Role and mechanisms of ferroptosis in cognitive impairment: From molecular pathways to therapeutic targets (Review)

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Abstract. Cognitive impairment remains an important global health concern, with the molecular mechanisms regulating its progression being a primary research focus. Ferroptosis, a unique form of programmed cell death characterized by iron-dependent lipid peroxidation, has been increasingly recognized for its essential role in the progression of various neurodegenerative diseases and diabetes-associated cognitive impairment. The present review summarizes current evidence on how ferroptosis contributes to cognitive decline and outlines its regulation through lipid, iron and glutathione metabolism; it further discusses how diverse upstream pathologies converge on ferroptosis as a shared mechanism underlying cognitive dysfunction. In addition, recent advances in ferroptosis-related biomarkers and therapeutic strategies are highlighted, with the aim of providing a clearer framework for understanding its pathogenic roles and guiding future clinical translation.

Contents

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Abbreviations: ACSL4, acyl-CoA synthetase long-chain family member 4; AD, Alzheimer's disease; CSF, cerebrospinal fluid; DACI, diabetes-associated cognitive impairment; GPX4, glutathione peroxidase 4; GSH, glutathione; GSK3β, glycogen synthase kinase 3β; LIP, labile iron pool; NRF2, nuclear factor erythroid 2-related factor 2; PD, Parkinson's disease; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; T2DM, type 2 diabetes mellitus; TREM1, triggering receptor expressed on myeloid cells 1

Key words: cognitive impairment, neurodegenerative diseases, ferroptosis, molecular mechanisms, therapeutic strategies

1. Introduction

Cell death is a fundamental biological process that governs cell fate, tissue regeneration and host immune responses (1). Among the various forms of cell death, ferroptosis has recently emerged as a unique, iron-dependent modality of programmed cell death that has gained significant scientific interest (2). Morphologically, biochemically and genetically, ferroptosis is distinct from other well-established cell death modalities, including apoptosis, necrosis and autophagy (3). Rather than being a stochastic or uncontrolled process, ferroptosis is precisely orchestrated by complex signaling pathways and metabolic networks; its core mechanism involves the dysregulation and interplay of three pivotal modules: Iron, lipid and amino acid metabolism (4,5).

Cognitive impairment represents a major global public health challenge, encompassing a clinical spectrum from mild cognitive impairment to severe dementia. This condition profoundly affects the quality of life of patients and imposes a significant socioeconomic burden (6). This dysfunction serves as a common pathological endpoint for a multitude of neurological disorders. The present review focuses on the following key categories of disorders closely associated with cognitive impairment: Neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD), which are pathologically characterized by the progressive loss of neurons in specific brain regions and the abnormal aggregation of functional proteins (7), and diabetes-associated cognitive impairment (DACI), which is caused mainly by factors such as insulin resistance and neuroinflammation (8).

Accumulating evidence indicates that ferroptosis plays a pivotal role in the pathophysiology of the aforementioned cognitive disorders. However, despite the rapid expansion of research into ferroptosis within the field of neuroscience, the existing body of knowledge remains relatively fragmented and unsystematized (9). Therefore, the present review aims

to systematically dissect the core molecular mechanisms of ferroptosis, elucidate its specific pathogenic roles in cognitive disorders including AD, PD and DACI as well as provide a comprehensive overview of emerging diagnostic biomarkers and therapeutic strategies targeting this cell death pathway. By synthesizing current research advancements, the present review aims to provide new perspectives on the common pathological pathways underlying these diseases and to establish a theoretical foundation to guide the development of effective clinical interventions.

Although several reviews have discussed the role of ferroptosis in neurodegenerative diseases, most have focused on a single disorder, isolated pathways or specific mechanistic aspects (7,10,11). By contrast, the novelty of the present review is its cross-disease perspective. The present review summarizes ferroptosis-related mechanisms across AD, PD and DACI, emphasizing both the common molecular features and the unique triggers in each disease. Moreover, the present review integrates recent progress in ferroptosis-related biomarkers and evaluates the translational potential of ferroptosis-targeted therapeutic strategies. By discussing the practical challenges, clinical feasibility and workflow integration of these biomarkers, the present review aims to bridge the gap between basic mechanistic research and clinical application.

2. Mechanisms of ferroptosis

Ferroptosis is a complex biological process regulated by the interplay of multiple metabolic pathways (Fig. 1); its hallmark feature is the uncontrolled, iron-dependent accumulation of lipid peroxides on cellular membranes (12), ultimately leading to the destruction of membrane integrity and cell death. Understanding the interplay among lipid metabolism, iron metabolism and the antioxidant defense system is fundamental to elucidating the role of ferroptosis in disease.

Lipid metabolism and peroxidation. Lipid peroxidation constitutes the final step of ferroptosis execution, the occurrence of which depends on specific lipid substrates and catalytic enzymes. Owing to its high lipid content, particularly its enrichment in polyunsaturated fatty acids (PUFAs), the brain is especially vulnerable to ferroptosis (13).

Critical role of PUFAs as substrates. PUFAs, especially arachidonic acid and adrenic acid, are the primary substrates for lipid peroxidation during ferroptosis. The bis-allylic hydrogen atoms within the molecular chains of these fatty acids are chemically labile and highly susceptible to abstraction, thereby initiating the chain reaction of lipid peroxidation (14). The content and composition of PUFAs within the cell membrane directly determine a cell's sensitivity to ferroptosis.

Enzymatic activation by acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3). PUFAs cannot be directly peroxidized; they must first be integrated into membrane phospholipids. This process is accomplished through the synergistic actions of two key enzymes: ACSL4 and LPCAT3. ACSL4 is responsible for esterifying PUFAs into their corresponding acyl-CoA derivatives, after which LPCAT3 catalyzes the incorporation of these activated PUFAs into membrane phospholipids to form phospholipid-containing polyunsaturated fatty acids (PL-PUFAs) (14). Consequently, ACSL4 is considered a critical 'gatekeeper' enzyme for ferroptosis, as its expression level and activity cellular sensitivity to ferroptosis; its high expression enriches the cell membrane with oxidizable PUFAs, effectively 'priming' the cell for ferroptosis (15).

Peroxidation cascade. Once incorporated into the membrane, PL-PUFAs are oxidized to phospholipid hydroperoxides (PL-PUFA-OOH) through enzymatic or non-enzymatic pathways. The enzymatic pathway is primarily catalyzed by members of the lipoxygenase family (16). The non-enzymatic pathway is driven by the Fenton reaction, which is catalyzed by intracellular labile Fe^{2+} (17). The accumulation of these PL-PUFA-OOH molecules disrupts the integrity and fluidity of the cell membrane, ultimately leading to membrane rupture, the release of the cellular contents and cell death (18).

Iron metabolism: The catalyst of death. Although iron is an essential trace element for life, its dyshomeostasis is a key catalyst for ferroptosis. Cells possess an intricate system to regulate iron uptake, storage, utilization and efflux; disruptions at any point can lead to ferroptosis.

Iron uptake and the labile iron pool (LIP). Extracellular Fe^{3+} typically binds to transferrin and enters cells via endocytosis through transferrin receptor 1 on the cell membrane. Within the acidic endosome, Fe^{3+} is reduced to Fe^{2+} by the six-transmembrane epithelial antigen of prostate 3 and is then released into the cytoplasm by divalent metal transporter 1, forming the highly redox-active LIP (19).

Fenton reaction. Fe^{2+} within the LIP is central to the catalysis of ferroptosis; it participates in the Fenton reaction, which decomposes H_2O_2, a byproduct of cellular metabolism, into highly reactive hydroxyl radicals. Hydroxyl radicals are among the most potent reactive oxygen species (ROS) and can non-specifically attack membrane PUFAs, thereby triggering intense lipid peroxidation (20).

Ferritinophagy. Cells store excess iron within ferritin, a spherical protein shell composed of 24 subunits, to mitigate the toxicity of free iron in the LIP (21,22). However, upon exposure to specific signaling cues, cells can degrade ferritin through a selective autophagic process known as ferritinophagy (23). This process is mediated by a specific cargo receptor, nuclear receptor coactivator 4, which recognizes and binds to ferritin, targeting it for lysosomal degradation (24). This process releases large amounts of stored iron into the LIP (23). Ferritinophagy is a key mechanism for rapidly increasing the iron content of the LIP when needed and is important for increasing cellular sensitivity to ferroptosis (25).

Antioxidant defense network. Cells have evolved a complex, multilayered antioxidant defense network to counteract the onset of ferroptosis. This network maintains cellular redox homeostasis by eliminating lipid peroxides or inhibiting their formation. These defense mechanisms can be broadly categorized into the canonical glutathione peroxidase 4 (GPX4)-dependent pathway and non-canonical, independent pathways.

Canonical GPX4/glutathione (GSH) defense axis. The canonical axis defending against ferroptosis is centered on the GPX4/GSH system (26). This pathway begins with the cell membrane-bound cystine/glutamate antiporter,

