DOI: 10.53469/jcmp.2024.06(09).28

Research Progress on the Intervention of Traditional Chinese Medicine in Signal Pathways Related to Acute Cerebral Infarction

Man Sun, Haizhe Zhou*

Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
Correspondence Author

Abstract: ***Acute cerebral infarction is a disease with high incidence, mortality, and disability rates. Its etiology is complex, and the exact pathogenesis is not yet fully understood. Current studies often involve inflammatory responses, apoptosis, oxidative stress, atherosclerosis, excitotoxicity, and free radical chain reactions. Signal pathways play a crucial role in the occurrence and development of this condition. Traditional Chinese medicine can improve the condition of patients with acute cerebral infarction by intervening in multiple signal pathways. This paper systematically reviews recent literature, identifying 11 key signal pathways, including NLRP3, TLR4/NF-κB, Nrf2/ARE, CD40/CD40L, JAK/STAT, PI3K/AKT, JNK/p38 MAPK, Wnt, Notch, RhoA/ROCK, and ERK1/2. The aim is to provide some reference for the research on traditional Chinese medicine treatments for acute cerebral infarction.***

Keywords: Traditional Chinese Medicine, Acute Cerebral Infarction, Signal Pathways, Research Progress**.**

1. Introduction

Acute cerebral infarction (ACI) is generally defined as an ischemic stroke occurring within two weeks, ranking as one of the top two causes of death worldwide [1]. It is characterized by five "highs": high mortality rate, high recurrence rate, high disability rate, high economic burden, and high social burden [2]. Early symptomatic and supportive treatments such as thrombolysis and antiplatelet therapy can significantly improve recovery and reduce long-term sequelae in ACI patients, making early intervention crucial. Although the exact pathogenesis of ACI is not fully understood, current research focuses on factors such as inflammatory responses, apoptosis, oxidative stress, atherosclerosis, excitotoxicity, and free radical chain reactions [3]. In recent years, traditional Chinese medicine (TCM) has shown great potential in ACI treatment due to its multi-component and multi-targeted therapeutic effects. This paper provides a review of the research on TCM interventions in signal pathways related to ACI.

2. NLRP3 Inflammasome Signaling Pathway

The NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome signaling pathway primarily consists of NLRP3, caspase-1, apoptosis-associated speck-like protein (ASC), and pro-inflammatory factors such as IL-1β, IL-18, and IL-8 [4]. NLRP3 is mainly expressed in dendritic cells, macrophages, and monocytes in the brain and is currently the most representative inflammasome [5]. When activated, NLRP3 enhances caspase-1 activity, and mature caspase-1 mediates the release of pro-inflammatory cytokines such as IL-1β and IL-18 [6], triggering an inflammatory response. Inflammation is a key pathological process in the progression of ACI, and the NLRP3 inflammasome pathway contributes to neuronal apoptosis and exacerbates brain tissue damage by activating related factors. Wang Yue et al. [7] conducted a study on 95 male SD rats, dividing them into different groups and measuring serum IL-1β, IL-18 levels, and NLRP3 and caspase-1 protein levels in brain tissue. They concluded that the Yiqi Shengqing Formula can inhibit the NLRP3 inflammasome pathway, reducing the levels of caspase-1, IL-1β, and IL-18 to alleviate neuroinflammation and pyroptosis in ACI. In a clinical study, Sun Qing et al. [8] found that the Huazhuo Jiedu Huoxue Tongluo Formula combined with Tongdu Tiaoshen acupuncture reduced the expression of NLRP3 mRNA, ASC mRNA, and caspase-1 mRNA in peripheral blood mononuclear cells of ACI patients, effectively inhibiting the NLRP3 inflammasome pathway and alleviating the inflammatory response, thus improving clinical efficacy. Zhou Ying [9] conducted a study on 18 SD rats and found that the Taohong Siwu Decoction reduced the protein levels of NLRP3, caspase-1, and IL-1β in the ischemic cortex of ACI rats, regulating the NLRP3 pathway and improving neurological deficits.

3. TLR4/NF-κB Signaling Pathway

The TLR4/NF-κB pathway is a classic inflammatory pathway composed of the upstream Toll-like receptor 4 (TLR4) and the downstream redox-sensitive transcription factor NF-κB (nuclear factor kappa B). TLR4 can be expressed in brain tissue and neurons. After the onset of ACI, changes in the permeability of the brain's vascular endothelium lead to the aggregation of immune cells such as macrophages and lymphocytes, which release large amounts of TLR4 [10]. TLR4 activates downstream NF-κB, inducing the transcription of pro-inflammatory factors such as TNF-α, IL-1β, and IL-10 [11], thereby promoting the inflammatory response. Li Yajun et al. [12] performed a study on rat models and found that treating rats with Naoluotong Granules reduced the infarct area and improved neurological deficits. The study measured levels of TLR4, NF-κB, and inflammatory factors like TNF-α and IL-1β in the brain tissue, concluding that the granules inhibited TLR4/NF-κB signaling. Similarly, Fu Beibei et al. [13] found that Astragaloside IV improved motor function in ACI rat models, potentially by inhibiting the NF-κB inflammatory signaling pathway. Wang Xiuli et al. [14] studied the effects of the Sanhan Qutan Kaiqiao Decoction combined with interventional

thrombolysis in treating 124 ACI patients. After treatment, patients showed a significant reduction in serum TLR4 and NF-κB levels compared to those receiving only interventional therapy, suggesting that the combination of traditional Chinese medicine and interventional treatment more effectively inhibited the TLR4/NF-κB pathway. This helped alleviate ischemia-reperfusion injury, accelerated neurological deficit repair, and delayed neurological recovery.

