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REVIEW

Traditional Chinese Medicine and Ferroptosis in Intracerebral Hemorrhage: A Potential Therapeutic Approach

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Abstract: Intracerebral hemorrhage (ICH) is a severe cerebrovascular disorder associated with high morbidity and mortality. Ferroptosis, a regulated form of cell death characterized by iron accumulation and lipid peroxidation, plays a critical role in secondary injury following ICH. Traditional Chinese Medicine (TCM) has demonstrated distinct therapeutic benefits in cerebrovascular disease, and emerging evidence suggests its potential to modulate ferroptosis. This review explores the therapeutic effects of TCM and TCM-based interventions for ICH, with a focus on their regulation of ferroptosis-related mechanisms. In ICH, ferroptosis is driven by disrupted iron metabolism, lipid peroxidation, oxidative stress, and neuroinflammation—key contributors to secondary brain injury. TCM interventions, including herbal medicines, active compounds, and acupuncture, may counteract these processes by restoring iron homeostasis and reducing oxidative stress, thereby improving neurological outcomes. Given the critical role of ferroptosis in ICH pathophysiology, TCM represents a promising avenue for targeting ferroptosis-related pathways and advancing therapeutic strategies.
Keywords: cell death, iron deposition, lipid peroxidation, acupuncture, traditional Chinese medicine

Introduction

Intracerebral hemorrhage (ICH) is defined as bleeding within the brain parenchyma resulting from the rupture of blood vessels in the absence of external trauma. It is a severe subtype of stroke, contributing to substantial morbidity and mortality worldwide. Approximately 2 million new cases of ICH are reported globally each year, and this number continues to rise. By 2050, the incidence of ICH is projected to double, highlighting its increasing burden on public health systems.[1,2] Despite advances in acute care, the prognosis for ICH survivors remains poor.

Beyond the primary brain injury caused by the mechanical impact of the hematoma, secondary brain injury (SBI)—driven by cerebral edema and ischemia-hypoxia in the perihematomal region—is a major contributor to long-term neurological dysfunction and disability.[3] Current management strategies, including early surgical hematoma evacuation and supportive care, mainly target the primary brain injury. However, SBI—characterized by cellular toxicity, blood-brain barrier (BBB) disruption, and metabolic disturbances—remains a significant therapeutic challenge.[4,5]

In recent years, ferroptosis, a regulated and non-apoptotic form of cell death, has attracted growing attention in the context of ICH.[6,7] Ferroptosis is driven by the excessive accumulation of iron ions that catalyze lipid peroxidation of

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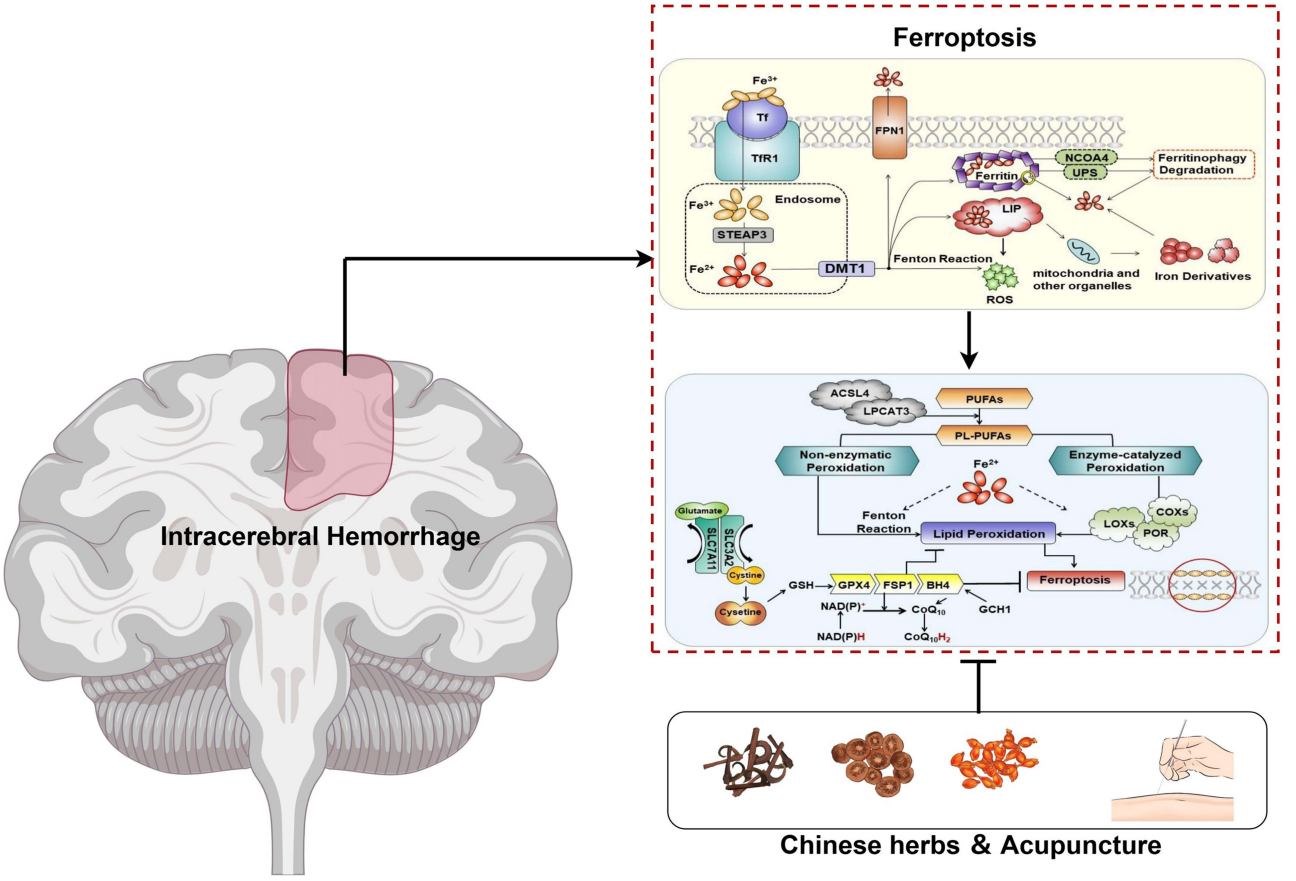
Graphical Abstract



cellular membranes. This process disrupts redox homeostasis and leads to the accumulation of lipid peroxides, resulting in oxidative damage and cellular demise.[8]

Growing evidence highlights the central role of ferroptosis in various diseases, including cardiovascular disorders,[9,10] neurodegenerative diseases (eg, Parkinson's disease),[11–13] and drug-induced liver injury. Importantly, therapeutic strategies targeting ferroptosis exhibit a dual nature: inducing ferroptosis has emerged as a novel anti-tumor strategy,[14,15] whereas inhibiting ferroptosis can protect healthy tissues in other pathological conditions.

Recent studies have further underscored the role of ferroptosis in the pathophysiology of SBI following ICH.[16,17] Post-ICH mechanisms involve multiple interconnected pathways, including iron dysregulation, neuroinflammation, cerebral vasospasm. Iron chelators such as deferiprone (DFP) and pyridoxal isonicotinoyl hydrazone (PIH) have demonstrated efficacy in reducing perihematomal iron deposition and lipid peroxidation in ICH models.[18] Notably, DFP also shows potential in ameliorating cerebral vasospasm after subarachnoid hemorrhage (SAH).[19] These findings position ferroptosis as a promising therapeutic target for mitigating SBI after ICH.

Recent reviews, including that by Sun et al,[20] have advanced our understanding of ferroptosis in ICH, primarily through the lens of molecular mechanisms and Western pharmacological interventions. However, such approaches often overlook integrative strategies—particularly the potential of Traditional Chinese Medicine (TCM) in modulating ferroptosis. This review aims to bridge this gap by exploring TCM-based interventions, offering a broader perspective on ICH treatment.