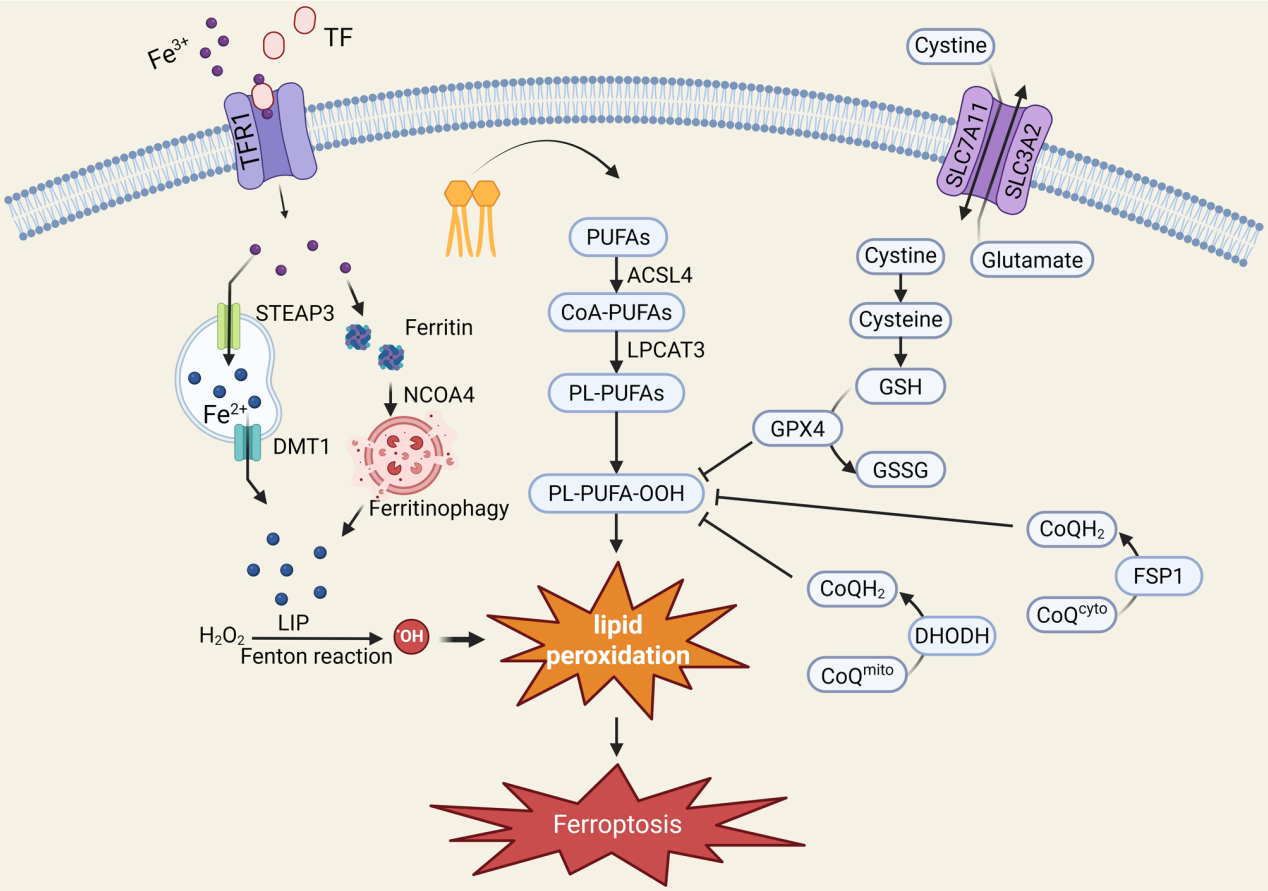

Figure 1. Core molecular mechanism of ferroptosis. ACSL4, acyl-CoA synthetase long-chain family member 4; DMT1, divalent metal transporter 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, oxidized glutathione; LIP, labile iron pool; LPCAT3, lysophosphatidylcholine acyltransferase 3; NCOA4, nuclear receptor coactivator 4; PL-PUFAs, phospholipid-containing PUFAs; PL-PUFA-OH, phospholipid PUFA alcohol; PL-PUFA-OOH, phospholipid PUFA hydroperoxide; PUFAs, polyunsaturated fatty acids; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STEAP3, six-transmembrane epithelial antigen of prostate 3; TF, transferrin; TFR1, transferrin receptor 1; CoQ, coenzyme Q10; DHODH, dihydroorotate dehydrogenase; FSP1, ferroptosis suppressor protein 1.

System Xc^- (27). Composed of the light chain subunit solute carrier family 7 member 11 (SLC7A11) and the heavy chain subunit SLC3A2, System Xc^- imports extracellular cystine, which is then rapidly reduced to cysteine intracellularly (28). Cysteine serves as the rate-limiting substrate for the synthesis of GSH (29). As the core effector molecule of this pathway, GPX4 is a unique selenoprotein and the only member of the GPX family capable of directly catalyzing the reduction of membrane phospholipid hydroperoxides (30). GPX4 utilizes GSH as a cofactor to efficiently reduce toxic lipid hydroperoxides into non-toxic phospholipid alcohols, thereby halting the lipid peroxidation chain reaction and effectively suppressing ferroptosis (31). Consequently, the inactivation of GPX4, either through the inhibition of System Xc^- or the depletion of intracellular GSH, represents a classic experimental method for inducing ferroptosis.

Non-canonical independent defense systems. In addition to the canonical GPX4/GSH axis, cells possess other parallel, GPX4-independent anti-ferroptotic pathways that provide additional layers of protection. One key non-canonical system is the ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10) pathway (32). Localized to the plasma membrane, FSP1 utilizes NADPH as an electron donor to reduce CoQ10 to its antioxidant form, ubiquinol. Ubiquinol acts as a lipophilic radical-trapping antioxidant that can effectively scavenge lipid peroxyl radicals, thus providing a critical alternative line of defense when GPX4 function is compromised. Another important independent anti-ferroptotic axis is the GTP cyclohydrolase-1/tetrahydrobiopterin (BH4) pathway (33). BH4 is not only a crucial enzyme cofactor but also a potent radical scavenger. Studies have shown that it exerts powerful anti-ferroptotic effects through two mechanisms: Protecting CoQ10 from depletion and directly inhibiting lipid peroxidation (34,35). In parallel to the plasma membrane-localized FSP1 system, a distinct, mitochondria-specific antioxidant axis that counteracts ferroptosis centered on the enzyme dihydroorotate dehydrogenase (DHODH) has been identified (36). DHODH is a flavoprotein of the electron transport chain that is anchored to the inner mitochondrial membrane, where it performs its canonical function in *de novo* pyrimidine synthesis (37). Crucially, this enzymatic process reduces CoQ10 to its active antioxidant form, ubiquinol (36). This dedicated mitochondrial pool of ubiquinol acts as a potent, radical-trapping antioxidant, directly neutralizing lipid peroxyl radicals within the inner mitochondrial membrane and thereby shielding the organelle from lipid peroxidation and subsequent ferroptotic collapse (38). Given that mitochondria are both a primary source of endogenous ROS and a central hub for

iron metabolism, their membranes are uniquely vulnerable to ferroptotic insults. This defense system thus provides a critical layer of localized protection specifically within this susceptible organelle, offering new insights for understanding cellular resilience and identifying potential therapeutic targets in neurodegenerative disorders where mitochondrial dysfunction is a core pathological feature.

Key transcriptional regulators. Nuclear factor erythroid 2-related factor 2 (NRF2) acts as the 'master regulator' of the cellular response to oxidative stress. Under oxidative or electrophilic stress, NRF2 is activated and translocates to the nucleus, where it binds to antioxidant response elements to initiate the transcription of a number of downstream genes. The proteins encoded by these genes have diverse functions, including promoting GSH synthesis, regenerating NADPH and upregulating iron storage proteins (ferritin), thereby constructing a robust, multilayered defense against ferroptosis (32).

The classic tumor suppressor p53 plays a complex, dual role in the regulation of ferroptosis. On the one hand, p53 can promote ferroptosis by inhibiting the expression of SLC7A11 (39). On the other hand, it can also suppress ferroptosis by regulating other metabolic pathways (such as activating CDKN1A/p21) (40). The ultimate effect of p53 is highly dependent on the cell type and the specific stress context (41).

The regulatory mechanisms of ferroptosis are not isolated but are intimately linked to the core metabolic activities of cells. The initiation of ferroptosis is deeply integrated with amino acid metabolism (glutamate/cystine balance), lipid metabolism (PUFA availability) and metal homeostasis (iron regulation). For instance, the activity of System Xc^- is directly linked to the levels of the neurotransmitter glutamate and the synthesis of the antioxidant GSH (42). The execution phase depends on the biological properties of the cell membrane and the activity of lipid-modifying enzymes (ACSL4 and LPCAT3) (20). Moreover, iron is a critical cofactor for core bioenergetic processes such as mitochondrial respiration and oxygen transport and the Fe^{2+} required for ferroptosis (32). This intrinsic connectivity implies that ferroptosis is not merely a simple 'death switch' but rather a composite reflection of the overall metabolic state of the cell. Any pathological process that can disrupt these interconnected metabolic hubs, such as mitochondrial dysfunction in PD or oxidative stress in AD, may inadvertently lower the cellular threshold for resistance to ferroptosis. This explains why ferroptosis has emerged as a common pathological pathway in multiple, seemingly unrelated diseases; it represents a shared downstream execution point where diverse upstream damage signals converge.

3. Molecular mechanisms of ferroptosis in cognitive impairment

The fundamental molecular mechanisms of ferroptosis are specifically activated and regulated in different disease contexts and are emerging as key factors driving the pathological progression of cognitive impairment (Table I). This section describes the specific mechanisms of ferroptosis in AD, PD and DACI.

Role of ferroptosis in AD. The regulation of ferroptosis can impact AD through multiple mechanisms, including the regulation of GSH levels, the Fenton reaction, amyloid-β (Aβ), lipid metabolism, iron metabolism and the NRF2 signaling pathway (Fig. 2).

Vicious cycle of iron dyshomeostasis and Aβ/tau. An abnormal increase in iron levels in the AD brain is a well-documented phenomenon, especially in the regions most severely affected by neurodegeneration (6). Iron dyshomeostasis is not only an epiphenomenon but is also strongly implicated in the core pathological processes of AD. On the one hand, excess iron ions can directly catalyze ROS production, exacerbating oxidative stress, while also promoting the generation and aggregation of Aβ and catalyzing the hyperphosphorylation of the tau protein. On the other hand, Aβ and tau aggregates can disrupt iron homeostasis, for instance, by interfering with the function of iron-efflux proteins, thereby further intensifying iron accumulation. This positive feedback loop, or 'vicious cycle', between iron and Aβ/tau significantly lowers the threshold for neuronal resistance to ferroptosis, rendering them exceptionally vulnerable (43).

Oxidative stress and the collapse of the GPX4/GSH system. The AD brain is in a state of chronic, sustained oxidative stress. Aβ oligomers and fibrils are themselves sources of ROS and can directly induce lipid peroxidation. Critically, a study has shown that the levels of GSH, a key antioxidant, are significantly reduced in the AD brain and that the extent of this depletion correlates positively with the severity of cognitive impairment (43). The depletion of GSH leads directly to the failure of the GPX4 antioxidant system, resulting in cells being unable to effectively neutralize lipid peroxides and thereby allowing the onset of ferroptosis.

Ferroptosis of microglia. In recent years, a new paradigm in AD pathology has emerged: The ferroptosis of microglia, the resident immune cells of the brain. In the pathological environment of AD, microglia are activated to clear Aβ plaques, damaged myelin, and cellular debris. However, this debris (particularly myelin) is rich in iron. During the phagocytosis and degradation of this iron-rich material, the microglia themselves can undergo ferroptosis due to iron overload (44). This process not only results in the loss of protective immune cells but also the release of proinflammatory cytokines and damage-associated molecular patterns during their death, further exacerbating the neuroinflammatory response (45). This process creates a self-amplifying cycle of damage that promotes neurodegeneration (46).

Key molecular evidence. Genetic studies have provided direct evidence for the involvement of ferroptosis in AD (47,48). Transcriptomic analyses of brain tissue samples from patients with AD have revealed significant alterations in the expression of a range of ferroptosis-related genes (FRGs). For example, the genes encoding transferrin receptor (TFRC), glucose transporters and the master antioxidant regulator NRF2 are closely associated with the pathological progression of AD (49).

Role of ferroptosis in PD. Ferroptosis is regulated by multiple interconnected pathways, including the GPX4/GSH system, iron and lipid metabolism, the NRF2 signaling pathway and mitochondrial function, in PD (Fig. 3).

Table I. Molecular mechanism of ferroptosis in cognitive impairment.

