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Review

Targeting the Nrf2-Keap1 Pathway to Suppress Ferroptosis in Ischemic Stroke: Repurposed Therapeutics and Translational Perspectives

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Abstract

Globally, ischemic stroke is the leading cause of mortality and long-term disability. Although reperfusion therapies have improved the patient outcomes, their benefits remain limited by narrow therapeutic windows and ischemia-reperfusion injury. Oxidative stress is the main contributor to the secondary neuronal damage, aggravating the lipid peroxidation, mitochondrial dysfunction, neuroinflammation, and ferroptosis. Therefore, targeting the Nrf2-Keap1 pathway has become a promising strategy for neuroprotection. The present review critically examines the molecular interaction between the oxidative stress, ferroptosis, and Nrf2 signaling, with particular emphasis on the translational potential of Nrf2-targeted pharmacotherapy. The repurposed and emerging Nrf2 modulators, including dimethyl fumarate, edaravone, N-acetylcysteine, and sulforaphane were evaluated for their mechanisms of action, preclinical and clinical evidence, and translational challenges. The review integrates mechanistic, preclinical, pharmacological, pharmacokinetic, safety, and available clinical evidence, with particular attention to therapeutic timing, Central Nervous System (CNS) exposure, combination strategies, biomarkers, and barriers to clinical translation. Overall, Nrf2-targeted modulation represents a promising mechanistic strategy for limiting ferroptosis and oxidative secondary injury after ischemic stroke, although its clinical therapeutic potential remains to be established.

Keywords

Ischemic stroke, Ferroptosis, Nrf2-Keap1 signaling, Drug repurposing, Pharmacological intervention, Neuroprotection

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1. Introduction

Ischemic stroke accounts for approximately 85-87% of all stroke cases and remains a major cause of mortality, long-term neurological disability, and healthcare burden worldwide [1,2]. Intravenous thrombolysis and mechanical thrombectomy have improved the treatment of acute ischemic stroke, but their benefits are limited by narrow therapeutic windows, delayed hospital presentation, strict eligibility criteria, and incomplete neurological recovery [3,4]. In addition, restoration of cerebral blood flow does not always prevent secondary brain injury. Ischemia and subsequent reperfusion trigger a series of interrelated processes, including excitotoxicity, mitochondrial dysfunction, oxidative stress, neuroinflammation, blood-brain barrier disruption, and regulated cell death [5]. Oxidative stress is particularly important because excessive reactive oxygen species (ROS) generation promotes lipid peroxidation, protein and DNA damage, and mitochondrial dysfunction. The limited clinical success of conventional antioxidant approaches has therefore increased interest in molecular pathways that regulate several components of ischemic brain injury rather than oxidative stress alone.

Ferroptosis has recently attracted considerable attention as a mechanism contributing to ischemic brain injury. It is an iron-dependent form of regulated cell death related to iron dysregulation, accumulation of lipid peroxides, and failure of cellular systems that normally remove the lipid peroxides [6,7]. Experimental studies have linked ischemic injury to increased iron availability, glutathione depletion, lipid peroxidation, and reduced glutathione peroxidase 4 (GPX4) activity, all of which may promote ferroptotic cell death [8]. Changes in ferroptosis-related biomarkers have also been reported in patients with ischemic stroke, providing early clinical evidence for the involvement of this pathway, although their clinical effectiveness has not yet been established [9,10].

The nuclear factor erythroid 2-related factor 2 (Nrf2)-Kelch-like ECH-associated protein 1 (Keap1) pathway is an important cellular defense system against oxidative stress [11]. Activation of Nrf2 increases the expression of genes involved in antioxidant defense, glutathione metabolism, iron regulation, and lipid peroxide detoxification [12,13]. Nrf2 therefore has a close relationship with ferroptosis, as its downstream targets influence several processes that determine the cellular susceptibility to ferroptotic injury. This relationship has led to growing interest in the Nrf2-ferroptosis axis as a potential target for neuroprotection after ischemic stroke. A previous review by Deng et al. [14] provided an important overview of the emerging relationship between Nrf2 signaling and ferroptosis in ischemic stroke and highlighted the potential of this pathway as a new therapeutic direction. The present review builds on this foundation by providing a more pharmacological and translational perspective on Nrf2-mediated ferroptosis regulation in ischemic stroke. In addition to recent mechanistic advances, it critically examines emerging therapeutic strategies and the key challenges that currently limit clinical translation.

2. Methodology

This review examined the role of Nrf2-Keap1 signaling in ferroptosis during ischemic stroke, focusing on pharmacological interventions, drug repurposing, pharmacokinetics, brain exposure, drug delivery, and barriers to clinical translation. Searches were conducted in PubMed/MEDLINE, Scopus, Web of Science Core Collection, ClinicalTrials.gov, and Google Scholar. The search terms covered ischemic stroke and ischemia-reperfusion injury, Nrf2-Keap1 signaling, oxidative stress, and ferroptosis. Search strategies were adapted to each database. Publications from 2023 to June 2026 received particular attention, although earlier studies were included when relevant. Additional searches covered individual drug candidates, pharmacokinetic properties, blood-brain barrier penetration, Central Nervous System (CNS) exposure, safety, and clinical evidence. Reference lists of relevant papers were also checked for further studies.

