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Original Article

Potential Anti-Inflammatory Effect of *Lamium Album* Extract through Caspase-3 and Cyclooxygenase-2 Genes Expression in a Rat Model of Middle Cerebral Artery Occlusion

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Abstract

Introduction: Stroke is one of the most common causes of death worldwide. Inflammation and apoptosis play an important role in the cascade of ischemic stroke.

Aim: The aim of the present study was to evaluate the pretreatment effects of *Lamium album* (*L. album*) extract on caspase-3 and cyclooxygenase-2 (COX-2) expression, infarct volume, and neurological deficit score in a rat model of middle cerebral artery occlusion (MCAO).

Materials and methods: Wistar male rats were randomly divided into three groups: 1) MCAO group (1 h after MCAO, reperfusion was allowed for 24 h by retracting the thread); 2) *L. album* + MCAO group [receiving *L. album* extract (100 mg/kg via intraperitoneal) for a week before MCAO]; 3) sham group. The expression level of caspase-3 and COX-2 in the core, penumbra, and subcortex regions was measured by real time-PCR technique. Infarct volume and neurological deficit score were also assessed.

Results: The mRNA expression of caspase-3 in the core, penumbra, and subcortex regions in *L. album* group was significantly reduced compared to MCAO group ($p<0.05$). Expression level of COX-2 in the subcortex of the rats exposed to *L. album* was statistically decreased relative to MCAO group ($p<0.05$). Infarct volume in the core, penumbra, and subcortex was significantly reduced in the *L. album* group compared with MCAO group ($p<0.001$, $p<0.001$, $p<0.05$, respectively). Neurological deficit score was remarkably decreased in the *L. album* group in comparison with the MCAO group ($p<0.05$).

Conclusions: It appears that pretreatment with *L. album* extract may attenuate brain tissue damage after ischemic stroke. The potential protective effects of this plant extract against this condition might be in part attributed to its anti-inflammatory and anti-apoptotic activities.

Keywords

caspase-3, cyclooxygenase-2, *Lamium album*, stroke

INTRODUCTION

Stroke is the second leading cause of death worldwide, after heart disease. Ischemic stroke including acute and chronic phases accounts for 80% of stroke cases.[1,2] Following the acute phase, disruption of the blood-brain barrier (BBB), migration of immune cells, activation of microglia, impaired cerebral homeostasis, and hypoxia occur.[3] Several studies have shown that inflammation, oxidative stress, and apoptosis play a key role in the pathogenesis of brain injury, although the exact mechanisms are not fully understood.[4] In the early stages of injury, the inflammatory response is essential for tissue repair but the overexpression of inflammatory and apoptotic factors such as tumour necrosis factor-**α** (TNF-α), interleukin1-β (IL1-β), cyclooxygenase-2 (COX-2), caspase-3 increases brain tissue damage.[5]

Following induction of cerebral ischemia, two regions of the core and penumbra develop in the brain. In the core, blood flow drops to less than 10%–25%. The penumbra lies between the normally perfused part and the area where the infarction is developing. Some previous studies reported that expression of caspase-3 and COX-2 genes was increased in both regions leading to cell death.[6,7] Therefore, use of anti-inflammatory and anti-apoptotic agents could be one of potentially effective interventions to reduce the complications of brain ischemia.[8]

Thrombolytic drugs were prescribed to treat ischemic stroke, but their use was limited because of complications such as intracranial hemorrhage, myocardial rupture, and immune system disorders. Furthermore, the lack of efficient and appropriate pharmacological treatment for ischemic stroke might explain the growing interest in traditional herbal medicines.[9] Therefore, exploring new therapeutic approaches to ischemic strokes seems to be essential. The use of medicinal herbs has increased due to their lower costs and fewer side effects than for chemical drugs.[10] Also, herbal treatment has increased the self-repair in cerebral infraction and has reduced cell death in the brain.

White dead nettle or *Lamium album* (*L. album*), is a plant of the *Lamiaceae* herb family used in traditional Chinese medicine, North Africa, and Europe in the treatment of several disorders such as trauma, paralysis, hypertension, cancer, and arthritis.[11] In some previous studies, anti-inflammatory, antioxidant, and free radical scavenging activities of *L . album* were reported.[12,13] Due to having extensive biological properties, its potential therapeutic effects are still being investigated.[14]

AIM

With regard to the role of inflammatory and apoptotic signalling pathways in the extent and severity of stroke injury, the aim of the present study was to evaluate the potential protective effects of *L. album* extract on caspase-3 and COX-2 expression, infarct volume (IV), and neurological deficit score (NDS) in a rat model of middle cerebral artery occlusion (MCAO).

