

Antioxidant and Antilipidemic Effects of Hydroalcoholic Extract of *Salvia officinalis* in a Cerebral Ischemia Model in Rats Fed a High-Fat Diet

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Research Article

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Abstract

Background and Objective

High-fat diet (HFD) is considered one of the main risk factors for ischemic stroke. Improving antioxidant defense and lipid profile through plant-based antioxidant compounds may help to reduce the negative outcomes of ischemia and HFD. Since *Salvia officinalis* (sage) contains strong antioxidant components, this study aimed to evaluate the effect of its hydroalcoholic extract (ESO) on antioxidant activity, lipid peroxidation, and other ischemic outcomes in rats.

Materials and Methods

Adult male Wistar rats were randomly divided into eight groups. Animals received a normal or high-fat diet for eight weeks, followed by ESO or vehicle treatment for four weeks. Cerebral ischemia was induced by middle cerebral artery occlusion (MCAO). Brain edema (brain water content), antioxidant enzyme activity, and malondialdehyde (MDA) levels were measured by standard biochemical methods.

Results

The findings showed that ESO treatment significantly reduced MDA level, brain water content, and serum lipids. At the same time, antioxidant activity was significantly increased compared with untreated groups.

Conclusion

These results suggest that ESO can improve antioxidant defense and decrease lipid peroxidation in ischemic conditions. Therefore, it may protect brain cells against oxidative stress and hyperlipidemia, and could be considered as a potential natural treatment for atherosclerotic ischemia.

Introduction

Stroke is a severe neurological disorder that can occur due to interrupted cerebral blood flow (ischemic stroke: IS) or rupture/bleeding of cerebral vessels (hemorrhagic stroke: HS). It remains a leading cause of death and long-term disability worldwide [1]

Dyslipidemia, particularly elevated LDL-cholesterol and triglycerides and reduced HDL-cholesterol is firmly linked to atherosclerosis and is associated with increased risk of ischemic stroke and poorer early outcomes, contemporary cohort analyses and reviews continue to support lipid control as a key preventive strategy [2]. In fact, examining the lipid profile of patients with ischemic and hemorrhagic

stroke shows alterations in triglyceride, LDL, and HDL levels in these patients. Analyses have shown that the risk of ischemic stroke decreases through lipid-lowering interventions [3].

Ischemic stroke (IS) is mainly caused by atherosclerosis, and about one-third of IS patients have atherosclerosis (4, 5). Atherosclerosis is a chronic inflammatory arterial disease characterized by lipid accumulation and oxidative modifications of LDL, which promote plaque formation and instability leading to thrombotic events and ischemic injury. Recent work highlights oxidative stress as a central mediator linking dyslipidemia to endothelial dysfunction and thrombosis [6]. Therefore, the most common and important feature of At is changes in the expression and activity of reactive oxygen species (ROS) alongside damage or loss of endogenous antioxidant systems, leading to oxidative stress induction [7]. Furthermore, ischemia-reperfusion injury leads to increased ROS production, enhanced lipid oxidation, and oxidative stress induced by these oxidized lipids causes neuronal damage, disruption of the blood-brain barrier function, and neuroinflammation. Targeting lipid-mediated mechanisms is a promising therapeutic approach for the prevention, control, and treatment of cerebral ischemia [8].

Free radicals are highly reactive molecules containing unpaired electrons that can attack biological macromolecules, leading to oxidative damage and tissue dysfunction. The most important free radicals in biological systems are ROS [9]. Under normal physiological conditions, ROS production is relatively low and excess ROS are cleared by antioxidant systems. However, during atherosclerosis, ROS production significantly increases while antioxidant system capacity decreases, leading to enhanced oxidative stress. ROS activate pro-atherosclerotic processes such as inflammation, endothelial dysfunction, and alterations in lipid metabolism [7]. Antioxidants are compounds that, due to their high oxidation potential, donate electrons to free radicals and neutralize them. Many antioxidant supplements naturally occur in fruits and vegetables and are consumed as part of the diet [10].

Salvia officinalis is commonly known as garden sage, common sage, or Dalmatian sage and has widespread use in traditional medicine. The extract of this plant contains phenolic compounds and flavonoids, and its hydroalcoholic extract contains more antioxidant compounds compared to other types of extracts. It has also been shown that the hydroalcoholic extract contains compounds such as rosmarinic acid, carnosic acid, and carnosol, which possess antioxidant properties and can scavenge oxygen free radicals. This extract neutralizes free radicals by donating hydrogen atoms [11]. that exhibit strong antioxidant and anti-inflammatory activities; recent preclinical studies report that sage extracts increase antioxidant enzyme activities, reduce lipid peroxidation and exert neuroprotective effects in models of neural injury [12–14].

Considering the above, increased free radicals play a significant role in the pathogenesis of atherosclerosis and cerebral ischemia by damaging macromolecules such as lipids and proteins. Therefore, strengthening antioxidant systems appears to be effective in reducing the consequences of atherosclerotic stroke. Since plants with effective antioxidant compounds have attracted much attention from researchers, we aimed in this study to investigate the effects of the hydroalcoholic extract of *Salvia Officinalis* on the outcomes of cerebral ischemia following a high-fat diet.

Materials and Methods

Preparation of High Fat Diet (HFD) and Extract

The high fat diet (HFD) was prepared according to a previous study [15]. Briefly, the regular feed was molded, and 200 g of sheep fat was added to every 800 g of powdered food. Distilled water was added to the powdered food to form a dough, which was thoroughly mixed by kneading. The dough mixture was then shaped into pellets and placed on racks for drying. The total drying time was 36 hours. After drying, the pellet strands were broken into short pieces and stored in the refrigerator. This feed was prepared weekly.

