The role of ferroptosis in Alzheimer's disease: Mechanisms and therapeutic potential (Review)

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Abstract. Alzheimer's disease (AD) is a prevalent neurodegenerative disorder characterized by insidious onset and progressive symptom deterioration. It extends beyond a simple aging process, involving irreversible and progressive neurological degeneration that impairs brain function through multiple etiologies. Iron dysregulation is implicated in the pathophysiology of AD; however, the precise mechanisms remain unclear. Additionally, vitamin E and selenium are key in regulating ferroptosis through their antioxidant properties. The present review examined the mechanistic pathways by which ferroptosis contributes to AD, the regulatory roles of vitamin E, selenium, ferrostatin-1, N-acetylcysteine and curcumin, and their potential as therapeutic agents to mitigate neurodegeneration.

Contents

1. Introduction

Alzheimer's disease (AD), the most prevalent form of dementia in the elderly, leads to a gradual decline in cognitive function. It is characterized by memory loss, language difficulty, impaired judgment, mood swings and, in advanced stages, loss of self-care ability (1). Epidemiological data reveals that >50 million individuals worldwide are affected by AD, with age-standardized prevalence of dementia in patients aged >60 is ~5-7% worldwide, making it one of the most expensive and fatal diseases globally (the absolute numbers of deaths have increased by 39%) (2). China has the highest number of patients with AD, with ~9.83 million individuals >60 years old diagnosed with AD (3). While the exact etiology of AD remains unclear, its development is linked to a range of factors, including genetic predisposition, abnormal protein aggregation, neurotransmitter imbalance and neuronal damage (4-6). Chinese Food and Drug Administration-approved treatments for AD include memantine, rivastigmine, galantamine and donepezil (7). In China, treatment recommendations for cognitive symptoms involve cholinesterase inhibitors, glutamate receptor antagonists such as memantine and combination therapy with both classes of drugs. Psychobehavioral symptoms are commonly managed with medications such as atypical antipsychotics and selective 5-hydroxytryptamine receptor agonists (8). The rise of artificial intelligence has led to the increasing use of data mining techniques, with complex network analysis based on graph theory offering a promising approach for clinical application (9,10). Topological indices expedite AD drug discovery by enabling rapid computational screening of compounds. They highlight promising candidates for further testing, bridging computational predictions and therapeutic development. Their integration with multi-omics data and machine learning holds promise for future breakthroughs in understanding and treating AD. Ashraf *et al* (11) employed quantitative structure-property association analysis to explore topological indices and drug properties for AD treatment. The analysis identified key structural features(such as topological indices) associated with drug efficacy, providing valuable insight for the design of more effective AD therapeutics (11). Despite the variety of mechanisms through which current drugs operate, most approved treatments fail to prevent the pathological progression of AD, and often exhibit limited efficacy or notable side effects (12,13). Thus, further research is key to improve understanding of the underlying mechanisms of AD and develop more effective therapies.

Ferroptosis, a distinct form of cell death driven by iron-dependent lipid peroxidation, serves a key role in several biological processes, including development, aging, immune regulation and cancer (14-16). Previous studies suggest that oxidative stress and iron overload contribute to neuronal death in AD (17,18). Iron, an essential trace element for the human body, is involved in numerous physiological functions such as

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erythropoiesis, energy metabolism, muscle function and cell cycle regulation (19). Elevated iron levels in the gray matter of patients with AD have been documented (1), along with dysregulated iron homeostasis and lipid peroxidation, hallmarks of ferroptosis that are implicated in AD pathology (20). Therapeutic strategies targeting ferroptosis to prevent or mitigate organ damage have gained attention (21,22).