Authors, year	Target	Intervention or drug	Effect on ferroptosis	Mechanism	Model	(Refs.)
A, Alzheimer's disease						
Cai *et al*, 2025	ROS	ATG7	Induce	Reduces the unfolded protein response and increases oxidative stress	*In vitro* and *in vivo*	(145)
Dixon *et al*, 2012	ROS	Ferrostatin-1	Inhibit	Suppresses fatty acid oxidation	*In vitro* and *in vivo*	(146)
Li *et al*, 2022	ROS	Liproxstatin-1	Inhibit	Suppresses fatty acid oxidation	*In vivo*	(147)
Long *et al*, 2022	Organelles	Mitochondrial/ lysosomal dysfunction	Induce	Mitochondria, lysosomes dysfunction leads to increased ROS production and disturbed iron metabolism	*In vivo*	(148)
Streit *et al*, 2025	Aβ/Tau protein	Aβ/Tau aggregation	Induce	Aβ/tau aggregation interacts with iron ions to promote oxidative stress and ferroptosis	*In vivo*	(44)
Conrad and Proneth, 2020	GPX4	Selenium	Inhibit	Activates GPX4	*In vivo*	(149)
Kalyanaraman, 2022	NRF2	N-acetylcysteine	Inhibit	Activates NRF2	*In vitro* and *in vivo*	(150)
Xu *et al*, 2025	Fe^{2+}/Fe^{3+}	Deferoxamine	Inhibit	Chelates excess iron and reduces Fenton reaction	*In vivo*	(151)
B, Parkinson's disease						
Negida *et al*, 2024	Fe^{2+}	DFP	Inhibit	Chelates excess iron in the substantia nigra	*In vivo*	(52)
Sun *et al*, 2023	GPX4	Dopamine oxidation	Induce	Dopamine oxidation product DAQ modifies GPX4 and mediates its ubiquitination degradation	*In vitro* and *in vivo*	(50)
Sun *et al*, 2023	GPX4	GPX4 overexpression	Inhibit	Reduces neuronal death by increasing GPX4 levels	*In vitro* and *in vivo*	(50)
Anandhan *et al*, 2022	NRF2	α-synuclein overexpression	Induce	Decreases NRF2 protein levels and impairs anti-oxidant defense	*In vivo*	(56)
Wang *et al*, 2025	ACSL4	Salsolinol	Induce	Upregulates ACSL4	*In vitro* and *in vivo*	(54)
Yan *et al*., 2025	ROS	Ferrostatin-1	Inhibit	Scavenges lipid free radicals and inhibits lipid peroxidation	*In vivo*	(55)
Angelova *et al*, 2020	α-synuclein	α-synuclein oligomers	Induce	Oligomers insert into cell membranes, causing abnormal calcium influx and lipid peroxidation	*In vivo*	(53)

Table I. Continued.

B, Parkinson's disease

Authors, year	Target	Intervention or drug	Effect on ferroptosis	Mechanism	Model	(Refs.)
Wang *et al*, 2025	Mitochondria	Mitochondrial dysfunction	Induce	Mitochondrial dysfunction, iron homeostasis imbalance and oxidative stress promote ferroptosis	*In vivo*	(59)
Li *et al*, 2025	m6A Demethylase FTO	BAP1	Induce	p53/SLC7A11	*In vitro* and *in vivo*	(39)
Wang *et al*, 2024	CR3	CR3 activation	Induce	NOX2	*In vitro* and *in vivo*	(60)
Lin *et al*, 2025	NOX4	NOX4 upregulation	Induce	Interacts with activated protein kinase Cα	*In vitro* and *in vivo*	(62)
Wang *et al*, 2024	NOX1	NOX1 upregulation	Induce	Triggers ferritinophagy	*In vitro* and *in vivo*	(61)
Lv *et al*, 2024	Melatonin MT1 receptors	Melatonin	Inhibit	SIRT1/NRF2/HO-1/GPX4	*In vitro* and *in vivo*	(58)
Zheng *et al*, 2024	LRRK2	LRRK2 overexpression	Induce	Regulates system Xc^-/GSH/GPX4	*In vitro* and *in vivo*	(51)

C, Diabetes-associated cognitive impairment

Xie *et al*, 2023	AMPK/GPX4	AMPK agonists	Inhibit	Activates AMPK, upregulates GPX4 expression and downregulates LCN2	*In vivo*	(63)
Xie *et al*, 2023	ROS	Liproxstatin-1	Inhibit	Reduces iron accumulation and oxidative stress	*In viv*o	(63)
Tang *et al*, 2022	Caveolin-1	Caveolin-1 overexpression	Inhibit	Improves mitochondrial homeostasis	*In vitro* and *in vivo*	(67)
Guo *et al*, 2023	Iron overload	Erythropoietin	Inhibit	Reduces iron overload and lipid peroxidation	*In vitro* and *in viv*o	(68)
Li *et al*, 2023	VDR/NRF2/HO-1	Vitamin D	Inhibit	Activates the NRF2/HO-1 pathway	*In vitro* and *in vivo*	(73)
Zhao *et al*, 2025	PERK	TREM1	Induce	Enhances ROS and promotes lipid peroxidation	*In vitro* and *in viv*o	(69)

Aβ, amyloid-β; ACSL4, acyl-CoA synthetase long-chain family member 4; AMPK, AMP-activated protein kinase; ATG7, autophagy related 7; BAP1, BRCA1 associated protein 1; Cav-1, caveolin-1; CR3, complement receptor 3; DAQ, dopamine quinone; DFP, deferiprone; FTO, FTO α-ketoglutarate dependent dioxygenase; GPX4, glutathione peroxidase 4; GSH, glutathione; HO-1, heme oxygenase 1; LCN2, lipocalin-2; LRRK2, leucine-rich repeat kinase 2; NOX, NADPH oxidase; NRF2, nuclear factor erythroid 2-related factor 2; PERK, PKR-like endoplasmic reticulum kinase; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SIRT1, sirtuin 1; SLC7A11, solute carrier family 7 member 11; TREM1, triggering receptor expressed on myeloid cells 1; VDR, vitamin D receptor.

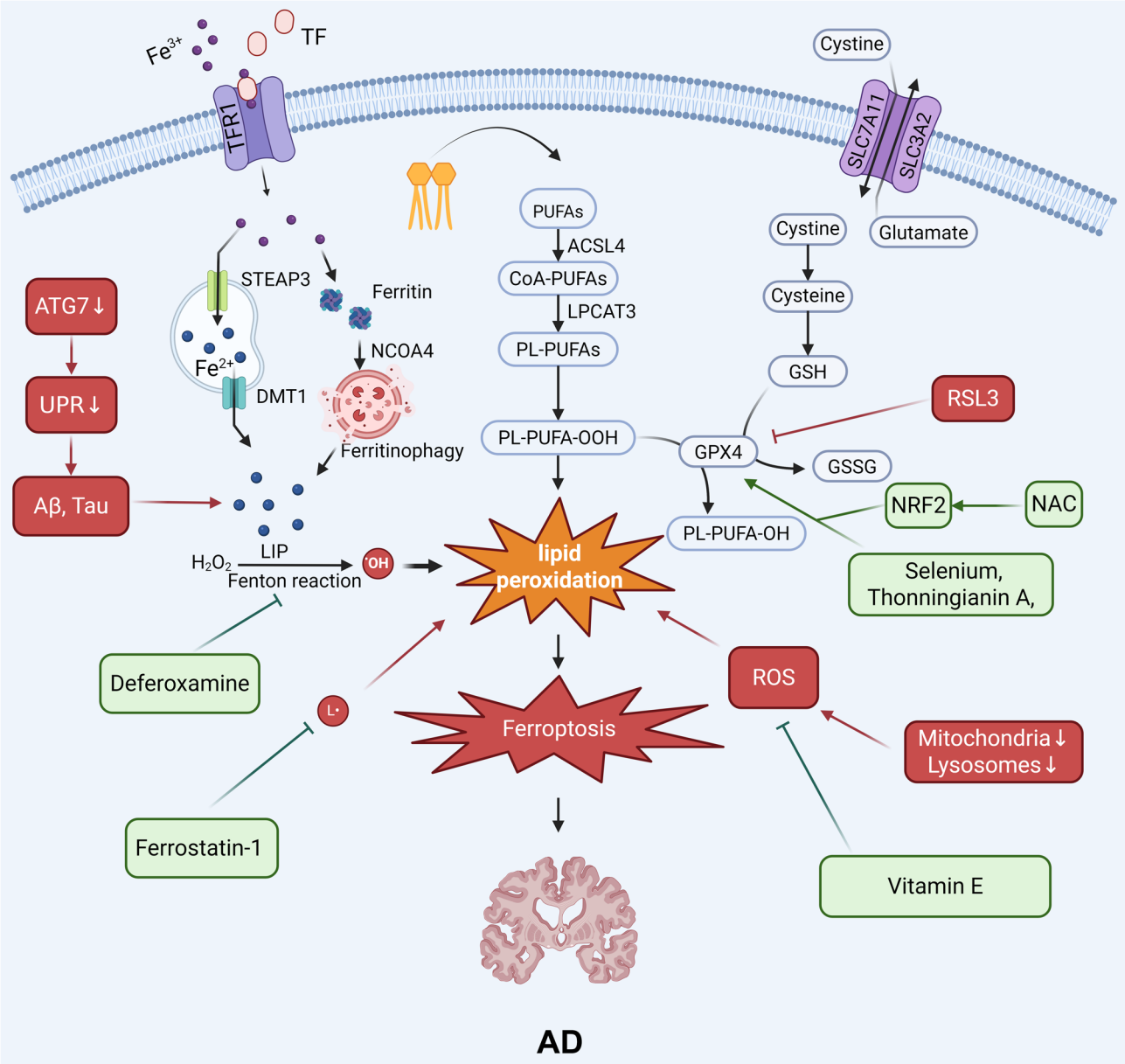

Figure 2. Role and regulatory mechanisms of ferroptosis in AD. The regulation of ferroptosis can impact AD through multiple mechanisms, including regulation of GSH levels, Fenton reaction, Aβ, lipid metabolism, iron metabolism and the NRF2 signaling pathway. AD, Alzheimer's disease; ACSL4, acyl-CoA synthetase long-chain family member 4; ATG7, autophagy related 7; Aβ, amyloid-β; DMT1, divalent metal transporter 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, oxidized glutathione; LIP, labile iron pool; LPCAT3, lysophosphatidylcholine acyltransferase 3; NAC, N-acetylcysteine; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid 2-related factor 2; PL-PUFAs, phospholipid-containing PUFAs; PL-PUFA-OH, phospholipid PUFA alcohol; PL-PUFA-OOH, phospholipid PUFA hydroperoxide; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; RSL3, RAS-selective lethal 3; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STEAP3, six-transmembrane epithelial antigen of prostate 3; TF, transferrin; TFR1, transferrin receptor 1; UPR, unfolded protein response.