TCM, with its holistic regulatory properties, has shown unique advantages in the management of cerebrovascular diseases. By modulating key molecular pathways, reducing neuroinflammatory responses, and enhancing antioxidative

defenses, TCM-based therapies have demonstrated potential in regulating ferroptosis.[21,22] Recent studies have identified specific herbal medicines, active components, and multi-herb formulations that target ferroptosis through diverse mechanisms. These interventions enhance neuronal antioxidant capacity, suppress neuroinflammation, and may improve neurological outcomes in ICH.[23]

This review aims to elucidate the mechanistic role of ferroptosis in the progression of ICH and to explore the therapeutic potential of TCM in targeting this pathway. By integrating the theoretical foundations of TCM with modern scientific research, this work seeks to provide insights and potential strategies for mitigating SBI and improving the prognosis of patients with ICH.[24]

Overview of Ferroptosis: Characteristics and Regulatory Mechanisms

Ferroptosis: A Unique Mode of Cell Death

In 2003, Stockwell et al identified a small molecule called erastin that could induce a rapid, irreversible, nonapoptotic form of death in engineered tumor cells.[25] This iron- and oxidation-dependent process was formally named ferroptosis in 2012. A key feature of ferroptosis is the accumulation of lipid peroxides, which disrupt membrane structure and compromise cellular integrity.

Cell membranes play a vital role in maintaining cellular integrity by compartmentalizing and protecting intracellular structures. When their integrity is compromised, cells may enter a lethal state. The most distinctive morphological hallmarks of ferroptosis include reduced mitochondrial size, loss of cristae, and increased membrane density.[26] This form of cell death is closely associated with disruption of redox homeostasis—driven by impaired glutathione (GSH) synthesis, GSH depletion, or glutathione peroxidase 4 (GPX4) inactivation—which weakens antioxidant defenses and leads to the accumulation of toxic lipid reactive oxygen species (ROS) within membranes. Iron plays a unique and indispensable role in this process by catalyzing ROS production in a way not observed with other divalent transition metals.[26]

Ferroptosis is also genetically regulated. Dixon et al identified six high-confidence genes essential for erastin-induced ferroptosis, primarily involved in iron regulation and mitochondrial fatty acid metabolism. This complexity was further demonstrated by Zhou et al, who developed the FerrDb database cataloging 259 genes and 95 associated diseases, highlighting the broad biological and pathological significance of ferroptosis.[27]

Within the context of ICH, ferroptosis plays a pivotal role in secondary brain injury (SBI). The lysis of erythrocytes following ICH releases heme, leading to a threefold increase in non-heme iron levels in the brain that persists for weeks and drives ferroptotic damage in perihematomal neurons. This vulnerability is intensified by the brain's high polyunsaturated fatty acid (PUFA) content and relatively low antioxidant capacity, making ICH a highly relevant and high-risk setting for ferroptosis research.

Essential Processes: Iron Deposition and Lipid Peroxidation in ICH

The Pivotal Role of Ferroptosis in ICH Pathophysiology

Growing interest in ferroptosis has led to a surge of studies examining its role in neurological diseases, including ICH. Several experimental investigations have demonstrated that ferroptosis inhibitors provide neuroprotection in ICH models, positioning ferroptosis as a compelling therapeutic target. The pathological environment created by ICH—marked by rapid iron accumulation from hematoma breakdown—overwhelms the brain's antioxidant defenses and exacerbates neuronal injury. As such, ferroptosis is now recognized as a critical driver of SBI following ICH.

The Trigger for Ferroptosis: Iron Deposition After ICH

Iron deposition is the key initiator of neuronal ferroptosis in the aftermath of ICH. During the acute phase, thrombin is rapidly produced to stop bleeding, leading to hematoma formation. Within hours, erythrocytes in the hematoma undergo lysis, releasing ferrous iron from heme via heme oxygenase-1 (HO-1)—a major source of toxic iron in the brain.[28,29] A rat model-based study revealed a threefold increase in non-heme iron levels following ICH, with elevated levels persisting for at least a month.[30]

The accumulation of iron in the perihematomal region creates a highly oxidative and cytotoxic microenvironment that promotes neuronal injury.[31,32] Supporting this, in vitro experiments by Chen-Roetling et al showed that overnight exposure to human hemoglobin killed approximately 75% of neurons and significantly increased levels of iron, malondialdehyde, and HO-1—underscoring iron's role in ferroptotic injury.[33] Further confirmation comes from studies using intraventricular injections of erythrocytes or their breakdown products, which also resulted in significant brain injury in animal models.

Moreover, iron amplifies the cytotoxicity of erythrocyte degradation products such as hemoglobin and heme. Therapeutic strategies such as iron chelators and ferroptosis inhibitors like ferrostatin-1 (Fer-1) have shown potential in reducing iron overload and attenuating brain injury. Wan et al reported that a combination of Fer-1 with other inhibitors provided greater protection against hemoglobin-induced neuronal death than monotherapy.[34] Additionally, upregulation of ferritin, which sequesters free iron, has been shown to enhance neuroprotection,[35] further underscoring iron's central role in ferroptosis and ICH-induced secondary damage.

Mediators of Ferroptosis: ROS Generation After ICH

Following ICH, ROS are generated from multiple sources, including endoplasmic reticulum (ER) stress, macrophage activation, mitochondrial dysfunction, erythrocyte degradation products, and glutamate excitotoxicity. Excessive ROS production damages lipids, proteins, and DNA, activating cell death pathways. Among these, ferroptosis is particularly relevant due to its dependence on iron-catalyzed lipid peroxidation.[29]

The brain's high oxygen consumption and abundance of PUFAs, combined with limited antioxidant reserves, make it especially susceptible to oxidative stress (OS) and ferroptosis.[36] Key pathways—such as the mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), and tumor necrosis factor (TNF) signaling pathways—are tightly linked to oxidative injury after ICH.[37] Iron-induced MAPK activation promotes ROS generation, while ROS also trigger NF-κB signaling, linking OS with inflammation.[38]

ICH rapidly impairs the brain's endogenous antioxidant defense systems, exacerbating oxidative damage.[29,38] A notable example is glutathione peroxidase 4 (GPX4), a central suppressor of ferroptosis. Zhang et al reported that GPX4 protein levels in rat brains declined significantly by 12 hours post-ICH, reaching their lowest point at 24 hours, particularly in neurons.[39] Enhancing nuclear factor erythroid 2–related factor 2 (Nrf2)—a key regulator of redox homeostasis—stimulates antioxidant enzyme activity and restores GPX4 levels, counteracting ferroptosis by supporting neurological recovery.

The hemoglobin–heme–iron axis is a major driver of OS after ICH. Ferrous iron released from erythrocytes promotes lipid peroxidation via Fenton reactions.[40] Meanwhile, excess hydrogen peroxide (H_2O_2) exacerbates redox imbalance and disrupts the BBB, allowing further iron infiltration.[4] In animal models, direct injection of ferrous iron into the cortex induced lipid peroxidation within 15 minutes. H_2O_2 is also generated by reactions between iron and lipid peroxides, perpetuating neuronal injury. These findings underscore ferroptosis as a compelling target for antioxidant-based therapy in ICH.