Studies were considered for inclusion if they examined Nrf2-Keap1 signaling, ferroptosis, or their interaction in ischemic stroke or cerebral ischemia-reperfusion injury, or provided relevant evidence on pharmacological interventions, drug repurposing, pharmacokinetics, CNS exposure, drug delivery, safety, or clinical translation. Experimental studies, clinical investigations, reviews, and meta-analyses were considered. Studies involving other diseases were included only when their findings informed mechanisms or pharmacological properties relevant to the review; such findings were treated as indirect evidence for ischemic stroke. Publications unrelated to these objectives, lacking sufficient information to support the relevant discussion, or addressing Nrf2-Keap1 signaling or ferroptosis without a clear connection to the review questions were excluded. Duplicate publications were removed where identified, and editorials without relevant supporting evidence were excluded. One reviewer assessed the literature for relevance to the review objectives. The evidence was appraised narratively, with findings from clinical studies distinguished from those obtained in animal models, cell-based experiments, and computational analyses. No quantitative synthesis or formal risk-of-bias assessment was performed. The database-specific search strategies and study-selection details are provided in Supplementary Material S1.

3. Redox-Mediated Mechanisms of Neuronal Injury in Ischemic Stroke

Oxidative stress is a key mediator of ischemic brain injury, arising from excessive reactive oxygen and nitrogen species generation during ischemia-reperfusion. The resulting lipid peroxidation, mitochondrial dysfunction, neuroinflammation, and blood-brain barrier disruption contributes to secondary neuronal injury and promote ferroptosis [5,15-17]. Ferroptosis is an iron-dependent form of regulated cell death characterized by increased lipid peroxidation and loss of membrane

integrity [6,7]. In ischemic stroke, disruption of iron homeostasis could increase the labile iron pool and promote ROS generation through iron-dependent reactions. Simultaneously, the depletion of glutathione, impaired cystine uptake through system Xc-(SLC7A11), and reduced GPX4 activity weaken the major cellular pathway responsible for detoxifying the phospholipid hydroperoxides [18,19]. These changes drive lipid peroxide accumulation and ferroptotic neuronal injury.

Ferroptosis is not regulated by GPX4 alone. Ferritinophagy could be mediated by nuclear receptor coactivator 4 (NCOA4), which could release the stored iron from ferritin and increase the ferroptotic susceptibility, while acyl-CoA synthetase long-chain family member 4 (ACSL4) promotes the incorporation of polyunsaturated fatty acids into membrane phospholipids that are susceptible to peroxidation [20,21]. On the other hand, the ferroptosis suppressor protein 1 (FSP1) limits the lipid peroxidation through regeneration of reduced coenzyme Q10 (CoQ10), and the GCH1-tetrahydrobiopterin (BH4) pathway providing an additional GPX4-independent antioxidant defense [20,22,23]. These pathways together suggest that ferroptotic injury results from the coordinated disruption of iron metabolism, lipid remodeling, glutathione-dependent defense, and alternative antioxidant systems. Evidence from patients with ischemic stroke also supports the clinical relevance of ferroptosis. Alterations in ferroptosis-related markers, including ACSL4, ferritin, heat shock protein 70 (HSP70), GPX4, and other redox-related molecules, have been reported in clinical studies and transcriptomic analyses [8-10,24]. However, these findings should be interpreted cautiously because most available evidence remains exploratory and the diagnostic or prognostic value of individual ferroptosis-related biomarkers has not yet been firmly established.

The Nrf2-Keap1 pathway is an important endogenous defense mechanism against oxidative stress and metabolic disturbances associated with cerebral ischemia. Stress-induced Nrf2 activation regulates the genes involved in antioxidant defense, glutathione metabolism, and iron homeostasis, thereby influencing the cellular susceptibility to ferroptosis [11,12]. Nrf2-dependent regulation of iron-handling proteins and the SLC7A11-GSH-GPX4 system could influence the intracellular iron availability and the detoxification of lipid peroxides. Nrf2 might also interact with complementary ferroptosis-regulatory systems, including FSP1 and GCH1-BH4, although the extent and context of these relationships in ischemic stroke remain to be fully established. The role of heme oxygenase-1 (HO-1), a prominent Nrf2 target, is particularly complex [25-28]. Transient HO-1 activation might be protective by facilitating the heme degradation, whereas continued activation might increase the labile iron pool and, when iron sequestration is insufficient, contribute to lipid peroxidation and ferroptotic injury [25,26]. Thus, the effects of Nrf2-HO-1 signaling might depend on the timing and extent of activation, cellular iron-handling capacity, and the stage of ischemic injury. Overall, the available evidence indicates that Nrf2 and ferroptosis are closely interconnected through pathways regulating redox balance, iron homeostasis, and lipid peroxidation. However, differences in experimental models, treatment timing, disease severity, and outcome measures limit direct comparison across studies. These factors suggest that therapeutic modulation of the Nrf2-ferroptosis axis might require coordinated regulation of multiple interacting pathways rather than sustained activation of a single downstream target. The major molecular interactions linking oxidative stress, Nrf2 signaling, and ferroptosis are summarized in Figure 1.

