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**Original Article**

# Aerobic exercise improves spatial memory in a rat model of meningitis

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## Abstract

Infections of the nervous system, such as acute bacterial meningitis, pose serious health problems that require immediate intervention. In experimental animals, exposure to lipopolysaccharide (LPS) is used to induce meningitis. Aside from drug intervention to reduce inflammation in meningitis, aerobic exercise helps to maintain the regulatory mechanisms of brain homeostasis through anti-inflammatory mechanisms. The aim of this study was to evaluate the effect of aerobic exercise on malondialdehyde (MDA), nuclear factor-kappa B (NF-κB), insulin-like growth factor 1 (IGF-1), endothelial nitric oxide synthase (eNOS), brain-derived neurotrophic factor (BDNF), apoptosis, and spatial memory. A four-week experimental study was conducted using 18 rats, which were randomly divided into three different groups (six rats per group): healthy rats as negative controls (non-meningitis), a treatment group treated with antibiotic treatment (meningitis group), and a third group (aerobic exercise group) treated with antibiotics and aerobic exercise following LPS-induced meningitis. Data were analyzed using a one-way analysis of variance (ANOVA) test, and the comparison between groups used the Bonferroni post-hoc test. The results showed that aerobic exercise significantly reduced MDA ($p$<0.001), NF-κB ($p$=0.035), and apoptosis ($p$=0.020) while increasing the serum levels of IGF-1 ($p$<0.001), eNOS ($p$=0.011), and BDNF ($p$=0.001) levels. Improvement in spatial memory was significant in the aerobic exercise group ($p$<0.001). This study suggested that aerobic exercise could be a promising adjunct therapy in meningitis management strategies, particularly due to its effect on improving spatial memory. Further clinical trials are needed to confirm these findings for clinical use.

**Keywords**: Aerobic exercise, spatial memory, meningitis, BDNF, MDA

## Introduction

Meningitis is an acute infection of the brain's protective membranes, particularly the arachnoid and pia mater, often caused by viruses or bacteria. It is characterized by central nervous system symptoms such as impaired consciousness, increased excitatory responses, elevated intracranial pressure, and neurological deficits [1,2]. Bacterial meningitis occurs when bacteria invade the meninges from bacteremia or a local infection [3]. After crossing the blood-brain barrier, these bacteria invade the meninges and central nervous system, leading to edema, increased intracranial pressure, and the release of inflammatory factors [4-6].



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When meningitis occurs, immune cells in the brain produce reactive nitrogen species (RNS) and reactive oxygen species (ROS), leading to oxidative stress, marked by increased malondialdehyde (MDA) levels [7-9]. This inflammation affects the hippocampus and other brain regions, resulting in glutamate excitotoxicity, brain-derived neurotrophic factor (BDNF) deficiency, and decreased insulin-like growth factor 1 (IGF-1), all of which impair neurogenesis and synaptic plasticity [10-13]. Additionally, disruptions in acetylcholine and neurotransmitter activity further reduce cognitive function and memory. Meningitis also triggers endothelial dysfunction, exacerbating oxidative stress and tissue damage [14,15].

While antibiotics like ceftriaxone are standard treatments for meningitis [16,17], aerobic exercise has shown promise in improving cognitive function and brain health [18]. Previous studies have suggested that both acute and regular aerobic exercise significantly increase BDNF levels, enhancing neuronal health, plasticity, and cognitive functions such as memory, attention, and executive function [19-22]. Thus, it is urgent to investigate aerobic exercise as a complementary intervention in meningitis treatment. Research on aerobic exercise is still limited in managing post-meningitis neurological deficit disorders, and the application of effective and safe aerobic exercise remains underreported. The aim of this study was to determine and analyze the effect of aerobic exercise on improving spatial memory in meningitis rat models by examining malondialdehyde (MDA), brain-derived neurotrophic factor (BDNF), nuclear factor-kappa B (NF-κB), insulin-like growth factor 1 (IGF-1), endothelial nitric oxide synthase, spatial memory, and apoptosis.

