

# Recent advances in potential therapeutic targets of ferroptosis-associated pathways for the treatment of stroke (Review)

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**Abstract.** Stroke is a severe neurological disease that is associated with high rates of morbidity and mortality, and the underlying pathological processes are complex. Ferroptosis fulfills a significant role in the progression and treatment of stroke. It is well established that ferroptosis is a type of programmed cell death that is distinct from other forms or types of cell death. The process of ferroptosis involves multiple signaling pathways and regulatory mechanisms that interact with mechanisms inherent to stroke development. Inducers and inhibitors of ferroptosis have been shown to exert a role in the onset of this cell death process. Furthermore, it has been shown that interfering with ferroptosis affects the occurrence of stroke, indicating that targeting ferroptosis may offer a promising therapeutic approach for treating patients of stroke. Hence, the present review aimed to summarize the latest progress that has been made in terms of using therapeutic interventions for ferroptosis as treatment targets in cases of stroke. It provides an overview of the relevant pathways and molecular mechanisms that have been investigated in recent years, highlighting the roles of inducers and inhibitors of ferroptosis in stroke. Additionally, the intervention potential of various types of Traditional Chinese Medicine is also summarized. In conclusion, the present review provides a comprehensive overview of the potential therapeutic targets afforded by ferroptosis-associated pathways in stroke, offering new insights into how ferroptosis may be exploited in the treatment of stroke.

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## 1. Introduction

Globally, stroke ranks as the second leading cause of death, and the primary cause of disability (1). It imposes a significant burden on patients, their families and society as a whole, with ~3 million new cases occurring each year (2,3). Stroke is usually referred to as an acute cerebrovascular disease, the main mechanism of which is the sudden rupture or blockage of blood vessels in the brain, resulting in an inability of blood to enter the brain, leading to a lack of blood sugar (4) and oxygen (5), resulting in metabolic changes (6), cell death (7) and brain damage. Stroke is usually divided into two major categories; namely, ischemic stroke (including cerebral infarction) and hemorrhagic stroke (including cerebral hemorrhage and subarachnoid hemorrhage) (8). Concurrently, ischemia-reperfusion injury often occurs during the treatment of stroke, especially when reperfusion therapies, such as vascular recanalization procedures, are employed (9). A close association exists among stroke, ischemia-reperfusion injury and hemorrhagic stroke, as abnormalities in cerebral blood supply are a common feature for all of these conditions, which may lead to either damage or death of neural cells (9). When treating stroke, it is essential to consider these distinct types of injury mechanisms and their corresponding therapeutic approaches. The incidence of stroke is increasing, due to the increasing population and aging (8). Long-term disability and cognitive impairment are considered to be major causes of stroke, which is characterized by high morbidity and disability rates; thereby, stroke generally requires the support of the healthcare system (10). Therefore, exploring different means of intervention therapy for the purposes of the treatment of stroke remains a current international concern.

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Ferroptosis is rapidly becoming understood to be one of the key cell death mechanisms associated with stroke (11). As is well known, ferroptosis is a type of programmed cell death that is distinct from other forms or types of cell death; it is characterized by an increase in the level of lipid peroxides, which are lethal substances that ultimately lead to oxidative stress and cell death (12). Ferroptosis differs from other forms of cell death in that morphologically, it typically manifests as increased cell volume, mitochondrial swelling and endoplasmic reticulum expansion (13); physiologically, ferroptosis involves processes such as excessive accumulation of iron ions and oxidative stress (14); and genetically, mutations or genetic variations in genes related to iron metabolism (15) or oxidative stress (16) may affect the occurrence and progression of ferroptosis (17). In addition, another characteristic of ferroptosis is that it is induced by abnormal oxidation in the intracellular microenvironment, primarily under the influence of glutathione peroxidase 4 (GPX4) activity (18). Decreased activity of GPX4 prevents the metabolism of lipid peroxides via GPX4-catalyzed glutathione (GSH) reduction reactions, resulting in the oxidation of divalent iron ions and the generation of reactive oxygen species (ROS) in lipids (19). As the cellular antioxidant capacity weakens and lipid ROS accumulate, the redox balance within cells is thereby disrupted, which induces cell death (20). Moreover, this process has also been shown to affect both upstream- and downstream-related proteins (or genes), thereby exerting different effects on the intracellular microenvironment, which ultimately influences the outcome of ferroptosis (21). The accumulation of iron ions is also one of the hallmark features of ferroptosis, accompanied by an accumulation of lethal levels of lipid peroxidation, which occurs in response to the Fenton reaction (22). The untimely increase or decrease in the intraorganismal level of iron, as the expression of iron in ferroptosis is a crucial process, will have a marked impact on the organism in question, eventually leading to the development of various diseases such as hemochromatosis or Parkinson's disease (15). In other words, the majority of the changes that occur with respect to the level of iron within organisms are primarily associated with iron metabolism (23). The interconversion between  $\text{Fe}^{3+}$  and  $\text{Fe}^{2+}$  generates toxic ROS that are often detrimental to cells, and hence iron metabolism is strictly regulated within the body (24). When the expression of proteins associated with iron metabolism is affected, this can influence either the intake or loss of iron, thereby impacting ferroptosis (25). Although the presence of ferroptosis was first demonstrated in cancer, given the increasing number of associated studies, ferroptosis has been shown to fulfill an important role within the nervous system (11,26-30), and common neurological disorders, including ischemic stroke (31), Alzheimer's disease (32) and Parkinson's disease (33), have been found to be closely associated with ferroptosis, the latter two being common neurodegenerative disorders wherein the molecular mechanism is mainly concerned with an aggregation of iron in the hippocampal region of the brain or in dense areas of the substantia nigra, and these responses have been shown to be inhibited by the ferroptosis inhibitor, ferrostatin-1 (Fer-1) (34-36).

In conclusion, a growing number of studies confirm the link between ferroptosis and stroke. The inherent pathological changes of stroke have been shown to be closely related to

the characteristics of ferroptosis, including iron metabolism disorders, lipid peroxidation, and elevated ROS levels. Ferroptosis may provide a promising therapeutic approach for treating stroke patients. Therefore, the present review provides a comprehensive overview of potential therapeutic targets provided by ferroptosis-related pathways in stroke, providing new insights into how ferroptosis can be exploited to treat stroke.