The hydroalcoholic extract of *Salvia officinalis* was obtained from Golestan Company (Tehran, Iran). The dose used in this experiment was determined based on a previous study [16]. In that study, three doses of the extract were tested, and 75 mg/kg was identified as the most effective dose. Therefore, the present study used a dose of 75 mg/kg of the hydroalcoholic extract.

Animals

A total of 144 adult male Wistar rats aged approximately 6–8 weeks, were obtained from the Animal Laboratory of Zanjan University of Medical Sciences and included in this study. Rats were housed under appropriate bioclimatic conditions, including 12 hours of light and 12 hours of darkness, temperature of 22–24°C, and 60% humidity. To adapt to the laboratory environment, the animals were transferred to the lab one week prior to the experiment. During this period, they had free access to food and water. All experimental procedures involving animals were conducted in accordance with institutional guidelines and approved by the Ethics Committee of Zanjan University of Medical Sciences, Zanjan, Iran (Approval No:IR.ZUMS.AEC.1404.026).

Experimental Groups

The animals were randomly divided into eight groups of 14 animals each as follows: Sham group (received a normal diet (ND) for 8 weeks and underwent surgical stress in the 12th week), HFD group (received only a high fat diet (HFD) for 8 weeks), MCAO group (received a normal diet (ND) for 8 weeks and then subjected only to brain ischemia induction by middle cerebral artery occlusion), Vehicle group (received HFD for 8 weeks, then ethanol for 4 weeks, followed by MCAO induction), HFD + MCAO group (received HFD for 8 weeks and underwent MCAO surgery at week 12), HFD + ESO group (received HFD for 8 weeks and then received hydroalcoholic extract of *Salvia officinalis* (ESO) by intraperitoneal injection for 4 weeks), ESO + MCAO group (received ESO for 4 weeks followed by MCAO induction), HFD + ESO + MCAO group (received HFD for 8 weeks, then ESO for 4 weeks, followed by MCAO induction). Each group was then randomly divided into two subgroups (n = 7). Brain edema was evaluated in the first subgroup, and biochemical analyses were performed in the second subgroup.

MCAO Model

Animals were anesthetized by intraperitoneal injection of ketamine (60 mg/kg) and xylazine (10 mg/kg). MCAO surgery was performed following the method described by Longa et al. [17]. Briefly, under microscopic surgery, a 3–0 nylon suture (403734PK5RE, Doccol, USA) was inserted through the external carotid artery (ECA) trunk into the right artery and advanced along the internal carotid artery (ICA) until reaching the anterior cerebral artery (ACA). The suture contact with the ACA blocked blood flow to the middle cerebral artery (MCA). This blockage was confirmed by resistance felt during suture advancement and insertion of about 20 mm of thread length from the ECA trunk. After 60 minutes of ischemia, reperfusion was allowed. Body temperature was monitored rectally with a digital thermometer and maintained at approximately 37°C.

Neurological Examination

Neurological function was assessed using a 0–5 point neurological score after 24 hours of reperfusion. The scoring scale was as follows: 0 = no neurological deficit, 1 = failure to extend the contralateral forepaw, 2 = circling to the contralateral side when held by the tail with feet on the floor, 3 = falling to the left and inability to bear weight on the affected side, 4 = no spontaneous walking and depressed consciousness, and 5 = death [17].

Brain Edema Evaluation

After sacrificing animals with a high dose of anesthetic, decapitation was performed and brains were removed. The cerebellum, brainstem, olfactory bulbs, and the two cerebral hemispheres were separated using a scalpel. The wet weight (WW) of the cerebral hemispheres was measured. Then, samples were dried in an oven (PID-C168 Zist Fanavar, Iran) at 120°C for 24 hours to measure dry weight (DW). Brain water content was calculated using the formula: $[(WW - DW) / WW] \times 100$ [18].

Measurement of Malondialdehyde (MDA), Catalase (CAT), Superoxide Dismutase (SOD), and Glutathione Peroxidase (GPx)

Because malondialdehyde (MDA) is the final product of lipid peroxidation, its level was measured in brain tissue to assess lipid peroxidation. The thiobarbituric acid reactive substances (TBARS) method using a spectrophotometer was employed for MDA measurement. The activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) enzymes were measured using commercial kits (Randox, UK). Catalase (CAT) activity was determined by Aebi's method using a spectrophotometer.

Blood Sampling

Twenty-four hours after ischemia induction, animals were anesthetized, and blood samples were collected from the heart. The samples were centrifuged at $7000 \times g$ for 10 minutes at room temperature to separate serum, which was stored at -20°C until biochemical analyses. Serum levels of cholesterol, triglycerides, and high-density lipoprotein (HDL) were measured by enzymatic colorimetry using special kits (Pars Azmon). Low-density lipoprotein (LDL) levels were calculated by the formula: $\text{LDL (mg/dL)} = \text{Total cholesterol} - (\text{HDL} + \text{TG}/5)$.

Statistical Analysis

Data were expressed as mean $\pm$ standard deviation (Mean $\pm$ SD). Statistical analyses were performed using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA). Neurological deficit scores were evaluated using the Mann–Whitney U test, while other quantitative data were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A p-value of less than 0.05 was considered statistically significant.

Results

Effect of Extract Treatment on Neurological Deficits

The results of the present study showed that MCAO induced cerebral ischemia in rats, as neurological deficits were observed in the MCAO group. On the other hand, treatment with the extract in the ESO group significantly reduced ($p \leq 0.05$) neurological deficits compared to the MCAO group. A high-fat diet in the HFD + MCAO group exacerbated neurological impairments, with a significant difference ($p \leq 0.05$) observed between this group and the MCAO group. Moreover, administration of the SO extract reduced ($p \leq 0.05$) neurological complications in the ESO + HFD + MCAO group compared to the HFD + MCAO group. Administration of the hydroalcoholic solvent alone did not induce any neurological deficits in the rats (Fig. 1).

