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REVIEW ARTICLE

Baicalein-loaded biomimetic PLGA nanoparticles for ferroptosis-targeted neuroprotection in cerebral ischemia–reperfusion injury

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Abstract

Cerebral ischemia–reperfusion injury (CIRI) contributes to secondary neurological injury following ischemic stroke, with ferroptosis increasingly recognized as an important mechanism involving iron dysregulation, lipid peroxidation, impaired glutathione-dependent antioxidant defenses, and mitochondrial dysfunction. This review summarizes the molecular mechanisms of ferroptosis in CIRI, evaluates evidence regarding baicalein, a bioactive flavonoid from *Scutellaria baicalensis* Georgi, and examines biomimetic nanocarrier strategies for ischemic stroke. A structured literature search was conducted in PubMed, Scopus, and Web of Science for publications from January 2015 to January 2026, focusing on CIRI and ferroptosis; baicalein and cerebral ischemia/neuroprotection; baicalein and ferroptosis; and poly(lactic-co-glycolic acid) (PLGA)-based and biomimetic nanocarrier strategies. The literature indicates that ferroptosis is closely associated with oxidative stress, iron dysregulation, impaired antioxidant defense, lipid peroxidation, mitochondrial dysfunction, and neuroinflammation in CIRI. Experimental evidence suggests that baicalein may modulate ferroptosis-related pathways, including those involving glutathione peroxidase 4 (GPX4) and acyl-CoA synthetase long-chain family member 4 (ACSL4), while also influencing oxidative and inflammatory responses. PLGA-based and biomimetic nanocarriers may improve the delivery of neuroprotective compounds, and platelet membrane camouflage may provide additional biomimetic properties relevant to targeted delivery. However, direct evidence integrating baicalein, PLGA-based delivery, and platelet membrane camouflage into a single ferroptosis-targeted platform for CIRI remains limited. This proposed integration represents a hypothesis-driven direction for future preclinical research. Further studies are needed to establish mechanistic validity, optimize delivery characteristics, evaluate pharmacokinetics and biosafety, and determine therapeutic efficacy in clinically relevant models.

Keywords: Cerebral ischemia–reperfusion injury; Ferroptosis; Baicalein; Poly(lactic-co-glycolic acid) nanoparticles; Biomimetic nanomedicine; Platelet membrane camouflage; Blood–brain barrier; Targeted drug delivery

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1. Introduction

Ischemic stroke accounts for 80%–90% of all strokes and remains a major cause of death and long-term neurological disability worldwide.[1] Although substantial advances have been made in reperfusion therapies, including intravenous thrombolysis and mechanical thrombectomy, neurological recovery remains incomplete in a considerable proportion of patients. Restoration of cerebral blood flow may be followed by cerebral ischemia–reperfusion injury, a complex secondary injury involving multiple interconnected pathological mechanisms, including oxidative stress, excitotoxicity, mitochondrial dysfunction, blood–brain barrier disruption, neuroinflammation, microvascular impairment, and various forms of regulated cell death.[1-3] These processes can contribute to progressive neuronal injury and impaired neurological recovery, providing a rationale for therapeutic strategies that target multiple pathological pathways.[3] Experimental studies have further demonstrated that baicalein may attenuate cerebral ischemia–reperfusion injury through modulation of ferroptosis-related pathways, including the glutathione peroxidase 4 (GPX4)/acyl-CoA synthetase long-chain family member 4 (ACSL4)/ACSL3 axis, and through suppression of ferroptosis and endoplasmic reticulum stress.[4,5] In parallel, biomimetic nanomedicine and platelet membrane-camouflaged delivery systems have emerged as promising approaches for improving targeted drug delivery in ischemia–reperfusion injury.[6,7]

Ferroptosis, which is closely associated with oxidative stress and iron dysregulation, has emerged as a potential therapeutic target in cerebral ischemia–reperfusion injury.[7] It is a regulated, iron-dependent form of cell death characterized by excessive lipid peroxidation, impaired glutathione-dependent antioxidant defenses, reduced GPX4 activity, and characteristic mitochondrial ultrastructural alterations. Increasing evidence suggests that ferroptosis contributes to neuronal injury following ischemic stroke, including injury occurring in the ischemic penumbra.[7] Accordingly, pharmacological modulation of ferroptosis has attracted growing interest as a potential neuroprotective approach for limiting secondary brain injury after ischemic stroke.[7]

Baicalein, a bioactive flavonoid derived from *Scutellaria baicalensis* Georgi, has demonstrated diverse pharmacological activities and neuroprotective potential in experimental models.[3] Experimental evidence suggests that baicalein can modulate ferroptosis-related pathways, including pathways involving GPX4 and ACSL4/ACSL3. However, these findings should be interpreted with appropriate mechanistic caution, as changes in individual ferroptosis-related markers do not, by themselves, establish ferroptotic cell death as the definitive mechanism underlying neuroprotection. Further investigation is therefore required to clarify the specific contribution of ferroptosis modulation to baicalein-mediated neuroprotection. To address drug-delivery limitations associated with neuroprotective compounds, nanotechnology-based delivery systems have emerged as a potential strategy.[8,9] Poly(lactic-co-glycolic acid) (PLGA) nanoparticles have received considerable attention because of their biodegradability, biocompatibility, capacity for drug encapsulation, and potential for controlled release. Baicalein has also been investigated for its neuroprotective effects by modulating nuclear factor-kappa B (NF-κB)- and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1)-related pathways, as well as AMP-activated protein kinase (AMPK)/nuclear factor erythroid 2–related factor 2 (NRF2) signaling, in experimental cerebral ischemia–reperfusion injury.[10] In addition, baicalein has been identified as a potential ferroptosis inhibitor in experimental research.[11] However, the available evidence does not establish ferroptosis inhibition as the sole mechanism responsible for the neuroprotective effects of baicalein, as its reported actions involve multiple interconnected cellular pathways. Platelet membrane-coated PLGA nanoparticles have been investigated as biomimetic delivery systems that may modify nanoparticle interactions with biological environments and injured vascular tissues.[12] Nanoparticle-based approaches have also been investigated for improving brain delivery of flavonoid compounds in cerebral ischemia.[13] More broadly, functionalized biomimetic nanoparticles have been explored for targeted therapeutic applications in cerebral ischemia–reperfusion injury.[14] Together, these findings provide a rationale for investigating PLGA-based and biomimetic strategies as potential delivery platforms for neuroprotective compounds such as baicalein.

In addition to summarizing the existing evidence, this review critically evaluates the strengths and limitations of current research and its translational relevance to ferroptosis-targeted neuroprotective strategies in cerebral ischemia–reperfusion injury. Particular attention is given to inconsistencies in experimental findings, unresolved mechanistic questions, and major barriers to clinical translation. Rather than considering baicalein, PLGA nanoparticles, and platelet membrane camouflage as separate therapeutic components, this review integrates these three elements into a coherent conceptual framework and critically examines the biological rationale for their combination. By doing so, the review aims not only to synthesize current knowledge but also to identify key research priorities and future directions required to evaluate the feasibility of biomimetic anti-ferroptotic nanomedicine for ischemic stroke.

2. Search strategy and selection criteria

A structured literature search was conducted to identify relevant and up-to-date evidence using three electronic databases: PubMed, Scopus, and Web of Science. Publications from January 2015 to January 2026 were considered. Combinations of Medical Subject Headings (MeSH) terms and free-text keywords were used, covering cerebral ischemia–reperfusion injury, ischemic stroke, ferroptosis, baicalein, biomimetic nanoparticles, platelet membrane coating, blood–brain barrier targeting, and PLGA.

The literature search was structured around four complementary concept groups to capture the distinct but interconnected evidence domains addressed in this review. The following search strategies were applied to the selected databases, with the date range restricted to January 2015 through January 2026. In PubMed, the search strategy was structured as follows:

(i) Search 1. Cerebral ischemia–reperfusion injury and ferroptosis: ("cerebral ischemia-reperfusion" OR "cerebral ischemia/reperfusion" OR "ischemic stroke" OR "brain ischemia") AND ("ferroptosis" OR "ferroptotic cell death" OR GPX4 OR ACSL4 OR SLC7A11).

(ii) Search 2. Baicalein and cerebral ischemia/neuroprotection: ("baicalein" OR "*Scutellaria baicalensis*") AND ("cerebral ischemia-reperfusion" OR "cerebral ischemia/reperfusion" OR "ischemic stroke" OR "brain ischemia" OR neuroprotection).

(iii) Search 3. Baicalein and ferroptosis: ("baicalein" OR "Scutellaria baicalensis") AND ("ferroptosis" OR "ferroptotic cell death" OR GPX4 OR ACSL4 OR "lipid peroxidation").

(iv) Search 4. PLGA, biomimetic nanocarriers, and brain-targeted delivery: ("PLGA" OR "poly(lactic-co-glycolic acid)" OR nanoparticle* OR "biomimetic nanoparticle*" OR "platelet membrane*" OR "cell membrane-coated nanoparticle*") AND ("brain delivery" OR "brain targeting" OR "nose-to-brain" OR "blood-brain barrier" OR "cerebral ischemia" OR "ischemic stroke" OR "ischemia-reperfusion").

The conceptual search structure was adapted to Scopus using the TITLE-ABS-KEY field and to the Web of Science Core Collection using the Topic (TS) field, with database-specific syntax and indexing conventions applied where necessary. The same four conceptual search domains and the January 2015–January 2026 date restriction were maintained across databases. Web of Science Topic searches cover title, abstract, author keywords, and Keywords Plus, while database-specific field syntax was adapted to the respective search interfaces.

The four searches retrieved 552, 84, 109, and 4,937 records, respectively, from PubMed, and 780, 473, 275, and 817 records, respectively, from Scopus. The corresponding Web of Science search records were exported and retained in Excel format as the underlying database for the four searches.

