Neuroprotective Mechanisms of Baicalin against Cerebral Ischemia-Reperfusion Injury and Recent Research Advances (Postprint)

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Abstract

Cerebral ischemia-reperfusion injury refers to the secondary damage that occurs to ischemic brain tissue during the process of restoring cerebral blood flow supply after cerebral blood flow interruption, resulting from multiple biological processes including energy metabolism disorder, oxidative stress, free radical damage, inflammatory response, blood-cerebrospinal fluid barrier disruption, cell apoptosis and necrosis. Cerebral ischemia-reperfusion injury not only exacerbates neuronal damage and even death, hindering the recovery of neurological function in patients, but also severely affects their quality of life. Therefore, effective prevention and treatment strategies for cerebral ischemia-reperfusion injury have become a current research focus in the field of cerebrovascular disease. Baicalin is a flavonoid compound extracted from the traditional Chinese medicine Scutellaria baicalensis, and accumulating evidence demonstrates that baicalin can effectively prevent cerebral ischemia-reperfusion injury through multiple pharmacological mechanisms. This article summarizes the neuroprotective effects of baicalin in various in vivo and in vitro experimental models of cerebral ischemia-reperfusion injury, and elaborates on the specific neuroprotective and pharmacological mechanisms by which baicalin prevents and treats cerebral ischemia-reperfusion injury through multi-target, multi-pathway approaches, including alleviating inflammatory response, reducing oxidative stress, regulating mitochondrial homeostasis, inhibiting cell apoptosis and pyroptosis, protecting the blood-cerebrospinal fluid barrier, maintaining astrocyte structure and function, and reducing neurotoxicity. The aim is to emphasize the potential role of baicalin in preventing and treating cerebral ischemia-reperfusion injury, provide a reference basis for further drug research and development, and offer perspectives on future applications of baicalin in cerebrovascular diseases.

Full Text

Neuroprotective Mechanism and Research Progress of Baicalin Against Cerebral Ischemia-Reperfusion Injury

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Abstract

Cerebral ischemia-reperfusion injury (CIRI) refers to secondary damage that occurs in ischemic brain tissue during the restoration of cerebral blood flow following interruption. This re-injury results from multiple biological processes including energy metabolism disorders, oxidative stress, free radical damage, inflammatory responses, blood-brain barrier disruption, and cell apoptosis and necrosis. CIRI not only exacerbates neuronal damage and death, impeding neurological recovery, but also severely compromises patients' quality of life. Consequently, developing effective prevention and treatment strategies for CIRI has become a major focus in cerebrovascular research. Baicalin, a flavonoid compound extracted from the traditional Chinese medicine *Scutellaria baicalensis*, has attracted increasing attention as evidence demonstrates its preventive efficacy against CIRI through diverse pharmacological mechanisms. This review systematically summarizes the neuroprotective effects of baicalin in various in vivo and in vitro experimental models of cerebral ischemia-reperfusion injury, and elaborates on its specific neuroprotective and pharmacological mechanisms. Baicalin prevents and treats CIRI through multi-target, multi-pathway approaches, including attenuating inflammatory responses, exerting antioxidant effects, regulating mitochondrial homeostasis, inhibiting apoptosis and pyroptosis, protecting the blood-brain barrier, maintaining astrocyte structure and function, and reducing neurotoxicity. We aim to highlight the potential role of baicalin in preventing and treating CIRI, provide a reference basis for further drug research and development, and offer perspectives on future applications of baicalin in cerebrovascular diseases.

Keywords: Brain ischemia; Cerebral ischemia-reperfusion injury; Baicalin; Neuroprotection

1. Literature Search Strategy

We conducted computerized searches of PubMed, Web of Science, CNKI, Wanfang Data, and VIP databases from inception to December 2024. Chinese search terms included "脑缺血再灌注损伤" or "脑缺血再灌注" and "黄芩苷". English search terms included "Injury, Ischemia-Reperfusion", "Ischemia-Reperfusion Injuries", "Ischemia-Reperfusion Injury", "Cerebral ischemia/reperfusion injury", "Cerebral ischemia-reperfusion injury", and "Baicalin". Inclusion criteria were studies addressing the relationship and mechanisms between baicalin and CIRI. Exclusion criteria were irrelevant literature, dissertations, unpublished studies, systematic reviews, and review articles.