2. Ferroptosis

Ferroptosis typically results from disruptions in iron metabolism, lipid peroxidation and decreased glutathione (GSH) levels or inactivation of GSH peroxidase 4 (GPX4) (14). In ferroptotic cells, mitochondria are smaller, with ruffled and reduced cristae and membrane rupture, while non-ferroptotic cells exhibit swollen mitochondria. Vitamin E, ferrostatin-1 (Fer-1) and liproxstatin-1 (Lip-1) inhibit ferroptotic cell death without affecting other cell death pathways (23). The molecular mechanisms underlying ferroptosis primarily involve lipid, iron and amino acid metabolism (Fig. 1). Lipid metabolism is key for ferroptosis, which is driven by the accumulation of lipid peroxides resulting from the oxidation of polyunsaturated fatty acids (PUFAs) (24). Enzymes regulating lipid metabolism serve a key role in ferroptosis during lipid peroxidation. Acyl-CoA synthetase long-chain family member 4, a key enzyme in phospholipid metabolism, facilitates the conversion of PUFAs, such as arachidonoyl and adrenic acid, into PUFA-CoA (25). GSH, synthesized from glutamate, cysteine and glycine via glutamine cysteine ligase and GSH synthetase, serves as the primary antioxidant in mammalian cells. During cellular transport, glutamate and cystine are exchanged between cells through system Xc^-, which is key for GSH synthesis (26). Cysteine, due to its limited intracellular availability, is the rate-limiting precursor in GSH synthesis. System Xc^-, consisting of subunits solute carrier family 7 member 11 (SLC7A11) and SLC3A2, exports glutamate when GSH is consumed in excess (27). Disruptions in iron metabolism lead to pathological conditions, with transferrin-Fe^{3+} complex formation occurring when transferrin binds external Fe^{3+} on the cell membrane, which is subsequently internalized by transferrin receptor 1 (24). Divalent metal transporter 1 mediates release of Fe^{3+} ions from the six-transmembrane epithelial antigen of prostate 3 endosome into the cytosol (28). Ferritin releases Fe^{2+} ions via ferroportin 1. In ferroptosis, free Fe^{2+} interacts with hydrogen peroxide to generate highly reactive lipid peroxides, resulting from the disruption of the balance between ferrous iron absorption, depletion and recycling (29).

3. Ferroptosis and AD pathology

Amyloid (A)β plaques and neurofibrillary tangles (NFTs). Aβ plaque accumulation is a hallmark pathological feature of AD, where abnormal Aβ aggregation disrupts synaptic function and impairs memory (30,31). Aβ, composed of 39-43 amino acids, is cleaved from amyloid precursor protein (APP) (32). APP is a highly conserved protein involved in synapse formation, dendritic growth and neuronal migration (33). Iron facilitates the dissociation of iron regulatory protein (IRP) 1 from the iron-responsive element (IRE) (34). Elevated intracellular iron levels disrupt the IRP/IRE signaling pathway, leading to increased expression of APP (35,36) and Aβ production. Additionally, Fe^{2+} binds to the N-terminal domain of Aβ, destabilizing its helical structure and promoting peptide aggregation by enhancing peptide-peptide interactions (37). Concurrently, τ hyperphosphorylation and its abnormal accumulation, coupled with impaired clearance, lead to the formation of NFTs, further compromising neuronal function. NFT formation is a key pathological hallmark of AD (38-41). Dysregulated iron homeostasis has been linked to τ hyperphosphorylation and NFT development (42). In the cortex and hippocampus of patients with AD, NFTs accumulate in response to increased iron levels (43). Excessive neuronal iron promotes NFT formation via the activation of CDK5 (Cyclin-dependent kinase 5)/P25 complexes and GSK-3β (Glycogen synthase kinase-3 beta) kinase pathways. Fe^{3+} also induces hyperphosphorylated τ aggregation by binding to the histidine residues of τ (44-46).

Microglia activation. Microglia are essential components of the central nervous system (CNS), serving key roles in energy metabolism, synaptic plasticity and ion homeostasis. In addition, microglia serve as resident immune cells, engaging in immune responses with memory-like behavior and maintaining brain homeostasis. During neurodegenerative processes, microglial activation is frequently observed, with increasing evidence suggesting that iron overload and disrupted iron homeostasis contribute to neurodegeneration in AD (47,48). As such, microglia serve a key role in neurological disorder. In response to infection or tissue injury, microglia rapidly adapt to the local environment, undergoing activation that can result in either beneficial or harmful outcomes. Kroner *et al* (49) demonstrated that elevated iron levels in microglia promote phagocytosis and drive a harmful M1 phenotype, which triggers the release of pro-inflammatory factors such as TNF-α, IL-1β, IL-6 and nitric oxide (NO), causing neuronal damage. Similarly, Rao *et al* (50) found that increased intracellular iron disrupts the neuromelanin-iron complex in neurons, releasing free iron ions that damage neurons and lead to neuromelanin leakage. This leakage further activates microglia towards the M1 phenotype, promoting release of neurotoxic agents, including TNF-α and IL-6 (50). Moreover, iron accumulation in activated microglia contributes to iron deposition within the CNS (51,52). In the M1 state, microglia express inducible NO synthase (iNOS), which converts arginine into NO. The resulting NO accumulation exacerbates glutamate-induced neurotoxicity, contributing to neuronal ferroptosis (53).

