Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

MiR-211 represses apoptosis of nerve cells in rats with cerebral infarction through PI3K/AKT signaling pathway

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ARTICLE INFO

Original paper

Article history:
Received: June 28, 2023
Accepted: November 09, 2023
Published: November 30, 2023

Keywords:

miR-211, cerebral infarction, PI3K/AKT signaling pathway, apoptosis

ABSTRACT

To investigate the effect of micro ribonucleic acid (miR)-211 on the apoptosis of nerve cells in rats with cerebral infarction through phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, a total of 36 Sprague-Dawley (SD) rats were randomly divided into sham operation group (n=12), model group (n=12) and miR-211 mimics group (n=12). Only the common carotid artery, external carotid artery, and internal carotid artery were exposed in the sham operation group, and the models of cerebral infarction were constructed *via* the suture method in the other two groups. After modeling, the rats in the sham operation group and model group were intraperitoneally injected with normal saline, while those in the miR-211 mimics group were given miR-211 mimics *via* intraperitoneal injection. At 2 weeks after the intervention, samples were collected. Neurological deficit in rats was assessed using the Zea-longa score, and a Nissl staining assay was performed to observe neuronal morphology. Western blotting (WB), quantitative polymerase chain reaction (qPCR) assay and enzyme-linked immunosorbent assay (ELISA) were employed to measure the relative protein expressions of PI3K and phosphorylated AKT (p-AKT), mRNA expression of miR-211 and content of B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X protein (Bax), respectively. Additionally, the apoptosis was detected *via* terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end labeling (TUNEL) assay. The neuronal morphology was normal in the sham operation group, while it was disordered in the model group, with damaged neurons. In the miR-211 mimics group, the morphology of neurons was improved. The Zea-longa score was higher in the model group and miR-211 mimics group than that in the sham operation group (P<0.05), while it was notably lower in the miR-211 mimics group than that in the model group (P<0.05). Compared with those in sham operation group, the relative protein expression levels of PI3K and p-AKT remarkably declined in model group and miR-211 mimics group (P<0.05), whereas they were clearly higher in miR-211 mimics group than those in model group (P<0.05). The relative expression level of miR-211 was lower in model group and miR-211 mimics group than that in sham operation group (P<0.05), while it was markedly higher in miR-211 mimics group than that in model group (P<0.05). In comparison with sham operation group, model group and miR-211 mimics group had remarkably increased content of Bax and lowered content of Bcl-2 (P<0.05), whereas compared with model group, miR-211 mimics group displayed reduced Bax content and notably raised Bcl-2 content (P<0.05). The apoptosis rate was distinctly higher in model group and miR-211 mimics group than that in sham operation group (P<0.05), while it was visibly lower in miR-211 mimics group than in model group (P<0.05). MiR-211 represses the apoptosis of nerve cells in rats with cerebral infarction by up-regulating the PI3K/AKT signaling pathway, thereby protecting nerves.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.12.24 Copyright: © 2023 by the C.M.B. Association. All rights reserved.

Introduction

Cerebral infarction, a very common cardiovascular and cerebrovascular disease in clinical practice, refers to damage to a large number of brain tissues and neurons caused by the pathological states of ischemia and hypoxia in brain tissues often due to dramatically reduced blood flow to the brain because of the occlusion of blood vessels to the brain (1, 2). Besides, cerebral infarction is one of the most common cardiovascular and cerebrovascular diseases in the elderly and also one of the important causes of vascular dementia, limb dysfunction and death in the elderly.

Its pathological responses are relatively complicated, mainly including inflammation, lipid peroxidation, overproduction of oxygen free radicals and excessive oxidative stress response in brain tissues and neurons due to ischemia, hypoxia and ischemia-reperfusion injury (3-5). These pathological responses can further lead to excessive apoptosis of brain neurons, resulting in changes in the normal physiological functions of the brain and affecting the movement and sensory functions of limbs, which are not conducive to neuron repair and regeneration after cerebral infarction.

The phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (AKT) signaling pathway, an important anti-apoptotic signaling pathway in the body, plays a good regulatory role in many pathological responses including apop-

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tosis. Studies have manifested that under physiological conditions, the PI3K/AKT signaling pathway is activated and thus inhibits the occurrence of excessive apoptosis, keeping apoptosis and anti-apoptosis balanced (6, 7). Micro ribonucleic acid (miR)-211, a member of the miRNA family in the body, has been proven to be involved in various physiological and pathological responses including apoptosis, and its expression level has an important effect on cerebral infarction (8-10). This study, therefore, aims to explore the effect of miR-211 on the apoptosis of nerve cells in rats with cerebral infarction through the PI3K/AKT signaling pathway.

Materials and Methods

Laboratory animals

A total of 36 Specific Pathogen Free (SPF) Sprague-Dawley (SD) rats aged 1 month old were purchased from Shanghai SLAC Laboratory Animal Co., Ltd., with license No. of SCXK (Shanghai, China) 2014-0003, and then fed with normal feed and sterile filtered water in a laboratory animal center with the light/dark cycle of 12 h/12 h and normal room temperature and humidity. This study was approved by the Animal Ethics Committee of Changchun University of Traditional Chinese Medicine Animal Center.

Experimental reagents and instruments

MiR-211 mimics (MCE, Monmouth Junction, NJ, USA), anti-PI3K and anti-phosphorylated AKT (p-AKT) primary antibodies and secondary antibodies (Abcam, Cambridge, MA, USA), Nissl and enzyme-linked immunosorbent assay (ELISA) kits (Beyotime, Shanghai, China), kits for terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end labeling (TUNEL) apoptosis assay and quantitative polymerase chain reaction (qPCR) (Vazyme, Nanjing, China), a fluorescence qPCR instrument (ABI, Applied Biosystems, Foster City, CA, USA), and a light microscope (Leica, Wetzlar, Germany).

Animal grouping and treatment

The 36 SD rats were divided into sham operation group (n=12), model group (n=12) and miR-211 mimics group (n=12) using a random number table, and then adaptively fed in the laboratory animal center for 7 d before experiments.

In sham operation group, only the common carotid artery, external carotid artery, and internal carotid artery were exposed, without blocking of the blood vessels, and after the operation, the rats were intraperitoneally injected with the same volume of normal saline. In the model group, the models of cerebral infarction were established and then (after the operation) intraperitoneally injected with normal saline. In the miR-211 mimics group, the rats were prepared into models of cerebral infarction and then (after the operation) intraperitoneally injected with 3 μM miR-211 mimics daily. Samples were collected after 14 consecutive d of intervention.

Modeling

The rats were anesthetized with 3% pentobarbital sodium solution *via* intraperitoneal injection at a dose of 5 mL/kg. After successful anesthesia, the rats were fixed in the supine position, and the neck was depilated, disinfected, and covered with a sterile towel. Then, a longitudinal incision (about 2 cm in length) was made in the front midline of the neck of rats to carefully separate and expose the common, external and internal carotid arteries. Next, the common and external carotid arteries were ligated with a silk thread, and the internal carotid artery was clamped with vessel forceps. After that, a suture line was inserted from the ligation site of the common carotid artery and slowly pushed into the branch of the middle cerebral artery after releasing the vessel forceps on the internal carotid artery. Thereafter, the internal carotid artery was ligated again, and the suture line was fixed. Afterward, the incision was rinsed with normal saline and sutured. 90 min later, the suture line was slowly drawn out.

Collection of samples

The rats were anesthetized by intraperitoneal injection of 3% pentobarbital sodium solution at a dose of 5 mL/kg. After successful anesthesia, samples were directly collected from 6 rats in each group, rinsed with normal saline, put into Eppendorf (EP) tubes and stored at -80°C for later use. Besides, for the remaining 6 rats, samples were collected through perfusion fixation. In other words, their chest cavity was cut open to expose the heart. Then, 400 mL of 4% paraformaldehyde was first infused into the heart from the left atrial appendage. Finally, the brain tissues were taken out and fixed in a 4% paraformaldehyde solution.

Zea-longa scoring

After 2 weeks of intervention, the symptoms and performance of each rat were independently evaluated by two researchers familiar with the Zea-longa scoring method in an open field using the Zea-longa scoring scale, so as to assess the neurological deficit of rats.