Herein, the animal model was induced by lipopolysaccharide (LPS) exposure, a component of gram-negative bacterial membranes like those of *Escherichia coli*. LPS activates the toll-like receptor 4 (TLR4) signaling pathway, the focal adhesion kinase (FAK), and myeloid differentiation factor 88 (MyD88) signaling pathway [23,24]. Subsequently, the signaling from TLR4/FAK/MyD88 is formed by activating interleukin-1 receptor-associated kinase 4 (IRAK4), causing a decrease in brain microvascular endothelial cells and tight junction (TJ) [23]. The reaction cascade could subsequently lead to microglial activation, resulting in the release of proinflammatory cytokines. In experimental models, LPS from *E. coli* can cross the blood-brain barrier, causing meningitis and leading to severe consequences, including cerebral infarction, subdural empyema, hearing loss, seizures, and cognitive impairment [25-27]. LPS exposure in animal models not only induces meningitis but also mimics the inflammatory and neurological damage seen in human cases, making it suitable to investigate the treatment for the disease, including the addition of aerobic exercise to the standard treatment [28-30].

# Methods

## Study design

An experimental study was conducted using male rats from December 2023 to March 2024 at the laboratory of the Institute of Biosciences, Universitas Brawijaya, Malang, Indonesia. The sample size was determined according to the World Health Organization (WHO) guideline for minimum sample size, with six rats per group. A total of 18 Wistar rats were double-blind, randomized, and allocated into three groups using simple random sampling via sequential allocation (placing the rats one by one into three labeled cages). The group assignment was blinded to the researchers handling the animals and those performing data analysis. The study was divided into three groups: a non-meningitis group (n=6), a meningitis group (n=6) that was exposed to *E. coli* LPS and treated with ceftriaxone for four weeks, and an aerobic exercise group (n=6) that was exposed to *E. coli* LPS, treated with ceftriaxone for two weeks, and then underwent two weeks of aerobic exercise.

## Animal model

A total of 18 male Wistar rats (*Rattus norvegicus*) were used in this study (non-meningitis, meningitis, and aerobic exercise group), with inclusion criteria were male rats of the Wistar strain, aged 4–8 weeks, body weight ranging from 250–300 grams, healthy and active. This was to avoid hormonal and pregnancy influences that could interfere with the research. Before the intervention, all rats acclimated to the environment for one week in 24×18×16 cm cages, with 12-

hour light and 12-hour dark cycle, while maintaining appropriate temperature and humidity levels. The rats received free access to standard feed and drinking water.

## Induction *Escherichia coli* bacterial infection

The infection of *E. coli* LPS in rats was induced using a liquid form at a concentration of 20 µg/mL. The *E. coli* LPS (O111:B4) was obtained from Sigma-Aldrich (Darmstadt, Germany). LPS was dissolved in water (5 mg/mL) and shaken until a homogeneous cloudy solution was formed. Anesthesia was administered using a combination of ketamine (100 mg/kg BW) and xylazine (10 mg/kg BW) intraperitoneally. Following this, the rats were injected with LPS (20 µg) into the subarachnoid space through the right frontolateral skull [29].

## Antibiotic administration and aerobic exercise

Ceftriaxone was administered subcutaneously to both the meningitis and aerobic exercise groups at a dose of 100 mg/kg BW twice daily for the duration of the experiment. The experiment lasted 4 weeks for both groups. In the meningitis group, ceftriaxone was given continuously for the full four weeks. In contrast, the aerobic exercise group received ceftriaxone only during the first two weeks (Weeks 1 and 2) and then underwent aerobic exercise during the subsequent two weeks (Weeks 3 and 4).

After the initial two weeks of ceftriaxone treatment, rats in the aerobic exercise group were housed separately in standard laboratory cages equipped with a treadmill. Aerobic exercise was performed in Weeks 3 and 4 with the following regimen: in Week 3, the rats ran at 5 m/min for 30 minutes daily, and in Week 4, they ran at 5 m/min for the first 5 minutes, 7 m/min for the next 5 minutes, and 8 m/min for the remaining 20 minutes daily. Aerobic exercise was conducted for a total of 14 days post-LPS injection. This protocol followed a previously published report [31].