## 2. Ferroptosis-associated pathways in stroke

Over previous years, ferroptosis has become an area of interest for researchers (12). Ferroptosis is a relatively recently discovered form of regulated cell death that is characterized by the accumulation of iron-dependent lipid peroxides (37). It has been implicated in various pathological conditions, including stroke (30). When the concept of ferroptosis was initially proposed, researchers identified key features of ferroptosis in HT-1080 cells using  $\text{H}_2\text{DCFDA}$  and C11-BODIPY fluorescent probes (38). These features included abnormal accumulation of lipid peroxides and ROS (38). Subsequently, molecular experimental techniques such as western blotting and polymerase chain reaction were used to investigate the changes in ferroptosis-related proteins and genes in stroke. The results revealed the involvement of various pathways, including iron metabolism, lipid peroxidation and oxidative stress in ferroptosis (39). Understanding the ferroptosis-associated pathways in stroke can guide the development of novel therapeutic strategies for stroke treatment (40). Targeting these pathways may help to mitigate oxidative stress (41), lipid peroxidation (30) and subsequent neuronal damage (42), ultimately improving stroke outcomes. However, further research is needed to fully elucidate the intricate molecular mechanisms involved in ferroptosis and their potential as therapeutic targets in stroke.

*Iron metabolism.* Iron metabolism is a crucial system in organisms, and it has been shown to be closely associated with ferroptosis (15). Ferroptosis not only influences the organism, but also has an impact on various other physiological processes. The overload of iron ions exacerbates the occurrence of cerebral hemorrhage, inducing the onset of ferroptosis (11). In the event of cerebral hemorrhage, blood vessels rupture, leading to the release of a substantial amount of blood and hemoglobin (43). Subsequently, microglia rapidly engulf the released hemoglobin and metabolize  $\text{Fe}^{2+}/\text{Fe}^{3+}$  (30). The accumulation of  $\text{Fe}^{2+}$  and  $\text{Fe}^{3+}$  signifies an iron overload due to excessive iron build-up, and this is a key factor in ferroptosis (15). Released  $\text{Fe}^{3+}$  ions enter cells by binding with transferrin receptors on the cell membrane (44). Once inside the cell,  $\text{Fe}^{3+}$  can be reduced to  $\text{Fe}^{2+}$  by ferric reductase, a process that is facilitated by hydroxyl radicals. Accumulated ROS resulting from this process lead to the peroxidization of membrane lipids, subsequently leading to a loss of cellular function and cell death. This phenomenon represents one of the characteristic features of ferroptosis (44). Alternatively, excess  $\text{Fe}^{3+}$  can enter the unstable iron pool through solute carrier family 39 member 14 (45), further promoting ferroptosis. Excess  $\text{Fe}^{2+}$  can be re-oxidized to  $\text{Fe}^{3+}$ , which is subsequently moved to the extracellular compartment, contributing to a series of iron metabolism processes associated with

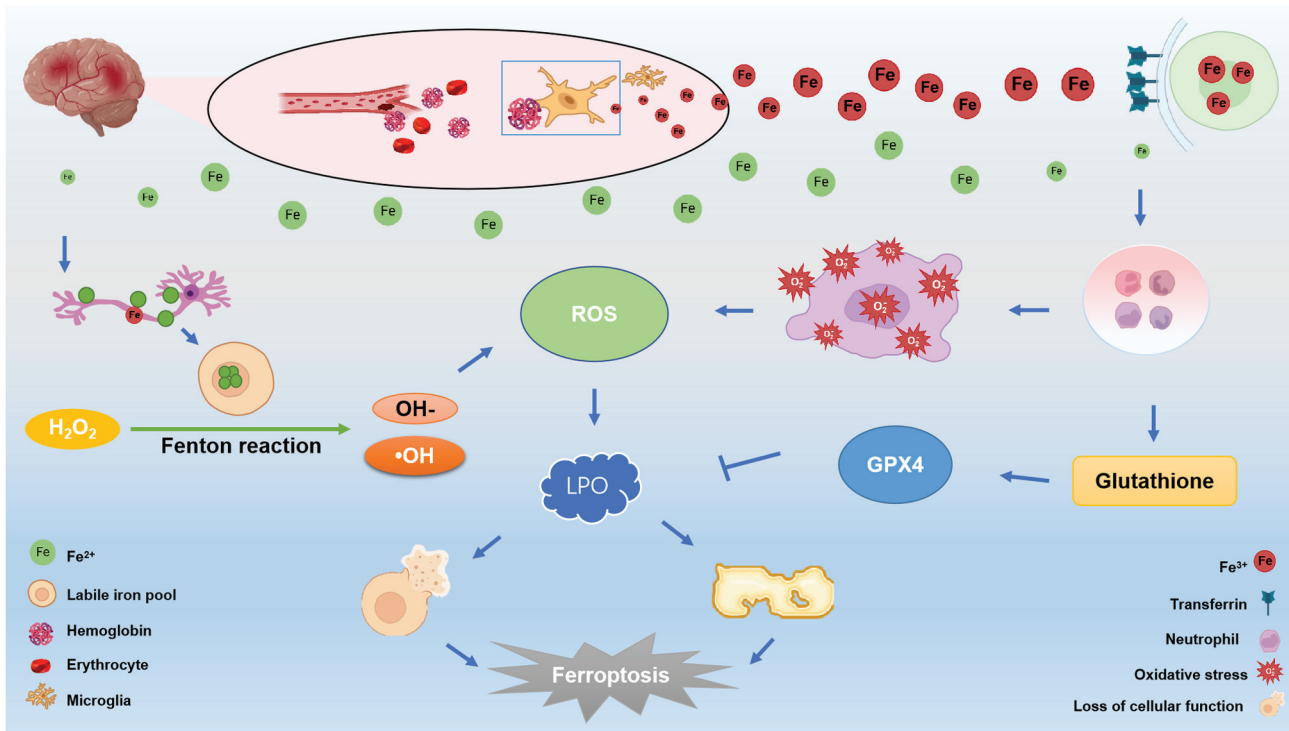


Figure 1. Mechanism of ferroptosis-related pathways during cerebral hemorrhage. When cerebral hemorrhage occurs, hemoglobin from red blood cells is released, which can trigger multiple pathways related to ferroptosis. These pathways include the activation of inflammation, where signals act on GPX4 and subsequently affect LPO, leading to ferroptosis. When oxidative stress occurs, changes in ROS within the body ultimately impact LPO and promote ferroptosis. The presence of unstable iron pools induces ferroptosis by affecting ROS levels. LPO, lipid peroxidation; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4.