4. Nrf2/ARE Signaling Pathway

The Nrf2 (nuclear factor erythroid 2-related factor 2)/ARE (antioxidant response element) signaling pathway is a classic oxidative stress reduction pathway that maintains redox balance in brain tissue cells and is involved in regulating oxidative stress, calcium transport, inflammatory damage, and apoptosis [15]. Nrf2 is a redox-sensitive transcription factor that controls the expression of various defense genes encoding antioxidant proteins and detoxification enzymes [16]. Under oxidative stress, Nrf2 is released from its upstream negative regulator Keap1, becomes more stable, and translocates to the nucleus to bind with ARE. This binding induces the expression of phase II detoxifying enzymes and antioxidant proteins, such as heme oxygenase-1 (HO-1), protecting cells from cytotoxicity and oxidative damage [17-18]. Lu Zhigang et al. [19] studied 70 ACI patients, dividing them into groups, and found that the treatment with Xingnaojing Injection reduced oxidative damage and alleviated acute ischemic injury by regulating the factors in the Nrf2/ARE pathway. Another experimental study [20] showed that the combination of Ligustrazine Injection with Xingnao Kaiqiao acupuncture could improve brain oxygen metabolism and protect brain cells by regulating the Nrf2/ARE signaling pathway, thus restoring neurological function. Wu Yifan et al. [21] conducted a study on 36 rats, detecting Keap1, Nrf2, and HO-1 protein levels, malondialdehyde (MDA) content, and levels of pro-inflammatory factors such as TNF-α and IL-18 in the hippocampus of the ischemic side. They found that the Bushen Qizhi Formula inhibited Keap1, increased Nrf2 and HO-1 levels in brain tissue, alleviated oxidative stress and inflammatory responses, and provided neuroprotection.

5. CD40/CD40L Signaling Pathway

Atherosclerosis is a chronic inflammatory disease that causes damage to arterial endothelial cells, leukocyte adhesion and proliferation, platelet activation, and lipid metabolism disorders. One of the main causes of ACI is the rupture of unstable atherosclerotic plaques, leading to thromboembolism and vascular occlusion [22], which is negatively correlated with plaque stability. CD40 is a type I transmembrane glycoprotein receptor, and its ligand, CD40L, is a trimeric type II transmembrane protein; both are members of the tumor necrosis factor (TNF) family [23]. The CD40/CD40L signaling pathway plays a key role in immune processes, such as T-cell activation and cytokine production [24]. These immune responses promote atherosclerosis development and rupture by enhancing the expression of inflammatory mediators, matrix metalloproteinases (MMPs), and coagulation factors [25]. Therefore, many scholars consider the CD40/CD40L signaling pathway as an important therapeutic target for ACI. Sun Hanjing et al. [26] conducted a study on 60 rats and found that, compared to the model group, the administration of Ligustrazine Injection reduced the expression of CD40 and CD40L proteins in brain tissue and the level of sCD40L in peripheral blood of acute cerebral infarction rats. This indicates that Ligustrazine can downregulate the CD40/CD40L pathway and effectively improve neurological function damage. Zhu Xing [26], through animal experiments, discovered that the Sanjie Tongmai Formula reduced the expression levels of CD40, CD40L, and NF-κBp65 in rat carotid artery tissues, and downregulated serum levels of pro-inflammatory factors such as TNF-α and IL-1β. This suggests that the formula regulates the CD40/CD40L pathway, thereby inhibiting the formation and rupture of atherosclerotic plaques. Li Qing et al. [27], in a clinical study, found that Ginkgolide B Injection significantly reduced the expression of CD40, sCD40L, and oxidative and inflammatory markers such as MDA and hs-CRP in the CD40/CD40L signaling pathway, thus alleviating oxidative stress damage and inflammatory reactions in the body.

6. JAK/STAT Signaling Pathway

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway plays a role in various biological processes, including cell proliferation, differentiation, apoptosis, inflammation, immunity, and hematopoiesis [28]. The JAK/STAT pathway consists mainly of three parts: JAK, STAT, and tyrosine kinase-associated receptors [29]. JAK is a non-receptor tyrosine kinase found in the cytoplasm and expressed in many cell types throughout the body. When cells are under stress, JAK becomes activated, forming phosphorylated JAK (p-JAK), which recruits and activates STAT to form p-STAT. Activated STAT proteins enter the nucleus, bind to DNA, and promote the transcription of inflammatory factors, accelerate apoptosis, and trigger oxidative stress. After the onset of ACI, the release of large amounts of cytokines such as TNF-α and IL-6 activates the JAK/STAT pathway, further triggering neuroinflammation, autophagy, and worsening neurological deficits [30]. Yu Xiaolan et al. [31] conducted a study on 36 rats, where they divided them into groups, modeled them with ACI, administered treatments, and measured the levels of high-mobility group box 1 (HMGB1), TNF-α, IL-1β, IL-6, malondialdehyde (MDA), and the expression of Jak2 and STAT3 in brain tissue. They found that puerarin reduced the expression of HMGB1, TNF-α, and IL-1β, thereby inhibiting the JAK/STAT pathway and improving neurological function and neuronal apoptosis in ACI rats. Similarly, Song Guangjie et al. [32] used middle cerebral artery occlusion (MCAO) to model ACI in rats and found that the levels of p-JAK1, p-STAT1, and caspase-3 in the ischemic brain tissue of the resveratrol-treated group were lower than those of the model group. There was no significant change in the levels of JAK1 and STAT1, indicating that resveratrol reduced neural apoptosis and neuroinflammation by inhibiting the phosphorylation of the JAK/STAT signaling pathway. Chen et al. [33], in a study of Buyang Huanwu Decoction, concluded that the decoction protects neurons, promotes angiogenesis, and improves cerebral blood supply in ACI rats by regulating the JAK/STAT pathway.

