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ORIGINAL RESEARCH

Syringaresinol mitigates cerebral ischemia-induced brain injury via NF-κB pathway inhibition and glial cell deactivation

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Abstract

Background: It is vital to clarify the pathogenesis and develop new effective therapies for the treatment of cerebral ischemia-reperfusion injury (CIRI). Syringaresinol (Syr), a furan lignan found in various medicinal herbs, may play a significant role in the treatment of CIRI. This study aims to investigate the effects of Syr on the progression of CIRI and to uncover the underlying mechanisms involved. **Methods**: A middle cerebral artery occlusion (MCAO) mouse model was developed to investigate CIRI. Mice were administered Syr at concentrations of 20 mg/kg and 40 mg/kg for 48 hours. The effects of Syr on cerebral infarction in the mice were evaluated using 2,3,5-triphenyltetrazolium chloride (TTC) assays. Immunostaining was conducted to detect Ionized calcium-binding adapter molecule 1 (Iba1) and glial fibrillary acidic protein (GFAP), while enzyme-linked immunosorbent assays (ELISA) were utilized to quantify levels of Interleukin (IL)-1β, Tumor Necrosis Factor (TNF)-α, IL-10 and IL-6. Furthermore, Terminal Deoxynucleotidyl Transferase (TdT)-mediated 2′-deoxyuridine 5′-triphosphate (dUTP) nick end labeling (TUNEL) assays were performed to assess the effects on the activation of cerebral glial cells, inflammation, and apoptosis in the brain tissues of Middle Cerebral Artery Occlusion Model (MCAO) mice. Immunoblotting was further performed to confirm the mechanism. **Results**: Syr was found to alleviate cerebral infarction in MCAO mice. Additionally, it reduces the activation of cerebral glial cells in these models. Our findings further demonstrate that Syr decreases inflammation within the brain tissues of MCAO mice. It also inhibits apoptosis in these tissues. Mechanistically, Syr suppresses the Nuclear Factor kappa-B (NF-κB) pathway, thereby alleviating CIRI. **Conclusions**: In summary, Syr mitigates CIRI by blocking glial activation and inhibiting the inflammatory response.

Keywords

Cerebral ischemia-reperfusion injury (CIRI); Syringaresinol; Cerebral infarction; Apoptosis; NF-κB pathway

1. Introduction

The brain is particularly vulnerable to ischemia and hypoxia, making ischemic cerebrovascular disease the second leading cause of death among various health conditions [1]. Treatment often involves methods such as mechanical thrombectomy and intravenous infusion of plasminogen activators, which aim to restore blood supply to the compromised brain tissues [2]. However, secondary damage that affects brain function after reperfusion, clinically known as cerebral ischemia-reperfusion injury (CIRI), remains a significant challenge. CIRI is a complex pathophysiological process characterized by the loss of intracellular calcium homeostasis, the generation of free radicals and the activation of apoptotic genes [3]. These interconnected processes contribute to a vicious cycle that ultimately results in cell apoptosis or necrosis. However, the exact mechanism underlying CIRI is still not fully understood. Therefore, it is essential to elucidate its pathogenesis and to develop new, effective therapeutic drugs for treating CIRI.

Syringaresinol is a furan lignan found in various medicinal herbs [4]. It possesses anti-inflammatory and antioxidant properties when derived from plant sources. Syr directly influences microglia and macrophages, facilitating the production of nitric oxide (NO) and related proteins, such as inducible nitric oxide synthase (iNOS). Additionally, it downregulates inflammatory signaling pathways [5]. Syr effectively alleviates neuropathic pain symptoms caused by oxaliplatin by modulating the inflammatory response of microglia in the spinal cord [6]. It also protects against acute lung injury associated with septicemia by inhibiting pyrodeath through the estrogen receptor-β signaling pathway. Additionally, Syr

reduces the phosphorylation levels of Nuclear Factor kappa-B (NF-κB), extracellular regulated protein kinases (ERK), c-Jun N-terminal kinase (JNK) and p38 [7]. Moreover, it significantly improves cardiac and renal function and fibrosis in rats [8]. Syr alleviates osteoarthritis by regulating the NF-κB pathway [9]. It prevents damage and death of cardiomyocytes caused by hypoxia/reoxygenation. However, the role of Syr in CIRI remains unclear.