Effect of Extract Treatment on Brain Edema

Brain edema was assessed by calculating the percentage of water content in the brain hemispheres. The study demonstrated that induction of cerebral ischemia led to water accumulation in the affected (right) brain hemisphere. Rats undergoing MCAO surgery showed a significant increase in brain water content compared to the sham group. Additionally, a significant difference ($p \leq 0.05$) in water content between the right and left hemispheres was observed in the MCAO group. This increase was further exacerbated in rats fed a high-fat diet prior to MCAO compared to those on a normal diet, with a significant difference ($p \leq 0.05$) between the MCAO and HFD + MCAO groups. Extract treatment significantly reduced ($p \leq 0.05$) brain water content; rats receiving the extract (ESO + MCAO and HFD + ESO + MCAO) showed a significant decrease ($p \leq 0.05$) in right hemisphere water content compared to the HFD + MCAO group (Fig. 2).

Effect of Extract Treatment on Lipid Peroxidation

Lipid peroxidation was evaluated by measuring malondialdehyde (MDA) levels. It was found that both cerebral ischemia induction and high-fat diet consumption significantly increased ($p \leq 0.05$) MDA levels in the MCAO and HFD groups compared to the sham group. Injection of the hydroalcoholic SO extract significantly reduced ($p \leq 0.05$) MDA levels in the extract-treated groups compared to the MCAO and HFD groups (Fig. 3).

Effect of Extract Treatment on Antioxidant Enzyme Levels

The levels of three antioxidant enzymes—catalase (Fig. 4A), superoxide dismutase (SOD) (Fig. 4B), and glutathione peroxidase (GPx) (Fig. 4C) were measured following cerebral ischemia induction in rats fed a high-fat diet. The results showed that both the high-fat diet and cerebral ischemia led to a significant decrease ($p \leq 0.05$) in the levels of these enzymes, with significant differences between the sham group and the MCAO, HFD, and HFD + MCAO groups ($p \leq 0.05$). Conversely, treatment with the hydroalcoholic sage extract enhanced the levels of these enzymes, with significant increases ($p \leq 0.05$) observed in the ESO + MCAO, HFD + ESO, and HFD + ESO + MCAO groups compared to the MCAO, HFD, and HFD + MCAO groups, respectively (Fig. 4).

Effect of Extract Treatment on Serum Lipid Levels

High-Density Lipoprotein (HDL)

The high-fat diet significantly decreased ($p \leq 0.05$) HDL levels in the HFD and HFD + MCAO groups compared to the sham group, while the decrease in the MCAO group was not statistically significant. Extract treatment caused significant changes in HDL levels in the ESO + MCAO and HFD + ESO + MCAO groups compared to the MCAO and HFD + MCAO groups, respectively.

Low-Density Lipoprotein (LDL)

The study results showed a significant increase in LDL levels in groups fed a high-fat diet compared to those on a normal diet, with the HFD and HFD + MCAO groups having significantly higher LDL levels than the sham group. Treatment with the hydroalcoholic sage extract significantly reduced LDL levels in the HFD + ESO + MCAO group compared to the HFD and HFD + MCAO groups. Although LDL levels decreased in the ESO + MCAO group after extract treatment, this reduction was not statistically significant.

Total Cholesterol (TC) and Triglycerides (TG)

Consumption of a high-fat diet significantly increased serum total cholesterol and triglyceride levels in the HFD and HFD + MCAO groups compared to the sham group, while ischemia induction alone did not cause a significant increase compared to sham. Extract administration in the ESO + HFD and HFD + ESO + MCAO groups significantly decreased serum total cholesterol and triglyceride levels compared to the

HFD and HFD + MCAO groups. Extract treatment also reduced these lipid levels in the ischemic groups, although this reduction was not statistically significant compared to the MCAO group.

Discussion

The present study was conducted to investigate the neuroprotective effects of a plant extract through enhancement of the antioxidant system and reduction of lipid peroxidation under a pseudo-atherosclerotic condition. Our results demonstrated that this extract can reduce serum lipid levels and increase the body's antioxidant activity, thereby effectively mitigating the consequences of atherosclerotic ischemia.

Since the onset of ischemic stroke, unlike hemorrhagic ones, is gradual, identifying and controlling risk factors that influence its progression is particularly important. Several studies have reported a strong correlation between the LDL/HDL ratio and the incidence of cerebral ischemia, suggesting that this ratio may serve as a predictive factor [19–21]. Elevated LDL and total cholesterol levels are associated with increased post-stroke complications and higher mortality rates [20]. High LDL promotes platelet adhesion and coagulation, thus facilitating thrombosis [22, 23]. Therefore, treatments that lower total cholesterol (TC) and LDL can prevent the progression of atherosclerosis and improve ischemic outcomes [24, 25].

Clinical and experimental studies have demonstrated that plant-derived polyphenols such as curcumin, resveratrol, and quercetin exert hypolipidemic and vascular-protective effects [26–30]. Similar to these compounds, *Salvia officinalis* (SO) has shown potent regulatory effects on cholesterol metabolism by reducing cholesterol synthesis, enhancing excretion, and inhibiting lipogenesis [31, 32]. Clinical investigations also report that SO can lower cholesterol, improve lipid profiles, and modulate insulin levels [33]. These properties are attributed to its rich content of phenolic and flavonoid compounds such as salvianolic acid, rosmarinic acid, carnosol, carnosic acid, and quercetin, which possess strong antioxidant activities [14, 34, 35].

