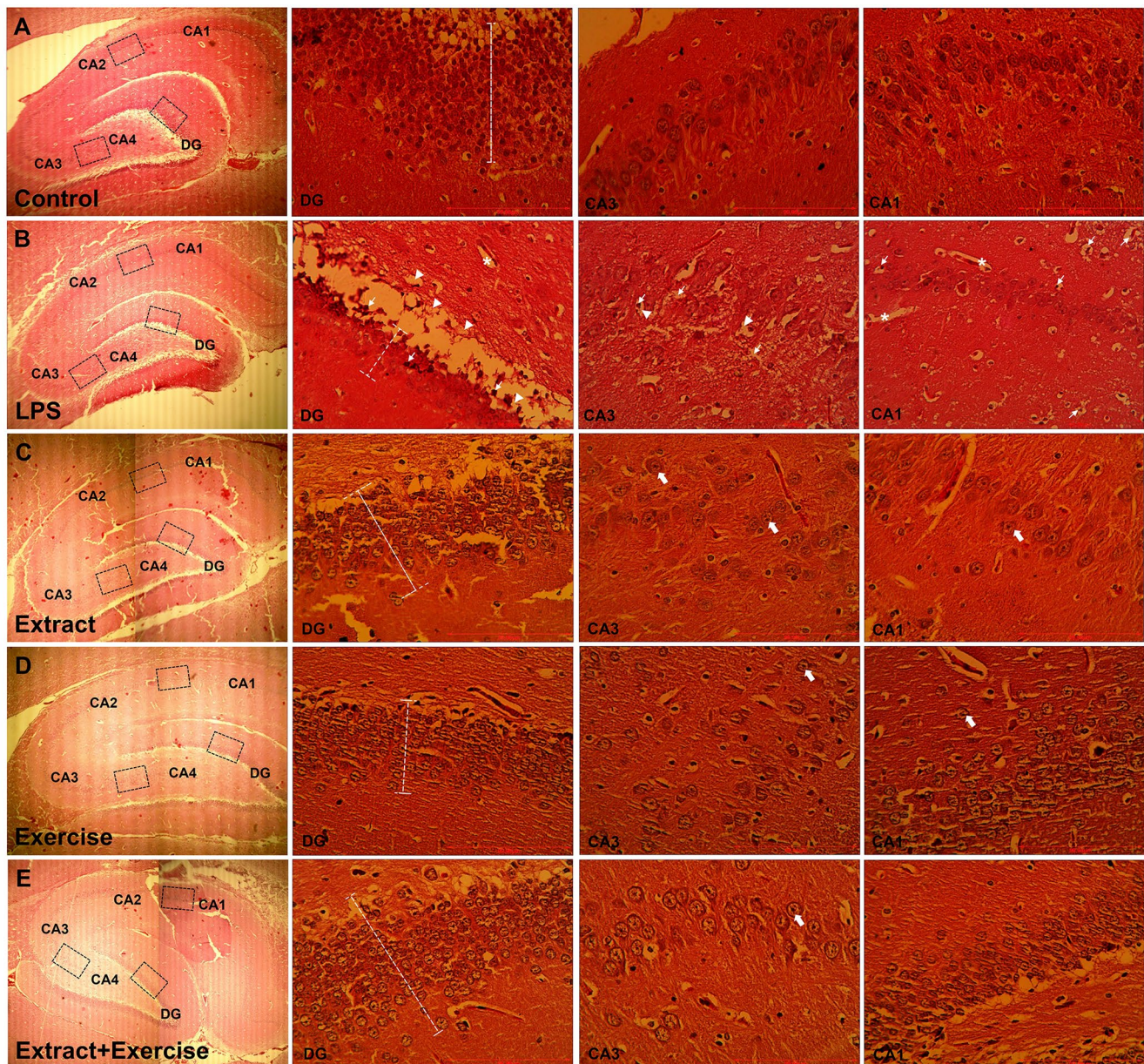


Fig. 5 Histological changes in the hippocampal regions of experimental groups. (A) Control group exhibits the normal thick layer and arrangement of the granular cells in the DG and the pyramidal neurons in CA3 and CA1 areas. (B) LPS group shows a significant reduction in the thickness of the granular cell layer in the DG, a significant increase in apoptotic neurons (arrow), and cytoplasm vacuolization (arrowhead) in the DG, CA3, and CA1 areas, accompanied by

demonstrated that LPS injection induced impairments in spatial learning and memory in the MWM via activation of neuroinflammation and oxidative stress, and decreased the cellular proliferation in the hippocampus. Our findings also demonstrated that treadmill running and supplementation of *Levisticum officinale* extract for four weeks improved memory deficits, decreased the expression of IL-6 mRNA and oxidative stress, and enhanced neurogenesis.