Nissl staining assay

The prepared paraffin-embedded tissues were made into sections (5 μm in thickness), put in 42°C warm water for spreading, collected using slides, baked, and prepared into paraffin tissue sections. Next, the paraffin tissue sections were sequentially soaked in xylene solution and graded ethanol for conventional deparaffinization and hydration. Afterward, the Nissl staining kits were used. The sections were firstly stained with hematoxylin for 5 min, soaked in pure water for 10 min, put in 95% ethanol for color separation for 5 s, permeabilized with xylene for 10 s, and mounted with neutral gum.

Western blotting (WB)

The cryopreserved brain tissues were added with lysis buffer, followed by an ice bath for 1 h and then centrifugation at 14,000 g for 10 min using a centrifuge. Next, the proteins were quantified *via* the bicinchoninic acid (BCA) method (Pierce, Rockford, IL, USA), and the protein concentration was calculated based on the absorbance values and standard curves obtained by a microplate reader. Thereafter, the proteins were denatured and separated through sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) during which the position of the Marker proteins was observed. When the Marker proteins were in a straight line at the bottom of the glass plate, the separation was stopped. Then, the proteins were trans-

Table 1. Primer sequences.

Name	Primer sequence
MiR-211	Forward primer: 5' GGATGGATTTAACCAGACGATT 3' Reverse primer: 5' CCCATTGGGACAGCTTGGATAT 3'
GAPDH	Forward primer: 5' ACGGCAAGTTCAACGGCACAG 3' Reverse primer: 5' GAAGACGCCAGTAGACTCCACGAC 3'

ferred onto a polyvinylidene fluoride (PVDF) membrane (Roche, Basel, Switzerland), and added with blocking solution for 1.5 h of reaction and incubated with anti-PI3K primary antibody (1:1000), anti-p-AKT primary antibody and (1:1000) and secondary antibody (1:1000) sequentially. After that, the membrane was rinsed and added with a chemiluminescent reagent for full development for 1 min in a dark place.

QPCR assay

The fresh brain tissues were added to the RNA extraction reagent for extraction of total RNAs. Next, the total RNAs extracted were reversely transcribed into complementary deoxyribose nucleic acids (cDNAs) using a reverse transcription kit. Then, a 20 μL system was designed for reaction under the following conditions: reaction at 53°C for 5 min, pre-denaturation at 95°C for 10 min, denaturation at 95°C for 10 s, and annealing at 62°C for 30 s, for 35 cycles. ΔCt value was calculated first, and then the difference in the expression of target genes was calculated. The primer sequences are shown in Table 1.

Detection of B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X protein (Bax) content in brain tissues through ELISA

The fresh tissues collected were minced. Then, ELISA was performed in accordance with the instructions of the ELISA kit: the samples were loaded and added with standard substance, biotinylated antibody working solution and enzyme conjugate working solution, followed by washing of the plate. Lastly, the microplate reader was utilized for detection at 450 nm.

TUNEL assay

The prepared paraffin-embedded tissues were made into sections (5 μm in thickness), put in 42°C warm water for spreading, collected using slides, baked, and prepared into paraffin tissue sections. Next, the paraffin tissue sections were sequentially soaked in xylene solution and graded ethanol for conventional deparaffinization and hydration. Afterward, the apoptosis in brain tissues was determined using the TUNEL apoptosis kit as per the instructions.

Statistical analysis

In this study, Statistical Product and Service Solutions (SPSS) 20.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Measurement data were expressed as mean ± standard deviation. *t*-test was utilized for data in line with normal distribution and homogeneity of variance, corrected *t*-test for those conforming to normal distribution and heterogeneity of variance, and non-parametric test for those not in line with normal distribution and homogeneity of variance. The rank sum test was applied for ranked data. For enumeration data, a chi-square test was employed.

Results

Zea-longa score

As shown in Figure 1, the Zea-longa score was obviously higher in the model group and miR-211 mimics group than that in the sham operation group, showing statistically significant differences ($p<0.05$), while it was notably lower in the miR-211 mimics group than that in the model group, with a statistically significant difference (P<0.05).