2. Neuroprotective Mechanisms of Baicalin in CIRI

2.1 Attenuating Inflammatory Response Neuroinflammation is an immune response triggered by cerebral ischemia and other stimuli in the brain' s innate immune system, characterized by activation of resident immune cells (microglia and astrocytes) and infiltration of peripheral immune cells. This process leads to increased expression of pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS), which cause blood-brain barrier disruption, neuronal damage, cerebral edema, and impaired neuroplasticity, ultimately exacerbating neurological deficits. While the most effective method to reduce acute cerebral ischemic damage is emergency restoration of cerebral blood flow, this reperfusion paradoxically triggers inflammatory cascades that cause secondary reperfusion injury. Therefore, inflammatory response represents a critical link in CIRI pathophysiology, and its attenuation constitutes an important therapeutic strategy.

Cerebral ischemia enhances expression of pro-inflammatory enzymes including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), accelerating ischemic brain injury progression. Inhibition of iNOS activity has been shown to reduce infarct volume in middle cerebral artery occlusion (MCAO) models, while COX-2 inhibition also ameliorates ischemic brain damage. Triggering receptor expressed on myeloid cells 2 (TREM2), a transmembrane receptor of the immunoglobulin superfamily predominantly expressed on microglia, plays a key role in regulating central nervous system inflammatory responses and phagocytosis of cellular debris. TREM2 activation reduces release of specific pro-inflammatory cytokases and suppresses neuroinflammation. WANG et al. demonstrated in a mouse cerebral ischemia-reperfusion injury (MCAO/R) model that baicalin upregulates TREM2, inhibits production of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and iNOS, effectively suppresses microglial activation and ROS production, enhances microglial phagocytic activity, promotes clearance of cellular debris, reduces infarct volume, and improves neurological deficits.

Toll-like receptors (TLRs) mediate inflammatory responses and participate in the pathophysiology of ischemic brain injury. Among the TLR family, TLR2

and TLR4 have been extensively studied and shown to be associated with initiating brain damage and inflammatory responses in ischemic stroke. TLR2/4 activation triggers nuclear factor- B (NF- B) transcription factor activation. As a downstream transcription factor of the TLR2/4 signaling pathway, NF- B is a key regulator involved in inducing expression of pro-inflammatory mediators such as iNOS, TNF-α, IL-1β, and COX-2. HAO et al. found that baicalin inhibits TNF-α, IL-6, iNOS, TLR2/4, and NF- B, attenuates inflammatory responses, reduces neurological scores, cerebral infarct volume, and brain water content, alleviates histomorphological changes, and suppresses immune cell infiltration, thereby improving ischemic stroke symptoms. LI et al. similarly demonstrated that baicalin effectively reduces elevated expression of TLR2/4, TNF-α, and IL-1β in OGD/R-treated PC12 cells and primary neurons, inhibits NF- B translocation from cytoplasm to nucleus, and significantly decreases expression of TLR2/4, TNF-α, and IL-1β in the hippocampus, mitigating post-injury inflammatory responses. XUE et al. observed that baicalin intervention in MCAO/R models reduces infarct volume in the ipsilateral cerebral cortex and hippocampal CA1 region, possibly through downregulating NF- B p65 expression.

IL-33, a member of the IL-1 family, is highly expressed in multiple human tissues, particularly the brain and spinal cord, and plays important roles in central nervous system pathophysiology. Interleukin-1 receptor-like 1 (IL-1RL1), also known as ST2, has a splice variant ST2L, and the IL-33/ST2L signaling pathway participates in various cardiovascular and cerebrovascular diseases. SUN et al. found that baicalin inhibits the IL-33/ST2L pathway in CIRI rats, reduces serum IL-6 and TNF-α levels, decreases microglial numbers and neurological deficit scores, reduces cerebral infarct area in a dose-dependent manner. These studies collectively demonstrate that baicalin improves neurological function by regulating multiple signaling pathways to attenuate inflammatory responses, representing an effective therapeutic agent for CIRI prevention and treatment.