pyknotic nuclei and several dilated blood vessels (star) compared to other groups. (C, D, E) Extract, Exercise and Extract + exercise groups indicate the normal thickness of the DG, CA3, and CA1 regions with the preservation of pyramidal cells with rounded vesicular nuclei and prominent nucleoli (thick arrow). Magnification 4× (first left column), 20×, Scale bar = 100 μm

We used the LPS model since LPS injection induces memory deficits and pathology similar to AD (Zakaria et al. 2017). Evidence indicates that systemic LPS injection induces memory impairments by activating inflammatory responses and neurodegeneration (Chowdhury et al. 2018; Batista et al. 2019; Amooheydari et al. 2022). Consistent with previous studies, our findings showed that systemic LPS deteriorated learning and memory of rats in the MWM,

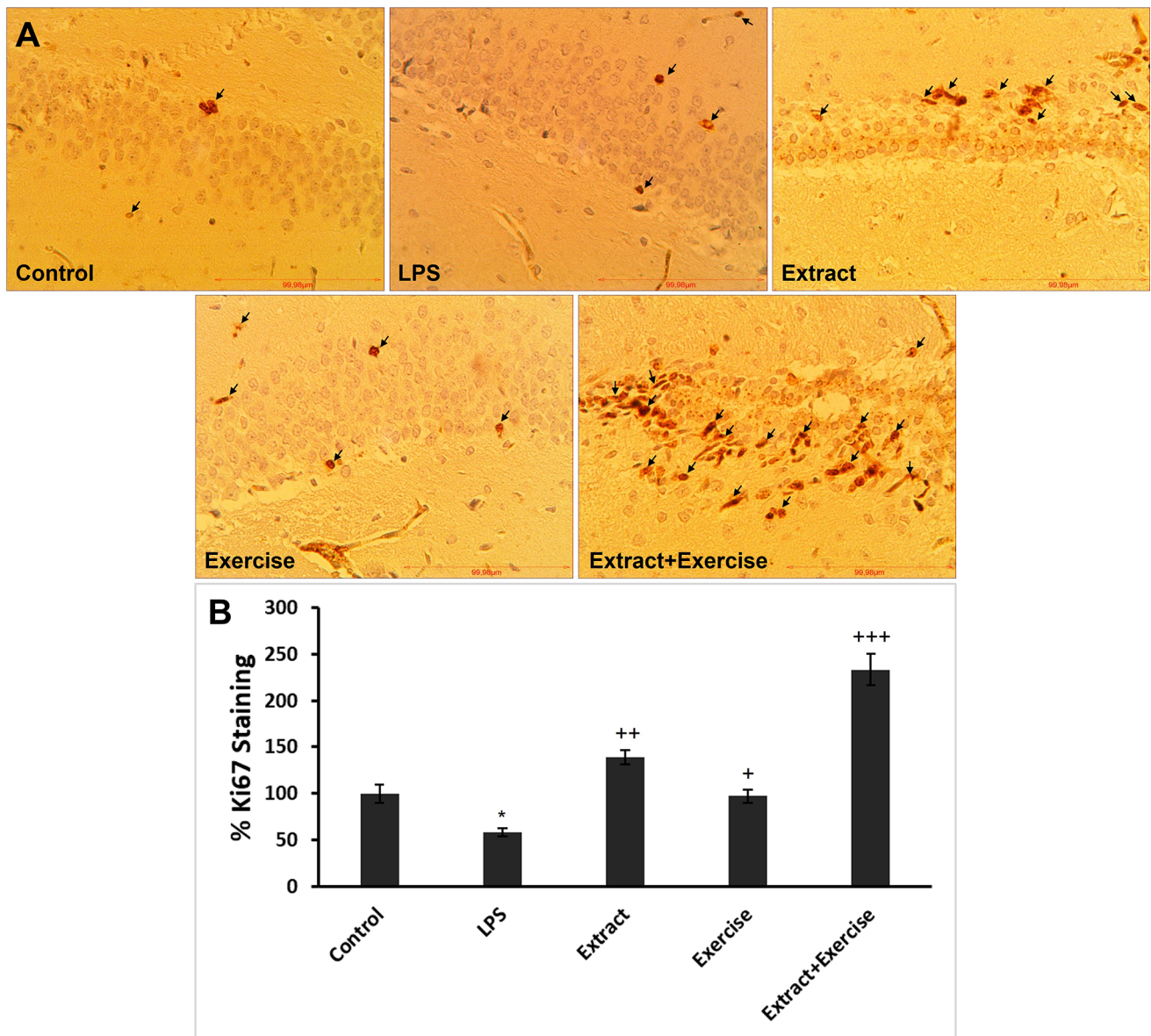


Fig. 6 Immunohistochemistry staining of the dentate gyrus of the hippocampus for the nuclear antigen Ki67 (A), and quantification analysis of Ki67 staining (B) in experimental groups. * $P < 0.05$ vs. the control

group, + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.001$ vs. the LPS group. Magnification 20 \times , Scale bar = 100 μm

since rats spent more time to find the hidden platform and less time on probe trial. Similarly, it was shown that acute systemic LPS deteriorates learning and memory of mice in MWM task (Ali et al. 2014), aversive memory (Lee et al. 2008), and performance in novel object recognition test (Ming et al. 2015).

Our results also indicated that treadmill exercise ameliorated spatial learning and memory impairments, as evident by a decrease in latency to find the hidden platform and an increase in time spent on the probe trial in exercised rats. The memory-enhancing effects of the exercise were previously shown in experimental animal models. For instance, it

was reported that treadmill running improves spatial memory impairments in the MWM in transgenic AD mice (Liu et al. 2011) and cerebral ischemia model (Cechetti et al. 2012).

Our findings also showed that *Levisticum officinale* extract, alone and in combination with treadmill exercise ameliorated learning and memory impairments in the MWM. Conclusively, our results indicate that treadmill running and *Levisticum officinale* extract are effective in protecting against memory deficits elicited by LPS in rats.