Neuronal morphology observed via Nissl staining assay

The neurons in the sham operation group had a complete structure and normal morphology, with more and full Nissl bodies. In the model group, the neurons were damaged, with disordered morphology, and Nissl bodies were less and splintery. In the miR-211 mimics group, the neuronal morphology was notably improved, and the neuronal structure was damaged, with more Nissl bodies.

Relative protein expression levels measured through WB

The PI3K and p-AKT protein expressions were higher in the sham operation group and lower in the model group (Figure 2A). The statistical results (Figure 2B) revealed that compared with the sham operation group, the model group and miR-211 mimics group displayed remarkably declined relative protein expression levels of PI3K and p-AKT, and the differences were statistically significant (P<0.05). Besides, the miR-211 mimics group exhibited clearly raised relative protein expression levels of PI3K and p-AKT in comparison with the model group, with statistically significant differences (P<0.05).

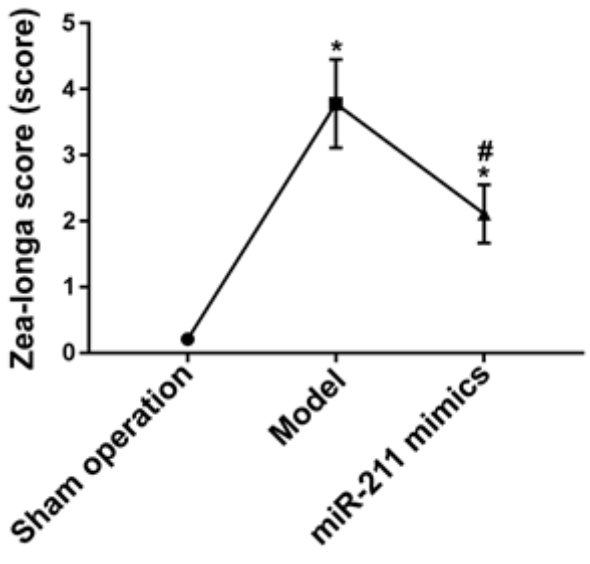

Figure 1. Zea-longa score in each group. Note: *P<0.05 *vs.* sham operation group, # P<0.05 *vs.* model group.

MRNA expression level measured by qPCR

The relative expression level of miR-211 was obviously lower in the model group and miR-211 mimics group than those in the sham operation group, displaying statistically significant differences (P<0.05), whereas it was significantly higher in miR-211 mimics group than that in the model group, and the difference was statistically significant (P<0.05) (Figure 3).

Results of ELISA

Compared with those in the sham operation group, the content of Bax evidently rose in the model group and miR-211 mimics group and that of Bcl-2 clearly declined in model group and miR-211 mimics group, and the differences were of statistical significance (P<0.05). The content of Bax was remarkably lower in the miR-211 mimics group than that in the model group, and that of Bcl-2 was markedly higher in the miR-211 mimics group than that in the model group, and the differences were statistically significant (P<0.05) (Figure 4).

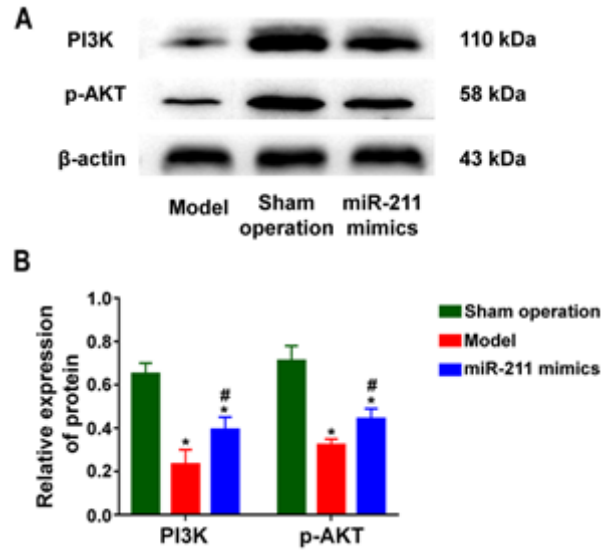

Figure 2. Protein expressions determined *via* WB. Note: (A) WB results and (B) relative protein expression levels in each group. *P<0.05 *vs.* sham operation group, #P<0.05 *vs.* model group.