Oxidative stress and neuronal loss. Ferroptosis, an iron-dependent form of cell death distinct from apoptosis and necrosis, is primarily triggered by oxidative stress, a key pathological process in AD. The accumulation of reactive oxygen species (ROS), a hallmark of oxidative stress, serves a key role in initiating ferroptosis. Oxidative stress affects numerous molecular pathways, including inhibition of the cystine/glutamate antiporter system, decreased expression of GPX4, disruption of iron homeostasis and lipid peroxidation, which is a major driver of ferroptosis activation (54). Excess lipid peroxide accumulation in cells, a key feature of

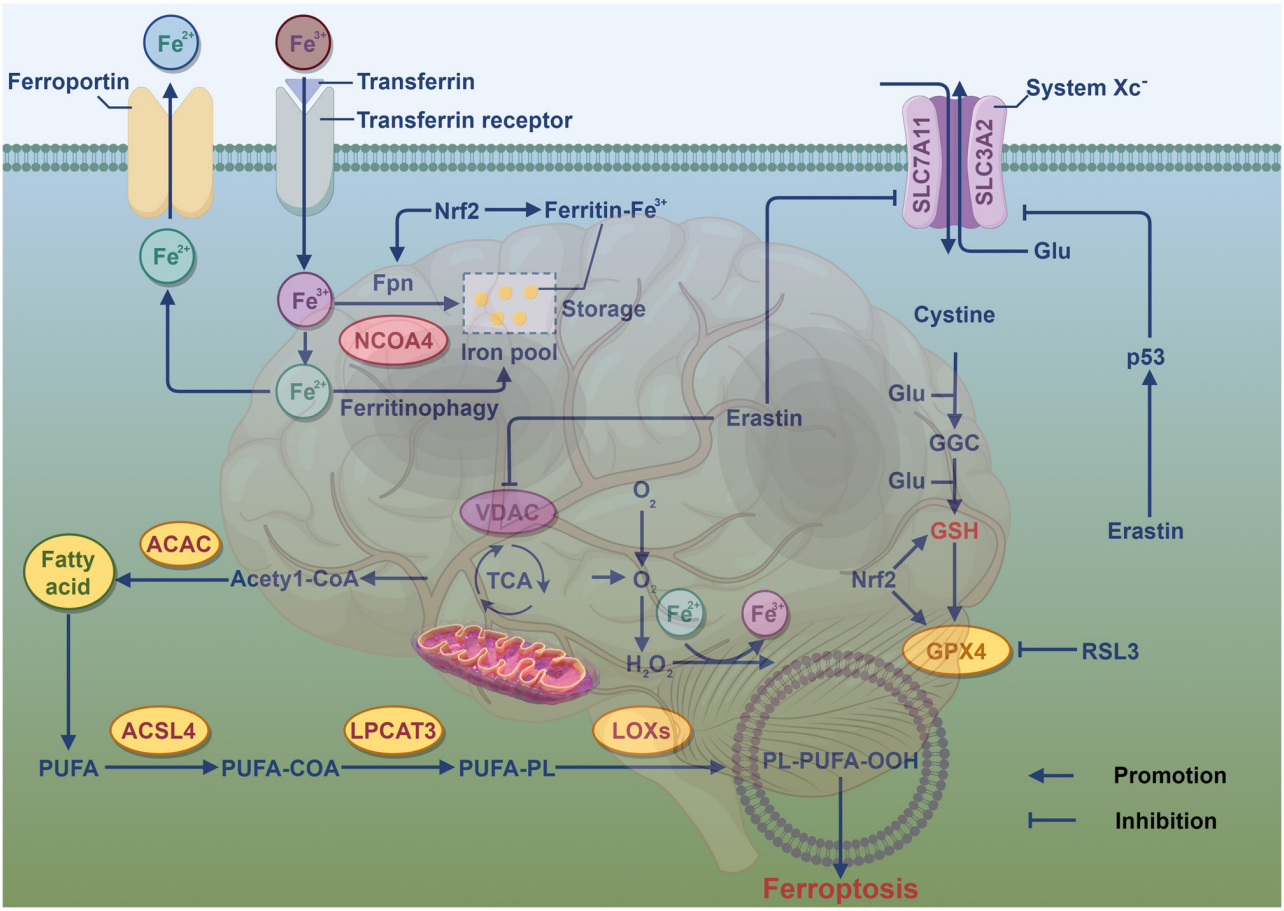

Figure 1. Molecular mechanisms of ferroptosis primarily involve lipid, iron and amino acid metabolism. Made with Figdraw.com. SLC7A11, solute carrier family 7a member 11; GGC, γ-glutamylcysteine; GSH, glutathione; GPX, glutathione peroxidase family; RSL, Ras-selective lethal small molecule; PL-PUFA-OOH, lipid peroxides; TCA, tricarboxylic acid; LOX, lipoxygenase; LPCAT, lysophosphatidylcholine acyltransferase; ACSL, acyl-CoA synthetase long-chain family; ACAC, acetyl-CoA carboxylase; VDAC, voltage-dependent anion channel); NCOA4, Nuclear receptor coactivator 4; Fpn, ferroportin.