After removing duplicates, the retrieved publications were initially screened by title and abstract for relevance to the scope of this review. Publications considered potentially relevant were subsequently assessed in full text. Studies were retained if they provided experimental, mechanistic, pharmacological, or technological evidence directly relevant to ferroptosis in cerebral ischemia–reperfusion injury, the neuroprotective or anti-ferroptotic effects of baicalein, or PLGA-based and biomimetic nanocarrier strategies relevant to brain-targeted delivery. Review articles were consulted to establish the scientific background, identify relevant concepts, and locate additional primary studies; however, primary experimental studies were preferentially considered when evaluating specific mechanistic or therapeutic evidence. Studies were excluded if they were unrelated to the predefined scope, duplicated publications, conference abstracts, editorials, letters, or non-English publications.[15] When a study addressed more than one relevant domain, it was included based on the specific evidence it contributed to the review. The selected studies were subsequently evaluated for methodological characteristics, mechanistic relevance, consistency of findings, and translational significance.

For studies investigating ferroptosis in cerebral ischemia–reperfusion injury, particular emphasis was placed on the strength of evidence supporting ferroptosis involvement and the potential relevance of ferroptosis-targeted interventions. Evidence concerning the pharmacology of baicalein and biomimetic nanomedicine was subsequently considered in relation to these mechanisms to develop an integrated conceptual framework for identifying current challenges and future therapeutic opportunities.

For the selected experimental studies, methodological characteristics were considered, including the experimental design, animal or cellular model, timing and duration of intervention, endpoints assessed, the degree of mechanistic evidence supporting ferroptosis involvement, translational relevance, and potential sources of bias. Greater interpretive weight was assigned to studies that evaluated multiple complementary molecular or biochemical features associated with ferroptosis, including GPX4, ACSL4, solute carrier family 7 member 11 (SLC7A11), lipid peroxidation, and iron metabolism, particularly when pharmacological or experimental evidence linked ferroptosis modulation to

the observed cellular or tissue injury.

Ferroptosis in ischemic stroke has been extensively discussed in previous reviews.[7] Related aspects of baicalein pharmacology, PLGA-based nanocarriers, and biomimetic nanoparticle strategies have also been addressed in separate areas of the literature.[16-18] However, based on the literature reviewed in the present study and the comparison summarized in Table 1, these areas appear to have been largely examined as separate topics rather than as components of a unified therapeutic concept. To the best of my knowledge, the integration of the anti-ferroptotic pharmacology of baicalein with PLGA-based nanocarriers incorporating platelet membrane camouflage for targeted delivery in cerebral ischemia–reperfusion injury has not been comprehensively addressed in previous reviews. The present review therefore integrates these fragmented areas to examine their biological rationale, translational challenges, and potential therapeutic implications.

3. Cerebral ischemia–reperfusion injury: pathophysiology and neuroinflammation

Cerebral ischemia–reperfusion injury is a complex pathological process initiated by cerebral ischemia and further modified during restoration of blood flow (Figure 1). Although reperfusion is essential for salvaging ischemic brain tissue, it can also contribute to secondary injury through multiple interconnected molecular and cellular mechanisms.[19] These mechanisms include energy failure, excitotoxicity, oxidative stress, mitochondrial dysfunction, blood–brain barrier disruption, sterile inflammation, microvascular injury, and several forms of regulated cell death.[20] Their interaction contributes to progressive neuronal injury, particularly within the ischemic penumbra, and provides multiple potential targets for limiting secondary brain damage.[19]

During the initial ischemic phase, interruption of oxygen and glucose supply causes rapid ATP depletion and loss of cellular energy homeostasis, leading to membrane depolarization and dysfunction of energy-dependent ion transport mechanisms, including the Na^+/K^+-ATPase [21]. Membrane depolarization and energy failure promote excessive glutamate release and sustained activation of ionotropic glutamate receptors, including N-methyl-*D*-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, thereby contributing to excitotoxic neuronal injury.[22] The resulting intracellular Ca^{2+} overload further contributes to mitochondrial dysfunction, activation of calcium-dependent proteases, cytoskeletal damage, and activation of multiple cell-death pathways.[21] Cells within the ischemic core undergo severe and often irreversible injury, whereas cells in the surrounding ischemic penumbra remain metabolically compromised but may retain therapeutic potential, making the penumbra a major target for neuroprotective interventions.[22]

During reperfusion, rapid restoration of oxygen availability can contribute to excessive generation of reactive oxygen species (ROS), thereby amplifying oxidative injury.[21] Mitochondrial electron transport chain dysfunction and activation of enzymatic ROS sources, including nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidases and xanthine oxidase, can increase oxidant production beyond endogenous antioxidant capacity.[19] Excessive ROS generation promotes lipid peroxidation, protein oxidation, DNA damage, mitochondrial membrane instability, and impairment of cellular bioenergetics.[23] Mitochondrial dysfunction may subsequently promote mitochondrial permeability transition, loss of mitochondrial membrane potential, and further propagation of oxidative injury, thereby contributing to a self-amplifying cycle of neuronal damage during reperfusion.[24]

Neuroinflammation is another major component of secondary injury following cerebral ischemia and reperfusion.[25] Activation of resident microglia, together with infiltration and interaction of peripheral immune cells, contributes to the production of pro-inflammatory cytokines, chemokines, nitric oxide, and other inflammatory mediators that can exacerbate tissue injury.[26] These inflammatory responses interact with oxidative stress and other injury pathways and may increase susceptibility to secondary neuronal damage within the ischemic microenvironment.[27] Thus, neuroinflammation should be considered as an interconnected component of cerebral ischemia–reperfusion injury rather than an isolated pathological process.

Blood–brain barrier disruption further contributes to cerebral ischemia–reperfusion injury by increasing communication between the injured brain and circulating peripheral factors. Loss of blood–brain barrier integrity can increase vascular permeability and allow circulating immune cells and inflammatory mediators to enter the ischemic brain. These changes contribute to edema, amplify inflammatory responses, and worsen neuronal injury. Maintenance of neurovascular unit integrity therefore remains an important component of limiting secondary brain damage following cerebral ischemia–reperfusion.

Neuronal death following cerebral ischemia–reperfusion injury is increasingly understood as the result of interactions among multiple regulated cell-death pathways rather than activation of a single isolated mechanism.[28] Apoptosis, necroptosis, pyroptosis,

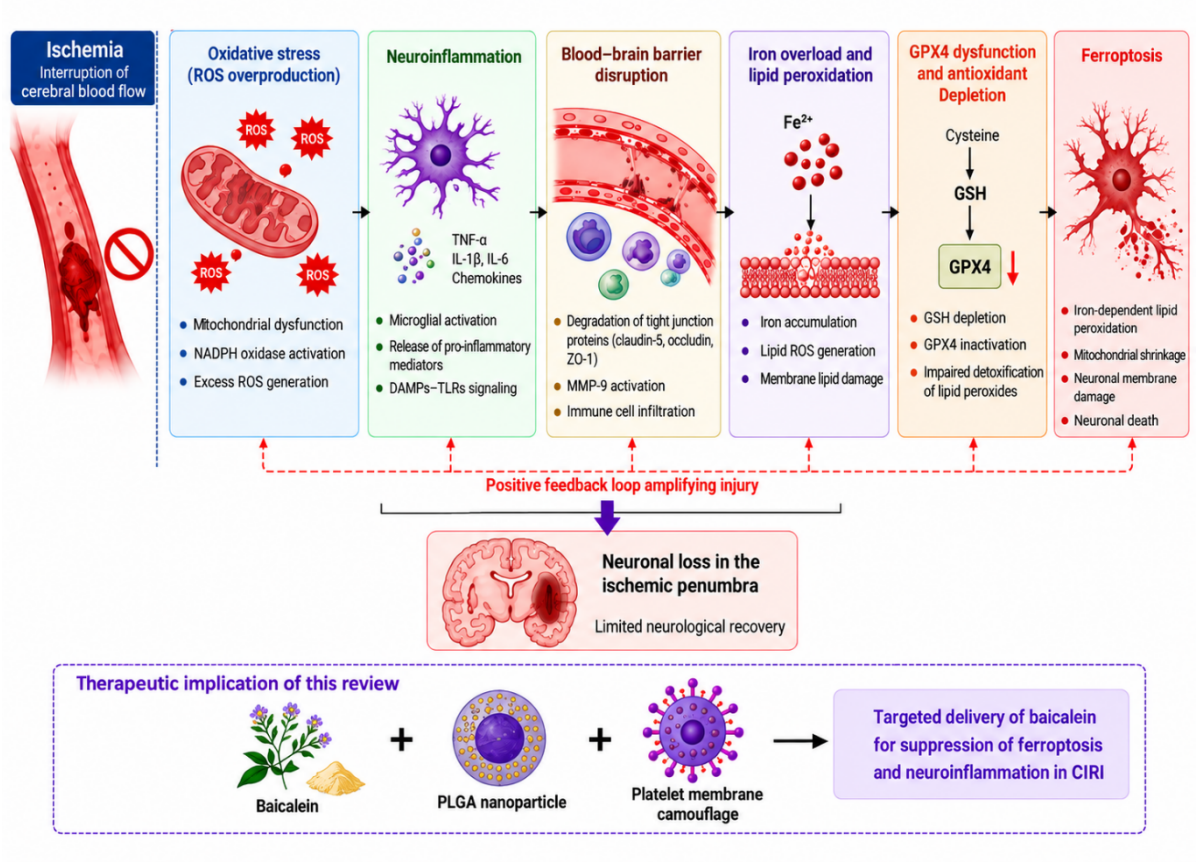


Figure 1. Pathophysiological cascade of cerebral ischemia–reperfusion injury (CIRI) and its relationship to ferroptosis. Schematic diagram of the major pathological events during CIRI. Excessive oxidative stress, neuroinflammation, blood–brain barrier disruption, iron overload, lipid peroxidation, and GPX4 dysfunction all contribute to ferroptosis and progressive neuronal loss in the ischemic penumbra following ischemia and subsequent reperfusion. The lower panel highlights the therapeutic concept proposed in this review: suppressing ferroptosis-mediated neuronal injury and enhancing targeted brain delivery by co-delivering baicalein with poly(lactic-co-glycolic acid) (PLGA) nanoparticles coated with platelet membranes.
Abbreviations: DAMP: Damage-associated molecular pattern; GPX4: Glutathione peroxidase 4; GSH: Glutathione; IL-1β: Interleukin-1 beta; MMP-9: Matrix metalloproteinase-9; NADPH: Nicotinamide adenine dinucleotide phosphate; ROS: Reactive oxygen species; TLRs: Toll-like receptors; TNF-α: Tumor necrosis factor-alpha; ZO-1: Zonula occludens-1.