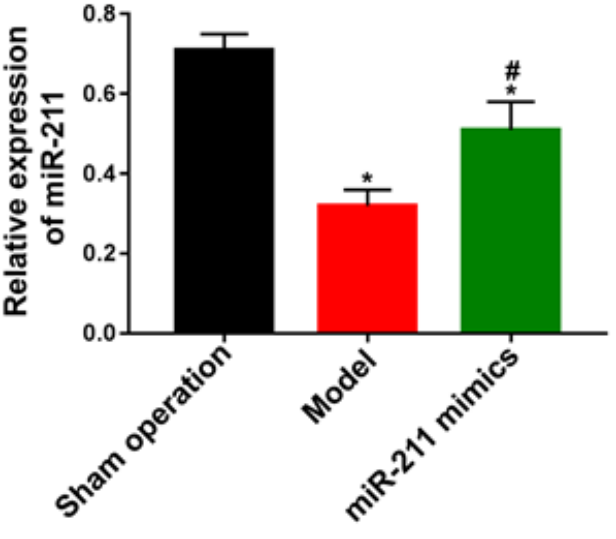

Figure 3. Relative expression level of miR-211 in each group. Note: *P<0.05 *vs.* sham operation group, #P<0.05 *vs.* model group.

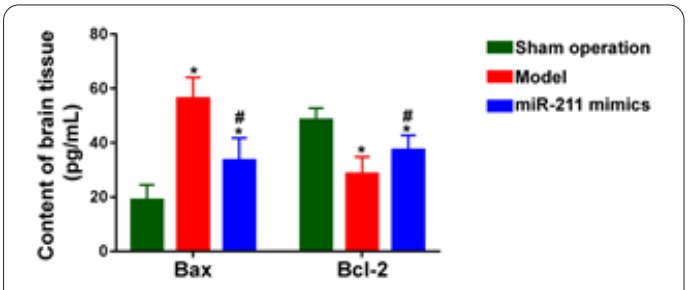

Figure 4. Content of Bcl-2 and Bax in each group. Note: *P<0.05 *vs.* sham operation group, #P<0.05 *vs.* model group.

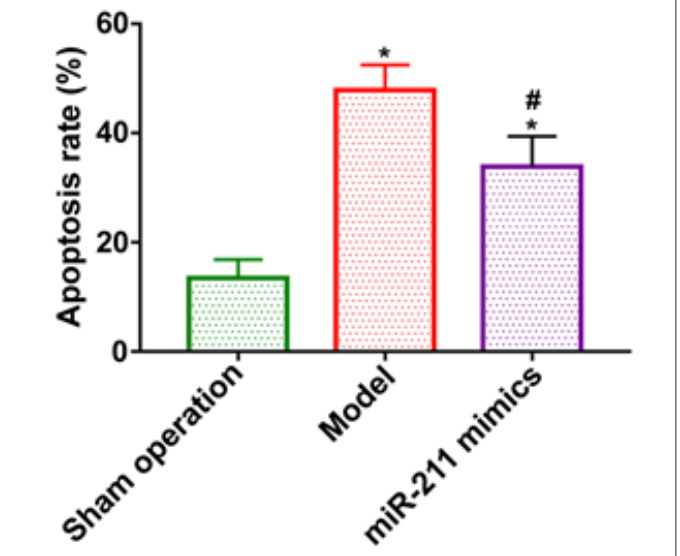

Figure 5. Apoptosis detected *via* TUNEL assay. The apoptosis rate of cells in each group. *P<0.05 *vs.* sham operation group, #P<0.05 *vs.* model group.

Apoptosis detected via TUNEL assay

The apoptotic cells were fewer in the sham operation group and more in the model group. The apoptosis rate was obviously higher in the model group and miR-211 mimics group than that in the sham operation group, showing statistically significant differences (P<0.05), while it was notably lower in the miR-211 mimics group than that in the model group, with a statistically significant difference (P<0.05) (Figure 5).

