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Targeting Ferroptosis-Inflammation Crosstalk: A Novel Strategy for the Prevention and Treatment of Myocardial Ischaemia Reperfusion Injury

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Abstract

Myocardial ischaemia-reperfusion injury (MIRI) is a major cause of residual myocardial damage following coronary revascularisation. Unfortunately, effective mechanism-based pharmacological interventions that can be translated into clinical practice remain limited. Emerging evidence indicates that ferroptosis and inflammation mutually reinforce each other and constitute a critical pathological process responsible for the amplification of myocardial injury during the early phase of reperfusion. Upon myocardial reperfusion, ferroptotic cardiomyocytes release damage-associated molecular patterns and disrupt tissue barriers, thereby activating the innate immune system and initiating inflammatory responses. In turn, inflammation promotes oxidative stress, dysregulation of iron metabolism and lipid

peroxidation through the activation of inflammatory signaling pathways and the release of pro-inflammatory mediators, ultimately exacerbating ferroptosis. This reciprocal interaction establishes a self-perpetuating vicious cycle that contributes to the progression of MIRI. Encouragingly, several Western medicines and bioactive compounds derived from traditional Chinese medicine have shown therapeutic potential in modulating MIRI. This review systematically summarizes the molecular mechanisms underlying the bidirectional interaction between ferroptosis and inflammation in MIRI and discusses emerging pharmacological strategies targeting this pathological network. Collectively, the available evidence suggests that future therapeutic approaches to MIRI should extend beyond reperfusion therapy, antioxidant treatment, or anti-inflammatory intervention alone and instead consider combined strategies that simultaneously suppress inflammation and ferroptosis. Such an integrated approach may provide a novel translational framework for early risk assessment, therapeutic response prediction and targeted intervention in patients with MIRI.

Keywords: ferroptosis; inflammation; myocardial ischaemia-reperfusion injury; bioactive compounds

1 | INTRODUCTION

Ischaemic heart disease (IHD) is one of the leading contributors to the global cardiovascular disease burden and remains a major public health cause of death and disability [1]. Unfortunately, despite a decline in the age-standardized mortality rate, the prevalence and overall disease burden of IHD continue to increase, driven

largely by population growth, population ageing, and persistent socioeconomic disparities worldwide [2]. Over the past three decades, the number of people living with IHD worldwide has increased dramatically from 96.9 million in 1990 to 197.22 million[3]. Accordingly, in patients presenting with acute ST-segment elevation myocardial infarction (STEMI) or high-risk acute coronary syndrome, the timely restoration of blood flow to ischemic myocardium is essential for limiting infarct size and improving clinical outcomes following acute myocardial infarction[4]. The 2023 European Society of Cardiology guidelines further emphasize that antithrombotic therapy, invasive assessment and myocardial revascularization constitute key components of the contemporary management of acute coronary syndromes[5]. However, the reperfusion process itself may induce myocardial ischemia-reperfusion injury (MIRI), which is characterized by metabolic dysregulation and structural damage within the myocardium. These pathological alterations can lead to cardiomyocyte death, endothelial and microvascular dysfunction, severe arrhythmias and even sudden cardiac death[6,7]. Although timely percutaneous coronary intervention and thrombolytic therapy can effectively restore coronary blood flow and improve survival in critically ill patients, reperfusion-related myocardial injury may account for nearly half of the final infarct size. Moreover, the persistent burden of post-reperfusion complications substantially compromises the overall clinical benefits of revascularization therapy[8].

The pathophysiology of myocardial ischemia-reperfusion injury (MIRI) is principally characterized by oxidative stress, intracellular Ca^{2+} overload and mitochondrial dysfunction, which subsequently trigger inflammatory responses and multiple forms of regulated cell death, ultimately resulting in irreversible cardiomyocyte injury. During ischemia, succinate accumulates substantially within the myocardium. Upon reperfusion, its rapid mitochondrial oxidation drives reverse

electron transport (RET) through mitochondrial complex I, leading to a burst of reactive oxygen species (ROS) and consequent oxidative damage to membrane lipids, proteins and DNA[9]. During myocardial ischemia, the interruption of oxygen and metabolic substrate supply impairs oxidative phosphorylation and causes a rapid decline in intracellular adenosine triphosphate (ATP) levels. ATP depletion suppresses the activity of the ATP-dependent Na^+/K^+-ATPase in the plasma membrane, resulting in intracellular Na^+ accumulation, disruption of transmembrane ionic gradients and increased K^+ loss[10]. Concurrently, enhanced anaerobic glycolysis leads to the accumulation of lactate and other acidic metabolites, causing intracellular and extracellular acidosis..Activation of the Na^+/H^+ exchanger (NHE) in response to acidosis further increases the intracellular Na^+ load[11]. Upon reperfusion, the elevated intracellular Na^+ concentration promotes reverse-mode operation of the Na^+/Ca^{2+}exchanger (NCX), resulting in excessive Ca^{2+} influx into the cytosol. Subsequent mitochondrial Ca^{2+} uptake induces mitochondrial Ca^{2+} overload and promotes the opening of the mitochondrial permeability transition pore (mPTP) [12]. Sustained mPTP opening causes dissipation of the mitochondrial membrane potential, impairment of ATP synthesis, mitochondrial swelling and the release of pro-apoptotic factors, ultimately contributing to cardiomyocyte necrosis and apoptosis.

In myocardial ischemia-reperfusion injury (MIRI), ferroptosis and inflammation contribute to the amplification of myocardial damage through distinct yet interconnected pathological pathways. Ferroptosis is a form of regulated cell death (RCD) characterized by the iron-dependent accumulation of lipid peroxides. Following reperfusion, dysfunction of mitochondrial electron transport chain complexes I and III promotes excessive reactive oxygen species (ROS) generation and oxidative stress, thereby creating a cellular environment that favors the initiation and progression of ferroptosis[13]. Under physiological conditions, intracellular iron

homeostasis is tightly regulated and excess iron is sequestered within ferritin to limit its redox activity. However, under ischemic, hypoxic and reperfusion-associated stress, nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy promotes the lysosomal degradation of ferritin and the subsequent release of labile iron[14]. In addition, oxidative stress induced by ischemia-reperfusion (I/R) injury impairs the endogenous antioxidant defense mechanisms that protect cells against ferroptosis. Glutathione (GSH) serves as an essential reducing cofactor for glutathione peroxidase 4 (GPX4), which suppresses ferroptosis by reducing phospholipid hydroperoxides to their corresponding non-toxic lipid alcohols. I/R injury not only accelerates GSH depletion but also disrupts the function of the cystine/glutamate antiporter system Xc^-, thereby inhibiting cystine uptake and limiting intracellular GSH biosynthesis[15]. The resulting impairment of the GSH-GPX4 antioxidant axis facilitates lipid peroxide accumulation and increases cardiomyocyte susceptibility to ferroptosis. Evidence suggests that mitochondrial glutathione (GSH) import is mediated primarily by the dicarboxylate carrier (DIC) and the 2-oxoglutarate carrier (OGC). Inhibition of these mitochondrial transporters disrupts GSH import, accelerates mitochondrial GSH depletion and increases cellular susceptibility to ferroptosis[16]. The transcription factor BTB and CNC homology 1 (BACH1) can promote the transcription of cation transport regulator-like protein 1 (CHAC1), a γ-glutamyl cyclotransferase that catalyses GSH degradation. Activation of BACH-CHAC1-GSH axis may therefore exacerbate GSH depletion and weaken cellular antioxidant defences during myocardial ischemia-reperfusion injury [17]. Emerging evidence suggests that oxidized phosphatidylcholines (OxPCs) generated during ischemia-reperfusion (I/R) serve as critical mediators of cardiomyocyte ferroptosis. Mechanistically, OxPCs impair glutathione peroxidase 4 (GPX4) activity and disrupt mitochondrial bioenergetic homeostasis, thereby promoting lipid peroxide accumulation and triggering extensive

ferroptotic cardiomyocyte death [18]. In myocardial ischemia-reperfusion (I/R) injury, dysregulation of the circular RNA FEACR-mediated nicotinamide phosphoribosyltransferase (NAMPT)-sirtuin 1 (SIRT1)-forkhead box O1 (FOXO1)-ferritin heavy chain 1 (FTH1) signaling axis exacerbates cardiomyocyte ferroptosis and compromises cardiac function. Accordingly, FEACR and its downstream effectors may represent promising therapeutic targets for attenuating ferroptosis-mediated myocardial injury following ischemia-reperfusion. In parallel with ferroptosis, inflammation constitutes another major pathological mechanism underlying myocardial ischemia-reperfusion injury. During ischemia and subsequent reperfusion, injured cardiomyocytes release damage-associated molecular patterns (DAMPs), including high-mobility group box 1 (HMGB1). These endogenous danger signals activate pattern-recognition receptors, such as Toll-like receptors (TLRs) and their downstream nuclear factor-κB (NF-κB) signaling pathway, thereby promoting the production of pro-inflammatory mediators including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6)[19]. Concurrently, the expression of adhesion molecules including P-selectin, E-selectin and intercellular adhesion molecule-1 (ICAM-1) is upregulated on vascular endothelial cells. This endothelial activation promotes the adhesion, transendothelial migration and subsequent infiltration of neutrophils and monocytes into the injured myocardium. Once recruited, these inflammatory cells release reactive oxygen species and proteolytic enzymes, thereby amplifying myocardial tissue damage and exacerbating coronary microvascular injury[20]. Furthermore, activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome promotes the maturation and secretion of interleukin-1β(IL-1β) and interleukin-18 (IL-18), while simultaneously inducing pyroptotic cell death. Collectively, these processes amplify the myocardial inflammatory response, expand infarct size, and exacerbate cardiac dysfunction.

The clinical relevance of myocardial ischemia-reperfusion injury (MIRI) is supported by a substantial body of clinical and evidence-based data. In clinical practice, a subset of patients with acute myocardial infarction continue to develop no-reflow, microvascular obstruction, intramyocardial haemorrhage and incomplete recovery of cardiac function despite successful restoration of epicardial coronary blood flow by primary percutaneous coronary intervention. These observations indicate that successful recanalization of the culprit coronary artery does not necessarily translate into complete reperfusion at the myocardial tissue level [21]. Moreover, several large-scale randomized controlled trials evaluating interventions targeting the mitochondrial permeability transition pore (mPTP), ischemic postconditioning (IPost) and remote ischemic conditioning (RIC) have failed to demonstrate consistent clinical benefits[22–24].Thus, although myocardial ischemia-reperfusion injury (MIRI) is supported by substantial pathophysiological evidence and well-characterized clinical manifestations, specific preventive and therapeutic strategies remain at an early stage of clinical translation. A growing body of evidence indicates that ferroptosis and inflammation are linked through bidirectional regulatory interactions and jointly contribute to the initiation and progression of MIRI. This review systematically outlines the core molecular mechanisms of ferroptosis and summarizes the pathophysiological roles of ferroptosis and inflammation in myocardial ischemia-reperfusion injury. On this basis, we highlight recent advances in the use of naturally derived bioactive compounds and conventional pharmacological agents to attenuate myocardial injury by modulating ferroptosis and inflammation related signaling pathways. We further discuss the limitations of the currently available evidence and the major challenges associated with clinical translation. Elucidating the mechanistic crosstalk between ferroptosis and inflammation may provide a rationale for the development of natural-product-based therapeutic strategies and identify promising

89 directions for the prevention and treatment of MIRI, as well as for the discovery and development of novel botanical therapeutics.