Steady-state GPX4/GSH system. The integrity of the GPX4/GSH antioxidant axis is critical for dopaminergic neuron survival. The oxidation product of dopamine can induce ferroptosis by covalently modifying GPX4 and mediating its ubiquitination and degradation (50). Conversely, experimental GPX4 overexpression exerts neuroprotective effects as it reduces neuronal death (50). This pathway is also targeted by other PD-related factors; the leucine-rich repeat kinase 2 (LRRK2) protein induces ferroptosis by acting on the System Xc^-/GSH/GPX4 pathway (51) and the m6A demethylase fat mass and obesity-associated protein can promote ferroptosis via the p53/SLC7A11 axis (39).

Iron metabolism. Given the central role of iron, therapeutic strategies have focused on its chelation. The drug deferiprone has been shown to inhibit ferroptosis by chelating excess iron within the substantia nigra *in vivo* (52). This result is compounded by the fact that α-synuclein aggregation, a hallmark of PD, can also induce ferroptosis through mechanisms such as membrane disruption and altered calcium influx (53).

Lipid metabolism. The regulation of lipid metabolism, particularly through the enzyme ACSL4, is a key control point. The PD-relevant neurotoxin salsolinol induces ferroptosis by upregulating ACSL4 expression (54). By contrast, the natural compound acteoside exerts a protective effect by

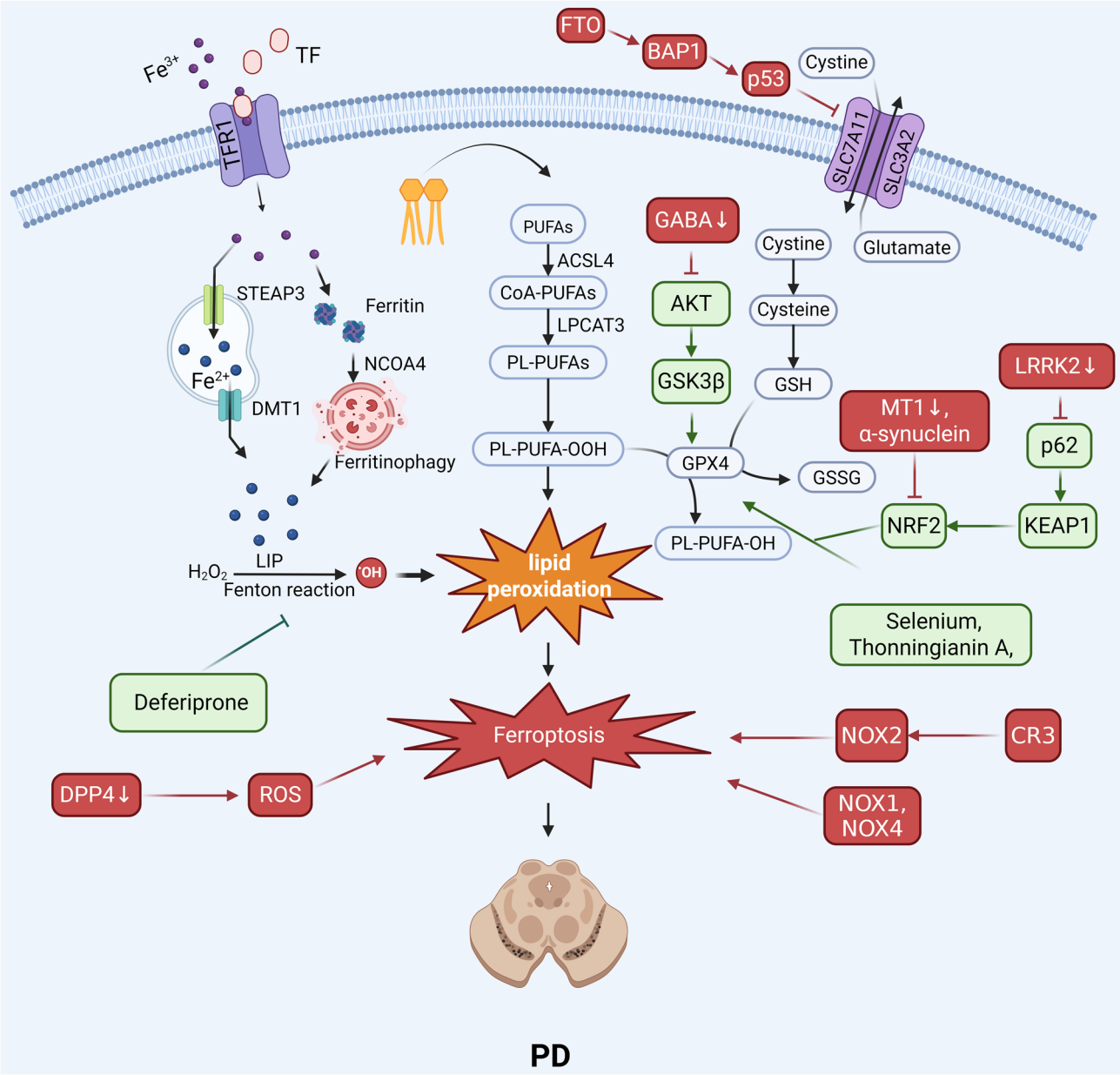

Figure 3. Role and regulatory mechanisms of ferroptosis in PD. Ferroptosis in PD is regulated by multiple interconnected pathways, including the GPX4/GSH system, iron and lipid metabolism, the NRF2 signaling pathway, and mitochondrial function. ACSL4, acyl-CoA synthetase long-chain family member 4; AKT, protein kinase B; BAP1, BRCA1 associated protein 1; CR3, complement receptor 3; DMT1, divalent metal transporter 1; DPP4, dipeptidyl peptidase-4; FTO, FTO α-ketoglutarate dependent dioxygenase; GABA, γ-aminobutyric acid; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, oxidized glutathione; GSK3β, glycogen synthase kinase 3β; KEAP1, kelch-like ECH-associated protein 1; LIP, labile iron pool; LPCAT3, lysophosphatidylcholine acyltransferase 3; LRRK2, leucine-rich repeat kinase 2; MT1, melatonin receptor 1; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid 2-related factor 2; NOX, NADPH oxidase; PD, Parkinson's disease; PL-PUFAs, phospholipid-containing PUFAs; PL-PUFA-OH, phospholipid PUFA alcohol; PL-PUFA-OOH, phospholipid PUFA hydroperoxide; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STEAP3, six-transmembrane epithelial antigen of prostate 3; TF, transferrin; TFR1, transferrin receptor 1.

downregulating ACSL4 (54). Downstream lipid peroxidation can be directly inhibited by radical-trapping antioxidants such as ferrostatin-1 (55).

NRF2 signaling pathway. The NRF2 antioxidant response pathway is a major defensive system whose impairment contributes to PD. Pathological α-synuclein upregulation induces ferroptosis by reducing NRF2 protein levels and impairing antioxidant defenses (56). The therapeutic activation of this pathway with compounds such as dimethyl fumarate, tert-butylhydroquinone and sulforaphane can inhibit ferroptosis by upregulating the expression of downstream antioxidant genes (57). Additionally, the activation of melatonin MT1 receptors can suppress ferroptosis through the sirtuin 1/NRF2/heme oxygenase 1 (HO-1)/GPX4 signaling cascade (58).

Mitochondrial metabolism and neuroinflammation. Mitochondrial dysfunction acts as a core driver of ferroptosis through a combination of iron homeostasis imbalance and oxidative stress (59). This oxidative environment is further exacerbated by neuroinflammatory processes. Microglial complement receptor 3 can induce ferroptosis via NADPH oxidase 2 (NOX2) (60), and other NADPH oxidases, including