Discussion

With the improvement of living standards and the acceleration of the pace of life of people, cerebral infarction has increased incidence and mortality rates and has become one of the major cardiovascular and cerebrovascular diseases endangering the quality of life, life and health of the elderly (11, 12). The greatest hazard of cerebral infarction is that it leads to hypoxia, ischemia and ischemia-reperfusion injury in brain tissues, as well as the loss of a large number of brain neurons, affecting the normal physiological functions of the brain, thus resulting in vascular dementia, memory loss, cognitive dysfunction, physical sensory and motor dysfunction of limbs, and even death in patients. For this reason, effectively preventing cerebral infarction and improving the recovery of the damaged nervous system and neurological function after cerebral infarction are crucial, which are conducive to the improvement of limb sensory and motor functions in patients with

cerebral infarction, thereby significantly improving their quality of life and reducing the financial burden of patients' families and the society. The pathological responses and mechanisms of cerebral infarction are very complex. Ischemic and hypoxic changes caused by a sharp decrease in blood supply to the brain, as well as ischemia-reperfusion injury, are able to induce such pathological responses as excessive inflammation of brain tissues, release of oxygen free radicals in quantity, and excessive oxidative stress and lipid peroxidation responses. These pathological responses further damage brain neurons, resulting in apoptosis, necrosis and even autophagy of a large number of brain neurons. As a result, the brain nervous system is damaged, normal physiological functions are destroyed, and tissue damage after cerebral infarction is exacerbated, which is not conducive to neuron repair and regeneration after injury. Hence, excessive apoptosis of nerve cells is considered as one of the important pathological responses and processes after cerebral infarction (13, 14). Studies have denoted that in the case of cerebral infarction, ischemia and hypoxia in local brain tissues can lead to the production of lots of inflammatory factors and cytokines therein, and these substances are capable of inducing abnormal expression of molecules closely related to apoptosis, such as Bax and Bcl-2, and promoting the apoptosis of a large number of neurons (15, 16). The PI3K/AKT signaling pathway, an important cell signal transduction pathway, has been confirmed to play a vital regulatory role in the physiological and pathological processes including the proliferation, differentiation, apoptosis and necrosis of cells. Studies have demonstrated that under physiological conditions, PI3K, the key molecule in the PI3K/AKT signaling pathway, stays at a high expression level, leading to a high level of p-AKT to maintain the activation of this signaling pathway. In addition, the PI3K/AKT signaling pathway has a good anti-apoptotic effect. Activation of such a signaling pathway increases the content of anti-apoptotic Bcl-2 and decreases the content of pro-apoptotic Bax, thereby maintaining the balance between apoptosis and anti-apoptosis. Therefore, from the perspective of the PI3K/AKT signaling pathway, inhibiting the apoptosis of a large number of nerve cells can further protect neurons after cerebral infarction, helping repair the nervous system after cerebral infarction (17, 18). In this study, it was confirmed that the levels of PI3K, the key molecule in the PI3K/AKT signaling pathway, and p-AKT were reduced in brain tissues of rats with cerebral infarction, indicating that the PI3K/AKT signaling pathway is suppressed in the pathological processes of cerebral infarction, which may be one of the major causes of apoptosis of a large number of neurons due to raised pro-apoptotic Bax content and lowered anti-apoptotic Bcl-2 content in brain tissues of rats with cerebral infarction, affecting the recovery of neurological function in rats with cerebral infarction.

Further research has reported that miR-211, a major member of the miRNA family, exerts an important regulatory effect on many downstream signaling pathways. Moreover, studies have manifested that miR-211 plays a crucial regulatory role in the physiological and pathological processes such as the proliferation, apoptosis, differentiation and autophagy of cells (19-22). The results of this study uncovered that miR-211 mimics significantly relieved neurological deficits in rats with cerebral infarction, increased the expression of PI3K, and maintained the level of p-AKT, implying that miR-211 facilitates the PI3K/AKT signaling pathway, which may be one of the important causes of inhibited neuronal apoptosis due to reduced Bax content and increased Bcl-2 content.

Conclusions

Therefore, it can be concluded that miR-211 up-regulates the PI3K/AKT signaling pathway to impede the apoptosis of nerve cells in rats with cerebral infarction, thus exerting a neuroprotective effect.

Conflict of Interest

The authors declared no conflict of interest.

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