MATERIALS AND METHODS

Twenty-four male Wistar rats, ranging in weight from 250 to 300 g, were obtained from the Animal Care Center of Guilan University of Medical Sciences (Rasht, Iran). The animals were adapted to the standard laboratory conditions (12 h light: 12 h dark cycles at 22°-24°**C**) one week before performing the experiment. The rats had free access to adequate water and food during the experiment.

All experiments were carried out based on the international principles for laboratory animal use and care as determined in the US guidelines (NIH publication #85-23, revised in 1985). The Ethics Committee of Guilan University of Medical Sciences (Iran, Rasht) approved all procedures in this study (IR.GUMS.REC.1395.291).

Study protocol

The animals were randomly divided into three groups: 1) MCAO group: 1 h after MCAO, reperfusion was allowed for 24 h by retracting the thread (n=9); 2) *L. album* + MCAO group with the rats receiving *L. album* extract [100 mg/kg via intraperitoneal (IP)] for a week before MCAO, on the 7th day, 1 h after MCAO, reperfusion was allowed for 24 h by retracting the thread (n=9); 3) the sham group: like the MCAO group, they underwent surgery, but their middle cerebral artery did not occlude (n=6). The animals' motor function was randomly assessed 24 h after ischemic induction, then the animals were euthanized and their brains were removed to examine the expression level of caspase-3 and COX-2 and IV.

Plant materials

The *L. album* for the study was collected from the Rasht region (Guilan Province, Iran). It was identified by Fatemeh Yousefbeyk, Department of Pharmacognosy, Guilan University of Medical Sciences (Rasht, Iran) (voucher specimen No. 202HGUM). The hydroalcoholic extract was prepared by macerating the powder of stems and leaves in 50% ethanol (10 ml/g powder) for 72 h at 40°C. The extract was then filtered through a 250-μm mesh, centrifuged for 10 min at 2000 rpm, and its supernatant was dried in a water bath (40°C). Based on our previous study, total phenolic and flavonoid content in *L. album* extract was 0.61 (mg GAL/g) and 2.10 (mg QE/g), respectively.[15]

MCAO induction

Induction of MCAO was performed according to the method of Longa et al.[16] In summary, the animals were anesthetized by IP injection of ketamine (75 mg/kg) and xylazine (10 mg/kg). 3-0 silicon-coated nylon was insert-

ed into the external carotid artery (17-20 mm), as long as low resistance was felt, which closed the middle cerebral artery opening from the anterior and posterior cerebral artery and the internal carotid artery. During surgery, body temperature was controlled by rectal thermometry and maintained at 37°C. One hour after occlusion, the sutures were carefully removed and the animals were perfused for 24 h. The surgical incisor was sutured and the animals were monitored until recovery.

NDS

NDS was randomly evaluated 24 h after MCAO according to Longa et al. study.[16] NDS: 0 = no motor impairment, 1 = weakness in the forelimb and rotation in the same direction while hanging from the tail, 2 = rotation to the contralateral side and normal posture during rest, 3 = weight intolerance while resting on the injury side, 4 = no spontaneous motor activity, and 5 = death.

IV evaluation

The animals were killed and their brains were removed rapidly and accurately 24 h after reperfusion. Eight coronal sections (2 mm thick, Brain Matrix, Tehran, Iran) were prepared from their brains. Sections were stained for 15 min at 37°C in 2% 2,3,5-triphenyltetrazolium chloride (TTC) solution (Merck, Germany). The slices were then digitally photographed by a camera (Canon, DSC-W310) connected to the computer. Unstained areas were defined as infarcts and were measured using image analysis software. The lesion volume was calculated by measuring the unstained and the stained areas in each hemisphere slice, and then summation all of the eight slices according to the method of Swanson et al.[17]: corrected IV = left hemisphere volume - (right hemisphere volume - IV).