7. PI3K/AKT Signaling Pathway

The phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway is widely present in various types of neurons and plays a crucial role in brain ischemia and neuronal apoptosis [33]. PI3K is a lipid kinase, and one of its key downstream target kinases is serine/threonine protein kinase (AKT). The PI3K/AKT signaling pathway functions by phosphorylating phosphatidylinositol to generate phosphatidylinositol trisphosphate (PIP3) under the influence of growth factors. PIP3, acting as a second messenger, activates AKT. Activated AKT regulates various downstream target genes such as Bcl-2-associated death promoter (Bad), apoptosis factor Caspase-9, NF-κB, and other target proteins, thus influencing biological processes like cell proliferation, differentiation, metabolism, and apoptosis [34]. Studies have shown that most neurotrophic factors can activate the PI3K/AKT pathway, inhibiting neuronal apoptosis, providing neuroprotection, and reducing blood-brain barrier disruption and cerebral edema [35]. Xie Taobo et al. [36] conducted a study on 60 SD rats, applying treatments and detecting the expression levels of p-PI3K/PI3K, p-AKT/AKT, and cleaved caspase-9 in brain tissue. Results indicated that the levels of these proteins were significantly higher in the ginkgo leaf extract-treated group compared to the model group, suggesting that the neuroprotective effects of ginkgo leaf extract in acute cerebral infarction (ACI) are closely related to the activation of the PI3K/AKT pathway, improving neurological function and protecting the blood-brain barrier. Du Jing et al. [37] found that the herbal compound hongcaoside could inhibit excessive mitochondrial autophagy in neurons by activating the PI3K/AKT pathway, providing neuroprotection in rats with ischemia-reperfusion injury. Additionally, Sun Jiahe [38], in animal studies, demonstrated that isorhamnetin (ISO) could activate the PI3K/AKT pathway, leading to the suppression of inflammatory cytokines IL-6, IL-1β, TNF-α, and an increase in superoxide dismutase (SOD) levels, thereby reducing oxidative stress and inflammation, and ultimately mitigating ischemia-reperfusion injury to brain cells.

8. JNK/p38 MAPK Signaling Pathway

The c-Jun N-terminal kinase/mitogen-activated protein kinase (JNK/p38 MAPK) pathway, also commonly referred to as the MAPK pathway, plays a crucial role in neuronal adaptation, proliferation, and differentiation. The MAPK signaling pathway is typically divided into three main subgroups: extracellular signal-regulated kinase (ERK)1/2, JNK, and p38 MAPK. p38 is a protein within the MAPK pathway that transmits signals from various physiological stress pathways, while JNK is a primary kinase in the MAPK pathway, closely linked to the pathogenesis of various diseases [39]. Recent studies have shown that the JNK and p38 pathways contribute to inflammatory responses and neuronal apoptosis in the pathophysiology of ischemia-reperfusion injury in the brain [40]. Thus, inhibiting the JNK/p38 MAPK pathway can effectively protect neural function after acute cerebral infarction (ACI). Yue Yun et al. [41] studied 90 SD rats with ACI and investigated the effects of crotonis fructus (a traditional Chinese medicine) on these rats and its relationship with the JNK/p38 MAPK pathway. They found that crotonis fructus exerted neuroprotective effects by inhibiting the activation of the JNK/p38 MAPK signaling pathway, downregulating the expression of apoptosis-related proteins (such as Bax), and reducing neuronal apoptosis. Astragaloside, an extract from the traditional Chinese herb Astragalus, has anti-oxidative, anti-inflammatory, and immune-enhancing properties. Wang Xianli et al. [42] discovered through experiments that astragaloside could inhibit the JNK/p38 MAPK signaling pathway, improve oxidative stress indicators, reduce inflammation, and enhance neurological function in ACI rat models.