2.2 Antioxidant Stress Oxidative stress is considered a major factor in numerous diseases including neurodegenerative disorders, multiple sclerosis, hypercholesterolemia, diabetes, and liver cirrhosis. Under normal physiological conditions, appropriate levels of ROS play crucial roles in important physiological processes and are rapidly scavenged by antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-px), and glutathione (GSH). However, excessive ROS is the primary cause of oxidative stress, leading to aggravated brain tissue damage. When the central nervous system undergoes oxidative stress, changes in malondialdehyde (MDA) content serve as a marker, closely associated with alterations in endogenous antioxidant enzymes such as SOD. Numerous studies have identified the nuclear factor E2-related factor 2 (Nrf2) pathway as one of the key and powerful intracellular antioxidant stress pathways. As a transcription factor highly sensitive to oxidative stress, Nrf2, once activated in oxidative stress environments, binds to antioxidant response elements (AREs) in the nucleus, inducing expression of other antioxi-

dant genes and promoting transcription of multiple antioxidant genes. CAO et al. investigated the protective effects of baicalin on transient global cerebral ischemia-reperfusion injury in gerbils, finding that baicalin significantly reduces MDA levels while increasing SOD, GSH, and GSH-px activities, suggesting that its neuroprotective effects against ischemia-reperfusion injury are related to its antioxidant properties.

Both ROS and reactive nitrogen species (RNS) are important neurotoxic factors in CIRI, which not only increase brain tissue susceptibility to ischemic injury but also trigger numerous molecular cascades leading to blood-brain barrier hyperpermeability, hemorrhage, inflammation, and cell death. Peroxynitrite ($ONOO^-$), a typical RNS, can easily cross plasma membranes and oxidize numerous intracellular molecules including lipids, DNA, and proteins, causing protein dysfunction and DNA damage. Increased $ONOO^-$ is closely associated with matrix metalloproteinase-9 (MMP-9) activation, cerebral hemorrhage, blood-brain barrier disruption, and infarct expansion in ischemic brain injury. Therefore, $ONOO^-$ represents an important therapeutic target for CIRI. XU et al. observed that baicalin inhibits 3-nitrotyrosine (3-NT, a biomarker of $ONOO^-$) formation in a rat focal cerebral ischemia-reperfusion model, effectively scavenges $ONOO^-$, exerts antioxidant effects, protects neurons from exogenous and endogenous $ONOO^-$-induced cytotoxicity, reduces neuronal death, and decreases infarct volume.

2.3 Regulating Mitochondrial Homeostasis Mitochondrial function is closely related to mitochondrial dynamics. Under physiological conditions, dynamin-related protein 1 (Drp-1) primarily exists in the cytoplasm; under stress conditions, Drp-1 overexpression and translocation to mitochondria can activate mitochondrial fission and promote apoptosis. Mitofusin-2 (MFN2) regulates mitochondrial fusion by targeting and tethering fusion proteins of adjacent mitochondria. Studies have shown that ROS overexpression is associated with mitochondrial dynamics and may play a role in mitochondrial dynamics during CIRI. Adenosine monophosphate-activated protein kinase (AMPK) has been reported to be activated after cerebral ischemia-induced neuronal injury and participates in regulation of mitophagy. LI et al. investigated the effects of baicalin on CIRI exacerbated by hyperglycemia, demonstrating that under in vitro high glucose (HG) conditions, HG causes Drp-1 upregulation and MFN2 downregulation, while OGD/R induces excessive ROS generation and mitochondrial dynamic damage. Baicalin intervention in PC12 cells reduces ROS expression and regulates AMPK activity, inhibits Drp-1 expression to reduce mitochondrial fission, promotes MFN2 production, increases Drp-1 Ser637 phosphorylation, induces mitophagy, alleviates mitochondrial dynamic damage, maintains mitochondrial homeostasis, promotes cell survival, and reduces infarct volume.

