Ferroptosis in neurodegenerative diseases: inhibitors as promising candidate mitigators

R.-F. ZHANG, M. ZENG, N. LV, L.-M. WANG, Q.-Y. YANG, J.-L. GAN, H.-H. LI, B. YU, X.-J. JIANG, L. YANG

School of Integrative Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China

R.-F. Zhang and M. Zeng contributed equally to this work and share first authorship

Abstract. – **Ferroptosis is a new form of iron-dependent programmed cell death, characterized by intracellular iron overload and lipid peroxidation. Several studies have revealed that ferroptosis is associated with the occurrence and development of various neurodegenerative diseases (NDs). Therefore, this paper reviews the mechanism and related genes of ferroptosis, focusing on the research of antiferroptosis drugs in NDs to provide theoretical support for future experimental research and clinical application.**

This work focuses on ferroptosis, and the authors searched the literature on PubMed related to ferroptosis using the keywords "neurodegenerative diseases" and "neurons". All articles were from August 2022 and earlier, excluding irrelevant or retracted articles, and articles from the last five years were used as the main inclusion criteria.

After collection and summary, it was found that ferroptosis in NDs was not only related to iron metabolism, lipid metabolism, and amino acid metabolism but also related to genes such as Nrf2, FSP1, VDACs, and p53. We also summarized drugs that inhibited ferroptosis in NDs and classified them according to their mechanism of action.

Ferroptosis was involved in the progression of NDs through its production mechanism and related genes. Targeting ferroptosis might be a new strategy for treating NDs.

Key Words:
   Ferroptosis, Neurodegenerative diseases, Iron metabolism, Lipid metabolism.

Introduction

Programmed cell deaths (PCDs), such as apoptosis, autophagy, programmed necrosis, and pyroptosis, are active and orderly phenomena of cellular self-destruction under gene regulation[1]. Besides determining organism development, PCD regulates the removal of damaged or undesirable cells, an organism's evolution, and the stability of a cell's internal environment[2]. It follows that PCD is diverse in its forms and carries a considerable deal of biological significance. However, PCD dysfunction has also been associated with various diseases, including neurodegenerative diseases (NDs)[3]. As a unique iron-reliant form of PCD, ferroptosis, first proposed by the Dixon team in 2012[4], differs from the other forms of PCD in terms of morphology and biochemistry[5]. From morphological aspects, ferroptosis is characterized by smaller mitochondria with fewer mitochondrial cristae[6], an increase in mitochondrial membrane density, and a rupture of the mitochondrial outer membrane without visible alterations to the nucleus[7]. From biochemical aspects, ferroptosis is characterized by excessive iron-dependent lipid peroxidation[8]. There is ongoing research[9-14] showing that several compounds or drugs can induce ferroptosis, such as erastin[9], lapatinib[10], RAS-selective lethal 3 (RSL3)[11], haloperidol[12], and piperlongumine[13], while the others inhibit ferroptosis, such as baicalein, deferoxamine (DFO), and ferrostatin-1 (Fer-1)[14]. Some recent studies[15] have linked ferroptosis to several genes, such as nuclear factor erythroid 2-related factor 2 (*Nrf2*), glutathione peroxidase 4 (*GPX4*), ferroptosis suppressor protein 1 (*FSP1*), *p53*, voltage-dependent anion channel (*VDAC*), NADPH oxidase 4 (*NOX4*), lipoxygenase (*LOX*), and acyl CoA synthase long-chain family member 4 (*ACSL4*), which are primarily involved in the iron metabolism pathway, lipid metabolism pathway, and the amino acid metabolism pathway.

Various diseases are also associated with ferroptosis[16-20], such as NDs[21]. Stroke, brain injury

Corresponding Authors: Xijuan Jiang, MD; e-mail: xijuanjiang@foxmail.com
Lin Yang, MD; e-mail: yanglin@tjutcm.edu.cn

(BI), and epilepsy are acute NDs[22], while chronic NDs include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS)[22]. Progressive neurological impairments resulting from neuronal cell death and loss commonly manifest in NDs[23]. Ferroptosis has been associated with various NDs[24]. First and foremost, iron accumulation in the brain, a prerequisite for developing neural ferroptosis, can be observed in patients with NDs such as AD[25] and PD[26]. Neural cells are susceptible to oxidative damage because of their high metabolism and low antioxidant defenses. As a result, excessive iron accumulation catalyzes the reactive oxygen species (ROS) formation through the Fenton reaction, resulting in neuronal damage[27]. Second, high levels of polyunsaturated fatty acids (PUFAs) are prevalent in the brain, resulting in lipid peroxidation as the main form of neuronal oxidative damage[28]. In addition, low activity of gpx4 and glutathione (GSH) was found in motor neuron degeneration, which is closely associated with ferroptosis[29]. Taken together, inhibiting neuronal ferroptosis offers new therapeutic targets for NDs. Therefore, this review aims to summarize the mechanisms of ferroptosis and its closely related genes, then focuses on anti-ferroptosis drugs in NDs and categorizes them by mechanisms of action to provide theoretical support for future experimental research and clinical applications.

Mechanisms of Ferroptosis and its Targeted Drugs

Free Iron Accumulation and Iron-Targeted Ferroptosis Inhibitors

As one of the most abundant essential and traceable elements in the human body, iron exists as ferrous iron and ferric[30]. Physiologically, iron is obtained from foods and primarily absorbed by the duodenum and upper jejunum through transferrin receptor 1 (TfR1)-mediated endocytosis of transferrin (Tf)-iron (III) (Fe^{3+}) complexes[31], and distal jejunal absorption of iron is possible in iron-deficient conditions[32]. Ferric is then converted to ferrous iron by the ferrireductase six-transmembrane epithelial antigens of prostate 3[33] and released into the cytoplasmic labile iron pool (LIP) divalent metal-ion transporter-1 (DMT1)[34]. It is also essential to maintain iron homeostasis through intracellular iron export. As the iron export protein, ferroportin (FPN) transports ex-

cessive ferrous iron from cells into plasma *via* its interaction with hepcidin[35]. Ceruloplasmin then oxidizes ferrous iron to ferric, binds to Tf in the plasma, and engages in the intracellular iron cycle again[36]. Ferrous iron overload occurs when there is an imbalance in the iron metabolism, causing the Fenton reaction (ferrous iron and hydrogen peroxide interaction) to form hydroxyl radicals (·OH, the most toxic ROS)[37]. A final consequence of ROS interacting with PUFA on lipid membranes is the generation of lipid ROS and lipid peroxides, leading to ferroptosis[38]. There is a large amount of evidence that abnormal iron accumulation in the brain contributes to various NDs[39]. For example, in early-onset AD patients, significant variations of iron distribution were observed and reflected the pattern of brain atrophy[40]. Further, an obvious iron overload in deep gray nuclei was found in an atypical presentation of AD, which helped to identify this condition[40]. Note that an intracellular iron overload can occur prior to developing senile plaques and neurofibrillary tangles (NFTs)[41]. A study[42] conducted on patients with PD, the second most common ND after AD, found that iron levels increase with the disease progression. An autopsy and neuroimaging study[43] revealed elevated iron levels exclusively in the substantia nigra (SN) in patients with PD. Similarly, the iron overload resulting from chronically administering ferric citrate induces PD-like phenotypes in middle-aged mice[44]. There has also been evidence[45] of increased iron levels in the basal ganglia of humans with manifest HD. Moreover, an iron overload following intracerebral hemorrhage (ICH) has been observed in both patients and animal models and has been linked to excessive ROS production around the hematoma[46]. An iron overload can be linked to NDs, including its key manifestations and pathogens.

Various iron homeostasis genes, such as heat shock protein family B (small) member 1 (*HSPB1*)[47], *Nrf2*[48], and nuclear receptor coactivator 4 (*NCOA4*)[49] are involved in ferroptosis. For example, *HSPB1* (also called *HSP27*) negatively regulates TfR1, the portal for iron uptake, and is a marker of ferroptosis[50,51]. The role of *HSPB1* in iron metabolism cannot be ignored either, as its phosphorylation blocks cytoskeleton-mediated iron absorption, leading to ferroptosis resistance[52]. Besides TfR1, *HSPB1* slightly induces ferritin heavy chain 1 (*FTH1*) expression[53], promoting the conversion of ferrous ions into ferric for storage in ferritin, thereby decreasing the free iron levels and inhibiting ferroptosis[54].

Using different behavioral tests[55,56], it was found that the overexpression of hspb1 ameliorates the symptoms of AD in APP/PS1 mice[55] as well as decreases the intracellular iron level in murine cells[56]. Moreover, a double transgenic mouse model overexpressing *APPswe* and *HSPB1* produced similar results[57]. There is evidence that the decrease in hspb1 in ALS patients will result in motor neuron death, which may be avoided by overexpressing hspb1[58]. Additionally, high-fat-diet-exacerbated PD animal models demonstrated decreased phosphorylation of hsp27 in the SN[59]. Therefore, NDs were strongly linked to *HSP27* abnormalities in these studies[55-59].

Considered a major regulatory factor for antioxidant resistance, Nrf2 is also a transcriptional regulator of *FTH1*, regulating iron metabolism against NDs[60,61]. For example, in PD and AD patients, the Nrf2 expression is altered in neurons, astrocytes, and in the brain of HD or stroke patients, respectively[62]. Similarly, the activation of Nrf2 inhibited neurodegeneration in several AD model mice[63]. Furthermore, there is a decreased expression of fth1 in PD model mice compared to that in healthy mice. In contrast, Nrf2 increases the expression of fth1 and enhances the iron storage capacity, thereby reducing susceptibility to ferroptosis in PD-associated PC12 cells[43]. Despite this, however, there is little evidence that Nrf2 influences ferroptosis through *FTH1*-mediated iron metabolism in NDs.

Nuclear receptor coactivator 4 (NCOA4), a ferritinophagy-specific cargo receptor, facilitates the transportation of *FTH1* to the autophagosome, where ferritinophagy occurs, and releases free iron into the cytosol[64]. Thus, overexpression of *NCOA4* promotes ferritin degradation and results in ferroptosis, while the genetic inhibition of *NCOA4* exerts the opposite effect[65]. For example, the reduction of fth1 levels promotes ferroptosis in PD models *in vivo* and *in vitro*, whereas the overexpression of fth1 suppresses ncoa4 expression, thus suppressing ferroptosis[66]. Furthermore, enhanced *NCOA4*-mediated ferritin (ferritinophagy) by dexmedetomidine protects HT-22 cells from neurotoxicity in a model of chemotherapy-induced cognitive dysfunction[67]. ALS has also been linked to iron ferritinophagy mediated by *NCOA4*, which can play a major role in the disease[68]. By increasing ncoa4 expression and reducing fth1 levels, formaldehyde can cause formaldehyde-related NDs[69]. Interestingly, overexpression and knockdown experiments have revealed that autophagy-related Beclin1 induces ferroptosis by

increasing the free iron levels[70]. Not only this but a significant decrease in Beclin1 levels was also observed in AD patients[71], so the relationship between Beclin1 and ferroptosis deserves further investigation in NDs. Furthermore, Tal-Beclin1, a Beclin1 activating peptide, is depicted to promote the ferroptosis induced by erastin, a small molecule inducer of ferroptosis *in vivo* and *vitro*[70]. As the only known cellular iron exporter, FPN knockout also causes increased iron-dependent ROS and ferroptosis, suggesting its anti-ferroptosis properties[72]. In the PD model, the reduction of FPN resulted in SN iron aggregation, thereby triggering an increase in iron-dependent ROS in neurons[73]. Meanwhile, the up regulation of FPN can decrease iron loading and ameliorate neuronal death after ICH[74]. Similar results were also observed in the models of AD[75] and early brain injury after subarachnoid hemorrhage[76]. In summary, iron metabolism involves multiple links, such as uptake, transport, storage, and export, and any disturbance in these links may lead to iron homeostasis imbalance and even ferroptosis. To prevent ferroptosis, it is, therefore, effective to regulate iron metabolism-related genes.

Current evidence[77] suggests that iron chelators, such as DFO, deferiprone (DFP), and ciclopirox olamine (CPX), can decrease the intracellular iron overload by binding ferrous iron, stimulating its excretion, preventing the generation of highly reactive ROS, and then inhibiting ferroptosis. For example, DFO can rescue iron overload-induced ferroptosis triggered by ferric ammonium citrate (FAC) in neuron-like PC12 cells by reducing iron levels[78]. Furthermore, DFP is used as an oral hydroxypyridinone-derived iron chelator for treating thalassemia, Friedreich's ataxia, and kidney disease in clinical practice[79]. According to the literature, DFP can also inhibit ferroptosis in the ketamine-sevoflurane-induced general anesthetic (GA) model by chelating iron as well as inhibiting the DMT1 expression[80]. Interestingly, the use of sevoflurane and ketamine in GA for surgery affects the iron metabolism[80], contributing to a postoperative cognitive decline in the elderly[81]. Thus, ferroptosis is linked to cognitive impairment in older people following anesthesia, and DFP is a candidate for its therapy. CPX is a broad-spectrum antifungal agent identified to functionally chelate intracellular iron[82]. It is well known that glutamate excitotoxicity is often observed in several NDs, such as stroke[83]. Studies[4] have reported that CPX can inhibit ferroptosis by reducing iron ions and ROS in glutamate-induced

organotypic hippocampal slice cultures (OHSC). Moreover, Baf-A1, a ferritinophagy inhibitor, can block fth1-mediated ferroptosis by inhibiting ferrous iron, ncoa4, lipid peroxidation levels, and excessive GSH consumption in a neurotoxin 6-hydroxydopamine (6-OHDA)-induced PD model[66]. In light of the above, the role of iron chelators in inhibiting ferroptosis has been gradually discovered. To make definitive conclusions, however, further research is needed.