90 2 | OVERVIEW OF FERROPTOSIS

91 2.1 | Definition of ferroptosis

92 In 2012, the term “ferroptosis” was first introduced by Dixon and colleagues to describe a distinct form of regulated cell death[25], Unlike apoptosis and autophagy,
93 ferroptosis is characterized by iron-dependent phospholipid peroxidation and the lethal accumulation of lipid peroxides. This process can be effectively suppressed by
94 iron chelators, further supporting the essential role of redox-active ferrous iron (Fe^{2+}) in ferroptotic cell death[26]. The excessive peroxidation of membrane
95 phospholipids containing polyunsaturated fatty acids (PUFA-PLs), accompanied by the accumulation of phospholipid hydroperoxides (PLOOHs) and the subsequent
96 loss of membrane integrity, represents a defining biochemical event in ferroptotic cell death[27]. At its core, ferroptosis reflects a disruption of redox homeostasis
97 arising from an imbalance between the accumulation of oxidative damage and insufficient antioxidant defence. Ferroptosis is morphologically, biochemically and
98 genetically distinct from apoptosis, necrosis and autophagy. Its characteristic ultrastructural features include shrunken mitochondria, increased mitochondrial membrane
99 density and reduced or absent mitochondrial cristae. By contrast, plasma membrane and nuclear morphology remain relatively preserved during the early stages with
100 no apparent nuclear shrinkage or chromatin condensation[28]. Studies have shown that treatment with ferroptosis inducers, such as erastin and RSL3, can induce

mitochondrial membrane depolarization and enhance mitochondrial reactive oxygen species production, thereby amplifying oxidative damage to membrane structures and facilitating ferroptotic cell death[29]. However, mitochondria-targeted antioxidants, such as MitoQ and MitoTEMPO, as well as iron chelators, can effectively suppress mitochondrial lipid peroxidation, thereby preserving mitochondrial morphology and preventing ferroptotic cell death[30]. At the biochemical level, intracellular glutathione (GSH) levels and glutathione peroxidase 4 (GPX4) activity are reduced, thereby impairing the GPX4-mediated reduction and detoxification of lipid hydroperoxides. Meanwhile, ferrous iron (Fe2+) catalyzes the conversion of hydrogen peroxide (H2O2) into highly reactive hydroxyl radicals (•OH) through the Fenton reaction. These radicals directly attack polyunsaturated fatty acid-containing phospholipids (PUFA-PLs), thereby initiating a self-propagating chain reaction of lipid peroxidation.[31]. Recent studies have highlighted the pivotal roles of genetic and epigenetic mechanisms in the regulation of ferroptosis. Canonical genetic regulation, exemplified by the transcriptional activation or repression of ferroptosis-related genes by transcription factors such as p53, BACH1, HNF4A, and HIC1, directly determines cellular susceptibility to ferroptosis[32–34].

3 | MOLECULAR MECHANISMS OF FERROPTOSIS

Dysregulated iron metabolism, the accumulation of lipid peroxides, the canonical GPX4-dependent defense pathway and GPX4-independent defense pathways constitute the four principal mechanistic components of ferroptosis. Through distinct but interconnected routes, these processes promote oxidative stress, alter lipid-

mediator signaling and amplify inflammatory responses, thereby driving excessive lipid peroxidation and ultimately triggering ferroptotic cell death.（Figure 1）

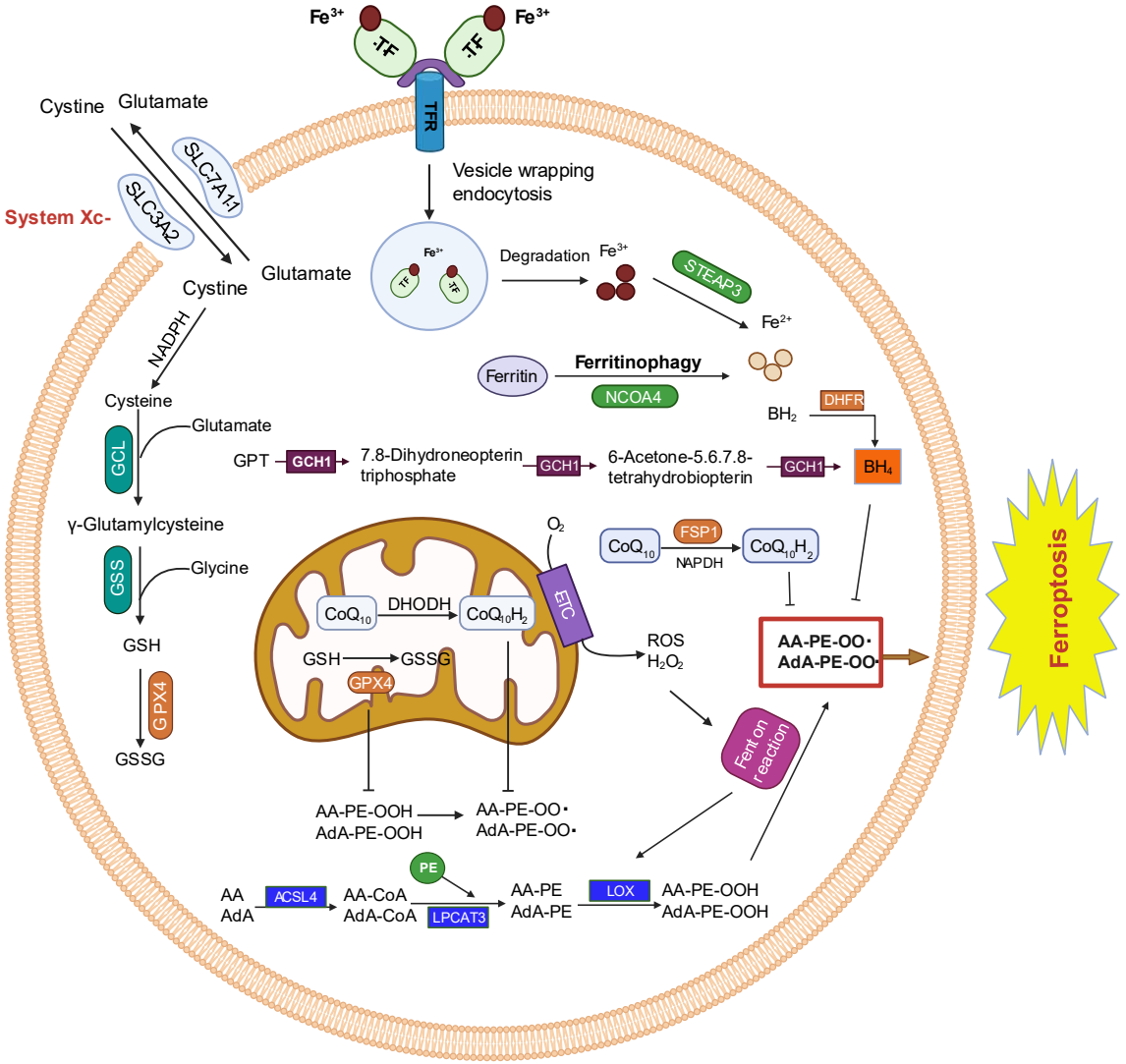

Fe3+
TF
TF
Fe3+
TFR
Vesicle wrapping endocytosis
Cystine
Glutamate
SLC7A11
SLC3A2
System Xc-
Cystine
Glutamate
Degradation
Fe3+
STEAP3
Fe2+
NADPH
Ferritin
Ferritinophagy
NCOA4
Cysteine
Glutamate
GCL
BH2
DHFR
GPT
GCH1
7,8-Dihydroneopterin triphosphate
GCH1
6-Acetone-5,6,7,8-tetrahydrobiopterin
GCH1
BH4
γ-Glutamylcysteine
GSS
Glycine
GSH
GPX4
GSSG
O2
ETC
CoQ10
DHODH
CoQ10H2
GSH
GSSG
GPX4
ROS
H2O2
CoQ10
FSP1
NAPDH
CoQ10H2
AA-PE-OO·
AdA-PE-OO·
Fenton reaction
AA-PE-OOH
AdA-PE-OOH
AA-PE-OO·
AdA-PE-OO·
PE
AA
AdA
ACSL4
AA-CoA
AdA-CoA
LPCAT3
AA-PE
AdA-PE
LOX
AA-PE-OOH
AdA-PE-OOH
Ferroptosis

Figure 1. Molecular mechanism of ferroptosis

3.1 | Iron dyshomeostasis

As an essential transition metal ion, iron is indispensable for the initiation and execution of ferroptosis and disruption of intracellular iron homeostasis can directly trigger this form of regulated cell death[35]. Iron-loaded transferrin binds to transferrin receptor 1 (TfR1) on the plasma membrane and the resulting transferrin-TfR1 complex is internalized into endosomes through receptor-mediated endocytosis. ATP-dependent proton pumps located on the endosomal membrane acidify the endosomal lumen to the pH of approximately 5.5. This acidic environment facilitates the dissociation of Fe^{3+} from transferrin after which Fe^{3+} is reduced to the more redox-active Fe^{2+} form, predominantly by the endosomal ferrireductase STEAP3. The resulting Fe^{2+} is subsequently transported from the endosomal lumen into the cytosol by divalent metal transporter 1 (DMT1), with ZIP8 and ZIP14 also contributing to cellular ferrous iron transport. In addition to transferrin-bound iron, lactoferrin (also known as lactotransferrin) and heme can serve as alternative iron sources and be internalized by cells through receptor-mediated endocytic pathways. In contrast to transferrin, lactoferrin retains a high affinity for iron under acidic conditions, such as those encountered at sites of infection and inflammation[36]. Under pathological conditions, heme released from extravasated erythrocytes following intramyocardial hemorrhage constitutes a critical exogenous source of iron. Its subsequent degradation liberates redox-active ferrous iron, thereby facilitating lipid peroxidation and triggering ferroptosis in cardiomyocytes[37]. Poly (rC) -binding proteins 1

and 2 (PCBP1/2) function as cytosolic iron chaperones that bind and deliver labile Fe^{2+} to specific recipient proteins, including ferritin for iron storage, non-haem iron enzymes for metal cofactor incorporation and ferroportin for cellular iron export[38].

Ferritin is the principal intracellular iron-storage protein and is composed of ferritin heavy-chain (FTH1) and light-chain (FTL) subunits. Iron regulatory protein 2 (IRP2), encoded by IREB2, is a key post-transcriptional regulator of cellular iron homeostasis and regulates ferritin expression in an iron-dependent manner. Under iron-deficient conditions, IRP2 binds to iron-responsive elements (IREs) within target mRNAs. This interaction stabilizes TFRC mRNA and thereby increases transferrin receptor 1 (TfR1) expression and iron uptake, while simultaneously repressing the translation of ferritin and ferroportin, resulting in reduced iron storage and export. Under iron-replete conditions, IRP2 is recognized by the F-box and leucine-rich repeat protein 5 (FBXL5) and subsequently degraded through the ubiquitin-proteasome pathway. The resulting loss of IRP2-mediated translational repression promotes ferritin synthesis, enabling excess intracellular iron to be safely sequestered and thereby limiting labile iron-mediated oxidative damage [39]. Lv reported that the IREB2 D826V variant upregulates FTH1 expression, thereby further activating genes involved in de novo lipogenesis[40]. In addition, nuclear receptor coactivator 4 (NCOA4) functions as a selective cargo receptor that targets ferritin for lysosomal degradation through ferritinophagy[41], the selective degradation of intracellular iron-storage ferritin releases substantial amounts of labile Fe^{2+}, thereby disrupting cellular iron homeostasis. The resulting expansion of the labile iron pool promotes Fe^{2+} accumulation, excessive reactive oxygen species (ROS) generation, and lipid peroxidation ultimately driving iron-dependent ferroptotic cell death[42]. Studies have demonstrated that nuclear receptor coactivator 4 (NCOA4) functions as a

selective cargo receptor by binding to ferritin heavy chain 1 (FTH1) and targeting ferritin to the autophagosome-lysosome pathway for degradation. This ATG5 and ATG7-dependent process, termed ferritinophagy promotes the lysosomal degradation of ferritin and the subsequent release of its sequestered iron into the intracellular labile iron pool [43].

Free heme is highly cytotoxic. Hemopexin (HPX), a high-affinity heme-binding protein, sequesters free heme to form heme-HPX complexes. These complexes are subsequently internalized via endocytosis and trafficked to endosomes. Within the endosomal membrane, heme-responsive gene 1 (HRG1), a heme transporter encoded by SLC48A1, mediates the translocation of heme from the endosomal lumen into the cytosol [44]. Cytosolic heme is degraded by heme oxygenase-1 (HO-1), which is encoded by the HMOX1 gene. HO-1 catalyzes the oxidative degradation of heme, yielding biliverdin, carbon monoxide (CO) and ferrous iron (Fe^{2+}) [45]. A fraction of the Fe^{2+} released from heme degradation is delivered by the iron chaperones poly (rC)-binding protein 1 and 2 (PCBP1/PCBP2) to non-heme iron-dependent enzymes, thereby contributing to the maintenance of cellular iron homeostasis. In contrast, excess labile Fe^{2+} expands the labile iron pool (LIP) and promotes Fenton chemistry, leading to excessive lipid peroxidation and ultimately triggering ferroptotic cell death. Notably, catecholamine stimulation has been shown to induce ferroptosis in cardiomyocytes by downregulating the transcriptional repressor BTB and CNC homology 1 (BACH1), thereby derepressing HO-1 expression. The resulting increase in HO-1 activity enhances intracellular labile iron accumulation and together with enhanced GPX4 degradation, promotes lipid peroxidation and

drives cardiomyocyte ferroptosis [46]. Doxorubicin (DOX) can also upregulate HO-1 through NRF2-mediated transcriptional activation, thereby enhancing heme catabolism and increasing the release of labile iron. The resulting iron accumulation promotes lipid peroxidation and ultimately contributes to ferroptotic cell death.