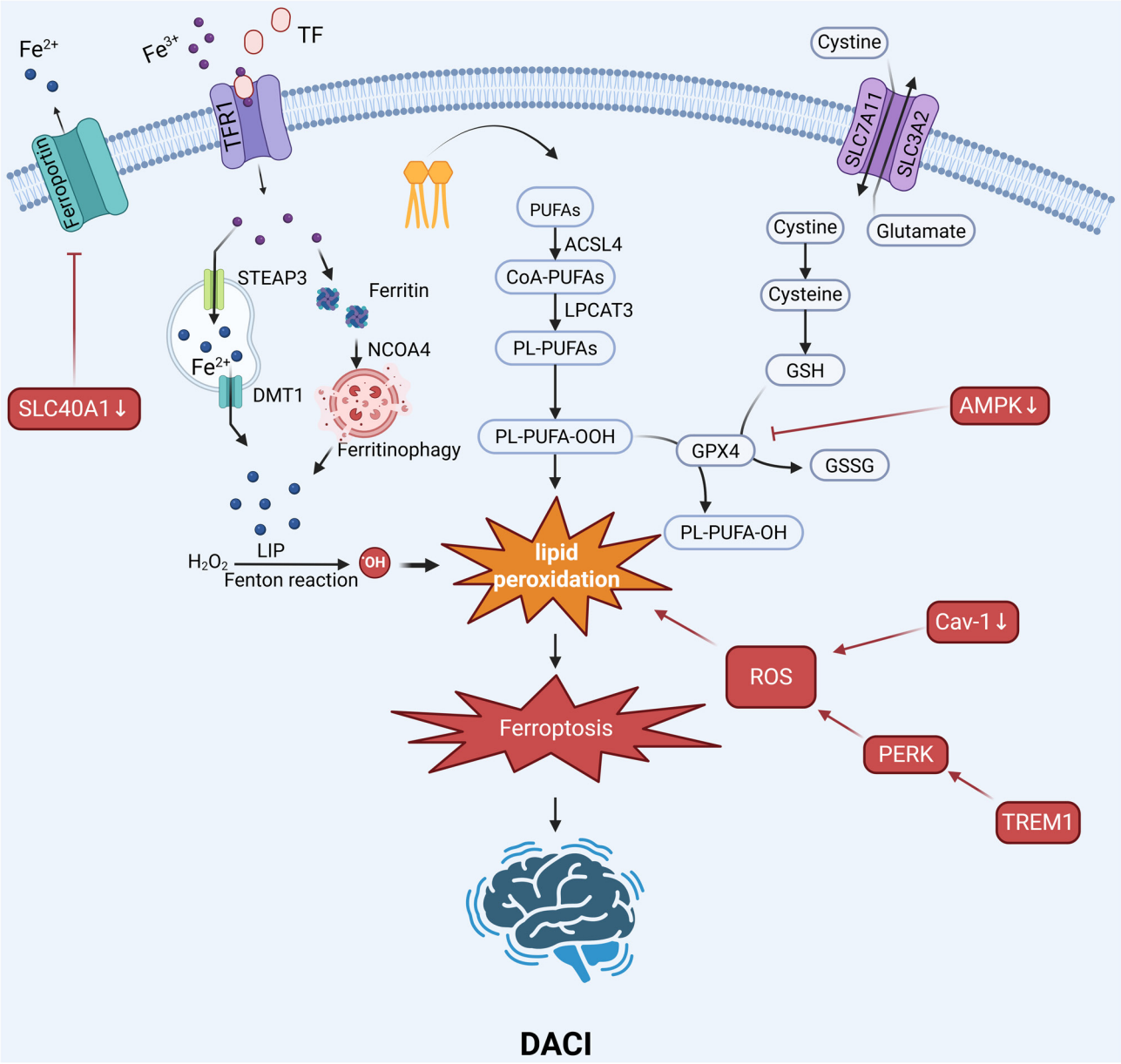

Figure 4. Role and regulatory mechanisms of ferroptosis in DACI. The regulation of ferroptosis can impact DACI through multiple mechanisms, including the modulation of the GPX4/GSH system, iron and ROS metabolism, mitochondrial homeostasis and the NRF2 and PERK signaling pathways. ACSL4, acyl-CoA synthetase long-chain family member 4; AMPK, AMP-activated protein kinase; Cav-1, caveolin-1; DACI, diabetes-associated cognitive impairment; DMT1, divalent metal transporter 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, oxidized glutathione; LIP, labile iron pool; LPCAT3, lysophosphatidylcholine acyltransferase 3; NCOA4, nuclear receptor coactivator 4; PERK, PKR-like endoplasmic reticulum kinase; PL-PUFAs, phospholipid-containing PUFAs; PL-PUFA-OH, phospholipid PUFA alcohol; PL-PUFA-OOH, phospholipid PUFA hydroperoxide; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; SLC40A1, solute carrier family 40 member 1; STEAP3, six-transmembrane epithelial antigen of prostate 3; TF, transferrin; TFR1, transferrin receptor 1; TREM1, triggering receptor expressed on myeloid cells 1.

NOX1 (61) and NOX4 (62), are also key contributors to the ferroptotic process.

Role of ferroptosis in DACI. The regulation of ferroptosis can affect DACI through multiple mechanisms, including the modulation of the GPX4/GSH system, iron and ROS metabolism, mitochondrial homeostasis and the NRF2 and PKR-like endoplasmic reticulum kinase (PERK) signaling pathways (Fig. 4).

Steady-state GPX4/GSH system. The metabolic state in DACI significantly affects the activity of the GPX4 antioxidant axis and the sensitivity of cells to ferroptosis. The AMP-activated protein kinase (AMPK) pathway, a key sensor of cellular energy, plays a protective role. AMPK agonists inhibit ferroptosis by activating AMPK, which subsequently upregulates GPX4 expression and downregulates lipocalin-2 expression *in vivo* (63). Additionally, berberine has been shown to protect against high glucose-induced damage to glomerular podocytes by activating the NRF2/HO-1/GPX4 pathway, thereby inhibiting ferroptosis (64).

Iron and ROS metabolism. The diabetic state creates a pro-ferroptotic environment characterized by iron dyshomeostasis (65). Extensive iron deposition is observed in the hippocampus of diabetic models and elevated plasma Fe^{2+} levels correlate with cognitive decline in patients (66,67).

The increased iron levels can catalyze the Fenton reaction, leading to lipid peroxidation. Therapeutic interventions aim to mitigate this iron-induced stress. Erythropoietin has been shown to inhibit ferroptosis by reducing iron overload and lipid peroxidation both *in vitro* and *in vivo* (68). Similarly, the antioxidant liproxstatin-1 can effectively inhibit ferroptosis by attenuating iron accumulation and oxidative stress *in vivo* (63).

PERK signaling pathway and neuroinflammation. Triggering receptor expressed on myeloid cells 1 (TREM1) is a key driver of microglial-mediated ferroptosis in individuals with DACI (69). Under high-glucose conditions, the expression of TREM1 is upregulated, activating the PERK pathway (69). This process leads to the inactivation of antioxidant systems and increased lipid peroxidation and ROS levels, ultimately inducing ferroptosis in microglia and exacerbating neuroinflammation.

Mitochondrial metabolism and homeostasis. Mitochondrial dysfunction is a core feature of DACI (70), contributing to both the ROS production and iron dysregulation that drive ferroptosis. The scaffolding protein Caveolin-1 is crucial for maintaining mitochondrial integrity (71). In diabetic models, Caveolin-1 expression is significantly reduced. Restoring its function via Caveolin-1 overexpression has been shown to inhibit ferroptosis by improving mitochondrial homeostasis, thereby mitigating cognitive decline both *in vitro* and *in vivo* (67).

NRF2 signaling pathway. The transcription factor NRF2 is a master regulator of the antioxidant response and a key target for inhibiting ferroptosis in individuals with DACI. Several compounds have been shown to confer protection by modulating this pathway. Quercetin inhibits ferroptosis by activating the NRF2/HO-1 pathway in models of diabetic nephropathy, a mechanism that is potentially relevant to DACI (72). Berberine also leverages this pathway, activating the NRF2/HO-1/GPX4 axis to suppress ferroptosis (64). Furthermore, vitamin D can inhibit ferroptosis by activating the vitamin D receptor, which in turn upregulates the NRF2/HO-1 signaling cascade, as shown in *in vitro* and *in vivo* models (73).

Summary. Although the initial etiologies of AD, PD and DACI are distinct, they all ultimately converge on the common cell death pathway of ferroptosis. These diseases share several core pathological features: Oxidative stress, neuroinflammation and mitochondrial dysfunction (74). Oxidative stress directly generates ROS to initiate lipid peroxidation (32); neuroinflammation, particularly the activation of microglia, alters iron metabolism and promotes ROS release (44); and mitochondrial dysfunction is a major source of both ROS and the LIP (75). The specific upstream triggers of each disease (such as Aβ, ischemia and hemorrhage) activate these common downstream pathological processes, which in turn are the direct upstream activators of the core ferroptosis machinery (iron overload, lipid peroxidation and antioxidant system depletion). Therefore, ferroptosis is not merely another form of cell death, it acts as a 'central executioner', a common endpoint where diverse neural injury signals converge. This recognition highlights the potential of ferroptosis as a therapeutic target. Theoretically, an effective antiferroptotic agent could possess broad value as a treatment for multiple mechanistically distinct cognitive disorders.

4. Roles of ferroptosis in the diagnosis and prognostic evaluation of cognitive impairment

Given the central role of ferroptosis in the pathological processes of various cognitive disorders, its associated molecules and metabolites hold immense potential as novel diagnostic and prognostic biomarkers. At present, diagnostic tools for neurodegenerative diseases primarily rely on the assessment of late-stage clinical symptoms or costly neuroimaging examinations and lack pathology-based biomarkers that would enable intervention in the early stages of the disease (76). The development of biomarkers that can reflect the state of ferroptosis in the brain is crucial for enabling early diagnosis, assessing disease progression and monitoring therapeutic responses (Table II).

Potential biomarkers in biofluids. Cerebrospinal fluid (CSF) and blood represent two vital biofluids for accessing pathological information regarding the central nervous system. Detecting changes in ferroptosis-related molecules within these biofluids holds promise for the development of minimally invasive diagnostic methods.

Iron metabolism-related proteins. Measuring the levels of iron homeostasis-related proteins in CSF or serum is a direct strategy. For example, multiple studies have shown that the levels of ferritin in the CSF of patients with AD are elevated and this increase is associated with faster rates of cognitive decline and brain atrophy, suggesting that CSF ferritin levels could be a valuable prognostic biomarker (77,78). Urbano *et al* (79) demonstrated that CSF ferritin levels are associated with the conversion from mild cognitive impairment to dementia. Furthermore, CSF iron levels correlate positively with tau protein levels (80). In the BioFINDER cohort study, CSF ferritin levels reaching a threshold value of 12.47 ng/ml predicted cognitive deterioration in patients with mild cognitive impairment (81). Moreover, Apolipoprotein E4 carrier status strengthens the diagnostic association between brain iron content and AD pathology (81). A study also found that patients with PD with substantia nigra hyperechogenicity exhibit significantly lower cognitive function than those without hyperechogenicity; among patients with PD and poorer cognitive function, CSF iron levels are significantly elevated while transferrin levels are significantly reduced (82). Additionally, the levels of transferrin and non-transferrin-bound iron may also reflect the status of iron load in the brain (77).

Lipid peroxidation products. Lipid peroxidation is the key step in the execution of ferroptosis and its metabolites are direct indicators of ferroptotic activity. Malondialdehyde and 4-hydroxynonenal are two major end-products of lipid peroxidation and their elevated levels in CSF or blood have been shown to be correlated with the pathological severity of AD and PD (33,83).

Antioxidant system components. The state of the antioxidant system reflects the capacity of the cell to resist ferroptosis. GSH is central to the GPX4 system and its reduced levels in CSF are closely associated with severe cognitive impairment in patients with AD, suggesting that GSH could serve as a marker for the failure of the brain's antioxidant capacity and the risk of ferroptosis (43).

Table II. Roles of ferroptosis in the diagnosis of cognitive impairment.

Authors, year	Biomarker	Biomarker type	Biofluid/tissue	Association with cognitive impairment	(Refs.)
Li *et al*, 2022	Ferritin	Protein	CSF and serum	Elevated in AD; CSF levels correlate with cognitive decline and brain atrophy.	(152)
Urbano *et al*, 2025	Ferritin	Protein	CSF	Elevated levels correlate with >15% risk of conversion to dementia.	(79)
Urbano *et al*, 2024	Ferritin	Protein	CSF	Positively correlates with tau protein levels.	(80)
Ayton *et al*, 2023	Ferritin	Protein	CSF	Associates with cognitive deterioration in MCI.	(81)
Majerníková *et al*, 2024	GPX4	Protein	Brain	Decreased expression accompanies AD pathological progression.	(86)
Majerníková *et al*, 2024	NCOA4	Protein	Brain	Decreased expression accompanies AD pathological progression.	(86)
Li *et al*, 2022	TF	Protein	CSF and serum	Reduced in patients with AD; reflects altered iron transport status.	(152)
Ko *et al*, 2021	MDA	Metabolite	CSF, serum and brain tissue	Elevated in neurodegenerative diseases; correlated with oxidative stress and ferroptosis activation.	(124)
Yang and Nao, 2023	4-HNE	Metabolite	CSF and brain tissue	Elevated in early AD and MCI; marks neurotoxic lipid peroxidation.	(153)
Sun *et al*, 2024	GSH	Metabolite	CSF and brain tissue	Decreased in AD hippocampus and cortex; correlated with severe cognitive impairment.	(43)
Mesa-Herrera *et al*, 2022	TFR	Protein	CSF	Elevated in patients with MCI vs. healthy controls.	(154)
Mayr *et al*, 2024	TFR	Protein	Brain tissue	Increased on degenerating neurons in AD; serves as potential early ferroptosis marker.	(155)
Ayton *et al*, 2020	Iron	Metabolite	Brain tissue	Correlated strongly with the rate of cognitive decline.	(156)
Shi *et al*, 2023	TFR	Protein	Brain tissue	Reduced in the brain of DACI animal models.	(157)
Yang *et al*, 2018	Iron	Metabolite	Brain tissue	Increased iron deposition in the hippocampus and caudate nucleus.	(158)
Hao *et al*, 2021	SLC40A1	Protein	Hippocampus	Decreased in the hippocampus of type 1 diabetes models.	(159)

AD, Alzheimer's disease; CSF, cerebrospinal fluid; DACI, diabetes-associated cognitive impairment; 4-HNE, 4-hydroxynonenal; GPX4, glutathione peroxidase 4; GSH, glutathione; MCI, mild cognitive impairment; MDA, malondialdehyde; NCOA4, nuclear receptor coactivator 4; PD, Parkinson's disease; SLC40A1, solute carrier family 40 member 1; TF, transferrin; TFR, transferrin receptor.