Lipid Peroxidation and Lipid Peroxidation-Targeted Ferroptosis Inhibitors

Lipids are the major components of cell membranes and organelle membranes, helping to maintain their integrity and molecular exchange functions[84]. However, it is well established that lipids are susceptible to peroxidation through enzymatic or non-enzymatic processes[85]. PUFA-containing phosphatidylethanolamine (PE) is more vulnerable to lipid peroxidation, particularly arachidonic acid (AA) and adrenal acid (ADA)[86]. It is true that the oxidation of lipids is a free radical-driven chain reaction, where reactive ROS begins the oxidation of PUFAs[87]. Non-enzymatic lipid peroxidation occurs when the ROS generated by the iron-dependent Fenton reactions oxidize the membrane phospholipids resulting in a lipid ROS accumulation[88]. Under iron accumulation conditions, Fenton chemistry significantly initiates NDs, such as AD, PD, and HD, by promoting free radical formation in cells[89]. A possible explanation for iron accumulation in the central nervous system (CNS) during NDs is inflammatory cells migrating into the affected areas and depositing iron there[89]. Somewhat differently, enzymatic lipid peroxidation is mediated by multi-enzymatic reactions. First, *ACSL4* catalyzes the conversion of AA or ADA to AA-CoA and ADA-CoA[90] and is in turn esterified into AA-PE and ADA-PE by lysophosphatidylcholine acyltransferase 3 (LPCAT3)[91], and lastly oxidized by LOX, particularly arachidonate lipoxygenase (ALOX) to the harmful lipid peroxidation product PE-AA-OOH or PE-ADA-OOH[92]. Lipid peroxides, once abundant, destroy the membrane bilayer and amplify their damage by reacting with the adjacent polyunsaturated lipids, thus causing ferroptosis[93]. In this manner, delaying lipid peroxidation will be effective in inhibiting ferroptosis. There is no doubt that lipid peroxidation has been

identified as a pathological marker in almost all NDs, such as AD[94], PD[95], and ALS[96]. In this context, the role of LOX in NDs is becoming more evident. For example, in AD models, the activation of LOX in microglia produces large amounts of ROS and causes enzymatic lipid peroxidation that affects microglia function[97]. Consequently, ferroptosis inhibitors counteracting lipid peroxidation hold many promises in treating NDs, including radical-trapping antioxidants (RTAs), NOX inhibitors, and LOX inhibitors.

Some RTAs, such as liproxstatin-1 (Lip-1), Fer-1, edaravone, tetrahydronaphthyridinols (THN), 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), phenothiazine, mitoquinone (MitoQ), BI-6c9, and resveratrol can inhibit ferroptosis by scavenging oxygen free radicals. For example, Lip-1 has been displayed to inhibit the RSL3-induced rat oligodendrocyte cell line (OLN-93) ferroptosis in a spinal cord injury (SCI) model by scavenging oxygen free radicals[98]. Fer-1, an inhibitor of ferroptosis, produced a similar outcome in a collagenase-induced ICH model[99]. A non-phenolic antioxidant, edaravone, acts as a powerful agent to improve neurological functions in disease conditions[100]. It was found that edaravone attenuates hippocampal neuronal ferroptosis by the activation of the silent information regulator 2 homolog 1 (Sirt1)/Nrf2/heme oxygenase-1 (*HO-1*)/GPX4 pathway in the chronic social defeat stress (CSDS) depression model mice[101]. As an RTA, THN, particularly lipophilic C12 THN, is highly effective against glutamate-induced ferroptosis in the hippocampal HT-22 cell line[102]. Furthermore, TEMPO[103] and phenothiazine[104] can inhibit ferroptosis in NDs by exploiting their ability to scavenge free radicals. The gasified form of TEMPO inhibits not only glutamate-induced ferroptosis in HT-22 cells but also protects neuronal cells from middle cerebral artery occlusion (MCAO) model-induced injury in CB-17 mice[103]. Phenothiazine, particularly it is derivative 51[104], as a diarylamine radical-trapping antioxidant, inhibits ferroptosis in an MCAO-induced ischemic stroke SD rat model by increasing GSH expression and reducing lipid peroxidation levels[.] MitoQ is a mitochondria-targeted ROS scavenger, and some experiments have demonstrated that mitoQ reverses RSL3-induced ferroptosis in an HT-22 brain ischemia model by inhibiting mitochondrial ROS production and then reducing the RSL3 toxicity[105]. BI-6c9, a pro-apoptotic protein Bid inhibitor, also plays a unique role in inhibiting ferroptosis. It has been demonstrated that BI-6c9

reverses the mitochondrial impairment caused by the mitochondrial transactivation of Bid by scavenging mitochondrial ROS and finally reverses the RSL3-induced ferroptosis in HT-22 cells[106]. A polyphenol found in many plants, resveratrol, is a potential therapeutic agent for NDs[107]. Like Fer-1, it inhibits (OGD/R)-induced ferroptosis in primary cortical neurons by its powerful antioxidant effect, as well as in MCAO-induced SD rats and RSL3-induced primary cortical neurons[108]. According to the abovementioned studies[98-108], RTA can inhibit ferroptosis and improve neuron survival in several NDs models, particularly ICH and stroke.

As ROS is mainly generated by NADPH oxidase (NOX)[109], its inhibitors, such as diphenyleneiodonium chloride (DPI) and GKT137831, help inhibit ferroptosis by reducing ROS production[110]. For instance, paraquat and maneb co-exposure cause dopaminergic neurodegenerative disorders as well as ferroptosis in the neuroblastoma cellular line SHSY5Y. DPI and GKT137831, as an inhibitor of nox, have some significant adverse effects on the abovementioned phenomenon by increasing the gpx4 levels and decreasing the intracellular MDA content[111]. In addition, vildagliptin (vilda), originally acting as a selective DPP-4 inhibitor, exerts neuroprotective effects in NDs by inhibiting oxidative stress[112] and potently inhibits ferroptosis by blocking the DPP-4-mediated nox activity in the ICH model[113].

LOX inhibitors [e.g., vitamin E, baicalein, zileuton, and N-acetylcysteine (NAC)] can resist ferroptosis by inhibiting LOX-mediated lipid peroxidation. There is an increased expression of LOX enzymes in stroke, AD, epilepsy, and ICH models, such as 15-lipoxygenase (15-LOX), 5-LOX, and ALOX[114-116]. Treatment of NDs by inhibiting LOX enzymes is another exciting prospect. Natural lipophilic antioxidant vitamin E is considered an adjunctive treatment for epilepsy, particularly in children[117]. Further studies[118] have depicted that it inhibits pentylenetetrazol-induced neuronal ferroptosis in epileptic rats by suppressing the 15-LOX-mediated overoxidation of PUFAs. Baicalin, derived from the root of *Scutellaria baicalensis Georgi*[119], has shown neuroprotective effects in posttraumatic epilepsy (PTE)[116]. Its treatment increases the gpx4 content by decreasing the 12/15-LOX levels, thereby reducing the FAC-induced lipid peroxidation in the HT-22 cell PTE model and further inhibiting ferroptosis. An effect consistent with this can also be observed in an *in vivo* model of $FeCl_3$-induced epilepsy[116]. Zileuton is an inhibitor of 5-LOX that

has pharmacologically demonstrated benefits in treating AD[120]. In addition to this, Zileuton can attenuate oxidative stress by inhibiting the LOX5 expression, thereby protecting HT-22 cells from glutamate-induced ferroptosis[121]. Several chronic neurological disorders, including AD, have been demonstrated[122] to benefit from NAC, a cysteine prodrug. According to recent studies[123], NAC inhibits ferroptosis by blocking the production of toxic lipids through ALOX in a heme-induced primary cortical neuronal ICH model.

There is a critical link between lipid peroxidation and acsl4, which is the target of rosiglitazone (ROSI)[124] and paeonol (PAN)[125]. ROSI is a proliferator-activated receptor gamma (PPARγ) agonist that has been shown to have neuroprotective effects in various NDs[126]. ROSI reduces lipid peroxidation levels and protects neurons from ferroptosis after an ischemic stroke by inhibiting acsl4[127]. PAN is a natural product isolated from *Paeonia Lactiflora pall*[128] that inhibits ferroptosis in an ICH model *in vivo* and *in vitro*. For example, in ICH model mice, PAN alleviated neuronal ferroptosis by suppressing the expression of acsl4[125], which could be degraded by direct binding to upf1. Moreover, the overexpression of LncRNA HOX transcript antisense RNA reversed the protective effect of PAN on the neurons through the UPF1/ acsl4 axis[125]. Consistent with this, in hemoglobin-induced primary cortical neurons or HT-22 cells, PAN was observed to protect neuronal cells from iron death through similar mechanisms[125].

Additionally, fatty acid synthesis is the upstream pathway that triggers ferroptosis[129]; therefore, drugs can inhibit ferroptosis by inhibiting fatty acid synthesis. For example, the transaminase inhibitor AOA can inhibit ferroptosis by silencing acyl-CoA synthase family member 2 (acsf2), thereby regulating the upstream of ferroptosis[4]. Interestingly, phase contrast images reveal that AOA treatment also blocks glutamate-induced ferroptosis in HT-22 cells[130].

Collectively, targeting lipid peroxidation-targeted ferroptosis inhibitors is a promising way to treat NDs. Research results obtained in a laboratory and a fundamental understanding of ferroptosis inhibitors counteracting lipid peroxidation lay the groundwork for clinical trials.

Amino Acid Metabolism Disorder and Their Related Ferroptosis Inhibitors

System Xc⁻ cystine/glutamate antiporter is widely distributed in the phospholipid bilayer[131] and works as an important component of the

antioxidant system[132]. In the brain, system Xc⁻ is expressed at the blood-brain barrier as well as throughout the brain parenchyma[133]. By regulating the production of GSH as described below, system Xc⁻ stimulates many ROS-dependent pathways[134]. First, cystine is taken up by system Xc⁻ in exchange for glutamate at a 1:1 ratio[135]. Upon introduction into cells, cystine converts to cysteine for the synthesis of GSH[136], which is the only substrate of gpx4 in mammals that eliminates lipid-based ROS[137]. In particular, gpx4 converts lipid peroxides into nontoxic lipid alcohols by oxidizing GSH to glutathione disulfide, blocking the lipid peroxidation chain reaction and thus playing a critical role in maintaining cellular redox homeostasis[138]. In a substantial body of literature, the amino acid metabolism disorder has been linked to NDs, and the system Xc⁻, as well as the GPX4 proteins, has been proposed as the molecular therapeutic target[139]. For instance, GSH levels are reduced in AD, which limits the activity of GSH-dependent enzymes, such as GPX4, leaving neurons vulnerable to oxidative stress damage[140]. According to a post-mortem study[141] on PD, reduced GSH levels and GSH depletion were found in the SN, which might be the first indicators of oxidative stress during the disease process. The results were similar for other NDs as well. Simultaneously, the inhibition of system Xc⁻ affects the glutamate release[142]; excess glutamate has neurotoxic effects, can overstimulate nerve cells and cause death[143]. For example, high glutamate concentrations have been detected in the cerebrospinal fluid of AD patients[144]. In addition, neuronal death due to the excitotoxicity of glutamate can be observed in various diseases, such as PD[145], ALS[146], and stroke[147]. Taken together, the inhibition of system Xc⁻ increases the impaired glutamate release and a decrease in GSH, and the low activity of GSH-dependent GPX4, leading to the accumulation of lipid ROS, lipid peroxides, and glutamate, ultimately leading to ferroptosis[148].

There are many chemosynthetic drugs that can inhibit ferroptosis by system Xc⁻ and up-regulating gpx4, such as 2-amino-5-chloro-N, 3-dimethylbenzamide (CDDO), dopamine (DA), β-mercaptoethanol (β-ME), sodium selenite (SS), idebenone, ebselen, and pioglitazone (PDZ). The triterpenoid CDDO blocks the gpx4 degradation by inhibiting the expression of heat shock protein 90, gpx4's chaperone protein, thus protecting the HT-22 cells from glutamate or erastin-induced ferroptosis[149]. The neurotransmitter DA blocks the degradation of gpx4 in HT-22 cells, thereby exerting a similar effect as CDDO[130]. A commonly used reducing agent in experiments, β-ME, bypasses the system Xc⁻ restricted by glutamate induction to provide cysteine for the GSH synthesis, thereby inhibiting HT-22 cell ferroptosis[102,150]. In SCI mice injected with SS, a common form of selenium, neurological recovery was observed by up regulating the SP1/GPX4 pathway, thus avoiding neuronal and oligodendrocyte ferroptosis after SCI[151]. Idebenone is a synthetic coenzyme Q10 (CoQ10) analog that is regularly used in the clinical treatment of AD[152]. Recent studies[153] showed that idebenone reduces lipid peroxidation levels and inhibits neuronal ferroptosis in a rotenone-induced PD rat's model by up-regulating gpx4. Moreover, ebselen, a potent glutathione peroxidase mimetic and neuroprotective agent, exhibited antiferroptosis by increasing gpx4 in erastin or RSL3-induced N27 neuronal cell models[154,155]. PDZ is a PPARγ agonist with potent neuroprotective effects in various NDs[156-158]. Both *in vivo* and *in vitro* ICH models revealed that the PDZ activated PPARγ and enhanced its antioxidant effects in concert with nrf2 while increasing the expression of nrf2 and gpx4-mediated ferroptosis suppressor genes[159].