The brain is the organ with the highest metabolic energy consumption, utilizing glucose or lactate as energy sources. In neurons, ATP production primarily

depends on glucose or lactate entering the tricarboxylic acid cycle via the pyruvate dehydrogenase (PDH) complex pathway. PDH complex activity is strictly regulated by allosteric and reversible phosphorylation. Pyruvate dehydrogenase kinase (PDK) phosphorylates serine residues on PDH (E1α) to inhibit PDH activity, thereby reducing energy supply. Therefore, PDK-PDH axis abnormalities play crucial roles in diseases closely related to mitochondrial bioenergetics. In ischemic stroke, neuronal PDH activity is impaired in ischemia-susceptible regions as early as 30 minutes after reperfusion, leading to subsequent energy deficiency and progressive neuronal damage. Existing evidence indicates that mitochondrial ROS production in ischemic tissue results from succinate accumulation mediated by succinate dehydrogenase (SDH) during ischemia and rapid succinate oxidation during early reperfusion. This event occurs almost simultaneously with changes in the PDK-PDH axis, suggesting a possible association between SDH activation and PDH inactivation, with the regulatory protein PDK potentially being a key link. PDK transcription is regulated by hypoxia-inducible factor-1 (HIF-1), a transcription factor that maintains intracellular homeostasis under hypoxic conditions. Previous studies have confirmed that baicalin inhibits SDH and regulates energy metabolism. LIU et al. found that baicalin can inhibit SDH activation under OGD/R conditions, regulate the SDH/ROS/PDK2 axis, reduce excessive ROS production, increase HIF-1 protein expression, decrease PDK2 in neurons and cerebral cortex, increase PDH activity, thereby improving neuronal ATP production and survival, and maintaining neuronal viability after acute ischemic stroke.

2.4 Inhibiting Cell Apoptosis and Pyroptosis

2.4.1 Inhibiting Neuronal Apoptosis Multiple signaling pathways and related genes regulate apoptosis, with the BCL-2 family being closely associated. Myeloid cell leukemia-1 (MCL-1) is a pro-survival gene in the BCL-2 family, initially identified as an immediate-early gene expressed during differentiation of ML-1 myeloid leukemia cells, functioning as an anti-apoptotic gene. Myocardin-related transcription factor-A (MRTF-A) is a powerful co-activator of serum response factor (SRF) and has been found to play key roles in cell proliferation, differentiation, migration, and apoptosis. Studies have shown that SRF/MRTF-A-driven transcription participates in promoting neuronal survival and inhibiting hypoxia/ischemia-induced apoptosis. ZHENG et al. established rat MACO/R models and H_2O_2-induced primary cortical neuron cultures to investigate baicalin' s effects on ischemia-induced neuronal apoptosis. The results indicated that baicalin significantly increases MRTF-A expression levels in ischemic brain tissue and primary cultured cortical neurons both in vivo and in vitro, enhances MCL-1 and BCL-2 transcription and expression, effectively inhibits neuronal apoptosis, markedly alleviates neurological deficits, and reduces cerebral infarct volume.

Elevated intracellular calcium concentration may be involved in various cellular activities including cell proliferation and apoptosis. Ischemic injury trig-

gers excessive glutamate release, causing increased intracellular Ca^{2+} concentration and resulting in excitotoxicity. Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is a key protein involved in Ca^{2+} signaling and plays a critical role in mediating cell death after acute excitotoxic injury, representing a promising neuroprotective target. WANG et al. found that baicalin inhibits ischemia-induced elevation of CaMKII phosphorylation levels in gerbil whole-brain ischemia-reperfusion models, cultured hippocampal neurons, and SH-SY5Y cells, thereby alleviating neuronal apoptosis and exerting neuroprotective effects. Another study also demonstrated that baicalin can inhibit microglial activation and inflammatory responses, suppressing neuronal apoptosis. N-methyl-D-aspartate receptors (NMDARs) are important excitatory amino acid receptors, and upregulation of NMDARs in neurons induces massive Ca^{2+} influx leading to increased caspase-3 activity. ZHOU et al. examined NMDAR1 expression in SH-SY5Y cells after OGD/R injury, finding that OGD/R induces increased NMDAR1 expression, while baicalin pretreatment reduces NMDAR1, caspase-3, and NF- B expression, inhibits cell apoptosis, alleviates CIRI, and reverses OGD/R-induced damage.