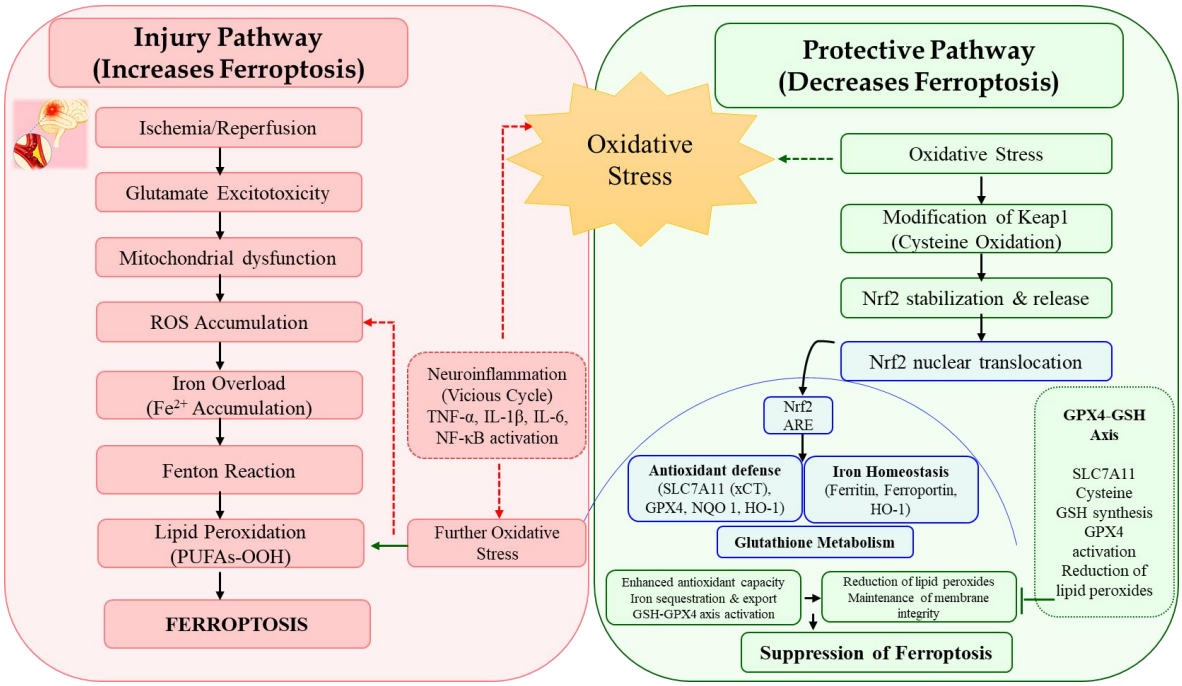


Figure 1. Molecular cross-talk between Nrf2 signaling and ferroptosis in ischemic stroke. Ischemia-reperfusion injury promotes ROS generation, mitochondrial dysfunction, iron accumulation, and lipid peroxidation, leading to ferroptotic neuronal death. Oxidative stress-induced activation of Nrf2 stimulates transcription of antioxidant and ferroptosis-regulatory genes, including SLC7A11, GPX4, FTH1, HO-1, and NQO1 [11,12]. These pathways enhance glutathione synthesis, maintain iron homeostasis, reduce lipid peroxidation, and suppress ferroptosis, thereby contributing to neuroprotection following cerebral ischemia [25-28].

4. Pharmacological Modulation of the Nrf2-Ferroptosis Axis in Ischemic Stroke

Evidence implicating the Nrf2-ferroptosis axis in ischemic brain injury has prompted investigation of pharmacological strategies targeting redox homeostasis, lipid peroxidation, and iron metabolism [10,12,27]. Several agents have shown neuroprotective effects in experimental stroke models through activation of Nrf2 or modulation of ferroptosis-related pathways, although the level and directness of evidence vary substantially among interventions. Among Nrf2-modulating agents, dimethyl fumarate (DMF), an established therapy for multiple sclerosis, has demonstrated neuroprotective effects in an experimental stroke model, accompanied by increased Nrf2 expression and reduced infarct burden [29]. Evidence from broader neuroinflammatory models further supports Nrf2-mediated cytoprotective effects of fumaric acid esters and their potential relevance to ischemic injury [30]. In ischemic stroke, Nrf2 activation has also been associated with modulation of ferroptosis and inflammatory responses related to blood-brain barrier injury [31]. Sulforaphane, a naturally occurring isothiocyanate and Nrf2 activator, has similarly shown experimental neuroprotective effects in cerebral ischemia, including effects linked to Nrf2-dependent antioxidant responses [32,33].