Injection of LPS causes memory deficits by multiple mechanisms such as expression of proinflammatory mediators (Chowdhury et al. 2018), enhanced oxidative stress

(Bai et al. 2016), impairment of neurogenesis (Ormerod et al. 2013), loss of cholinergic neurons (Houdek et al. 2014) and apoptosis.

Systemic LPS is known to produce inflammatory responses mainly via activating TLR4, subsequently NF- κ B transcriptional activation of inflammatory genes, such as TNF- α and IL-6, and eventually loss of synapses, neurons and memory deficits (Brown 2019). The high production of IL-6 following LPS injection was shown to impair spatial and working memory in rodents (Chen et al. 2008; Dugan et al. 2009). It was also demonstrated that over-expression of IL-6 and TNF- α induces memory impairment in transgenic animal models (Zheng et al. 2016). In this study, we observed that LPS increased the mRNA expression of IL-6 in the hippocampus, which is consistent with prior studies (Chowdhury et al. 2018). Our findings also showed that treadmill running for four weeks decreased mRNA expression of IL-6 in the hippocampus, indicating the anti-inflammatory activity of exercise training against LPS-induced neuroinflammation in rats. The anti-inflammatory effect of treadmill exercise has been shown in several animal models such as cerebral ischemia (Zhang et al. 2017), Parkinson's disease (Shahidani et al. 2022) and the transgenic AD mouse model (Leem et al. 2011). In line with this, it was shown that the expression of IL-6 and TNF- α was decreased in the brain of transgenic mice after treadmill training (Leem et al. 2011). While studies in the transgenic models of AD have reported the beneficial impact of exercise on cognitive function and pathology in AD, a few studies have evaluated the impact of exercise on LPS-induced neuroinflammation and memory deficits (Kelly 2018). In this context, several studies reported that treadmill running did not change LPS-induced expressions of IL-1 β and TNF- α in the hippocampus (Wu et al. 2007), while other studies reported opposite results. For example, Mota and Kelly (2020) have shown that exercise exerts neuroprotective effects against LPS-induced impairment of spatial recognition memory along with down-regulation of TNF- α , IL-1 β and IL-10 mRNA expression in the mice hippocampus (Mota and Kelly 2020). In line with this study, our study indicated that treadmill running reduced the mRNA expression of IL-6 in the hippocampus of LPS-administered rats.