Mechanistic Contributors to Ferroptosis in ICH

Extensive evidence indicates that iron contributes to various neurotoxic processes following ICH, including OS, inflammation, BBB disruption, coagulation cascade activation, and other pathological mechanisms.[29,34] All of these factors converge to promote SBI. One of the earliest pathological responses is leukocyte infiltration, which begins within hours of hemorrhage and amplifies inflammatory damage.[41,42]

Microglia, the brain's resident immune cells, are rapidly activated after ICH and release inflammatory mediators such as TNF-α and interleukin-1 beta (IL-1β).[43,44] While M2-polarized microglia support the clearance of cellular debris and may limit iron accumulation, rapid iron deposition after ICH promotes sustained M1 polarization, which worsens neurological outcomes.[45,46] Interactions between overactivated microglia and infiltrating leukocytes further escalate post-ICH neuroinflammation.[43] HO-1 expression, predominantly induced in endothelial cells and microglia/macrophages, contributes to ongoing iron release from the hematoma.[38] Huang et al[47] showed that the ferroptosis inhibitor ferrostatin-1 (Fer-1) enhanced M2 polarization, promoted microglial phagocytosis, and attenuated inflammation in a murine ICH model.

ICH also activates the coagulation cascade, triggering prothrombin cleavage and substantial thrombin release. Thrombin has a well-documented dual role in brain injury: at low concentrations, it is neuroprotective, but at high levels, it is neurotoxic.[48,49] Thrombin activity increases significantly within one hour of ICH onset,[50] initiating chemokine and adhesion molecule expression, enhancing leukocyte infiltration, activating glial cells,[51] and upregulating matrix metalloproteinases (MMP-2 and MMP-9), which degrade extracellular matrix components and compromise BBB integrity.[52]

Crucially, thrombin and iron interact in a synergistic and pathological manner. Thrombin upregulates brain HO-1 and the transferrin/transferrin receptor (Tf/TfR) system, accelerating hematoma breakdown and iron uptake.[53] However, excess iron potentiates thrombin-induced edema and neurotoxicity. Co-administration of iron-loaded Tf (holo-Tf) and thrombin worsens brain edema more than either factor alone.[54] These interactions highlight iron's central role in ferroptosis and its contribution to post-ICH brain injury.

Role of Iron in Ferroptosis

Iron is essential for numerous cellular functions, including mitochondrial respiration and enzymatic reactions. However, it also acts as a potent pro-oxidant. In the presence of H_2O_2, ferrous iron catalyzes the Fenton reaction, generating hydroxyl radicals and promoting oxidative damage.[55] This dual nature places iron at the heart of ferroptosis.

Iron contributes to ferroptosis through multiple mechanisms: it promotes ROS production,[56] drives lipid peroxidation, and acts as a cofactor for iron-dependent oxidoreductases.[57] In the context of ICH, hematoma-derived Fe^{2+} accumulates in perihematomal regions, where it fuels lipid peroxidation and directly contributes to neuronal death via ferroptosis.

Cellular Iron Metabolism and Regulation

Iron homeostasis is tightly regulated at both systemic and cellular levels. In the context of ferroptosis, regulation of intracellular iron is particularly important (Figure 1). The amount of intracellular iron depends on the balance between iron uptake, storage, and export.

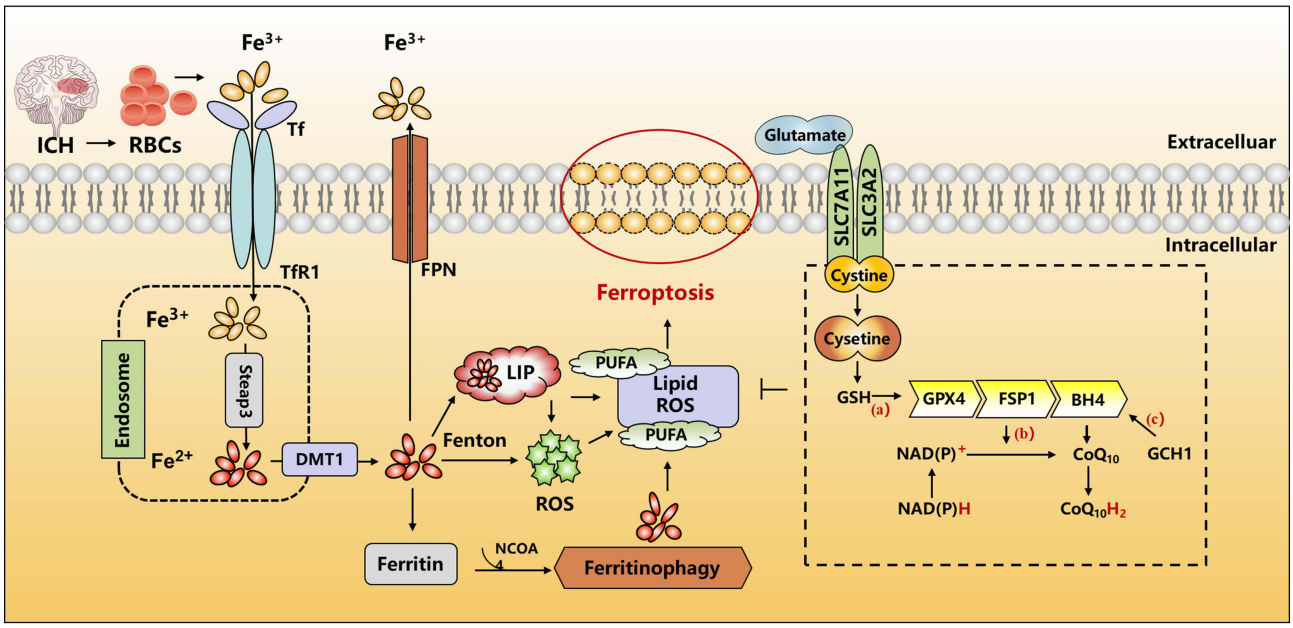


Figure 1 Mechanism of ferroptosis following intracerebral hemorrhage (ICH). ICH causes the extravasation of red blood cells (RBCs) into brain tissue. Upon lysis, RBCs release hemoglobin, which is degraded into heme, releasing iron into the surrounding microenvironment.[58–60] Extracellular Fe^{3+} binds transferrin (Tf) and is internalized via transferrin receptor 1 (TfR1)-mediated endocytosis. Within endosomes, Fe^{3+} is reduced to Fe^{2+} by Steap3 and transported into the cytoplasm via DMT1. Cytoplasmic Fe^{2+} enters the labile iron pool (LIP), where it may be stored in ferritin, released via ferritinophagy, or exported by ferroportin 1 (FPN1).[61,62] Excess Fe^{2+} catalyzes the Fenton reaction, generating reactive oxygen species (ROS) that drive lipid peroxidation of polyunsaturated fatty acids (PUFAs), ultimately inducing ferroptosis and neuronal damage.[63] Three major ferroptosis-suppressing pathways counteract this process: (**a**) the System xc^-–GSH–GPX4 axis, in which imported cystine is reduced to cysteine for glutathione (GSH) synthesis, enabling glutathione peroxidase 4 (GPX4) to detoxify lipid peroxides;[64–67] (**b**) the FSP1–CoQ10–NAD(P)H pathway, where ferroptosis suppressor protein 1 (FSP1) reduces oxidized CoQ10 to $CoQ10H_2$ via NAD(P)H oxidoreductase activity, protecting membranes from lipid peroxidation;[68,69] and (**c**) GCH1–BH4 axis, where GTP cyclohydrolase 1 (GCH1) promotes tetrahydrobiopterin (BH4) synthesis, enhancing CoQ10 production and scavenging ROS to reduce oxidative stress.[70]

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Iron uptake begins with Tf, which binds ferric iron (Fe^{3+}) and interacts with TfR1 on the cell surface. The Tf-TfR1 complex is internalized via receptor-mediated endocytosis.[58] Within acidic endosomes, Fe^{3+} is released from Tf and reduced to Fe^{2+} by the ferrireductase six-transmembrane epithelial antigen of the prostate 3 (Steap3).[59] Fe^{2+} is then transported into the cytoplasm by divalent metal ion transporter-1 (DMT1).[60] The Tf-TfR1 complex is recycled back to the membrane.