ferroptosis. Moreover, the presence of this free iron stimulates the production of lipid ROS via participating in the inflammatory response (46), inducing oxidative stress (47), and the Fenton reaction (22). Consequently, there is an accumulation of lipid ROS *in vivo*, which leads to DNA (48), protein (49) and lipid damage (50), ultimately resulting in cell death. Studies have also demonstrated that neurons require both the ferroptosis inhibitory factor, GPX4, and genes involved in the GPX4-synthesis pathway to survive under conditions of oxidative stress (21,51,52). GPX4 utilizes GSH to reduce peroxidized lipids, thereby preventing lipoatrophy (53). This suggests that neurons are prone to undergoing ferroptosis when exposed to oxidative stress (54). Additionally, the excess iron ions metabolized by microglia are expelled through the transferrin receptor system, leading to a significant accumulation of iron in neurons (55). Subsequently, the neurons undergo the classical reaction of ferroptosis (the Fenton reaction) (56). This reaction catalyzes the generation of ROS, further promoting lipid peroxidation and leading to lipid peroxide accumulation, ultimately inducing ferroptosis (57) (Fig. 1).

**Lipid peroxidation.** Lipid peroxidation is a process in which lipids lose hydrogen atoms due to the activity of free radicals or lipid peroxidases (58). This leads to oxidation, fragmentation and the shortening of lipid carbon chains, resulting in the generation of lipid free radicals, lipid hydroperoxides and reactive aldehydes (such as malondialdehyde and 4-hydroxynonenal) (59). Ultimately, this process causes the oxidative degradation of lipids, thereby damaging the cells. The end product of the Fenton reaction,  $\cdot\text{OH}$ , fulfills a crucial

role in ferroptosis (60). The increase in  $\cdot\text{OH}$  radicals induces oxidative damage, leading to ferroptosis, and an exacerbation of the edema response at the site of cerebral hemorrhage (61,62). Building upon this, in the event of a cerebral hemorrhage, ferroptosis occurring in the affected region triggers the release of iron ions from blood cells (63). These iron ions instigate oxidative stress reactions, leading to the production of  $\cdot\text{OH}$  radicals that subsequently target DNA, proteins, and lipid membranes. The resulting damage to these components often aligns with the manifestation of ferroptosis in the brain. Furthermore, the regions affected by ferroptosis are subjected to significant iron accumulation. This accumulation of iron has two subsequent effects. First, it stimulates microglia to continue engulfing the hemoglobin that is released from blood cells, leading to the secretion of yet more iron ions, creating a positive feedback loop (64). Secondly, the accumulating iron participates in various redox reactions in the brain, resulting in an increase in the production of  $\cdot\text{OH}$  radicals (65) (Fig. 2). In other words, when cerebral hemorrhage occurs, there can be a positive feedback system loop promoting ferroptosis through  $\text{Fe}^{\cdot\text{OH}}/\text{DNA damage}/\text{Fe}$  and  $\text{Fe}/\text{microglia}/\text{Fe}$  interactions. Consequently, the brain is subjected to further oxidative damage. This oxidative damage, in the presence of interleukin and nitric oxide, further compromises the integrity of the blood-brain barrier, ultimately leading to the development of cerebral edema at the site of hemorrhage (66).

Lipoxygenases (LOXs), a key component in the process of ferroptosis, have gained significant attention in recent years (67). One study demonstrated that conducting diphenyl-1-pyrenylphosphine experiments using HEK-293

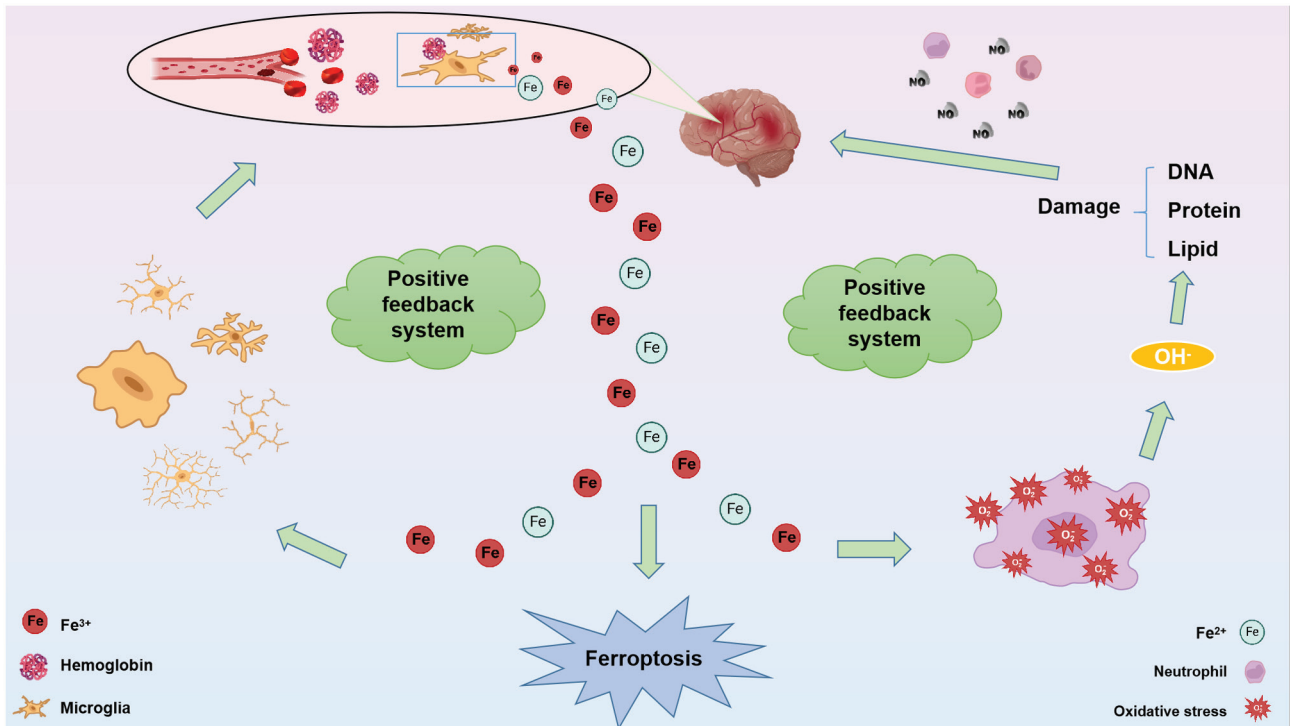


Figure 2. Positive feedback effect of microglia on ferroptosis during cerebral hemorrhage. When cerebral hemorrhage occurs, the injured area undergoes ferroptosis. The occurrence of ferroptosis prompts blood cells to release iron ions. The presence of iron ions leads to the generation of  $\cdot\text{OH}$  through oxidative stress reactions, further inducing ferroptosis. On the other hand, iron ions also stimulate microglia cells, causing blood cells to secrete more iron ions, forming a positive feedback loop.  $\cdot\text{OH}$ , hydroxyl radical.