Brain-derived neurotrophic factor (BDNF) and caspase-3 are two key regulatory factors in cerebral ischemia, playing critical roles in ischemia-induced neuronal death. CAO et al. found that baicalin exerts anti-apoptotic effects and protects ischemia-injured neurons by upregulating BDNF expression and reducing caspase-3 activity. LUO et al. demonstrated that baicalin reduces lactate dehydrogenase leakage, promotes neural stem cell proliferation, alleviates cell apoptosis, and protects hippocampal neural stem cells in OGD/R injury model rats. XU et al. observed that baicalin inhibits neuronal apoptosis by reducing $ONOO^-$-induced cytotoxicity and alleviating nerve injury. Therefore, baicalin' s anti-apoptotic effects are crucial in preventing and treating CIRI.

2.4.2 Inhibiting Neuronal Pyroptosis Pyroptosis plays a key role in the development of cardiovascular and cerebrovascular diseases. The NLRP3 inflammasome is a protein complex composed of NLRP3, ASC, and p-caspase-1 located in the cytoplasm. During inflammatory responses in vivo, the NLRP3 inflammasome triggers caspase-1 cascade reactions, converting inactive forms of IL-1β and IL-18 into active forms, leading to caspase-1-dependent programmed cell death, namely pyroptosis. AMPK influences energy metabolism, neuronal repair, and angiogenesis in ischemic brain tissue. Studies have shown that the AMPK signaling pathway can inhibit NLRP3 inflammasome activity and plays an important role in mediating systemic inflammatory responses. ZHENG et al. explored the specific molecular mechanisms of baicalin' s neuroprotective effects in vivo and in vitro, finding that after successful MCAO/R modeling, rats showed significantly increased infarct volume, altered neuronal ultrastructure, activated NLRP3 inflammasome, and markedly increased expression of NLRP3, ASC, cleaved caspase-1, IL-1β, and IL-18 compared with the sham group. However, baicalin intervention effectively reversed these phenomena in a dose-dependent manner. Furthermore, in vitro experiments revealed that baicalin treatment

significantly increased p-AMPK expression after OGD/R in neurons. When compound C (a specific AMPK signaling pathway inhibitor) blocked the AMPK pathway, NLRP3 inflammasome expression also increased. Additionally, they found that MCAO/R-induced damaged neurons recovered to near-normal structure with clearly visible organelles after baicalin intervention, further highlighting baicalin' s neuroprotective biological activity. In summary, these results indicate that baicalin alleviates cerebral ischemia-reperfusion-induced neurological damage by regulating the AMPK signaling pathway to inhibit NLRP3 inflammasome-dependent pyroptosis.

2.5 Protecting the Blood-Brain Barrier The blood-brain barrier, formed by brain microvascular endothelial cells connected through tight junction complexes, is essential for controlling substance exchange between peripheral circulation and the central nervous system, maintaining CNS homeostasis and normal function. Tissue plasminogen activator (t-PA) has a limited therapeutic window of 4.5 hours after ischemic stroke; use beyond this window carries risks of hemorrhagic transformation (HT) and neurotoxicity, with blood-brain barrier disruption playing a key role in HT during thrombolytic therapy. Blood-brain barrier disruption and HT can be mediated by various pathological factors, including matrix metalloproteinases (MMPs). $ONOO^-$ plays a critical role in blood-brain barrier disruption and brain injury during CIRI. In animal models of ischemic stroke with delayed t-PA treatment, $ONOO^-$ decomposition catalysts can inhibit MMP activation, prevent blood-brain barrier disruption, reduce HT, and improve neurological outcomes. CHEN et al. validated that baicalin, as a medicinal plant active compound, can attenuate HT damage during cerebral ischemia-reperfusion with delayed t-PA treatment. The specific mechanism involves baicalin directly scavenging $ONOO^-$ and attenuating t-PA-mediated HT by inhibiting $ONOO^-$-mediated MMP-9 activation, thereby protecting blood-brain barrier integrity, reducing cell death, cerebral hemorrhage, and brain edema, and ultimately improving neurological outcomes and reducing mortality in ischemic stroke. Moreover, t-PA activity assays showed that baicalin does not affect t-PA fibrinolytic function, suggesting that baicalin is a potential candidate for combination therapy with t-PA in acute ischemic stroke.