In the present study, pretreatment with hydroalcoholic extract of *Salvia officinalis* significantly improved antioxidant enzyme activities and reduced lipid peroxidation following cerebral ischemia. This suggests that SO mitigates ischemic outcomes—including neurological deficits and cerebral edema—through enhancing endogenous antioxidant defense mechanisms.

Malondialdehyde (MDA), a major product of lipid peroxidation, is widely recognized as a marker of oxidative stress. Previous studies have demonstrated that treatment with aqueous or hydroalcoholic extracts of SO increases antioxidant enzyme activities such as superoxide dismutase (SOD) and catalase (CAT), while reducing MDA production [35–37]. The antioxidant effects of phenolic compounds are mainly attributed to their reactive hydroxyl groups, which can neutralize free radicals and delay lipid oxidation [38, 39]. Moreover, polyphenols suppress reactive oxygen species (ROS) generation by inhibiting oxidases, preventing LDL oxidation, and protecting mitochondrial integrity, thereby exerting neuroprotective effects [40, 41].

Several studies have shown that resveratrol and quercetin, compounds present in SO, enhance antioxidant enzyme activities (SOD, CAT, and glutathione peroxidase) and reduce neuronal MDA levels, thereby protecting against ischemia-induced oxidative injury [42–47].

Collectively, the results of the present study suggest that *Salvia officinalis* enhances endogenous antioxidant activity, reduces oxidative stress induced by a high-fat diet and cerebral ischemia, and attenuates ischemic injury through decreasing lipid peroxidation. These findings are supported by the observed reductions in MDA levels and improvements in antioxidant enzyme activities in ESO-treated rats. Nonetheless, further studies are warranted to confirm these findings through histopathological assessments and evaluation of free radical levels.

Abbreviations

HFD

High-Fat Diet

ND

Normal Diet

SO

Salvia officinalis

ESO

Extract of *Salvia officinalis* (Hydroalcoholic Extract)

MCAO

Middle Cerebral Artery Occlusion

ROS

Reactive Oxygen Species

MDA

Malondialdehyde

CAT

Catalase

SOD

Superoxide Dismutase

GPx

Glutathione Peroxidase

LDL

Low-Density Lipoprotein

HDL

High-Density Lipoprotein

TC

Total Cholesterol

TG

Triglycerides

IS
Ischemic Stroke
HS
Hemorrhagic Stroke
ACA
Anterior Cerebral Artery
ICA
Internal Carotid Artery
ECA
External Carotid Artery
SD
Standard Deviation
SPSS
Statistical Package for the Social Sciences
TBARS
Thiobarbituric Acid Reactive Substances
ANOVA
Analysis of Variance.

Declarations

Ethics declarations

All experimental procedures involving animals were conducted in accordance with institutional guidelines and approved by the Ethics Committee of Zanzan University of Medical Sciences, Zanzan, Iran (Approval No:IR.ZUMS.AEC.1404.026).

Author Contribution

E.G. and M.F. conceptualized the study and designed the methodology. E.G. and M.F and H.M. conducted the literature review and collected data. M.F and A.R. performed the analysis and interpretation of results. E.G. and M.F and M.HS. wrote the main manuscript text. E.G. prepared Figures. All authors reviewed and critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Data Availability

All data supporting the findings of this study are included within the article.