Other agents have been investigated through mechanisms involving oxidative stress, antioxidant defense, iron metabolism, or ferroptosis-related pathways. Edaravone has demonstrated clinical activity in acute ischemic stroke, while preclinical evidence has linked some of its neuroprotective effects to the Sirt1/Nrf2/HO-1/GPx4 pathway [34-36]. NAC has also entered clinical investigation, including a randomized pilot trial and a systematic review [37,38]. Melatonin has predominantly preclinical support in stroke, whereas curcumin has been evaluated experimentally through mechanisms involving oxidative stress and Nrf2/HO-1 signaling [39,40]. Additional studies have implicated Nrf2 activation and ferroptosis-related pathways in cerebral ischemia, although much of this evidence remains mechanistic or preclinical [41-43]. These findings support the biological plausibility of pharmacological modulation of the pathway but do not establish equivalent therapeutic efficacy across agents.

Ferroptosis may also be approached through complementary mechanisms that do not depend exclusively on direct Nrf2 activation. Iron chelation with deferoxamine might reduce redox-active iron and thereby limit iron-dependent lipid peroxidation; it has also been evaluated clinically in ischemic stroke [44]. Recent experimental and mechanistic studies have linked ferritinophagy, Nrf2-regulated pathways, and ferroptotic injury to cerebral ischemia-reperfusion, while broader translational and related mechanistic literature provides additional context for these pathways [45-48]. Ferroptosis inhibitors such as ferrostatin-1 and liproxstatin-1 represent experimental approaches for suppressing lipid peroxidation and ferroptotic cell death. However, the cited evidence is derived largely from broader ferroptosis research rather than direct therapeutic studies in ischemic stroke, and their efficacy and translational relevance in ischemic stroke remain to be established [49,50]. Taken together, the pharmacological evidence suggests that the Nrf2-ferroptosis pathway can be influenced at several levels, including Nrf2 activation, strengthening of endogenous antioxidant defenses, regulation of iron homeostasis, and inhibition of ferroptotic signaling. Although these approaches target different aspects of the pathway, they may ultimately reduce oxidative and iron-dependent neuronal injury after ischemia. This suggests that Nrf2 and ferroptosis are closely linked components of the cellular response to ischemic injury and may need to be considered together when evaluating potential therapeutic strategies. The major pharmacological approaches targeting the Nrf2-ferroptosis axis in ischemic stroke are summarized in Figure 2.

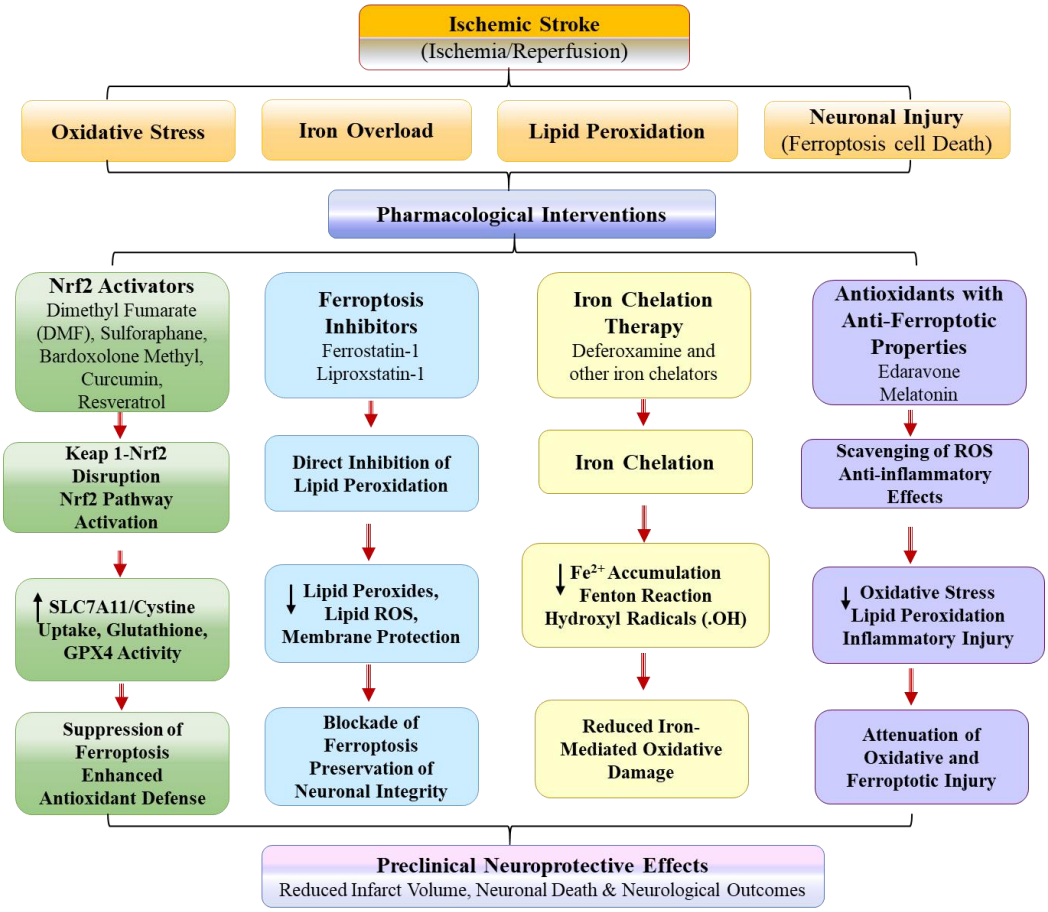


Figure 2. Pharmacological modulation of the Nrf2-ferroptosis axis in ischemic stroke. Representative approaches include Nrf2 activation, enhancement of endogenous antioxidant defenses, direct inhibition of ferroptosis, and modulation of iron availability, which might collectively reduce oxidative stress, lipid peroxidation, and iron-dependent neuronal injury [11,12,19-23,25-29,51].