Genetic and transcriptomic biomarkers. Using high-throughput sequencing technologies, researchers can identify ferroptosis-related molecular markers at the genetic and transcriptomic levels.

FRGs. Through bioinformatics methods, the expression profile of a set of FRGs can be analyzed in patient tissues or peripheral blood cells to construct prognostic models. For example, in AD research, an FRG signature composed of genes such as DNA damage inducible transcript 4, mucin 1 and CD44 was found to not only distinguish patients with AD from healthy controls but also to predict disease severity and immune cell infiltration in the brain (43). Such multigene signatures offer greater robustness and predictive power than single-gene markers.

Single-gene markers. Certain genes that play key roles in the ferroptosis pathway may also serve as independent prognostic indicators based on their expression levels. Measuring the expression levels of genes such as TFRC or SLC7A11 in brain tissue or blood from patients with neurodegenerative diseases could provide clues for assessing ferroptotic activity and disease progression (49).

Imaging biomarkers. Neuroimaging techniques, particularly magnetic resonance imaging (MRI), represent a non-invasive, *in vivo* method for assessing iron deposition in the brain and can serve as an indirect means of evaluating ferroptosis risk. Advanced MRI sequences, such as T2* relaxometry, are highly sensitive to iron deposition. Compared with elderly individuals negative for AD biomarkers, cognitively normal elderly individuals positive for AD biomarkers show significantly higher R2* levels in the caudate nucleus, putamen and globus pallidus, suggesting increased iron content (84). In PD research, this technique can be used to precisely quantify the iron content in the substantia nigra region and has been found to be closely correlated with disease severity and motor deficits (85). This method is useful not only for diagnosis but also for tracking disease progression and evaluating the efficacy of iron-targeted therapies.

Challenges in clinical translation. Although numerous potential biomarkers have been identified, the vast majority are still in the preclinical or early clinical research stages (11). Transforming these research findings into stable, reliable and easily accessible clinical diagnostic tools remains a significant challenge.

Optimal timing of assessment. Given the insidious and progressive nature of neurodegenerative diseases, the utility of a single biomarker measurement is questionable. Early in the disease course, ferroptotic processes may be subtle and localized, potentially yielding false-negative results. Longitudinal monitoring, therefore, represents a more clinically meaningful approach. Tracking the trajectory of changes in a panel of ferroptosis-related markers within accessible biofluids offers greater prognostic value than a single snapshot measurement. This dynamic monitoring is essential for identifying high-risk individuals, tracking disease progression and evaluating therapeutic responses.

Biomarker sources and accessibility. Biomarker sources profoundly impact clinical feasibility. While analysis of postmortem brain tissue is the gold standard for research, it is not relevant for clinical diagnosis. A study on human postmortem brain tissue has revealed that the pathological progression of AD is accompanied by decreased expression of nuclear receptor coactivator 4 and GPX4 in gray matter (86). Meanwhile, research using human brain organoid models has demonstrated that ferroptosis inhibitors (Ferrostatin-1) can block Aβ pathology, reduce lipid peroxidation and restore iron storage function in AD organoids (86).

By contrast, CSF provides a more direct window into central nervous system pathology, yet the invasiveness of lumbar puncture limits its utility for routine screening or frequent monitoring. Consequently, developing biomarkers in easily accessible peripheral biofluids, such as blood, is a key priority. However, this approach faces several challenges, including the potential for the blood-brain barrier (BBB) to mask or dilute CNS-specific signals and the difficulty in distinguishing brain-derived markers from those originating systemically (87,88). In particular, the development of peripheral blood biomarkers that can accurately reflect the state of local ferroptosis within the brain is key and represents a major hurdle for future research. Future research must therefore focus on identifying markers capable of specifically crossing the BBB and on developing ultrasensitive technologies for reliable peripheral detection.

Integrating ferroptosis biomarkers into clinical workflows. A major challenge in translating ferroptosis research from the laboratory to clinical practice is how to integrate ferroptosis biomarkers into current diagnostic pathways for cognitive impairment. A stepwise clinical workflow may provide a practical framework for this translation (Fig. 5).

At the first stage, ferroptosis-related tests could be added to primary care as part of low-cost, population-wide screening. For individuals at increased risk, such as those >65 years of age, with a family history of dementia or with comorbid type 2 diabetes mellitus (T2DM) (89-91), routine blood tests may be expanded to include serum ferritin and transferrin levels. These tests could be combined with simple cognitive assessments, such as the Montreal Cognitive Assessment or the Mini-Mental State Examination (92,93). Individuals who show both mild cognitive changes and abnormal iron metabolism could be flagged as high-risk and referred for specialist evaluation. This approach is affordable and easy to implement, but its specificity is low as ferritin and related markers are affected by inflammation and liver disease (94).

At the specialist evaluation stage, diagnosis could be refined in memory clinics or neurology departments using more specific ferroptosis biomarkers. Key measurements include lipid peroxidation markers such as malondialdehyde and 4-hydroxynonenal, antioxidant defense markers such as GPX4 activity and the GSH/oxidized GSH ratio and advanced MRI-based assessments such as quantitative susceptibility mapping to quantify brain iron deposition (95,96). These ferroptosis markers should be interpreted together with established diagnostic tools, including CSF Aβ42, phosphorylated tau, total tau and Aβ PET imaging (97). Signs of increased ferroptosis activity, when combined with these biomarkers, may improve diagnostic accuracy and help with differential diagnosis. The main barriers at this stage are the lack of standardized laboratory assays and the high cost and limited availability of advanced imaging.

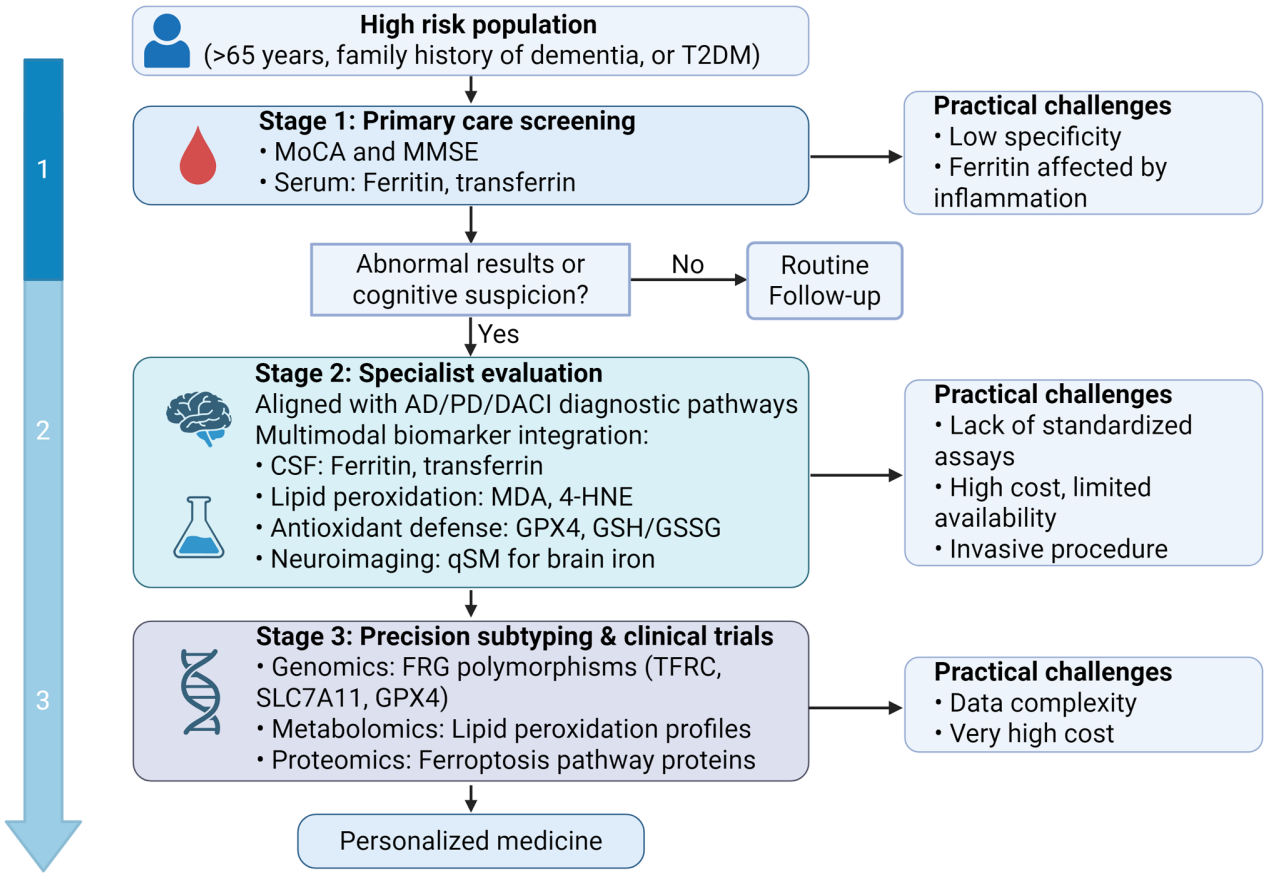

Figure 5. Clinical workflow for ferroptosis biomarkers in cognitive impairment diagnosis. MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; T2DM, type 2 diabetes mellitus; CSF, cerebrospinal fluid; MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; GPX4, glutathione peroxidase 4; GSH/GSSG, reduced/oxidized glutathione ratio; qSM, quantitative susceptibility mapping; AD, Alzheimer's disease; PD, Parkinson's disease; DACI, diabetes-associated cognitive impairment; FRG, ferroptosis-related gene; TFRC, transferrin receptor; SLC7A11, solute carrier family 7 member 11.