Similarly, some natural drugs can inhibit ferroptosis by increasing the GPX4 expression, such as carvacrol (CAR), galangin, glycyrrhizin (GL), ginkgolide B (GB), paeoniflorin (PF), and forsythoside A (FA). For example, carvacrol, a monoterpenoid found in many aromatic plants, is neuroprotective[160,161]. In gerbils, CAR reduces lipid peroxidation by up-regulating gpx4, thus inhibiting neuronal ferroptosis after ischemia/reperfusion (I/R)[162]. Galangin is the main component of the natural medicine galangal that has neuroprotective and antioxidant properties[163,164]. Some studies[165] have found that galangin enhances the antioxidant capacity of neurons, thus inhibiting ferroptosis after I/R injury by activating slc7a11/gpx4. GL is a triterpenoid saponin extracted from licorice that is useful in AD, ICH, and so on[166]. As a consequence of inhibiting the HMGB1 translocation dependent on ROS, GL elevates the GPX4 expressions in neonates with OGD-induced I/R brain injury and prevents the ferroptosis of cortical neurons due to oxidative stress[167]. Among the main components of ginkgo biloba, GB, has neuroprotective effects in AD, stroke, and other brain diseases[168,169]. In SAMP/8 mice (a model of AD), it activates the Nrf2/GPX4 pathway, enhancing the antioxidant capacity against ferroptosis[170]. PF is a water-soluble monoterpene glycoside extracted from the root of *Paeonia Lactiflora*, which has been used in treat-

ing neurodegenerative diseases[171]. For example, in a 1-methyl-4-phenylpyridinium (MPP)-induced PD model of primary dopaminergic neurons, PF exerts its neuroprotective effect against ferroptosis by increasing the GPX4 expression through the regulation of the protein kinase B (Akt)/Nrf2/GPX4 pathway[172]. FA is a natural drug with various pharmacological properties, including anti-inflammatory, antioxidant, and neuroprotective properties, and is found in large quantities in *Forsythia suspensa*[173]. There is now proof that FA protects erastin-exposed HT-22 cells from ferroptosis in AD models by targeting the activation of the Nrf2/GPX4 pathway[174].

Moreover, some drugs, such as curcumin, gastrodin (GAS), tetrahydroxy stilbene glycoside (TSG), alpha-lipoic acid (LA), and salidroside inhibit ferroptosis in NDs by activating nrf2-related signaling and up-regulating gpx4 or system Xc⁻. For example, curcumin, a natural antioxidant compound extracted from the plants of the *Zingiberaceae* and *Araceae* families, is a promising neuroprotective agent[175]. Several studies[176] have reported that curcumin nanoparticles activate the Nrf2/HO-1 pathway to enhance the antioxidant capacity of erastin-induced HT-22 cells, avoiding ferroptosis after ICH. GAS, a major component of *gastrodia elata*, plays a similar role in glutamate-induced HT-22 cells *through* the Nrf2/HO-1 pathway[177]. There is promising evidence that TSG, an extract of another natural medicine, *polygonum multiflorum*, helps treat AD[178]. In an APP/PS1 transgenic AD mouse model, TSG intervention increased the GPX4 expression by activating the kelch-like ECH-associated protein 1 (Keap1)/Nrf2/antioxidant responsive element (ARE) pathway and inhibited neuronal ferroptosis[179]. The universal antioxidant and iron chelator LA is known to be beneficial in inhibiting ferroptosis[180]. In a PD model induced by MPP, LA decreased the ferrous iron levels and ROS, thereby inhibiting ferroptosis by activating the phosphoinositide 3-kinases (PI3Ks)/Akt/Nrf2 pathway[181]. Salidroside is a natural drug that has been reported to have potential therapeutic value in neurodegenerative diseases[182]. Salidroside also exerts neuroprotective effects by activating the Nrf2/HO-1 pathway to attenuate neuronal ferroptosis in Aβ1-42-induced AD mice and gluconate-exposed-exposed HT-22 cells[183].

Taken together, multiple drugs have been developed and tested in recent years with potential activity against ferroptosis, particularly by regu-

lating system Xc⁻ and GPX4. Note that the results of this study are based on laboratory research, but no clinical confirmation has been obtained (Table 1).

Ferroptosis-Related Genes

Nrf2

As is well known, Nrf2 is the master transcriptional regulator of the antioxidant gene expression that plays a critical role in the antioxidant response in cells[184]. Under normal physiological conditions, Keap1 binds to and retains Nrf2 in the cytoplasm, preventing its nuclear translocation[185]. In contrast, upon exposure to oxidative stress, the Nrf2-Keap1 complex is disrupted, and subsequently, Nrf2 is released and translocated to the nucleus[186]. This process is regulated by the autophagy receptor p62 that binds to Keap1 and then promotes the activation of Nrf2[187]. In the nucleus, Nrf2 binds to the antioxidant response elements and promotes the expression of antioxidant genes, such as *HO-1*, to counteract oxidative stress[188], as well as many ferroptosis-related genes such as *SLC7A11*, *GPX4*, and *FTH1*[189-191]. Several studies[192] have reported that Nrf2 has emerged as an important target for NDs because of its role in neuronal resistance to oxidative stress and glutamate-induced excitotoxicity and, finally, in maintaining neuronal survival in neurological injury. For example, it has been reported that Nrf2 expression is significantly reduced in the hippocampal neurons of AD patients[193]. The same decrease can be observed in many NDs, such as PD[194] and ALS[195]. Furthermore, the Nrf2 agonists EPI-743 and sulforaphane inhibit oxidative stress and ferroptosis by increasing the nuclear translocation of Nrf2 in the fibroblasts of Friedreich's ataxia patients[196]. Therefore, Nrf2 has been widely viewed as the primary therapeutic target of NDs. (Figure 1).

FSP1

A study[197] in 2019 discovered that FSP1, also called apoptosis-inducing factor mitochondria-associated 2 (AIFM2, or PRG3), can inhibit ferroptosis independently of GSH. As a cotranslational lipidic modification, FSP1 is targeted to the plasma membrane through myristoylation, where it decreases CoQ10 to create ubiquinol through the FSP1/CoQ10 pathway. Known as a lipophilic antioxidant, ubiquinol traps radicals, halting lipid peroxidation and finally inhibiting ferroptosis[198].
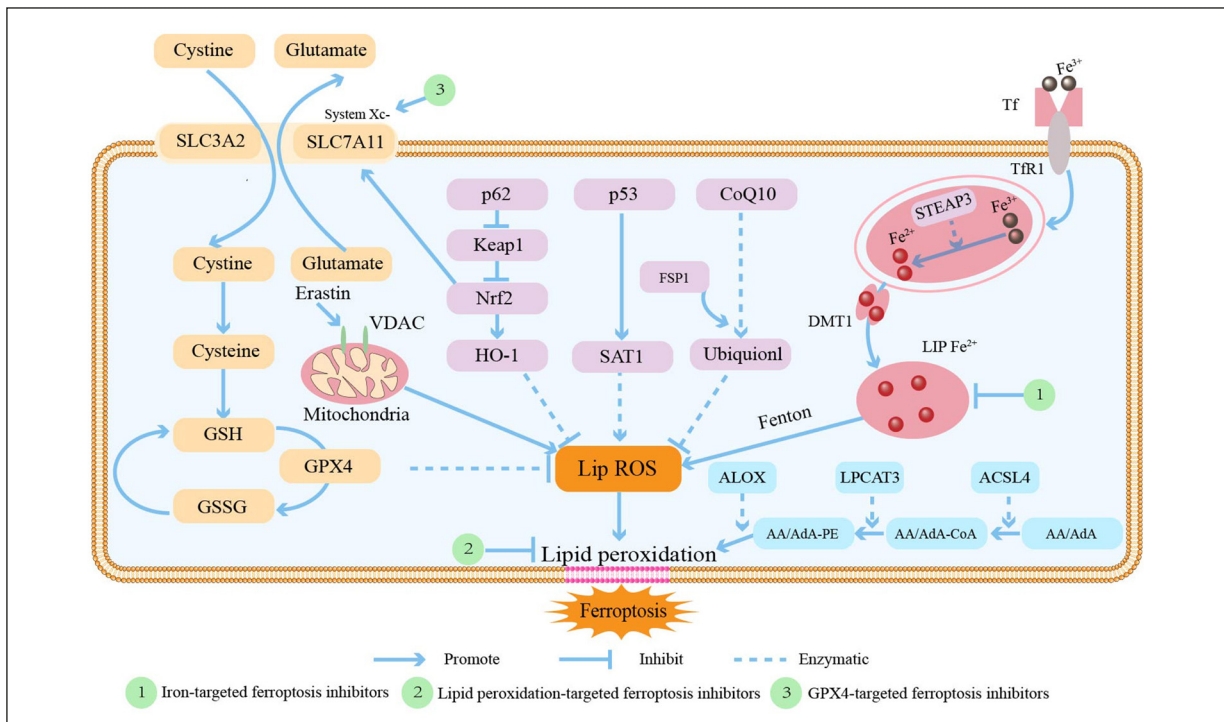
Figure 1. Overview of the mechanism of ferroptosis.

Interestingly, ferroptosis is related to FSP1 in brain disorders[199], which is also a potential neuroprotective target against ferroptosis in the models of neonatal hypoxic-ischemic brain injury, acute spinal cord injury, and PD[200-202]. For example, FSP1 was up-regulated, and ferroptosis was observed in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mice models. Apoferritin prevents MPTP-induced ferroptosis partly by inhibiting the downregulation of FSP1[203]. In general, the role of FSP1 in NDs is still in its infancy, and in-depth research is needed.

VDACs

VDACs are the most abundant proteins in the mitochondrial outer membrane in their three isoforms: VDAC1, VDAC2, and VDAC3[204]. VDAC, an ion channel protein, can regulate the exchange of metabolites, ions, and ATP between mitochondria and cytoplasm[205]. Erastin, as a ferroptosis activator, binds to VDAC2/3 and promotes its opening, generating hyperpolarization in the mitochondria, increasing ROS production, and eventually triggering ferroptosis[206]. Meanwhile, high levels of glutamate in HT-22 cells up-regulate the VDAC protein expression, resulting in a loss of the mitochondrial membrane poten-

tial, increased ROS production, and ATP consumption, finally leading to ferroptosis[206]. While 4,4'-diisothiocyanatostilbene-2,2'-disulfonate as a VDAC inhibitor can decrease mitochondrial ROS levels and effectively inhibit cell death[206]. In other words, VDACs are involved in ferroptosis occurrence and development and can be a potential target for its intervention.

p53

Tumor suppressor p53 is a transcription factor that plays a key role in regulating cell cycles[207]. In response to DNA damage, p53 engenders cell-cycle arrest, senescence, and apoptosis, which constrains cell growth[208]. Additionally, p53 increases the spermidine/spermine N1-acetyltransferase 1 (SAT1) expression, a rate-limiting enzyme in polyamine catabolism, facilitating the decomposition of polyamine spermine, which functions as a free radical scavenger[209,210]. As a result, a p53-induced overexpression of SAT1 results in the peroxidation of lipids and ferroptosis by accelerating the decomposition of polyamine spermine[211]. SAT1 also produces a significant amount of hydrogen peroxide during the polyamine decomposition process, ultimately leading to ferroptosis that can be rescued by the ferro-

Table I. Common ferroptosis inhibitors.

Drugs	Model	Dose	Mechanism or pathway of action	Signal	Refs.
DFO	FAC-induced PC12-NGF cell PD model	Unknown	Iron chelator	GPX4, FTH1 ↑ DMT1, TfR1, FPN, ACSL4, ROS ↓	[78]
DFP	Ketamine-and sevoflurane-induced-hippocampal neuronal GA model	100 μM	Iron chelator	GHS, SOD2 ↑ DMT1, MDA, ROS ↓	[80]
CPX	Glutamate-induced OHSC	5 μM	Iron chelator	ROS ↓	[4]
Baf-A1	6-OHDA-induced PC12 cell PD model	100 nM	Autophagy inhibitor	GPX4, FTH1 ↑ NCOA4 ↓	[66]
Lip-1	RSL3-induced OLN-93 cell line SCI model	1 μM	RTA	GPX4, GSH, FSP1 ↑ MDA, ROS ↓	[98]
Fer-1	Collagenase-induced C57BL/6 mouse ICH model Hb-induced OHSC ICH model	*In vivo*: 1 pmol of Fer-1 *In vitro*: 10 μM	RTA	MDA,4-HNE, ROS, PTGS2 ↓	[99]
Edaravone	C57BL/6J mouse CSDS model	10 mg/kg	RTA	GSH, SOD, GPX4, GSH-PX, Nrf2, HO-1 ↑ MDA, ROS ↓	[101]
C12-THN TEMPO	Glutamate-induced HT-22 cells MACO-induced CB-17 mouse stroke model Glutamate-induced HT-22 cell stroke model	100 nM *In vivo*: 0.1-g cotton soaked in 5-mL tempo *In vitro*: 10 μL	RTA RTA	ROS ↓ ROS, 4-HNE ↓	[102] [103]
Phenothiazine derivative 51	MCAO-induced SD rat stroke model	0.01, 0.1, 1 μM	RTA	GSH ↑ ROS, MDA ↓	[104]
MitoQ	RSL3-induced HT-22 cells	0.1-1.5 μM	RTA	ROS, lipid peroxidation ↓	[105]
BI-6c9	Erastin- and glutamate-induced HT-22 cells	10 μM	BID inhibitor	ROS ↓	[106]
Resveratrol	MCAO-induced SD rat stroke model OGD/R-induced primary cortical neuron stroke model	*In vivo:* 30 mg/kg *In vitro:* 5, 10, 20 μM	RTA	GPX4, GSH ↑ ROS, ACSL4, Fe2+ ↓	[108]
DPI	PQ- and maneb-induced SHSY5Y cells	1 μM	NOX inhibitor	GSH, GPX4 ↑ ROS, MDA ↓	[111]
GKT137831	PQ- and maneb-induced SHSY5Y cells	0.5 μM	NOX inhibitor	GSH, GPX4 ↑ ROS, MDA ↓	[111]
Vilda	Collagenase-induced C57BL/6J mouse ICH model	50 mg/kg/d	DPP-4 inhibitor	GPX4 ↑ MDA, Fe2+ ↓	[113]
Vitamin E	PTZ-induced SD rat chronic epilepsy model	200 mg/kg	ALOX inhibitor	GPX4, GSH ↑MDA, ROS, 15-LOX ↓	[118]
Baicalein	FeCl3-induced C57BL/ 6J mouse PTE model FAC-induced HT-22 cell PTE model	*In vivo:* 100 mg/kg *In vitro:* 1, 2, 4, 8, 16, 32 μM	ALOX inhibitor	GPX4 ↑ ROS, PTGS2, 4-HNE, 12/15-LOX ↓	[116]
Zileuton	Glutamate-induced HT-22 cells	1, 10, 50, 100 μM	ALOX inhibitor	ROS, 5-LOX, lipid peroxidation ↓	[121]
NAC	Collagenase-induced ICH model Hemin-induced primary cortical neuronal ICH model	*In vivo:* 300 mg/kg *In vitro:* 1 mM	ALOX inhibitor	GSH ↑ ALOX5 ↓	[123]

Table I *(Continued)*. Common ferroptosis inhibitors.