CIRI results in a range of pathological processes, including cell damage (such as apoptosis, necrosis and ferroptosis), oxidative stress, inflammatory responses, disruption of the blood-brain barrier (BBB), remodeling of the extracellular matrix (ECM), angiogenesis, cardiomyocyte hypertrophy and fibrosis [10]. Key signaling pathways involved in these processes include Notch, Phosphatidylinositol 3-kinase/Protein kinase B (PI3K/Akt), Hypoxia-inducible factor-1 (HIF-1) and Wingless-Type MMTV Integration Site Family (Wnt). Importantly, NF-κB is a significant transcriptional regulator in cells, playing a crucial role in gene expression [10]. A thorough understanding of NF-κB's role in CIRI can provide new directions for research into its prevention and treatment. As a transcription factor, NF-κB is essential for cell survival and inflammation, and it can mediate the production of various pro-inflammatory proteins in astrocytes [11, 12]. Furthermore, selective inhibition of NF-κB can suppress astrocyte activation, down-regulate chemokines released by these cells, and reduce the infiltration of macrophages and T cells, ultimately decreasing secondary inflammatory damage [13].

In this study, we investigate the potential effects and mechanisms of Syr on CIRI. Our findings suggest that Syr alleviates CIRI by inhibiting the NF-κB pathway and deactivating glial cells. These findings position Syr as a promising therapeutic agent for the management of CIRI.

2. Materials and methods

2.1 Middle cerebral artery occlusion (MCAO) model construction

Male C57BL/6 mice (10–12 weeks) from the SLAC Animal Center (Shanghai, China) were housed at 22 °C in the animal feeding room of the Laboratory Animal Center of Nanchong Central Hospital. The mice were kept for one week after being moved to the feeding room. All animals had a chow diet and water freely before surgery. All experimental protocols were carried out under the approval of the People's Hospital of Xinjiang Uygur Autonomous Region (Approve number: SYDW2023052301). For MCAO surgery, mice were anesthetized by intraperitoneal injection of pentobarbital sodium (20 mg/kg). To perform the occlusion of the origin of the middle cerebral artery, a nylon microfilament was inserted into the internal carotid artery and established reperfusion after ischemia for 90 min [3]. Mice were separated into 4 groups (n = 6): (1) sham, (2) MCAO, (3) MCAO + Syr (20 mg/kg in Dimethyl sulfoxide, DMSO), (4) MCAO + Syr (40 mg/kg in DMSO) for 48 h according to the previous study [8]. Syr was bought from MCE (HY-N8307, Princeton, NJ, USA) and given by intraperitoneal injection [9]. The mice were sacrificed by cervical dislocation. The successful construction of the MCAO model was evaluated manually using the neurological deficit score and histological analysis using ImageJ (USA).

2.2 Neurological deficit score

The neurological deficit score was given according to the previous study [3] after the MCAO model construction: 0, no significant neurological defect; 1, slight neurological deficit, unable to fully extend contralateral forelimbs; 2, medium focal neurologic impairment with contralateral circling; 3, severe focal neurological dysfunction; 4, unconsciousness.

2.3 TTC (2,3,5-triphenyltetrazolium chloride) staining

After reperfusion, the brain tissue was sliced by frozen optimal cutting temperature compound (OCT) embedding and cut into 5 sections with 1 mm between each section. Brain sections were stained with 1% TTC solution and protected from light. The brain tissue samples were embedded in paraffin wax. The infarct tissues cannot be stained, and normal tissues were stained with red. Representative pictures were obtained and were manually quantified with ImageJ software.