In the cytoplasm, iron has three major fates: (a) entry into the labile iron pool (LIP), from which it is delivered to mitochondria and other organelles and incorporated into iron-containing cofactors such as heme and Fe-S clusters;[61] (b) storage in ferritin, which sequesters excess iron and prevents ROS generation;[62] and (c) export from the cell via ferroportin 1 (FPN1), the only known iron exporter.

Iron release from ferritin occurs via two pathways. In ferritinophagy, ferritin is degraded through autophagy in a process mediated by nuclear receptor coactivator 4 (NCOA4), which responds to intracellular iron levels.[71,72] Alternatively, ferritin can be degraded through the ubiquitin–proteasome system (UPS), providing another route for iron mobilization.[71,73]

The level of cellular iron is tightly regulated to prevent both deficiency and toxicity. One of the primary regulatory mechanisms is the iron-responsive element/iron regulatory protein (IRE/IRP) system, which controls the post-transcriptional expression of genes involved in iron homeostasis. IREs are conserved stem-loop structures located in the untranslated regions (UTRs) of mRNAs encoding proteins such as transferrin receptor 1 (TfR1), divalent metal transporter-1 (DMT1), and ferritin.[74] IRPs—comprising two homologs, IRP1 and IRP2—respond dynamically to intracellular iron levels by binding to these IREs.

Under iron-deficient conditions, IRPs bind to IREs in the 3'-UTRs of TfR1, DMT1, and ferritin mRNAs, stabilizing these transcripts and promoting iron uptake. Concurrently, IRPs bind to IREs in the 5'-UTR of ferritin mRNA, suppressing its translation and thereby reducing iron storage. Conversely, under iron-replete conditions, IRPs lose their RNA-binding activity, resulting in the degradation of TfR1 and DMT1 mRNAs and allowing ferritin translation to increase iron sequestration. This finely tuned regulatory system ensures iron availability for essential cellular functions while preventing oxidative damage associated with excess free iron, which is particularly relevant in ferroptosis following ICH.

Iron Catalyzes ROS Production and Lipid Peroxidation

Cells maintain redox homeostasis through a coordinated network of antioxidative enzymes and compounds that regulate the balance between ROS production and clearance. Disruption of this balance induces excessive ROS accumulation,[75] leading to cell death and tissue damage.[76,77] While both proteins and lipids are susceptible to oxidative modifications by ROS, not all ROS sources contribute equally to ferroptosis.[73]

Iron plays a central role in ROS generation. It catalyzes the Fenton and Haber–Weiss reactions, directly producing highly reactive hydroxyl radicals, which have extremely high reaction rate constants.[63] Among these, hydroxyl radicals are considered the most damaging. The Fe- and Cu-catalyzed Fenton reaction is the predominant source of hydroxyl radicals in vivo and serves as a primary trigger for non-enzymatic lipid peroxidation by attacking polyunsaturated fatty acids (PUFAs).

Beyond initiating lipid peroxidation, iron also contributes to downstream processes by being incorporated into iron-containing proteins and enzymes. These include heme and iron–sulfur (Fe–S) clusters, which are essential components of ROS-producing enzymes and redox systems, further amplifying lipid peroxidation.[73]

Iron-dependent lipoxygenases (LOXs), particularly 15-LOX-1, also catalyze lipid oxidation. LOXs oxidize linoleic acid (LH) and molecular oxygen (O2), directly producing lipid hydroperoxides (LOOH)—one of the main enzymatic pathways involved in lipid peroxidation, a hallmark of ferroptosis, and a critical step in this process. The underlying reactions are broadly divided into non-enzymatic and enzymatic mechanisms (Figure 1).

Non-Enzymatic Lipid Peroxidation

Lipid autoxidation is a self-propagating chain reaction between lipids and molecular oxygen, consisting of three main phases: initiation, propagation, and termination.[78,79] During initiation, oxygen-centered radicals such as hydroxyl radicals

abstract hydrogen atoms from PUFAs, generating carbon-centered lipid radicals. These radicals then react with molecular oxygen to form lipid peroxyl radicals, which further abstract hydrogen atoms from adjacent fatty acids—producing the first LOOH and new radicals, perpetuating the cycle.[79,80] This propagation step is facilitated by the close packing of fatty acid chains in lipid bilayers.[81]

LOOH can undergo reductive cleavage by reduced metals like Fe^{2+}, yielding lipid alkoxyl and lipid peroxyl radicals that further accelerate peroxidation.[80,81] The chain reaction continues until essential reactants—lipids, oxygen, or peroxide radicals—are depleted or until radical-trapping antioxidants, such as GSH or vitamin E, neutralize the radicals.[82] In ICH, this process is exacerbated by the release of Fe^{2+} during erythrocyte lysis, which accelerates lipid peroxidation in neuronal membranes.

Enzyme-Mediated Lipid Peroxidation

Enzymatic lipid peroxidation is primarily mediated by LOXs, cyclooxygenases (COXs), and cytochrome P450 oxidoreductase (POR), with LOXs playing a particularly dominant role in LOOH formation.[83] LOXs stereospecifically oxidize PUFAs to generate hydroperoxy derivatives, which are subsequently converted into bioactive lipid mediators that influence cellular signaling and metabolic processes. LOX activity is regulated by several protein kinases and divalent metal ions,[83] among which iron serves as an essential cofactor.

The excess accumulation of lipid peroxides compromises cell membrane integrity by altering its structure, fluidity, and composition, ultimately impairing cell viability.[84] Furthermore, lipid peroxides not only amplify ROS production but also generate secondary aldehydic byproducts such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE).[75,80,85] These highly reactive and cytotoxic aldehydes can modify proteins, nucleic acids, and lipids—even at sites distant from their origin—disrupting cellular function.[80] Additionally, they act as signaling molecules that influence gene expression and promote pathological changes.[84]

Major Pathways Regulating Ferroptosis

Three key regulatory pathways of ferroptosis have been identified to date (Figure 1a–1c), although the process is likely governed by a broader and more complex signaling network. The first is the System xc^-/GSH/GPX4 axis (Figure 1a). System xc- is a cystine/glutamate antiporter that mediates the uptake of extracellular cystine in exchange for intracellular glutamate. Once inside the cell, cystine is reduced to cysteine, which serves as a precursor for glutathione (GSH) synthesis.[64] System xc^- is composed of two subunits: the light chain SLC7A11, responsible for cystine uptake,[65] and the heavy chain SLC3A2, which stabilizes SLC7A11.[66,67,86] Inhibition of system xc^- disrupts cystine transport, leading to GSH depletion and GPX inactivation. This results in the accumulation of lipid peroxides and ultimately induces ferroptotic cell death.[67,86,87] GPX4 is the only member of the GSX family capable of reducing lipid peroxides within complex membrane environments.[88] Two classical ferroptosis inducers, erastin and RSL3, inhibit GPX4 through distinct mechanisms: erastin depletes GSH by inhibiting system xc^- (an indirect effect),[86] while RSL3 directly binds to GPX4's nucleophilic residues, inactivating GPX4.[86,89]

The second pathway is the FSP1/CoQ10/NAD(P)H axis (Figure 1b). Ferroptosis suppressor protein 1 (FSP1) offers protection against ferroptosis through a mechanism independent of GPX4. FSP1 undergoes N-myristoylation, a lipid modification that enables its localization to the plasma membrane.[68] In addition, FSP1 possesses an N-terminal hydrophobic sequence that facilitates its association with the lipid bilayers of the plasma membrane.[69] Once localized, FSP1 functions as a NAD(P)H-dependent oxidoreductase, converting oxidized coenzyme Q10 (CoQ10) into its reduced form ($CoQ10H_2$). This reduced CoQ10 acts as a lipid-soluble antioxidant that halts the propagation of lipid peroxides and protects against ferroptosis.[69]