Drugs	Model	Dose	Mechanism or pathway of action	Signal	Refs.
ROSI	MCAO-induced ischemic stroke model	0.4 mg/kg	Lipid peroxidation	GSH, SOD, GPX4 ↑ PTGS2, ROS, MDA, ACSL4↓	[127]
PAN	Collagenase-induced ICH model Hemin-induced primary cortical neuronal and HT-22 cell ICH model	*In vivo:* 5, 10, 15 mg/kg *In vitro:* 10, 20, and 40 mM	ACSL4 inhibitor	GPX4, SLC7A11 ↑ ROS, MDA, Fe2+ ↓	[125]
AOA	Glutamate-induced HT-22 cells	2 mM	Transaminase inhibitor	ACSF2↓	[130]
CDDO	Erastin- and glutamate-induced HT-22 cells	10 μM	HSP90 inhibitor	System Xc−, GSH, GPX4 ↑ ROS, MDA ↓	[149]
DA	Glutamate-induced HT-22 cells	5 μM	GPX4	GPX4 ↑	[130]
β-ME	Glutamate-induced HT-22 cells	100 nM	System Xc−	GSH ↑	[150]
SS	Contusion SCI model	2.5 μM	GPX4	GSH↑ MDA, 4-HNE, Fe2+ ↓	[151]
Idebenone	Rotenone-induced PD model	200 mg/kg	GPX4	GSH, SOD↑ MDA ↓	[153]
Ebselen	Erastin- or RSL3-induced N27 cell stroke model	10 μM	GPX4	GPX4↑	[155]
PDZ	Autologous blood-induced ICH model Heme-induced primary neuron ICH model	*In vivo:* 30 mg/kg *In vitro:* 10 μM	PPARγ agonist	GPX4, Nrf2, SLC11A7 ↑ MDA, 4-HNE, NCOA4, SAT1 ↓	[159]
CAR	I/R-induced stroke model	25, 50, 100 mg/kg	GPX4	GSH, GSH-PX, FPN1, SOD ↑ ROS, Fe2+, TfR1, MDA ↓	[162]
Galangin	I/R-induced stroke model	25, 50, 100 mg/kg	SLC7A11/ GPX4 pathway ↑	GSH, SOD, GSH-PX ↑ MDA, 4-HNE, ROS, Fe2+ ↓	[165]
GL	Hypoxia-ischemia-induced HIBD model OGD-induced primary cortical neuron HIBD model	*In vivo:* 20 mg/kg *In vitro:* 55 μM	HMGB1/ GPX4 pathway ↑	SOD, GSH ↑ MDA, ROS ↓	[167]
GB	AD model	*In vivo:* 20, 30, 40 mg/kg	Nrf2/GPX4 signaling pathway ↑	SOD, HO-1, GSH, FTH1 ↑ Fe2+, MDA, TfR1, NCOA4, ROS ↓	[170]
PF	MPP-induced primary dopaminergic neuron PD model	10 μM	Akt/Nrf2/GPX4 signaling pathway ↑	GSH ↑ ROS ↓	[172]
FA	Erastin-exposed HT22 cells AD model	40 μM, 80 μM	Nrf2/GPX4 signaling pathway ↑	FTH, GSH ↑ DMT1, MDA, ROS ↓	[174]
Curcumin	Collagenase-induced ICH model Erastin-induced HT-22 cells ICH model	*In vivo:* 20 mg/kg *In vitro:* 2.5, 5, and 10 μM	Nrf2/HO-1 signaling pathway ↑	GPX4 ↑ ROS ↓	[176]
GAS	Glutamate-induced HT-22 cells	1, 5, 25 μM	Nrf2/HO-1 pathway	FPN1 ↑ ROS, ACSL4, PTGHS2, MDA, ACSL4, Fe2+ ↓	[177]

Continued

Table I *(Continued)*. Common ferroptosis inhibitors.

Drugs	Model	Dose	Mechanism or pathway of action	Signal	Refs.
TSG	AD model	60, 120, 180 mg/kg	Keap1/Nrf2/ARE signaling pathway ↑	GSH, GPX4 ↑ ROS, DMT1, ACSL4, NCOA4 ↓	[179]
LA	MMP-induced PC12 cell PD model	0, 0.1, 1, 10, 20 mM	PI3K/Akt/Nrf2 signaling pathway ↑	GPX4, SLC7A11, GSH ↑ MDA, 4-HNE, Fe2+, ROS ↓	[181]
Salidroside	Aβ1−42-induced AD model glutamate-induced HT-22 cell AD model	*In vivo:* 50 mg/kg *In vitro:* 10, 20,40, 80, 160, 320 μM	Nrf2/HO-1 pathway ↑	SOD, GSH, GPX4, SLC7A11 ↑ ROS, Fe2+, MDA ↓	[183]

ptosis inhibitor Fer-1 but not by other cell death inhibitors[212]. The p53-induced ferroptosis is also involved in the progression of NDs, such as the MPP-induced PD model *in vitro*[213]. MPP reduces the levels of GSH, SLC7A11, and GPX4 through the amino acid pathway, resulting in ferroptosis in PC12 cells. Pretreatment with the p53 inhibitor pyrethrin-α reverses these phenomena, indicating that MPP-induced ferroptosis is p53-dependent[213]. Overall, p53 inhibits cystine uptake and limits GSH synthesis, thereby increasing the ROS levels and the susceptibility of cells to ferroptosis by the downregulation of slc7a11[214].

This figure displays the three regulatory pathways of ferroptosis and the several genes that affect ferroptosis. The first one is regulated by iron metabolism. After ferric ions enter the cell through the Tf and TfR1-mediated transport to ferrous iron, they are transported by DMT1 to LIP, where excessive iron accumulation triggers an iron overload, which causes a Fenton reaction to generate ROS and further leads to ferroptosis. Drugs (i.e., DFO, DFP, and CPX) inhibit ferroptosis through this pathway. Furthermore, the regulatory mechanism of lipid metabolism is illustrated, taking AA as an example. AA is linked to CoA by the catalytic action of acsl4 to form AA-CoA and, subsequently, AA-PE through LPCAT3. AA-PE formation can be converted to lipid peroxides through LOX-mediated enzymatic or non-enzymatic effects, ultimately leading to cellular ferroptosis. Drugs (i.e., Lip-1, Fer-1, edaravone, and AOA) can attenuate lipid peroxidation by trapping lipid ROS and inhibiting the activity of lipid peroxidation-related enzymes. The third category is the related pathways surrounding glutamate metabolism. System Xc⁻ regulates the uptake of cystine, which

is rapidly reduced to cysteine upon entry into the cell and is involved in the synthesis of GSH. GSH is an important substrate for the role of GPX4, which helps to scavenge lipid peroxides and thus inhibit ferroptosis. Drugs (i.e., CDDO, DA, and β-ME) can target system Xc⁻, GPX4, and their related pathways to inhibit ferroptosis. It is also advisable to introduce some genes affecting the occurrence of ferroptosis, such as *Nrf2*, *FSP1*, *VDAC*, and *p53*.

Conclusions

Ferroptosis, an iron-dependent cell death phenomenon, has attracted widespread attention in the scientific community since its discovery in 2012. Although originally observed in cancer cells, ferroptosis has been linked to different NDs. This article provided an overview of the ferroptosis-related mechanisms in NDs: iron metabolism, lipid peroxidation, and amino acid metabolism, as well as ferroptosis-related genes such as *Nrf2*, *FSP1*, *p53*, and *VDAC* (Figure 1). Moreover, we classified ferroptosis inhibitors targeting these mechanisms and elucidated their efficacy, targets, and signaling pathways in specific models (Table I). Taken together, ferroptosis inhibitors have overlapping and unique functions, showing considerable potential in treating NDs. In summary, this review is expected to help you understand the links between ferroptosis and NDs and how it can be targeted by therapeutics accordingly.

However, some challenges should be overcome. As a starting point, these inhibitors exhibit good antiferroptosis activity in the laboratory, but their clinical role is unknown. To further explore

their therapeutic effects on humans, clinical trials are required. Second, there are several inhibitors targeting the same disease or the same target, yet they are not compared in terms of efficacy. The third question is whether ferroptosis inhibitors effective in one ND are also effective in another. In conclusion, these findings must be further investigated for clarity to better understand the specificity of inhibitors and how to target ferroptosis biomarkers for more effective treatment of NDs.

Conflict of Interest

The authors declare that this work was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

Authors' Contribution

Ruifeng Zhang and Miao Zeng drafted the manuscript. Xijuan Jiang and Lin Yang designed and supervised the manuscript. Nuan Lv verified the contents and revised the manuscript. Luming Wang, Qiuyue Yang, Jiali Gan, Huhu Li, Bin Yu critically revised the manuscript. All authors reviewed and approved the final manuscript.

References

1) Nunes T, Bernardazzi C, de Souza HS. Cell Death and Inflammatory Bowel Diseases: Apoptosis, Necrosis, and Autophagy in the Intestinal Epithelium. Biomed Res Int 2014; 2014: 1-12.

2) Liu L, Li H, Hu D, Wang Y, Shao W, Zhong J, Yang S, Liu J, Zhang J. Insights into N6-methyladenosine and programmed cell death in cancer. Mol Cancer 2022; 21: 32.

3) Giorgi C, Romagnoli A, Pinton P, Rizzuto R. Ca2+ signaling, mitochondria and cell death. Curr Mol Med 2008; 8: 119-130.

4) Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, Morrison BR, Stockwell BR. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell 2012; 149: 1060-1072.

5) Lee J, You JH, Kim MS, Roh JL. Epigenetic reprogramming of epithelial-mesenchymal transition promotes ferroptosis of head and neck cancer. Redox Biol 2020; 37: 101697.

6) Dong X, Tan Y, Zhuang D, Hu T, Zhao M. Global Characteristics and Trends in Research on Ferroptosis: A Data-Driven Bibliometric Study. Oxid Med Cell Longev 2022; 2022: 8661864.

7) Demuynck R, Efimova I, Naessens F, Krysko DV. Immunogenic ferroptosis and where to find it? J Immunother Cancer 2021; 9: e003430.

8) Amaral EP, Costa DL, Namasivayam S, Riteau N, Kamenyeva O, Mittereder L, Mayer-Barber KD, Andrade BB, Sher A. A major role for ferroptosis in Mycobacterium tuberculosis-induced cell death and tissue necrosis. J Exp Med 2019; 216: 556-570.

9) Lachaier E, Louandre C, Ezzoukhry Z, Godin C, Maziere JC, Chauffert B, Galmiche A. Ferroptosis, a new form of cell death relevant to the medical treatment of cancer. Med Sci (Paris) 2014; 30: 779-783.

10) Ma S, Henson ES, Chen Y, Gibson SB. Ferroptosis is induced following siramesine and lapatinib treatment of breast cancer cells. Cell Death Dis 2016; 7: e2307.

11) Dachert J, Schoeneberger H, Rohde K, Fulda S. RSL3 and Erastin differentially regulate redox signaling to promote Smac mimetic-induced cell death. Oncotarget 2016; 7: 63779-63792.

12) Bai T, Wang S, Zhao Y, Zhu R, Wang W, Sun Y. Haloperidol, a sigma receptor 1 antagonist, promotes ferroptosis in hepatocellular carcinoma cells. Biochem Biophys Res Commun 2017; 491: 919-925.

13) Yamaguchi Y, Kasukabe T, Kumakura S. Piperlongumine rapidly induces the death of human pancreatic cancer cells mainly through the induction of ferroptosis. Int J Oncol 2018; 52: 1011-1022.

14) Kabiraj P, Valenzuela CA, Marin JE, Ramirez DA, Mendez L, Hwang MS, Varela-Ramirez A, Fenelon K, Narayan M, Skouta R. The neuroprotective role of ferrostatin-1 under rotenone-induced oxidative stress in dopaminergic neuroblastoma cells. Protein J 2015; 34: 349-358.

15) Koppula P, Zhang Y, Zhuang L, Gan B. Amino acid transporter SLC7A11/xCT at the crossroads of regulating redox homeostasis and nutrient dependency of cancer. Cancer Commun (Lond) 2018; 38: 12.

16) Zhou Z, Ye TJ, Bonavita G, Daniels M, Kainrad N, Jogasuria A, You M. Adipose-Specific Lipin-1 Overexpression Renders Hepatic Ferroptosis and Exacerbates Alcoholic Steatohepatitis in Mice. Hepatol Commun 2019; 3: 656-669.

17) Xu W, Deng H, Hu S, Zhang Y, Zheng L, Liu M, Chen Y, Wei J, Yang H, Lv X. Role of Ferroptosis in Lung Diseases. J Inflamm Res 2021; 14: 2079-2090.