9. Wnt Signaling Pathway

The Wnt signaling pathway is crucial for various biological processes, including cell proliferation, differentiation, migration, and stem cell renewal. It consists of two main pathways: the canonical pathway and the non-canonical pathway. The canonical Wnt/β-catenin pathway plays a key role in neuronal survival, neurogenesis, and axon extension [43]. This pathway involves Wnt ligands and transmembrane receptors, primarily Frizzled (Fz) and low-density lipoprotein receptor-related proteins 5/6 (LRP5/6). When cells are stimulated, Wnt ligands bind to Fz and LRP5/6, leading to an increase in free β-catenin levels, which can then enter the nucleus to promote the transcription of target genes, inducing cell proliferation, differentiation, and maturation [44]. The non-canonical Wnt signaling pathways include the Wnt/PCP (Planar Cell Polarity) pathway, which regulates cellular activities through ROCK and JNK signaling, and the Wnt/Ca2+ pathway, which acts as a mediator of calcium signaling, increasing cytosolic Ca2+ concentrations to trigger the expression and effects of downstream cytokines [45]. Research indicates that both the canonical and non-canonical Wnt pathways can protect neurons by regulating processes such as brain vascular remodeling, blood-brain barrier formation, and neuronal proliferation and differentiation [46]. Yu Lihua et al. [47] treated ACI model rats with kidney-tonifying and blood-activating formulas and assessed the levels of LRP5 and β-catenin in their cerebral cortex. Results showed that both formulations suppressed the canonical Wnt signaling pathway, reducing LRP5 protein expression while enhancing β-catenin protein expression, thus promoting the proliferation and differentiation of endogenous neural stem cells after ischemia-reperfusion. Soy isoflavones, extracted from soybeans, have been shown to reduce intracellular Ca2+ concentrations by inhibiting the Wnt/Ca2+ signaling pathway, thus mitigating neuronal damage [48]. Berberine, a bioactive alkaloid extracted from the traditional herb Coptis chinensis, exhibits antibacterial, lipid-regulating, and anti-inflammatory properties [49]. Yao Yan et al. [50] found that berberine activated the Wnt/β-catenin signaling pathway, upregulating the expression of Wnt-1 and β-catenin proteins in brain tissue, which alleviated inflammatory responses and inhibited neuronal apoptosis, thereby protecting neurological function in rats with acute cerebral infarction.

10. Notch Signaling Pathway

The Notch signaling pathway is essential for regulating intercellular communication during embryonic development. It is a transcriptionally activated pathway composed of Notch receptors, Notch ligands, and CSL-DNA binding proteins [51]. Mammalian cells express four homologous Notch receptors (Notch1, Notch2, Notch3, and Notch4), which are

type I transmembrane proteins consisting of an extracellular region, a transmembrane region, and an intracellular region. There are five recognized Notch ligands in humans and mice: DLL1, DLL3, DLL4, and JAG1/2, which play roles in regulating cell differentiation, intercellular communication, apoptosis induction, and cell proliferation. CSL proteins act as transcriptional repressors and can form complexes that activate transcription [52]. The Notch signaling pathway functions as follows: when a Notch receptor binds to a ligand, it undergoes proteolytic cleavage, releasing a functional fragment that translocates into the nucleus and binds to CSL, thereby regulating the transcription of downstream genes [53]. Studies indicate that after acute cerebral infarction (ACI), the Notch signaling pathway is involved in regulating neuronal apoptosis, angiogenesis in ischemic areas, and the inflammatory response [54-56]. Chen Pingting et al. [57] conducted experiments on male SD rats, observing the levels of Notch1, Notch2, and Hes1 (a target gene of the Notch pathway that promotes neuronal proliferation) in the hippocampus following ACI. They found that Danlong Xingnao Formula upregulated the Notch signaling pathway, promoting the proliferation of neural stem cells (NSCs) in the central nervous system, thereby providing neuroprotective and regenerative effects. Xie Qing et al. [58] discovered that Sangqi Shouwu Tablets (which nourish the liver and kidneys, invigorate Qi, and activate blood circulation) increased the expression of Notch1, NICD (Notch intracellular domain), and Hes1, resulting in a higher number of Nissl bodies and promoting neuronal proliferation, thus improving neuronal deficits in rats. Zhang Yuzhou et al. [59] found that Rhein, an important anthraquinone compound extracted from rhubarb, could inhibit the Notch signaling pathway. This inhibition reduced the release of inflammatory factors, such as intercellular adhesion molecule-1 (ICAM-1) and TNF-α, from microglial cells, thereby mitigating inflammation after ACI, reducing infarct size, and improving neurological function.

11. RhoA/ROCK Signaling Pathway

The RhoA/ROCK signaling pathway is a G protein-coupled receptor signaling pathway, where Rho (including RhoA, RhoB, and RhoC) is a primary member of the Rho GTPase family, and ROCK (Rho-associated coiled-coil forming protein kinase) is the most significant downstream effector of Rho. ROCK is divided into two isoforms: ROCK1, predominantly expressed in non-neuronal tissues (like the liver, lung, spleen, and testis), and ROCK2, which is mainly found in the brain, muscle, and heart. Upon receiving activation signals from Rho, ROCK undergoes phosphorylation at multiple amino acid sites, leading to its activation and mediating a series of phosphorylation / dephosphorylation reactions [59]. Research has shown that the RhoA/ROCK pathway plays a critical role in mediating the effects of myelin-associated inhibitors, causing cytoskeletal reorganization, growth cone collapse, and suppression of neurite extension, making it an important pathological mechanism in neural damage [60]. Activation of this pathway can exacerbate neuroinflammation and cytotoxicity. Na Lisa et al. [61] conducted experiments on rats, measuring levels of TNF-α, IL-1β, IL-6, Bax, RhoA, ROCK1, and ROCK2 in the hippocampus. They found that leech extract significantly downregulated inflammatory and apoptotic markers, potentially via inhibition of the RhoA/ROCK signaling pathway. Wang Yue et al. [62] used Yiqi Shengqing Decoction to treat ACI model rats, assessing levels of inflammatory factors, blood-brain barrier (BBB) permeability, and matrix metalloproteinases alongside RhoA/ROCK pathway proteins. Their results indicated that Yiqi Shengqing Decoction could inhibit the RhoA/ROCK pathway, reduce inflammatory markers, and lessen BBB permeability, thereby mitigating neuronal damage and improving neurological function. Leech extract (HDR) is a bioactive substance derived from the saliva of the leech, known for its properties as a natural thrombin inhibitor, along with its ability to suppress inflammation and cell apoptosis.