2.4 Immunofluorescence staining

The brain tissues were dehydrated, fixed and embedded and then were sliced into 25 μm sections. Then, the sections were blocked with goat serum for one hour. The sections were further incubated with primary antibodies targeting Ionized calcium-binding adapter molecule 1 (Iba1) (ab178847, Abcam, Cambridge, UK) and glial fibrillary acidic protein (GFAP) (ab7260, Abcam, Cambridge, UK) at 4 °C overnight. After washing with Phosphate Buffered Saline (PBS), the sections were stained with secondary antibodies (488 or 555 secondary antibodies, ab150077 and 150078, Abcam, Cambridge, UK) for 1 h. Finally, the sections were blocked with anti-quenching agents and followed by capture with a confocal fluorescence microscope [3].

2.5 ELISA

The blood samples were collected before the end of the MCAO experiment. The serum levels of IL-1β (ab197742), TNF-α (ab208348), IL-10 (ab255729) and IL-6 (ab222503) were detected with ELISA kit (Abcam, Cambridge, UK) under the manufacturer's guidelines and previous study [9]. The intensity in each well was detected with a microplate reader.

2.6 TUNEL and immuno-staining

Sliced sections were treated with 20 mg/mL proteinase K at 37 °C for 10 minutes. Slices were incubated with a TUNEL reaction mixture or NeuN antibody (Abcam, Cambridge, UK, ab177487, 1:200) at 37 °C in humidified conditions with 4′,6-diamidino-2-phenylindole (DAPI) staining. Each image was evaluated, photographed with a confocal microscope, and manually analyzed with ImageJ (USA).

2.7 Western blotting

The sample was isolated from the infarct region and lysed for protein extraction. The extracted proteins were quantitated, separated by Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE), and transferred to the Polyvinylidene Fluoride (PVDF) membrane. The membranes were cultured with 5% BSA for 1 hour. Then, the membranes were incubated with primary antibodies at 4 ℃ overnight. Primary antibodies targeting p-p65 (ab76302, Abcam, Cambridge, UK, 1:1000), p65 (ab32536, Abcam, Cambridge, UK, 1:1000), p-IκBα (ab133462, Abcam, Cambridge, UK, 1:1000), IκBα (ab32518, Abcam, Cambridge, UK, 1:1000) and β-actin (ab8226, Abcam, Cambridge, UK, 1:1000) were incubated with membranes. Then, secondary antibodies were added to the membranes for 1 h, imaged after chemiluminescence, and analyzed manually with ImageJ (USA).

2.8 Statistics

GraphPad software was used to perform the statistical analysis. Data were represented as mean ± Standard Deviation (SD). One-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test determined the statistical differences between different groups. Shapiro-Wilk test was used to test the normality of the data in this study. Data that do not exhibit a normal/Gaussian distribution was analyzed via a non-parametric equivalent. Each experiment was repeated 3 times. $p < 0.05$ was considered statistically significant.

3. Results

3.1 Syr alleviates cerebral infarction in MCAO mice

A MCAO mice model was constructed to examine Syr's effects on cerebral infarction, and neurological deficit scores were evaluated. As illustrated in Fig. 1A, there was a statistically significant increase in neurological deficit scores following the establishment of the MCAO model. Notably, treatment with Syr improved these deficit scores in a dose-dependent manner. The size of the brain infarction was assessed using TTC staining, allowing for quantification of the infarct area (Fig. 1B). The MCAO group displayed a larger infarction size; however, Syr treatment markedly reduced the area of infarction induced by MCAO (Fig. 1B). These results demonstrate that Syr alleviates cerebral infarction in MCAO mice.

3.2 Syr alleviates the activation of cerebral glial cells in MCAO mice

To investigate the activation of cerebral glial cells in this model, we assessed the number of glial cells in the different groups using immunofluorescence. As illustrated in (Fig. 2A,B), the MCAO group showed increased Iba1 (microglia) and GFAP (astrocyte)-positive mice. Conversely, treatment with Syr significantly reduced the number of Iba1 and GFAP-positive mice. This suggests that Syr alleviates the activation of cerebral glial cells in MCAO mice.