autophagy-associated cell-death processes, and ferroptosis have all been implicated in the dynamic ischemic microenvironment and may exhibit substantial molecular crosstalk.[27] Among these pathways, ferroptosis has received particular attention because it intersects with several major components of ischemia–reperfusion injury, including oxidative stress, iron dysregulation, glutathione-dependent antioxidant defense, and lipid peroxidation.[29] The interaction between ferroptotic and inflammatory signaling pathways may further contribute to neuronal injury, supporting continued investigation of ferroptosis as a potential target within broader multi-mechanistic neuroprotective strategies.[30]

Ferroptosis is a distinct form of regulated cell death characterized by iron-dependent phospholipid peroxidation and subsequent loss of membrane integrity.[28,31] Despite significant advances in understanding the pathophysiological mechanisms of cerebral ischemia–reperfusion injury, several important questions remain unresolved.[21] Most experimental studies have been conducted in young and otherwise healthy animals, which may not adequately reflect the clinical heterogeneity of stroke patients, who are often older and frequently have pre-existing comorbidities such as hypertension, diabetes mellitus, and atherosclerosis.[32] Furthermore, the relative contribution of individual pathological mechanisms—including oxidative stress, neuroinflammation, ferroptosis, apoptosis, and microvascular dysfunction—may vary according to the severity and duration of ischemia, the timing of reperfusion, and the temporal stage of injury.[33]

These factors should therefore be considered when interpreting mechanistic findings, particularly because clinical translation of interventions targeting a single pathological pathway has often shown limited success.[34] Collectively, these limitations support the development of multi-targeted therapeutic strategies designed to address multiple interconnected pathological mechanisms rather than focusing exclusively on a single molecular pathway.[35]

4. Ferroptosis mechanisms in stroke

Ferroptosis is a distinct form of regulated cell death characterized by iron-dependent phospholipid peroxidation and subsequent catastrophic membrane damage.[27] Since its first description in 2012, ferroptosis has been increasingly recognized as an important mechanism contributing to neuronal loss during cerebral ischemia–reperfusion injury.[36] Unlike apoptosis, necrosis, or pyroptosis, ferroptosis exhibits distinct morphological and biochemical characteristics, including mitochondrial shrinkage, increased mitochondrial membrane density, diminished or absent cristae, and disruption of the outer mitochondrial membrane, without the typical hallmarks of apoptosis, such as chromatin condensation or caspase activation.[31,37]

Oxidative stress, mitochondrial dysfunction, iron accumulation, glutathione depletion, and lipid peroxidation are closely interconnected processes involved in ferroptotic injury.[27] Within the ischemic penumbra, these mechanisms may interact to promote progressive neuronal damage and expansion of ischemic injury.[36] Accordingly, pharmacological targeting of ferroptosis has emerged as a promising therapeutic approach for reducing secondary brain injury following ischemic stroke.[38,39] The major molecular pathways involved in ferroptosis and the proposed anti-ferroptotic actions of baicalein are summarized in Figure 2.

4.1. Glutathione peroxidase 4 and the glutathione system

Glutathione peroxidase 4 is considered a major endogenous antioxidant defense against ferroptosis. Using reduced glutathione as an essential cofactor, GPX4 converts phospholipid hydroperoxides into their corresponding non-toxic lipid alcohols. Therefore, maintenance of the GPX4–glutathione antioxidant system is essential for preventing uncontrolled lipid peroxidation and subsequent membrane damage.[28]

The progressive impairment of endogenous antioxidant defenses and the complex interaction between oxidative stress and other pathological mechanisms may contribute to neuronal injury following cerebral ischemia–reperfusion. However, the precise contribution of individual molecular pathways should be interpreted cautiously because preclinical stroke models have important translational limitations.[36]

Reduced GPX4 expression has been associated with increased lipid peroxidation, mitochondrial damage, and cellular injury in experimental models relevant to ferroptosis.[27,40] Conversely, interventions aimed at preserving or restoring GPX4 activity have been investigated as potential approaches to attenuate ferroptotic injury. Some of these interventions may act by modulating antioxidant pathways, including the NRF2/SLC7A11/GPX4 signaling axis.[28] Collectively, these observations support the potential importance of preserving GPX4 function as one component of strategies to reduce ferroptosis-related neuronal injury after cerebral ischemia–reperfusion.[28] Disruption of the GPX4–glutathione antioxidant system represents an important mechanistic link between oxidative stress and ferroptosis-associated neuronal injury (Figure 2).

Recent studies also suggest that GPX4 activity may be regulated through complementary mechanisms beyond transcriptional regulation.[28] Post-translational mechanisms, including ubiquitination, deubiquitination, protein stabilization, and intracellular protein degradation, represent additional levels of regulation relevant to ferroptosis.[41] Based on these findings, therapeutic interventions aimed at regulating GPX4 protein homeostasis may provide a complementary approach to conventional antioxidant strategies and warrant further investigation as potential neuroprotective interventions in ischemic stroke.[42]

4.2. Lipid peroxidation and membrane damage

Lipid peroxidation represents a hallmark and an irreversible execution stage of chemically induced ferroptosis. This process begins with the iron-dependent oxidation of polyunsaturated fatty acid (PUFA)-containing phospholipids, leading to progressive loss of membrane integrity, disruption of cellular homeostasis, and ultimately irreversible neuronal death. Phosphatidylethanolamines, particularly PUFA-containing phosphatidylethanolamine species, are highly susceptible to oxidative modification and represent important substrates for ferroptotic membrane injury.[27,43]

The susceptibility of neuronal membranes to ferroptosis is strongly influenced by phospholipid-remodeling enzymes, particularly ACSL4 and lysophosphatidylcholine acyltransferase 3 (LPCAT3). ACSL4 catalyzes the conversion of long-chain PUFAs into PUFA-CoA derivatives, whereas LPCAT3 incorporates these activated fatty acid derivatives

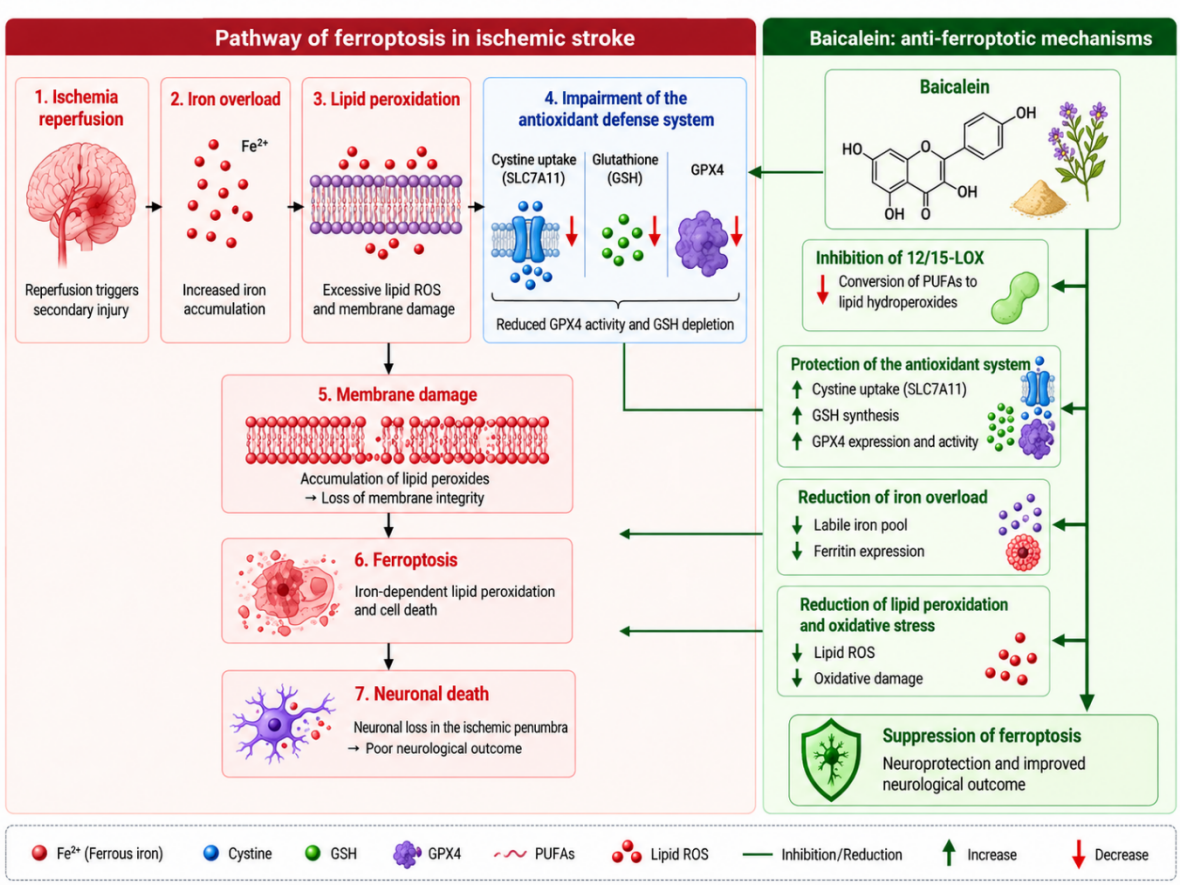


Figure 2. Molecular mechanisms of ferroptosis in cerebral ischemia–reperfusion injury. Ferroptosis is a novel type of cell death distinct from necrosis and apoptosis, and baicalein exerts anti-ferroptotic effects in cerebral ischemia–reperfusion injury. Iron accumulation, glutathione depletion, GPX4 inactivation, and phospholipid peroxidation ultimately lead to iron-mediated neuronal death via ferroptosis in cerebral ischemia–reperfusion. The ability of baicalein to inhibit ferroptosis is achieved through the inhibition of 12/15-lipoxygenase (12/15-LOX), the maintenance of the GPX4–glutathione (GSH) antioxidant system, the decrease of iron overload in the cell, the reduction of phospholipid peroxidation, and, ultimately, the suppression of ferroptosis. Image created by the authors with Microsoft PowerPoint.