Quantitative real-time PCR

The brain tissue pieces were immediately transferred to liquid nitrogen until assessment of COX-2 and caspase-3 gene expression. In brief, total RNA was extracted based on the manufacturer instructions (YEKTA TAJHIZ AZMA, Iran). The purity of the extracted RNA was assessed by measuring the absorbance at 260/280 nm using the Nanodrop spectrophotometer (Thermo Fisher Scientific Inc., USA). Then the extracted RNA was treated with DNase to eliminate possible contamination. HyperScript™ First-strand Synthesis Kit (GeneAll, South Korea) was used to synthesize cDNA at 55°C for 60 min in accordance with the protocols explained by the manufacturer's instructions. To quantify the mRNA expression level of caspase-3 and COX-2, real-time PCR was performed by using the ABI instrument (StepOne™, USA). GAPDH was used as housekeeping gene for normalization of COX-2 and caspase-3 expression levels. The PCR primers (forward and reverse) of the studied genes were designed with Primer3web (version 4.0.0) **(Table 1)**. The designed PCR primers were tested using the Primer-BLAST system available at the National Center for Biotechnology Information (NCBI). All steps were based on our previous study.[15]

Statistical analysis

Data are presented as mean ± SD as appropriate. Inter-group comparisons were performed using the one-way analysis of variance (ANOVA) followed by post-hoc Tukey's test. $P<0.05$ was considered statistically significant for the tests. SPSS 16 software was used for data analysis. Graphs were designed by GraphPad Prism 5.04 (Graphpad Software, Inc).

RESULTS

Pretreatment with *L. album* extract decreased NDS

NDS test was used to evaluate the motor function of rats in different experimental groups. NDS in the rats pretreated with *L. album* extract was significantly reduced compared to MCAO group ($p<0.05$). Therefore, pretreatment with this extract improved motor activity **(Table 2)**.

L. album extract reduced IV

TTC stained coronal sections of the brains showed that IV in the core, penumbra, and subcortex regions of the rats

Table 1. PCR primer sequences for the real time PCR analysis of selected genes

Genes name	Sequence (5′ → 3′)	Annealing	Product size
Cox-2-F	ATGATCTACCCTCCCCACGT	54°C×30 s	119
Cox-2-R	ACTCTGTTGTGCTCCCGAAG		
Caspase-3-F	GCTGGACCCGTATTGAGA	55°C×30 s	142
Caspase-3-R	CCATGACCCGTCCCTTGAAT		
GAPDH-F	CCACAGTCCATGCCATCACT	60°C×25 s	101
GAPDH-R	TGCAGGGATGATGTTCTGGG		

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Table 2. Distribution of neurologic deficit score (NDS) in experimental groups (n=4)

Experimental groups	NDS in each group						Total (N)	*P* value
	0	1	2	3	4	5		
MCAO	0	0	3	4	2	0	9	$p<0.05$*
L. album pretreatment	2	2	2	2	1	0	9	

pretreated with *L. album* extract was significantly lower than that in the MCAO group ($p<0.001$, $p<0.001$, $p<0.05$, respectively) **(Fig. 1)**.

Pretreatment with *L. album* extract decreased caspase-3 and COX-2 genes expression in the core, penumbra, and subcortex

The expression level of caspase-3 was increased in the core, penumbra, and subcortex in the MCAO group compared with that in the sham group **(Fig. 2)**. In the rats pretreated with *L. album* extract, mRNA level of caspase-3 was decreased relative to MCAO group ($p<0.05$) **(Fig. 2)**. Pretreatment with *L. album* extract for a week significantly reduced COX-2 expression in the subcortex region compared to the MCAO group ($p<0.05$) **(Fig. 3)**.

DISCUSSION

In this experimental study, we investigated the potential protective effects of *L. album* extract on caspase-3 and COX-2 expressions (as apoptotic and inflammatory markers) in the MCAO model. The main findings were: (1) *L. album* protected the brain from ischemia; (2) *L. album* decreased caspase-3 and COX-2 expression level in core, penumbra, and subcortex regions; (3) *L. album* decreased the extent of lesion and improved motor activity.