The third pathway is the GCH1/BH4 axis (Figure 1c). Tetrahydrobiopterin (BH4) is a redox-active cofactor involved in the biosynthesis of neurotransmitters, nitric oxide, and aromatic amino acids.[70] Its synthesis is regulated by GTP cyclohydrolase 1 (GCH1), the rate-limiting enzyme in this pathway, which is allosterically controlled by the GTPCHI feedback regulatory protein. Overexpression of GCH1 leads to increased production of BH4, which has potent free radical-scavenging activity.[70] Elevated BH4 levels not only neutralize OS but also facilitate the conversion of phenylalanine into 4-hydroxybenzoate, a CoQ10 precursor, thereby enhancing antioxidant defenses. Moreover, GCH1

overexpression alters lipid profiles and protects specific phospholipid subclasses from oxidative degradation, particularly in response to ferroptosis-inducing agents such as imidazole ketone erastin.

Traditional Chinese Medicine and Ferroptosis in ICH Treatment

Explaining Ferroptosis After ICH from the Perspective of TCM Theory

In TCM theory, the hematoma formed after ICH is described as "blood stasis"—a pathological state arising from disrupted circulation and the extravasation of blood into brain tissue. "Blood stasis" encompasses more than just stagnant blood; it also includes secondary pathological products such as phlegmatic turbidity and "heat evil", collectively referred to as "toxins". The damaging effects of these toxins are analogous to the cellular injury caused by iron accumulation and lipid-derived ROS attack on cell membranes.

In TCM, qi is described as an invisible, dynamic, warm-natured force essential for sustaining physiological function. Qi governs blood movement; therefore, when blood stasis obstructs qi flow, stagnation ensues. This stagnation may transform into "heat evil", disrupting the normal interplay of qi and blood, and accelerating the formation of additional toxins (Figure 2). TCM interprets heat evil and its toxic byproducts in terms similar to inflammatory cytokines and OS markers in modern medicine. Notably, the oxidative damage, inflammation, and iron dysregulation seen after ICH closely align with TCM concepts of stasis and toxicity. The core pathological events of ferroptosis—iron deposition and lipid peroxidation—are also deeply integrated into this interpretation.

To address these pathological patterns, TCM therapies employ principles such as "blood activating and stasis dissolving", "heat clearing and fire purging", "detoxification", and "damp clearing".[90,91] These approaches aim to restore balanced iron homeostasis—conceptually akin to modulating the hepcidin–ferroportin axis—and exert effects comparable to anti-inflammatory, antioxidative, and pro-angiogenic interventions recognized in contemporary biomedical science.

Ferroptosis, as a multifactorial and adjustable cell death process, provides ample opportunity for therapeutic intervention. Research has demonstrated that TCM interventions—including isolated herbal constituents (Table 1), compound decoctions (Table 2), and acupuncture (Table 3)—can regulate key ferroptosis-related processes such as GPX4 activity, iron metabolism, and ROS production. These effects collectively confer neuroprotection and offer new therapeutic avenues to reduce brain injury after ICH.

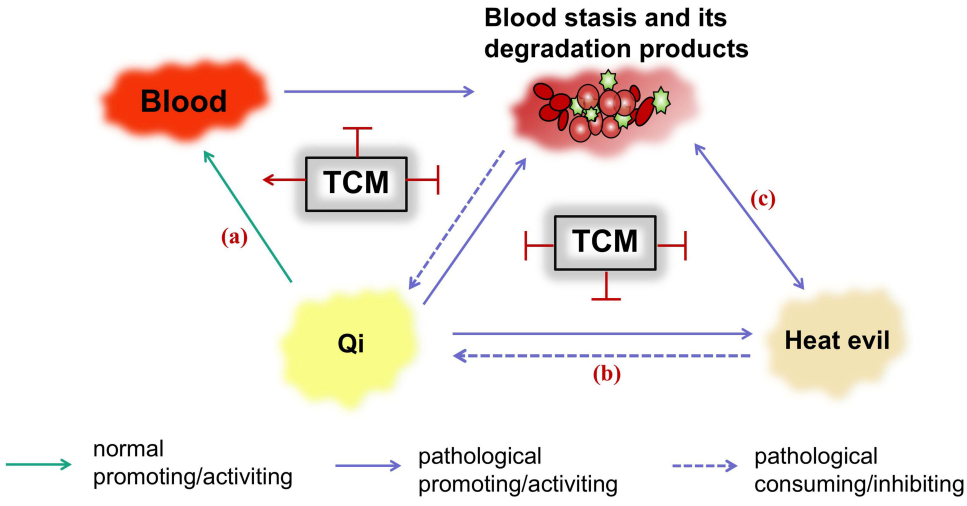

Figure 2 Pathological cascade triggered by qi and blood dysregulation, and intervention pathways in Traditional Chinese Medicine (TCM). (**a**) Relationship between qi and blood: under normal conditions, qi promotes blood circulation. When qi becomes stagnant, blood flow is impaired, leading to blood stasis. (**b**) Relationship between qi and heat evil: If qi cannot circulate normally, it stagnates and gradually transforms into heat evil. In turn, heat evil consumes qi, weakening its ability to promote blood circulation. (**c**) Relationship between heat evil and blood stasis: heat evil accelerates the formation of blood stasis, while persistent blood stasis generates additional heat evil, forming a pathological feedback loop. Heat evil accelerates the formation of blood stasis, while persistent blood stasis generates additional heat evil, forming a pathological feedback loop.

Table 1 Ingredients of Chinese Herbs/ Nature Products for ICH Treatment by Regulating Ferroptosis

Ingredients	Herbs/ Nature Products	Effect of herbs/ Nature Products	Botanical Origin	Targets/Pathways	Ref
Baicalin	Huangqin	Clearing heat and toxin	*Scutellaria baicalensis* Georgi	SLC7A11/GXP4 DMT1	[92]
Paeonol	Mudanpi etc.	Clearing heat, removing blood stasis	*Paeonia* × *suffruticosa* Andrews,etc.	HOTAIR/UPF1/ ACSL4SLC7A11/ GPX4	[93]
Curcumin	Jianghuang, Yujin etc.	Activating qi Removing blood stasis	*Curcuma longa* L.	Nrf2/HO-1/GPX4	[94]
Dauricine	Shandougen	Clearing heat and toxin	*Sophora tonkinensis* Gagnep.	GPX4/GSR	[95]
Isorhynchophylline	Gouteng	Soothing the liver clearing heat	*Uncaria macrophylla* Wall.	TP53/SLC7A11	[96]
Crocin	Honghua, Zhizi, etc.	Removing blood stasis clearing heat	*Crocus sativus* L.,etc.	Nrf2/GPX4	[97]
Naringenin	Zhishi, Chenpi etc.	Activating qi resolving phlegm	*Citrus*×*aurantium* L.,etc.	Nrf2/GPX4	[41]
Resveratrol	Huzhang	Clearing heat and toxin removing blood stasis	*Polygonum cuspidatum* Siebold & Zucc.	System xc^-/GPX4	[98]
Dihydromyricetin	Tengcha	Clear heat and eliminate dampness, invigorate blood and unblock meridians	*Ampelopsis acerifolia* W. T.Wang	LCN2/System xc^-	[99]
Epicatechin	Jixueteng, etc.	Invigorate blood and unblock meridians	*Spatholobus suberectus* Dunn,etc.	Nrf2, AP-1	[100]
Epigallocatechin gallate	Tea	Clearing heat and toxin	*Camellia sinensis* (L). Kuntze	Nrf2/GPX4, System xc^-	[101]
Salvianolic acid A	Danshen	Invigorate blood, dispel stasis, unblock meridians, and relieve pain, clear heat from the blood	*Salvia miltiorrhiza* Bunge	Akt /GSK-3β/Nrf2/ GPX4	[102]
Artesunate	Qinghao	Clear heat and eliminate dampness	*Artemisia annua* L.	AMPK/mTORC1/ GPX4	[103]
Eupatilin	Alye	Warming Meridian, Removing blood stasis	*Artemisia argyi Levl.et Vant.*	SOX2/SLC7A11	[104]
Withaferin A	Nanfeizuiqie	Reinforce the healthy qi, Clearing heat and toxin	Withania Somnifera	Tf, FTH1, 4-HNE	[105]
Cinnamaldehyde	Rougui	Returning fire to its origin	*Cinnamomum cassia* (L). D. Don	SLC7A11/GPX4	[106]
Panaxadiol	Renshen	Replenishing vital energy	*Panax ginseng* C. A. Mey.	ACSL4/GPX4	[107]
Hesperidin	Chenpi, Zhishi, etc	Regulating qi-flowing for activating stagnancy	*Citrus reticulata Blanco, Citrus aurantium* L.	Nrf2/GPX4	[108]