12. ERK1/2 Signaling Pathway

The extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway is a downstream component of the MAPK pathway, functioning through a three-tiered kinase cascade to transmit extracellular signals into the cell, thereby regulating processes like cell proliferation, apoptosis, and differentiation. When a cell is stimulated, receptor dimerization occurs, activating the Ras-Raf pathway, which subsequently phosphorylates serine/threonine and tyrosine residues to activate ERK1/2. Once activated, ERK1/2 translocates to the nucleus to bind with transcription factors, promoting the expression of target genes and producing various cellular effects. Research has demonstrated that ERK1/2 is acutely activated following acute cerebral infarction (ACI) and regulates downstream apoptotic proteins, inhibiting cell apoptosis and protecting brain tissue [63]. Gao Bai et al. [64] used polygonum cuspidatum extract (also known as resveratrol glycoside, recognized for its anti-infective and anti-apoptotic properties) to treat ACI model rats, finding that it activated the ERK1/2 pathway in brain tissue, suppressing the expression of apoptotic factors like Caspase-3, Bax, and Bcl-2, thus regulating apoptosis and improving brain injury in ACI mice. Liu Menghan's study also indicated that the "Bujin Kaiqiao Decoction" could block ferroptosis by regulating ERK1/2 in diabetic rats with ischemic stroke, providing neuroprotection [64]. Ba Qinghua reported that activating the ERK1/2 signaling pathway could also activate the Nrf2/HO-1 pathway, thereby alleviating oxidative stress responses, reversing neuronal apoptosis, and mitigating neurological damage in rats [65].

In summary, numerous studies suggest that during traditional Chinese medicine treatment of ACI, multiple signaling pathways exert various physiological effects, including suppressing inflammatory responses and oxidative stress, reducing apoptosis, improving BBB permeability, and promoting neuronal repair and proliferation. Furthermore, several pathways may work synergistically to enhance neurological recovery post-ACI.

13. Summary

The etiology of acute cerebral infarction (ACI) is highly complex, and its pathological mechanisms remain incompletely understood. However, signaling pathways have been identified as key contributors to the neurological deficits associated with ACI. Targeted treatment strategies based on these signaling pathways have become a focal point in research. Despite this, there are several shortcomings in the

use of traditional Chinese medicine (TCM) to treat ACI based on signaling pathways that need to be addressed: 1) Independent Pathway Functions: Current research often treats each signaling pathway in isolation, with limited exploration of their interactions. 2) Integration of Perspectives: Most studies on signaling pathways and their roles are based on Western biomedical principles, with insufficient consideration of TCM concepts and therapeutic approaches. 3) Clinical Evidence Gap: Much of the existing research relies on animal models, with a lack of large-scale clinical trials and insufficient evidence supporting clinical efficacy. Moving forward, research into the mechanisms of TCM should aim to integrate TCM perspectives with Western biomedical principles. This can involve conducting large-scale, rigorously designed clinical studies to further elucidate the precise mechanisms by which TCM impacts diseases.

References

[1] Vasu S, Luis G, R D Y. Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions. [J]. Neurology, 2021.

[2] Wang Yongjun, Li Zixiao, Gu Hongqiu, et al. China Stroke Report 2020 (Chinese version) (1) [J]. Chinese Stroke Journal, 2022, 17(05): 433-447.

[3] Yi Zhen, He Xincui. Research Progress on Factors Affecting Early Neurological Recovery After Intravenous Thrombolysis Treatment for Acute Cerebral Infarction [J]. Sino-Foreign Medical Research, 2024, 22(18): 165-170.

[4] Yi Zhen, He Xincui. Research Progress on Factors Affecting Early Neurological Recovery After Intravenous Thrombolysis Treatment for Acute Cerebral Infarction [J]. Sino-Foreign Medical Research, 2024, 22(18): 165-170.

[5] Sun K, Zhang J, Yang Q, et al. Dexmedetomidine exerts a protective effect on ischemic brain injury by inhibiting the P2X7R/NLRP3/Caspase-1 signaling pathway. Brain Res Bull. 2021;174:11-21.

[6] Wu Jingyue, Chen Xiaofan, Wang Xiaoqin, et al. Evaluation of serum NLRP3 inflammasome signaling pathway-related factors in assessing thrombus formation and its clinical application value in patients with acute cerebral infarction. Journal of Translational Medicine, 2023, 12(05): 255-261.

[7] Wang Yue, Quan Xingmiao, Wang Yu, et al. Effects of Yiqi Shengqing formula on neuronal pyroptosis in ischemic stroke rats by regulating the HIF-1α/NLRP3 signaling pathway. Tianjin Medical Journal, 2024, 52(04): 350-355.