ferroptosis, results from a free radical chain reaction. Oxygen radicals insert into the C-H bonds of PUFAs, generating lipid hydroperoxides and elevating levels of ROS, which induce ferroptosis (55). Malondialdehyde, a byproduct of lipid peroxidation, is a marker for both ferroptosis and oxidative stress (56). Furthermore, oxidative stress impairs the antioxidant defense system by decreasing expression of key enzymes such as GSH, catalase, superoxide dismutase and GPX, thus accelerating ferroptosis (56,57). Neuronal loss, a defining characteristic of neurodegenerative disease, is associated with cognitive decline in AD (58). Elevated iron levels promote ROS production, depleting intracellular GSH levels and accelerating lipid peroxidation. This cascade leads to ferroptosis, contributing to neuronal death (59). Bao *et al* (60) found downregulation of the ferroptosis regulator GPX4 in both $Fpn^{fl/fl/NEXcre}$ (NEX-Cre mice were mated with Fpn-floxed (Fpnfl/fl) mice to generate conditional $Fpn^{fl/fl/NEXcre}$ mice.) and APPswe/PS1dE9 (Carrying genetically modified mice with AD-related mutations: a chimeric mouse/human APP with the Swedish mutation and human PSEN1 lacking exon 9) mouse models compared with controls. Additionally, mRNA expression of iron response element binding protein 2, encodes a master regulator of iron metabolism), and CS (citrate synthase, regulating the mitochondrial fatty acid metabolism) was upregulated in both models, while ACSF2 ((acyl-CoA synthetase family member 2, regulating the mitochondrial fatty acid metabolism) was upregulated only in APPswe/PS1dE9 mice. These findings suggest that ferroptosis is activated in the hippocampus of both mouse models.

4. Pathways regulating ferroptosis in AD

Kelch-like ECH-associated protein 1 (Keap1)/Nrf2)/antioxidant response element (ARE) pathway. In cellular defense against oxidative stress, the Keap1/Nrf2/ARE signaling pathway regulates the expression of various proteins involved in detoxification and antioxidant defense, positioning it as a potential target for AD treatment (61). Nrf2, a transcription factor that is highly responsive to oxidative stress, serves a key role in mitigating lipid peroxidation and ferroptosis (62). Under physiological conditions, Keap1 suppresses Nrf2 by facilitating its ubiquitination and degradation via the ubiquitin-proteasome system. By contrast, during oxidative stress, Nrf2 dissociates from Keap1, translocates to the nucleus, forms a heterodimer with small musculoaponeurotic fibrosarcoma oncogene homolog proteins and binds to ARE, thereby enhancing the transcription of antioxidant genes (63-65). Nrf2 regulates key components of anti-ferroptotic pathways, positioning it as a central modulator of lipid peroxidation and ferroptosis (62). In the nucleus, Nrf2 induces the expression

of cytoprotective genes that mitigate ferroptosis by regulating iron metabolism and enhancing antioxidant defenses. This includes the upregulation of ferritin heavy and light chain, ferroportin, transferrin receptor and heme oxygenase-1 (HO-1), alongside increased production of NADPH, GSH and CoQ10 (coenzyme Q10) which counter lipid peroxidation and suppress ferroptosis (66,67). Moreover, the detachment of the DLG motif of Nrf2 from Keap1 prevents its ubiquitination and degradation, thus strengthening antioxidant defenses and inhibiting ferroptosis (68).