Ferroportin (FPN), a plasma membrane iron exporter, mediates the efflux of intracellular Fe^{2+} through an alternating-access transport mechanism and thereby plays a pivotal role in maintaining cellular iron homeostasis. Structurally, FPN contains metal-binding sites that become accessible to cytosolic Fe^{2+} in the inward-facing conformation. Upon Fe^{2+} binding, conformational rearrangement of FPN switches the transporter to an outward-facing state, enabling the release of Fe^{2+} into the extracellular space. Because the negatively charged membrane potential would otherwise impose an electrochemical barrier to the efflux of positively charged Fe^{2+}, FPN operates as an electroneutral Fe^{2+}/H^{+} antiporter. Specifically, the export of one Fe^{2+} ion is coupled to the counter-transport of two H^{+} ions into the cytosol, thereby facilitating iron efflux while maintaining overall charge neutrality across the plasma membrane [47]. Following export from the cell, Fe^{2+} is oxidized to Fe^{3+} by the ferroxidase activity of ceruloplasmin (CP) or the membrane-associated ferroxidase hephaestin (HEPH). The resulting Fe^{3+} subsequently binds to transferrin for systemic transport and distribution to sites of iron utilization or storage. In addition, Ca^{2+} has been shown to act as a cofactor that modulates the iron-export activity of ferroportin (FPN). Notably, Ca^{2+} itself is not transported by FPN but instead regulates FPN-mediated Fe^{2+} transport [48]. Downregulation of ferroportin (FPN) expression or inhibition of its iron-export activity impairs cellular iron efflux, resulting in intracellular iron retention and expansion of the labile iron pool. The resulting iron overload enhances Fenton chemistry and promotes the accumulation of lipid peroxides, thereby increasing cellular susceptibility to ferroptosis.Hepcidin negatively regulates

ferroportin (FPN) by binding to FPN and promoting its internalization and subsequent degradation, thereby suppressing cellular iron export. In contrast, the gain-of-function FPN variant p.Y333H confers resistance to hepcidin-mediated regulation, allowing sustained iron efflux despite elevated hepcidin levels. This dysregulated iron export increases circulating iron availability and ultimately promotes iron accumulation in parenchymal tissues [49]. Under inflammatory conditions, pro-inflammatory cytokines stimulate hepcidin expression, which in turn promotes the internalization and subsequent degradation of ferroportin (FPN). This hepcidin-mediated suppression of FPN impairs cellular iron efflux, thereby resulting in intracellular iron retention and accumulation [50]. Studies have shown that prominin-2 (PROM2), a pentaspan transmembrane glycoprotein, promotes the formation of ferritin-containing multivesicular bodies (MVBs) and facilitates the subsequent export of ferritin-bound iron through exosome secretion. This exosome-mediated iron efflux effectively reduces the intracellular labile iron pool (LIP) available to fuel ferroptotic lipid peroxidation, thereby limiting cellular susceptibility to ferroptosis[51]. In addition, intracellular labile Fe^{2+} catalyzes the conversion of hydrogen peroxide (H_2O_2) into highly reactive hydroxyl radicals (·OH) through Fenton chemistry. These hydroxyl radicals readily attack polyunsaturated fatty acid-containing phospholipids (PUFA-PLs), thereby initiating and propagating lipid peroxidation chain reactions. This iron-dependent radical-mediated lipid oxidation represents a major mechanism through which oxidative stress compromises membrane integrity and induces cellular injury [52]. In addition to promoting non-enzymatic lipid peroxidation through Fenton chemistry, iron also contributes to enzymatic lipid oxidation. Lipoxygenases (LOXs) are non-heme iron-dependent enzymes that require catalytic iron for the oxidation of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs), whereas cytochro me P450 oxidoreductase (POR) promotes lipid

peroxidation through flavin-dependent electron transfer. Together, these enzymatic pathways facilitate the accumulation of lipid peroxides and contribute to ferroptotic cell death (ou et al., 2020).（Figure 2）

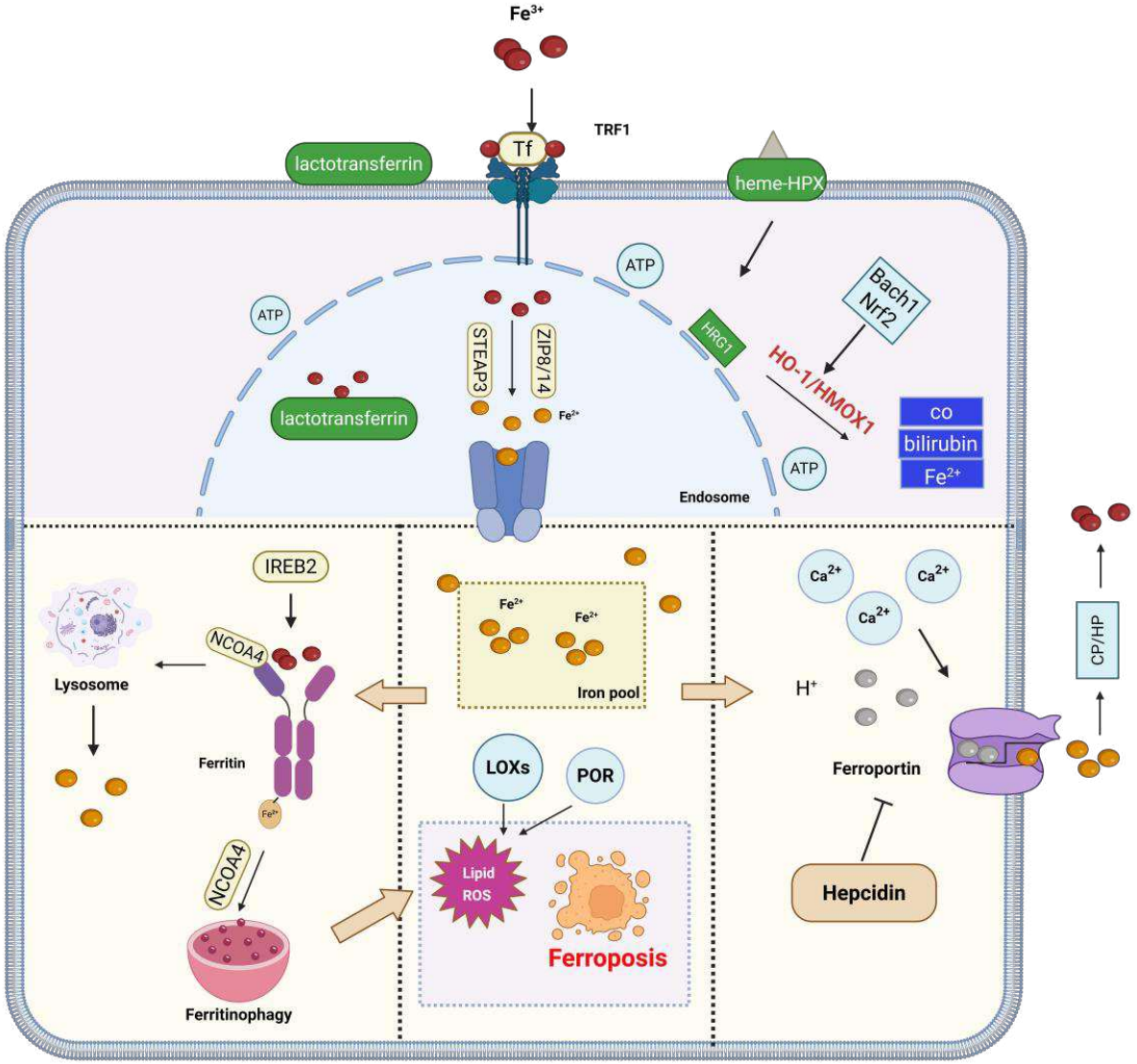

Fe3+
TRF1
Tf
lactotransferrin
heme-HPX
ATP
ATP
ATP
STEAP3
ZIP8/14
Fe2+
HRG1
Bach1
Nrf2
HO-1/HMOX1
CO
bilirubin
Fe2+
lactotransferrin
Endosome
IREB2
NCOA4
Lysosome
Ferritin
Fe2+
NCOA4
Ferritinophagy
Fe2+
Fe2+
Iron pool
LOXs
POR
Lipid
ROS
Ferroposis
Ca2+
Ca2+
Ca2+
H+
Ferroportin
Hepcidin
CP/HP

Figure 2. Schematic for the regulation of iron homeostasis

3.2 | Accumulation of lipid peroxides

Cellular fatty acids are incorporated into various lipid species, including triacylglycerols, phospholipids and cholesteryl esters, while a substantial fraction is sequestered within lipid droplets (LDs) for storage. Upon activation of lipophagy, lipid droplets undergo autophagic degradation, resulting in the mobilization and release of stored fatty acids, which can subsequently participate in diverse pathological processes. Ferroptosis exhibits marked selectivity toward specific lipid substrates and is particularly dependent on the peroxidation of membrane phospholipids. Among these substrates, polyunsaturated fatty acids (PUFAs) are especially susceptible to oxidative attack because their multiple carbon-carbon double bonds confer a high vulnerability to free-radical-mediated oxidation. Once incorporated into membrane phospholipids, PUFA-containing phospholipids (PUFA-PLs) can undergo radical-initiated lipid peroxidation and propagate self-amplifying oxidative chain reactions, ultimately compromising membrane integrity and promoting ferroptotic cell death [54]. Long-chain acyl-CoA synthetase 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are key determinants of cellular susceptibility to ferroptosis [55], ACSL4 and LPCAT3 act cooperatively to regulate the esterification and remodeling of polyunsaturated fatty acids (PUFAs) within membrane phospholipids, thereby critically determining cellular susceptibility to ferroptosis. ACSL4 catalyzes the CoA-dependent activation of free fatty acids, with a preference for long-chain PUFAs, generating fatty acyl-CoAs and PUFA-CoAs, respectively. These activated fatty acyl-CoAs can subsequently be partitioned into different lipid metabolic pathways: a fraction is incorporated into

194 triacylglycerols (TAGs) for lipid storage, whereas PUFA-CoAs serve as essential substrates for subsequent phospholipid remodeling. LPCAT3 then catalyzes the
195 incorporation of PUFA acyl chains into membrane phospholipids, thereby enriching cellular membranes with oxidation-prone PUFA-containing phospholipids
196 (PUFA-PLs). The accumulation of PUFA-PLs provides susceptible substrates for lipid peroxidation and consequently enhances cellular sensitivity to ferroptosis[56].
197 Triacsin C is a broad-spectrum inhibitor of long-chain acyl-CoA synthetases (ACSLs) that inhibits ACSL1 and ACSL4 activity, thereby suppressing the conversion of
198 free fatty acids including PUFAs, into their corresponding fatty acyl-CoA derivatives and consequently limiting PUFA esterification. Mechanistically, triacsin C acts
199 as a competitive inhibitor with respect to fatty acid substrates by competing for substrate-binding sites on ACSLs. Rosiglitazone, a member of the thiazolidinedione
200 (TZD) class, is a well-established ligand and agonist of peroxisome proliferator-activated receptor γ (PPAR γ). However, its inhibitory effect on ACSL activity is
201 independent of PPARγ activation, indicating a PPARγ-independent mechanism of ACSL inhibition [57]. Rosiglitazone has been reported to directly interact with
202 ACSL4 through its thiazolidinedione moiety, thereby selectively inhibiting ACSL4 enzymatic activity. Consequently, ACSL4 inhibition reduces fatty acid activation
203 and alters the metabolic channeling of fatty acids into diacylglycerol (DAG) and triacylglycerol (TAG) synthesis, ultimately perturbing phospholipid biosynthesis and
204 membrane lipid remodeling.