3.3 Syr alleviates inflammation in MCAO mice

The serum concentrations of inflammatory cytokines were significantly elevated in the MCAO group compared to the sham group. Treatment with Syr significantly decreased the levels of IL-1β, IL-6 and TNF-α while substantially increasing the level of IL-10 (Fig. 3). In conclusion, our findings suggest that Syr effectively alleviates inflammation in MCAO mice.

3.4 Syr alleviates brain cell apoptosis in MCAO mice

Given the increased infarction size in the MCAO group and the reduction in infarction area following Syr treatment, we analyzed the type of cell death in these groups. We calculated the number of TUNEL-positive cells for each group. The MCAO group exhibited a significant rise in neuron cells (NeuN positive) with TUNEL staining. In contrast, treatment with Syr led to a decrease in TUNEL-positive cells, indicating a protective role of Syr against brain cell apoptosis (Fig. 4).

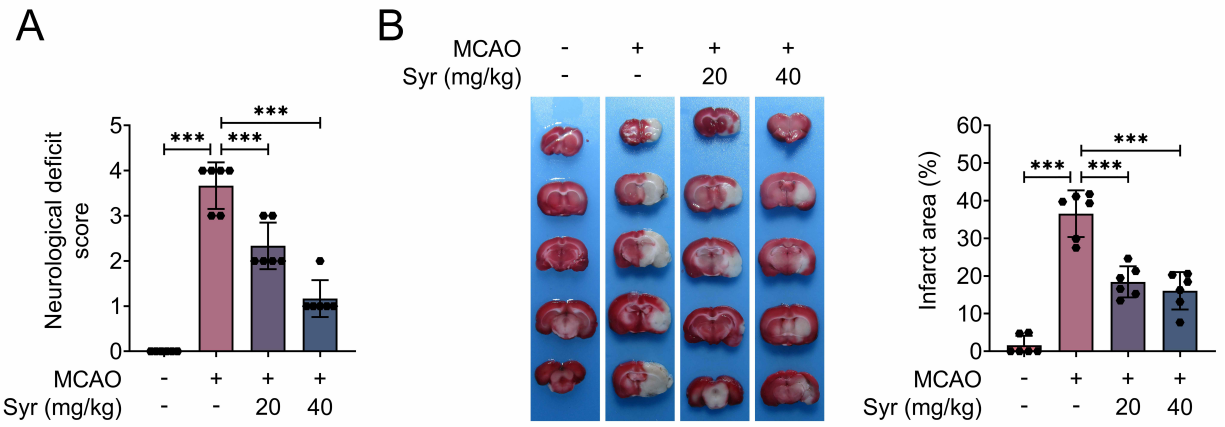

FIGURE 1. Syringaresinol alleviates cerebral infarction in MCAO mice. (A) The Neurological deficit score in the brain tissues from the sham, MCAO, MCAO + Syr (20 mg/kg), MCAO + Syr (40 mg/kg) groups. (B) The TTC staining of normal sham, MCAO, MCAO + Syr (20 mg/kg), MCAO + Syr (40 mg/kg) groups. The quantification has been conducted. ***$p <$ 0.001. Syr: Syringaresinol, MCAO: Middle cerebral artery occlusion.