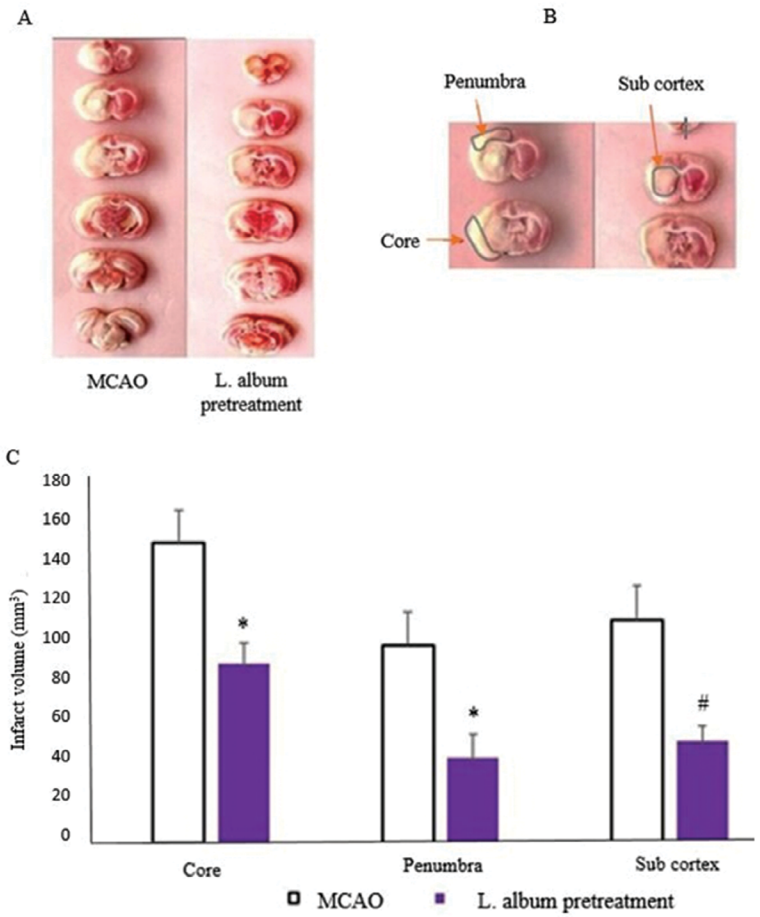

Figure 1. (**A**) TTC stained sections for each group; (**B**) Core, penumbra and subcortex; (**C**) The effect of pretreatment with *L. album* (100 mg/kg) on infarct volume (IV) in the core, penumbra, and subcortex regions. *L. album* group considerably exhibited less IV relative to the MCAO group. Data are presented as mean ±*SD* (n=4). * $p<0.001$, # $p<0.05$.

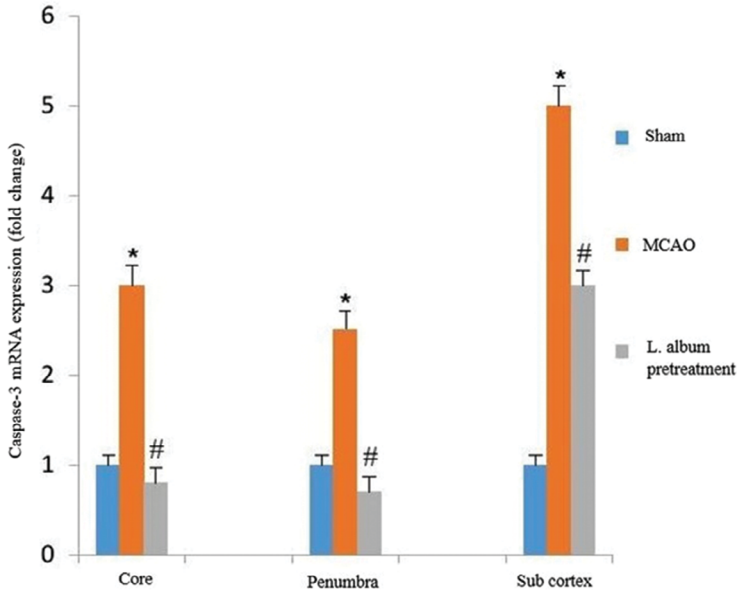

Figure 2. Effect of *L. album* extract on caspase-3 gene expression in core, penumbra, and subcortex. Values are expressed as mean ± SD (n=5). * $p<0.05$ compared with sham group; # $p<0.05$ compared with *L. album* + MCAO group.