Abbreviations: 12/15-LOX: 12/15-lipoxygenase; GPX4: Glutathione peroxidase 4; GSH: Glutathione; PUFA: Polyunsaturated fatty acid; ROS: Reactive oxygen species; SLC7A11: Solute carrier family 7 member 11.

into membrane phospholipids, generating substrates that are highly susceptible to peroxidation and promoting lipid peroxide accumulation. Increased ACSL4 expression has been associated with enhanced lipid peroxidation and aggravated ischemic neuronal injury in experimental models of cerebral ischemia–reperfusion, suggesting that ACSL4 is an important mechanistic regulator and potential therapeutic target in ferroptosis.[28]

12/15-Lipoxygenase (12/15-LOX) is an important enzyme involved in the oxidation of PUFA-containing phospholipids and may contribute to the propagation of ferroptotic membrane damage. Experimental studies have implicated 12/15-LOX in cerebral ischemia–reperfusion injury and associated lipid peroxidation. Moreover, pharmacological inhibition or genetic suppression of 12/15-LOX has been associated with reduced ischemic brain injury and improved neurological outcomes, supporting its potential as a therapeutic target for limiting ferroptotic damage. This mechanism is particularly relevant to the present review because baicalein has been investigated as a 12/15-LOX inhibitor with potential anti-ferroptotic and neuroprotective effects in ischemic stroke.[28]

Lipid peroxidation products, including malondialdehyde, 4-hydroxynonenal, and F_2-isoprostanes, are commonly used as indicators of oxidative membrane damage and lipid peroxidation associated with ferroptotic injury. In addition to their value as biomarkers, reactive lipid-derived products such as malondialdehyde and

4-hydroxynonenal may contribute to tissue injury through covalent modification of proteins, nucleic acids, and membrane components, thereby perpetuating oxidative damage beyond the initial ischemic insult. Collectively, these observations support the inhibition of lipid peroxidation as an important therapeutic strategy for preserving neuronal membrane integrity and reducing ferroptosis after cerebral ischemia–reperfusion injury.[27,28]

4.3. Iron overload and dysregulated iron metabolism

Iron dysregulation is a central feature of ferroptosis and contributes to oxidative membrane damage during cerebral ischemia–reperfusion injury.[27] Excess intracellular ferrous iron (Fe^{2+}) can catalyze Fenton reactions, generating highly reactive hydroxyl radicals that initiate and propagate lipid peroxidation, thereby contributing to neuronal injury.[44] During cerebral ischemia–reperfusion, several complementary mechanisms may disrupt iron homeostasis, including hemoglobin degradation following microvascular injury, increased transferrin receptor–mediated iron uptake, impaired intracellular iron sequestration, and reduced iron export.[45] Collectively, these alterations can expand the labile iron pool and thereby promote ferroptotic cell death.[27]

Ferritin is a heteropolymeric iron-storage complex composed of ferritin heavy (FTH1) and light (FTL) chains and plays an important role in maintaining cellular iron homeostasis by safely sequestering excess iron and limiting its toxicity.[27] Ferritin can undergo selective autophagic degradation through a process known as ferritinophagy, which is mediated by nuclear receptor coactivator 4 (NCOA4). This process promotes the release of stored iron and can increase the labile iron pool, thereby facilitating ferroptosis.[28,44] Experimental evidence suggests that dysregulation of the NCOA4–ferritin axis may increase neuronal susceptibility to ferroptosis, while reduced ferritin levels and increased transferrin receptor activity can further exacerbate oxidative damage during cerebral ischemia–reperfusion injury.[27,45]

Given the established role of iron overload in ferroptotic damage, modulation of iron metabolism has emerged as an attractive therapeutic strategy.[44] Iron chelators such as deferoxamine can reduce intracellular redox-active iron, suppress Fenton chemistry, and attenuate lipid peroxidation, thereby limiting neuronal injury in experimental stroke models.[27,45] Nanotechnology-based delivery systems may further advance this therapeutic concept by improving targeted delivery to the brain and prolonging drug retention within ischemic tissue.[46,47] Collectively, these findings support the regulation of iron metabolism as a potential strategy for limiting ferroptosis and improving neurological outcomes after cerebral ischemia–reperfusion injury.[48]

Beyond the classical pathways governing iron uptake and storage, a growing body of evidence suggests that regulatory molecules such as hepcidin, ferroportin, and iron regulatory proteins 1 and 2 (IRP1 and IRP2) may influence susceptibility to ferroptosis by modulating intracellular iron homeostasis.[27] The temporal regulation of these pathways during ischemia-reperfusion remains incompletely understood. However, their interaction with oxidative stress and lipid peroxidation highlights iron metabolism as an important therapeutic target in ferroptosis.[44] Further elucidation of these regulatory networks may facilitate the development of more precise neuroprotective strategies aimed at reducing secondary neuronal injury following cerebral ischemia–reperfusion.[28]

4.4. Mitochondrial damage and reactive oxygen species generation

Mitochondria play an important role in ferroptosis as both major sources of ROS and important targets of ROS-induced injury.[49,50] Cerebral ischemia–reperfusion can disrupt the mitochondrial electron transport chain, promoting the generation of superoxide and hydrogen peroxide and thereby contributing to oxidative stress, iron-dependent lipid peroxidation, and amplification of ferroptotic signaling. Ferroptosis is characterized by distinct mitochondrial morphological alterations, including mitochondrial shrinkage, increased mitochondrial membrane density, reduced or absent cristae, and disruption of the outer mitochondrial membrane. These structural changes reflect severe mitochondrial dysfunction and have been associated with neuronal injury.[49,51]

The ferroptotic cascade may be further amplified by oxidative damage to mitochondrial membranes.[52] During ischemia–reperfusion injury, cardiolipin, a mitochondria-specific phospholipid that is susceptible to oxidative modification, can undergo oxidation, potentially compromising mitochondrial membrane integrity.[53,54] Preservation of mitochondrial quality-control mechanisms and organelle homeostasis has also been associated with reduced ferroptotic injury and improved neuronal survival in experimental studies.[55]

Several mitochondrial regulatory pathways may contribute to ferroptosis progression.[56] Mitochondrial dysfunction and altered mitochondrial membrane homeostasis may contribute to neuronal injury during ischemia-reperfusion and provide an important mechanistic link between mitochondrial damage and regulated cell-death pathways.[57-59] These interconnected

processes may form a self-amplifying cycle in which mitochondrial dysfunction promotes oxidative stress and lipid peroxidation, thereby further increasing susceptibility to ferroptotic neuronal injury.[60]

Collectively, available evidence supports ferroptosis as a promising therapeutic target in cerebral ischemia–reperfusion injury; however, substantial challenges remain before ferroptosis-targeted strategies can be translated into clinical practice.[7] Ferroptosis does not occur in isolation but interacts with other regulated cell-death pathways, including apoptosis and pyroptosis, as well as with mitochondrial dysfunction and neuroinflammation within the dynamic ischemic microenvironment.[61] Consequently, therapeutic strategies directed at a single molecular pathway may provide limited or incomplete neuroprotection in this multifactorial disease.[61] Furthermore, although several biomarkers, including GPX4, ACSL4, SLC7A11, lipid peroxidation products, and proteins involved in iron metabolism, are commonly used to evaluate ferroptosis, no universally accepted biomarker panel for reliably assessing ferroptotic activity *in vivo* has been established.[7] Most available evidence is also derived from preclinical studies using relatively homogeneous experimental models, whereas clinical ischemic stroke is highly heterogeneous and influenced by factors such as age, hypertension, and diabetes.[7] These limitations highlight the need for multifunctional therapeutic strategies capable of simultaneously targeting interconnected pathological mechanisms while also addressing drug-delivery and brain-targeting challenges.[62,63] Accordingly, multimodal therapeutic approaches that combine modulation of several pathological pathways with improved drug-delivery strategies may offer advantages over conventional single-target interventions.[62,63] Naturally derived compounds with multi-target pharmacological properties have therefore attracted increasing attention and provide the rationale for the following discussion of baicalein.[64]

5. Baicalein as a multi-target ferroptosis modulator

The discovery of ferroptosis as a key process in cerebral ischemia–reperfusion injury has led to the emergence of a class of potential multi-target drugs.[65] One of the most promising naturally derived bioactive compounds that have attracted the interest of researchers as multi-target ferroptosis modulators is baicalein,[3] a principal bioactive flavonoid from *S. baicalensis* Georgi. Unlike traditional antioxidants that mainly scavenge ROS, baicalein has been reported to influence several interconnected processes relevant to ferroptosis, including lipid peroxidation, intracellular iron balance, the GPX4-mediated antioxidant system, NRF2 signaling, mitochondrial injury, and neuroinflammation.[3] Through these complementary mechanisms, baicalein can block the ferroptosis pathway at several levels, instead of targeting a single molecule.[3] It interrupts the ferroptotic cascade at multiple stages rather than acting on a single molecular target.[3] The neuroprotective effects of baicalein against cerebral ischemia–reperfusion injury are summarized in Figure 3 and are mainly attributed to its anti-ferroptotic actions

Importantly, the pharmacological profile of baicalein extends beyond direct ferroptosis inhibition.[3] The antioxidant, anti-inflammatory, mitochondrial protective, and iron-regulatory effects suggest that it can help maintain neuronal viability after a cerebral ischemia–reperfusion event, as suggested by experimental evidence.[10] The integrated mechanism of action differentiates baicalein from several experimental ferroptosis inhibitors that have been developed to target a single signaling molecule, suggesting that it could be a disease-modifying therapeutic candidate as opposed to a traditional antioxidant.[3]

Despite these beneficial pharmacological properties, baicalein has not yet entered clinical practice due to several unfavorable physicochemical and pharmacokinetic properties, such as low aqueous solubility, low oral bioavailability, rapid systemic elimination, and poor blood–brain barrier penetration. This has led to efforts to develop drug-delivery systems that enable translation of the broad anti-ferroptotic activity of baicalein.[66]

5.1. Inhibition of 12/15-lipoxygenase

One well-studied and pharmacologically relevant molecular target regulated by baicalein is 12/15-LOX.[67] 12/15-LOX is a key enzyme that catalyzes the oxidation of phospholipids rich in PUFAs, leading to lipid peroxide accumulation and membrane injury caused by ferroptosis. Baicalein directly inhibits this enzyme, interrupting one of the earliest processes involved in ferroptosis after cerebral ischemia–reperfusion.[67]