5. Drug Repurposing Strategies Targeting the Nrf2-Ferroptosis Axis

Drug repurposing offers a practical starting point for investigating new treatments for ischemic stroke, particularly when the pharmacological properties and safety profiles of existing drugs are already well documented [52,53]. Several of these drugs also affect pathways related to oxidative stress, antioxidant defense, iron metabolism, or cellular stress responses, making them relevant to the Nrf2-ferroptosis pathway despite having been developed for other indications. DMF, for example, is an established treatment for multiple sclerosis and can activate Nrf2-related responses. Experimental studies in ischemic stroke have provided evidence for Nrf2-dependent cytoprotection, supporting further investigation of this approach [29,30]. Sulforaphane has similarly been studied as an Nrf2 activator and has shown neuroprotective effects in experimental ischemic stroke models [32,33,54]. Other studies have examined the xCT/GPX4 system and AMPK/Nrf2 signaling, highlighting their involvement in the regulation of ferroptosis during ischemic injury [55,56].

Some drugs may be relevant to this area through broader antioxidant, metabolic, or iron-regulating effects. Edaravone has been investigated extensively in the context of ischemic stroke, but its clinical use and neuroprotective effects do not, by themselves, establish that Nrf2 activation or ferroptosis inhibition is responsible for its effects [34-36]. Similarly, N-acetylcysteine (NAC) has been evaluated clinically in acute ischemic stroke, including the NACTLYS pilot trial, but its therapeutic value in this setting remains to be established [37,38]. Melatonin, metformin, and statins have also been examined in experimental or clinical studies involving antioxidant defense, metabolic regulation, and Nrf2-associated mechanisms [39,54,57-60]. Deferoxamine represents a different strategy by targeting redox-active iron, thereby addressing a key component of ferroptotic injury without directly activating Nrf2 [44,45].

These examples show that repurposing approaches within the Nrf2-ferroptosis field are not pharmacologically uniform. Some agents have relatively direct effects on Nrf2 or ferroptosis-related pathways, whereas others may influence these pathways as part of broader antioxidant, metabolic, or iron-regulatory actions. Their relevance to ischemic stroke also varies according to the strength of preclinical evidence, clinical experience, dosing requirements, and available information on pharmacokinetics and CNS exposure. Table 1 summarizes these features, together with the main safety and translational issues associated with each agent. Overall, existing clinical experience can provide a useful starting point for drug development, but stroke-specific studies are still needed to determine whether the proposed mechanisms can be achieved at clinically relevant doses and whether they translate into meaningful neurological benefit.

Table 1. Selected pharmacological strategies targeting the Nrf2-ferroptosis axis in ischemic stroke.