18) Bano I, Horky P, Abbas SQ, Majid M, Bilal A, Ali F, Behl T, Hassan S, Bungau S. Ferroptosis: A New

Road towards Cancer Management. Molecules 2022; 27: 2129.

19) Zhao WK, Zhou Y, Xu TT, Wu Q. Ferroptosis: Opportunities and Challenges in Myocardial Ischemia-Reperfusion Injury. Oxid Med Cell Longev 2021; 2021: 9929687.

20) Belavgeni A, Meyer C, Stumpf J, Hugo C, Linkermann A. Ferroptosis and Necroptosis in the Kidney. Cell Chem Biol 2020; 27: 448-462.

21) Wu H, Wang Y, Tong L, Yan H, Sun Z. Global Research Trends of Ferroptosis: A Rapidly Evolving Field With Enormous Potential. Front Cell Dev Biol 2021; 9: 646311.

22) Gallucci M, Limbucci N, Catalucci A, Caulo M. Neurodegenerative diseases. Radiol Clin North Am 2008; 46: 799-817.

23) Ahmad K, Balaramnavar VM, Chaturvedi N, Khan S, Haque S, Lee YH, Choi I. Targeting Caspase 8: Using Structural and Ligand-Based Approaches to Identify Potential Leads for the Treatment of Multi-Neurodegenerative Diseases. Molecules 2019; 24: 1827.

24) Thayyullathil F, Cheratta AR, Alakkal A, Subburayan K, Pallichankandy S, Hannun YA, Galadari S. Acid sphingomyelinase-dependent autophagic degradation of GPX4 is critical for the execution of ferroptosis. Cell Death Dis 2021; 12: 26.

25) Guo JP, Pan JX, Xiong L, Xia WF, Cui S, Xiong WC. Iron Chelation Inhibits Osteoclastic Differentiation In Vitro and in Tg2576 Mouse Model of Alzheimer's Disease. PloS One 2015; 10: e139395.

26) Xu SF, Zhang YH, Wang S, Pang ZQ, Fan YG, Li JY, Wang ZY, Guo C. Lactoferrin ameliorates dopaminergic neurodegeneration and motor deficits in MPTP-treated mice. Redox Biol 2019; 21: 101090.

27) Bennett C, Mohammed F, Alvarez-Ciara A, Nguyen MA, Dietrich WD, Rajguru SM, Streit WJ, Prasad A. Neuroinflammation, oxidative stress, and blood-brain barrier (BBB) disruption in acute Utah electrode array implants and the effect of deferoxamine as an iron chelator on acute foreign body response. Biomaterials 2019; 188: 144-159.

28) Ko CJ, Gao SL, Lin TK, Chu PY, Lin HY. Ferroptosis as a Major Factor and Therapeutic Target for Neuroinflammation in Parkinson's Disease. Biomedicines 2021; 9: 1679.

29) Reichert CO, De freitas FA, Sampaio-Silva J, Rokita-Rosa L, Barros PL, Levy D, Bydlowski SP. Ferroptosis Mechanisms Involved in Neurodegenerative Diseases. Int J Mol Sci 2020; 21: 8765.

30) Tomasz G, Ewa W, Jolanta M. Biomarkers of iron metabolism in chronic kidney disease. Int Urol Nephrol 2021; 53: 935-944.

31) Zhu BM, Mclaughlin SK, Na R, Liu J, Cui Y, Martin C, Kimura A, Robinson GW, Andrews NC, Hennighausen L. Hematopoietic-specific Stat5-null mice display microcytic hypochromic anemia associated with reduced transferrin receptor gene expression. Blood 2008; 112: 2071-2080.

32) Kopec Z, Starzynski RR, Jonczy A, Mazgaj R, Lipinski P. Role of Iron Metabolism-Related Genes in Prenatal Development: Insights from Mouse Transgenic Models. Genes (Basel) 2021; 12: 1382.

33) Li Y, Huang X, Wang J, Huang R, Wan D. Regulation of Iron Homeostasis and Related Diseases. Mediators Inflamm 2020; 2020: 6062094.

34) Qian ZM, Ke Y. Brain iron transport. Biol Rev Camb Philos Soc 2019; 94: 1672-1684.

35) Ganz T. Systemic iron homeostasis. Physiol Rev 2013; 93: 1721-1741.

36) Vogt AS, Arsiwala T, Mohsen M, Vogel M, Manolova V, Bachmann MF. On Iron Metabolism and Its Regulation. Int J Mol Sci 2021; 22: 4591.

37) Li L, Yang Z, Fan W, He L, Cui C, Zou J, Tang W, Jacobson O, Wang Z, Niu G, Hu S, Chen X. In Situ Polymerized Hollow Mesoporous Organosilica Biocatalysis Nanoreactor for Enhancing ROS-Mediated Anticancer Therapy. Adv Funct Mater 2020; 30: 1907716

38) Battaglia AM, Chirillo R, Aversa I, Sacco A, Costanzo F, Biamonte F. Ferroptosis and Cancer: Mitochondria Meet the "Iron Maiden" Cell Death. Cells 2020; 9: 1505.

39) Schneider SA, Dusek P, Hardy J, Westenberger A, Jankovic J, Bhatia KP. Genetics and Pathophysiology of Neurodegeneration with Brain Iron Accumulation (NBIA). Curr Neuropharmacol 2013; 11: 59-79.

40) Kuchcinski G, Patin L, Lopes R, Leroy M, Delbeuck X, Rollin-Sillaire A, Lebouvier T, Wang Y, Spincemaille P, Tourdias T, Hacein-Bey L, Devos D, Pasquier F, Leclerc X, Pruvo JP, Verclytte S. Quantitative susceptibility mapping demonstrates different patterns of iron overload in subtypes of early-onset Alzheimer's disease. Eur Radiol 2022; doi: 10.1007/s00330-022-09014-9.

41) Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biol 2018; 14: 450-464.

42) Lancione M, Donatelli G, Del PE, Campese N, Frosini D, Cencini M, Costagli M, Biagi L, Lucchi G, Tosetti M, Godani M, Arnaldi D, Terzaghi M, Provini F, Pacchetti C, Cortelli P, Bonanni E, Ceravolo R, Cosottini M. Evaluation of iron overload in nigrosome 1 via quantitative susceptibility mapping as a progression biomarker in prodromal stages of synucleinopathies. Neuroimage 2022; 260: 119454.

43) Li J, Jia B, Cheng Y, Song Y, Li Q, Luo C. Targeting Molecular Mediators of Ferroptosis and Oxidative Stress for Neurological Disorders. Oxid Med Cell Longev 2022; 2022: 3999083.

44) Huang C, Ma W, Luo Q, Shi L, Xia Y, Lao C, Liu W, Zou Y, Cheng A, Shi R, Chen Z. Iron overload resulting from the chronic oral administration of ferric citrate induces parkinsonism phenotypes in middle-aged mice. Aging (Albany NY) 2019; 11: 9846-9861.

45) Jurgens CK, Jasinschi R, Ekin A, Witjes-Ane MN, Middelkoop H, Van der Grond J, Roos RA. MRI T2 Hypointensities in basal ganglia of premanifest Huntington's disease. PLoS Curr 2010; 2: RRN1173.

46) Chen W, Guo C, Jia Z, Wang J, Xia M, Li C, Li M, Yin Y, Tang X, Chen T, Hu R, Chen Y, Liu X, Feng H. Inhibition of Mitochondrial ROS by MitoQ Alleviates White Matter Injury and Improves Outcomes after Intracerebral Haemorrhage in Mice. Oxid Med Cell Longev 2020; 2020: 8285065.

47) Jaune-Pons E, Vasseur S. Role of amino acids in regulation of ROS balance in cancer. Arch Biochem Biophys 2020; 689: 108438.

48) Lovatt M, Adnan K, Kocaba V, Dirisamer M, Peh G, Mehta JS. Peroxiredoxin-1 regulates lipid peroxidation in corneal endothelial cells. Redox Biol 2020; 30: 101417.

49) Gao M, Monian P, Pan Q, Zhang W, Xiang J, Jiang X. Ferroptosis is an autophagic cell death process. Cell Res 2016; 26: 1021-1032.

50) Peng Y, Chang X, Lang M. Iron Homeostasis Disorder and Alzheimer's Disease. Int J Mol Sci 2021; 22: 12442.

51) Sun X, Ou Z, Xie M, Kang R, Fan Y, Niu X, Wang H, Cao L, Tang D. HSPB1 as a novel regulator of ferroptotic cancer cell death. Oncogene 2015; 34: 5617-5625.

52) Razaghi A, Heimann K, Schaeffer PM, Gibson SB. Negative regulators of cell death pathways in cancer: perspective on biomarkers and targeted therapies. Apoptosis 2018; 23: 93-112.

53) Mou Y, Wang J, Wu J, He D, Zhang C, Duan C, Li B. Ferroptosis, a new form of cell death: opportunities and challenges in cancer. J Hematol Oncol 2019; 12: 34.

54) Hu W, Zhou C, Jing Q, Li Y, Yang J, Yang C, Wang L, Hu J, Li H, Wang H, Yuan C, Zhou Y, Ren X, Tong X, Du J, Wang Y. FTH promotes the proliferation and renders the HCC cells specifically resist to ferroptosis by maintaining iron homeostasis. Cancer Cell Int 2021; 21: 709.

55) Toth ME, Szegedi V, Varga E, Juhasz G, Horvath J, Borbely E, Csibrany B, Alfoldi R, Lenart N, Penke B, Santha M. Overexpression of Hsp27 ameliorates symptoms of Alzheimer's disease in APP/PS1 mice. Cell Stress Chaperones 2013; 18: 759-771.

56) Chen H, Zheng C, Zhang Y, Chang YZ, Qian ZM, Shen X. Heat shock protein 27 downregulates the transferrin receptor 1-mediated iron uptake. Int J Biochem Cell Biol 2006; 38: 1402-1416.

57) Hoshino T, Murao N, Namba T, Takehara M, Adachi H, Katsuno M, Sobue G, Matsushima T, Suzuki T, Mizushima T. Suppression of Alzheimer's disease-related phenotypes by expression of heat shock protein 70 in mice. J Neurosci 2011; 31: 5225-5234.

58) Laskowska E, Matuszewska E, Kuczynska-Wisnik D. Small heat shock proteins and protein-misfolding diseases. Curr Pharm Biotechnol 2010; 11: 146-157.

59) Morris JK, Bomhoff GL, Stanford JA, Geiger PC. Neurodegeneration in an animal model of Parkinson's disease is exacerbated by a high-fat diet. Am J Physiol Regul Integr Comp Physiol 2010; 299: R1082-R1090.

60) Sun X, Ou Z, Chen R, Niu X, Chen D, Kang R, Tang D. Activation of the p62-Keap1-NRF2 pathway protects against ferroptosis in hepatocellular carcinoma cells. Hepatology 2016; 63: 173-184.

61) Calkins MJ, Johnson DA, Townsend JA, Vargas MR, Dowell JA, Williamson TP, Kraft AD, Lee JM, Li J, Johnson JA. The Nrf2/ARE pathway as a potential therapeutic target in neurodegenerative disease. Antioxid Redox Signal 2009; 11: 497-508.

62) Zhang X, Wu Q, Wang Z, Li H, Dai J. Keap1-Nrf2/ARE signal pathway activated by butylphthalide in the treatment of ischemic stroke. Am J Transl Res 2022; 14: 2637-2646.

63) Murphy K, Llewellyn K, Wakser S, Pontasch J, Samanich N, Flemer M, Hensley K, Kim DS, Park J. Mini-GAGR, an intranasally applied polysaccharide, activates the neuronal Nrf2-mediated antioxidant defense system. J Biol Chem 2018; 293: 18242-18269.

64) Santana-Codina N, Gableske S, Quiles DRM, Malachowska B, Jedrychowski MP, Biancur DE, Schmidt PJ, Fleming MD, Fendler W, Harper JW, Kimmelman AC, Mancias JD. NCOA4 maintains murine erythropoiesis via cell autonomous and non-autonomous mechanisms. Haematologica 2019; 104: 1342-1354.

65) Zhou Y, Shen Y, Chen C, Sui X, Yang J, Wang L, Zhou J. The crosstalk between autophagy and ferroptosis: what can we learn to target drug resistance in cancer? Cancer Biol Med 2019; 16: 630-646.

66) Tian Y, Lu J, Hao X, Li H, Zhang G, Liu X, Li X, Zhao C, Kuang W, Chen D, Zhu M. FTH1 Inhibits Ferroptosis Through Ferritinophagy in the 6-OHDA Model of Parkinson's Disease. Neurotherapeutics 2020; 17: 1796-1812.

67) Chen J, Wang J, Li C, Ding H, Ye J, Xia Z. Dexmedetomidine reverses MTX-induced neurotoxicity and inflammation in hippocampal HT22 cell lines via NCOA4-mediated ferritinophagy. Aging (Albany NY) 2021; 13: 6182-6193.

68) Wang JC, Ramaswami G, Geschwind DH. Gene co-expression network analysis in human spinal cord highlights mechanisms underlying amyotrophic lateral sclerosis susceptibility. Sci Rep 2021; 11: 5748.

69) Hu Y, Wu L, Yang SQ, Wei HJ, Wang CY, Kang X, Jiang JM, Zhang P, Tang XQ. Formaldehyde induces ferritinophagy to damage hippocampal neuronal cells. Toxicol Ind Health 2021; 37: 685-694.

70) Song X, Zhu S, Chen P, Hou W, Wen Q, Liu J, Xie Y, Liu J, Klionsky DJ, Kroemer G, Lotze MT, Zeh HJ, Kang R, Tang D. AMPK-Mediated BECN1 Phosphorylation Promotes Ferroptosis by Directly Blocking System Xc(-) Activity. Curr Biol 2018; 28: 2388-2399.