Our results also demonstrated that treatment with *Levisticum officinale* extract, alone and in combination with treadmill exercise decreased mRNA expression of IL-6 in the hippocampus, indicating the anti-inflammatory activity of *Levisticum officinale* extract in LPS-induced neuroinflammation. The anti-inflammatory effect of *Levisticum officinale* was shown in previous studies (Złotek et al. 2019; Jakubczyk et al. 2020). Collectively, the beneficial impact of treadmill running and *Levisticum officinale* on memory dysfunction in LPS-injected rats could be partly attributed

to anti-inflammatory activity of treadmill running and *Levisticum officinale*.

Evidence indicates a strong relation between oxidative stress and memory deficits in AD (Barnham et al. 2004). Production of high amounts of reactive oxygen species (ROS) during oxidative stress causes oxidative damage to lipids, proteins, DNA, and eventually neurodegeneration. MDA is considered as an index of lipid peroxidation. SOD and CAT scavenge free radicals or prevent their formation. SOD changes the superoxide anion to H₂O₂, which is removed by CAT (Ighodaro and Akinloye 2018). Administration of LPS causes the increased generation of ROS and development of oxidant/antioxidant imbalance (Bai et al. 2016, which leads to neuronal damage. Oxidative damage to synapses in the cerebral cortex and hippocampus contributes to memory deficits (Ahmadi et al. 2017). In this study, LPS induced memory deficits along with brain tissue oxidative stress since hippocampal MDA levels were increased, whereas the activities of SOD and CAT were decreased. Consistent with this, it was shown that LPS caused oxidative damage in brain tissues and memory deficits (Ali et al. 2016). According to our results, exercise training for four weeks reduced MDA levels in the serum and hippocampus and potentiated antioxidant defence of the brain by increasing SOD activity in the hippocampus. Therefore, the results demonstrate the protective action of exercise against LPS through its antioxidant activity. Consistent with our findings, previous reports have demonstrated the neuroprotective action of exercise by removing ROS and decreasing lipid peroxidation. For instance, studies in transgenic AD mice have shown that running wheel reduces lipid peroxidation and enhances glutathione level in the cerebral cortex (García-Mesa et al. 2011). It was also revealed that swimming exercise for four months increases SOD activity in the hippocampus and cerebral cortex of normal rats (Devi and Kiran 2004). Moreover, an enhancement in the expression of the SOD enzyme in the hippocampus of transgenic mice following three weeks of treadmill running has been reported (Um et al. 2011).

According to the present results, treatment with *Levisticum officinale* extract, alone and in combination with treadmill exercise decreased MDA level and enhanced SOD activity in the hippocampus, indicating the antioxidant activity of *Levisticum officinale* in LPS-treated rats. Previous studies have also shown the antioxidant activity of *Levisticum officinale*. For example, it was demonstrated that aqueous extract of *Levisticum officinale* protects against the adverse impacts of paraquat on hepatocytes due to its antioxidant activity (Afarnehan et al. 2017). Taken together, the positive influence of treadmill exercise and *Levisticum officinale* on memory deficits could also be attributed to their antioxidant activity.

However, decreased neurogenesis is also involved in cognitive decline in AD, and targeting neurogenesis may ameliorate cognitive dysfunction in AD (Babcock et al. 2021). It was also revealed that neuroinflammation and oxidative stress negatively influences neurogenesis and cognition (Ryan and Nolan 2016; Suwannakot et al. 2022). In line with this, previous studies have shown the detrimental impacts of LPS and proinflammatory mediators on neurogenesis (Monje et al. 2003; Borsini et al. 2015). For example, it was revealed that systemic LPS injection reduces the proportion of doublecortin-positive new cells, demonstrating that LPS decreases neuronal differentiation (Monje et al. 2003). Similarly, in another study it was shown that the intracortical LPS injection reduced the production of new neurons (Ekdhahl et al. 2003). It was also demonstrated that neurogenesis was reduced in the hippocampus in transgenic mice overexpressing IL-6 in astrocytes (Vallieres et al. 2002). Consistent with prior studies, present results showed that systemic LPS reduced neurogenesis, possibly due to the enhanced mRNA expression of IL-6 and oxidative stress in the hippocampus. Our results also showed that treadmill exercise enhanced neurogenesis, which is in agreement with previous studies. For instance, it was demonstrated that running wheel protects against reductions in hippocampal neurogenesis in the aged brain (Littlefield et al. 2015). Our results also demonstrated that *Levisticum officinale* extract alone and in combination with exercise enhanced neurogenesis in the hippocampus, which could be due to their anti-inflammatory and antioxidant activities. Collectively, according to our results, treadmill running and *Levisticum officinale* extract may improve spatial memory partly by synergistic effects on enhancing neurogenesis in LPS-treated rats.