Agent	Nrf2-Ferroptosis Relevance	Dose/Regimen	Reported PK/CNS Exposure	Safety/Toxicity	Evidence Level	Directness to Ischemic Stroke	Translational Status & Major Limitations
Edaravone [34-36]	Free-radical scavenging and reduction of oxidative stress and lipid peroxidation; experimental evidence also links edaravone to Nrf2/HO-1/GPx4-associated responses, although its effects are not attributable exclusively to Nrf2 signaling.	Clinical IV regimens have been evaluated in acute ischemic stroke; the optimal stroke-specific regimen remains uncertain.	Clinical experience provides substantial systemic exposure information, but quantitative human brain/CSF exposure in acute ischemic stroke remains insufficiently characterized	Generally well tolerated in clinical studies; safety remains an important consideration in translation to acute ischemic stroke.	Clinical RCTs and meta-analyses	Direct - clinical ischemic stroke	Clinical studies provide evidence of use in acute ischemic stroke, but they do not establish that any clinical benefit is mediated specifically by Nrf2 activation or ferroptosis suppression. The relationship between brain exposure, pathway engagement, and functional outcome remains insufficiently defined.
N-acetylcysteine (NAC) [37,38]	Supports endogenous antioxidant defenses and has potential relevance to glutathione-dependent ferroptosis regulation.	Oral and IV regimens vary across clinical studies; an optimal stroke-specific dose has not been established.	Systemic exposure varies with route; stroke-specific quantitative brain/CSF exposure remains insufficiently characterized.	Generally well tolerated in clinical investigation; gastrointestinal or infusion-related adverse effects may occur.	Pilot RCT and clinical evidence synthesis	Direct - clinical ischemic stroke	Early clinical investigation supports further evaluation in ischemic stroke, but does not establish efficacy or a pathway-specific therapeutic effect. Larger controlled studies, together with stroke-specific exposure and target-engagement data, are needed.
DMF [29,30]	Activates Nrf2-associated antioxidant and cytoprotective responses, with experimental evidence of neuroprotection after ischemic stroke.	Stroke-specific therapeutic dosing has not been established; experimental dosing differs from clinical use in other indications.	Stroke-specific brain/CSF exposure and molecular target engagement remain insufficiently characterized.	Safety and tolerability in acute ischemic stroke have not been established.	Preclinical stroke study plus mechanistic/ neuroinflammatory evidence	Direct - preclinical ischemic stroke	Experimental stroke findings provide a rationale for further investigation. Its safety, effective dosing, CNS target engagement, and efficacy in acute ischemic stroke have not been established. Clinical experience in other indications cannot substitute for stroke-specific evidence.
Metformin [57]	Activates AMPK-associated Nrf2 antioxidant responses in experimental cerebral ischemia, with potential relevance to ferroptosis-related redox regulation.	Experimental cerebral-ischemia regimens differ across models; an optimal stroke-specific therapeutic regimen has not been established.	Stroke-specific systemic and CNS exposure-response relationships remain insufficiently characterized.	Safety and tolerability in acute ischemic stroke have not been established.	Preclinical cerebral ischemia evidence	Indirect/related - cerebral ischemia; not stroke-specific	Experimental evidence involving cerebral ischemia supports mechanistic investigation, but its relevance to acute ischemic stroke treatment depends on the model and treatment conditions studied. Stroke-specific dosing, treatment timing, CNS exposure, and clinical benefit remain to be established.
Sulforaphane [32,33]	Electrophilic activator of Nrf2 signaling that enhances endogenous antioxidant and cytoprotective responses, providing a mechanistic rationale for relevance to ferroptosis-related redox injury.	Experimental dosing and formulation vary across studies; an optimal formulation and stroke-specific regimen remain uncertain.	Stroke-specific pharmacokinetic and quantitative brain/CSF exposure data remain insufficiently characterized.	Safety and tolerability in acute ischemic stroke remain unestablished.	Preclinical stroke evidence and broader pharmacological evidence	Direct - preclinical ischemic stroke	Preclinical stroke findings support further investigation of Nrf2-related neuroprotection. Formulation-dependent exposure, an appropriate treatment regimen, target engagement, and clinical efficacy in ischemic stroke remain unresolved.

Agent	Nrf2-Ferroptosis Relevance	Dose/Regimen	Reported PK/CNS Exposure	Safety/Toxicity	Evidence Level	Directness to Ischemic Stroke	Translational Status & Major Limitations
Deferoxamine [44]	Chelates redox-active iron and may reduce iron-dependent lipid peroxidation and ferroptosis-related injury.	IV administration has been clinically evaluated using a 10 mg/kg bolus followed by 20, 40, or 60 mg/kg/day continuous infusion.	Stroke-specific quantitative human CNS pharmacokinetic data remain limited.	Clinical safety and tolerability have been evaluated in acute ischemic stroke; dose-related tolerability remains an important consideration.	Clinical randomized trial with preclinical rationale	Direct - clinical ischemic stroke	Clinical investigation of iron chelation provides information relevant to feasibility and tolerability, but does not establish ferroptosis-specific neuroprotection. The relationship between iron chelation, CNS exposure, treatment timing, and functional outcomes requires further clarification.
Melatonin [39]	Modulates oxidative stress and antioxidant pathways, with potential relevance to ferroptosis through regulation of redox homeostasis.	Experimental regimens vary across preclinical stroke studies.	Stroke-specific CNS exposure-response data remain limited.	Stroke-specific safety, dose, timing, and target-engagement data remain insufficient.	Preclinical stroke evidence summarized in review	Direct - preclinical ischemic stroke	Preclinical findings support investigation of its antioxidant effects in cerebral ischemia, but do not establish clinical efficacy through Nrf2-ferroptosis modulation. Stroke-specific target engagement, treatment timing, exposure, and functional benefit remain uncertain.

Note: Abbreviations: AMPK, AMP-activated protein kinase; CNS, central nervous system; CSF, cerebrospinal fluid; GPx4, glutathione peroxidase 4; IV, intravenous; Nrf2, nuclear factor erythroid 2-related factor 2; PK, pharmacokinetics.

The current evidence base and the major translational uncertainties associated with Nrf2-ferroptosis-targeted interventions in ischemic stroke are summarized in Figure 3.