Baicalein inhibition of 12/15-LOX has consistently been shown to decrease lipid peroxide production, maintain membrane integrity, reduce neuronal degeneration, and markedly improve neurological outcomes in experimental stroke models.[68] These protective effects include decreased cerebral infarct volume, decreased brain edema, and suppression of secondary inflammatory responses, suggesting that 12/15-LOX inhibition is not only involved in ferroptosis inhibition but also in other mechanisms of neuroprotection.[68]

Beyond direct enzyme inhibition, baicalein affects multiple downstream signaling pathways influenced by 12/15-LOX activity.[67] There is emerging evidence that

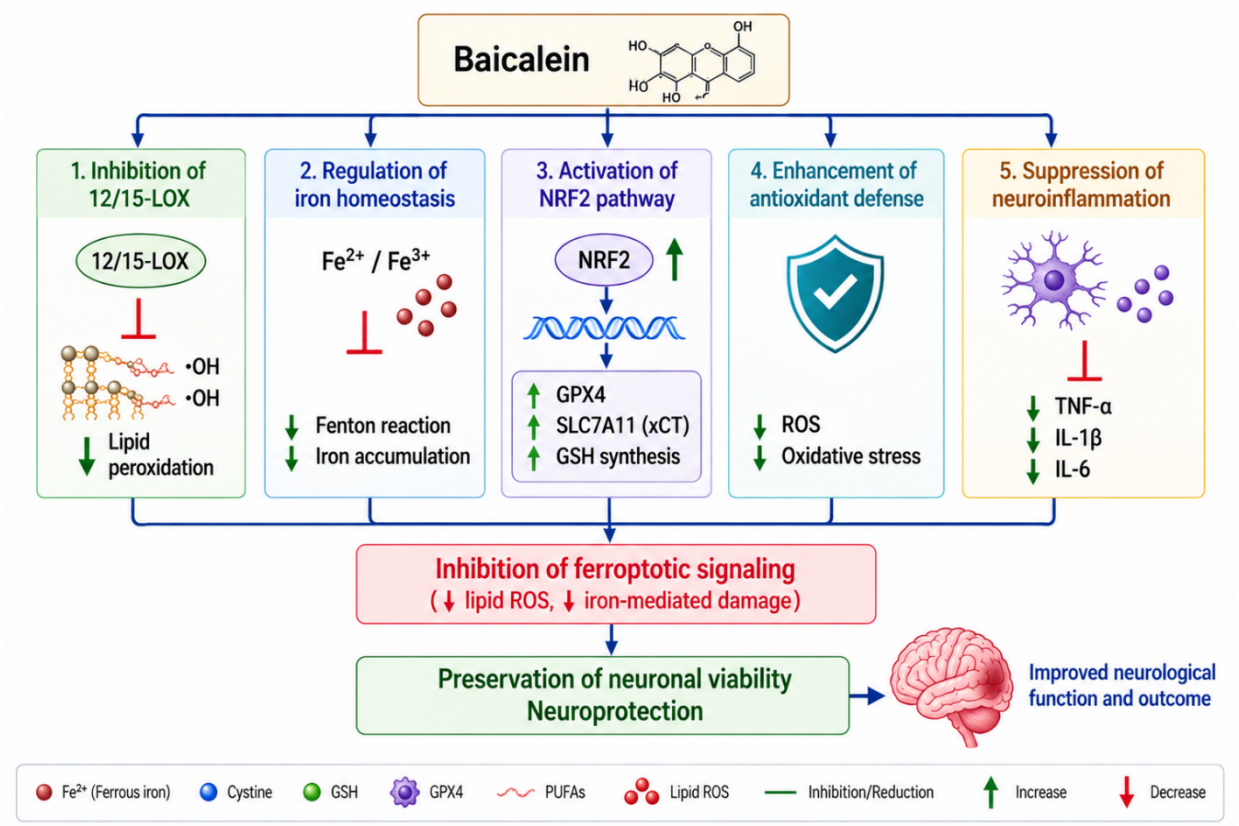


Figure 3. Multi-target anti-ferroptotic mechanisms of baicalein in cerebral ischemia–reperfusion injury. Baicalein has multi-target anti-ferroptotic mechanisms in cerebral ischemia–reperfusion injury. The multiple complementary mechanisms of action of baicalein include inhibition of the inflammation-enhancing 12/15-lipoxygenase (12/15-LOX), regulation of iron homeostasis, induction of the NRF2/GPX4 antioxidant pathway, enhancement of endogenous antioxidant defenses, and inhibition of neuroinflammation. These concerted activities halt lipid peroxidation and ferroptotic signaling, maintain neuronal viability, and enhance neurological outcomes after cerebral ischemia–reperfusion injury.
Abbreviations: GPX4: Glutathione peroxidase 4; GSH: Glutathione; IL-1β: Interleukin-1 beta; NRF2: Nuclear factor erythroid 2–related factor 2; ROS: Reactive oxygen species; SLC7A11: Solute carrier family 7 member 11; TNF-α: Tumor necrosis factor-alpha.

inhibition of 12/15-LOX is associated with regulation of transcriptional networks related to oxidative stress, inflammation, and neuronal survival, including peroxisome proliferator-activated receptor gamma (PPARγ)-mediated signaling pathways.[10,67] These findings suggest that 12/15-LOX inhibition may be an early event in a more complex and global neuroprotective mechanism rather than merely a biochemical event.[67,69]

More recently, baicalein-mediated 12/15-LOX inhibition has been shown to strongly correlate with inhibition of molecular markers of ferroptosis, such as decreased phospholipid oxidation, decreased accumulation of lipid peroxides, and maintenance of neuronal membrane stability.[3] Taken together, these observations strongly suggest 12/15-LOX as one of the major molecular targets leading to anti-ferroptosis activity of baicalein, offering a solid mechanistic framework for its therapeutic potential in cerebral ischemia–reperfusion injury.[67,69]

5.2. Regulation of iron homeostasis and antioxidant defense

In addition to inhibiting 12/15-LOX, baicalein exerts broad-spectrum anti-ferroptotic activity through coordinated regulation of intracellular iron homeostasis and antioxidant defense systems. Baicalein does not act on a single molecular pathway; instead, it simultaneously inhibits iron-dependent oxidative reactions, corrects redox imbalance, and enhances endogenous cytoprotective mechanisms, thereby interrupting several steps of the ferroptotic cascade. One of the biggest benefits of using baicalein instead of traditional antioxidants is this integrated pharmacological profile.[3,10]

The anti-ferroptotic effect of baicalein may be attributed to one of its key effects: decreasing intracellular redox-

active iron levels. Fe^{2+} catalyzes lipid peroxidation, while catalytically inactive Fe^{3+} inhibits it, reducing hydroxyl radical generation and thereby reducing iron-dependent lipid peroxidation by baicalein. The preservation of iron homeostasis not only decreases oxidative membrane damage but also breaks the amplification loop of iron overload, mitochondrial dysfunction, and ferroptosis-associated neuronal injury.[3]

Baicalein also enhances the intrinsic antioxidant system by activating the NRF2 signaling pathway, the master antioxidant pathway that improves neuronal resistance to ferroptotic injuries after ischemia-reperfusion[10]. NRF2 activation induces transcription of cytoprotective genes such as *GPX4*, *SLC7A11*, *HMOX1*, and *NQO1*, which are involved in glutathione biosynthesis, iron metabolism, ROS detoxification, and removal of lipid hydroperoxides. Maintenance of this innate defense system protects intracellular antioxidant levels, maintains mitochondrial function, and improves neuronal resistance to ferroptotic injury after ischemia-reperfusion.[10]

Available evidence suggests that baicalein may help maintain the GPX4–glutathione antioxidant axis, an important endogenous defense mechanism against ferroptosis. Active GPX4 helps prevent the accumulation of phospholipid hydroperoxides and preserve membrane integrity, thereby limiting lipid peroxidation-associated cellular damage. Baicalein may therefore influence cellular antioxidant homeostasis beyond direct free-radical scavenging, although the extent to which these effects specifically mediate ferroptosis inhibition remains to be established.[3]

Taken together, these findings suggest that baicalein may influence multiple interconnected processes relevant to ferroptosis, including iron metabolism, endogenous antioxidant defenses, GPX4 activity, lipid peroxidation, and cellular redox balance. However, the extent to which these effects collectively constitute a direct multi-target ferroptosis-modulating mechanism remains to be established. This integrated pharmacological activity provides strong mechanistic support for combining baicalein with advanced drug delivery systems to maximize its therapeutic effect in cerebral ischemia–reperfusion injury.[67] Baicalein is a multi-target therapeutic agent that regulates multiple interconnected ferroptosis-related pathways (Figure 3), making it an effective antioxidant for treating ferroptosis.

Importantly, the apparent multi-target activity of baicalein should not be interpreted as independent activity at the same target across different pathways. Instead, many of these biological responses are mechanistically related, given the strong relationships among the electron transport system, iron metabolism, inflammatory signaling, and lipid peroxidation.[10,67] Modulation of one pathway can thus secondarily affect multiple other pathways, which may account for the wide range of pharmacological effects observed in experimental studies.