[8] Sun Qing, Zhao Jianwen, Wang Feng, et al. Study on the efficacy of Huazhuo Jiedu Huoxue Tongluo formula combined with Tongdu Tiaoshen acupuncture in treating acute cerebral infarction and its effects on the NLRP3 signaling pathway. Chinese Journal of Emergency in Traditional Chinese Medicine, 2024, 33(07): 1200-1204.

[9] Zhou Ying. Investigation of the effects and mechanisms of Taohong Siwu Decoction on cellular pyroptosis after acute cerebral infarction based on the DRP1/NLRP3 pathway [D]. Beijing University of Chinese Medicine, 2021. DOI:10.26973/d.cnki.gbjzu.2021.000498.

[10] Song Shigeng, Han Ruili, Wang Yimin. Correlation between peripheral blood MIF and TLR4 levels and the severity of cerebral edema in patients with acute cerebral infarction. Guangdong Medical Journal, 2021, 42(09): 1119-1122.

[11] TANG XH, CHEN XX, LI XJ, et al. The TL R 4 mediated inflamma tory signal pathway might be involved in drug resistance in drug-re sistant epileptic rats[J]. J Neuroimmunol, 2022, 365: 577802.

[12] Li Yajun, Li Liangyong, Wu Yunhu, et al. Investigation of the effects of Naoluotong granules on acute cerebral infarction model rats based on the TLR4/NF-κB signaling pathway. Journal of Traditional Chinese Medicine, 2023, 38(02): 360-366. DOI:10. 16368/j. issn. 1674-8999.2023.02.062.

[13] Fu Beibei, Zheng Yongqiang, Xu Yue. Effects of astragaloside IV on improving neural motor function in rats with acute cerebral infarction and its impact on NF-κB p65 and IKKβ proteins in the infarct-side cerebral cortex. China Journal of Emergency Traditional Chinese Medicine, 2019, 28(01): 25-28.

[14] Wang Xiuli, Feng Yulong, Ding Ru. The efficacy of modified Sanhan Qutan Kaiqiao Decoction combined with interventional thrombolysis in the treatment of acute cerebral infarction and its impact on related signaling pathways. Journal of Medical Forum, 2023, 44(23): 97-101.

[15] Wang Xiuli, Feng Yulong, Ding Ru. The efficacy of modified Sanhan Qutan Kaiqiao Decoction combined with interventional thrombolysis in the treatment of acute cerebral infarction and its impact on related signaling pathways. Journal of Medical Forum, 2023, 44(23): 97-101.

[16] WANG Y W J, XIANG Y, WANG R Q, et al. Sulforaphane enhances Nrf2-mediated antioxidant responses of skeletal muscle induced by exhaustive exercise in HIIT mice[J]. Food Science and Human Wellness, 2022, 11(5): 1355-1361.

[17] Kaspar JW, Niture SK, Jaiswal AK. Nrf2:INrf2 (Keap1) signaling in oxidativestress [J]. Free Radic Biol Med 2009; 47(9):1304-1309.

[18] Stefanson AL, Bakovic M. Dietary regulation of Keap1/Nrf2/ARE pathway: focus on plant-derived compounds and trace minerals. Nutrients. 2014;6(9):3777-3801.

[19] Lu Zhigang, Huang Jiabian, Liu Yun, et al. "Effects of Xingnaojing Injection on the Keap1-Nrf2/ARE Oxidative Stress Pathway in Acute Cerebral Infarction." Guangdong Medical Journal, 2016, 37(20): 3127-3129.Chen Jing, Liu Jing, Wang Namei, et al. "Effects of Chuanxiongzine Injection Combined with Xingnao Kaiqiao Acupoint Acupuncture on Neurological Function and the Keap1-Nrf2/ARE Signaling Pathway in Patients with Acute Cerebral Infarction." Chinese Journal of Traditional Chinese Medicine for Emergencies, 2023, 32(05): 883-886.

[20] Wu Yifan, Fu Chen, Luo Chaoqin, et al. "Effects of Buxin Qizhi Formula on Cognitive Function in Ischemic Stroke Rats by Regulating the Keap1/Nrf2/ARE Signaling Pathway." Journal of Beijing University of Chinese Medicine, 2022, 45(07): 654-662.

[21] Wang Yin, Hou Lichun, Wang Chen, et al. "Relationship between Serum PAF, P-Selectin, and Carotid Atherosclerotic Plaque Stability in Patients with Acute