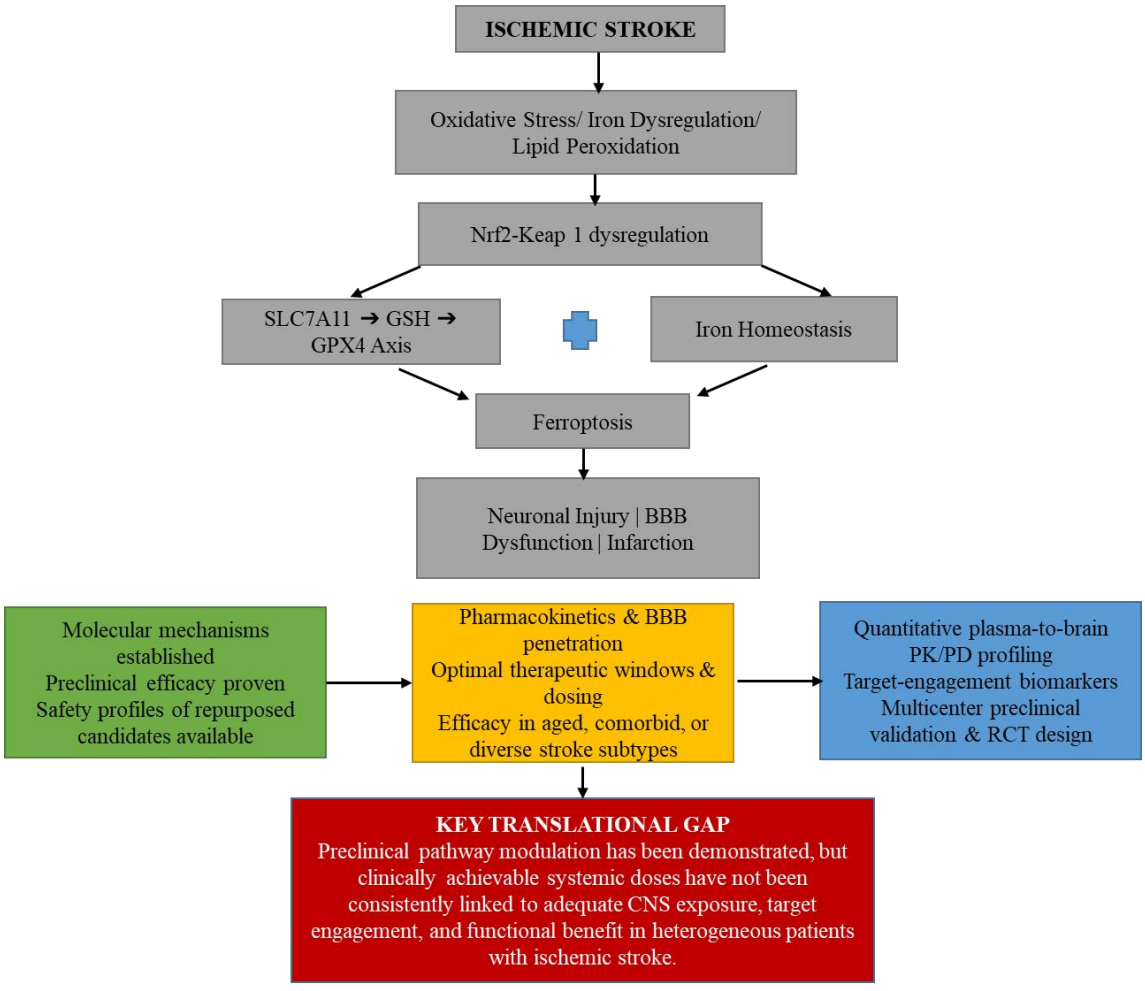


Figure 3. Nrf2-Keap1/ferroptosis axis and translational gap in ischemic stroke.

6. Translational Challenges, Limitations, and Future Directions

Although experimental studies implicate Nrf2 signaling and ferroptosis in ischemic brain injury, the evidence supporting therapeutic intervention remains uneven. Much of the mechanistic evidence comes from cell-based experiments and animal models, in which treatment conditions can be controlled more closely than in clinical practice. These models have helped establish links between antioxidant defenses, iron handling, lipid peroxidation, and neuronal injury, but they do not establish that manipulating these pathways will improve outcomes in patients. Differences in age, vascular comorbidities, stroke severity, and reperfusion status may also affect treatment responses [1,2,47,58,59,61,62]. Findings therefore need confirmation in models that better reflect clinical stroke, including treatment after ischemia has occurred and, where appropriate, in the setting of reperfusion.

Treatment timing is a particular limitation. Several experimental interventions are administered before ischemia or soon after reperfusion, whereas treatment in clinical practice usually begins after neurological symptoms develop. Because oxidative stress, iron accumulation, and lipid peroxidation change over the course of ischemic injury, an intervention that is protective at one experimental time point may not be effective at a later stage [4,42]. This uncertainty is relevant to both Nrf2 activators and ferroptosis inhibitors. Studies should establish the treatment window, duration of effect, and interaction with reperfusion before experimental efficacy is taken as evidence of likely clinical benefit.

Pharmacokinetic evidence also needs to be linked to target engagement in the injured brain. Systemic drug exposure does not establish that a sufficient concentration reaches the relevant brain tissue. Cerebral perfusion, blood-brain barrier disruption, infarct characteristics, and reperfusion can all influence CNS distribution [18,19,62]. Although edaravone has clinical pharmacokinetic data, these do not by themselves establish the concentration achieved at the site of ischemic injury [63]. For other candidates, quantitative brain or cerebrospinal fluid exposure and exposure-response relationships remain inadequately characterised. Future studies should therefore determine whether the concentrations associated with neuroprotection in experimental models can be achieved safely in the clinical setting and whether those concentrations produce the intended molecular effects.