cells revealed the formation of lipid hydroperoxides catalyzed by LOX (68). Based on the findings of this study, it is hypothesized that LOX activity may enhance the accumulation of lipid hydroperoxides within cells, thereby promoting ferroptosis. This may be associated with a specific ferroptotic pathway, such as the hypoxia-inducible factor-prolyl hydroxylase domain pathway (69). Therefore, measuring LOX activity and the levels of lipid hydroperoxides may serve as valuable assays for assessing the occurrence of ferroptosis (70), given that LOX activation may drive this process (71).

**System Xc<sup>-</sup>.** It is widely recognized that elevated levels of glutamate can exert neurotoxic effects on the brain during disease conditions (72). In response to this neurotoxic effect, system Xc<sup>-</sup> fulfills a crucial function. System Xc<sup>-</sup> is a heterodimeric cystine/glutamate antiporter protein that consists of two core components: Solute carrier family 7 member 11 (SLC7A11), serving as the catalytic subunit, and solute carrier family 3 member 2, which acts as an anchoring protein (73). In the context of stroke and its relevance to ferroptosis, particular attention has been focused on the SLC7A11 gene, which encodes a sodium-independent member of the anionic amino acid transport system (51). Its highly specific role in transporting cysteine (74) and glutamate (75) has been shown to be of great importance. In general, system Xc<sup>-</sup> facilitates the extracellular transport of high intracellular concentrations of glutamate, whereas the anionic form of cysteine is transported in exchange for glutamate (76). The intracellularly transported cysteine is subsequently utilized for the synthesis of cysteine and GSH (77). GSH, a tripeptide composed of glutamate,

cysteine and glycine, fulfills critical roles in various physiological functions, including the scavenging of free radicals, acting as an antioxidant (78) and maintaining cellular redox balance (79). GSH also activates various enzymes that influence cellular metabolic processes, and serves as an essential intracellular antioxidant in brain diseases (such as Parkinson's disease), contributing to the scavenging of free radicals and preserving redox balance both inside and outside of cells (80).

System Xc<sup>-</sup> functions within the central nervous system, where microglia, the representative immune cells, are activated from a resting state and migrate to the injured brain (81). Activated microglia can exert anti-neuroinflammatory effects (82). However, it will inhibit the release of glutamate (83), which has the consequence of inhibiting the protective effects mediated by GSH in stroke. Following a stroke, two main areas are primarily affected: i) The infarct zone (where cell death occurs due to ischemia) (84); and ii) the surrounding ischemic penumbra (85). Alterations in glutamate are known to induce the occurrence of ferroptosis during a stroke, with a significant increase in extracellular glutamate levels released by neurons in these areas (86). Consequently, the balance between system Xc<sup>-</sup> and glutamate transport is disrupted, leading to both a reduced intracellular uptake of glutamate and an inhibition of GSH synthesis due to the lack of necessary raw materials (87). Ultimately, this impairment in the cellular antioxidant defense results in an accumulation of lipid ROS, with the subsequent induction of ferroptosis.

GPX4, a downstream target of GSH action, functions as a unique intracellular antioxidant enzyme acting on membrane lipid repair, which is able to directly reduce peroxidized

phospholipids produced in cell membranes (88,89), and it converts toxic lipid ROS into non-toxic lipid alcohols with the aid of GSH, which thereby reduces the level of oxidative damage to cells (90). However, the generation of large amounts of lipid ROS during stroke disrupts this oxidative balance, resulting in both a large accumulation of lipid ROS and the development of peroxidation, which is the main feature of ferroptosis (42). In addition, lipid ROS have also been shown to directly react with polyunsaturated fatty acids (PUFAs) on lipid membranes via oxidation, which directly leads to the occurrence of ferroptosis in cells (91).

*AMP-activated protein kinase (AMPK) signaling pathway.* AMPK has a critical role in ferroptosis following cerebral hemorrhage. AMPK is an energy sensor widely present in various tissues and cells. For instance, when it is present in brain tissue and microglial cells, it can alleviate secondary damage from cerebral haemorrhage (92). It regulates cellular energy metabolism balance (93), and participates in the regulation of multiple biological processes, including glycogen synthesis (94), fatty acid synthesis (95) and mitochondrial biogenesis (96). Studies have found that *Spatholobi Caulis* (SC) has the ability to activate AMPK (97). Subsequent 2,7-dichlorodihydrofluorescein diacetate experiments using HepG2 cells revealed that the combined effect of arachidonic acid (AA) and iron led to increased intracellular ROS production (97). However, pretreatment with SC suppressed the production of ROS when combined with AA and iron. This suggests that AMPK may possess antioxidant capacity (97). In *in vivo* experiments, using a mouse liver injury model, it was shown that oral administration of SC (which activates AMPK) could alleviate liver damage mediated by acute acetaminophen (by enhancing oxidative stress and increasing cell injury), exerting antioxidant effects (97). Therefore, both *in vivo* and *in vitro* experiments indicate that AMPK can play a role in protecting against oxidative damage, possibly by inhibiting ferroptosis to provide neuroprotection (97). Furthermore, *in vitro* and *in vivo* models of intracerebral hemorrhage were created by treating BV2 cells with hemoglobin and intraventricular injection of type IV collagenase into Sprague-Dawley rats, respectively. *In vitro* experiments showed a phosphorylation reaction of AMPK after initial intervention with AMPK inhibitors in BV2 cells. Subsequently, pharmacological intervention led to upregulation of ROS and lipid peroxidation levels (positive regulators of ferroptosis) in BV2 cells, and silenced GPX4 (a key negative regulator of ferroptosis) levels through the AMPK signaling pathway (92). In *in vivo* experiments, iron deposition at the site of brain injury was observed through Perl's staining (92). So, both *in vitro* and *in vivo* experiments have demonstrated the occurrence of ferroptosis during cerebral hemorrhage. Additionally, the AMPK signaling pathway, targeting GPX4 (a negative regulator of ferroptosis), was found to be involved in neuroprotection (92). Moreover, in the field of tumor research, it has been shown that AMPK can reduce the occurrence of ferroptosis by regulating intracellular lipid synthesis metabolism (98). When ferroptosis occurs, the AMPK-mediated phosphorylation of acetyl-coenzyme A carboxylase is considered to inhibit ferroptosis by limiting the production of PUFAs (99). However, the specific role and mechanism of AMPK in the field of cerebral hemorrhage