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Figures

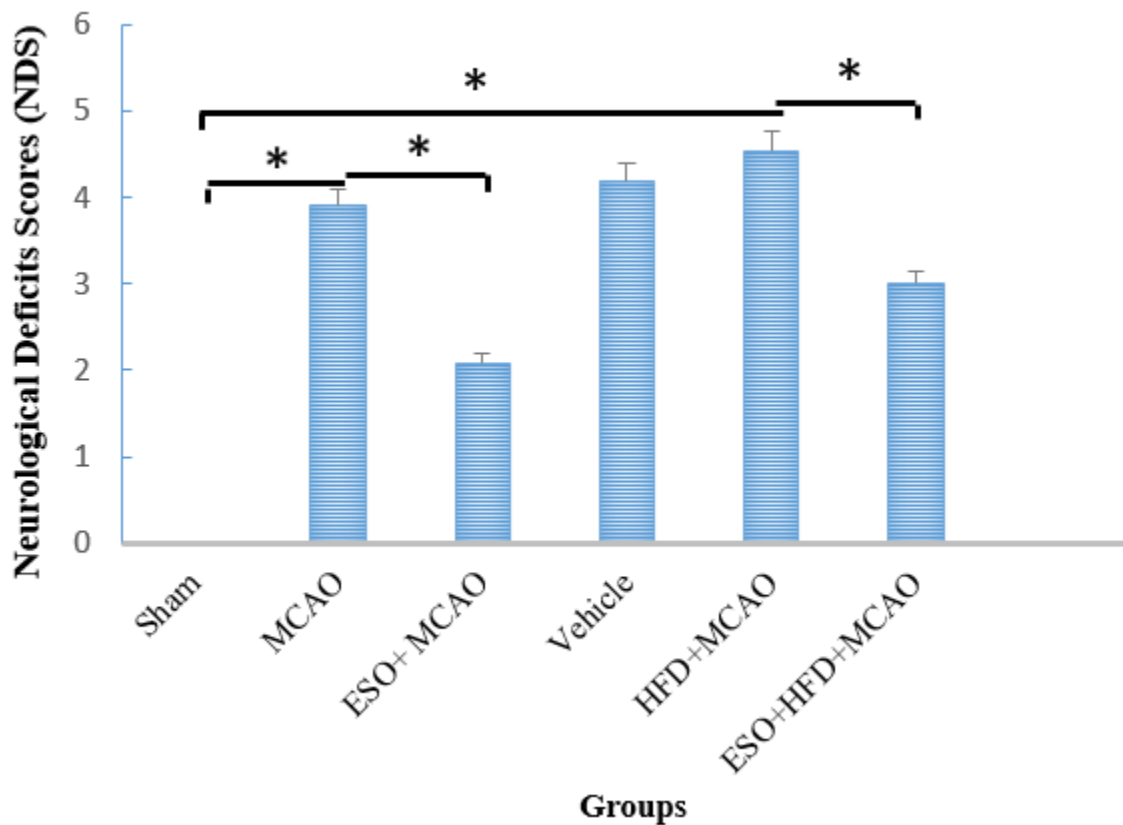


Figure 1

Reduction of neurological deficits following SO extract injection. Neurological performance assessment 24 hours after cerebral ischemia induction showed that MCAO and high-fat diet (HFD) caused neurological deficits in rats. Pretreatment with *Salvia officinalis* (SO) extract significantly decreased neurological deficit scores compared with the MCAO and HFD+MCAO groups (* $p \leq 0.05$).

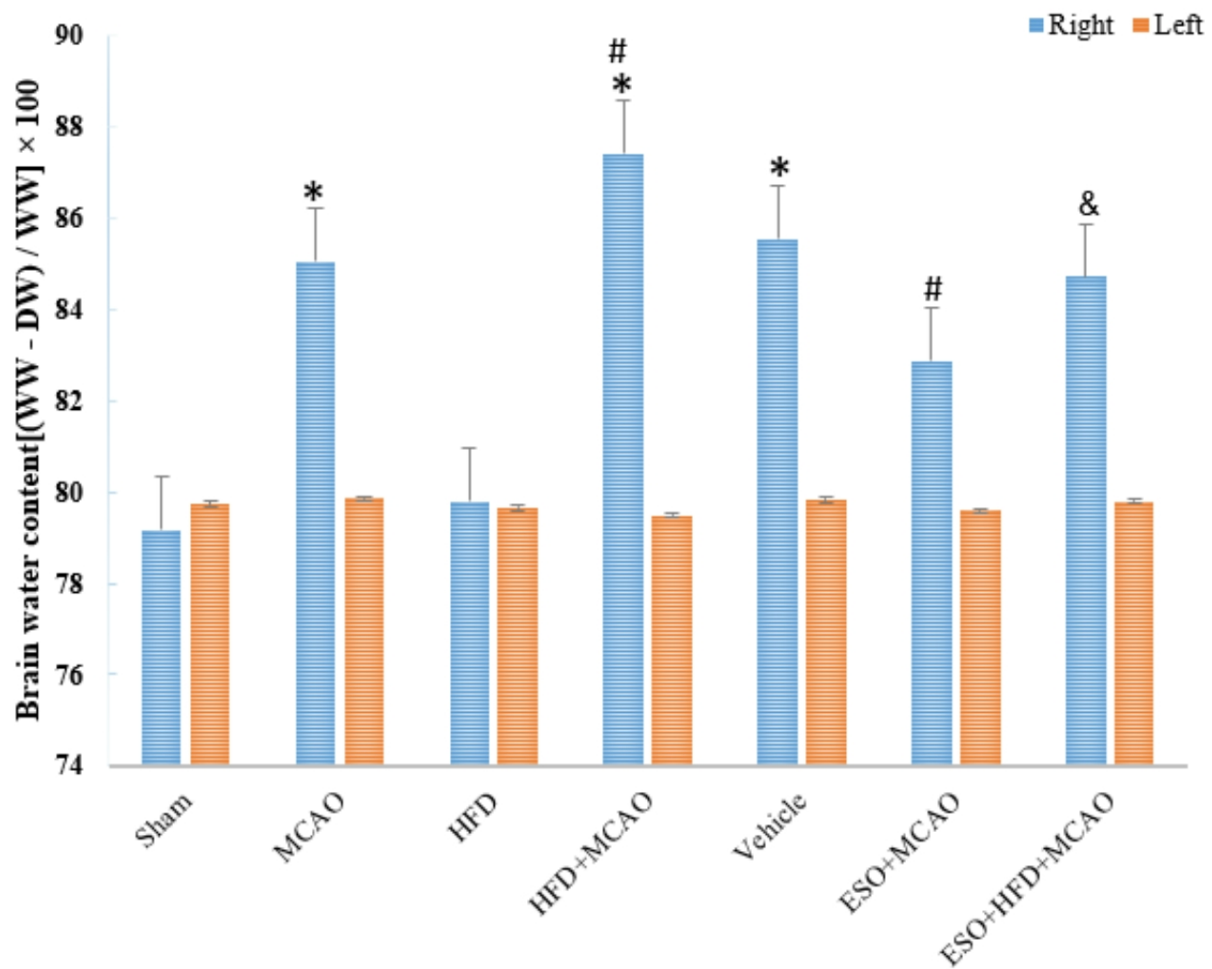


Figure 2

Improvement of brain edema following SO pretreatment. Evaluation of brain water content in the left (normal) and right (injured) hemispheres showed that cerebral ischemia and HFD significantly increased brain water content in the right hemisphere compared with the left hemisphere and sham group. Pretreatment with SO extract significantly reduced brain water content in the ESO+MCAO and ESO+HFD+MCAO groups compared with MCAO and HFD+MCAO groups (* $p \leq 0.05$ Compared to the Sham group; # $p \leq 0.05$ Compared to the MCAO group; & $p \leq 0.05$ Compared to the HFD+MCAO group).