205 The abundance of polyunsaturated fatty acids (PUFAs) within membrane phospholipids is a critical determinant of cellular susceptibility to ferroptosis. Notably,
206 ACSL4 exhibits a pronounced substrate preference for highly unsaturated fatty acids (HUFAs), particularly arachidonic acid (AA) and adrenic acid (AdA), thereby

promoting their activation and subsequent incorporation into membrane phospholipids that are highly susceptible to lipid peroxidation[58]. ACSL4 catalyzes the CoA-dependent activation of arachidonic acid (AA) and adrenic acid (AdA), generating the corresponding PUFA acyl-CoA derivatives, arachidonoyl-CoA and adrenoyl-CoA. These activated PUFAs subsequently serve as substrates for LPCAT3-mediated phospholipid remodeling, resulting in their esterification into membrane phospholipids and the generation of oxidation-prone phospholipid species, including AA- and AdA-containing phosphatidylethanolamines (PE-AA and PE-AdA). Mechanistically, during the Lands cycle, LPCAT3 catalyzes the reacylation of lysophospholipids by incorporating PUFA acyl-CoAs, particularly arachidonoyl-CoA, into the sn-2 position of the glycerophospholipid backbone. This process enriches membrane phospholipids with AA and other PUFAs, thereby expanding the pool of peroxidation-susceptible phospholipid substrates that can promote ferroptosis [59]. In macrophages, ACSL4 deficiency markedly reduces the cellular pool of highly unsaturated fatty acyl-CoAs (HUFA-CoAs) and consequently decreases the incorporation of HUFAs into phosphatidylcholine (PC) [60].

Lipoxygenases (LOXs) constitute a family of non-heme iron-dependent dioxygenases that catalyze the regio- and stereospecific oxygenation of polyunsaturated fatty acids (PUFAs) and thereby contribute to the selective oxidation of PUFA-containing phospholipids (PUFA-PLs). In certain LOX isoforms, the N-terminal polycystin-1, lipoxygenase, α-toxin (PLAT) domain facilitates membrane association, thereby positioning the catalytic domain in close proximity to membrane-embedded lipid substrates. This membrane-targeting configuration enables LOXs to access and oxidize esterified PUFAs within phospholipids, promoting the formation of phospholipid hydroperoxides and facilitating lipid peroxidation (Mohammadyani et al., 2017). The lipoxygenase (LOX) family comprises multiple isoforms with

distinct substrate and positional specificities. Among these, 5-lipoxygenase (5-LOX; ALOX5), 12-lipoxygenase (12-LOX; ALOX12) and 15-lipoxygenases (15-LOXs; ALOX15/ALOX15B) catalyze the regioselective oxygenation of arachidonic acid (AA) at different carbon positions, generating hydroperoxyeicosatetraenoic acid intermediates and their downstream bioactive lipid mediators. These pathways give rise to hydroxyeicosatetraenoic acids (HETEs), depending on the LOX isoform and cellular context, contribute to the biosynthesis of leukotrienes and lipoxins, which are important regulators of inflammatory responses. Several pharmacological agents, including zileuton, MK-886, baicalein, cinnamyl-3,4-dihydroxy-α-cyanocinnamate (CDC) and AA-861, have been used to inhibit or modulate specific components of LOX-dependent lipid metabolism. Zileuton, CDC and AA-861 directly inhibit 5-LOX activity and thereby suppress the 5-LOX-dependent biosynthesis of leukotrienes. In contrast, MK-886 does not directly inhibit 5-LOX but targets 5-lipoxygenase-activating protein (FLAP; encoded by ALOX5AP), thereby disrupting FLAP-dependent activation of ALOX5 and consequently attenuating leukotriene biosynthesis. Baicalein is widely used as a pharmacological inhibitor of 12/15-LOX and has been extensively employed in experimental models of ischemic and oxidative tissue injury. 15-Lipoxygenase (15-LOX) exhibits potent oxidative activity toward phosphatidylethanolamine species containing two polyunsaturated fatty acyl chains (di-PUFA-PEs). Notably, di-PUFA-PEs are enriched at endoplasmic reticulum-mitochondria contact sites (EMCSs), rendering these membrane contact regions particularly susceptible to phospholipid peroxidation and potentially establishing localized hotspots of lipid peroxidation.

The generation of lipid peroxides is critically dependent on iron-mediated oxidative reactions. As a redox-active transition metal, iron catalyzes the formation of

highly reactive oxygen-centered radicals, particularly through Fenton chemistry, which readily attack polyunsaturated fatty acid-containing phospholipids (PUFA-PLs) within cellular membranes. This iron-dependent radical oxidation initiates lipid peroxidation and promotes the propagation of self-amplifying lipid peroxidation chain reactions, ultimately leading to the accumulation of lipid peroxides [61]. Excess intracellular labile Fe^{2+} reacts with hydrogen peroxide (H_2O_2) through Fenton chemistry, generating highly reactive hydroxyl radicals (·OH). These radicals abstract hydrogen atoms, particularly from the bis-allylic positions of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs), thereby generating carbon-centered lipid radicals (L·). The resulting lipid radicals rapidly react with molecular oxygen (O_2) to form lipid peroxyl radicals (LOO·), which subsequently abstract hydrogen atoms from adjacent PUFA-containing phospholipids to generate lipid hydroperoxides (LOOH) and new lipid radicals. This self-propagating radical cycle drives the chain propagation of lipid peroxidation, leading to the progressive accumulation of phospholipid hydroperoxides. Under physiological conditions, glutathione peroxidase 4 (GPX4) functions as a key lipid peroxide-detoxifying enzyme that uses reduced glutathione (GSH) as an essential reducing substrate to convert toxic lipid hydroperoxides (LOOHs) into their corresponding non-toxic lipid alcohols (LOHs). By eliminating phospholipid hydroperoxides before they can propagate further radical reactions, the GPX4-GSH antioxidant system effectively terminates lipid peroxidation chain reactions and thereby preserves membrane redox homeostasis [62]. SLC7A11 (xCT), the light-chain subunit of the cystine/glutamate antiporter system Xc^-, mediates the uptake of extracellular cystine in exchange for intracellular glutamate. Following its intracellular reduction to cysteine, imported cystine provides an essential precursor for glutathione (GSH) biosynthesis, thereby maintaining the cellular GSH pool required for GPX4-dependent reduction of lipid

hydroperoxides and suppression of lipid peroxidation [63]. When the SLC7A11-GSH-GPX4 antioxidant axis is compromised, cells lose the capacity to efficiently detoxify phospholipid hydroperoxides (PLOOHs), resulting in their excessive accumulation within cellular membranes. Progressive phospholipid peroxidation destabilizes the lipid bilayer, increases membrane permeability, disrupts ionic homeostasis, and ultimately causes loss of membrane integrity. These membrane-damaging events collectively culminate in ferroptotic cell death [64]. The NADPH oxidase (NOX) family represents an important enzymatic source of reactive oxygen species (ROS) and contributes to the regulation of cellular redox homeostasis. NOX-derived ROS can promote oxidative modification of membrane lipids and thereby facilitate lipid peroxidation. Moreover, hydroxyeicosatetraenoic acids (HETEs) generated through 12/15-lipoxygenase (12/15-LOX)-dependent arachidonic acid metabolism can stimulate NOX activation, leading to further ROS production. This reciprocal interaction between LOX-derived lipid mediators and NOX-dependent ROS generation establishes a feed-forward oxidative amplification loop that exacerbates lipid peroxidation and oxidative cellular injury [65]. The mitochondrial electron transport chain (ETC) represents a major intracellular source of reactive oxygen species (ROS), particularly under conditions of mitochondrial dysfunction or excessive electron flux. Mitochondria-derived ROS can promote the oxidative modification of membrane lipids and thereby contribute to the initiation and propagation of lipid peroxidation. Acetyl-CoA occupies a central metabolic branch point between lipid biosynthesis and mitochondrial oxidative metabolism. In the lipogenic pathway, acetyl-CoA is carboxylated to malonyl-CoA by acetyl-CoA carboxylase (ACC), providing an essential precursor for de novo fatty acid synthesis. Alternatively, acetyl-CoA enters the tricarboxylic acid (TCA) cycle, generating the reducing equivalents NADH and $FADH_2$, which subsequently donate electrons to the ETC to support

oxidative phosphorylation and ATP production. Increased ACC activity elevates malonyl-CoA levels, thereby promoting fatty acid synthesis while suppressing mitochondrial fatty acid oxidation, in part through inhibition of carnitine palmitoyltransferase 1 (CPT1). Consequently, reduced fatty acid oxidation may limit mitochondrial oxidative stress and attenuate ROS-associated lipid peroxidation under specific metabolic conditions.（Figure 3.）

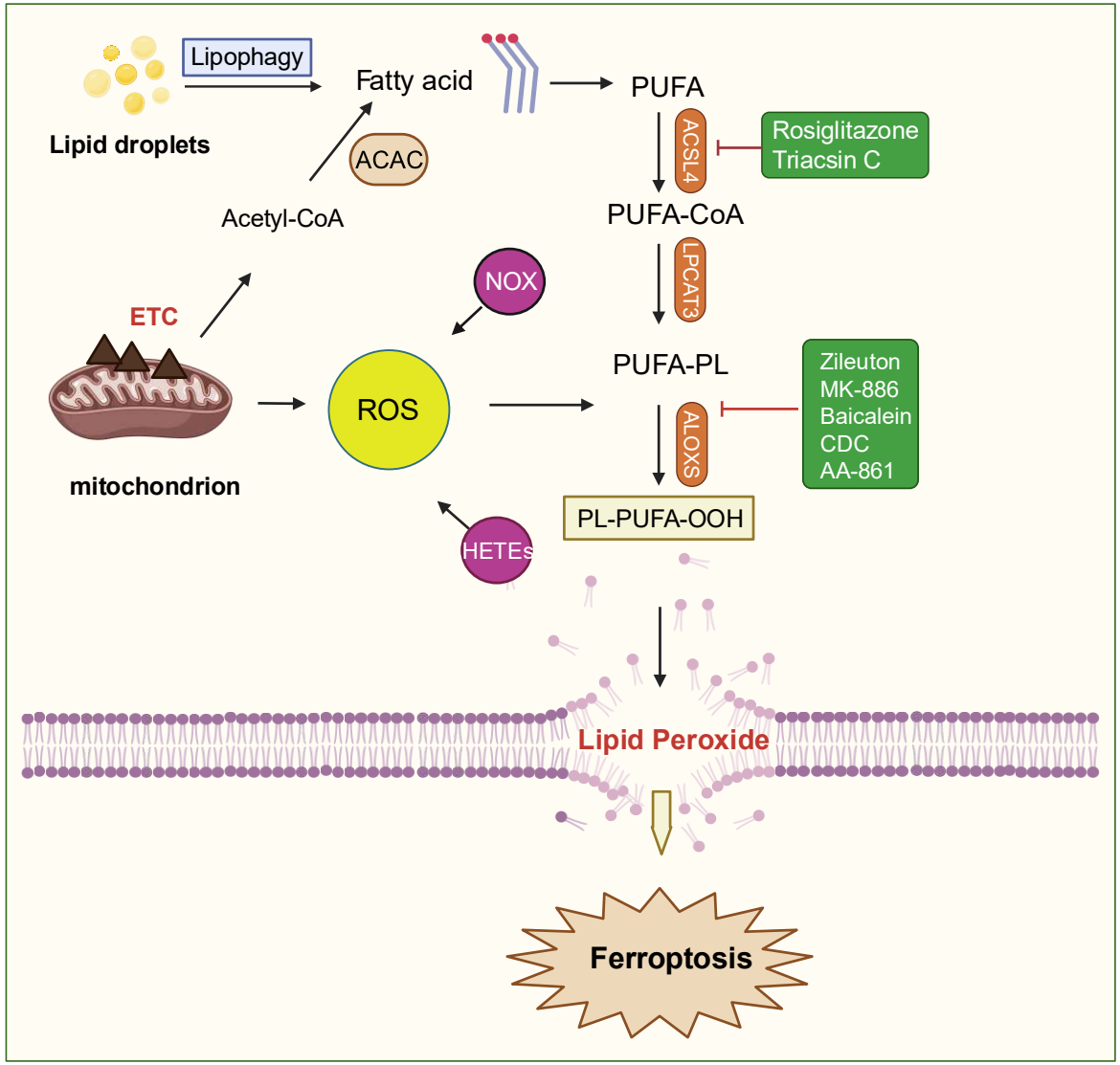

Lipophagy
Lipid droplets
Fatty acid
ACAC
Acetyl-CoA
PUFA
ACSL4
Rosiglitazone
Triacsin C
PUFA-CoA
LPCAT3
NOX
ETC
ROS
PUFA-PL
Zileuton
MK-886
Baicalein
CDC
AA-861
ALOXS
mitochondrion
PL-PUFA-OOH
HETEs
Lipid Peroxide
Ferroptosis