## Morris water maze test

The Morris water maze (MWM) was used to evaluate spatial memory. The rats were required to swim in water tanks to find submerged platforms and exit the water. The non-toxic, white-painted pool (diameter of 100 cm and height of 40 cm) was filled with water at a temperature of 22°C. A transparent platform, 10 cm in diameter, was located 1 cm below the water level. Before testing, the rats were given a trial to swim and find the platform within 60 seconds. If unsuccessful, they were directed by the experimenter towards the platform.

## Endpoints

The humane endpoints of this study were defined by poor health conditions in the rats. Rats exhibiting signs such as piloerection, dull, rough, oily fur, or fur loss were excluded from the study. Additionally, rats that died during treatment were excluded. Other exclusion criteria included loose skin, a drastic decrease in body weight post-adaptation, slightly closed eyelids, sunken eyes, or chromodacryorrhea. Rats that became excessively aggressive, then passive, refused to eat or drink, and frequently slept in the cage were also excluded. At the end of the experiment (Week 4), all remaining animals were euthanized using intraperitoneal anesthesia with ketamine (100 mg/kg BW) and xylazine (10 mg/kg BW). Following anesthesia, the rats were dissected, and their brains were examined.

## Enzyme-linked immunosorbent assay (ELISA)

Sixteen milliliters of blood was collected via cardiac puncture under general anesthesia. The samples were centrifuged at 3,000 rpm for 15 minutes at 4°C to separate the serum, which was then aliquoted (minimum 500 µL) and stored at -80°C. Before analysis, serum samples were thawed at room temperature for 30 minutes. The concentrations of MDA, NF-κB, eNOS, and IGF-1 were measured using ELISA kits from eBioscience Co. (San Diego, CA, USA), following the manufacturer's instructions.

Briefly, 100 µL of serum, standards, controls, and blanks were added to a 96-well plate pre-coated with specific antibodies and incubated for two hours at room temperature. The wells were washed three times with wash buffer, and then 100 µL of biotin-conjugated detection antibody was added and incubated for one hour at room temperature. The well plates were washed again, and 100 µL of streptavidin-horseradish peroxidase (SA-HRP) conjugate was added and incubated

for 30 minutes in the dark. Following a final wash, 100 µL of 3,3',5,5'-tetramethylbenzidine substrate solution was added and incubated for 10–15 minutes in the dark until color development. The reaction was stopped by adding 100 µL of stop solution. Absorbance was measured at 450 nm using a microplate reader, with each measurement performed in a triplicate.

### Immunohistochemistry of brain-derived neurotrophic factor (BDNF)

Immunohistochemistry (IHC) staining began by washing the dissected brain with phosphate-buffered saline (PBS) at pH 7.4 for three cycles of five minutes each at room temperature. The aim was to increase BDNF expression in the hippocampus. The slides were washed using PBS (pH 7.4, 3×5 minutes), followed by blocking unspecific protein using 3% PBS containing 0.25% Triton X BDNF expression. The slides were washed again with PBS (pH 7.4, 3×5 minutes) and given to rats modeled with meningitis. Next, the slides were incubated overnight at 4°C with an anti-BDNF mature polyclonal rabbit (Santa Cruz).

After incubation, the slides were washed in PBS (pH 7.4, 3×5 minutes) and then incubated in a secondary antibody labeled biotin-conjugated for 60 minutes. This was followed by washing the slides in PBS (pH 7.4, 3×5 minutes). The slides were then incubated in SA-HRP for 40 minutes, washed with PBS (3×5 minutes), dripped with diaminobenzidine (DAB), and incubated for 10 minutes. After DAB incubation, the slides were washed using distilled water (3×5 minutes). Then, it was counterstained in Mayer's hematoxylin, incubated for 10 minutes, and washed using distilled water. Once dried, it was continued with installation using a bundle and covered with a glass cover. Observations were made under 40× magnification. Positive glial cell counts were performed at 10 fields of view, and the average was calculated. Positive cells are indicated by a brown-tinged cytoplasm.