71) Wang S, Wang L, Qin X, Turdi S, Sun D, Culver B, Reiter RJ, Wang X, Zhou H, Ren J. ALDH2 contributes to melatonin-induced protection against APP/PS1 mutation-prompted cardiac anomalies through cGAS-STING-TBK1-mediated regulation of mitophagy. Signal Transduct Target Ther 2020; 5: 119.

72) Geng N, Shi BJ, Li SL, Zhong ZY, Li YC, Xua WL, Zhou H, Cai JH. Knockdown of ferroportin accelerates erastin-induced ferroptosis in neuroblastoma cells. Eur Rev Med Pharmacol Sci 2018; 22: 3826-3836.

73) Ma L, Gholam AM, Dharmasivam M, Richardson V, Quinn RJ, Feng Y, Pountney DL, Tonissen KF, Mellick GD, Yanatori I, Richardson DR. Parkinson's disease: Alterations in iron and redox biology as a key to unlock therapeutic strategies. Redox Biol 2021; 41: 101896.

74) Bao WD, Zhou XT, Zhou LT, Wang F, Yin X, Lu Y, Zhu LQ, Liu D. Targeting miR-124/Ferroportin signaling ameliorated neuronal cell death through inhibiting apoptosis and ferroptosis in aged intracerebral hemorrhage murine model. Aging Cell 2020; 19: e13235.

75) Bao WD, Pang P, Zhou XT, Hu F, Xiong W, Chen K, Wang J, Wang F, Xie D, Hu YZ, Han ZT, Zhang HH, Wang WX, Nelson PT, Chen JG, Lu Y, Man HY, Liu D, Zhu LQ. Loss of ferroportin induces memory impairment by promoting ferroptosis in Alzheimer's disease. Cell Death Differ 2021; 28: 1548-1562.

76) Zhang H, Ostrowski R, Jiang D, Zhao Q, Liang Y, Che X, Zhao J, Xiang X, Qin W, He Z. Hepcidin Promoted Ferroptosis through Iron Metabolism which Is Associated with DMT1 Signaling Activation in Early Brain Injury following Subarachnoid Hemorrhage. Oxid Med Cell Longev 2021; 2021: 9800794.

77) Taher AT, Saliba AN, Kuo KH, Giardina PJ, Cohen AR, Neufeld EJ, Aydinok Y, Kwiatkowski JL, Jeglinski BI, Pietropaolo K, Berk G, Viprakasit V. Safety and pharmacokinetics of the oral iron chelator SP-420 in beta-thalassemia. Am J Hematol 2017; 92: 1356-1361.

78) Zeng X, An H, Yu F, Wang K, Zheng L, Zhou W, Bao Y, Yang J, Shen N, Huang D. Benefits of Iron Chelators in the Treatment of Parkinson's Disease. Neurochem Res 2021; 46: 1239-1251.

79) Aminzadeh-Gohari S, Weber DD, Vidali S, Catalano L, Kofler B, Feichtinger RG. From old to new - Repurposing drugs to target mitochondrial energy metabolism in cancer. Semin Cell Dev Biol 2020; 98: 211-223.

80) Wu J, Yang JJ, Cao Y, Li H, Zhao H, Yang S, Li K. Iron overload contributes to general anaesthesia-induced neurotoxicity and cognitive deficits. J Neuroinflammation 2020; 17: 110.

81) Jungwirth B, Zieglgansberger W, Kochs E, Rammes G. Anesthesia and postoperative cognitive dysfunction (POCD). Mini Rev Med Chem 2009; 9: 1568-1579.

82) Wang F, Lv H, Zhao B, Zhou L, Wang S, Luo J, Liu J, Shang P. Iron and leukemia: new insights for future treatments. J Exp Clin Cancer Res 2019; 38: 406.

83) Yue L, Zhao L, Liu H, Li X, Wang B, Guo H, Gao L, Feng D, Qu Y. Adiponectin Protects against Glutamate-Induced Excitotoxicity via Activating SIRT1-Dependent PGC-1alpha Expression in HT22 Hippocampal Neurons. Oxid Med Cell Longev 2016; 2016: 2957354.

84) Sophia D, Manoharan S. Hypolipidemic activities of Ficus racemosa Linn. bark in alloxan induced diabetic rats. Afr J Tradit Complement Altern Med 2007; 4: 279-288.

85) Balihodzic A, Prinz F, Dengler MA, Calin GA, Jost PJ, Pichler M. Non-coding RNAs and ferroptosis: potential implications for cancer therapy. Cell Death Differ 2022; 29: 1094-1106.

86) Kagan VE, Mao G, Qu F, Angeli JP, Doll S, Croix CS, Dar HH, Liu B, Tyurin VA, Ritov VB, Kapralov AA, Amoscato AA, Jiang J, Anthonymuthu T, Mohammadyani D, Yang Q, Proneth B, Klein-Seetharaman J, Watkins S, Bahar I, Greenberger J, Mallampalli RK, Stockwell BR, Tyurina YY, Conrad M, Bayir H. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol 2017; 13: 81-90.

87) Stoyanovsky DA, Tyurina YY, Shrivastava I, Bahar I, Tyurin VA, Protchenko O, Jadhav S, Bolevich SB, Kozlov AV, Vladimirov YA, Shvedova AA, Philpott CC, Bayir H, Kagan VE. Iron catalysis of lipid peroxidation in ferroptosis: Regulated enzymatic or random free radical reaction? Free Radic Biol Med 2019; 133: 153-161.

88) Forcina GC, Dixon SJ. GPX4 at the Crossroads of Lipid Homeostasis and Ferroptosis. Proteomics 2019; 19: e1800311.

89) Andersen HH, Johnsen KB, Moos T. Iron deposits in the chronically inflamed central nervous system and contributes to neurodegeneration. Cell Mol Life Sci 2014; 71: 1607-1622.

90) Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, Irmler M, Beckers J, Aichler M, Walch A, Prokisch H, Trumbach D, Mao G, Qu F, Bayir H, Fullekrug J, Scheel CH, Wurst W, Schick JA, Kagan VE, Angeli JP, Conrad M. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol 2017; 13: 91-98.

91) Conrad M, Pratt DA. The chemical basis of ferroptosis. Nat Chem Biol 2019; 15: 1137-1147.

92) Yan N, Zhang JJ. The Emerging Roles of Ferroptosis in Vascular Cognitive Impairment. Front Neurosci 2019; 13: 811.

93) Kim S, Kang SW, Joo J, Han SH, Shin H, Nam BY, Park J, Yoo TH, Kim G, Lee P, Park JT. Characterization of ferroptosis in kidney tubular cell death under diabetic conditions. Cell Death Dis 2021; 12: 160.

94) Tretyakova N, Goggin M, Sangaraju D, Janis G. Quantitation of DNA adducts by stable isotope dilution mass spectrometry. Chem Res Toxicol 2012; 25: 2007-2035.

95) Del HP, Garcia-Redondo A, de Bustos F, Molina JA, Sayed Y, Alonso-Navarro H, Caballero L, Arenas J, Agundez JA, Jimenez-Jimenez FJ. Oxidative stress in skin fibroblasts cultures from patients with Parkinson's disease. Bmc Neurol 2010; 10: 95.

96) Angelova PR, Esteras N, Abramov AY. Mitochondria and lipid peroxidation in the mechanism of neurodegeneration: Finding ways for prevention. Med Res Rev 2021; 41: 770-784.

97) Czapski GA, Czubowicz K, Strosznajder JB, Strosznajder RP. The Lipoxygenases: Their Regulation and Implication in Alzheimer's Disease. Neurochem Res 2016; 41: 243-257.

98) Fan BY, Pang YL, Li WX, Zhao CX, Zhang Y, Wang X, Ning GZ, Kong XH, Liu C, Yao X, Feng SQ. Liproxstatin-1 is an effective inhibitor of oligodendrocyte ferroptosis induced by inhibition of glutathione peroxidase 4. Neural Regen Res 2021; 16: 561-566.

99) Li Q, Han X, Lan X, Gao Y, Wan J, Durham F, Cheng T, Yang J, Wang Z, Jiang C, Ying M, Koehler RC, Stockwell BR, Wang J. Inhibition of neuronal ferroptosis protects hemorrhagic brain. JCI Insight 2017; 2: e90777.

100) Guo Z, Wu HT, Li XX, Yu Y, Gu RZ, Lan R, Qin XY. Edaravone protects rat astrocytes from oxidative or neurotoxic inflammatory insults by restoring Akt/Bcl-2/Caspase-3 signaling axis. IBRO Rep 2020; 8: 122-128.

101) Dang R, Wang M, Li X, Wang H, Liu L, Wu Q, Zhao J, Ji P, Zhong L, Licinio J, Xie P. Edaravone ameliorates depressive and anxiety-like behaviors via Sirt1/Nrf2/HO-1/Gpx4 pathway. J Neuroinflammation 2022; 19: 41.

102) Zilka O, Shah R, Li B, Friedmann AJ, Griesser M, Conrad M, Pratt DA. On the Mechanism of Cytoprotection by Ferrostatin-1 and Liproxstatin-1 and the Role of Lipid Peroxidation in Ferroptotic Cell Death. ACS Cent Sci 2017; 3: 232-243.

103) Mizuno H, Kubota C, Takigawa Y, Shintoku R, Kannari N, Muraoka T, Obinata H, Yoshimoto Y, Kanazawa M, Koshiishi I, Torii S. 2,2,6,6-Tetramethylpiperidine-1-oxyl acts as a volatile inhibitor of ferroptosis and neurological injury. J Biochem 2022; 172: 71-78.

104) Yang W, Liu X, Song C, Ji S, Yang J, Liu Y, You J, Zhang J, Huang S, Cheng W, Shao Z, Li L, Yang S. Structure-activity relationship studies of phenothiazine derivatives as a new class of ferroptosis inhibitors together with the therapeutic effect in an ischemic stroke model. Eur J Med Chem 2021; 209: 112842.

105) Jelinek A, Heyder L, Daude M, Plessner M, Krippner S, Grosse R, Diederich WE, Culmsee C. Mitochondrial rescue prevents glutathione peroxidase-dependent ferroptosis. Free Radic Biol Med 2018; 117: 45-57.

106) Neitemeier S, Jelinek A, Laino V, Hoffmann L, Eisenbach I, Eying R, Ganjam GK, Dolga AM, Oppermann S, Culmsee C. BID links ferroptosis to mitochondrial cell death pathways. Redox Biol 2017; 12: 558-570.

107) Tellone E, Galtieri A, Russo A, Giardina B, Ficarra S. Resveratrol: A Focus on Several Neurodegenerative Diseases. Oxid Med Cell Longev 2015; 2015: 392169.

108) Zhu H, Huang J, Chen Y, Li X, Wen J, Tian M, Ren J, Zhou L, Yang Q. Resveratrol pretreatment protects neurons from oxygen-glucose deprivation/reoxygenation and ischemic injury through inhibiting ferroptosis. Biosci Biotechnol Biochem 2022; 86: 704-716.

109) Sultan MT, Choi BY, Ajiteru O, Hong DK, Lee SM, Kim HJ, Ryu JS, Lee JS, Hong H, Lee YJ, Lee H, Suh YJ, Lee OJ, Kim SH, Suh SW, Park CH. Reinforced-hydrogel encapsulated hMSCs towards brain injury treatment by trans-septal approach. Biomaterials 2021; 266: 120413.

110) Dachert J, Ehrenfeld V, Habermann K, Dolgikh N, Fulda S. Targeting ferroptosis in rhabdomyosarcoma cells. Int J Cancer 2020; 146: 510-520.

111) Hou L, Huang R, Sun F, Zhang L, Wang Q. NADPH oxidase regulates paraquat and maneb-induced dopaminergic neurodegeneration through ferroptosis. Toxicology 2019; 417: 64-73.

112) Yossef RR, Al-Yamany MF, Saad MA, El-Sahar AE. Neuroprotective effects of vildagliptin on drug induced Alzheimer's disease in rats with metabolic syndrome: Role of hippocampal klotho and AKT signaling pathways. Eur J Pharmacol 2020; 889: 173612.

113) Zhang Y, Zhang X, Wee YV, Xue M. Vildagliptin improves neurological function by inhibiting apoptosis and ferroptosis following intracerebral hemorrhage in mice. Neurosci Lett 2022; 776: 136579.

114) Cheng G, Zhao W, Xin Y, Huang G, Liu Y, Li Z, Zhan M, Li Y, Lu L, van Leyen K, Liu Y. Effects of ML351 and tissue plasminogen activator combination therapy in a rat model of focal embolic stroke. J Neurochem 2021; 157: 586-598.

115) Pourabdi L, Kucukkilinc TT, Khoshtale F, Ayazgok B, Nadri H, Farokhi AF, Forootanfar H, Akbari T, Shafiei M, Foroumadi A, Sharifzadeh M, Shafiee AM, Abaee MS, Firoozpour L, Khoobi M, Mojtahedi MM. Synthesis of New 3-Arylcoumarins Bearing N-Benzyl Triazole Moiety: Dual Lipoxygenase and Butyrylcholinesterase Inhibitors With Anti-Amyloid Aggregation and Neuroprotective Properties Against Alzheimer's Disease. Front Chem 2021; 9: 810233.

116) Li Q, Li QQ, Jia JN, Sun QY, Zhou HH, Jin WL, Mao XY. Baicalein Exerts Neuroprotective Effects in FeCl3-Induced Posttraumatic Epileptic Seizures via Suppressing Ferroptosis. Front Pharmacol 2019; 10: 638.

117) Muller KI, Bekkelund SI. Epilepsy in a patient with ataxia caused by vitamin E deficiency. BMJ Case Rep 2011; 2011: bcr0120113728.