2.6 Maintaining Astrocyte Structure and Function Astrocytes are key structural and functional components of the neurovascular unit, playing crucial roles in maintaining normal brain function and responding to ischemic injury. After ischemic stroke, astrocytes promote neurogenesis, synaptogenesis, and axonal remodeling, thereby facilitating neurological recovery. The critical involvement of astrocytes makes them excellent therapeutic targets for improving post-stroke functional outcomes. BDNF, one of the most important neurotrophic factors, promotes neuronal survival and repairs brain damage after ischemia-reperfusion. Studies have shown that BDNF provides neuroprotection against ischemic stress and inflammation and can reduce apoptosis. TrkB is the endogenous high-affinity receptor for BDNF; after BDNF binds to TrkB, tyrosine

residues in the intracellular domain are autophosphorylated, subsequently activating downstream phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways. The PI3K/Akt and MAPK/ERK1/2 cascades are key signaling pathways promoting neuronal survival and plasticity, providing essential protective effects for neuronal activity after ischemic stroke. LI et al. investigated the neuroprotective mechanism of baicalin in neuron-astrocyte coculture systems under OGD/R conditions, demonstrating that baicalin maintains reactive astrocyte characteristics and significantly increases expression of cyclic AMP response element-binding protein (CREB) and BDNF levels in the co-culture system. By increasing BDNF and its receptor TrkB expression, baicalin promotes release of downstream signaling regulators PI3K/Akt and MAPK/ERK1/2, inhibits inflammatory responses and apoptosis, protects astrocytes, and promotes neuronal recovery.

Aquaporin-4 (AQP4) and transient receptor potential vanilloid receptor 4 (TRPV4) channels are both highly expressed on astrocyte cell membranes. Studies have found that the AQP4/TRPV4 complex is essential for maintaining astrocyte volume. During cerebral ischemia, AQP4 regulation alters cell membrane permeability, subsequently activating and maintaining opening of TRPV4 channels, facilitating Ca^{2+} influx. When osmotic pressure differences develop between intra- and extracellular compartments, water enters cells, ultimately leading to neuronal swelling. ZHENG et al. found that baicalin can inhibit AQP4/TRPV4 expression, further suppress Ca^{2+} influx, reduce water entry into cells after cerebral ischemia-reperfusion, maintain astrocyte structure and function, and protect brain tissue.

2.7 Reducing Neurotoxicity Glutamic acid (Glu) is an excitatory neurotransmitter released by neurons, and Glu excitotoxicity represents a challenge in acute ischemic stroke treatment and a key target for improving neuronal survival. Astrocytes absorb Glu and mediate its conversion to glutamine, ensuring the Glu-glutamine cycle between neurons and astrocytes and maintaining brain function in multiple aspects. Glutamine synthetase (GS), primarily expressed in central nervous system astrocytes, plays a critical role in the Glu-glutamine cycle. GS synthesizes glutamine from Glu and ammonia in an ATP-dependent manner, maintaining neurotransmitter homeostasis by promoting Glu clearance. Therefore, alterations in GS expression and activity are closely associated with neurological dysfunction. SONG et al. investigated baicalin's mechanism against excitotoxicity using primary astrocytes from MCAO/R rats, finding that mitochondrial SDH activation leads to excessive ROS production through reverse electron transport (RET) under OGD/R conditions, increasing astrocyte GS carbonylation and proteasomal degradation. Baicalin intervention reduces SDH-mediated oxidative stress, inhibits ROS production, maintains GS protein stability against oxidative stress, increases astrocyte Glu processing, and protects neurons from excitotoxicity. ZHENG et al. also found that baicalin can inhibit TRPV4 expression in MCAO/R rats, further suppress Ca^{2+} influx, effectively

reduce Glu content in brain tissue, alleviate excitotoxicity, and protect brain tissue after ischemia-reperfusion. These studies collectively suggest that reducing neurotoxicity is an effective strategy for baicalin in CIRI prevention.