Figure 3. excessive accumulation of lipid peroxides

3.3 | The canonical GPX4-dependent defence pathway

The System Xc^--GSH-GPX4 axis represents a canonical and central antioxidant defense pathway against ferroptosis, primarily by maintaining membrane lipid redox homeostasis and limiting the accumulation of lipid peroxides. System Xc^- is a heterodimeric cystine/glutamate antiporter composed of the light-chain subunit xCT, encoded by SLC7A11 and the heavy-chain subunit 4F2hc (CD98hc), encoded by SLC3A2, which are covalently linked through a disulfide bond. Functionally, System Xc^- mediates the Na^+-independent uptake of extracellular cystine in exchange for intracellular glutamate at a 1:1 stoichiometric ratio, thereby sustaining intracellular cysteine availability for glutathione (GSH) biosynthesis and supporting GPX4-dependent detoxification of lipid hydroperoxides [66]. Within System Xc^-, the xCT subunit is responsible for substrate recognition and cystine/glutamate exchange, whereas the 4F2hc subunit primarily contributes to transporter stability and proper localization at the plasma membrane. Following cellular uptake, cystine is rapidly reduced to cysteine (Cys) under the intracellular reducing environment. Cysteine subsequently serves as a rate-limiting precursor for glutathione (GSH) biosynthesis and provides the thiol (-SH) group that constitutes the principal redox-active moiety of GSH. This cysteine-derived thiol enables GSH to function as an essential reducing substrate in cellular antioxidant defense [67]. Glutamate-cysteine ligase (GCL) catalyzes the rate-limiting step of glutathione (GSH) biosynthesis and therefore serves as a major determinant of cellular GSH synthetic capacity. Glutamate not only functions as the intracellular exchange substrate for System Xc^- but also constitutes one of the three amino acid precursors required for GSH

synthesis. In the first step of GSH biosynthesis, GCL catalyzes the ATP-dependent ligation of glutamate and cysteine (Cys) to generate γ-glutamylcysteine (γ-Glu-Cys). Subsequently, glutathione synthetase (GSS) catalyzes the addition of glycine (Gly) to γ-glutamylcysteine, resulting in the formation of GSH. Because cysteine availability frequently represents a rate-limiting factor for GSH biosynthesis, intracellular cysteine levels critically determine the cellular capacity to maintain GSH-dependent antioxidant defense and thereby constitute an important upstream determinant of ferroptosis susceptibility. The activity of System Xc^- critically influences intracellular glutathione (GSH) biosynthesis and cellular reducing capacity by controlling cystine availability. However, its activity is tightly regulated by multiple transcription factors and signaling pathways. Nuclear factor erythroid 2-related factor 2 (NRF2) promotes xCT expression and thereby enhances cellular resistance to oxidative stress and ferroptosis. Activating transcription factor 4 (ATF4), which is activated as part of the integrated stress response under conditions such as amino acid deprivation, similarly upregulates xCT expression to maintain intracellular cysteine availability and support GSH synthesis. In contrast, the tumor suppressor p53 can negatively regulate xCT/SLC7A11 through both transcription-dependent and transcription-independent mechanisms, thereby restricting cystine uptake and increasing cellular susceptibility to ferroptosis. When System Xc^- function is impaired and extracellular cystine uptake becomes insufficient, cells can engage the transsulfuration pathway as an alternative source of cysteine. Through this metabolic route, sulfur derived from methionine is transferred through the homocysteine-cystathionine pathway to generate cysteine, thereby partially compensating for diminished cystine uptake and sustaining intracellular cysteine and GSH availability[68]. Moreover, supplementation with N-acetylcysteine (NAC) or related cysteine-donating derivatives can suppress ferroptosis by replenishing intracellular cysteine

289 availability, thereby supporting glutathione (GSH) biosynthesis and reinforcing cellular antioxidant capacity against lipid peroxidation (Chen et al., 2024). Although
290 D-cysteine (D-Cys) is not directly incorporated into glutathione (GSH), supplementation with D-Cys can promote the cellular uptake of L-cysteine (L-Cys), thereby
291 transiently maintaining intracellular cysteine and GSH levels. This compensatory effect partially preserves GSH-dependent antioxidant capacity and provides temporary
292 protection against ferroptotic cell death [69]. Studies have demonstrated that several small-molecule compounds, including erastin and its derivatives, sulfasalazine and
293 sorafenib, can inhibit or interfere with System Xc^- activity, thereby restricting cystine uptake and depleting intracellular cysteine and glutathione (GSH). The resulting
294 GSH deficiency compromises GPX4-dependent detoxification of phospholipid hydroperoxides, leading to the accumulation of lipid peroxides and consequently
295 increasing cellular susceptibility to ferroptosis (Fujii et al., 2020). Ferroptosis induced by this class of compounds is associated with mitochondrial function and
296 mitochondrial lipid peroxidation, while endocytic processes can further perturb intracellular iron homeostasis and expand the labile iron pool, thereby enhancing iron-
297 dependent lipid peroxidation and promoting ferroptotic cell death. Notably, supplementation with coenzyme A (CoA) has been reported to selectively suppress
298 ferroptosis triggered by xCT inhibitors, but not that induced by direct GPX4 inhibitors, suggesting that CoA-dependent metabolic processes may specifically modulate
299 ferroptosis arising from impaired cystine uptake. Coenzyme A (CoA) can covalently modify mitochondrial thioredoxin reductase 2 (TXNRD2) at the cysteine residue
300 Cys-483 through a post-translational modification termed CoAlation, thereby supporting the reductive capacity of the mitochondrial thioredoxin system and maintaining
301 mitochondrial redox homeostasis[70]. Collectively, these findings identify the mitochondrial thioredoxin system as a critical redox defense machinery mediating the

anti-ferroptotic effect of CoA, linking CoA-dependent modification of TXNRD2 to the preservation of mitochondrial redox homeostasis and suppression of ferroptotic cell death.

Glutathione peroxidase 4 (GPX4) is a key antioxidant enzyme that suppresses ferroptosis by directly reducing phospholipid hydroperoxides (PLOOHs) within cellular membranes. Unlike other members of the glutathione peroxidase family, GPX4 possesses the unique capacity to efficiently reduce complex membrane-embedded phospholipid hydroperoxides. GPX4 is a selenoprotein whose catalytic active site contains a selenocysteine (Sec) residue, which enables the enzyme to recognize and directly reduce membrane-associated phospholipid hydroperoxides to their corresponding non-toxic phospholipid alcohols, thereby limiting the propagation of lipid peroxidation and protecting cells from ferroptotic death [71]. GPX4 utilizes reduced glutathione (GSH) as a reducing substrate to convert cytotoxic phospholipid hydroperoxides (PLOOHs) into their corresponding, relatively non-toxic phospholipid alcohols (PLOHs), concomitantly oxidizing GSH to glutathione disulfide (GSSG). Through this catalytic process, GPX4 efficiently detoxifies polyunsaturated fatty acid-containing phospholipid hydroperoxides (PUFA-PL-OOHs), thereby limiting the propagation of lipid peroxidation and preventing oxidative membrane damage from progressing beyond a reversible threshold [72]. GPX4 utilizes reduced glutathione (GSH) as a reducing substrate to convert cytotoxic phospholipid hydroperoxides (PLOOHs) into their corresponding, relatively non-toxic phospholipid alcohols (PLOHs), concomitantly oxidizing GSH to glutathione disulfide (GSSG). Through this catalytic process, GPX4 efficiently detoxifies polyunsaturated fatty acid-containing phospholipid hydroperoxides (PUFA-PL-OOHs), thereby limiting the propagation of lipid peroxidation and preventing oxidative

membrane damage from progressing beyond a reversible threshold [73]. In addition, the efficiency of intracellular selenium utilization represents an important determinant of GPX4 expression and activity. Peroxiredoxin 6 (PRDX6) has been reported to function as a selenium-acceptor protein that facilitates intracellular selenium utilization, thereby promoting the biosynthesis and maintaining the expression of the selenoprotein GPX4. Through this mechanism, PRDX6 may indirectly reinforce GPX4-dependent antioxidant defense and modulate cellular susceptibility to ferroptosis [74]. In summary, the System Xc^--GSH-GPX4 axis constitutes a central antioxidant defense mechanism against lipid peroxidation. System Xc^- maintains the intracellular supply of cysteine by importing extracellular cystine, which is subsequently reduced to cysteine (Cys) in the intracellular reducing environment. Cysteine then serves as a key, and frequently rate-limiting, precursor for glutathione (GSH) biosynthesis, thereby sustaining the GSH pool required for GPX4 activity. Using GSH as a reducing substrate, GPX4 catalyzes the reduction of membrane phospholipid hydroperoxides (PLOOHs) to their corresponding phospholipid alcohols, thereby limiting the propagation of lipid peroxidation and ultimately maintaining membrane lipid redox homeostasis.（Figure 4.）

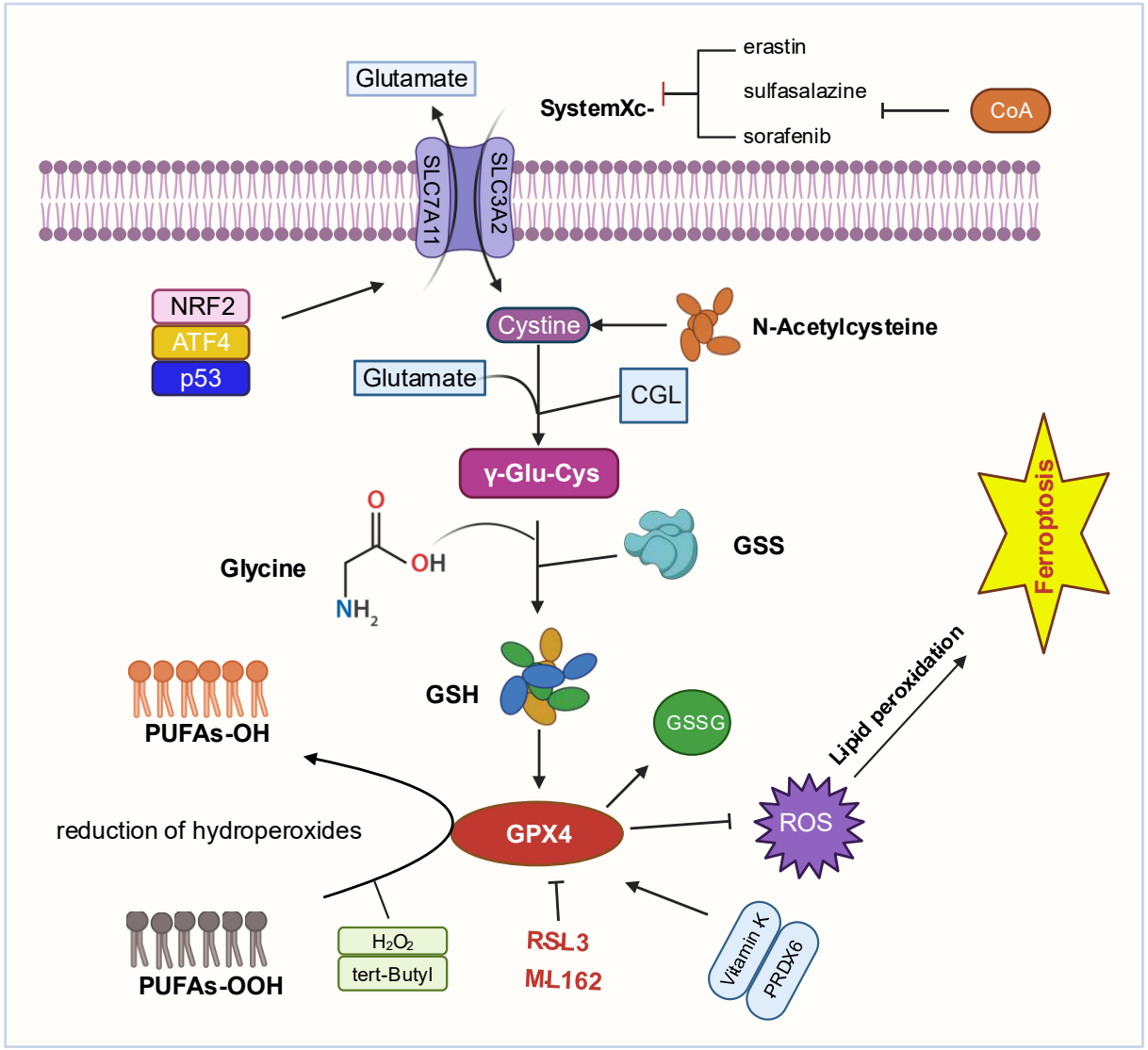

Glutamate
SystemXc-
erastin
sulfasalazine
sorafenib
CoA
SLC7A11
SLC3A2
NRF2
ATF4
p53
Cystine
N-Acetylcysteine
Glutamate
CGL
γ-Glu-Cys
Glycine
GSS
Ferroptosis
GSH
PUFAs-OH
GSSG
Lipid peroxidation
reduction of hydroperoxides
GPX4
ROS
PUFAs-OOH
H2O2
tert-Butyl
RSL3
ML162
Vitamin K
PRDX6