Table 2 Preparations of TCM for ICH Treatment by Regulating Ferroptosis

Preparations of TCM	Composition	Effect of Composition	Targets/Pathways	Ref
Zhilonghuoxue tongyu Capsule	Huangqi, Dilong, Shuizhi, Daxueteng, Guizhi	Invigorating qi and promoting blood circulation Removing blood stasis	TP53 GPX4	[109]
Annaopingchong Derection	Longgu, Muli, Niuxi, Baijili, Gouteng, Zexie, Mudanpi, Zhizi, Huangqin, Baishao, Dahuang, Gancao	Soothing the liver for calming endogenous wind, Nourishing blood,Clearing heat	System xc^-/GPX4 Tf/TfR	[110]
Naotaifang	Huangqi, Chuanxiong, Dilong, Jiangcan	Invigorating qi, Promoting blood circulation, Activating collaterals	TfR GSH/GPX4	[111]
Zhongfeng Xingnao Decoction	Hongshen, Chuanxiong, Sanqi, Dahuang	Awakening the mind and opening the orifices, Removing blood stasis and resolving phlegm, Clearing heat and extinguishing wind	System xc^-/GPX4 Tf/TfR	[112]
Didang Tang	Dahuang, Taoren, Shuizhi, Mengchong	Removing blood stasis, Clearing heat	SLC7A11 GPX4	[113]

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Table 3 Acupuncture for ICH Treatment by Regulating Ferroptosis

Mk	Acupoints	Effect	Targets/Pathways	Ref
Acupuncture	DU20-penetrating-GB7	Regulating the qi and blood circulation of the whole head	miR-23a-3p, Nrf2/HO-1/GPX4	[114]
Scalp Acupuncture	DU20-penetrating-GB7		p62/Keap1/Nrf2, FTH1,GPX4	[95]

Notes: DU20: Baihui; GB7: Qubin.

Active Ingredients of Chinese Herbs

Although research on the role of individual herbal constituents in regulating ferroptosis after ICH remains limited, several studies offer promising insights (Table 1). Specific active compounds from traditional Chinese herbs have demonstrated anti-ferroptotic effects and improved neurological outcomes in ICH models. For instance, baicalin, derived from *Scutellaria baicalensis* Georgi (Huangqin), has been shown to upregulate GPX4 expression while reducing iron uptake by downregulating DMT1 in neural cells.[115] Similarly, paeonol, extracted from *Paeonia* × *suffruticosa* Andrews (Mudanpi), alleviates ACSL4-dependent neuronal ferroptosis,[21] and crocin from *Carthamus tinctorius* L. (Honghua), mitigates ICH-induced ferroptosis by promoting Nrf2 nuclear translocation.[97]

Table 1 summarizes eighteen active ingredients from different herbs. Among them, eight possess blood-activating properties, nine have heat-clearing properties, two promote qi, five exhibit detoxifying properties, and two reinforce healthy qi. This classification suggests that TCM strategies targeting "heat evil" and "blood stasis" may play a central role in modulating ferroptosis after ICH.

A study by Liu et al used transcriptomic analysis to compare perihematomal tissue and contralateral normal tissue from ICH patients. By intersecting the identified differentially expressed genes (DEGs) with known ferroptosis-related genes, they uncovered 45 ferroptosis-associated DEGs.[37] KEGG pathway enrichment analysis indicated that many of these genes were involved in TNF signaling and OS responses, with MAPK1 emerging as a key hub gene. These findings support the hypothesis that herbs with blood-activating, heat-clearing, and detoxifying effects may be particularly relevant for anti-ferroptotic therapy via antioxidant and anti-inflammatory mechanisms. In the same study, Liu et al developed an ICH rat model to investigate MAPK1-related targets, providing a foundation for further mechanistic investigations.[37]

While not all herbal compounds have been explicitly studied in the context of ferroptosis, several are known to affect related processes such as iron metabolism and lipid peroxidation. For example, puerarin, extracted from *Pueraria alopecuroides* Craib (Gegen)[116] reduces both lipid accumulation and iron overload.[117] Similarly, emodin, derived from *Rheum palmatum* L. (Dahuang) protects neurons from oxidative injury by activating the Nrf2/ARE pathway.[118] These compounds represent promising candidates for future research into TCM-based modulation of ferroptosis after ICH.

Moreover, hematoma clearance is critical for the treatment of intracerebral hemorrhage (ICH). Studies have reported that Panax notoginseng saponins enhance hematoma absorption mediated by the glymphatic system, upregulate Nrf2 expression, reduce neuroinflammation, and protect brain tissue from damage. These findings underscore the potential of targeting ferroptosis suppression and glymphatic system function as an effective therapeutic strategy for ICH. Numerous herbal extracts, such as Panax notoginseng saponins, demonstrate neuroprotective effects through these mechanisms. Although not all are directly linked to ICH, they represent a promising group of bioactive compounds with therapeutic potential, particularly in mitigating iron-dependent neuronal injury and supporting broader neurovascular recovery.[119]

Preparations of TCM

In TCM, the root cause of "blood stasis" is often attributed to abnormalities in the circulation of qi and blood. According to this framework, qi stagnation of deficiency impairs blood flow, making the regulation of their interaction a central therapeutic goal in ICH treatment. Consequently, many TCM compound formulas used in ICH management emphasize harmonizing qi and promoting blood circulation. Classic prescriptions such as Buyang Huanwu Decoction, Didang Decoction, and Xuefu Zhuyu Decoction exemplify this therapeutic approach (Table 2).[92,93]

Given that blood stasis is a key pathological mechanism in ICH, TCM commonly employs therapies aimed at activating blood and removing stasis. A systematic review has shown that such treatments can reduce hematoma volume

while minimizing adverse effects.[94] Among the components of these formulas, insect-derived medicines—recognized in TCM for their potent stasis-resolving effects—are often included. These agents enhance hematoma absorption, reduce inflammation, and support neurological recovery.[109,114,120] For example, Naoxueshu liquid and Didang Tang, widely used preparation containing leeches, exemplifies this strategy. It replenishes qi, activates blood, removes stasis, and has been shown to reduce both inflammation and hematoma volume in ICH patients.[113,114] Its key active component, hirudin, is a natural thrombin inhibitor that facilitates hematoma clearance.