3. Discussion and Outlook

Scutellaria baicalensis is a widely used traditional Chinese medicine with thousands of years of medicinal history. Baicalin, as a flavonoid natural compound considered the main active component of *Scutellaria*, has been investigated for disease prevention and treatment due to its extensive pharmacological effects. Current evidence demonstrates that baicalin alleviates post-ischemia-reperfusion neurological damage through multi-target, multi-pathway approaches including attenuating inflammatory responses, exerting antioxidant effects, regulating mitochondrial homeostasis, inhibiting apoptosis and pyroptosis, protecting the blood-brain barrier, maintaining astrocyte structure and function, and reducing neurotoxicity. These findings provide new biological targets and potential mechanisms for CIRI treatment.

However, several issues remain. First, current research on baicalin for CIRI primarily relies on cellular and animal models, with insufficient clinical validation of its efficacy and safety in humans. Due to interspecies differences, current basic experiments cannot comprehensively elucidate its therapeutic mechanisms. Second, while specific mechanisms of post-ischemia-reperfusion neurological damage continue to expand with molecular biology advances, current research mainly focuses on single pathways without revealing deep connections between mechanisms. Additionally, drug dosages and optimal dosing lack uniform standards, and poor bioavailability limits widespread application.

Future research should employ advanced detection technologies and multidisciplinary approaches to explore baicalin' s drug dosage, pharmacokinetics, especially brain pharmacokinetics, and analyze deep connections between pathways and additional potential mechanisms. Second, extensive clinical trials are needed to clarify baicalin' s therapeutic effects and safety in humans, providing more reliable evidence for CIRI prevention and treatment. Furthermore, although numerous studies have shown baicalin can prevent and treat diseases by regulating various programmed and non-programmed cell death modalities, current research on baicalin regulating cell death in CIRI only involves apoptosis and pyroptosis. Therefore, investigating baicalin' s mechanisms through regulating other cell death modalities represents a future research direction that may further supplement and 完善 its molecular mechanisms and targets for CIRI prevention. In summary, baicalin demonstrates significant potential against post-ischemia-reperfusion neurological injury and can provide more options for ischemic stroke prevention and treatment, though specific mechanisms and applications require further refinement.

Table 1 Neuroprotective mechanisms of baicalin in CIRI

Animal/Cell Model	Intervention	Key Molecular Changes	Neuroprotective Effect
Male C57BL/6J mice and BV2 cells	MCAO/R and OGD/R	TREM2 ↑, IL-1β ↓, TNF-α ↓, iNOS ↓	Attenuating inflammatory response
Rat BMEC (CP-R108) and adult male SD rats	OGD/R and MCAO/R	TNF-α ↓, IL-6 ↓, iNOS ↓, TLR2 ↓, TLR4 ↓, NF- B ↓	Attenuating inflammatory response
Female Wistar rats and PC12 cells	MCAO/R and OGD/R	TLR2/4 ↓, TNF-α ↓, IL-1β ↓, NF- B p65 ↓	Attenuating inflammatory response
Adult male Wistar rats	MCAO/R	NF- B p65 ↓	Attenuating inflammatory response
Adult male Mongolian gerbils	MCAO/R	MDA ↓, SOD ↑, GSH ↑, GSH-px ↑	Antioxidant stress
Male SD rats and SH-SY5Y neurons	MCAO/R and OGD/R	3-NT ↓, $ONOO^-$ ↓	Antioxidant stress
Adult male SD rats and PC12 cells	MCAO/R and OGD/R	AMPK ↑, ROS ↓, Drp-1 ↓, Drp-1 Ser637 ↑, MFN2 ↑	Regulating mitochondrial homeostasis
Male SD rats and mouse neuroblastoma N2a cells	MCAO/R and OGD/R	SDH ↓, ROS ↓, HIF-1 ↑, PDK2 ↓, PDH ↑	Regulating mitochondrial homeostasis
Adult male SD rats and primary cortical neurons from neonatal SD rats	MCAO/R	MRTF-A ↑, MCL-1 ↑, BCL-2 ↑	Inhibiting cell apoptosis
Adult male Mongolian gerbils and SH-SY5Y cells	Whole-brain ischemia-reperfusion	CaMKII ↓	Inhibiting cell apoptosis
SH-SY5Y cells	OGD/R	NMDAR1 ↓, caspase-3 ↓, NF- B ↓	Inhibiting cell apoptosis
Male SD rats and human SH-SY5Y neuroblastoma cells	MCAO/R and OGD/R	3-nitrotyrosine ↓	Inhibiting cell apoptosis