p53/SLC7A11 pathway. This process is initiated when unsaturated FAs in cell membranes undergo catalytic lipid peroxidation, driven by divalent iron or esteroxygenases, leading to cell death (69-71). The p53 protein, a key human tumor suppressor, regulates the expression of oncogenes and downstream signaling pathways, contributing to biological effects (72-75): Beyond its role in cancer, p53 is highly expressed in the brain, where it influences dendritic growth, oxidative stress response, apoptosis and autophagy, making p53 dysfunction and associated pathways noteworthy in the pathogenesis of AD (76-78). SLC7A11, a key ferroptosis regulator, is a transmembrane protein that is part of the system Xc^-, responsible for cystine import into cells for cysteine synthesis and GSH production (79,80). Downregulation of SLC7A11 disrupts cysteine metabolism, leading to decreased intracellular cystine and GSH levels, impairing GPX4 activity and triggering lipid peroxide accumulation and ferroptosis (79,81,82). Studies indicate that p53 binds the SLC7A11 promoter, suppressing its expression and limiting GSH production, thereby promoting ferroptosis (83,84). Aristolochic acid, mediated by p53, may limit ferroptosis in liver cancer to enhance tumor growth. The p53(3KR) mutant, lacking acetylation due to lysine-to-arginine substitutions at three residues, decreases expression of SLC7A11 without affecting other p53 targets such as CDKN1A/p21 (involved in cell cycle progression) or BAX (involved in apoptosis). By contrast, the p53(4KR98) mutant, with an additional lysine 98 substitution, does not downregulate SLC7A11 (85-87).

GSH/GPX4 pathway. In AD, excessive lipid peroxide accumulation is a key initiator of ferroptosis, with elevated markers of lipid peroxidation observed in neurons. Iron accumulation drives the Fenton and Haber-Weiss reactions, generating ROS that induce lipid peroxidation, leading to oxidative damage to subcellular structures (88). GPX4 and GSH are key regulators of ferroptosis. GSH, containing a thiol group derived from cysteine, serves as a vital antioxidant, neutralizing ROS and reactive nitrogen species, maintaining cellular redox balance and detoxifying xenobiotics (89). GPX4, a selenium (Se)-dependent enzyme, relies on a Se-containing amino acid residue to execute its reductive function (90). It converts lipid hydroperoxides into less harmful lipid alcohols, preventing oxidative damage (91,92). The active site of GPX4, selenocysteine, alternates between reduced and oxidized states to sustain its catalytic activity. In the presence of peroxides, the selenolate form of GPX4 is oxidized to selenic acid, which is regenerated to its active form by two molecules of reduced GSH, converting lipid hydroperoxides into non-toxic lipid alcohols and generating oxidized GSH (16,92-94). This highlights the key role of GPX4 synthesis and its associated pathways in the regulation of ferroptosis.

5. Ferroptosis inhibitors and AD

Given the mechanisms underlying ferroptosis in AD, researchers have focused on its inhibition as a potential therapeutic strategy. Growing evidence suggests that targeting ferroptosis may offer benefits for CNS disorders, driving the development of effective inhibitors (24,95). This approach presents promising therapeutic opportunities for AD management (Table I; Fig. 2). As AD is characterized by iron accumulation in brain cells, exacerbating oxidative damage and cognitive decline (96-100), these inhibitors show therapeutic promise. Vitamin E, Se, Fer-1, N-acetylcysteine (NAC) and curcumin exhibit antioxidant and neuroprotective properties (101-131).

Vitamin E. Vitamin E, an antioxidant in AD treatment, inhibits ferroptosis primarily by preventing lipid peroxidation (101). It consists of two subclasses: Tocotrienols and tocopherols, with four saturated analogs (α, β, γ and δ) (132,133). These lipophilic compounds, along with their derivatives, serve as radical-trapping antioxidants, preventing the formation of phospholipid hydroperoxides. As the dominant form in tissue, α-tocopherol exerts its antioxidant effects by interrupting the chain reaction of lipid oxidation. Specifically, the oxidative conversion of α-tocopherol produces α-tocopherol quinone, which is reduced to α-tocopherol hydroquinone. This reduction is key for inhibiting the enzymatic activity of 15-lipoxygenase, primarily by converting its non-heme Fe^{3+} to an inactive Fe^{2+} state. This inhibition disrupts the ferroptotic signaling cascade, effectively preventing lipid peroxidation and mitigating ferroptosis (106). α-tocopherol transfer protein (TTP), which is abundant in the brain, regulates α-tocopherol levels and distribution (107). Vitamin E or TTP deficiency induce oxidative stress in the brain. Studies show that patients with AD exhibit reduced vitamin E levels in plasma, serum and cerebrospinal fluid, and those receiving vitamin E supplementation experience slower cognitive decline and decreased oxidative stress compared with placebo-treated individuals (101,108). These findings suggest that vitamin E deficiency contributes to neurodegeneration, while supplementation may offer protection against ferroptotic stress.