Cerebral Infarction." Journal of Stroke and Neurological Diseases, 2018, 35(12): 1076-1078.
[22] Angeli F, Verdecchia P, Savonitto S, et al. Soluble CD40 ligand and outcome in patients with coronary artery disease undergoing percuta neous coronary intervention [J]. Clin Chem Lab Med, 2022, 60(1):118-126.
[23] Daub S, Lutgens E, Münzel T, et al. CD40/CD40L and related signal ing pathways in cardiovascular health and disease-the pros and cons for cardioprotection [J]. Int J Mol Sci, 2020, 21(22): 8533.
[24] Tian Qi, Hao Chunyan, Duan Hubin. "Relationship between CD40/CD40L and Ischemic Stroke." Hainan Medical Journal, 2023, 34(15): 2269-2272.
[25] Zhu Xing. "Experimental Study on the Intervention of Sanjie Tongmai Formula on the CD40/CD40L Signaling Pathway in Atherosclerotic Rats." Changchun University of Traditional Chinese Medicine, 2020.
[26] Zhu Xing. "Experimental Study on the Intervention of Sanjie Tongmai Formula on the CD40/CD40L Signaling Pathway in Atherosclerotic Rats." Changchun University of Traditional Chinese Medicine, 2020.
[27] Xin P, Xu X, Deng C, et al. The role of JAK/STAT signaling pathway and its inhibitors in diseases. Int Immunopharmacol. 2020;80:106210.
[28] Satriotomo I, Bowen KK, Vemuganti R. JAK2 and STAT3 activation contributes to neuronal damage following transient focal cerebral ischemia. J Neurochem. 2006;98(5):1353-1368.
[29] Satriotomo I, Bowen KK, Vemuganti R. JAK2 and STAT3 activation contributes to neuronal damage following transient focal cerebral ischemia. J Neurochem. 2006;98(5):1353-1368.
[30] O'Callaghan JP, Kelly KA, Van Gilder RL, Sofroniew MV, Miller DB. Early activation of STAT3 regulates reactive astrogliosis induced by diverse forms of neurotoxicity. PLo S One. 2014;9(7):e102003.
[31] Yu Xiaolan, Li Guangnan, Zhao Ting. "Effects of Puerarin on Neurological Function, Neuronal Apoptosis, and the Jak2/STAT3 Signaling Pathway in Rats with Cerebral Infarction." Shanxi Medical Journal, 2020, 49(03): 243-246.
[32] Song Guangjie, Fang Yi, Chen Li, et al. "Mechanism of the JAK1/STAT1 Signaling Pathway in Resveratrol Mitigating Focal Cerebral Ischemia-Reperfusion Injury in Rats." Chinese Journal of Geriatrics, 2023, 43(03): 700-704.
[33] Zhou JD, Li XX, Zhang TJ, et al. Micro RNA-335/ID4 dysregulation predicts clinical outcome and facilitates leukemogenesis by activating PI3K/Akt signaling pathway in acute myeloid leukemia [J]. Aging (Albany NY), 2019, 11(10): 3376-3391
[34] Xiong LL, Xue LL, Jiang Y, et al. Suppression of PDGF induces neu ronal apoptosis after neonatal cerebral hypoxia and ischemia by in hibiting P-PI3K and P-AKT signaling pathways [J]. Brain Res, 2019; 1719: 77-88.
[35] Palabiyik O, Tastekin E, Doganlar ZB, et al. Alteration in cardiac PI3K/Akt/m TOR and ERK signaling pathways with the use of growth hormone and swimming, and the roles of mi R21 and mi R133 [J]. Biomed Rep, 2019, 0(0): 1-10
[36] Xie Taobo, Zhong Chunzheng, Fu Yaotian, et al. "Effects and Mechanism of Ginkgo Biloba Extract on Blood-Brain Barrier Function and the PI3K/AKT Signaling Pathway in a Rat Model of Acute Cerebral Infarction." Chinese Journal of Geriatrics, 2021, 41(20): 4467-4471.
[37] Liang Qun, Yang Yang, Li Shuai, et al. "Effects of 'Stroke No. 1' on the PI3K/Akt Signaling Pathway and GSK-3β Protein Expression in Rats with Acute Intracerebral Hemorrhage." Chinese Journal of Traditional Chinese Medicine for Emergencies, 2022, 31(04): 565-567+572.
[38] Sun Jiahe. "Neuroprotective Effect of Rhei Radix et Rhizoma Extract on Rat Cerebral Ischemia-Reperfusion Injury by Regulating the PI3K/Akt Signaling Pathway." Clinical Research of Traditional Chinese Medicine, 2024, 16(16): 81-86.
[39] Dou Yawei, Wang Hongtao, Tian Wei, et al. "Expression of Insulin Signaling Pathway-Related Proteins in Lung Tissue of Patients with Pulmonary Emphysema." Shaanxi Medical Journal, 2017, 46(10): 1386-1388.
[40] Xu Zuqing, Wang Shiyang, Wang Xiao, et al. "Effects of Oleuropein on Neuronal Apoptosis and the JNK/p38 MAPK Signaling Pathway in Rats with Cerebral Ischemia-Reperfusion Injury." Chinese Journal of Geriatrics, 2021, 41(02): 334-338.
[41] Yue Yun, Wang Peipei, Yuan Zhaohe, et al. "Mechanism of Baduo Powder in Intervening Cerebral Ischemia-Reperfusion Injury by Affecting JNK/p38 MAPK and Neuronal Apoptosis in the Cortical Region of Rats." Chinese Journal of Tissue Engineering Research, 2024, 28(08): 1186-1192.
[42] Wang Xianli, Liu Yan, Li Ting, et al. "Effects of Astragaloside on Neurological Function in a Rat Model of Acute Cerebral Infarction by Activating the JNK/p38 MAPK Signaling Pathway." Hebei Medical Journal, 2024, 46(06): 816-820.
[43] Li Lin, Zhou Yunpeng, Liu Xican, et al. "Effects of Baicalin on Rotational Behavior and Apoptosis of Dopaminergic Neurons in the Substantia Nigra of Parkinson's Rats Based on the Wnt/β-Catenin Signaling Pathway." Chinese Journal of Immunology, 2022, 38(04): 395-401.
[44] [44] Nusse R, Clevers H. Wnt/β-Catenin Signaling, Disease, and Emerging Therapeutic Modalities. Cell. 2017;169(6):985-999.
[45] De A. Wnt/Ca2+ signaling pathway: a brief overview. Acta Biochim Biophys Sin (Shanghai). 2011; 43(10): 745-756.
[46] Liao Kexin, Xiao Aijiao, Xiao Yisheng. "Research Progress on Traditional Chinese Medicine in the Treatment of Cerebral Ischemia/Reperfusion Injury Based on the Wnt Signaling Pathway." Chinese Pharmacological Bulletin, 2022, 38(09): 1297-1302.
[47] Yu Lihua, Hu Jianpeng, Wang Jian, et al. "Effects of Two Traditional Chinese Medicine Formulas on the Expression of LRP5 and β-Catenin in the Frontal and Parietal Cortex of Rats with Focal Cerebral Ischemia-Reperfusion." Journal of Liaoning University of Traditional Chinese Medicine, 2014, 16(04): 17-20.
[48] Li Li, Wang Mengzhe, Liu Saisai, et al. "Soy Isoflavones Mitigate Calcium Overload Induced by Cerebral Ischemia-Reperfusion in Rats by Inhibiting the Wnt/Ca^{2+} Signaling Pathway." Journal of Southern Medical University, 2024, 44(06): 1048-1058.