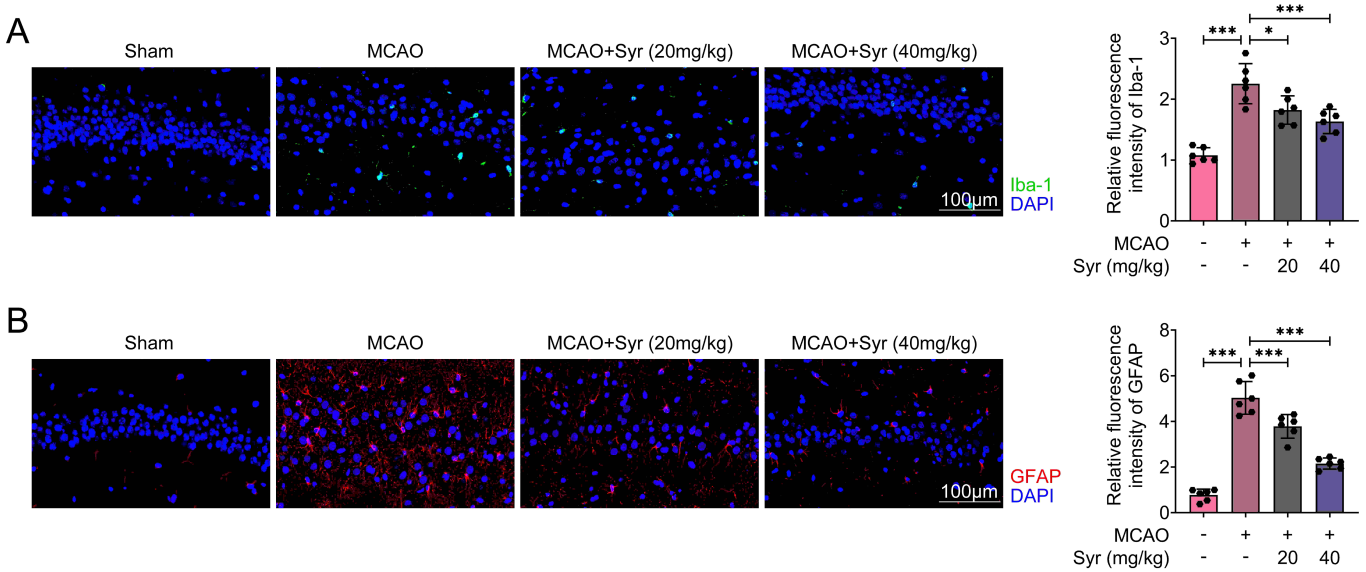

FIGURE 2. Syringaresinol alleviates the activation of cerebral glial cells in MCAO mice. (A,B) Immunostaining assays showed Iba1 and GFAP staining in the brain tissues from sham, MCAO, MCAO + Syr (20 mg/kg), MCAO + Syr (40 mg/kg) groups. The quantification has been conducted. $*p < 0.05$, $***p < 0.001$. Syr: Syringaresinol; MCAO: Middle cerebral artery occlusion; Iba1: Ionized calcium-binding adapter molecule 1; DAPI: 4′,6-diamidino-2-phenylindole; GFAP: glial fibrillary acidic protein.