and ferroptosis have yet to be fully elucidated. When AMPK activation protects neurons from damage caused by cerebral hemorrhage through a series of antioxidant, anti-inflammatory and anti-apoptotic pathways, this may result in a reduction in the occurrence of ferroptosis (98). However, following cerebral hemorrhage, AMPK activation may increase the levels of intracellular free iron ions, which, in turn, may exacerbate oxidative stress and cell damage, potentially contributing to ferroptosis (92). Therefore, the mechanism of action of AMPK in cerebral hemorrhage may potentially exert an impact on ferroptosis. However, the current research findings are both inconsistent and limited. Further research is needed to address this issue.

*Sirtuin 2 (SIRT2)-P53 signaling pathway.* The SIRT2-p53 pathway exerts neuroprotective effects by modulating GPX4 and SCL7A11, inhibiting the occurrence of ferroptosis (100). SIRT2 is a NAD<sup>+</sup>-dependent deacetylase predominantly localized in the cytoplasm and has been demonstrated to be involved in the mechanisms of neuroinflammation- and neuroimmunology-related diseases (101). Additionally, P53, a tumor suppressor protein, has also been implicated in ferroptosis. In the context of ferroptosis, P53 has been shown to regulate the expression of key genes involved in iron metabolism, lipid peroxidation and antioxidant defense. P53 inhibits cystine uptake and sensitizes cells to ferroptosis by inhibiting the expression of SLC7A11, a key component of cystine/glutamate retrotransporters. Previously, the traumatic brain injury model using the controlled cortical impact (CCI) injury method found that knockdown of P53 could significantly block ferroptosis after CCI. In addition, inhibition of SIRT2 led to upregulation of acetylation and expression of P53, exacerbating ferroptosis after CCI. In other words, P53-mediated ferroptosis is involved in the pathogenesis of TBI, and SIRT2 exerts a neuroprotective effect on TBI by inhibiting P53-mediated ferroptosis (100).

*Nuclear receptor coactivator 4 (NCOA4) signaling pathway.* The overall role of NCOA4 in cerebral stroke has been controversial, and its specific effects on ferroptosis, contributing to this process, have yet to be fully elucidated. Currently, studies on NCOA4 have revealed its potential dual role in either promoting (102) or inhibiting ferroptosis (103). Moreover, investigations on ovarian cancer cell models with manipulated NCOA4 expression have implicated NCOA4 in the processes of both formation and degradation of intracellular iron storage autophagosomes (104). Furthermore, in ovarian cancer cells, it has been observed that up-regulation of C-MYC (a gene regulating tumor proliferation) leads to a significant reduction in ROS content (104). On the other hand, overexpression of NCOA4 reverses these changes. These findings suggest that C-MYC may exert an inhibitory effect on ferroptosis in ovarian cancer cells through NCOA4-mediated ferritin autophagy (104). The process of NCOA4-mediated ferritin autophagy appears to play a role in suppressing ferroptosis in ovarian cancer cells (104). Autophagy-associated pathways induce an excessive degradation of ferritin, leading to an increase in the amount of free iron in neurons. Therefore, when cerebral ischemia occurs, NCOA4 may promote the release of iron ions and trigger ferroptosis in cells (105). Due to the large impact of NCOA4 in cerebral ischemia-reperfusion

Table I. Common ferroptosis inducers and their potential targets and mechanisms of action.

Ferroptosis inducers	Potential targets	Mechanisms of action	(Refs.)
Erastin	Inhibit system Xc <sup>-</sup>	Inhibit the uptake of system Xc <sup>-</sup> cystine	(113)
Sulfasalazine		Inhibit system Xc <sup>-</sup>	(114)
Glutamate		Reduce the activity of system Xc <sup>-</sup>	(115)
RSL3	Inhibit GPX4 pathway	Combined with GPX4 to reduce GPX4	(116)
ML162		Combined with GPX4 to reduce GPX4	(117)
iFSP1	Others <sup>a</sup>	Inhibit FSP1 activity and inactivate GPX4	(118)
Hemin		Increase unstable iron in cells	(119)
Lapatinib		Increase the expression of transferrin	(120)

<sup>a</sup>Used to display categories other than those already listed. RSL3, RAS-selective lethal 3; ML162, 2-chloro-N-(3-chloro-4-methoxyphenyl)-N-(2-oxo-2-(phenethylamino)-1-(thiophen-2-yl)ethyl)acetamide; iFSP1, FSP1 inhibitor; Xc<sup>-</sup>, cystine/glutamate antiporter; GPX4, glutathione peroxidase 4.

injury, it has been shown that the autophagy-related 5 (ATG5)-ATG7-NCOA4 pathway also has an important role in ferroptosis (106). Notably, NCOA4 is a selective autophagy receptor that is essential for mediating ferritin phagocytosis in certain tissues (for example, brain tissue) and cells (for example, red blood cells) (107,108). However, other studies have found that, under conditions such as hypoxic-ischemic brain injury, NCOA4 may protect cells from excessive damage caused by free iron ions via regulating intracellular iron metabolism. In this case, NCOA4 is considered as a factor that inhibits ferroptosis (109,110).

### 3. Ferroptosis inducers and stroke

In animal models of ischemic stroke and associated clinical specimens, it was found that, when cerebral ischemia-reperfusion occurs, an increase in the level of iron ions exacerbates neuronal damage (111). However, subsequent research has indicated that there may be a close link between the increase in the level of iron ions and ferroptosis. The increase in iron undoubtedly exacerbates the occurrence of ferroptosis, and so, iron may act as a catalyst for the occurrence of ferroptosis, or serve a role as an inducer (112). Therefore, when a stroke occurs, is it possible that some of the inducers associated with ferroptosis may accelerate progression of the stroke, thereby leading to more serious consequences (Table I) (113-120).