Figure 4. GPX4-dependent canonical antioxidant pathway

3.4 | GPX4-independent ferroptosis-defence pathways

When the System Xc^--GSH-GPX4 axis is compromised, as occurs upon System Xc^- inhibition, GSH depletion,or GPX4 inactivation, GPX4 and GSH-independent ferroptosis defense mechanisms become particularly important in restraining lipid peroxidation. These parallel antioxidant systems suppress phospholipid peroxidation through several complementary mechanisms, including lipophilic radical trapping, reduction and regeneration of coenzyme Q, tetrahydrobiopterin (BH4) metabolism, compartmentalized mitochondrial antioxidant defense and remodeling of membrane lipid composition. Collectively, these mechanisms limit the accumulation and propagation of phospholipid peroxides, thereby preventing the execution of ferroptotic cell death.（Figure 5.）

3.4.1 | The FSP1-CoQ10-NAD(P)H axis

When the System Xc^--GSH-GPX4 axis is compromised, cells can engage alternative antioxidant defense mechanisms in which endogenous or exogenous lipophilic antioxidants directly trap lipid radicals and terminate lipid peroxidation chain reactions. Ferroptosis suppressor protein 1 (FSP1, formerly known as AIFM2) is an endogenous ferroptosis suppressor that functions as a plasma membrane-associated flavoprotein oxidoreductase. N-terminal myristoylation facilitates the localization of FSP1 to cellular membranes, particularly the plasma membrane, where it establishes a GPX4-independent antioxidant defense system. Mechanistically,

FSP1 utilizes reduced nicotinamide adenine dinucleotide (NADH) or reduced nicotinamide adenine dinucleotide phosphate (NADPH) as electron donors to reduce oxidized coenzyme Q10 (ubiquinone-10, CoQ10) to its highly antioxidant reduced form, ubiquinol-10 ($CoQ10H_2$). The resulting $CoQ10H_2$ acts as a lipophilic radical-trapping antioxidant, thereby limiting the propagation of membrane lipid peroxidation and suppressing ferroptotic cell death [75]. As a lipophilic antioxidant, reduced coenzyme Q10 (ubiquinol-10, $CoQ10H_2$) can directly scavenge lipid peroxyl radicals ($LOO\cdot$), thereby terminating the propagation of lipid peroxidation chain reactions and protecting cellular membranes from oxidative damage. In addition to its canonical CoQ-dependent radical-trapping activity, FSP1 has also been reported to promote plasma membrane repair through the recruitment of the endosomal sorting complex required for transport III (ESCRT-III) machinery to the plasma membrane. This membrane-repair response helps preserve plasma membrane integrity and provides an additional mechanism through which FSP1 may suppress ferroptotic cell death [76]. Scimilarly, vitamin E can act as an exogenously supplied lipophilic radical-trapping antioxidant, thereby limiting the propagation of lipid peroxidation and protecting cellular membranes from oxidative damage.

3.4.2 | The DHODH-CoQ10-$CoQH_2$ axis

Dihydroorotate dehydrogenase (DHODH), a flavin-dependent enzyme located in the mitochondrial inner membrane (IMM), catalyzes the oxidation of dihydroorotate (DHO) to orotate (OA), thereby contributing to de novo pyrimidine biosynthesis. Meanwhile, DHODH transfers electrons generated during DHO oxidation to ubiquinone (CoQ10) in the IMM, leading to the formation of ubiquinol (CoQH2)[77]. When mitochondrial ROS levels are elevated and GPX4 activity is

compromised, DHODH functions as an anti-lipid peroxidation defense system at the mitochondrial inner membrane (IMM), thereby protecting mitochondrial membrane lipids from peroxidative damage. Notably, inhibition of mitochondrial complex III disrupts the regeneration of oxidized CoQ10, thereby limiting the availability of the electron acceptor required for DHODH catalysis and consequently impairing DHODH activity[78]. Furthermore, studies employing neutron reflectometry and other biophysical approaches have demonstrated that the catalytic domain of DHODH penetrates into the hydrophobic region of the lipid bilayer, allowing it to interact directly with CoQ10 embedded within the membrane core. This structural feature provides a rationale for the development of ferroptosis-inducing agents that competitively target the CoQ10-binding site of DHODH, thereby disrupting DHODH-mediated electron transfer and weakening its anti-lipid peroxidation capacity.

3.4.3 | The GCH1-BH4-DHFR axis

GTP cyclohydrolase 1 (GCH1), the rate-limiting enzyme in de novo tetrahydrobiopterin (BH4) biosynthesis, promotes the production of BH4, a potent endogenous radical-trapping antioxidant. BH4 directly inhibits membrane lipid autoxidation and thereby helps preserve cellular redox homeostasis [79]. Overexpression of GCH1 elevates intracellular BH4/BH2 levels and suppresses the peroxidation of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs). Meanwhile, dihydrofolate reductase (DHFR) regenerates BH4 by reducing its oxidized form, 7,8-dihydrobiopterin (BH2), thereby sustaining the BH4 redox cycle and reinforcing cellular antioxidant capacity [80]. Evidence indicates that folic acid supplementation enhances DHFR-mediated BH4 regeneration, thereby increasing the BH4/BH2 ratio and

363 alleviating aortic valve calcification [81].

364 **3.4.4 | Other GPX4-independent mechanisms**

365 The FSP1-mediated non-canonical vitamin K cycle represents an additional GPX4-independent ferroptosis defense pathway. FSP1 catalyzes the reduction of
366 vitamin K to vitamin K hydroquinone, a potent phenolic radical-trapping antioxidant that inhibits lipid peroxidation and consequently confers resistance to ferroptosis
367 [82]. SCD1 is a key enzyme responsible for the biosynthesis of monounsaturated fatty acids (MUFAs) from saturated fatty acids. By enriching MUFAs in membrane
368 phospholipids, SCD1 decreases the relative abundance of highly peroxidizable PUFAs including arachidonic acid (AA) and adrenic acid (AdA), thereby rendering
369 membrane lipids less susceptible to peroxidation (Sen et al., 2023). Farnesoid X receptor (FXR) activation enhances the expression of multiple ferroptosis defense
370 proteins, including FSP1, GPX4 and SCD1, thereby suppressing lipid peroxidation and conferring resistance to ferroptosis [83].

371

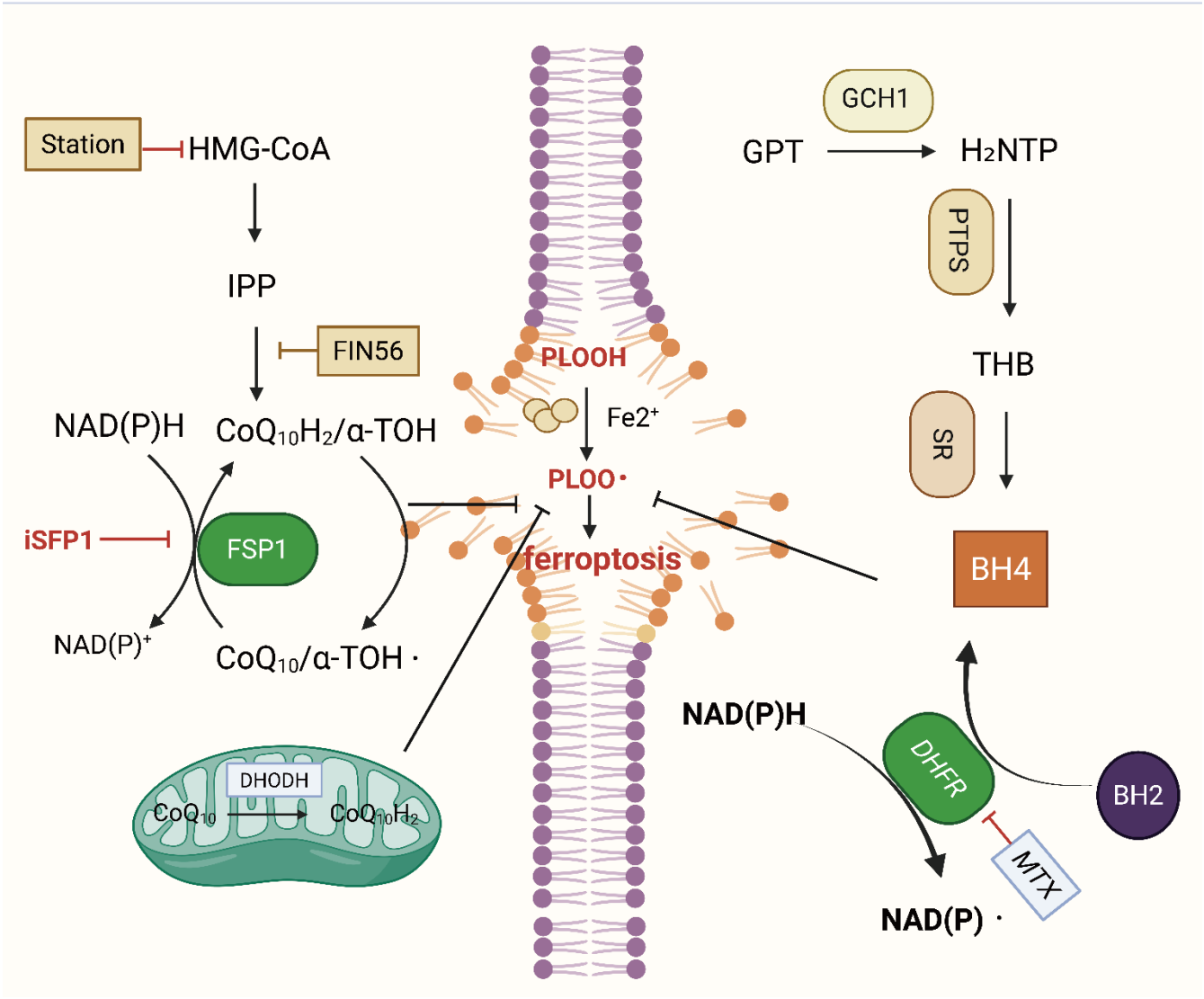

Station
HMG-CoA
IPP
FIN56
NAD(P)H
CoQ10H2/α-TOH
iSFP1
FSP1
NAD(P)+
CoQ10/α-TOH ·
DHODH
CoQ10
CoQ10H2
PLOOH
Fe2+
PLOO·
ferroptosis
GCH1
GPT
H2NTP
PTPS
THB
SR
BH4
NAD(P)H
DHFR
BH2
MTX
NAD(P) ·

Figure 5. GPX4-independent classical ferroptosis defense pathway

4 | MECHANISMS BY WHICH FERROPTOSIS TRIGGERS INFLAMMATION

Lipid peroxidation during ferroptosis disrupts plasma membrane integrity, resulting in membrane rupture and the release of oxidative damage-associated signals. These signals can be sensed by the immune system, thereby initiating and amplifying downstream inflammatory cascades [84]. In contrast to the immunologically "silent" nature of apoptosis, ferroptosis is a lytic form of regulated cell death accompanied by marked plasma membrane permeabilization [85], which facilitates the release of abundant damage-associated molecular patterns (DAMPs) into the extracellular milieu. DAMPs are endogenous molecules that acquire immunostimulatory properties following cellular damage or stress as a consequence of altered localization, extracellular release, abundance or molecular state. Representative DAMPs include high-mobility group box 1 (HMGB1), adenosine triphosphate (ATP) and heat shock proteins (HSPs). Upon recognition by pattern-recognition receptors (PRRs) on immune cells, these DAMPs activate downstream pro-inflammatory signaling pathways, thereby initiating and amplifying inflammatory responses.