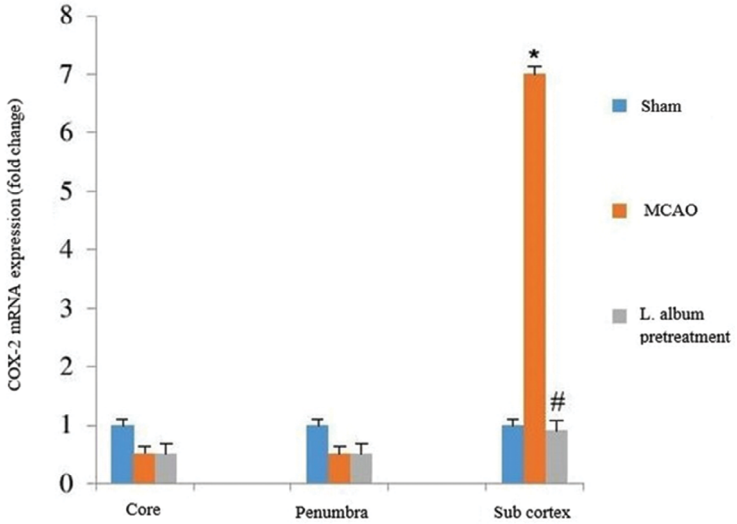

Figure 3. Effect of *L. album* extract on COX-2 gene expression in core, penumbra, and subcortex. Values are expressed as mean ± SD (n=5). * $p<0.05$ compared with sham group; # $p<0.05$ compared with the *L. album* + MCAO group.

L. album, a herbal plant with anti-inflammatory and neuroprotective properties, is used in traditional Chinese medicine to treat various diseases. Its antioxidant compounds include iridoid, kaempferol, and verbascoside, which have been studied for beneficial effects on stroke and neurodegenerative diseases.[11] The extract of this plant has a high percentage of iridoid. In a study conducted by Ya et al., pretreatment with iridoid reduced the expression level of caspase-3, TNFα, as well as improved activity of microglia cells in the ischemic stroke model.[18] It was concluded that *L. album* extract might exert neuroprotective effects by inhibiting the inflammatory and apoptotic pathways.

It was previously documented that caspase-3 could have a fundamental role in the execution phase of programmed cell death. The expression level of this apoptotic marker in cerebral ischemia was increased in penumbra and core regions. Also, the important role of caspase-3 in the progression of lesion extent and behavioural impairment associated with injury was reported. It was determined that neurons were main population undergoing apoptosis 1 h after ischemia.[19,20] In a study performed by Zhang et al., 1 h after MCAO induction, the expression level of caspase-3 in the penumbra region was increased, which was directly associated with motor dysfunction.[21] In the present study, pretreatment with *L. album* decreased the mRNA expression of caspase-3. It was shown that the injury caused by ischemia stimulated microglial cells, and immune cells in brain, which in turn increased the extent of the lesion in part by

releasing inflammatory factors and increasing oxygen free radical levels. These factors could stimulate the apoptotic pathway, which was ultimately associated with increased caspase-3 expression. It seems that antioxidant compounds of *L. album* might have an effective role in controlling stroke in part by reducing caspase-3, ROS, and iNOS.[22,23] Other *Lamiaceae* family such as *Scutellaria Baicalensis* due to having antioxidant properties decreased caspase-3 expression in MCAO model. These herbal extracts partly by reducing caspase expression might be protective against cerebral ischemia and neurodegenerative diseases.[23,24] For further investigation about the potential neuroprotective role of *L. album* extract, the COX-2 expression level following MCAO was measured. The role of COX-2 in important brain functions such as memory consolidation and synaptic activity was proposed. It was shown that brain injury stimulated the COX-2 expression, which could be a cause of cell death.[25] The neurotoxicity mechanism of this enzyme has not been well understood. Superoxide radicals as products of the COX-2 reaction could increase brain tissue damage by nitric oxide.[26] Regarding the role of this marker in neuroinflammation, inhibition of its expression may be an appropriate approach to prevent stroke complications. Im et al. reported that the COX-2 expression level in neurons was increased 12 h and 48 h after cerebral ischemia in the penumbra.[27] But, in the present study, the COX-2 level was increased only in the subcortex, on the other hand, the expression level of COX-2 was decreased in rats pretreated with *L. album* extract. The extract of this plant decreased the expression level of this isoenzyme in other organs. The study of Khanaki et al. demonstrated that *L. album* reduced hepatic tissue injury in diabetic rats to some extent by reducing COX-2 expression.[15] In several previous studies, the beneficial effects of *Lamiaceae* plants on COX-2 expression in cerebral ischemia models were investigated. *Hyptis fruticosa Salzm* belong to this family that showed neuroprotective effects by inhibiting the COX-2 expression.[28]