### Preparation of apoptosis using hematoxylin and eosin staining

Apoptosis was assessed using hematoxylin and eosin staining. To further clarify the level of apoptosis, caspase-3 was used as a marker. The brains of dissected rats were fixed in a 10% formalin solution and covered with paraffin. A 5-µm thick section was obtained at the hippocampal level, stained with hematoxylin and eosin, and examined under a light microscope for histological examination.

### Statistical analysis

Data distribution was assessed using the Shapiro-Wilk test. For normally distributed data, a one-way analysis of variance (ANOVA) test was employed, followed by the Bonferroni post-hoc analysis. If $p<0.05$, the outcome was considered statistically significant. Data analysis was performed using SPSS software, version 24 (IBM, New York, USA).

## Results

### Biomarker levels following aerobic exercise

At the end of the observation, no rats were dropped out due to death or adverse effects. Data comparing several biomarkers across three experimental groups are presented in **Figure 1**. Aerobic exercise significantly reduced serum MDA ($p<0.001$), NF-κB ($p=0.035$), and IGF-1 ($p=0.000$). On the other hand, eNOS levels were significantly elevated in the aerobic exercise group as compared to meningitis ($p=0.011$) and non-meningitis groups ($p=0.043$). Significant improvements among rats undergoing aerobic exercise were also observed in BDNF ($p=0.001$) and caspase-3 ($p=0.020$), where the levels were reversed to that of normal conditions.

### Aerobic exercise improves spatial memory

The average escape latency of the animals observed during the Morris water maze test is presented in **Figure 2**. The escape latency improved in meningitis rats undergoing aerobic exercise ($p<0.001$). There was no significant difference in the escape latency between the non-meningitis and aerobic exercise groups ($p=0.101$).