5.3. Evidence from experimental stroke models

The mechanisms outlined above have been consistently observed in preclinical models of cerebral ischemia–reperfusion injury, with growing evidence that they lead to meaningful neuroprotection across a variety of experimental models.[3,10,70] Baicalein regulates multiple interconnected processes related to ferroptosis, such as maintaining GPX4 activity, inhibiting lipid peroxidation, controlling iron levels, sustaining intracellular glutathione levels, and restoring cellular redox balance.[3,10,64] This integrated pharmacological profile can break the ferroptotic pathway at a stage preceding the final irreversible damage of neuronal membranes, offering a more comprehensive neuroprotection than targeting single molecules.[7,71]

Baicalein consistently demonstrates neuroprotective effects extending beyond ferroptosis.[3,10,70] Experimental studies have shown that baicalein can attenuate oxidative stress and neuroinflammatory signaling while supporting mitochondrial function and other pro-survival pathways following cerebral ischemia–reperfusion injury.[10] These changes include reduced oxidative stress, inhibited neuroinflammatory signaling, maintained mitochondrial function, and activation of various pro-survival pathways. These complementary actions suggest that the neuroprotective effects of baicalein may involve multiple pathological processes beyond ferroptosis, rather than being attributable exclusively to ferroptosis inhibition.[10]

In experimental stroke models, the molecular actions of baicalein are consistently linked to functional outcomes.[72] Baicalein has been shown to significantly reduce cerebral infarct volume, improve neurological deficit scores, preserve neuronal morphology, and attenuate biochemical markers of oxidative stress and ferroptosis.[10] Overall, these results offer strong preclinical support for the neuroprotective effects of ferroptotic signaling modulation both structurally and functionally following cerebral ischemia–reperfusion injury.[73]

Although these results are promising, the available evidence is largely limited to experimental studies, and several key translational issues remain that impede the clinical use of baicalein.[3] Despite its broad spectrum of pharmacological activity, poor aqueous solubility, low oral bioavailability, and rapid systemic clearance limit its therapeutic potential. Thus, it is important to enhance the pharmacokinetic profile of baicalein for its potential clinical applications.[3]

Nanotechnology in drug delivery systems has been proposed as a solution to address these challenges, as it can improve drug stability and bioavailability, extend systemic circulation, and promote targeted delivery to the brain.[74] The biodegradable PLGA nanoparticles would thus be one of the most promising platforms for optimizing the therapeutic efficacy of baicalein with reduced loss of the drug in the systemic circulation.[75] For this reason, the following discussion explores the rationale for using PLGA-based nanocarriers as an advanced strategy for the delivery of therapeutic agents, which are targeted against ferroptosis, to treat cerebral ischemia-reperfusion injury.[72]

While several experimental drugs have shown anti-ferroptotic activity in ischemic stroke, most exert their anti-ferroptotic effects through a single molecular mechanism, such as radical trapping or iron chelation.[76,77] Baicalein, on the other hand, has a broad spectrum of pharmacologic action and simultaneously targets lipid peroxidation, oxidative stress, inflammatory signaling, iron homeostasis, and endogenous antioxidant defenses.[72] However, the extended mechanistic picture does not necessarily reflect improved therapeutic utility; comparative studies conducted under standardized experimental conditions and with well-designed designs need to be performed to evaluate this.[7,76]

A comparative summary of the principal anti-ferroptotic mechanisms, therapeutic evidence, advantages, and limitations of baicalein and representative ferroptosis-modulating agents is presented in Table 1.

Although baicalein has a broad pharmacological profile, key challenges remain that must be addressed to enhance its clinical potential as a neuroprotective agent. Comparisons between studies are difficult because most mechanistic studies have used experimental models with relatively uniform dosing regimens, treatment schedules, and short observation periods.[74] Moreover, the exact molecular mechanisms by which baicalein regulates ferroptosis are still far from fully understood, and most of the reported biological effects of baicalein could be caused by its action on multiple pathways other than ferroptosis, including oxidative stress, inflammatory signaling, mitochondrial homeostasis, and iron metabolism.[3,72] This complexity makes it difficult to interpret experimental results and suggests the need for more comprehensive mechanistic studies using standardized ferroptosis-specific biomarkers and functional validation strategies. Although preclinical evidence is promising, clinical evidence supporting the use of baicalein in ischemic stroke remains extremely limited.[67] Future investigations should thus confirm not only its anti-ferroptotic mechanisms but also the pharmacokinetic limitations that hinder its therapeutic translation.[70,75]

The therapeutic potential of baicalein in cerebral ischemia–reperfusion injury is substantially constrained by its unfavorable physicochemical and pharmacokinetic properties, including poor aqueous solubility, limited bioavailability, rapid systemic elimination, and inadequate penetration across the blood-brain barrier.[3] These limitations may markedly reduce the amount of drug reaching ischemic brain tissue following systemic administration and consequently restrict its therapeutic applicability.[3,78] Therefore, the development of an efficient drug-delivery platform is essential for maximizing the therapeutic potential of baicalein while preserving its broad anti-ferroptotic activity.[72,73,79]

Among the biodegradable polymeric nanocarriers

Table 1. Comparative profile of baicalein and representative anti-ferroptotic agents

Agent	Principal anti-ferroptosis mechanism	Evidence in stroke	Advantages	Major limitations	Clinical status
Baicalein	Multi-target anti-ferroptotic activity	MCAO	12/15-LOX inhibition; antioxidant and ferroptosis-related pathways	Limited brain exposure	Preclinical
Fer-1	Ferroptosis inhibition/ Radical trapping	MCAO	Direct ferroptosis inhibition	Poor stability; pharmacokinetic limitations	Experimental
Lip-1	Ferroptosis inhibition/ Radical trapping	MCAO	Potent lipid-radical trapping	Pharmacokinetic limitations	Experimental
DFO	Iron chelation	MCAO	Clinically established iron chelator	Limited brain penetration	Clinical use; stroke evidence preclinical
Edaravone	ROS scavenging; indirect ferroptosis modulation	Clinical + MCAO	Clinically used neuroprotective agent	Limited ferroptosis specificity	Clinical

Abbreviations: DFP: Deferiprone; Fer-1: Ferrostatin-1; Lip-1: Liproxstatin-1; MCAO: Middle cerebral artery occlusion; ROS: Reactive oxygen species; 12/15-LOX: 12/15-lipoxygenase.

currently available, PLGA has emerged as one of the most extensively investigated platforms because of its biocompatibility, biodegradability, versatility, and capacity to encapsulate hydrophobic compounds.[80] The polymeric matrix of PLGA can provide a suitable microenvironment for hydrophobic compounds such as baicalein, potentially protecting the encapsulated drug from premature degradation while improving its stability and enabling controlled drug release. These properties make PLGA an attractive platform for delivering hydrophobic neuroprotective agents following ischemic stroke.[3]

Several nanocarrier platforms, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric micelles, dendrimers, and inorganic nanoparticles, have been investigated for brain-targeted drug delivery. Each platform has distinct advantages and limitations depending on the physicochemical properties of the therapeutic cargo and the intended clinical application.[81] Among these systems, PLGA remains one of the most extensively investigated biodegradable polymers because of its favorable safety profile, controllable degradation kinetics, compatibility with hydrophobic compounds, and extensive experience in biomedical applications.[81]

An important advantage of PLGA nanoparticles is their tunable drug-release profile.[82,83] Drug release can be modulated by adjusting formulation characteristics, including the lactide-to-glycolide ratio and polymer molecular weight, allowing optimization of degradation kinetics to meet therapeutic requirements.[84] A higher lactide content generally prolongs polymer degradation and may contribute to more sustained drug release, whereas a higher glycolide fraction can accelerate polymer hydrolysis and drug release.[84] Such tunability may facilitate the development of sustained-release formulations designed to maintain drug exposure during the post-ischemic period.

Several formulation approaches have been used to encapsulate bioactive compounds within PLGA nanoparticles, with emulsion-solvent evaporation and nanoprecipitation among the most widely used methods.[85] These approaches can achieve efficient drug encapsulation while maintaining drug stability and generating nanoparticles with controlled release characteristics.[84] Experimental studies have demonstrated that PLGA nanoparticles can improve drug stability, prolong systemic exposure, and provide controlled drug release, properties that may enhance the delivery of baicalein.[84,86,87]

Beyond drug encapsulation, PLGA nanoparticles offer a versatile platform for surface engineering, allowing incorporation of functional coatings and targeting ligands without fundamentally altering the polymeric core,[87] biodistribution, tissue accumulation, and therapeutic performance, thereby extending the potential applications of PLGA-based drug-delivery systems.[84]

Collectively, these characteristics establish PLGA as an attractive carrier for baicalein and provide a technological foundation for the development of biomimetic nanomedicine. Nevertheless, passive PLGA nanoparticles alone may struggle to achieve efficient and selective accumulation in ischemic brain tissue because of systemic clearance mechanisms and the restrictive properties of the blood–brain barrier.[88] These limitations have encouraged the development of biomimetic surface-engineering strategies, particularly platelet membrane camouflage, which is discussed in **Section 6**.

Despite its favorable characteristics, PLGA has several formulation-related limitations, including initial burst release, potential local acidification during polymer degradation, variable drug-loading efficiency depending on the physicochemical properties of the encapsulated compound, and batch-to-batch variability associated with nanoparticle preparation.[83,84] Furthermore, optimization of particle size, surface characteristics, encapsulation efficiency, and release kinetics often requires extensive formulation development, making direct comparison among published studies difficult.[82] From a translational perspective, large-scale manufacturing, long-term storage stability, reproducibility, and regulatory standardization remain important challenges that must be addressed before PLGA-based formulations can achieve broader clinical application.[88] Thus, although PLGA provides a versatile drug-delivery platform, its therapeutic performance ultimately depends on appropriate formulation design and integration with effective targeting strategies.[87]

6. Platelet membrane camouflage strategy

Recent advances in biomimetic nanomedicine have expanded nanoparticle-based drug-delivery systems by integrating synthetic nanocarriers with naturally derived cell membranes. Among the various cell membrane sources investigated for biomimetic drug delivery, platelet membranes have attracted particular interest as a biomimetic surface-engineering strategy because they retain biologically relevant membrane components that may be exploited for therapeutic delivery.[89,90] Platelet membrane-based nanocarriers have also been investigated for ischemic stroke because of the natural involvement of platelets in vascular injury, inflammation, and thrombotic processes.[91]

Unlike conventional surface-modification strategies, platelet membrane camouflage can provide nanoparticles

with biological properties derived from native platelet membranes. These properties may include reduced immune recognition, prolonged systemic circulation, and enhanced interactions with injured vascular environments.[6] Such characteristics provide a biological rationale for investigating platelet membrane-coated nanoparticles as a targeted drug-delivery strategy in ischemic stroke.[91] The proposed design of platelet membrane-coated baicalein-loaded PLGA nanoparticles and their potential therapeutic mechanism in cerebral ischemia-reperfusion injury are illustrated in Figure 4.