[49] Chen Meilin, Li Zhiqi, Fan Qiqi, et al. Research progress on pharmacological action of berberine and its related mechanism [J]. Chinese Herbal Medicine, 2022, 53(18): 5861-5872.
[50] Yao Yan, Gu Juxian, Zhao Li, et al. Therapeutic effect of berberine on acute cerebral infarction in rats and its mechanism [J]. Shandong Medicine, 2023, 63(12):48-52.
[51] Vieceli Dalla Sega F, Fortini F, Aquila G, Campo G, Vaccarezza M, Rizzo P. Notch Signaling Regulates Immune Responses in Atherosclerosis. Front Immunol. 2019;10:1130.
[52] Zhou Qiang, Li Zhaohui. Research progress of Notch signaling pathway in cerebral ischemia [J]. Journal of Clinical Pathology, 2015, 35(03):449-454.
[53] Wang Lifeng, Chen Li, Peng Daozhen, et al. Research progress on the mechanism of Notch signaling pathway in cerebral ischemia injury [J]. Journal of Practical Medicine, 2011, 27(23):4337-4338.
[54] Cheng YL, Choi Y, Seow WL, et al. Evidence that neuronal Notch-1 promotes JNK/c-Jun activation and cell death following ischemic stress. Brain Res. 2014; 1586:193-202.
[55] Li S, Zyang X, Wang Y, Ji H, Du Y, Liu H. DAPT protects brain against cerebral ischemia by down - regulating the expression of Notch 1 and nuclear factor κB in rats. Neurol Sci. 2012;33(6):1257-1264.
[56] Al Haj Zen A, Oikawa A, Bazan-Peregrino M, Meloni M, Emanueli C, Madeddu P. Inhibition of delta-like-4-mediated signaling impairs reparative angiogenesis after ischemia. Circ Res. 2010; 107(2): 283-293.
[57] Chen Pingting, Zhou Xiaoqing, Cao Zebiao, et al. Effect of Danlong Xingnao recipe on Notch signaling pathway related protein expression in hippocampus of rats with cerebral ischemia-reperfusion [J]. journal of traditional chinese medicine university of hunan, 2016, 36(01): 10-14.
[58] Xie Qing, Wei Danxia, Gu Lihua, et al. Protective effect and mechanism of Sangqi Shouwu tablet on cerebral ischemia-reperfusion injury in rats [J]. China Journal of Gerontology, 2022, 42(15):3791-3796.
[59] Mueller BK, Mack H, Teusch N. Rho kinase, a promising drug target for neurological disorders. Nat Rev Drug Discov. 2005;4(5):387-398.
[60] Zhao Y, Xu J. Sanggenon C Ameliorates Cerebral Ischemia-Reperfusion Injury by Inhibiting Inflammation and Oxidative Stress through Regulating RhoA-ROCK Signaling. Inflammation. 2020;43(4):1476-1487.
[61] Na Lisha, Qu Na, Yu Xue, et al. Effects of Hirudin on the Apoptosis and Inflammatory Reaction of Neurons in Rats with Cerebral Infarction [J]. China Journal of Immunology, 2024, 40(08):1640-1645.
[62] Wang Yue, Shao Yue, Quan Xingmiao, et al. Effects of YiQi Shengqing recipe on blood-brain barrier and neuroinflammation in stroke rats by regulating RhoA/ROCK signaling pathway [J]. China Journal of Gerontology, 2024, 44(17):4266-4270.
[63] Zhu YM, Wang CC, Chen L, et al. Both PI3K/Akt and ERK1/2 pathways participate in the protection by dexmedetomidine against transient focal cerebral ischemia/reperfusion injury in rats. Brain Res. 2013; 1494:1-8.
[64] Gao Bai, Xian Jianfei, Cong Shuyan, et al. Effect of polydatin on ERK1/2 signal pathway in brain tissue of mice with acute cerebral infarction [J]. China Journal of Gerontology, 2023, 43(13):3297-3301.
[65] Ba Qinghua, Cui Chuanju. Effect and mechanism of salidroside on cerebral ischemia-reperfusion in rats [J]. chinese journal of practical nervous diseases, 2022, 25(01):92-97.