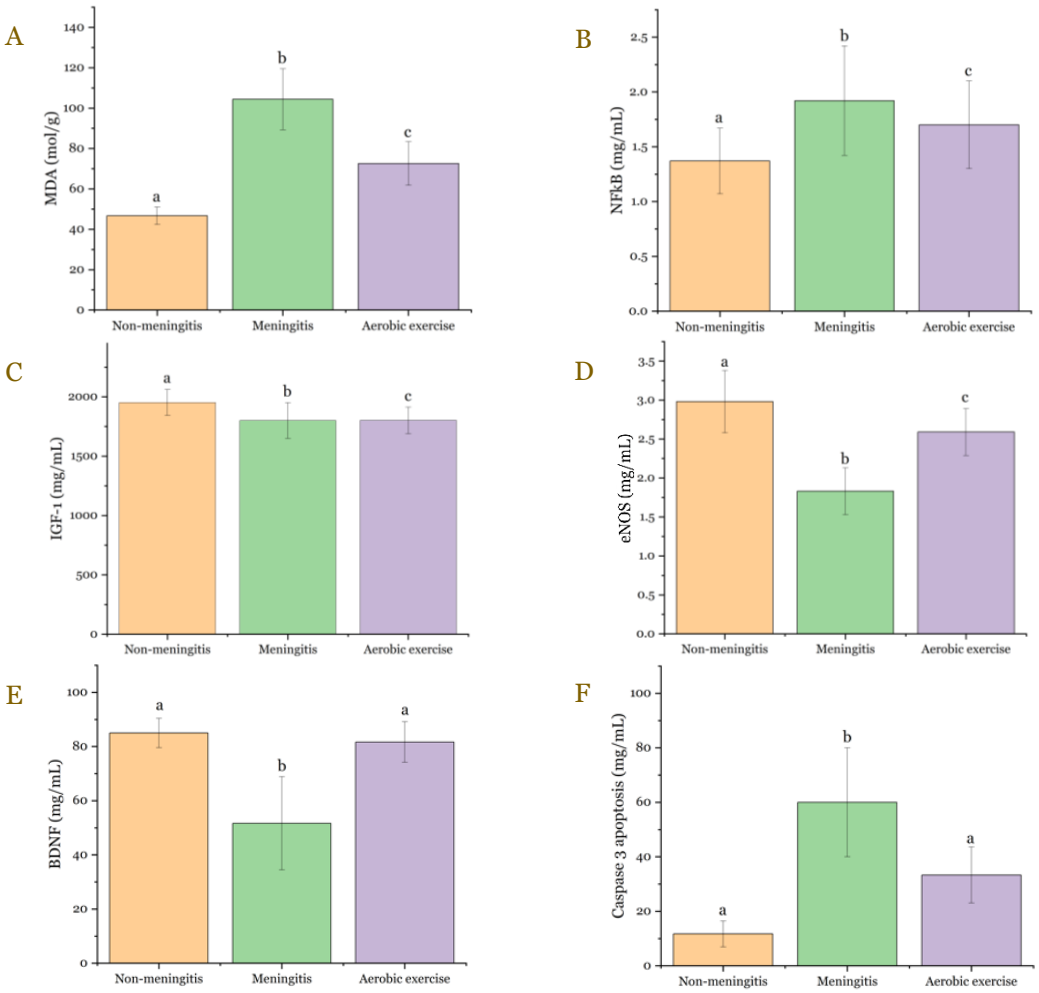


Figure 1. Effect of aerobic exercise on meningitis rats based on MDA (A), NF-κB (B), IGF-1 (C), eNOS (D), BDNF (E), and apoptosis (F). Data are presented as mean±SD (n=6). Different alphabets indicate statistical significance at $p<0.05$.

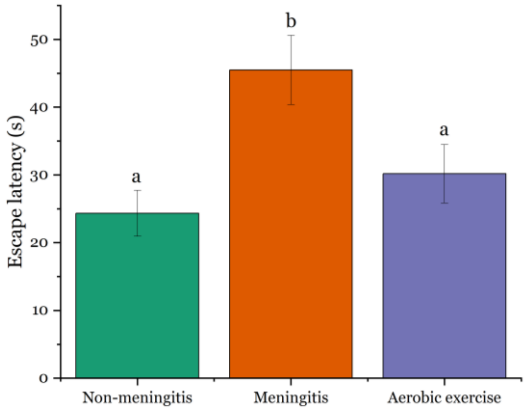


Figure 2. The effect of aerobic exercise on escape latency of meningitis rats during Morris water maze test. The escape latency indicates the spatial memory ability. Data are presented as mean±SD (n=6). Different alphabets indicate statistical significance at p<0.05.

## Histopathology of brain-derived neurotrophic factor (BDNF)

Histopathological images of hippocampal brain tissue to assess BDNF in each group through immunohistochemistry after treatment are presented in **Figure 3**. IHC staining revealed that 90% of brain tissue in the non-meningitis group showed strong positivity, indicating intact cells with no cytoplasmic or nuclear damage. This was similar to findings observed in the aerobic exercise group, where BDNF antigen and antibody binding reactions were observed in glial cells. Both groups exhibited numerous cells with mediators involved in brain damage repair.

Histochemistry images of brain tissue from the non-meningitis group showed normal neuron cells without edema or abnormalities. In contrast, the treatment groups (indicated with arrows) showed edematous stroma, few inflammatory cells, and dilated blood vessels. Histology images of this group also showed neuron cells with some inflammatory cell infiltration. Brain tissue in the aerobic exercise treatment group showed neuron cells appearing largely normal with only slight edema. These findings suggested that aerobic exercise significantly improves brain condition.