6.1. Immune evasion and prolonged circulation

Platelet membrane camouflage has emerged as an important biomimetic surface-engineering strategy because membrane-based approaches may help nanocarriers reduce recognition and clearance by components of the mononuclear phagocyte system.[92] CD47 biomimicry may provide a physiological "self-recognition" signal that contributes to reduced macrophage-mediated phagocytosis and improved systemic persistence of nanocarriers.[93] Consequently, platelet membrane-coated nanoparticles may exhibit prolonged systemic circulation and improved opportunities for delivery to ischemic tissues compared with non-camouflaged nanocarriers.[6]

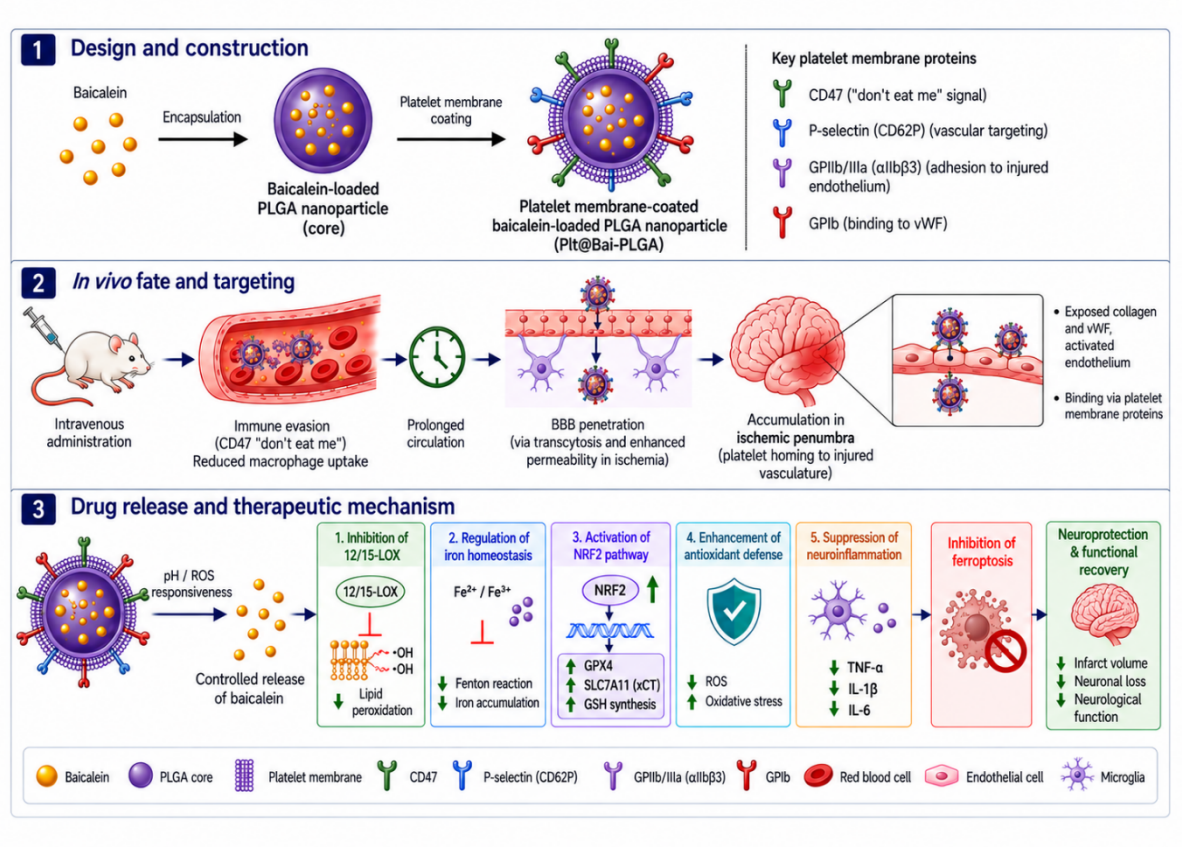


Figure 4. Design and therapeutic mechanism of platelet membrane-coated baicalein-loaded PLGA nanoparticles for cerebral ischemia–reperfusion injury. Schematic illustration of the proposed biomimetic nanoplatform for targeted delivery of baicalein in cerebral ischemia–reperfusion injury. Baicalein is encapsulated within a PLGA nanoparticle core and subsequently coated with a platelet membrane to enhance immune evasion, prolong systemic circulation, facilitate blood-brain barrier penetration, and promote selective accumulation within the ischemic penumbra. Controlled release of baicalein at the target site suppresses ferroptosis through multiple complementary mechanisms, ultimately preserving neuronal viability and improving neurological recovery.

Abbreviations: 12/15-LOX: 12/15-lipoxygenase; BBB: Blood–brain barrier; GPX4: Glutathione peroxidase 4; GSH: Glutathione; IL-1β: Interleukin-1 beta; NRF2: Nuclear factor erythroid 2–related factor 2; PLGA: Poly(lactic-co-glycolic acid); ROS: Reactive oxygen species; SLC7A11: Solute carrier family 7 member 11; TNF-α: Tumor necrosis factor-alpha; vWF: von Willebrand factor.

These membrane-associated components retain biological functions involved in platelet adhesion and interactions with activated endothelial cells and injured vascular surfaces, providing a rationale for their use in biomimetic drug-delivery systems.[94] Thus, platelet membrane camouflage may provide a complementary approach for improving the biological performance and targeting characteristics of polymeric nanocarriers.[5]

6.2. Blood–brain barrier targeting

Although blood–brain barrier integrity can be transiently disrupted following cerebral ischemia–reperfusion, this pathological alteration does not necessarily ensure efficient delivery or retention of therapeutic agents within ischemic brain tissue.[95,96] Effective delivery of free drugs to the ischemic penumbra may remain limited because of rapid systemic elimination and insufficient tissue retention. Platelet membrane-coated nanoparticles represent a potential biomimetic strategy for improving therapeutic delivery by combining synthetic nanocarriers with biologically derived membrane components.[5]

Experimental studies have investigated cell membrane-functionalized biomimetic nanoparticles to improve nanoparticle delivery and accumulation in ischemic brain tissue.[96] Membrane-camouflaged biomimetic nanoparticle systems have been investigated as potential approaches for improving therapeutic delivery and treatment strategies in ischemic stroke.[97] Collectively, these findings support further investigation of nanoparticle-based delivery strategies designed to improve targeted therapeutic approaches for ischemic stroke.[46]

6.3. Ischemic penumbra targeting

Beyond prolonging systemic circulation, platelet membrane camouflage has been investigated as a strategy to enhance nanoparticle delivery and accumulation within ischemic brain tissue.[96] Native platelet membrane proteins, including glycoproteins, integrins, and selectins, retain biologically relevant functions involved in platelet adhesion and interactions with vascular and cellular targets.[98] These biological targeting properties may support preferential nanoparticle accumulation within ischemic brain regions, where targeted therapeutic intervention may help preserve vulnerable but potentially viable tissue.[96]

Preclinical investigations have evaluated cell membrane-coated nanoparticles for their potential to improve brain delivery, cellular interactions, and therapeutic performance compared with non-camouflaged nanocarriers.[96] Reported therapeutic benefits of membrane-camouflaged nanoparticle systems in experimental ischemic stroke models include improved drug delivery and attenuation of pathological processes associated with ischemic injury.[98] These observations provide a rationale for further investigating targeted nanocarrier strategies in combination with therapeutic agents that may modulate ferroptosis, including baicalein.[28]

Importantly, the performance of cell membrane-functionalized nanoparticles can be influenced by several formulation-related variables, including nanoparticle size, membrane-to-core ratio, preservation of membrane components, coating methodology, and physicochemical stability of the final formulation.[96] Variations in these parameters may influence circulation, targeting behavior, cellular interactions, and overall therapeutic performance.[97] Therefore, rigorous physicochemical characterization, standardized formulation protocols, and appropriate quality control are important for meaningful comparison among preclinical studies and for supporting future translational development.[97]

Collectively, platelet membrane camouflage provides a biomimetic interface that may complement the drug-delivery properties of PLGA nanoparticles.[98] By integrating biomimetic surface engineering with nanoparticle-based drug delivery, this approach provides a rationale for further development of targeted nanomedicine strategies for ischemic stroke and related ischemic brain injury.[99]

7. Biomimetic cell-membrane nanoparticles in experimental MCAO models

The middle cerebral artery occlusion (MCAO) model is one of the most widely used preclinical models for investigating ischemic stroke and evaluating potential therapeutic strategies because it reproduces important features of cerebral ischemic injury.[100] Consequently, the MCAO model provides an important experimental platform for evaluating biomimetic nanomedicines and nanoparticle-based therapeutic strategies for ischemic stroke.[96]

Recent advances in biomimetic nanotechnology have led to the development of diverse cell membrane-functionalized nanoparticle systems employing membranes derived from different cellular sources, including platelets, erythrocytes, immune cells, stem cells, and other biologically derived materials.[96] Although these platforms differ in membrane source, fabrication method, and therapeutic cargo, they generally share the principle of incorporating biologically derived membrane components to modify nanoparticle behavior and therapeutic delivery.[97] Depending on the membrane source and nanoparticle design, these systems may improve selected aspects of systemic circulation, immune evasion, tissue interactions, and therapeutic delivery in ischemic stroke.[46]

Across experimental studies of ischemic stroke, biomimetic nanoparticle systems have been investigated for their potential to improve therapeutic delivery and treatment outcomes compared with conventional drug formulations or non-camouflaged nanocarriers .[96] Reported outcomes in experimental studies include attenuation of pathological processes associated with ischemic brain injury, with specific effects varying according to the therapeutic cargo, nanoparticle design, and experimental model.[28] The development of biomimetic systems using different membrane sources suggests that cell membrane camouflage may represent a versatile strategy whose potential applications depend on the biological properties of the selected membrane source and therapeutic objective.[46]

Nevertheless, different membrane sources possess distinct biological characteristics that may influence nanoparticle behavior and therapeutic applications.[89] For example, platelet-derived membranes may be useful for interactions with injured vascular environments, erythrocyte-derived membranes may support prolonged circulation, and immune cell-derived membranes may provide biologically relevant interactions with inflammatory environments. Other membrane sources, including mesenchymal stem cell– and exosome-derived systems, have also been investigated for their potential applications in targeted therapeutic delivery.[101] Collectively, these diverse biological properties provide a basis for investigating and optimizing targeted drug-delivery strategies for ischemic stroke.[102]

Table 2 summarizes representative biomimetic cell membrane-coated nanoparticle platforms evaluated in experimental MCAO models, highlighting the diversity of membrane sources, therapeutic cargoes, reported therapeutic effects, and proposed biological advantages.