It should be noted that in our previous studies, we reported the presence of flavonoids and phenolic acids in the *Levisticum officinale* extract by the HPLC method (Amraie et al. 2020; Ghaedi et al. 2019). Evidence indicates that phenolic acids and flavonoids possess anti-inflammatory and antioxidant properties (Amraie et al. 2020). Conclusively, the anti-inflammatory and antioxidant properties of *Levisticum officinale* extract could be due to the existence of flavonoids and phenolic acids in the extract.

It is noteworthy that other mechanisms might also be involved in the beneficial impact of exercise and plant extract on memory function in LPS injected rats. Previous studies have demonstrated that systemic LPS injection influences microglial phenotype, neuronal structure and function (Lonnemann et al. 2022), BDNF expression and A β formation (Lee et al. 2008; Beheshti et al. 2019). For instance, it was shown that neuroinflammation and activated microglia following LPS challenge reduces dendritic spine density in hippocampal neurons, and impairs LTP and cognitive

abilities (Lonnemann et al. 2022; Hosseini et al. 2021). Evidence also indicates that treadmill exercise reduces the glial cell response (Mota and Kelly 2020; Zhang et al., 2022) and enhances structural and functional synaptic plasticity in the hippocampus and prefrontal cortex (Tsai et al. 2018; Mu et al. 2022). For instance, it was demonstrated that treadmill running for nine days improved memory performance in the object displacement task and reduced the microglia and astrocytes activation in the mouse brain following a single injection of LPS (Mota and Kelly 2020). In another studies, treadmill running enhanced CA1 neurons LTP, dendritic complexity (branch and length) and spine density of hippocampal neurons and upregulated the expression of BDNF in the mice hippocampus (Tsai et al. 2018; Lin et al. 2012). Therefore, above mechanisms may also involve in the positive influence of exercise and extract on memory deficits in LPS exposed rats due to their anti-inflammatory activity.

To sum up, treadmill running and *Levisticum officinale* extract, alone and combined together, ameliorated learning and memory impairments, decreased the mRNA expression of IL-6 and MDA level, and enhanced antioxidant enzymes activity and neurogenesis in the hippocampus. Comparing their effects revealed that *Levisticum officinale* extract possesses more antioxidant activity than exercise training, since the extract caused a more significant decrease in lipid peroxidation and increase in antioxidant enzymes activity in the hippocampus compared to exercise training. Furthermore, the synergistic effects of the plant extract and exercise training on neurogenesis in the hippocampus was found. The complementary mechanism of action of this combination on neurogenesis needs more studies; however, one possible mechanism could be related to antioxidant and anti-inflammatory activities of the extract and exercise.

Conclusion

The advantageous effects of running exercise and *Levisticum officinale* extract on memory impairments induced by LPS are possibly due to the antioxidant and anti-inflammatory activity and enhancing neurogenesis. Thus, treadmill exercise and *Levisticum officinale* could be used as a useful strategy for alleviating memory dysfunction in inflammatory disorders such as AD.

Author contributions ZR, IP designed the study; EA acquired data; ZR, IP, HS, EA analyzed and interpreted the data; ZR prepared the draft of the paper; ZR, IP, HS critically revised the article. All authors approved final version of the article.

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Data availability On request from the corresponding author.

Declarations

Ethical approval and consent to participate The maintenance and treatment of animals were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publication, 8th edition, 2011). The Ethic Committee for Animal Experiments at Isfahan University of Medical Sciences approved the study (Ethical code: IR.MUI.REC.1396.1.067).

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

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