Se. Se, an essential trace element involved in GPX4 synthesis, is incorporated into several proteins in the body (109). Known for its antioxidant properties, Se also serves a role in inhibiting ferroptosis (102,110). Clinical studies suggest Se may have potential in mitigating cognitive decline (111,134). In a mouse model of stroke, intracerebroventricular sodium selenate treatment elevates GPX4 levels by activating transcription factors activating enhancer binding protein 2γ and specificity protein 1, while also providing protection against excitotoxicity and endoplasmic reticulum stress-induced cell death independent of GPX4 (102). Decreased Se levels in the brains of patients with AD are associated with disease progression. In primary neuronal cultures, Se was shown to decrease Aβ production by downregulating 4-hydroxy-2-nonenal-induced β-secretase transcription, thus preventing Aβ-associated toxicity (102).

Table I. Ferroptosis inhibitors and their mechanisms.

First author/s, year	Subject	Mechanism	(Refs.)
Hinman *et al*, 2018	Vitamin E	Inhibits ferroptosis by inhibiting lipid peroxidation	(106)
Ashram *et al*, 2020			(107)
Gugliandolo *et al*, 2017			(101)
Kryscio *et al*, 2017			(108)
Conrad *et al*, 2020	Selenium	Antioxidant activity; inhibits ferroptosis by upregulating GPX4	(109)
Alim *et al*, 2019			(102)
Ingold *et al*, 2018			(110)
Cardoso *et al*, 2017			(111)
Dixon *et al*, 2012	Ferrostatin-1	Prevents the accumulation of lipid reactive oxygen species, inhibits oxidative stress and decreases lipid peroxidation	(27)
Skouta *et al*, 2014			(112)
Li *et al*, 2017			(103)
Fang *et al*, 2019			(113)
Miotto *et al*, 2020			(114)
Asano *et al*, 2017			(115)
Kalyanaraman *et al*, 2022	N-acetylcysteine	Activates Nrf2; controls the expression of metallothionein, ferritin and iron transporter	(116)
Fan *et al*, 2017			(117)
Kerins *et al*, 2018			(118)
Rojo de la Vega *et al*, 2018			(119)
Hara *et al*, 2017			(120)
Pocernich *et al*, 2000			(121)
Koppal *et al*, 1999			(122)
Pocernich *et al*, 2001			(123)
Dodson *et al*, 2019	Curcumin	Decreases expression levels of GPX4 and increase levels of HO-1 and Nrf2	(62)
Prasad *et al*, 2014			(124)
Wei *et al*, 2022			(125)
Hirata *et al*, 2019			(126)
Ikawa *et al*, 2021			(104)
Hirata *et al*, 2021			(127)
Hirata *et al*, 2022			(128)
Friedmann Angeli *et al*, 2014	Liproxstatin-1	Decreases oxidative stress and blocks lipid peroxidation	(129)
Li *et al*, 2022			(130)
Fan *et al*, 2021			(131)

GPX4, glutathione GSH peroxidase 4; HO-1, heme oxygenase-1.

Se-containing compounds inhibit ferroptosis by upregulating GPX4. A clinical trial demonstrated that oral sodium selenate supplementation increases brain Se levels without notable side effects, and participants with improved Se levels do not exhibit worsening Mini-Mental State Examination scores over time (108). However, Kryscio *et al* (108) revealed that both Se and vitamin E have adverse effects on progression of AD in male patients. Thus, current evidence does not definitively support a potential therapeutic role of Se in AD, and further clinical trials are needed to clarify its effects.

Fer-1. Fer-1, the first synthetic ferroptosis inhibitor, has served as a pivotal reference compound (27). It effectively prevents oxidative lipid damage and cell death in disease models, including Huntington's disease, periventricular leukomalacia, renal dysfunction, cerebral hemorrhage and cardiomyopathy (103,112,113). As a highly specific ferroptosis inhibitor, Fer-1 surpasses phenolic antioxidants in its ability to suppress ferroptosis, particularly by inhibiting lipid ROS accumulation induced by erastin or RSL3 in HT-1080 human fibrosarcoma cells) (27). The anti-ferroptotic action of Fer-1 primarily arises from its capacity to scavenge alkoxyl radicals and reactive species generated by ferrous iron in lipid hydroperoxides. Additionally, it reduces labile iron, as confirmed by calcein fluorescence assays, further supporting its iron-complexing properties (114). In HT-22 (mouse hippocampal neurons