Inducers of ferroptosis may generally be grouped into categories, based on the effects of targeted interventions at different sites. In general, class I ferroptosis inducers that are typically used are erastin (113) (which inhibits Xc<sup>-</sup> cystine uptake), glutamate (121) (which inhibits glutamate transfer to reduce Xc<sup>-</sup> activity) and sulfasalazine (122) (which inhibits Xc<sup>-</sup> in the cell membrane). However, the most common class I ferroptosis inducer is erastin and was first discovered before the concept of ferroptosis came into existence (38). It was then shown that the newly discovered compound erastin had no effect on either the apoptosis or necrosis of cells, but it was found that lipophilic ROS were involved in the process of ferroptosis of cells (113). After the concept of ferroptosis had been confirmed, further studies identified that erastin inhibited Xc<sup>-</sup> cystine uptake, and therefore it was categorized as a class I

inducer of ferroptosis for medical research (123,124). Previous studies have revealed that erastin-induced ferroptosis is a significant feature of intracerebral hemorrhage. In a mouse model of intracerebral hemorrhage (collagenase model), it was observed that the mRNA expression of GPX4, a crucial regulator of ferroptosis, was increased. This finding suggests that ferroptosis is regulated in the context of intracerebral hemorrhage (125). Moreover, cell experiments were conducted using rat PC12 cells, and the results indicated a distinct decrease in the survival rate of these cells when treated with erastin. This decrease in cell survival strongly suggests the occurrence of ferroptosis in response to erastin treatment (125). In various investigations examining the link between stroke and ferroptosis, erastin has been utilized to trigger ferroptosis, revealing its potential neuroprotective effect in alleviating stroke symptoms (126). However, further experimental investigations are needed to fully understand the precise mechanism by which erastin induces ferroptosis during stroke. It is hypothesized that erastin may play a valuable role in providing neuroprotection during strokes in the future.

The commonly used class II ferroptosis inducers are RAS-selective lethal 3 (RSL3) (127), 2-chloro-N-(3-chloro-4-methoxyphenyl)-N-(2-oxo-2-(phenethylamino)-1-(thiophen-2-yl)ethyl)acetamide (128) and cisplatin (which binds to GSH and inactivates GPX4) (129). However, the most commonly used class II ferroptosis inducer is RSL3, predominantly since RSL3 is an inducer that can either indirectly or directly induce the occurrence of ferroptosis (130). The main effect of RSL3 is that it can directly bind to GPX4 protein, thereby inactivating GPX4, at which point the production of lipid ROS is increased, leading to the occurrence of ferroptosis (131). Furthermore, it has been shown in other studies that the protective effects against cerebral ischemia-reperfusion injury, achieved by inhibiting ferroptosis, are partially diminished upon induction by RSL3 (125,132). In the context of cerebral hemorrhage ischemia-reperfusion injury, the action of RSL3 has been found to worsen the incidence of ferroptosis (133). However, the precise underlying mechanisms of this action have not yet been fully elucidated, necessitating further experimental and theoretical investigations.

There are also class III and class IV ferroptosis inducers, which similarly intervene in the process of ferroptosis through a

Table II. Common ferroptosis inhibitors including their potential targets and mechanisms of action.

Ferroptosis inhibitors	Potential targets	Mechanisms of action	(Refs.)
Deferoxamine mesylate	Inhibition of Fenton reaction	Iron chelating agents	(144)
Deferiprone		Reduce unstable iron in cells	(145)
Ferrostain-1	Antioxidant	Inhibition of lipid peroxidation	(146)
Liproxstain-1		Impact Nrf2/GPX4 pathway	(147)
VKH2		Inhibition of lipid oxidation	(148)
XJB-5-131		Clear ROS	(149)
Inhibition GPX4	Inhibit classical ferroptosis pathway protein	Key proteins of the ferroptosis pathway	(150)
Troglitazone		Inhibiting ACSL4 function and reducing the production of lipid peroxidation raw materials	(151)
Zileuton		Inhibiting 5-LOX	(152)

VKH2, vitamin K hydroquinone; ACSL4, acyl-CoA synthetase long-chain family member 4; 5-LOX, 5-lipoxygenase; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4.

Table III. Summary of the target sites of some ferroptosis inhibitors, including their specific target sites and specific targeting properties.

Ferroptosis inhibitors	Targets	(Refs.)
DFO	Fe <sup>2+</sup>	(153)
CPX		(154)
Ferrostain-1	Iron and trace lipid	(146)
Liproxstain-1	hydroperoxides in liposomes	(147)
GPX4	GSH to GSSG L-OOH to L-OH	(155)

DFO, deferoxamine; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, oxidized glutathione; L-OOH, lipid hydroperoxide; L-OH, lipid hydroxide; CPX, ciclopirox.

number of different pathways. The more commonly used class III ferroptosis inducers are FSP1 inhibitor (which inhibits FSP1 activity and reduces coenzyme Q10 production) (134), statins (which inhibit the mevalonate pathway) (135,136), and class IV ferroptosis inducers, such as heme (which increases the amount of intracellular iron in the unstable state) (137) and artemisinin (which induces ferritin autophagy, causing the release of iron in the unstable state) (138). These ferroptosis inducers are representative in research related to cerebral stroke and can mitigate the occurrence of cerebral stroke by inducing ferroptosis (125,126).