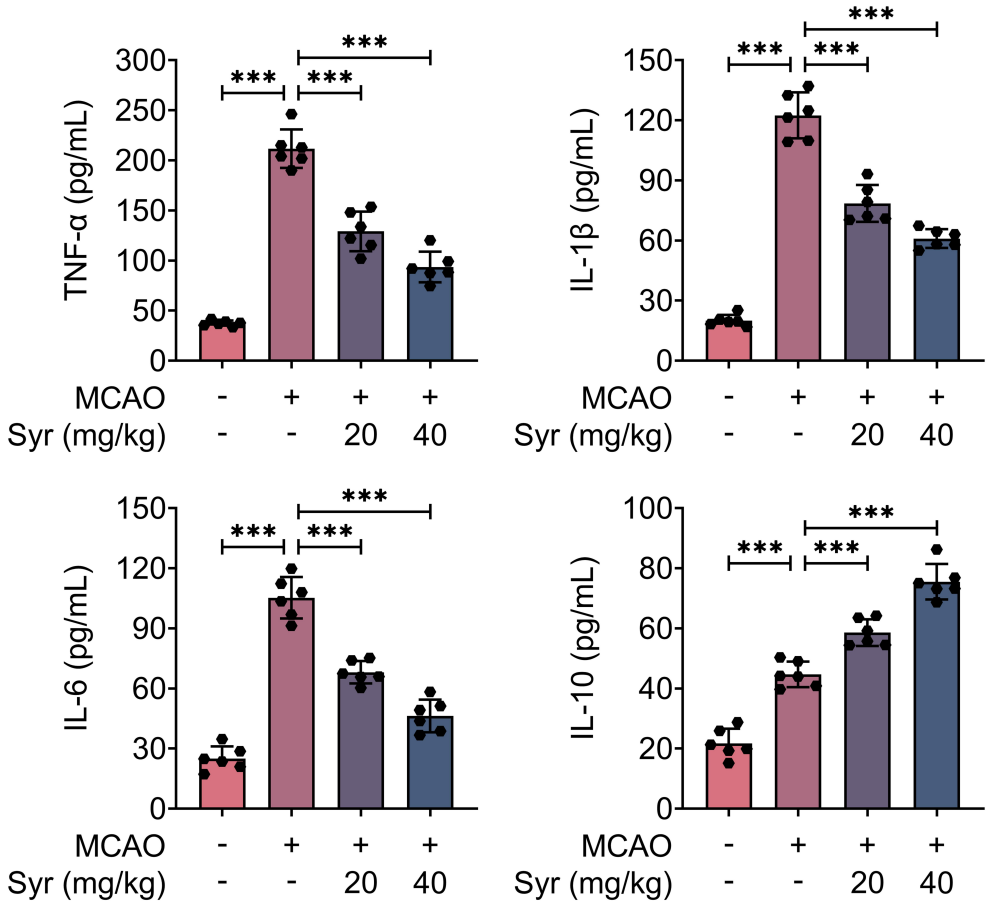

FIGURE 3. Syringaresinol alleviates inflammation in MCAO mice. The secretion of IL-6, IL-10, IL-1β and TNF-α level in the serum from sham, MCAO, MCAO + Syr (20 mg/kg), MCAO + Syr (40 mg/kg) groups were assessed by ELISA kit. $***p < 0.001$. Syr: Syringaresinol; MCAO: Middle cerebral artery occlusion; IL: Interleukin; TNF-α: Tumor Necrosis Factor-α.