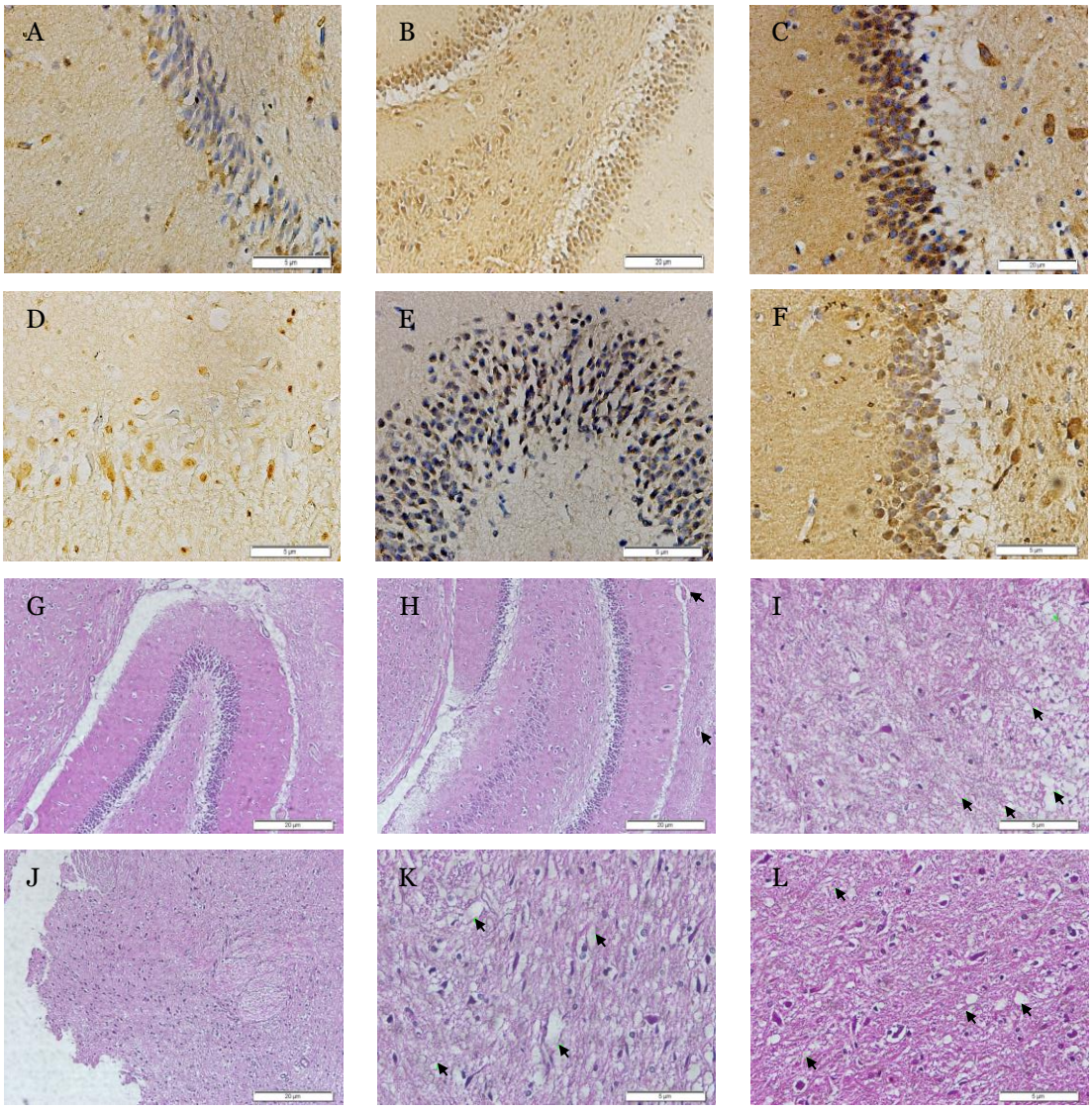


Figure 3. Immunohistochemistry between groups (A-F). Hematoxylin and eosin apoptosis with arrows indicate neuron cells with some areas of slight edema (G-L).