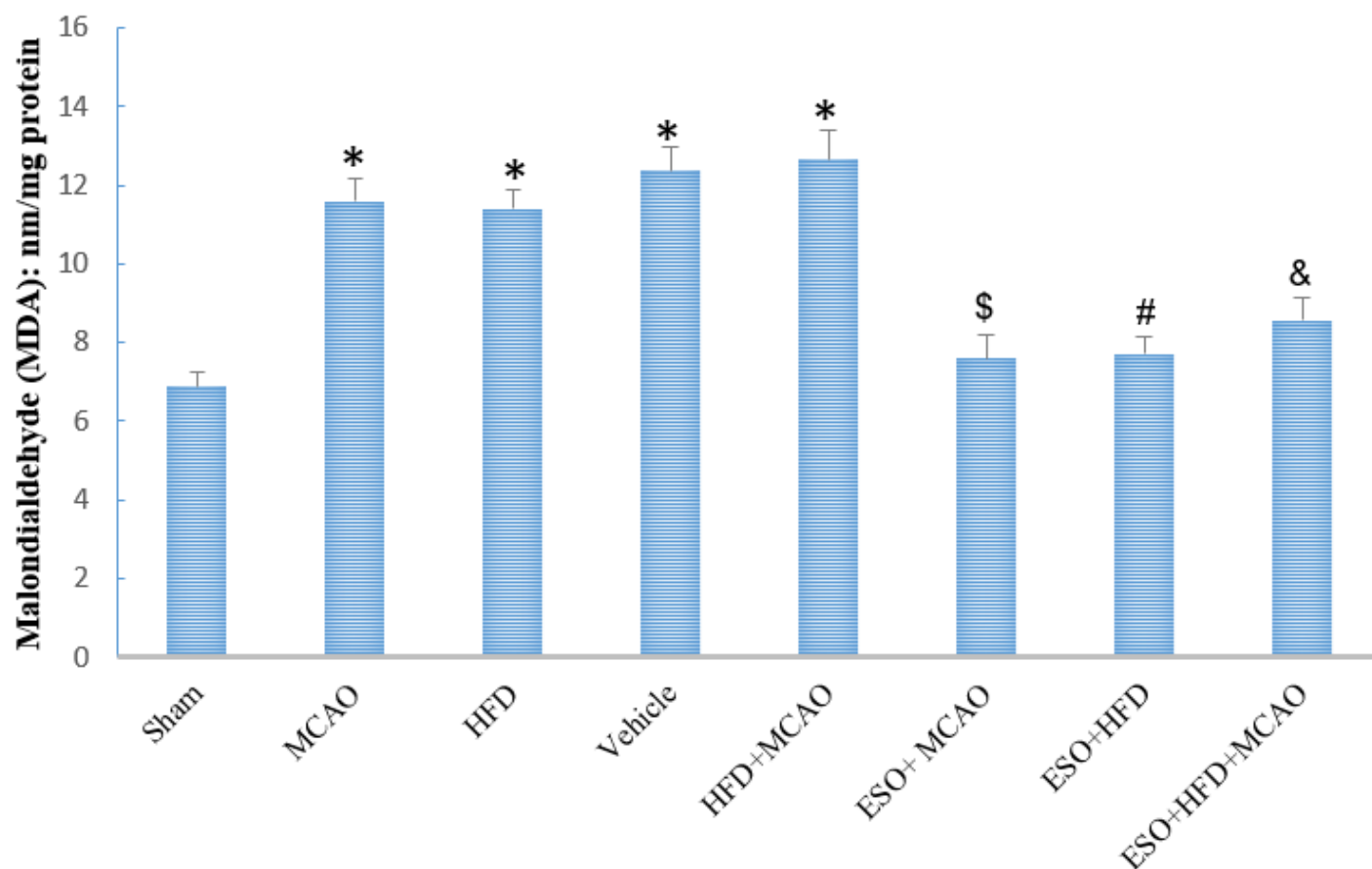


Figure 3

Reduction of lipid peroxidation by SO pretreatment. Cerebral ischemia and HFD increased malondialdehyde (MDA) levels in brain tissue, with significant differences observed between the MCAO and HFD+MCAO groups and the sham group. SO extract injection significantly reduced MDA levels in ESO+MCAO and ESO+HFD+MCAO groups compared with corresponding control groups (* $p \leq 0.05$ Compared to the Sham group; # $p \leq 0.05$ Compared to the HFD group; & $p \leq 0.05$ Compared to the HFD+MCAO group).