#### 4. Ferroptosis inhibitors and stroke

Following a stroke, various forms of cell death occur in the body, the main ones of which are apoptosis (139), necrosis (140)

and autophagy (141). It has been shown that the use of different inhibitors to inhibit apoptosis, necrosis and autophagy is more effective than the use of any of these inhibitors in isolation, as in the case of cerebral hemorrhage, where caspase inhibitors have been shown to be unsuccessful in terms of inhibiting hemoglobin-induced neuronal death (142). Therefore, when ferroptosis was initially discovered, its inhibitors were also investigated within the field of stroke research (143). Currently in the medical field, a number of ferroptosis inhibitors have been identified, for which specific information for commonly used inhibitors such as Fer-1 is shown in Table II (144-152). In addition, with respect to the ferroptosis inhibitors summarized in the present review and those that are similar to them in terms of their function, their specific target sites have been identified, as shown in Table III (146,147,153-155). Both *in vitro* and *in vivo* experiments have shown that the levels of molecular markers of ferroptosis are increased when cerebral hemorrhage occurs. Experiments performed *in vivo* have shown that the mortality rate may be reduced by ~80% with the use of ferroptosis inhibitors (156,157). *In vitro* experiments performed in a previously published study (140) have confirmed the occurrence of ferroptosis without autophagy or apoptosis. Therefore, as a novel form of cell death that is distinct from apoptosis, necrosis, autophagy and other types of cell death, the use of certain inhibitors targeting ferroptosis may have more pronounced therapeutic effects with regard to the treatment of stroke (40). The present review provided detailed information on several different inhibitors of ferroptosis. Deferoxamine (DFO) is an iron chelator that can act on iron ions to inhibit the occurrence of ferroptosis (158). GPX4, as an important negative regulator of ferroptosis (159), may also effectively suppress the occurrence of ferroptosis (150). Fer-1, a commonly used inhibitor of ferroptosis, has been shown to have a significant role in terms of inhibiting ferroptosis (146). Additionally, when combined with inhibitors of other types of programmed cell death, Fer-1 has also been shown to exert inhibitory effects on ferroptosis (160). These

effects can alleviate adverse reactions caused by stroke, thereby demonstrating that it has some therapeutic potential in terms of the treatment of stroke (161).

*DFO can relieve stroke.* DFO induces ferroptosis during a stroke; DFO is an iron chelator that is able to reduce the accumulation and precipitation of iron in cells or tissues by binding to ferric ( $\text{Fe}^{3+}$ ) ions to form a stable complex, thereby allowing the removal of excess iron from cells (158). In the general field of cancer research, DFO has been shown to have good antioxidant activity (162); it acts as an anti-proliferative agent, and can induce apoptosis in cancer cells (163). At present, extensive research is being performed on the use of DFO in various iron overload-associated brain diseases (representing a class of neurological disorders caused by excessive accumulation of iron ions in the body, such as thalassemia). DFO has been shown to help regulate iron balance in the body, and to reduce neurological damage and functional impairments associated with iron overload (164). Similarly, significant research has also been performed on the role of DFO in neurodegenerative diseases (such as diseases that are characterized by neuronal cell death and functional impairments, including Alzheimer's disease, Parkinson's disease and Huntington's disease, which are associated with oxidative stress, abnormal neurodevelopment and protein aggregation) (153). Upon reviewing the literature, DFO has been shown to reduce the level of cell death through reducing free radicals (165), and to promote wound healing and healing in diabetic patients (166), although due to the potential toxicity of DFO itself (167), the research remains only at an early stage (160). In addition, animal experiments were used to demonstrate that the treatment of mice with DFO, wherein the aging process was simulated, led to a marked alleviation of the occurrence of ferroptosis, with the consequent inhibition of the increase of age spots in mice due to iron overload, thereby achieving the desired protective effect of delaying aging (168). In investigating the neurological and cognitive functions of aged mice in a study focused on the auditory cortex, the effect of alleviating ferroptosis in the brain was achieved by treatment with DFO, suggesting that DFO may be used to treat auditory and cognitive impairment resulting from age-associated problems (169). It is noteworthy that, although DFO primarily functions as an iron chelator in ferroptosis (158), investigations utilizing rodent models propose that DFO could impact stroke through gene-mediated mechanisms (69,170). Therefore, the role of DFO in ferroptosis warrants further investigation.

*Fer-1 alleviates stroke.* Fer-1 has been shown to inhibit ferroptosis during stroke (161). Traditionally, the most direct way to inhibit ferroptosis has been to utilize appropriate ferroptosis inhibitors. In the field of stroke-related research, the most commonly used ferroptosis inhibitor is Fer-1, whose main effects are to scavenge ROS and to inhibit erastin, the aforementioned class I inducer of ferroptosis (113,171). The effect of Fer-1 was verified with experimentally administered ventricular Fer-1 in experiments with rats, where it was found to inhibit erastin-induced accumulation of ROS in the cytoplasm and lipids, resulting in a decrease in ROS and lower levels of ferroptosis, demonstrating that Fer-1 could appreciably slow down the onset of ferroptosis in the brain (171). Notably, when

Fer-1 intervention was present in the ventricles, the levels of iron deposition and neuronal degeneration were both significantly reduced, reducing the level of cellular damage, while also improving long-term motor and cognitive function (172). After a stroke, iron tends to accumulate in the damaged area, where it participates in oxidative stress reactions, leading to more cell damage and inflammatory responses (173). In addition, free iron is able to promote abnormal protein aggregation and neurodevelopmental abnormalities (174). The inhibitor Fer-1 may reduce oxidative stress reactions by reducing levels of free iron ions, thereby reducing cell damage and inflammatory responses following a stroke (166). Furthermore, inhibiting ferroptosis may also lead to the aggregation of abnormal proteins and abnormalities in neurodevelopment (175). Fer-1 exerts protective effects on cerebral ischemia-reperfusion injury by activating the Akt/GSK-3 $\beta$  pathway, indicating that ferroptosis may become a novel target in the treatment of ischemic stroke in the future (176). However, at present, few studies have reported on the specific effects and associated pathways of Fer-1 following a stroke, and therefore our knowledge is currently relatively limited; further experimental and clinical studies are required to explore its underlying mechanisms of action, and the potential therapeutic effects.

*Effects of Traditional Chinese Medicine (TCM) on ferroptosis.* Through clinical trial studies, TCM combined with the influencing factors associated with ferroptosis has been shown to be more effective than single-drug treatment for stroke (177,178). It is well established that TCM herbs have antioxidant, anti-inflammatory and blood-brain barrier-protective effects, and that they can prevent stroke in advance by various means (179-181). For example, Danhong injection, a standardized injection comprising danshen (*Salvia miltiorrhiza*) and saffron, has been shown in studies to improve ferroptosis in ischemic stroke (182,183). In addition, moxibustion (a form of therapy that entails the burning of mugwort leaves), as one of the more frequently used treatments, has an important role in the treatment of cerebral infarction. It has been found that moxibustion can reduce neurological damage and neuronal death, reduce the accumulation of ROS and inhibit ferroptosis (184). In conclusion, the effects of certain Chinese medicines and their active ingredients on stroke both involve multiple pathways and are multi-targeted. In addition, the intervention of Chinese medicines on ferroptosis has been shown to be more stable and safer to use compared with small-molecule inducers or inhibitors of ferroptosis (185). For example, astragaloside IV can alleviate brain injury by inhibiting the ferroptosis-associated sequestosome-1/kelch-like ECH associated protein 1/nuclear factor erythroid 2-related factor 2 pathway (177,186). In addition, there are studies reporting that TCM treatment can reduce the side effects of drug toxicity in patients via targeting ferroptosis, leading to significant improvements in patient safety and quality of life (187,188). The impact that specific Chinese medicines and their active constituents have on stroke involves multiple pathways and targets, and these are summarized in Table IV (125,182,189-191).