## Discussion

This present study showed that aerobic exercise has significant results in improving the brains of meningitis rats on MDA, NF-κB, IGF-1, eNOS, BDNF, apoptosis, and spatial memory. The administration of ceftriaxone antibiotics improved the molecular system of MDA as indicated by a reaction of increased ROS and improved the activation of NF-κB, which is activated due to stress inhibited by ceftriaxone antibiotics to reduce its activity. The function of NF-κB becomes cell cycle activation for spurring cell proliferation and inhibition apoptosis [32]. It was able to improve the circulation of IGF-1 and eNOS, which inhibit meningeal inflammation [33,34].

The results of the present study proved that aerobic exercise in the treatment group was able to reduce NF-κB levels significantly. These findings support the role of aerobic exercise in improving oxidative stress by reducing NF-κB, thus minimizing brain damage. The results of this present study proved that aerobic exercise in the treatment group significantly increased eNOS

levels. Aerobic exercise as an antioxidant can improve endothelial function, which contains NOS1-3 and produces nitric oxide (NO), which widely mediates neurotransmission, cytotoxicity, and vascular regulation. In cells, NO interacts with mitochondrial respiration, activates metabolic regulatory pathways and reduces oxidative stress [34]. Previous studies have shown that moderate-intensity and long-term exercise activates endogenous antioxidant production and increases blood flow. These reactions generate shear stress, which is able to increase the antioxidant superoxide dismutase (SOD) and glutathione peroxidase (GPx) that are responsible for ROS scavenging [35,36]. Oxidative stress may activate NF-κB. The activation of NF-κB increases the extracellular matrix and stimulates cell proliferation, which raises the intracranial pressure and may lead to brain nerve damage, including edema and inflammation in the brain [37,38]. Aerobic exercise reduces the activation of the inhibitor of kappa B alpha (IκBα)/ NF-κB pathway and decreases IL-6, TNFα, and F4/80 (macrophage markers) at the mRNA level in db/db+Ex [39].

Moderate aerobic exercise has been recognized as one of the most effective ways to improve brain plasticity [40]. Aerobic exercise affects cognitive function with an increase in neurotrophic factors (**Figure 4**). Neurotrophins such as BDNF, insulin-like growth factor growth factor, and nerve growth factor are endogenous proteins that have been described as factors that regulate cell proliferation and differentiation in the developing central nervous system. Aerobic exercise as an antioxidant can improve the central nervous system (CNS). IGF-1 can cross the blood-brain barrier (brain membrane) and enter the cerebrospinal fluid, performing neurogenesis and neuroprotection through autocrine/paracrine or endocrine effects. This affects metabolic regulation in the CNS, increases other nerve growth factors, clearance of protein aggregates, and angiogenesis [41]. Aerobic exercise in the treatment group has shown the potential to increase internal antioxidants and trigger neuroplasticity in the hippocampus derived from the brain. Neurotrophic factors and N-methyl-D-aspartate receptor (NMDAR) expression in rats, indicating changes in synaptic plasticity. Aerobic exercise affects oxygen consumption in the brain and the activation of antioxidants that induce the growth of new nerve cells (neurogenesis) and synaptic plasticity, which is associated with delayed memory decline, decreased incidence of dementia, decreased depression and anxiety, improved cognitive function, including executive function and information processing speed, and reduced hippocampal atrophy in humans [18].