4.1 | Release of DAMPs

DAMPs released from damaged cells activate innate immune signaling and drive sterile inflammation and their release represents a pivotal step linking ferroptosis to inflammatory responses. High-mobility group box 1 (HMGB1) is a highly conserved non-histone nuclear protein that serves as a DNA chaperone to maintain

chromatin organization. Upon translocation to the cytoplasm, HMGB1 interacts with beclin 1 (BECN1) and can facilitate autophagy-related processes associated with ferroptosis. Following either active secretion or passive release, extracellular HMGB1 functions as a prototypical DAMP, regulating inflammatory and immune responses through receptor-dependent signaling or direct cellular uptake [86]. The subcellular localization and release of HMGB1 are tightly regulated by its acetylation status. Acetylation reduces the affinity of HMGB1 for DNA, facilitating its dissociation from chromatin and subsequent nuclear-to-cytoplasmic translocation [87]. During ferroptosis, acetylated HMGB1 translocates from the nucleus to the cytoplasm and is subsequently released into the extracellular space through an autophagy-dependent mechanism, thereby acquiring its function as a damage-associated molecular pattern (DAMP). Both class I and class II ferroptosis inducers have been shown to promote HMGB1 release. Notably, genetic ablation of the autophagy-related genes ATG5 or ATG7, or pharmacological inhibition of autophagic flux with bafilomycin A1, suppresses HMGB1 release, supporting an essential role for autophagy in this process [88]. Suppression of histone deacetylases (HDACs), including SIRT1 and SIRT2, enhances HMGB1 acetylation. Ferroptosis-associated autophagy further promotes HMGB1 hyperacetylation by inhibiting HDAC activity, thereby facilitating its translocation and subsequent extracellular release. Extracellular acetylated HMGB1 can then engage receptors such as the receptor for advanced glycation end products (AGER/RAGE), triggering downstream pro-inflammatory and immune signaling cascades [89]. HMGB1 activates the AIM2 inflammasome in macrophages and drives pro-inflammatory M1 macrophage polarization through TLR2-, TLR4- and RAGE/NF-κB-dependent signaling pathways, thereby amplifying the inflammatory response [90].

ATP primarily functions as an intracellular energy carrier that supports cellular metabolism. Following tissue injury, substantial amounts of intracellular ATP are released into the extracellular milieu, generating a high-concentration DAMP signal. Extracellular ATP is recognized by immune cells through purinergic P2X receptors (P2XRs). Notably, extracellular ATP has been shown to activate P2X7R signaling, thereby promoting immune activation and suppressing regulatory T-cell (Treg) function, which may further aggravate tissue damage [91]. The P2X receptor family consists of seven subtypes (P2X1-P2X7), all of which are ATP-gated non-selective cation channels. P2X7R has a relatively low affinity for ATP and is therefore preferentially activated under pathological conditions in which extracellular ATP accumulates to high concentrations, such as at sites of inflammation. Notably, reasearchers suggested that P2X7R may also be activated by non-nucleotide agonists, including circulating histones H3/H4 (cH3/cH4) and the antimicrobial peptide LL-37, providing an alternative ATP-independent mechanism for P2X7R activation and subsequent inflammatory signaling [92].

Under physiological conditions, heat shock proteins (HSPs) primarily reside within cells and function as molecular chaperones that regulate protein folding, stabilization, trafficking and degradation, thereby preserving cellular proteostasis and homeostasis. During ferroptosis, HSPs can be released into the extracellular microenvironment, including through extracellular vesicles (EVs), and subsequently function as damage-associated molecular patterns (DAMPs) recognized by the immune system. In differentiated THP-1 macrophages, HSPA1A has been shown to engage Toll-like receptors (TLRs) and activate the MyD88/p38 MAPK/NF-κB signaling axis, promoting the secretion of the pro-inflammatory cytokines IL-1β and TNF-α as well as the immunoregulatory cytokines IL-4 and IL-10. These findings

411 suggest that extracellular HSPA1A may exert context-dependent, dual immunomodulatory effects [93]. MyD88 functions as a central adaptor protein that initiates
412 downstream signaling cascades following TLR activation. Subsequent activation of tumor necrosis factor receptor-associated factor 6 (TRAF6) represents a pivotal
413 step coupling MyD88-dependent TLR signaling to the NF-κB and MAPK pathways. Conversely, speckle-type POZ protein (SPOP) can negatively regulate TLR-driven
414 inflammatory signaling by interfering with MyD88 oligomerization, thereby constraining excessive inflammatory responses and limiting inflammation-associated
415 tissue damage [94].

416 **4.2 | Lipid mediators alter the conformation and function of inflammatory signalling proteins**

417 Excessive accumulation of polyunsaturated fatty acid-containing phospholipid hydroperoxides (PUFA-PL-OOH) represents a defining feature of ferroptosis.
418 Through non-enzymatic free-radical chain reactions, phospholipid peroxidation generates highly reactive lipid-derived products, including 4-hydroxynonenal (4-HNE),
419 malondialdehyde (MDA) and oxidized phospholipids (OxPLs). These lipid-derived electrophiles can covalently modify proteins, DNA and other biomacromolecules,
420 generating oxidation-associated molecular patterns that may act as DAMPs. Recognition of these modified molecules by pattern-recognition receptors, such as
421 scavenger receptors and Toll-like receptors, signals cellular oxidative injury and promotes activation of innate immune responses [95]. 4-Hydroxynonenal (4-HNE) is
422 a prototypical α,β-unsaturated aldehyde produced during the peroxidation of ω-6 polyunsaturated fatty acids, particularly arachidonic acid. As a highly reactive
423 electrophile, 4-HNE preferentially forms covalent adducts with cysteine, histidine, and lysine residues, thereby modifying the conformation and function of target

proteins. 4-HNE-modified proteins have been implicated in the propagation and modulation of inflammatory signaling. Notably, under certain conditions, 4-HNE can directly interact with NLRP3 and suppress inflammasome assembly and activation [96]. Malondialdehyde (MDA) is a major reactive aldehyde generated during the decomposition of peroxidized polyunsaturated fatty acids, including arachidonic acid. MDA can covalently modify protein amino groups and promote intermolecular cross-linking. In particular, MDA-modified apolipoprotein B generates oxidation-specific neoepitopes that can be recognized by C-reactive protein and natural IgM antibodies, thereby facilitating the clearance of apoptotic cells and oxidatively modified molecules [97]. Oxidized phospholipids (OxPLs), particularly their truncated forms (Tr-OxPLs), can act as damage-associated molecular patterns (DAMPs) and be recognized by scavenger receptors and Toll-like receptors (TLRs), thereby triggering inflammatory signaling. Tr-OxPLs further engage CD36-dependent signaling to activate Src kinases and NF-κB, ultimately compromising endothelial barrier integrity and promoting the expression of pro-inflammatory mediators [98].

5 | INFLAMMATORY REGULATION OF FERROPTOSIS-RELATED SIGNALLING

The inflammatory microenvironment profoundly influences cellular sensitivity to ferroptosis by reshaping the threshold for lipid peroxidation through cytokine signaling, redox imbalance, lipid metabolic reprogramming and immune cell interactions. Mechanistically, inflammatory signaling can exacerbate ferroptosis by impairing the System Xc^--GSH-GPX4 antioxidant defense axis, enlarging the labile Fe^{2+} pool, increasing the abundance of peroxidation-prone PUFA-containing

phospholipids (PUFA-PLs), and potentiating ROS- and lipoxygenase (LOX)-driven lipid peroxidation (Figure 6B)

5.1 | NF-κB signalling

Diverse pathological stimuli, including lipopolysaccharide (LPS), hypoxia and certain environmental pollutants, can trigger NF-κB activation through Toll-like receptor (TLR)-dependent and other signaling pathways. Once activated, NF-κB drives the transcription and subsequent release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, thereby establishing a self-reinforcing positive-feedback loop that sustains and amplifies the inflammatory response [99]. NF-κB activation is positively associated with increased expression of pro-inflammatory cytokines, thereby aggravating the inflammatory response. In parallel, it promotes the generation of reactive oxygen species (ROS), which oxidatively attack polyunsaturated fatty acids (PUFAs) in cellular membranes, ultimately leading to lipid peroxidation [100]. Studies have demonstrated that activated NF-κB can suppress the expression of SLC7A11 and GPX4. SLC7A11, which constitutes the light-chain subunit of system Xc^-, is responsible for mediating cystine uptake. Downregulation of SLC7A11 restricts cystine availability and subsequently reduces glutathione (GSH) synthesis, thereby further compromising GPX4-mediated detoxification of lipid peroxides. Consequently, excessive accumulation of lipid peroxides promotes the onset of ferroptosis [101].

5.2 | JAK–STAT signalling

Inflammatory cytokines, such as IFN-γ, engage the cell-surface receptor complex consisting of IFNGR1 and IFNGR2, leading to the activation of JAK1 and JAK2 and subsequent phosphorylation of STAT1. Activated STAT1 then translocates into the nucleus, where it directly binds to the promoter region of SLC7A11 and transcriptionally represses its expression [102]. SLC7A11 serves as a critical regulator of the system Xc^--GSH-GPX4 antioxidant axis. Suppression of SLC7A11 transcription limits GSH synthesis, thereby compromising GPX4-mediated antioxidant defense and promoting the persistent accumulation of lipid peroxides. Meanwhile, the pro-inflammatory cytokine IL-6 engages the IL-6R/gp130 receptor complex on the cell surface, leading to JAK2 activation and subsequent phosphorylation of STAT3. Phosphorylated STAT3 translocates into the nucleus and binds to the promoter region of HAMP, which encodes hepcidin, thereby enhancing HAMP transcription and promoting hepatic hepcidin synthesis and secretion [103]. Elevated hepcidin binds to ferroportin 1 (FPN1), the major cellular iron exporter, and induces its internalization and degradation. This process suppresses cellular iron efflux, resulting in intracellular iron retention and tissue iron accumulation while reducing circulating iron availability . Experimental studies have shown that suppression of JAK2/STAT3 signaling and hepcidin expression alleviates the inflammatory response induced by cerebral ischemia-reperfusion injury, thereby reducing neuronal iron accumulation and ultimately mitigating ferroptosis [104]. ACSL4 is a critical determinant of ferroptosis, as its expression directly modulates the incorporation of polyunsaturated fatty acids (PUFAs) into membrane phospholipids and consequently influences susceptibility to lipid peroxidation. Interestingly, the transcriptional regulation of ACSL4 by STAT3 appears to be context-dependent and bidirectional.In experimental models of acute kidney injury (AKI) and Lipin3 deficiency-induced liver injury, activation of STAT3 by JAK1 enhances ACSL4 expression, thereby

increasing cellular susceptibility to ferroptosis and ultimately promoting ferroptotic cell death [105].

5.3 | The NLRP3 inflammasome

Activation of the NLRP3 inflammasome facilitates the maturation and release of IL-1β and IL-18, thereby exacerbating oxidative stress through increased ROS production and disruption of the cellular antioxidant defense system. Consequently, lipid peroxidation products, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), accumulate excessively, ultimately increasing cellular susceptibility to ferroptosis. In experimental models of placental oxidative stress, ferroptosis has been shown to be positively associated with NLRP1 inflammasome activation. Notably, pharmacological inhibition of ferroptosis reduces the expression of inflammasome-associated mediators, including NLRP1, NLRP3, IL-1β and caspase-1 [105].

5.4 | cGAS–STING signalling

In response to pathogen invasion, cellular damage or mitochondrial stress, the aberrant presence of DNA in the cytosol triggers activation of the cGAS–STING signaling pathway. cGAS, a principal cytosolic DNA sensor, recognizes and binds to cytosolic DNA, subsequently catalyzing the synthesis of cyclic GMP-AMP (cGAMP) from ATP and GTP as a second messenger [106]. Binding of cGAMP to endoplasmic reticulum (ER)-resident STING induces a conformational rearrangement and oligomerization of STING. The activated STING complex then traffics from the ER through the Golgi apparatus to the trans-Golgi network (TGN) in a COPII-

dependent manner, where it recruits and activates TANK-binding kinase 1 (TBK1). This subcellular translocation of STING is essential for the initiation and propagation of downstream signaling [107]. The trans-Golgi network (TGN), characterized by sphingomyelin- and cholesterol-enriched lipid domains, functions as a specialized signaling platform that enables STING-dependent TBK1 activation and subsequent downstream signal transduction. STING acts as a molecular scaffold to facilitate TBK1-mediated phosphorylation of interferon regulatory factor 3 (IRF3). Once phosphorylated, IRF3 undergoes dimerization and translocates into the nucleus, where it drives the transcription of type I interferons, including IFN-β, together with a broad range of inflammatory mediators. Moreover, activation of the cGAS–STING pathway induces type I interferon production, which may suppress dihydroorotate dehydrogenase (DHODH) expression, thereby increasing mitochondrial reactive oxygen species (ROS) generation and lipid peroxidation and ultimately sensitizing cells to ferroptosis [108]. NCOA4 serves as a key cargo receptor for ferritinophagy, mediating the delivery of ferritin to the autophagosome-lysosome system for degradation and subsequent release of labile iron. Specific residues within the CBD of STING, including Q237, E316, and S322, interact with the coiled-coil domain of NCOA4. This STING-NCOA4 interaction promotes ferritin degradation and intracellular iron accumulation, thereby enhancing reactive oxygen species (ROS) generation and lipid peroxidation, while simultaneously amplifying the inflammatory response [109]. Experimental evidence indicates that activation of the cGAS–STING signaling pathway promotes ferritinophagy in microglia during cerebral ischemia-reperfusion injury (CIRI), accompanied by upregulation of NCOA4 and downregulation of FTH1. In contrast, inhibition of cGAS attenuates ferritinophagy and consequently mitigates oxidative stress [110].