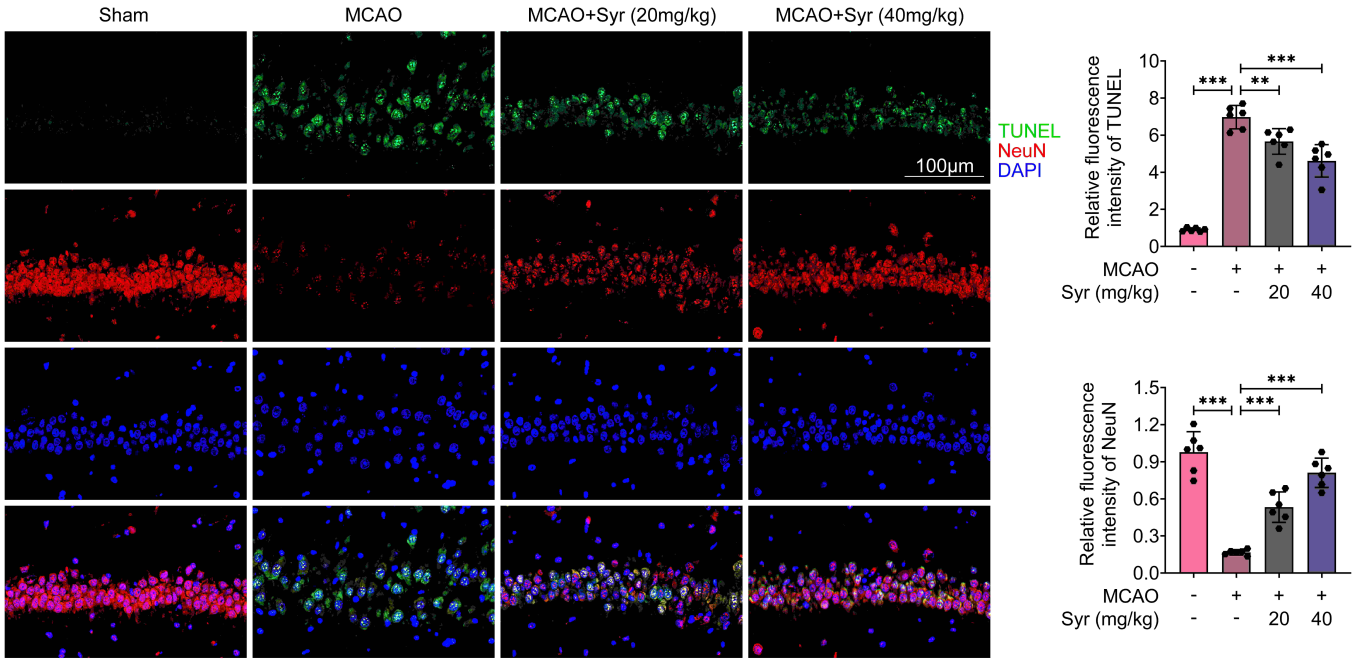

FIGURE 4. Syringaresinol alleviates brain neuron apoptosis in MCAO mice. TUNEL staining assay showed the apoptosis degree of brain tissues in sham, MCAO, MCAO + Syr (20 mg/kg), MCAO + Syr (40 mg/kg) groups. Green panel indicates TUNEL, apoptosis cells. Red panel indicates NeuN, Neurons. $^{**}p < 0.01$, $^{***}p < 0.001$. Syr: Syringaresinol; MCAO: Middle cerebral artery occlusion; TUNEL: TdT-mediated dUTP nick end labeling; DAPI: 4′,6-diamidino-2-phenylindole.

3.5 Syr Inhibits the NF-κB Pathway in MCAO Mice

The NF-κB signaling pathway is activated in the MCAO mouse model. We investigated the potential effects of Syr on the NF-κB pathway. MCAO mice displayed elevated levels of p-p65 and p-IκBα, along with a decreased level of IκBα. However, treatment with Syr significantly reduced the levels of p-p65 and p-IκBα while restoring the levels of IκBα in the brains of MCAO mice (Fig. 5). Therefore, we concluded that Syr inhibits the NF-κB pathway in MCAO mice.

4. Discussion

The mechanism behind CIRI primarily involves a reduction in intracellular calcium ion concentration following ischemia and subsequent reperfusion. This reduction can lead to intracellular calcium overload, mitochondrial dysfunction, and changes in cell membrane potential [14]. A key aspect of CIRI is the infiltration and activation of inflammatory cells, which disrupt energy metabolism and membrane function in both tissues and cells. This ultimately results in increased tissue damage and cell death [15]. Ischemia-reperfusion injury entails intricate pathophysiological processes, and the interactions among various components and influencing factors remain inadequately understood. CIRI is associated with excessive formation of free radicals, excitotoxicity due to amino acids, intracellular calcium overload, inflammatory responses, and apoptosis [16]. Current treatments for CIRI primarily involve neuroprotective agents such as edaravone and butylphthalein, among others [15]. Our research indicates that Syr may mitigate CIRI by inhibiting glial activation and reducing the inflammatory response. Consequently, it shows potential as a therapeutic option for CIRI.

Syringaresinol exhibits a range of biological activities, including antioxidant, anti-inflammatory, and antitumor properties [17]. Additionally, it possesses anti-aging properties and provides cardiovascular protection [18]. Syr can promote neuron growth, stimulate the proliferation of T and B cells, and exhibit selective cytotoxic effects while inhibiting various enzymes [19]. In this study, MCAO mice were administered Syringaresinol at dosages of 20 mg/kg and 40 mg/kg, following the methodology of a previous study [8]. Our results indicate that Syr alleviates CIRI by reducing cerebral infarction, glial cell activation, inflammation and apoptosis in brain tissues of the MCAO mice model. Moreover, it can slow down immunosenescence by regulating the intestinal flora of the mice [20]. Syr also alleviates oxidative damage to cells caused by aging in the skin, and we observed its effects on apoptosis within the brain tissue of the MCAO mice.