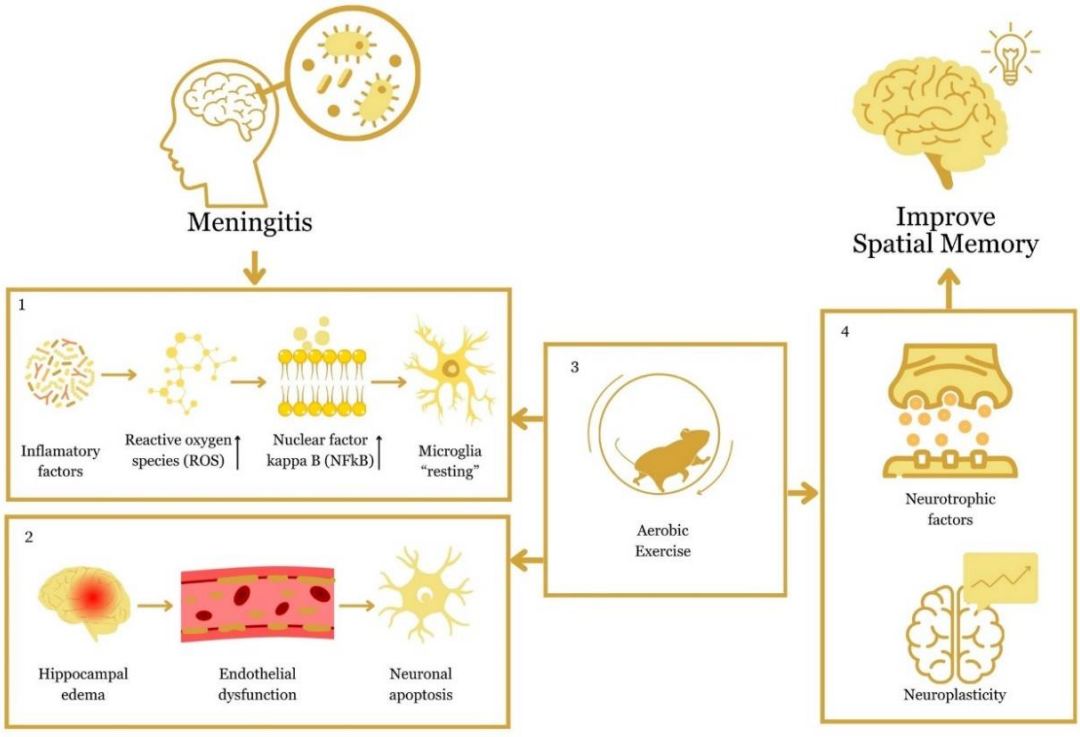


Figure 4. Illustration of aerobic exercise mechanisms in improving spatial memory in a rat model of meningitis.

The present study also has several limitations. First, it was conducted only on male rats, limiting the generalizability of the findings to females. Additionally, the dosage of exercise was restricted to moderate intensity, so the effects of lower or higher-intensity exercise remain unknown. The exercise intervention involved in this study was only moderate-intensity for two weeks, which may not fully capture the effects of different exercise intensities or longer durations and may limit the generalizability of the findings to other populations and exercise modalities. The present study did not include any clinical follow-up, making it unclear whether the observed effects are sustained over time. This present study was conducted on rats, which limits the direct applicability of the findings to human physiology and cognitive processes. Additionally, the specific conditions and responses observed in animal models may not fully replicate the complexities of human brain functions and the long-term effects of interventions.

## Conclusion

The findings of this study suggested that aerobic exercise significantly reduced the effects that arise due to acute meningitis in the rat brain, such as neuronal loss, neuroinflammation, and oxidative stress, which led to neuronal damage and cognitive deficits, including memory impairment. Aerobic exercise appeared to alleviate these effects by improving molecular and biochemical systems by enhancing antioxidant defense mechanisms and promoting neurogenesis, stimulating the formation of new neuron cells, particularly in regions like the hippocampus, which is crucial for memory. Future research should incorporate both male and female subjects, varied exercise protocols, and long-term follow-up to provide more comprehensive insights into sex-related differences in response to exercise post-meningitis. Long-term follow-up studies are also crucial to determine whether the observed benefits on brain repair and cognitive function are sustained over time or if they diminish once the exercise intervention is discontinued.

### Ethics approval

This research was approved by the Research Ethics Committee of Universitas Brawijaya, Malang, Indonesia (No: 031-KEP-UB-2023). All treatment of animals was carried out according to the ethical guidelines and regulations for the care and use of laboratory animals.

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### Competing interests

All the authors declare that there are no conflicts of interest.

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### Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

## How to cite

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