118) Zhang X, Wu S, Guo C, Guo K, Hu Z, Peng J, Zhang Z, Li J. Vitamin E Exerts Neuroprotective Effects in Pentylenetetrazole Kindling Epilepsy via Suppression of Ferroptosis. Neurochem Res 2022; 47: 739-747.

119) Woo AY, Cheng CH, Waye MM. Baicalein protects rat cardiomyocytes from hypoxia/reoxygenation damage via a prooxidant mechanism. Cardiovasc Res 2005; 65: 244-253.

120) Di Meco A, Lauretti E, Vagnozzi AN, Pratico D. Zileuton restores memory impairments and reverses amyloid and tau pathology in aged Alzheimer's disease mice. Neurobiol Aging 2014; 35: 2458-2464.

121) Liu Y, Wang W, Li Y, Xiao Y, Cheng J, Jia J. The 5-Lipoxygenase Inhibitor Zileuton Confers Neuroprotection against Glutamate Oxidative Damage by Inhibiting Ferroptosis. Biol Pharm Bull 2015; 38: 1234-1239.

122) Kanazirska MV, Fuchs PM, Chen L, Lal S, Verma J, Vassilev PM. Beneficial effects of lysosome-modulating and other pharmacological and nanocarrier agents on amyloid-beta-treated cells. Curr Pharm Biotechnol 2012; 13: 2761-2767.

123) Karuppagounder SS, Alin L, Chen Y, Brand D, Bourassa MW, Dietrich K, Wilkinson CM, Nadeau CA, Kumar A, Perry S, Pinto JT, Darley-Usmar V, Sanchez S, Milne GL, Pratico D, Holman TR, Carmichael ST, Coppola G, Colbourne F, Ratan RR. N-acetylcysteine targets 5 lipoxygenase-derived, toxic lipids and can synergize with prostaglandin E2 to inhibit ferroptosis and improve outcomes following hemorrhagic stroke in mice. Ann Neurol 2018; 84: 854-872.

124) Chen J, Li X, Ge C, Min J, Wang F. The multifaceted role of ferroptosis in liver disease. Cell Death Differ 2022; 29: 467-480.

125) Jin ZL, Gao WY, Liao SJ, Yu T, Shi Q, Yu SZ, Cai YF. Paeonol inhibits the progression of intracerebral haemorrhage by mediating the HOTAIR/UPF1/ACSL4 axis. ASN Neuro 2021; 13: 17590914211010647.

126) Xu Q, Park Y, Huang X, Hollenbeck A, Blair A, Schatzkin A, Chen H. Diabetes and risk of Parkinson's disease. Diabetes Care 2011; 34: 910-915.

127) Chen J, Yang L, Geng L, He J, Chen L, Sun Q, Zhao J, Wang X. Inhibition of Acyl-CoA Synthetase Long-Chain Family Member 4 Facilitates Neurological Recovery After Stroke by Regulation Ferroptosis. Front Cell Neurosci 2021; 15: 632354.

128) Li N, Fan LL, Sun GP, Wan XA, Wang ZG, Wu Q, Wang H. Paeonol inhibits tumor growth in gastric cancer in vitro and in vivo. World J Gastroenterol 2010; 16: 4483-4490.

129) Shimada K, Skouta R, Kaplan A, Yang WS, Hayano M, Dixon SJ, Brown LM, Valenzuela CA, Wolpaw AJ, Stockwell BR. Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis. Nat Chem Biol 2016; 12: 497-503.

130) Tang HM, Tang HL. Cell recovery by reversal of ferroptosis. Biol Open 2019; 8: bio043182.

131) Ho CH, Huang JH, Sun MS, Tzeng IS, Hsu YC, Kuo CY. Wild Bitter Melon Extract Regulates LPS-Induced Hepatic Stellate Cell Activation, Inflammation, Endoplasmic Reticulum Stress, and Ferroptosis. Evid Based Complement Alternat Med 2021; 2021: 6671129.

132) Novgorodov SA, Voltin JR, Gooz MA, Li L, Lemasters JJ, Gudz TI. Acid sphingomyelinase promotes mitochondrial dysfunction due to glutamate-induced regulated necrosis. J Lipid Res 2018; 59: 312-329.

133) Lewerenz J, Maher P. Control of redox state and redox signaling by neural antioxidant systems. Antioxid Redox Signal 2011; 14: 1449-1465.

134) Cai Y, Yang Q, Liao M, Wang H, Zhang C, Nambi S, Wang W, Zhang M, Wu J, Deng G, Deng Q, Liu H, Zhou B, Jin Q, Feng CG, Sassetti CM, Wang F, Chen X. xCT increases tuberculosis susceptibility by regulating antimicrobial function and inflammation. Oncotarget 2016; 7: 31001-31013.

135) Maher P. The effects of stress and aging on glutathione metabolism. Ageing Res Rev 2005; 4: 288-314.

136) Li LB, Chai R, Zhang S, Xu SF, Zhang YH, Li HL, Fan YG, Guo C. Iron Exposure and the Cellular Mechanisms Linked to Neuron Degeneration in Adult Mice. Cells 2019; 8: 198.

137) Wang TX, Liang JY, Zhang C, Xiong Y, Guan KL, Yuan HX. The oncometabolite 2-hydroxyglutarate produced by mutant IDH1 sensitizes cells to ferroptosis. Cell Death Dis 2019; 10: 755.

138) Zhang L, Liu W, Liu F, Wang Q, Song M, Yu Q, Tang K, Teng T, Wu D, Wang X, Han W, Li Y. IMCA Induces Ferroptosis Mediated by SLC7A11 through the AMPK/mTOR Pathway in Colorectal Cancer. Oxid Med Cell Longev 2020; 2020: 1675613.

139) Lewerenz J, Hewett SJ, Huang Y, Lambros M, Gout PW, Kalivas PW, Massie A, Smolders I, Methner A, Pergande M, Smith SB, Ganapathy V, Maher P. The cystine/glutamate antiporter system x(c)(-) in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxid Redox Signal 2013; 18: 522-555.

140) More SS, Vince R. Potential of a gamma-glutamyl-transpeptidase-stable glutathione analogue against amyloid-beta toxicity. Acs Chem Neurosci 2012; 3: 204-210.

141) Serra D, Henriques JF, Serra T, Bento SA, Bronze MR, Dinis T, Almeida LM. An Anthocyanin-Rich Extract Obtained from Portuguese Blueberries Maintains Its Efficacy in Reducing Microglia-Driven Neuroinflammation after Simulated Digestion. Nutrients 2020; 12: 3670.

142) Mesci P, Zaidi S, Lobsiger CS, Millecamps S, Escartin C, Seilhean D, Sato H, Mallat M, Boillee S. System xC- is a mediator of microglial function and its deletion slows symptoms in amyotrophic lateral sclerosis mice. Brain 2015; 138: 53-68.

143) Northcutt AL, Hutchinson MR, Wang X, Baratta MV, Hiranita T, Cochran TA, Pomrenze MB,

Galer EL, Kopajtic TA, Li CM, Amat J, Larson G, Cooper DC, Huang Y, O'Neill CE, Yin H, Zahniser NR, Katz JL, Rice KC, Maier SF, Bachtell RK, Watkins LR. DAT isn't all that: cocaine reward and reinforcement require Toll-like receptor 4 signaling. Mol Psychiatry 2015; 20: 1525-1537.

144) Fuchsberger T, Martinez-Bellver S, Giraldo E, Teruel-Marti V, Lloret A, Vina J. Abeta Induces Excitotoxicity Mediated by APC/C-Cdh1 Depletion That Can Be Prevented by Glutaminase Inhibition Promoting Neuronal Survival. Sci Rep 2016; 6: 31158.

145) Strecker K, Schwarz J. Parkinson's disease: emerging pharmacotherapy. Expert Opin Emerg Drugs 2008; 13: 573-591.

146) Soo KY, Farg M, Atkin JD. Molecular motor proteins and amyotrophic lateral sclerosis. Int J Mol Sci 2011; 12: 9057-9082.

147) Castillo J, Davalos A, Noya M. Progression of ischaemic stroke and excitotoxic aminoacids. Lancet 1997; 349: 79-83.

148) Yang WS, Sriramaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, Cheah JH, Clemons PA, Shamji AF, Clish CB, Brown LM, Girotti AW, Cornish VW, Schreiber SL, Stockwell BR. Regulation of ferroptotic cancer cell death by GPX4. Cell 2014; 156: 317-331.

149) Wu Z, Geng Y, Lu X, Shi Y, Wu G, Zhang M, Shan B, Pan H, Yuan J. Chaperone-mediated autophagy is involved in the execution of ferroptosis. Proc Natl Acad Sci U S A 2019; 116: 2996-3005.

150) Sasseville LJ, Morin M, Coady MJ, Blunck R, Lapointe JY. The Human Sodium-Glucose Cotransporter (hSGLT1) Is a Disulfide-Bridged Homodimer with a Re-Entrant C-Terminal Loop. Plos One 2016; 11: e154589.

151) Chen YX, Zuliyaer T, Liu B, Guo S, Yang DG, Gao F, Yu Y, Yang ML, Du LJ, Li JJ. Sodium selenite promotes neurological function recovery after spinal cord injury by inhibiting ferroptosis. Neural Regen Res 2022; 17: 2702-2709.

152) Swerdlow RH. Treating neurodegeneration by modifying mitochondria: potential solutions to a "complex" problem. Antioxid Redox Signal 2007; 9: 1591-1603.

153) Avci B, Gunaydin C, Guvenc T, Yavuz CK, Kuruca N, Bilge SS. Idebenone Ameliorates Rotenone-Induced Parkinson's Disease in Rats Through Decreasing Lipid Peroxidation. Neurochem Res 2021; 46: 513-522.

154) Cabungcal JH, Counotte DS, Lewis E, Tejeda HA, Piantadosi P, Pollock C, Calhoon GG, Sullivan E, Presgraves E, Kil J, Hong LE, Cuenod M, Do KQ, O'Donnell P. Juvenile antioxidant treatment prevents adult deficits in a developmental model of schizophrenia. Neuron 2014; 83: 1073-1084.

155) Tuo QZ, Masaldan S, Southon A, Mawal C, Ayton S, Bush AI, Lei P, Belaidi AA. Characterization of Selenium Compounds for Anti-ferroptotic Activity in Neuronal Cells and After Cerebral Ischemia-Reperfusion Injury. Neurotherapeutics 2021; 18: 2682-2691.

156) Hunter RL, Choi DY, Ross SA, Bing G. Protective properties afforded by pioglitazone against intrastriatal LPS in Sprague-Dawley rats. Neurosci Lett 2008; 432: 198-201.

157) Sauerbeck A, Gao J, Readnower R, Liu M, Pauly JR, Bing G, Sullivan PG. Pioglitazone attenuates mitochondrial dysfunction, cognitive impairment, cortical tissue loss, and inflammation following traumatic brain injury. Exp Neurol 2011; 227: 128-135.

158) Quan Q, Qian Y, Li X, Li M. Pioglitazone Reduces beta Amyloid Levels via Inhibition of PPARgamma Phosphorylation in a Neuronal Model of Alzheimer's Disease. Front Aging Neurosci 2019; 11: 178.

159) Duan C, Jiao D, Wang H, Wu Q, Men W, Yan H, Li C. Activation of the PPARgamma Prevents Ferroptosis-Induced Neuronal Loss in Response to Intracerebral Hemorrhage Through Synergistic Actions With the Nrf2. Front Pharmacol 2022; 13: 869300.

160) Wijesundara NM, Lee SF, Cheng Z, Davidson R, Rupasinghe H. Carvacrol exhibits rapid bactericidal activity against Streptococcus pyogenes through cell membrane damage. Sci Rep 2021; 11: 1487.

161) Chen W, Xu B, Xiao A, Liu L, Fang X, Liu R, Turlova E, Barszczyk A, Zhong X, Sun CL, Britto LR, Feng ZP, Sun HS. TRPM7 inhibitor carvacrol protects brain from neonatal hypoxic-ischemic injury. Mol Brain 2015; 8: 11.

162) Guan X, Li X, Yang X, Yan J, Shi P, Ba L, Cao Y, Wang P. The neuroprotective effects of carvacrol on ischemia/reperfusion-induced hippocampal neuronal impairment by ferroptosis mitigation. Life Sci 2019; 235: 116795.

163) Kong Y, Feng Z, Chen A, Qi Q, Han M, Wang S, Zhang Y, Zhang X, Yang N, Wang J, Huang B, Zhang Q, Xiang G, Li W, Zhang D, Wang J, Li X. The Natural Flavonoid Galangin Elicits Apoptosis, Pyroptosis, and Autophagy in Glioblastoma. Front Oncol 2019; 9: 942.

164) Li S, Wu C, Zhu L, Gao J, Fang J, Li D, Fu M, Liang R, Wang L, Cheng M, Yang H. By improving regional cortical blood flow, attenuating mitochondrial dysfunction and sequential apoptosis galangin acts as a potential neuroprotective agent after acute ischemic stroke. Molecules 2012; 17: 13403-13423.

165) Guan X, Li Z, Zhu S, Cheng M, Ju Y, Ren L, Yang G, Min D. Galangin attenuated cerebral ischemia-reperfusion injury by inhibition of ferroptosis through activating the SLC7A11/GPX4 axis in gerbils. Life Sci 2021; 264: 118660.

166) Zhang X, Yang H, Yue S, He G, Qu S, Zhang Z, Ma B, Ding R, Peng W, Zhang H, Yang Z, Dou K, Tao K, Li X. The mTOR inhibition in concurrence with ERK1/2 activation is involved in excessive autophagy induced by glycyrrhizin in

hepatocellular carcinoma. Cancer Med 2017; 6: 1941-1951.