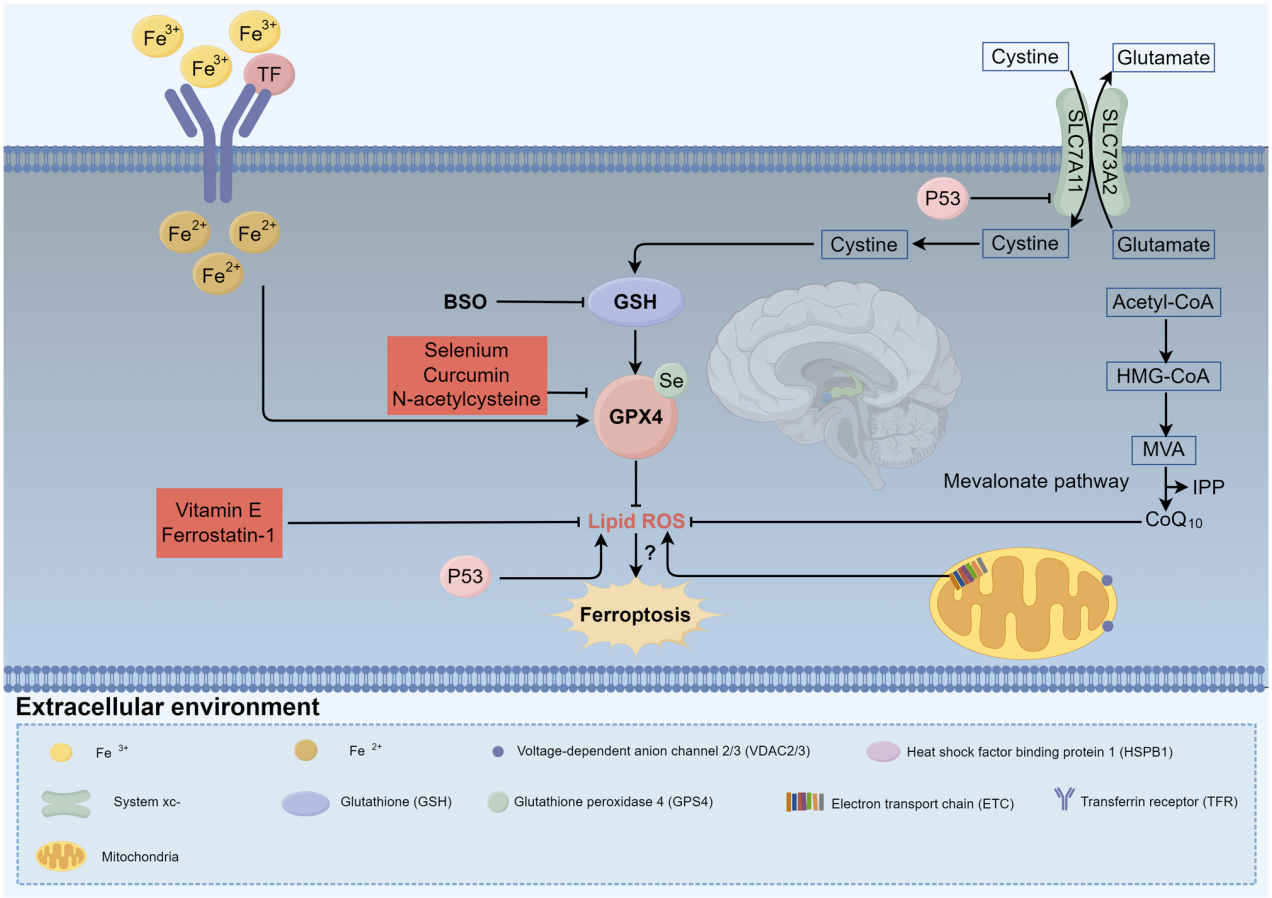

Figure 2. Potential ferroptosis inhibitors in the treatment of Alzheimer's disease. Made with Figdraw.com. SLC7A11, solute carrier family 7a member 11; HMG, 3-hydroxy-3-methylglutaryl; MVA, mevalonate; IPP, isopentenyl pyrophosphate; CoQ_{10}, coenzyme Q10; ROS, reactive oxygen species; GSH, Glutathione; GPX, glutathione peroxidase family; BSO, buthionine sulfoximine; TF, transferrin.

cells) cells, Fer-1 notably decreases both cytoplasmic and lipid ROS levels, counteracts glutamate-induced suppression of GSH and GPX activity and protects against oxidative toxicity. Furthermore, Fer-1 mitigates oxidative stress by downregulating prostaglandin endoperoxide synthase 2 while upregulating GPX4 and Nrf2, thereby decreasing lipid peroxidation (115). Despite its documented efficacy *in vitro* and *in vivo* in alleviating oxidative stress and preventing iron deficiency, Fer-1 remains untested in clinical trials (114). Further investigation is required to assess its therapeutic potential, safety and clinical effectiveness for treating AD.