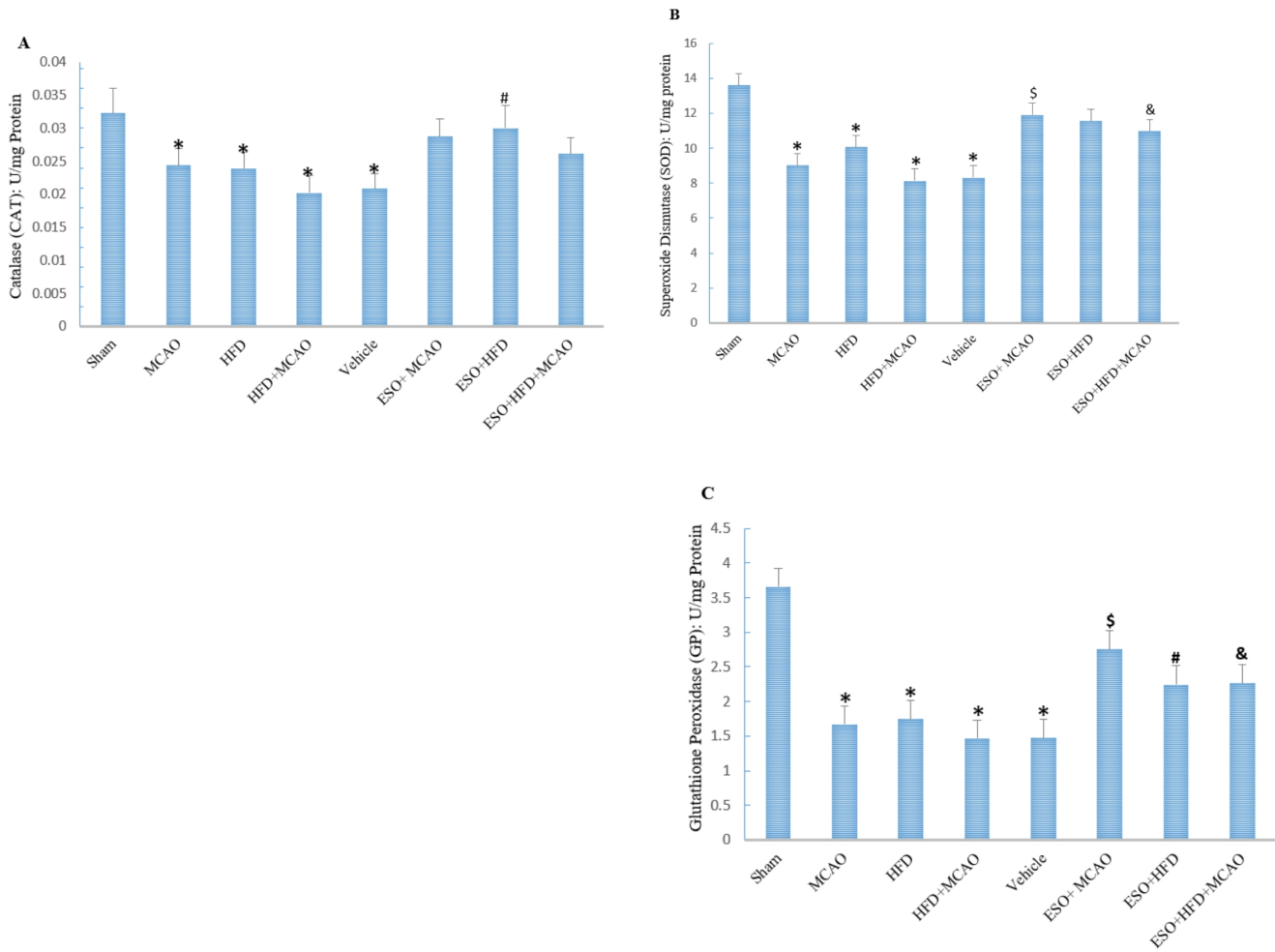


Figure 4

Enhancement of brain antioxidant activity after SO treatment. Results indicated that cerebral ischemia and high-fat diet (HFD) reduced the activity of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in MCAO, HFD, and HFD+MCAO groups compared with the sham group. SO extract injection significantly increased these enzyme levels in ESO+MCAO and ESO+HFD+MCAO groups compared with corresponding control groups (* $p \leq 0.05$ Compared to the Sham group; [#] $p \leq 0.05$ Compared to the HFD group; [&] $p \leq 0.05$ Compared to the HFD+MCAO group).

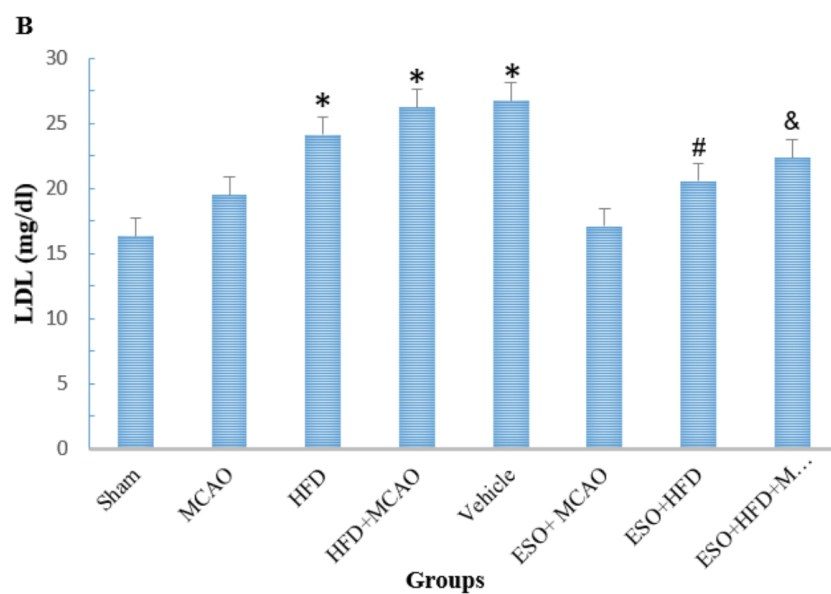
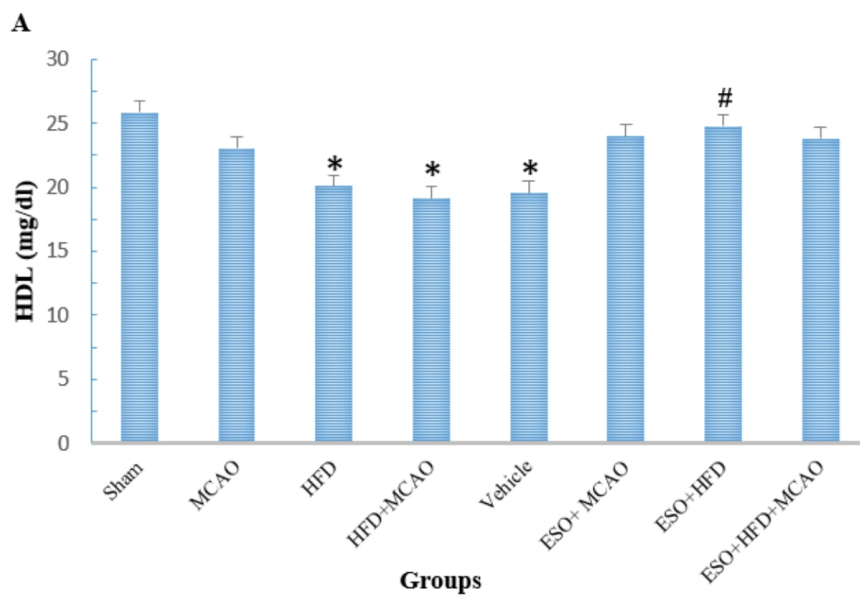