The existing clinical evidence also needs to be interpreted according to what each study actually tested. Edaravone has been investigated clinically in ischemic stroke, and NAC has undergone early clinical investigation, including the NACTLYS pilot study [34-38]. These studies provide clinical information about the agents, but they do not establish that their effects are mediated by Nrf2 activation or ferroptosis suppression. Their pharmacological actions are broader, and a clinical outcome alone cannot identify which pathway contributed to that outcome. By comparison, the evidence supporting DMF and sulforaphane in ischemic stroke is predominantly preclinical [29,30,32,33]. Ferrostatin-1 and liproxstatin-1 remain experimental approaches; evidence of ferroptosis inhibition in experimental systems is not sufficient to establish their suitability for clinical use in stroke [49,50]. These candidates should therefore not be treated as equivalent in terms of clinical evidence or translational development.

Biomarker interpretation is another unresolved issue. Markers such as GPX4, ACSL4, ferritin, malondialdehyde, 4-hydroxynonenal, and glutathione-related measures can provide information about redox status, iron handling, or lipid peroxidation [8-10,20,21]. However, changes in these markers do not necessarily demonstrate ferroptotic cell death specifically, nor do they establish that a treatment improves outcomes by suppressing ferroptosis. Their value for identifying patients who might respond to pathway-directed treatment also remains uncertain. Combining molecular measurements with clinical characteristics and imaging may help clarify pathway activity, but proposed biomarkers need validation before they can be used to select patients or monitor target engagement [10,24].

Any future treatment would also need to be evaluated along with established reperfusion therapies, including thrombolysis and mechanical thrombectomy in eligible patients [3,4]. A candidate that reduces injury in a model without clinically relevant reperfusion conditions may behave differently when used as an adjunct to reperfusion. Studies should assess whether treatment timing affects efficacy and whether combination treatment introduces additional safety concerns. The aim should be to establish an additional, clinically meaningful benefit rather than simply a change in an oxidative stress marker or an experimental measure of tissue injury.

Drug-delivery approaches, including nanoparticles, liposomes, extracellular vesicles, and intranasal formulations, may help address inadequate CNS exposure [62,64-69]. Nevertheless, increased brain delivery is only an intermediate outcome. These approaches must demonstrate target engagement and functional benefit, while also addressing toxicity, biodistribution, manufacturing consistency, and feasibility in acute stroke care [70]. Similarly, the biological complexity of the Nrf2-ferroptosis axis complicates therapeutic design. Nrf2 signaling, glutathione metabolism, iron handling, and lipid peroxidation interact with other pathways, including NCOA4-mediated ferritinophagy and cGAS-STING signaling [45,51]. The consequences of pathway modulation may therefore depend on the timing and cellular context of treatment, rather than on activation or inhibition of a single molecular target.

The next stage of research should address these gaps in a defined sequence: establish reproducible effects in clinically relevant ischemia models; determine dose, treatment window, brain exposure, and target engagement; and assess functional outcomes and safety under conditions that include reperfusion where appropriate. Mechanism-linked biomarkers should be validated rather than assumed to indicate ferroptosis or predict treatment response. Candidates with adequate preclinical evidence and feasible pharmacological profiles could then be considered for appropriately designed

clinical studies. Until these requirements are met, the Nrf2-ferroptosis axis should be regarded as a supported mechanistic target under investigation, not a clinically validated treatment strategy.

7. Conclusion

The Nrf2-ferroptosis axis is a plausible therapeutic target for limiting oxidative and iron-dependent injury after ischemic stroke. Experimental evidence supports interactions among Nrf2 signaling, antioxidant defenses, iron homeostasis, lipid peroxidation, and ferroptotic cell death. However, the strength and directness of the evidence vary substantially between therapeutic candidates. Edaravone and NAC have been investigated clinically in ischemic stroke, but their clinical effects do not establish that Nrf2 activation or ferroptosis suppression mediates benefit. Evidence for several other candidates remains predominantly preclinical, while experimental ferroptosis inhibitors have not yet established clinical utility in stroke. The principal barrier to translation is therefore not the absence of a biological rationale, but the lack of sufficient evidence connecting pathway modulation to safe and meaningful clinical benefit. Further studies need to establish appropriate treatment windows, effective CNS exposure, target engagement, and functional benefit under clinically relevant conditions, including along with reperfusion treatment. At present, the Nrf2-ferroptosis axis warrants further investigation, but neither the pathway nor the candidate interventions considered here can be regarded as an established therapeutic strategy for ischemic stroke.

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Ethics Statement

Not applicable.

Informed Consent

Not applicable.

Data Availability Statement

No new datasets were generated during this study. The information presented in this review is based on previously published literature, which is appropriately cited in the manuscript.

Author Contributions

GT is the sole author of the manuscript.

Conflict of Interest

The author declares no competing interests. The manuscript has not been published or submitted elsewhere for consideration.

Generative AI Statement

The author declares that ChatGPT (OpenAI) was used solely for language editing and grammatical refinement during the preparation of this manuscript. AI assistance was limited to improving language, grammar, and readability in selected sections of the manuscript. No generative AI tools were used to develop the scientific content, interpret the literature, or formulate the conclusions. The author takes full responsibility for the scientific content, interpretation, accuracy, and conclusions presented in the manuscript.

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