Despite these advances, an important research and translational gap remains. Based on the literature identified in the present review, the simultaneous integration of baicalein, PLGA nanoparticles, and platelet membrane camouflage into a single biomimetic nanoplatform for ferroptosis-targeted neuroprotection in cerebral ischemia–reperfusion injury has not been extensively investigated. These three components address complementary therapeutic challenges: baicalein has been investigated for its potential to modulate ferroptosis-related pathways[28], nanoparticle-based delivery systems may support targeted therapeutic strategies in ischemic stroke[46], and biomimetic cell membrane-based approaches provide a basis for exploring biologically informed nanocarrier design.[102] Their integration therefore represents a rational hypothesis for future investigation rather than an established therapeutic platform.

Although biomimetic nanoparticles derived from

Table 2. Representative biomimetic cell membrane-coated nanoparticle systems evaluated in MCAO models

Membrane source	Therapeutic cargo	Major therapeutic effects	Principal advantage
Platelet membrane	Deferoxamine	↓ Iron overload; ↓ infarct volume; improved neurological function	Vascular injury targeting; immune evasion
Platelet membrane	Ginkgolide B	↑ GPX4; ↓ ROS; ↓ neuroinflammation	Ferroptosis modulation; ischemic targeting
Platelet membrane	Fat extract (RGD-PLT@ PLGA-FE)	Enhanced angiogenesis and neurogenesis; improved functional recovery	Dual vascular targeting
RBC membrane	Nanozyme	↓ Oxidative stress; ↓ neuronal apoptosis	Prolonged circulation; BBB penetration
RBC + platelet hybrid membrane	Nanovesicles	BBB protection; ↓ astrocyte/microglial activation	Combined circulation and targeting
Neutrophil membrane	Leonurine	↓ Neuroinflammation; BBB protection	Inflammation-guided targeting
Mesenchymal stem cell membrane	PB-006	↓ Infarct volume; ↑ tissue repair	Tissue-homing capability
Monocyte membrane	Rapamycin	↓ Inflammation; improved neurological recovery	Targeting inflamed endothelium
Microglial membrane (M2)	Catalase nano-scavenger	↓ ROS; M2 polarization	Anti-inflammatory microenvironment
Exosome-derived membrane	Quercetin	↓ Infarct volume; ↑ neuronal survival	Efficient neuronal targeting

Abbreviations: BBB: Blood–brain barrier; GPX4: Glutathione peroxidase 4; RBC: Red blood cell; ROS: Reactive oxygen species.

different cell membranes have been investigated in experimental ischemic stroke models, direct comparison among these platforms remains challenging because of heterogeneity in membrane source, nanoparticle formulation, therapeutic cargo, route of administration, dosing regimen, experimental model, and outcome assessment.[102] Consequently, it remains premature to conclude that any single membrane source is universally superior. Rather, the suitability of a biomimetic platform likely depends on the intended therapeutic objective and the biological properties of the selected membrane source.[101] For example, different membrane sources may be selected according to their distinct biological properties and the intended therapeutic objective, including applications related to vascular injury, inflammatory processes, or tissue repair.

Future head-to-head comparative studies employing standardized experimental designs will therefore be essential to define the relative therapeutic advantages of individual biomimetic strategies.

8. Research gap and therapeutic potential

Nevertheless, these areas have largely evolved as partially independent research fields, and their integration into a unified therapeutic strategy remains limited. This fragmentation highlights a key research and translational gap in developing integrated ferroptosis-targeted therapeutic strategies for cerebral ischemia–reperfusion injury.[102]

Accumulating evidence indicates that ferroptosis contributes to secondary neuronal injury following cerebral ischemia–reperfusion, and pharmacological modulation of ferroptosis-related pathways has therefore emerged as a potential therapeutic approach.[28] PLGA nanoparticles and platelet membrane-based biomimetic strategies have also been investigated as complementary approaches for improving drug-delivery performance and biologically informed targeting.[101] However, these approaches have predominantly been investigated independently, with each addressing different components of the therapeutic challenge.

This fragmented approach represents an important limitation because ischemic brain injury involves multiple interconnected pathological processes, including oxidative stress, iron dysregulation, mitochondrial dysfunction, neuroinflammation, and lipid peroxidation.[46,103] This complexity provides a rationale for investigating multifunctional therapeutic strategies that combine targeted drug delivery with pharmacological modulation of multiple pathological pathways.[102]

Based on the literature identified in the present review, the simultaneous integration of baicalein, PLGA nanoparticles, and platelet membrane camouflage into a single biomimetic platform for ferroptosis-targeted neuroprotection in cerebral ischemia–reperfusion injury has not been extensively investigated. These components provide complementary functions: baicalein may modulate multiple ferroptosis-related pathways, PLGA nanoparticles provide a versatile platform for drug encapsulation and controlled release, and platelet membrane camouflage represents a biomimetic surface-engineering strategy that may modify nanocarrier interactions with biological environments.

The proposed platform should therefore be considered a hypothesis-driven therapeutic concept rather than an experimentally validated treatment. Platelet membrane-mediated surface engineering may potentially influence the biological distribution and interactions of the proposed nanocarrier, while sustained release from the PLGA matrix may prolong drug availability following administration.

Collectively, these complementary properties provide a rationale for investigating whether an integrated biomimetic platform could improve therapeutic delivery and modulate multiple pathological processes associated with cerebral ischemia–reperfusion injury.[102] Importantly, this concept requires rigorous experimental validation. Future studies should characterize the physicochemical properties of the formulation, drug-loading efficiency, release kinetics, membrane integrity, biological interactions, pharmacokinetic behavior, tissue distribution, and ferroptosis-related molecular effects before concluding therapeutic efficacy. Thus, the proposed platform provides a rational framework for future preclinical investigation rather than evidence of established therapeutic or clinical efficacy.[102]

From a translational perspective, several sequential barriers must be addressed before this concept can progress toward clinical development. First, the proposed formulation would require rigorous standardization of nanoparticle size, surface characteristics, drug loading, release kinetics, platelet membrane integrity, and batch-to-batch reproducibility. Second, its pharmacokinetic and biodistribution profiles would need to be established to determine whether membrane camouflage and PLGA-based delivery provide a meaningful advantage over free baicalein or non-camouflaged nanoparticles. Third, safety assessment would need to address acute and chronic toxicity, immunological responses, potential effects on coagulation and platelet-related biological functions, and the consequences of repeated administration. These considerations are particularly relevant to platelet

membrane-based systems because their biological functionality may provide targeting advantages but may also introduce additional manufacturing and safety requirements. Finally, demonstration of reproducible therapeutic efficacy in clinically relevant animal models, including aged animals and models incorporating common stroke comorbidities, along with standardized manufacturing and regulatory characterization, would be necessary before considering progression toward first-in-human evaluation.

9. Conclusion

Cerebral ischemia–reperfusion injury remains a major therapeutic challenge in ischemic stroke because of its multifactorial pathophysiology, in which ferroptosis represents an important contributor to secondary neuronal injury. This review integrates current evidence regarding the molecular mechanisms of ferroptosis, the pharmacological potential of baicalein in relation to ferroptosis, the drug-delivery properties of PLGA nanoparticles, and the biological rationale for platelet membrane camouflage. Collectively, these areas provide a scientific basis for exploring biomimetic nanomedicine as a potential approach for addressing multiple interconnected pathological mechanisms involved in ischemic stroke.[28,102]

Although these components have individually been investigated in relevant pharmacological or nanomedicine contexts, evidence supporting their integration into a single biomimetic platform for ferroptosis-targeted neuroprotection following cerebral ischemia–reperfusion remains limited. The proposed combination of baicalein, PLGA nanoparticles, and platelet membrane camouflage therefore represents a rational hypothesis-driven therapeutic concept that may potentially address several pharmacological and drug-delivery limitations associated with conventional neuroprotective approaches.[102]

The proposed nanoplatform may provide complementary therapeutic advantages by combining controlled drug delivery with a pharmacological agent that may influence ferroptosis-related and other pathological processes associated with cerebral ischemia–reperfusion injury. However, these anticipated advantages remain hypothetical and require rigorous physicochemical, *in vitro*, and *in vivo* validation before concluding therapeutic performance, comparative efficacy, or clinical translation.[28,102]

Future development of ferroptosis-targeted therapeutic strategies for cerebral ischemia–reperfusion injury will potentially depend not only on identifying additional neuroprotective compounds but also on effectively integrating disease-relevant pharmacology with advanced drug-delivery technologies. The proposed combination of baicalein, PLGA nanoparticles, and platelet membrane camouflage illustrates how advances in molecular pharmacology, pharmaceutical sciences, and biomaterials engineering may be integrated into a hypothesis-driven strategy for future investigation.

Future preclinical development should proceed through a stepwise translational framework. Initial studies should establish the physicochemical characteristics, drug-loading capacity, release kinetics, membrane integrity, and formulation stability of the proposed nanoplatform. This should be followed by systematic evaluation of biological interactions, pharmacokinetic behavior, tissue distribution, cellular uptake, and therapeutic release profiles. Mechanistic studies should evaluate ferroptosis-related effects using complementary molecular, biochemical, and functional endpoints rather than relying solely on nonspecific markers of oxidative stress. Comparative experiments involving free baicalein, baicalein-loaded PLGA nanoparticles without membrane coating, appropriate empty nanoparticle controls, and the complete platelet membrane-coated formulation would be important for determining the contribution of individual formulation components to the observed biological effects.

In addition, future studies should investigate dose–response relationships, treatment windows, sex- and age-related differences[104], clinically relevant comorbidities, long-term neurological outcomes, biosafety, manufacturing reproducibility, and regulatory feasibility. Importantly, successful translation would require the demonstration of a reproducible benefit–risk profile and a manufacturing process capable of producing a well-characterized and consistent product under appropriate quality and regulatory standards. Such studies will be essential for determining whether the proposed biomimetic platform can progress beyond a conceptual strategy toward a therapeutically relevant approach for ischemic stroke.[28,102]

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