167) Zhu K, Zhu X, Liu S, Yu J, Wu S, Hei M. Glycyr-rhizin Attenuates Hypoxic-Ischemic Brain Damage by Inhibiting Ferroptosis and Neuroinflammation in Neonatal Rats via the HMGB1/GPX4 Pathway. Oxid Med Cell Longev 2022; 2022: 8438528.

168) Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Hamano N, Li SD, Chougule M, Shoyele SA, Gupta U, Ajazuddin, Alexander A. Recent advancements in the field of nanotechnology for the delivery of anti-Alzheimer drug in the brain region. Expert Opin Drug Deliv 2018; 15: 589-617.

169) Lv Z, Yang Y, Wang J, Chen J, Li J, Di L. Optimization of the Preparation Conditions of Borneol-Modified Ginkgolide Liposomes by Response Surface Methodology and Study of Their Blood Brain Barrier Permeability. Molecules 2018; 23: 303.

170) Shao L, Dong C, Geng D, He Q, Shi Y. Ginkgolide B protects against cognitive impairment in senescence-accelerated P8 mice by mitigating oxidative stress, inflammation and ferroptosis. Biochem Biophys Res Commun 2021; 572: 7-14.

171) Ma XH, Duan WJ, Mo YS, Chen JL, Li S, Zhao W, Yang L, Mi SQ, Mao XL, Wang H, Wang Q. Neuroprotective effect of paeoniflorin on okadaic acid-induced tau hyperphosphorylation via calpain/Akt/GSK-3beta pathway in SH-SY5Y cells. Brain Res 2018; 1690: 1-11.

172) Wang L, An H, Yu F, Yang J, Ding H, Bao Y, Xie H, Huang D. The neuroprotective effects of paeoniflorin against MPP(+)-induced damage to dopaminergic neurons via the Akt/Nrf2/GPX4 pathway. J Chem Neuroanat 2022; 122: 102103.

173) Wang HM, Wang LW, Liu XM, Li CL, Xu SP, Farooq AD. Neuroprotective effects of forsythiaside on learning and memory deficits in senescence-accelerated mouse prone (SAMP8) mice. Pharmacol Biochem Behav 2013; 105: 134-141.

174) Wang C, Chen S, Guo H, Jiang H, Liu H, Fu H, Wang D. Forsythoside A Mitigates Alzheimer's-like Pathology by Inhibiting Ferroptosis-mediated Neuroinflammation via Nrf2/GPX4 Axis Activation. Int J Biol Sci 2022; 18: 2075-2090.

175) Kose T, Vera-Aviles M, Sharp PA, Latunde-Dada GO. Curcumin and (-)- Epigallocatechin-3-Gallate Protect Murine MIN6 Pancreatic Beta-Cells Against Iron Toxicity and Erastin-Induced Ferroptosis. Pharmaceuticals (Basel) 2019; 12: 26.

176) Yang C, Han M, Li R, Zhou L, Zhang Y, Duan L, Su S, Li M, Wang Q, Chen T, Mo Y. Curcumin Nanoparticles Inhibiting Ferroptosis for the Enhanced Treatment of Intracerebral Hemorrhage. Int J Nanomedicine 2021; 16: 8049-8065.

177) Jiang T, Cheng H, Su J, Wang X, Wang Q, Chu J, Li Q. Gastrodin protects against glutamate-induced ferroptosis in HT-22 cells through Nrf2/HO-1 signaling pathway. Toxicol in Vitro 2020; 62: 104715.

178) Zhang L, Guo Y, Shi S, Zhuge Y, Chen N, Ding Z, Jin B. Tetrahydroxy stilbene glycoside attenuates endothelial cell premature senescence induced by H2O2 through the microRNA-34a/SIRT1 pathway. Sci Rep 2022; 12: 1708.

179) Gao Y, Li J, Wu Q, Wang S, Yang S, Li X, Chen N, Li L, Zhang L. Tetrahydroxy stilbene glycoside ameliorates Alzheimer's disease in APP/PS1 mice via glutathione peroxidase related ferroptosis. Int Immunopharmacol 2021; 99: 108002.

180) Suh JH, Shigeno ET, Morrow JD, Cox B, Rocha AE, Frei B, Hagen TM. Oxidative stress in the aging rat heart is reversed by dietary supplementation with (R)-(alpha)-lipoic acid. Faseb J 2001; 15: 700-706.

181) Liu L, Yang S, Wang H. alpha-Lipoic acid alleviates ferroptosis in the MPP(+) -induced PC12 cells via activating the PI3K/Akt/Nrf2 pathway. Cell Biol Int 2021; 45: 422-431.

182) Chen X, Liu J, Gu X, Ding F. Salidroside attenuates glutamate-induced apoptotic cell death in primary cultured hippocampal neurons of rats. Brain Res 2008; 1238: 189-198.

183) Yang S, Xie Z, Pei T, Zeng Y, Xiong Q, Wei H, Wang Y, Cheng W. Salidroside attenuates neuronal ferroptosis by activating the Nrf2/HO1 signaling pathway in Abeta1-42-induced Alzheimer's disease mice and glutamate-injured HT22 cells. Chin Med 2022; 17: 82.

184) Hecker L, Logsdon NJ, Kurundkar D, Kurundkar A, Bernard K, Hock T, Meldrum E, Sanders YY, Thannickal VJ. Reversal of persistent fibrosis in aging by targeting Nox4-Nrf2 redox imbalance. Sci Transl Med 2014; 6: 231r-247r.

185) Zhang Y, Xue W, Zhang W, Yuan Y, Zhu X, Wang Q, Wei Y, Yang D, Yang C, Chen Y, Sun Y, Wang S, Huang K, Zheng L. Histone methyltransferase G9a protects against acute liver injury through GSTP1. Cell Death Differ 2020; 27: 1243-1258.

186) Weerachayaphorn J, Amaya MJ, Spirli C, Chansela P, Mitchell-Richards KA, Ananthanarayanan M, Nathanson MH. Nuclear Factor, Erythroid 2-Like 2 Regulates Expression of Type 3 Inositol 1,4,5-Trisphosphate Receptor and Calcium Signaling in Cholangiocytes. Gastroenterology 2015; 149: 211-222.

187) Zhang W, Feng C, Jiang H. Novel target for treating Alzheimer's Diseases: Crosstalk between the Nrf2 pathway and autophagy. Ageing Res Rev 2021; 65: 101207.

188) Ji H, Xiao F, Li S, Wei R, Yu F, Xu J. GRP78 effectively protect hypoxia/reperfusion-induced myocardial apoptosis via promotion of the Nrf2/HO-1 signaling pathway. J Cell Physiol 2021; 236: 1228-1236.

189) Shen B, Zhao C, Wang Y, Peng Y, Cheng J, Li Z, Wu L, Jin M, Feng H. Aucubin inhibited lipid accumulation and oxidative stress via Nrf2/HO-1 and AMPK signalling pathways. J Cell Mol Med 2019; 23: 4063-4075.

190) Li X, Zou Y, Xing J, Fu YY, Wang KY, Wan PZ, Zhai XY. Pretreatment with Roxadustat (FG-4592) Attenuates Folic Acid-Induced Kidney Injury through Antiferroptosis via Akt/GSK-3beta/Nrf2 Pathway. Oxid Med Cell Longev 2020; 2020: 6286984.

191) Seiwert N, Wecklein S, Demuth P, Hasselwander S, Kemper TA, Schwerdtle T, Brunner T, Fahrer J. Heme oxygenase 1 protects human colonocytes against ROS formation, oxidative DNA damage and cytotoxicity induced by heme iron, but not inorganic iron. Cell Death Dis 2020; 11: 787.

192) Habas A, Hahn J, Wang X, Margeta M. Neuronal activity regulates astrocytic Nrf2 signaling. Proc Natl Acad Sci U S A 2013; 110: 18291-18296.

193) Wang CY, Zhang Q, Xun Z, Yuan L, Li R, Li X, Tian SY, Xin N, Xu Y. Increases of iASPP-Keap1 interaction mediated by syringin enhance synaptic plasticity and rescue cognitive impairments via stabilizing Nrf2 in Alzheimer's models. Redox Biol 2020; 36: 101672.

194) Kwon SH, Lee SR, Park YJ, Ra M, Lee Y, Pang C, Kim KH. Suppression of 6-Hydroxydopamine-Induced Oxidative Stress by Hyperoside Via Activation of Nrf2/HO-1 Signaling in Dopaminergic Neurons. Int J Mol Sci 2019; 20: 5832.

195) Dehghan E, Zhang Y, Saremi B, Yadavali S, Hakimi A, Dehghani M, Goodarzi M, Tu X, Robertson S, Lin R, Chudhuri A, Mirzaei H. Hydralazine induces stress resistance and extends C. elegans lifespan by activating the NRF2/SKN-1 signalling pathway. Nat Commun 2017; 8: 2223.

196) La Rosa P, Petrillo S, Turchi R, Berardinelli F, Schirinzi T, Vasco G, Lettieri-Barbato D, Fiorenza MT, Bertini ES, Aquilano K, Piemonte F. The Nrf2 induction prevents ferroptosis in Friedreich's Ataxia. Redox Biol 2021; 38: 101791.

197) Doll S, Freitas FP, Shah R, Aldrovandi M, Da SM, Ingold I, Goya GA, Xavier DST, Panzilius E, Scheel CH, Mourao A, Buday K, Sato M, Wanninger J, Vignane T, Mohana V, Rehberg M, Flatley A, Schepers A, Kurz A, White D, Sauer M, Sattler M, Tate EW, Schmitz W, Schulze A, O'Donnell V, Proneth B, Popowicz GM, Pratt DA, Angeli J, Conrad M. FSP1 is a glutathione-independent ferroptosis suppressor. Nature 2019; 575: 693-698.

198) Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, Roberts MA, Tong B, Maimone TJ, Zoncu R, Bassik MC, Nomura DK, Dixon SJ, Olzmann JA. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature 2019; 575: 688-692.

199) Lamade AM, Anthonymuthu TS, Hier ZE, Gao Y, Kagan VE, Bayir H. Mitochondrial damage & lipid signaling in traumatic brain injury. Exp Neurol 2020; 329: 113307.

200) Peeples ES, Genaro-Mattos TC. Ferroptosis: A Promising Therapeutic Target for Neonatal Hypoxic-Ischemic Brain Injury. Int J Mol Sci 2022; 23: 7420.

201) Shao C, Chen Y, Yang T, Zhao H, Li D. Mesenchymal Stem Cell Derived Exosomes Suppress Neuronal Cell Ferroptosis Via lncGm36569/miR-5627-5p/FSP1 Axis in Acute Spinal Cord Injury. Stem Cell Rev Rep 2022; 18: 1127-1142.

202) Guiney SJ, Adlard PA, Bush AI, Finkelstein DI, Ayton S. Ferroptosis and cell death mechanisms in Parkinson's disease. Neurochem Int 2017; 104: 34-48.

203) Song LM, Xiao ZX, Zhang N, Yu XQ, Cui W, Xie JX, Xu HM. Apoferritin improves motor deficits in MPTP-treated mice by regulating brain iron metabolism and ferroptosis. iScience 2021; 24: 102431.

204) Yang Y, Luo M, Zhang K, Zhang J, Gao T, Connell DO, Yao F, Mu C, Cai B, Shang Y, Chen W. Nedd4 ubiquitylates VDAC2/3 to suppress erastin-induced ferroptosis in melanoma. Nat Commun 2020; 11: 433.

205) Salinas T, El FS, Ubrig E, Sauter C, Duchene AM, Marechal-Drouard L. Molecular basis for the differential interaction of plant mitochondrial VDAC proteins with tRNAs. Nucleic Acids Res 2014; 42: 9937-9948.

206) Zuo S, Yu J, Pan H, Lu L. Novel insights on targeting ferroptosis in cancer therapy. Biomark Res 2020; 8: 50.

207) Ellis NA, Huo D, Yildiz O, Worrillow LJ, Banerjee M, Le Beau MM, Larson RA, Allan JM, Onel K. MDM2 SNP309 and TP53 Arg72Pro interact to alter therapy-related acute myeloid leukemia susceptibility. Blood 2008; 112: 741-749.

208) Barshishat S, Elgrably-Weiss M, Edelstein J, Georg J, Govindarajan S, Haviv M, Wright PR, Hess WR, Altuvia S. OxyS small RNA induces cell cycle arrest to allow DNA damage repair. Embo J 2018; 37: 413-426.

209) Zhang Z, Guo M, Shen M, Kong D, Zhang F, Shao J, Tan S, Wang S, Chen A, Cao P, Zheng S. The BRD7-P53-SLC25A28 axis regulates ferroptosis in hepatic stellate cells. Redox Biol 2020; 36: 101619.

210) Ha HC, Sirisoma NS, Kuppusamy P, Zweier JL, Woster PM, Casero RJ. The natural polyamine spermine functions directly as a free radical scavenger. Proc Natl Acad Sci U S A 1998; 95: 11140-11145.

211) Hassannia B, Vandenabeele P, Vanden BT. Targeting Ferroptosis to Iron Out Cancer. Cancer Cell 2019; 35: 830-849.

212) Ou Y, Wang SJ, Li D, Chu B, Gu W. Activation of SAT1 engages polyamine metabolism with p53-mediated ferroptotic responses. Proc Natl Acad Sci U S A 2016; 113: E6806-E6812.

213) Li S, Wang M, Wang Y, Guo Y, Tao X, Wang X, Cao Y, Tian S, Li Q. p53-mediated ferroptosis is required for 1-methyl-4-phenylpyridinium-induced senescence of PC12 cells. Toxicol in Vitro 2021; 73: 105146.

214) Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, Baer R, Gu W. Ferroptosis as a p53-mediated activity during tumour suppression. Nature 2015; 520: 57-62.