Another commonly used insect medicine is Dilong (earthworm), which supports nerve regeneration, exerts anticoagulant effects, and demonstrates antioxidant properties.[121,122] However, the use of blood-activating formulas, particularly those containing insect medicines, raises concerns about the potential risk of rebleeding. To address this, it is essential to assess coagulation function, hemorrhage volume, and vascular integrity before initiating circulation-promoting treatments.

Recent studies have also explored the timing of blood-activating and stasis-resolving therapy in acute cerebral hemorrhage.[123] Determining the optimal intervention window remains an ongoing challenge, and further research is needed to establish standardized clinical risk assessment protocols. One notable advantage of TCM lies in its flexible prescription principles—herbs can be added, removed, or substituted to match the individual patient's condition. This customizability offers a path toward maximizing therapeutic efficacy while minimizing the risk of complications such as rebleeding.

Acupuncture in TCM

Acupuncture, a core modality in TCM, has been shown to inhibit ferroptosis in neurons in rat models following ICH induction.[66] In a recent study, Li et al reported that acupuncture attenuated neuronal ferroptosis by modulating iron metabolism—specifically by reducing iron accumulation through regulation of the DMT1/FPN1 ratio.[124] It also decreased lipid content in neurons and suppressed lipid peroxidation, key processes involved in ferroptosis. To date, two studies have directly examined acupuncture's role in regulating ferroptosis after ICH, both using the same acupoint combination (Table 3 and Figure 3).

Scalp acupuncture (SA)—a modern adaptation of traditional acupuncture—integrates classical meridian theory with the cortical functional zones of the brain. It is especially valued in neurological rehabilitation for its simplified acupoint selection, robust needling response, and strong therapeutic effects, making it particularly suitable for treating cerebrovascular diseases such as ICH.

Both studies utilized the "Baihui-penetrating-Qubin" acupoint combination, which is widely used in stroke treatment. Baihui, located at the top of the head, is believed to regulate meridian qi and improve neurological function by enhancing

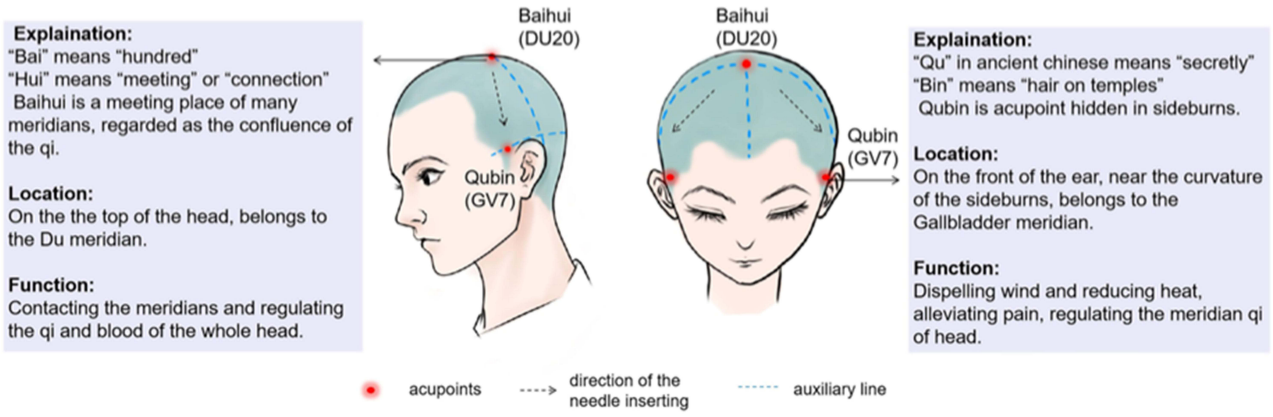

Figure 3 Schematic illustration of the Baihui-penetrating-Qubin acupoint technique. This figure illustrates the Baihui-penetrating-Qubin acupuncture method. Baihui (GV20), located at the vertex of the head, is traditionally used to activate qi and promote cerebral circulation. Qubin (GB7), positioned along the gallbladder Meridian, governs the regulation and movement of qi.[95,114] The integration of these two acupoints in the Baihui-penetrating-Qubin technique aims to enhance cerebral blood flow by restoring qi dynamics. This method has long been employed in stroke therapy and is now being explored for its potential role in modulating ferroptosis, inflammation, and oxidative stress in ICH.

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the circulation of qi and blood in the upper body. Qubin, located along the gallbladder meridian, is known as the "doorshaft" of qi movement and is thought to regulate directional flow—ascending, descending, inward, and outward. By stimulating these two acupoints simultaneously, acupuncture helps restore qi dynamics and thereby promotes cerebral blood flow and neurological recovery.

In addition to manual acupuncture, electroacupuncture (EA) has shown neuroprotective effects in ICH models. Studies have reported that EA can inhibit apoptosis, enhance angiogenesis, reduce BBB permeability, and regulate mitophagy.[125,126] However, research on EA's role in regulating ferroptosis, specifically in hemorrhagic stroke, remains limited. Most existing studies focus on ischemic stroke or ischemia–reperfusion injury.[127,128] This gap highlights an important area for future exploration—investigating how EA may influence ferroptosis pathways in the setting of ICH could uncover new therapeutic mechanisms and expand TCM-based treatment strategies for hemorrhagic stroke.

Discussion

Ferroptosis is an iron-dependent form of programmed cell death, and in recent years, its association with intracerebral hemorrhage (ICH) has garnered increasing attention. Ferroptosis is closely linked to oxidative stress (OS) and lipid peroxidation, both of which play pivotal roles in the secondary injury following ICH.[26] After an intracerebral hemorrhage, iron ions released from the hematoma may exacerbate neuronal damage, while ferroptosis inhibitors, by modulating iron metabolism or scavenging free iron, have shown promising therapeutic potential.

While ferroptosis inhibitors, especially iron chelators and modulators of iron metabolism, have shown potential, their clinical translation remains limited. Among them, deferoxamine (DFX), an FDA-approved iron chelator, has progressed to clinical trials. DFX reduces OS and lipid peroxidation by binding free iron. Although preclinical models suggest that DFX may reduce white matter injury and perihematomal edema, meta-analyses have reported inconsistent effects on neurological recovery.[129,130]

Several barriers hinder clinical application: (1) limited BBB penetration restricts effective intracerebral drug delivery;[131] (2) chronic toxicity, including auditory, retinal, and hematological adverse effects, limit long-term use;[132] (3) short plasma half-lives of agents like LIP1 and DFX necessitate frequent dosing;[123,133] (4) narrow therapeutic focus on lipid peroxidation fails to address broader iron imbalance and GPX4 dysfunction;[134] (5) low oral bioavailability and dose-related central nervous system depression reduce effectiveness;;[133,135] (6) drug interactions, particularly with immunosuppressants, heighten bleeding and infection risks;[133,136] and (7) natural chelators often lack validated safety and efficacy data, despite encouraging preclinical data.[137]

To improve treatment efficacy, ferroptosis-targeted therapies must shift from single-target agents to integrated, multi-pathway strategies. Future strategies should focus on multi-functional modulators that regulate both iron homeostasis and lipid peroxidation. Delivery via advanced systems such as nanocarriers with BBB-transmigrating peptides or sustained-release platforms is particularly promising.[20,134,138] Rational drug design can enhance natural chelators' metabolic stability and reduce off-target toxicity.[123,139] Tissue-specific engineering and metabolic bypass activation may further minimize systemic iron depletion. Preclinical studies would benefit from using physiologically relevant models, such as cerebral organoids and ICH models incorporating HFE gene variants, to better mimic human disease.[140,141] In clinical settings, adaptive trial designs that enable real-time drug monitoring and dose optimization could replace traditional protocols.[142,143]

Emerging tools, such as machine learning, stimuli-responsive nanomaterials, and near-infrared-triggered nanoparticles, offer novel solutions for precise, spatiotemporal-controlled drug delivery to hemorrhagic sites.[144–146] These innovations must tackle the persistent challenges of therapeutic precision, bioavailability, and clinical translatability that currently limit ferroptosis-based interventions.