The advanced research stage focuses on precision subtyping and clinical trial applications. Multi-omics approaches, such as metabolomics to identify lipid peroxidation profiles and genomics to characterize polymorphisms in ferroptosis-regulating genes, may allow more accurate pathological classification. Although these approaches are currently limited by high cost and complex data processing, they show strong potential for identifying patient groups that may benefit from ferroptosis-targeted treatments.

5. Aging as a key modulator of ferroptosis susceptibility

Advanced age is the most significant non-modifiable risk factor for major cognitive disorders, including AD, PD and DACI (98-100). A compelling body of evidence suggests that the aging process itself fosters a 'pro-ferroptotic' state in the brain, thereby lowering the threshold for neurodegeneration (101,102). This connection is rooted in several age-related physiological changes that directly impinge on the core regulatory axes of ferroptosis.

Physiological aging systematically increases neuronal susceptibility to ferroptosis through the synergistic action of four interconnected mechanisms. First, normal aging is associated with the progressive dysregulation of iron homeostasis, often leading to iron accumulation in vulnerable brain regions such as the hippocampus and substantia nigra (52). This expands the labile, catalytically active iron pool, providing ample 'fuel' to initiate destructive lipid peroxidation via the Fenton reaction. Second, the efficiency of endogenous antioxidant systems decreases with age, a core feature of which is the reduction in the levels of the master intracellular antioxidant, GSH (103,104). As GPX4 is entirely dependent on GSH to neutralize toxic lipid peroxides, the depletion of GSH directly weakens the cell's most critical line of defense against ferroptosis (105). Third, age-related mitochondrial dysfunction is another key contributor. Senescent mitochondria not only produce more ROS due to inefficient electron transport but also exhibit impaired iron-sulfur cluster biogenesis, leading to improper iron handling and accumulation within the mitochondria, thus creating a potent internal source of oxidative stress (106,107). Finally, although the total brain lipid content may decrease with age, the enzymes responsible for incorporating PUFAs into membrane phospholipids remain active, ensuring the continued presence of the necessary substrates for the final execution step of ferroptosis (75).

In summary, age-dependent changes such as increased catalytic iron levels, weakened antioxidant defenses, elevated mitochondrial-derived oxidative stress and sustained membrane vulnerability to peroxidation, collectively place neurons in the aging brain in a fragile state. This underlying vulnerability explains why the pathological triggers of various neurodegenerative diseases can converge on ferroptosis in the

aging brain. Therefore, ferroptosis emerges as a core mechanism that intimately links age, the most universal risk factor, to cognitive decline, the shared pathological outcome.

6. Targeting ferroptosis for the treatment of cognitive impairment

Given the core pathogenic role of ferroptosis in various cognitive disorders, targeting this pathway has emerged as a highly attractive and novel therapeutic strategy. To this end, researchers have developed or screened a range of drugs and compounds capable of inhibiting ferroptosis through various approaches and have validated their neuroprotective effects using various disease models (Table III).

AD. Cognitive impairment in AD is closely associated with disrupted iron homeostasis, excessive oxidative stress and the accumulation of Aβ and tau proteins, which collectively promote ferroptosis. Several natural compounds have been found to be effective at modulating ferroptosis-related pathways to counteract these processes.

A common strategy involves activating the NRF2 signaling pathway, a master regulator of antioxidant responses. For example, ganoderic acid A activates the NRF2/SLC7A11/GPX4 axis (108), whereas saponins derived from *Astragalus membranaceus* act on the NOX4/NRF2 pathway to restore iron balance (109). Lignans from *Schisandra chinensis* activate the NRF2/FPN1 pathway, reducing phosphorylated tau levels and improving cognitive function (110). Similarly, avicularin enhances cognition by modulating NOX4/NRF2 signaling (111) and artemisinin derivatives increase NRF2 activity by targeting its inhibitor kelch-like ECH-associated protein 1 (Keap1) (112).

Some compounds work by directly supporting the GPX4/GSH antioxidant defense system. Thonningianin A, a newly identified ferroptosis inhibitor, activates GPX4 through the AMPK/NRF2 pathway (113). Total lignans from *Schisandra* increase the activity of the NADK/NADPH/GSH system to reduce Aβ deposition (114) and schisandrin B downregulates glycogen synthase kinase 3β (GSK3β) expression to promote NRF2/GPX4 signaling (115). Clinical studies suggest that selenium may help slow cognitive decline (116,117). Reduced selenium levels in the brains of patients with AD are associated with disease progression. In addition, selenium-loaded nanospheres can deliver selenium, an essential cofactor for GPX4, and markedly improve cognition in AD models (118).

Other strategies target molecules other than NRF2 and GPX4. Berberine reduces oxidative damage by inhibiting the JNK/p38 MAPK pathway (119). Neuritin protects against cognitive impairment by activating PI3K/Akt (120), whereas ghrelin mitigates neuroinflammation by acting on the bone morphogenetic protein 6/SMAD1 pathway (121). In addition, tetrahedral framework nucleic acids have been developed to directly neutralize Aβ toxicity and restore synaptic integrity (122).

PD. The degeneration of dopaminergic neurons in PD is fueled by iron overload, mitochondrial dysfunction and oxidative stress, all of which are tightly linked to ferroptosis. Therapeutic strategies have therefore focused on disrupting these pathological cycles.

Iron chelation remains a straightforward intervention. Deferoxamine (DFO) has been shown to preserve dopaminergic neurons in animal models (123). However, the clinical outcomes associated with deferiprone, an oral iron chelator, have been inconsistent. For instance, one trial reported worsening motor symptoms in patients with early-stage PD, highlighting the complexity of iron-targeted therapy (52,60,124).

Several natural compounds activate endogenous antioxidant pathways to increase the resilience of the brain to oxidative stress. Acteoside inhibits ACSL4 (54) while simultaneously activating NRF2 (125). Granulathiazole A reduces α-synuclein accumulation through NRF2/HO-1 activation (126) and betulinic acid improves behavioral outcomes by reducing ROS levels (127). Dingzhen pills, a traditional herbal formulation, inhibit the cyclic GMP-AMP synthase/stimulator of interferon genes pathway to protect dopaminergic neurons (128).

Efforts have also been directed at modulating key proteins in the ferroptosis cascade. γ-aminobutyric acid from *Lactobacillus reuteri* alleviates pathology by activating the Akt/GSK3β/GPX4 axis (129), emodin upregulates the mitochondrial protein ubiquitin-cytochrome C reductase core protein 1 to suppress ferroptosis (130) and corilagin protects neurons by regulating the Toll-like receptor 4/Src/NOX2 pathway (131). Additionally, the inhibition of LRRK2 has been linked to reduced ferroptotic damage via the p62/Keap1/NRF2 axis (132) and teneligliptin, a dipeptidyl peptidase-4 inhibitor, decreases ROS levels and prevents ferroptosis (133).

DACI. Therapeutic interventions for DACI often target the metabolic dysregulation that creates a pro-ferroptotic environment. Several repurposed diabetes drugs and natural compounds have been shown to exert neuroprotective effects by inhibiting ferroptosis. The GLP-1 receptor agonist liraglutide improves cognition by repairing mitochondria and modulating the GPX4/SLC7A11 pathway (134).

Activation of the NRF2 antioxidant pathway is a common strategy. The natural product sinomenine improves cognition by regulating the EGF/NRF2/HO-1 pathway (135). Artemisinin has also been shown to ameliorate cognitive impairment in T2DM mice by activating NRF2 (136). Other compounds work by inhibiting inflammatory signaling; dihydromyricetin alleviates hippocampal ferroptosis by inhibiting the JNK pathway (137).

Other approaches aim to correct the iron and ROS imbalance directly. Erythropoietin has been shown to improve cognition by reducing iron overload and lipid peroxidation in diabetic models (68). Resveratrol inhibits the ability of microRNA-9-3p to upregulate SLC7A11 expression, thereby improving cognition in the context of DACI (138).

7. Conclusions and future directions

Ferroptosis, a distinct form of iron-dependent cell death driven by lipid peroxidation, has emerged as a key pathological mechanism underlying multiple cognitive disorders, including AD, PD and DACI. Preclinical studies have consistently shown that targeting ferroptosis with drugs such as iron chelators, lipid peroxidation inhibitors or NRF2 activators can produce

Table III. Strategies for targeting ferroptosis to treat cognitive impairment.

A, Alzheimer's disease

Authors, year	Drug	Target	Ferroptosis inducer or inhibitor	Biological function	Model	(Refs.)
Clarke *et al*, 2025	SBH	FAC	Inhibit	Alleviates iron-induced death of hippocampal neurons	*In vitro* and *in vivo*	(160)
Ding *et al*, 2025	Schisandrin B	GSK3	Inhibit	Inhibits the activation of GSK3β and regulates the NRF2/GPX4 signaling pathway	*In vitro* and *in vivo*	(115)
Wang *et al*, 2025	ANO6	TMEM30A	Inhibit	Reduces GPX4 and lipid peroxidation	*In vitro*	(161)
Sun *et al*, 2025	Berberine	JNK-p38MAPK	Inhibit	Reduces the expression levels of ROS and lipid peroxide levels	*In vitro* and *in vivo*	(119)
Lu *et al*, 2025	WY118	tau phosphorylation and MAPK	Inhibit	Inhibits ferroptosis	*In vitro*	(162)
Ramesh and Govindaraju, 2025	MiR-7a	Klf4	Inhibit	Targets labile iron levels, GPX4/NRF2 pathways and mitochondrial damage	*In vivo*	(163)
Wang *et al*, 2025	AS	NOX4/NRF2	Inhibit	Restores brain iron homeostasis and lipid peroxidation balance	*In vivo*	(109)
Wu *et al*, 2025	STL	NADK/NADPH/GSH	Inhibit	Reduces Aβ deposition and improves cognition	*In vitro* and *in vivo*	(114)
Lu *et al*, 2025	Ganoderic acid A	NRF2	Inhibit	Activates the NRF2/SLC7A11/GPX4 pathway	*In vitro* and *in vivo*	(108)
Zheng *et al*, 2025	MK886	PRKCI/AKT	Inhibit	Reduces Aβ deposition and improves cognition	*In vitro* and *in vivo*	(164)
Song *et al*, 2025	Neuritin	PI3K/Akt	Inhibit	Enhances NADK activity and improves cognition	*In vitro* and *in vivo*	(120)
Meng *et al*, 2025	Lignans	NRF2/FPN1	Inhibit	Reduces p-Tau and neuronal loss and improves cognition	*In vitro* and *in vivo*	(110)
Guo *et al*, 2025	Ghrelin	BMP6/SMAD1	Inhibit	Inhibits neuroinflammation and improves cognition	*In vitro* and *in vivo*	(121)
Feng *et al*, 2025	Hederagenin	PPARα/NRF2/GPX4	Inhibit	Reduces ROS and lipid peroxidation	*In vitro*	(165)
Tian *et al*, 2025	Catalpol	HSPA5/ GPX4	Inhibit	Improves cognition and reduces Aβ 1-40 and Aβ 1-42	*In vitro*	(166)
Li *et al*, 2024	Avicularin	NOX4/NRF2	Inhibit	Improves cognition	*In vitro* and *in vivo*	(111)
Tan *et al*, 2024	tFNAs	Aβ	Inhibit	Improves cognition	*In vivo*	(122)
Wang *et al*, 2023	CLNDSe	GPX1/4	Inhibit	Improves cognition	*In vivo*	(118)
Yong *et al*, 2024	Thonningianin A	GPX4	Inhibit	Enhances GPX4 via the AMPK/NRF2 pathway	*In vitro* and *in vivo*	(113)
Deng *et al*, 2025	Artemisinin	KEAP1	Inhibit	Improves cognition	*In vitro* and *in vivo*	(112)

Table III. Continued.