Animal/Cell Model	Intervention	Key Molecular Changes	Neuroprotective Effect
SD rats	OGD/R	LDH leakage ↓, NSCs ↑	Inhibiting cell apoptosis
SD rats and neurons	MCAO/R and OGD/R	caspase-1 ↓, IL-1β ↓, IL-18 ↓	Inhibiting pyroptosis
Male SD rats	MCAO/R	$ONOO^-$ ↓, MMP-9 ↓, HT ↓	Protecting blood-brain barrier
Neonatal SD rat neuron-astrocyte co-cultures	OGD/R	BDNF ↑, TrkB ↑, PI3K/Akt ↑, MAPK/ERK1/2 ↑	Maintaining astrocyte structure and function
Male SD rats	MCAO/R	AQP4/TRPV4 ↓, Ca^{2+} ↓, Glu ↓	Maintaining astrocyte structure and function
Male SD rats and astrocytes	MCAO/R and OGD/R	SDH ↓, ROS ↓, GS ↑	Reducing neurotoxicity
Male SD rats	MCAO/R	TRPV4 ↓, Ca^{2+} ↓, Glu ↓	Reducing neurotoxicity

Note: TREM2=triggering receptor expressed on myeloid cells 2, IL-1β=interleukin-1β, TNF-α=tumor necrosis factor-α, iNOS=inducible nitric oxide synthase, IL-6=interleukin-6, TLR2/4=Toll-like receptor 2/4, NF- B=nuclear factor- B, MDA=malondialdehyde, SOD=superoxide dismutase, GSH=glutathione, GSH-px=glutathione peroxidase, BDNF=brain-derived neurotrophic factor, caspase-3=cysteine-aspartic acid protease-3, $ONOO^-$=peroxynitrite, AMPK=adenosine monophosphate-activated protein kinase, ROS=reactive oxygen species, Drp-1=dynamin-related protein 1, MFN2=mitofusin-2, SDH=succinate dehydrogenase, HIF-1=hypoxia-inducible factor-1, PDK2=pyruvate dehydrogenase kinase 2, PDH=pyruvate dehydrogenase, MRTF-A=myocardin-related transcription factor-A, MCL-1=myeloid cell leukemia-1, BCL-2=B-cell lymphoma-2, CaMKII=Ca^{2+}/calmodulin-dependent protein kinase II, NMDAR1=N-methyl-D-aspartate receptor, LDH=lactate dehydrogenase, NLRP3=NOD-like receptor protein 3, IL-18=interleukin-18, MMP-9=matrix metalloproteinase-9, HT=hemorrhagic transformation, PI3K=phosphatidylinositol 3-kinase, Akt=protein kinase B, MAPK=mitogen-activated protein kinase, ERK1/2=extracellular signal-regulated kinase 1/2, AQP4=aquaporin-4, TRPV4=transient receptor potential vanilloid receptor 4, Glu=glutamate, GS=glutamine synthetase.

Author Contributions: QIN Wenxiu was responsible for conceptualization, design, and manuscript writing; KONG Qingjie and WEI Gang conducted literature searches; SUN Huiying edited and organized tables; WANG Qi revised and proofread the manuscript; XU Junfeng provided overall supervision and management.

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