As TCM research in ICH advances, various effective herbal monomers, compound formulas, and acupuncture methods have been identified.[147,148] Multiple studies have examined their roles in modulating post-hemorrhagic inflammation and apoptosis. TCM's unique therapeutic models—targeting neurotoxicity, ferroptosis, and neuroimmune responses—are increasingly recognized as valuable contributions to hemorrhagic stroke treatment.

In contrast to the single-target approach used by Sun et al,[20] who explored ferroptosis inhibitors like Liproxstatin-1 with limited attention to long-term safety, this review emphasizes TCM's multi-target approach. For example,

acupuncture has demonstrated ability to reduce OS in clinical trials,[149] while herbal compounds like baicalin inhibit lipid peroxidation, synergistically complementing Western pharmacological approaches.[150]

Within TCM, ferroptosis aligns conceptually with "blood stasis", "toxicity", and "phlegm-dampness". Iron accumulation and lipid peroxidation, key features of ferroptosis, parallel the idea of "blood stasis", where disrupted flow and vascular congestion result from iron deposition.[151] Toxic lipid peroxides generated via the Fenton reaction reflect the TCM notion of "toxicity", signifying persistent tissue injury from accumulated harmful substances.[152,153] Moreover, lipid and glucose metabolism disorders common after ICH align with the "phlegm-dampness" concept, as lipid accumulation mirrors endogenous phlegm obstructing qi and blood circulation.[154] These analogies offer a bridge between molecular pathology and traditional diagnostics.

Active components in TCM regulate ferroptosis through various mechanisms. We have compiled evidence in the text regarding active components of Chinese herbal medicine, herbal preparations, and non-pharmacological interventions (such as acupuncture) that effectively mitigate the progressive deterioration of intracerebral hemorrhage, demonstrating significant therapeutic effects. Moreover, it has been found that certain components, such as Astragaloside IV, Tanshinone I, and Danhong Injection—although not yet directly linked to intracerebral hemorrhage—can also inhibit lipid peroxidation and protect against neuronal damage through targets like Nrf2/GPX4 and ACSL4, suggesting their potential to exert neuroprotective effects following intracerebral hemorrhage.[155,156] However, validating TCM scientifically remains challenging. Randomized controlled trials (RCTs) have yielded inconsistent results. For instance, a double-blind, multicenter study published in *The Lancet* found no significant difference in clinical outcomes between Xingnao Injection and placebo in acute ICH patients.[157] These findings do not negate TCM's clinical relevance but highlight the difficulty of applying standardized research designs to inherently multi-target therapies. They also underscore the need for stratified study designs and personalized interventions.

While Sun et al[20] provide a solid foundation for ferroptosis-targeted ICH therapies, their focus on Western single-target interventions overlooks the synergistic potential of integrative approaches. TCM's multi-pathway, low-toxicity regulation of ferroptosis offers a compelling alternative for cerebrovascular disease treatment. However, the complexity of herbal formulas complicates mechanistic analysis and standardization. Although progress in ferroptosis-related signaling has enhanced our understanding,[158,159] further work is needed to explore crosstalk between ferroptosis and other forms of programmed cell death. Integrating multi-omics research with TCM theory may help unravel these interactions.

Systems-level studies are crucial to reveal molecular synergies among TCM components and clarify their therapeutic logic. Technologies such as AI, big data analytics, and network pharmacology can accelerate the identification of active ingredients and therapeutic targets. Additionally, developing research models that reflect the multi-target nature of TCM will strengthen the scientific foundation for its application.

Acupuncture, a core TCM modality, is increasingly recognized for its neuroprotective role in ICH. Research shows that EA—which combines traditional needling with low-frequency microcurrent to enhance stimulation—at GV20-GB7, GV26, and PC6 improves neurological function through several mechanisms: (1) promoting autophagy by upregulating expression of mitophagy protein LC3, suppressing p62, and activating the mTOR/S6K1 pathway;[160] (2) inhibiting apoptosis by suppressing caspase-3/9 expression and modulating p53 levels;[161,162] (3) attenuating ferroptosis through NFE2L2 signaling and miR-23a-3p downregulation;[163] and (4) reducing inflammation by downregulating NLRP3, IL-1β, and IL-18.[164]

Scalp penetration needling reduces serum IL-6 and modulates the plasma endothelin (ET)/ calcitonin gene-related peptide (CGRP) ratio. EA at GV20-GB7 relieves cerebral edema by regulating AQP4. Although limited, existing studies suggest that GV20–GB7 needling may influence ferroptosis via antioxidant, anti-inflammatory, and miRNA pathways.[160,165] Additional acupoints like GV26 and PC6 may further enhance these effects by synergistically inhibiting apoptosis.[165,166] EA at GV20 and GV14 improves cerebral iron metabolism by downregulating hepcidin, ferritin, and TfR expression, thereby alleviating neurological deficits after ICH.[167,168] Further exploration of acupoint combinations and their mechanisms will help clarify acupuncture's role in regulating ferroptosis and support its integration into post-ICH neurorehabilitation.

This comprehensive approach bridges macro-level therapeutic evaluation with molecular-level mechanistic research, advancing TCM from empirical application to precision medicine. By combining traditional theory with modern technology, TCM's multi-target potential can be systematized, standardized, and globalized to provide robust, evidence-based strategies for ICH prevention and treatment.

Conclusion

Our comprehensive review highlights the pivotal role of ferroptosis in the pathophysiology of ICH and underscores the therapeutic potential of TCM in regulating this form of cell death. Growing evidence shows that TCM interventions—including herbal compounds, multi-herb formulations, and acupuncture—can enhance neuronal antioxidant capacity, modulate iron metabolism, and reduce neuroinflammation, collectively offering a promising strategy for mitigating SBI after ICH. By elucidating the molecular pathways through which TCM influences ferroptosis, this review provides novel insights and identifies potential multi-target therapeutic approaches for improving neurological outcomes in ICH patients. Future research should aim to validate these mechanisms through rigorous experimental and clinical studies and explore the integration of TCM into standardized treatment frameworks for ferroptosis-related neurological disorders.

Abbreviations

ICH, Intracerebral hemorrhage; TCM, Traditional Chinese medicine; ACD, Accidental cell death; RCD, Regulatory cell death; GSH, Glutathione; GPX4, Glutathione peroxidase 4; ROS, Reactive oxygen species; OS, Oxidative Stress; Tf, Transferrin; TfR1, Transferrin receptor-1; Steap3, Six-transmembrane epithelial antigen of the prostate 3; DMT1, Divalent metal-ion transporter-1; LIP, Labile iron pool; NCOA4, Nuclear receptor coactivator 4; UPS, Ubiquitin-proteasome system; POR, Cytochrome P-450; LOXs, Iron-dependent lipoxygenases; LOOH, Lipid hydroperoxide; PUFAs, Polyunsaturated fatty acids; COXs, Cyclooxygenases; 4-HNE, 4-Hydroxynonenal; GCH1, GTP Cyclohydrolase1; HO-1, Heme oxygenase-1; TNF-α, Tumor necrosis factor-α; IL-1β, Interleukin-1 beta; MMPs, Metalloproteinases; ERs, Endoplasmic reticulum stress; MAPK, Mitogen-activated protein kinase; NK-κB, Nuclear factor kappa-B; Nrf2, Nuclear factor erythroid 2-like 2.

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Disclosure

The authors report no conflicts of interest in this work.

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