A, Alzheimer's disease						
Authors, year	Drug	Target	Ferroptosis inducer or inhibitor	Biological function	Model	(Refs.)
Gong *et al*, 2025	Danggui Shaoyao San	ACSL4	Inhibit	Downregulates ACSL4 expression via the AMPK/Sp1 pathway	*In vivo*	(57)
Gugliandolo *et al*, 2017	Vitamin E	ROS	Inhibit	Reduces oxidative stress	*In vivo*	(167)
B, Parkinson's disease						
Fu *et a*l, 2025	Dingzhen pills	cGAS-STING	Inhibit	Improves movement disorders and promotes the recovery of dopaminergic neurons in the substantia nigra	*In vivo*	(128)
Dong *et al*, 2025	GABA	AKT-GSK3β-GPX4	Inhibit	Alleviates MPTP-induced PD	*In vivo*	(129)
Huang *et al*, 2025	Teneligliptin	ROS	Inhibit	Alleviates MPTP-induced PD	*In vitro* and *in vivo*	(133)
Yusun *et al*, 2025	Emodin	UQCRC1	Inhibit	Upregulates mitochondrial complex III component UQCRC1	*In vitro* and *in vivo*	(130)
Xiao *et al*, 2025	Astragenol	VDR	Inhibit	Improves movement disorders and reduces serum and brain tissue inflammatory factors	*In vitro* and *in vivo*	(168)
Pandey *et al*, 2025	Betulinic acid	ROS	Inhibit	Improves behavioral deficits, restores tyrosine hydroxylase levels and reduces α-synuclein accumulation	*In vivo*	(127)
Wang *et al*, 2025	GDF15	cGAS-STING	Inhibit	Improves Parkinson's symptoms	*In vitro* and *in vivo*	(169)
Liu *et al*, 2025	LRRK2	p62-Keap1-NRF2	Inhibit	Reduces apoptosis of midbrain dopaminergic neurons	*In vitro* and *in vivo*	(132)
Lei *et al*, 2025	Corilagin	TLR4/Src/NOX2	Inhibit	Reduces loss of TH-positive neurons	*In vitro* and *in vivo*	(131)
Lei *et al*, 2024	DFO	Labile iron pool	Inhibit	Alleviates the loss of dopaminergic neurons and behavioral disorders	*In vivo*	(123)
Han *et al*, 2024	Acteoside	NRF2	Inhibit	Improves cognition	*In vitro* and *in vivo*	(125)
Zhao *et al*, 2024	JWA	NCOA4	Inhibit	Ameliorates DA neuron loss	*In vitro* and *in vivo*	(170)
Kong *et al*, 2024	Granulathiazole A	NRF2/HO-1	Inhibit	Reduce accumulation of α-synuclein	*In vitro* and *in vivo*	(126)
Fu *et al*., 2024	Ndfip1	ACSL4	Inhibit	Improves motor dysfunction and antagonizes the loss of dopaminergic neurons	*In vitro* and *in vivo*	(171)

Table III. Continued.

Authors, year	Drug	Target	Ferroptosis inducer or inhibitor	Biological function	Model	(Refs.)
B, Parkinson's disease						
Wang *et al*, 2024	DMF	NRF2	Inhibit	Activates the NRF2 pathway and upregulates downstream antioxidant genes	*In vivo*	(172)
Wang *et al*, 2025	Acteoside	ACSL4	Inhibit	Reduces PUFA incorporation into phospholipids	*In vitro* and *in vivo*	(54)
C, Diabetes-associated cognitive impairment						
Hu *et al*, 2025	Resveratrol	miR-9-3p/ SLC7A11	Inhibit	Improves cognition	*In vitro* and *in vivo*	(138)
Zhao *et a*l, 2025	LP17	PERK	Inhibit	Reduces ROS and improves cognition	*In vitro* and *in vivo*	(69)
Wang *et al*, 2024	Artemisinin	NRF2	Inhibit	Improves cognitive impairment and reduces the loss of hippocampal neurons	*In vivo*	(136)
Wang *et al*, 2023	Dihydromyricetin	JNK	Inhibit	Reduces inflammation and improves cognition	*In vivo*	(137)
Guo *et al*, 2023	Erythropoietin	Iron overload	Inhibit	Improves cognition	*In vitro* and *in vivo*	(68)
Chen *et al*, 2023	Sinomenine	EGF/NRF2/HO-1	Inhibit	Improves cognition	*In vitro* and *in vivo*	(135)
An *et al*, 2022	Liraglutide	GPX4/SLC7A11	Inhibit	Repairs mitochondria and improves cognition	*In vivo*	(134)

ACSL4, acyl-CoA synthetase long-chain family member 4; AMPK, AMP-activated protein kinase; ANO6, anoctamin 6; AS, *Astragalus membranaceus*; Aβ, amyloid-β; BMP6, bone morphogenetic protein 6; cGAS, cyclic GMP-AMP synthase; CLNDSe, double selenium nanosphere; DA, dopamine; DFO, deferoxamine; DMF, dimethyl fumarate; EGF, epidermal growth factor; FAC, ferric ammonium citrate; FPN1, ferroportin 1; GABA, γ-aminobutyric acid; GDF15, growth differentiation factor 15; GPX4, glutathione peroxidase 4; GSH, glutathione; GSK3, glycogen synthase kinase 3; HO-1, heme oxygenase-1; HSPA5, heat shock protein family A (Hsp70) member 5; JNK, c-Jun N-terminal kinase; KEAP1, Kelch-like ECH-associated protein 1; Klf4, Krüppel-like factor 4; LRRK2, leucine-rich repeat kinase 2; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NADK, NAD kinase; NADPH, nicotinamide adenine dinucleotide phosphate; NCOA4, nuclear receptor coactivator 4; Ndfip1, Nedd4 family interacting protein 1; NOX, NADPH oxidase; NRF2, nuclear factor erythroid 2-related factor 2; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PPARα, peroxisome proliferator-activated receptor α; PRKCI, protein kinase C iota; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SBH, salicylaldehyde benzoylhydrazone; SLC7A11, solute carrier family 7 member 11; Sp1, specificity protein 1; STING, stimulator of interferon genes; STL, Schisandra total lignans; T2DM, type 2 diabetes mellitus; tFNAs, tetrahedral framework nucleic acids; TH, tyrosine hydroxylase; TLR4, Toll-like receptor 4; TMEM30A, transmembrane protein 30A; UQCRC1, ubiquinol-cytochrome c reductase core protein 1; VDR, vitamin D receptor.

significant neuroprotective effects. However, translating these promising findings into clinical success remains a formidable challenge.

One of the major pharmacological barriers is the BBB, which restricts the entry of most therapeutic agents into the central nervous system. A number of compounds with robust *in vitro* efficacy, such as DFO and certain natural products, fail to exert therapeutic effects *in vivo* due to their poor BBB permeability (139). Thus, improving drug delivery across the BBB (through molecular optimization or nanotechnology-based delivery systems) is a critical priority.

Target specificity and off-target effects represent other challenges. Iron homeostasis plays dual roles in maintaining normal brain function and contributes to pathology. Broad-spectrum iron chelation, as highlighted by the 'Deferiprone Paradox', risks impairing physiological processes while attempting to block ferroptosis. Similarly, electrophilic NRF2 activators may non-specifically react with other thiol-containing proteins, causing cytotoxicity (140). Future therapeutics must achieve high specificity and ideally be selectively activated under pathological conditions.

A number of currently available ferroptosis modulators also face limitations in drug-like properties, such as poor water solubility, instability and suboptimal pharmacokinetics, which hinder their development into clinically viable agents (141). Improving these characteristics through medicinal chemistry is essential.

Compounding these pharmacological issues is the lack of reliable biomarkers for monitoring ferroptosis in the human brain. In the absence of validated protein, metabolite or genetic markers in CSF or blood, identifying patients most likely to benefit from ferroptosis-targeting therapies, assessing the treatment response or dose adjustment are difficult (9). Most proposed biomarkers are still in the exploratory stage and require rigorous clinical validation.

Several innovative strategies should be prioritized to overcome these obstacles. Nanodelivery systems can facilitate BBB penetration, improve drug solubility and stability, and enable targeted delivery to pathological brain regions (142,143). Combination therapies that integrate ferroptosis inhibitors with other modalities, such as dopamine replacement therapy for PD, anti-Aβ or anti-tau agents for AD and anti-inflammatory drugs for chronic neuroinflammation, may yield synergistic benefits. Personalized medicine approaches that incorporate individual disease stages, genetic profiles and biomarker status are critical for optimizing therapeutic outcomes. Furthermore, mechanistic research is essential to elucidate the unresolved aspects of ferroptosis, including the final molecular executors and the crosstalk between ferroptosis and other cell death pathways, such as apoptosis and autophagy. These insights will inform the discovery of more precise and effective drug targets. At present, the field of ferroptosis is at a critical inflection point, shifting from mechanistic discovery to translational application. While preclinical data highlight its therapeutic potential (74), clinical progress has been slow due to unresolved delivery and diagnostic issues (144). Animal models are indispensable for mechanistic exploration but cannot fully replicate the long-term, multifactorial progression of human neurodegenerative diseases.

Therefore, the future of ferroptosis-targeted therapy depends not only on discovering new inhibitors or inducers but also on solving the core issues of how to deliver the right drug to the right brain region in the right patient and how to reliably monitor ferroptosis in clinical settings. Interdisciplinary collaboration among researchers from the neuroscience, pharmacology, medicinal chemistry and biomarker fields is essential. Without such concerted efforts, the enormous therapeutic promise of ferroptosis modulation may remain confined to the preclinical realm.

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Availability of data and materials

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Authors' contributions

JM and WX provided supervision and assisted with writing and editing. SG conducted the literature search and drafted and compiled the manuscript and created the figures. DK, SF, YL, XY and ZJ provided constructive suggestions for the article and contributed to its design and structuring. JM and WX modified and adjusted the figures, ensuring their accuracy and clarity. All authors have 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 that they have no competing interests.

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