In this experiment, the effects of *L. album* on the IV and NDS were evaluated. This extract significantly reduced the extent of injury and motor impairment, which may be due to the inhibition of caspase-3 and COX-2 expression in different regions of the brain following cerebral ischemia. It was shown that the ischemic stroke was associated with the production of inflammatory factors such as IL-1β, COX-2, NO, IL-6, and TNF-α.[29] Uncontrolled inflammation can stimulate programmed cell death and progression of injury. Therefore, the management of ischemia at the early stages might prevent the progression of injury and could reduce its complications.[30] In the present study, *L. album* extract reduced the level of caspase-3 in the core, penumbra, and subcortex. Also, this extract inhibited COX-2 expression in the subcortex, alleviated inflammation and reduced cell death, thereby led to a decrease in the extent of lesion and motor impairment.

In the present study, practically all main regions of the rat brain were examined separately. Moreover, the total phenolic and flavonoids contents of *L. album* were evaluated. However, some limitations should be considered: 1) the enzymatic activity of COX-2 and caspase-3 was not evaluated. 2) One dose of this plant extract was utilized.

The potential protective effects of this plant extract against this condition might be in part attributed to its anti-inflammatory activity. Further investigation of the neuroprotective effects of *L. album* on chronic inflammatory processes, microglial cell activity, and adhesion molecules in neurodegenerative diseases is warranted.

CONCLUSIONS

It appears that pretreatment with *L. album* extract may attenuate brain tissue damage after ischemic stroke. The potential protective effects of this plant extract against this condition might be in part attributed to its anti-inflammatory and anti-apoptotic activities, although further studies in this field are needed.

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Conflict of interest

The authors declare that they have no conflict of interest in this study.

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Потенциальный противовоспалительный эффект экстракта *Lamium Album* через экспрессию генов Caspase-3 и Cyclooxygenase-2 в крысиной модели с окклюзией средней мозговой артерии

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Резюме

Введение: Инсульт является одной из наиболее частых причин смерти во всём мире. Воспаление и апоптоз играют важную роль в каскаде ишемического инсульта.

Цель: Цель настоящего исследования заключалась в оценке воздействия экстракта *Lamium album (L. album)* до лечения на экспрессию caspase-3 и cyclooxygenase-2 (COX-2), объём инфаркта и оценку неврологического дефицита в крысиной модели среднего мозга. окклюзия артерии (MCAO).

Материалы и методы: Крысы-самцы линии Wistar были случайным образом разделены на три группы: 1) группа MCAO (через 1 ч после MCAO реперфузию давали в течение 24 ч путём оттягивания нити); 2) группа *L. album* + MCAO [получение экстракта *L. album* (100 мг/кг внутрибрюшинно) за неделю до MCAO]; 3) фиктивная группа. Уровень экспрессии caspase-3 и COX-2 в сердцевине, полутени и подкорке измеряли методом PCR в реальном времени. Также оценивали объём инфаркта и балл неврологического дефицита.

Результаты: Экспрессия мРНК caspase-3 в центральной, полутеневой и подкорковой областях в группе *L. album* была значительно снижена по сравнению с группой MCAO ($p<0.05$). Уровень экспрессии ЦОГ-2 в подкорке крыс, подвергшихся воздействию *L. album*, был статистически снижен по сравнению с группой MCAO ($p<0.05$). Объём инфаркта в сердцевине, полутени и подкорке был значительно уменьшен в группе *L. album* по сравнению с группой MCAO ($p<0.001$, $p<0.001$, $p<0.05$ соответственно). Показатель неврологического дефицита был значительно снижен в группе *L. album* по сравнению с группой MCAO ($p<0.05$).

Заключение: Похоже, что предварительная обработка экстрактом *L. album* может ослабить повреждение тканей головного мозга после ишемического инсульта. Потенциальные защитные эффекты этого растительного экстракта от этого состояния могут быть частично связаны с его противовоспалительной и антиапоптотической активностью.

Ключевые слова

caspase-3, cyclooxygenase-2, *Lamium album*, инсульт