NF-κB is prominently present in the nervous system, including cerebrovascular endothelial cells, nerve cells, astrocytes, microglia, and oligodendrocytes. Numerous studies have shown that NF-κB becomes activated following CIRI [21]. A range of drugs modulate NF-κB activation and reduce CIRI, indirectly highlighting the neurotoxic effects of NF-κB activation. Our research reveals that Syr alleviates CIRI by inhibiting glial activation and suppressing the inflammatory response mediated by the NF-κB pathway. During CIRI, the NF-κB signaling pathway is activated, leading to the expression of several related genes [21]. NF-κB is a vital nuclear transcription factor that regulates the expression of several genes [22]. It is present in eukaryotic cells and plays a crucial role in immunity, cell growth, and apoptosis [23]. In recent years, NF-κB sites have been discovered in both nerve cells

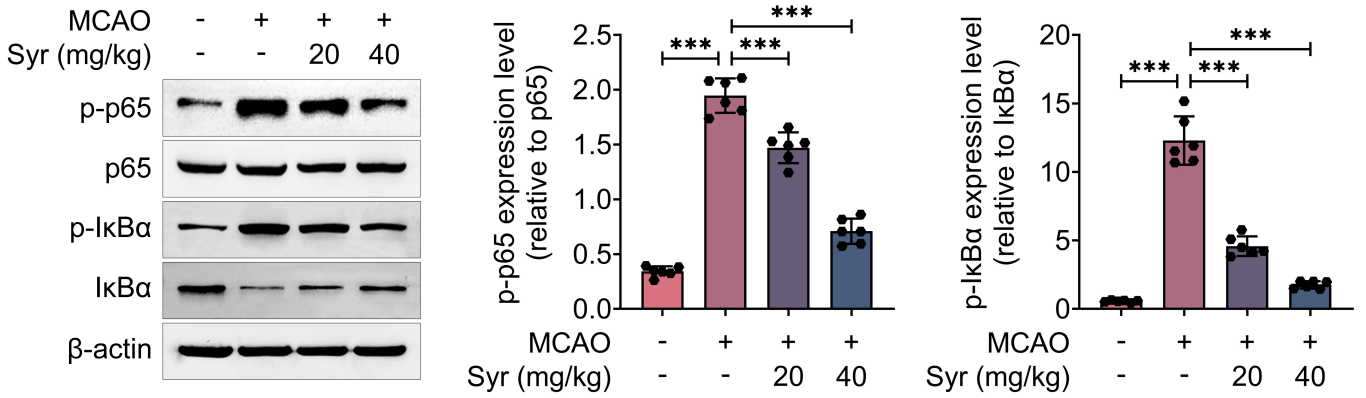

FIGURE 5. Syringaresinol inhibits the NF-κB pathway in MCAO mice. Immunoblot assay detected the protein and phosphorylation levels of p-p65 and p-IκBα in sham, MCAO, MCAO + Syr (20 mg/kg), MCAO + Syr (40 mg/kg) groups from the infarct region. ***$p < 0.001$. Syr: Syringaresinol; MCAO: Middle cerebral artery occlusion.

and cerebrovascular endothelial cells, which are closely related to cell death during cerebral ischemia [24]. Notably, this study further confirmed that this pathway could act as a significant target for addressing CIRI.

Furthermore, the secretion of inflammatory cytokines was positively correlated with the intensity of the inflammatory response [25]. When inflammation occurs in the body, various inflammatory factors, such as IL-1β, TNF-α, IL-10 and IL-6, are secreted in the serum [26, 27]. Measuring these serum inflammatory factors provides insight into the body's inflammation levels, especially in CIRI. Interestingly, we observed the effects of Syr on the inflammation in the CIRI mice model via the detection of these factors.

The limitation of this study is the absence of in-depth mechanisms to elucidate the role of the NF-κB pathway in the remission of CIRI by Syr. To gain deeper insight into the molecular mechanisms, specific inhibitors of this pathway are necessary. Employing multiple omics approaches and regression experiments could further elucidate the underlying mechanisms.

5. Conclusions

In conclusion, our findings indicate that Syringaresinol alleviates CIRI by inhibiting the NF-κB pathway and deactivating glial cells. These findings suggest that Syringaresinol has significant potential as a therapeutic agent for treating CIRI.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

CFW and XYH—performed material preparation and the experiments. RT and CLZ—performed data collection and analysis. HYL—written the first draft of the manuscript. All authors contributed to the study conception and design. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region (Approve number: SYDW2023052301).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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