## 5. Discussion

The present review provides a comprehensive overview of the potential therapeutic targets of ferroptosis-associated

Table IV. Summary of how certain TCM utilize ferroptosis to treat stroke, including an overview of specific pathways and target points through which these Chinese medicines engage with ferroptosis to address stroke.

TCM	Ferroptosis pathway	Therapeutic target	Clinical trial stages	Regulatory bodies	(Refs.)
<i>Salvia miltiorrhiza</i>	Reduced expression of Lip ROS	NRF2	Pharmaceutical research stage	NO	(189)
Angong Niu Huang Wan	Activate PPAR $\gamma$ /AKT/GPX4 pathway	GPX4	Listed for use	National Medical Products Administration	(190)
<i>Scutellaria baicalensis</i>	Reduce iron deposition	Fe	Preclinical biological research stage	NO	(125)
Danhong	SATB1/SLC7A11/HO-1 axis	SLC7A11	Preclinical biological research stage	NO	(182)
Astragaloside IV	ACSL4-related pathways	ACSL4	Pharmaceutical research stage	NO	(191)

TCM, Traditional Chinese Medicine; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; Lip, lipid; NRF2, nuclear factor erythroid 2-related factor 2; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$ ; AKT, protein kinase B; SATB1, special AT-rich sequence-binding protein 1; HO-1, heme oxygenase-1; ACSL4, acyl-CoA synthetase long-chain family member 4; NO, records have not yet been approved.

pathways in stroke, providing novel insights into the application of ferroptosis in the treatment of stroke. Ferroptosis is a relatively recently discovered form of cell death that was first proposed by the laboratory of Brent R. Stockwell in 2012 (38). It is characterized by an excessive accumulation of lipid peroxides, and this accumulation is dependent on iron ions (192). Ferroptosis distinguishes itself from other forms of cell death, such as apoptosis, necrosis, autophagy (193,194) and pyroptosis, in terms of its morphological and biological features, and its underlying mechanistic regulation (44). It is also associated with inflammation and oxidative stress, along with other pathological processes (195). The characteristic morphological changes observed in ferroptosis primarily include mitochondrial atrophy, a ruptured outer membrane, reduced cristae, a compressed inner membrane and intact nuclei (196). By contrast, apoptosis and necrosis typically exhibit swollen mitochondria and fragmented nuclei (197). In recent years, the role of ferroptosis in various pathological processes has gained significant attention. Although ferroptosis was initially identified in studies that were associated with cancer, it has been demonstrated to fulfill a crucial role in the progression and toxicity of numerous neurological diseases, including stroke (198), Parkinson's disease (199) and Alzheimer's disease (32). Multiple reviews have highlighted ferroptosis as a promising target for various neurological disorders, and these reviews have also summarized the major regulators and associated studies in this field (178,200,201). The present review focused on summarizing the ferroptosis-associated pathways in stroke and discussed the potential therapeutic interventions using inhibitors and inducers of ferroptosis, with the ultimate goal of alleviating the impact of stroke.

The collection of studies published on ferroptosis in stroke to date have provided a comprehensive and informative overview of the field. By summarizing the findings from

these studies, specific research goals have been identified that should guide targeted and precise investigations in the area of ferroptosis in stroke. This approach allows results to be achieved faster and more efficiently, avoiding unnecessary detours. By summarizing this article, important signaling pathways of iron death in stroke, and inhibitors and inducers of iron death can be refined. Intervening in the signaling pathways of iron death and applying inducers can slow down the occurrence of stroke. This improved understanding will enable more accurate interventions for stroke management, specifically targeting ferroptosis. In conclusion, several preclinical studies (202,203) have confirmed the protective effect of ferroptosis inhibitors in stroke, and have highlighted the potential of these inhibitors as novel therapeutic drugs for stroke treatment.

Although ferroptosis-associated pathways are potential targets for the treatment of stroke, there remain certain limitations that need to be addressed. First, although iron overload is a key factor in ferroptosis, it remains unclear whether other metal ions also serve a role in this process, or whether alternative forms of cell death involving different metal ions also have a participatory role (204). Further investigations are needed to explore these possibilities. Additionally, despite the numerous studies that have been published on stroke and ferroptosis, very few of these have translated into clinical applications. Although it has been established that neuronal cells in the brain are particularly susceptible to ferroptosis, the effects of ferroptosis on other cell types in the brain have yet to be fully elucidated (51). Further studies exploring the effects of ferroptosis on various brain cell types are necessary to guide future research directions. In summary, targeting ferroptosis-associated pathways represents a promising approach for stroke treatment. However, there is a need for further research to improve understanding of the roles and potential targets of ferroptosis-associated pathways in stroke, which will provide valuable insights for the prevention and treatment of stroke.

The present review focused on the impact of ferroptosis on stroke and studied whether intervening in the ferroptosis pathway can prevent and treat stroke. Inhibiting ferroptosis pathways has shown promise in reducing neuronal cell death, protecting brain tissue, and improving functional outcomes in stroke models. This therapeutic approach not only provides new therapeutic avenues beyond traditional approaches, but also highlights the importance of understanding the mechanisms of ferroptosis in developing more effective stroke therapies. Therefore, the exploration of ferroptosis inhibitors or inducers represents a major advance in stroke treatment and provides new strategies for the prevention and treatment of cerebral stroke.

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### Availability of data and materials

Not applicable.

### Authors' contributions

BGZ and MTH conceptualized the study; HD was responsible for methodology and visualization; HD, YPM, MMC and ZHQ were responsible for the writing, reviewing and editing of the manuscript; and MTH and BGZ provided supervision and corrections. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare they have no competing interests.

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