NAC. NAC, a cysteine precursor, is used to treat acetaminophen overdose and is listed as an essential medicine by the World Health Organization (116). In addition to its role in treating acute poisoning, NAC is recognized for its pro-neurogenic and neuroprotective effects in neurodegenerative and psychiatric disorder (120). NAC can cross the blood-brain barrier and mitigate age-associated memory decline (117,120). NAC may prevent ferroptosis by activating Nrf2, which regulates the expression of metallothioneins, ferritins and ferroportins, thereby preventing iron accumulation. Other Nrf2-dependent genes, including GPX4, GSH and NADPH synthesis genes, as well as epigenetic regulators of lipid hydroperoxides, contribute to its ferroptosis-inhibitory effects (117-119). In AD, NAC has potential as a GSH precursor, enhancing antioxidant defenses (120). Rat and gerbil studies have demonstrated that intraperitoneal NAC administration protects against oxidative damage induced by acrolein, peroxynitrite, hydroxyl radicals and 3-nitropropionic acid while increasing GSH levels in the brain and synaptosomes (119-123).

Curcumin. Curcumin, a polyphenolic compound initially identified as diferuloylmethane in turmeric rhizomes, has demonstrated protective effects against oxidative damage resulting from iron accumulation in cells (124). Curcumin treatment has been shown to decrease expression of GPX4 while increasing levels of heme-oxygenase (HO-1) and Nrf2 (124). As a key regulator of oxidative stress, Nrf2 governs the expression of ARE-dependent genes (62,125). Hirata *et al* (126) developed hybrid molecules that combine the oxidized indole structure of neuroprotective agents with the polyphenolic structure of curcumin, applying them to mouse hippocampal HT22 cells. These hybrids exhibited superior neuroprotective effects and lower cytotoxicity compared with curcumin alone, activated ARE, chelated ferrous ions and scavenged ROS, thereby protecting cells from oxidative stress and ferroptosis, ultimately promoting neuronal survival (104,127,128).

Lip-1. Lip-1, a derivative of quinoxaline spirocyclic compounds, is a potent ferroptosis inhibitor first identified in 2014 through small molecule compound library screening (129). Lip-1

primarily exerts its effects by inhibiting lipid peroxidation. Li *et al* (130) demonstrated that Lip-1 alleviates memory deficits in a mouse model of lipopolysaccharide (LPS)-induced cognitive impairment. Moreover, Lip-1 reduced microglial activation and the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α, while mitigating oxidative stress, lipid peroxidation, mitochondrial damage and neuronal injury following LPS exposure. Further studies have revealed that Lip-1 not only prevents mitochondrial lipid peroxidation but also restores the expression of key molecules involved in ferroptosis regulation, including GSH, GPX4 and ferroptosis suppressor protein 1 (135,136). These findings suggest that GPX4 inhibition may induce ferroptosis in oligodendrocytes, with Lip-1 serving as a potent ferroptosis antagonist. Therefore, Lip-1 holds promise as a therapeutic candidate for CNS disease (131).

6. Conclusion

Research on iron-lowering strategies in AD has been limited, likely due to the predominant focus on amyloid-lowering treatments, which have generally yielded unfavorable results (137,138). Nevertheless, studies involving iron chelators in cell and animal models of AD have demonstrated promising outcomes (95,139). While iron metabolism and lipid peroxidation trigger ferroptosis under pathological conditions, the precise mechanisms remain incompletely understood and warrant further investigation. Additionally, iron chelating agents, including chloroiodohydroxyquine and its derivatives, as well as antioxidants, have shown efficacy in animal models of AD, though clinical trials are yet to be conducted (27,106,116). Ferroptosis may serve as a key target pathway for advancing AD treatment strategies.

In conclusion, the present review summarized the role of ferroptosis in the pathology of AD and how mechanisms such as iron metabolism disorders, lipid peroxidation and GSH depletion lead to neuronal damage, as well as the role of ferroptosis inhibitors such as vitamin E, Se and Fer-1 as potential therapeutic strategies. Keap1/Nrf2/ARE, p53/SLC7A11 and GSH/GPX4 signaling pathways underlie the pathological mechanism of AD, positioning them as a potential direction for future research.

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Authors' contributions

HZ and ZJ wrote and reviewed the manuscript. 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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