Figure 5

Improvement of serum lipid profile in SO-treated groups. Analysis of serum lipids showed that cerebral ischemia and HFD decreased HDL levels (A) and increased LDL levels compared with the sham group. SO extract administration in the ESO+HFD group significantly increased HDL levels and decreased LDL levels in ESO+HFD and ESO+HFD+MCAO groups compared with HFD and HFD+MCAO groups (* $p \leq 0.05$

Compared to the Sham group; # $p \leq 0.05$ Compared to the HFD group; & $p \leq 0.05$ Compared to the HFD+MCAO group).

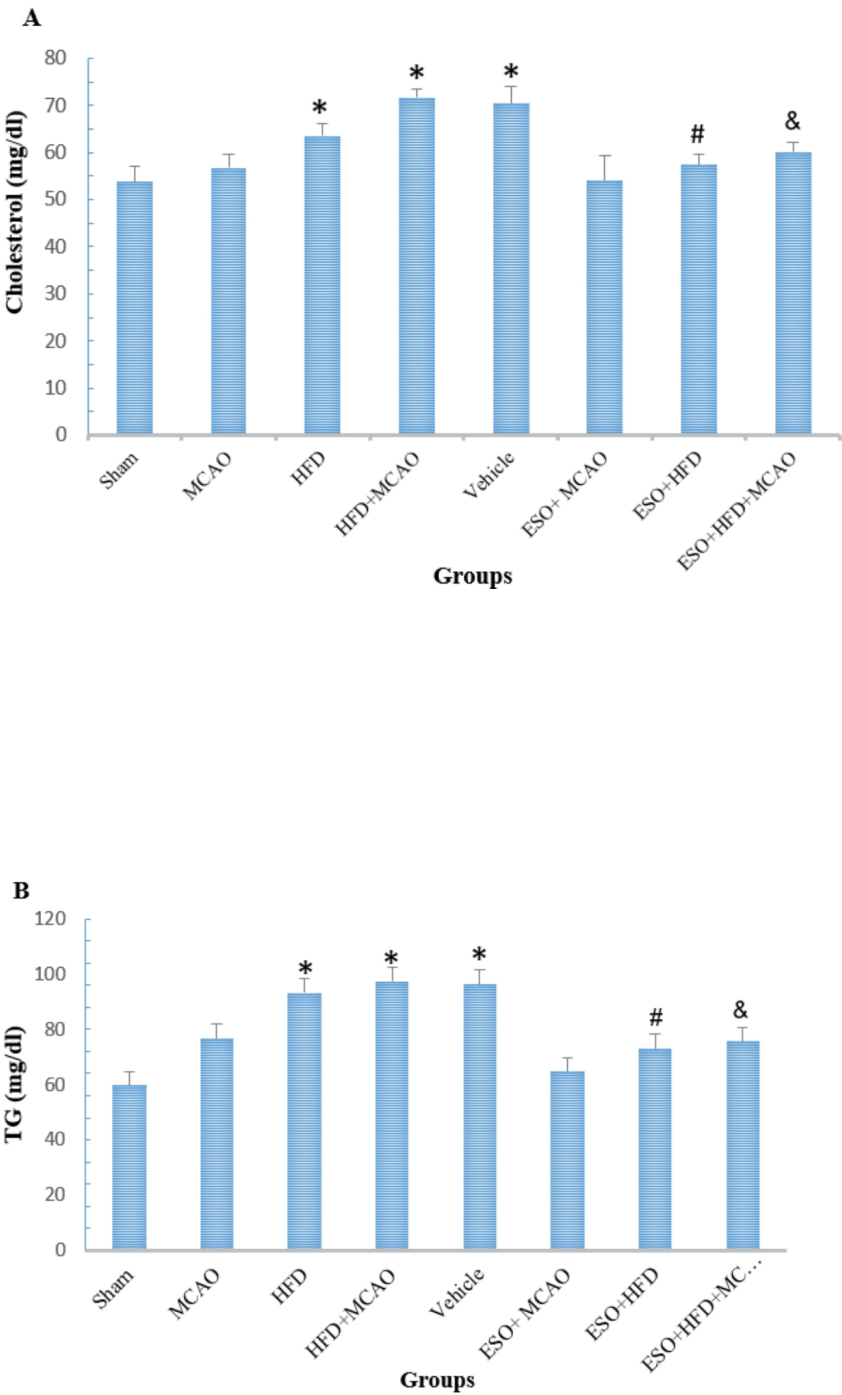


Figure 6

Reduction of serum lipid levels following extract treatment. Administration of a high-fat diet and induction of cerebral ischemia resulted in a significant elevation of total cholesterol (A) and triglyceride (B) levels in the blood of rats in the HFD and HFD+MCAO groups compared to sham group. Conversely,

rats that received the extract of *Salvia officinalis* exhibited a statistically significant reduction in serum cholesterol and triglyceride concentrations compared to those that did not undergo extract treatment (* $p \leq 0.05$ Compared to the Sham group; # $p \leq 0.05$ Compared to the HFD group; & $p \leq 0.05$ Compared to the HFD+MCAO group).