5.5 | MAPK signalling

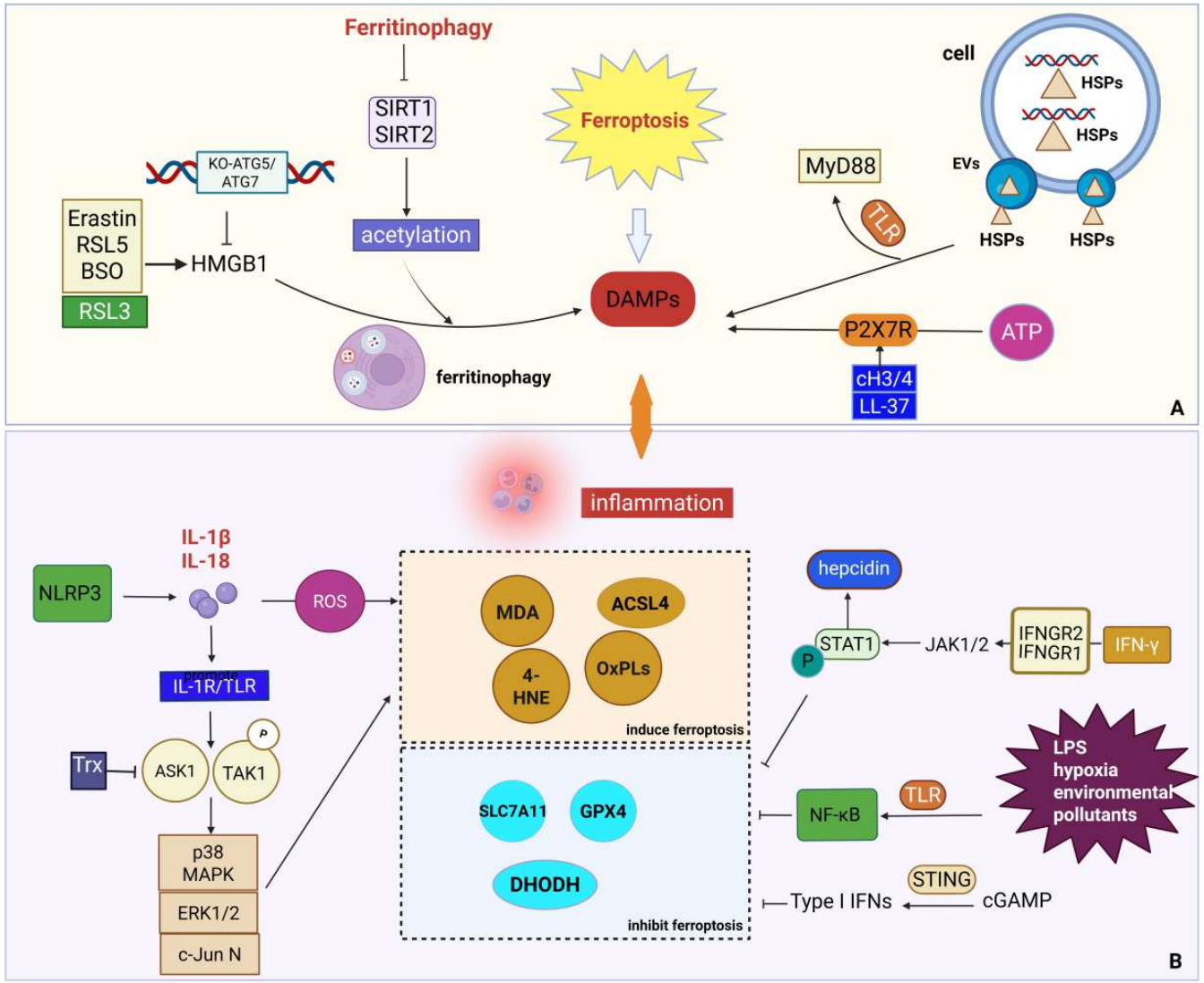
The mitogen-activated protein kinase (MAPK) pathway constitutes a key signaling cascade that coordinates cellular responses to stress, inflammation and tissue injury. Inflammatory signaling is an important upstream driver of MAPK activation. In response to pathological stimuli, engagement of Toll-like receptors (TLRs), tumor necrosis factor receptors (TNFRs) and interleukin-1 receptors (IL-1Rs) activates upstream kinases, including transforming growth factor-β-activated kinase 1 (TAK1) and apoptosis signal-regulating kinase 1 (ASK1), thereby triggering downstream MAPK signaling cascades [111]. Activated TAK1 and ASK1 can trigger multiple downstream MAPK signaling cascades. Previous studies have demonstrated that IL-1β promotes c-Jun N-terminal kinase (JNK) activation through TAK1-dependent signaling, whereas disruption of TAK1 activation markedly suppresses JNK signaling. Activated TAK1 subsequently phosphorylates and activates MAPK kinases 3 and 6 (MKK3 and MKK6), leading to selective activation of the downstream p38 MAPK signaling cascade [112]. Under basal conditions, thioredoxin (Trx) directly associates with apoptosis signal-regulating kinase 1 (ASK1) and maintains it in an inactive state. In response to oxidative stress, oxidation of Trx induces its dissociation from ASK1, thereby relieving ASK1 inhibition and triggering the downstream p38 MAPK and c-Jun N-terminal kinase (JNK) signaling cascades. Extracellular signal-regulated kinases 1/2 (ERK1/2), JNK, and p38 MAPK constitute the three major MAPK signaling modules, each of which may exert distinct and context-dependent effects on the regulation of ferroptosis.

Activation of p38 MAPK enhances the expression of NADPH oxidases (NOXs) and lipoxygenases (ALOXs), thereby promoting excessive ROS production and

the oxidative modification of polyunsaturated fatty acids (PUFAs), ultimately facilitating ferroptosis. Moreover, JNK/p38 activation has been shown to promote ROS accumulation and activate the ATM/p53 signaling axis, leading to subsequent upregulation of NOX4. Concurrently, ATM/p53-dependent activation of p38 increases the expression of ALOX12/15, thereby driving phospholipid peroxidation and enhancing ferroptotic susceptibility [113]. Activation of p38 MAPK suppresses the expression of SLC7A11 and GPX4, thereby impairing the cellular antioxidant defense system and promoting ferroptosis. Experimental evidence has shown that the ferroptosis inducer erastin activates p38 MAPK while decreasing the mRNA and protein expression of SLC7A11 and GPX4. Notably, treatment with a p38 MAPK inhibitor partially reverses these changes, supporting a regulatory role for p38 MAPK in erastin-induced ferroptosis [114]. Glutamate-induced excitotoxicity promotes ferroptosis through the activation of p38 MAPK, thereby downregulating SLC7A11 and GPX4 expression [115]. Nrf2 is a key transcription factor involved in the regulation of ferroptosis. In response to stimuli such as inflammation and ischemia-reperfusion injury, Nrf2 is activated and translocates into the nucleus, where it promotes the transcription of a series of antioxidant and cytoprotective genes, thereby suppressing ferroptosis. HO-1 catalyzes heme degradation, leading to the release of Fe^{2+}. The liberated Fe^{2+} can generate hydroxyl radicals through the Fenton reaction, thereby further promoting the peroxidation of polyunsaturated fatty acid-containing phospholipids. Notably, the interplay between p38 and Nrf2 is context-dependent and they may exert bidirectional regulatory effects under different cellular conditions.p38 can inhibit Nrf2 nuclear translocation through the glycogen synthase kinase-3β (GSK-3β) axis, thereby suppressing the transcription of Nrf2 downstream target genes, such as SLC7A11 and HO-1. Conversely, in RAW264.7 macrophages, ethyl pyruvate-induced glutathione depletion activates p38 MAPK, which

512 subsequently promotes Nrf2 nuclear translocation and HO-1 expression, highlighting the context-dependent regulatory relationship between p38 and Nrf2 [116].

513 Activation of JNK modulates the activity of transcription factors, including c-Jun/AP-1, thereby altering the expression of genes involved in lipid metabolism
514 and antioxidant defense and ultimately increasing cellular susceptibility to membrane lipid peroxidation. As a major component of the activator protein-1 (AP-1)
515 transcriptional complex, c-Jun can cooperate with Ets family proteins to regulate the transcription of the glutathione S-transferase Ya (GST Ya) gene [117].
516 Glutathione S-transferases (GSTs) constitute an important component of the cellular antioxidant defense system, and increased GST expression enhances cellular
517 resistance to oxidative stress and may consequently mitigate ferroptotic damage. The antioxidant/electrophile response element (ARE/EpRE) located within the
518 regulatory region of the GST Ya subunit gene comprises two adjacent AP-1-binding sites. Fos/Jun heterodimers within the AP-1 transcription factor complex
519 specifically bind to the ARE/EpRE and contribute to the basal transcriptional regulation of the GST Ya gene. Moreover, intracellular glutathione availability
520 modulates GST Ya expression by influencing Fos/Jun induction and AP-1 activation. Pinkus proposed that iron-chelating quinones, such as doxorubicin, are more
521 potent than non-chelating quinones in inducing AP-1 DNA-binding activity and GST Ya gene expression, an effect that may be attributable to their enhanced capacity
522 to generate hydroxyl radicals [118].


Ferritinophagy
SIRT1
SIRT2
acetylation
Ferroptosis
cell
HSPs
HSPs
EVs
HSPs
HSPs
MyD88
TLR
KO-ATG5/
ATG7
Erastin
RSL5
BSO
RSL3
HMGB1
DAMPs
P2X7R
ATP
cH3/4
LL-37
ferritinophagy
A
inflammation
IL-1β
IL-18
NLRP3
ROS
MDA
ACSL4
4-
HNE
OxPLs
induce ferroptosis
hepcidin
STAT1
P
JAK1/2
IFNGR2
IFNGR1
IFN-γ
IL-1R/TLR
Trx
ASK1
TAK1
P
p38
MAPK
ERK1/2
c-Jun N
SLC7A11
GPX4
DHODH
inhibit ferroptosis
NF-κB
TLR
LPS
hypoxia
environmental
pollutants
STING
Type I IFNs
cGAMP
B

523

Figure 6. Mechanism of ferroptosis-inflammation crosstalk

6 | NATURAL BIOACTIVE COMPOUNDS

In recent years, growing in vivo and in vitro evidence has demonstrated that bioactive monomeric compounds derived from traditional Chinese medicine (TCM) can modulate ferroptosis-related signaling pathways and key molecular targets, thereby attenuating iron overload and lipid peroxidation, preserving mitochondrial function and cellular redox homeostasis, and ultimately suppressing ferroptosis in cardiomyocytes and alleviating myocardial ischemia–reperfusion injury. To date, the major classes of bioactive compounds reported to exert these effects include flavonoids, polyphenols, alkaloids, saponins, and polysaccharides （Table 1）

6.1 | Flavonoids

Puerarin, a naturally occurring isoflavone, has exhibited substantial cardioprotective effects in a growing body of preclinical studies. Evidence from various animal models, including rats, mice and rabbits, indicates that puerarin can reduce myocardial infarct size, improve cardiac function and decrease serum levels of creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH) [119,120]. Ferroptosis has recently emerged as a novel form of regulated cell death, offering a new perspective for understanding the cardioprotective effects of puerarin. In myocardial ischemia-reperfusion (I/R) injury models, puerarin markedly increases the protein expression of glutathione peroxidase 4 (GPX4) and ferritin heavy chain 1 (FTH1), while decreasing the levels of the lipid peroxidation products malondialdehyde (MDA) and 4-

536 hydroxynonenal (4-HNE). These findings suggest that puerarin may alleviate myocardial I/R injury, at least in part, by suppressing ferroptosis-associated lipid
537 peroxidation. Moreover, prostaglandin-endoperoxide synthase 2 (PTGS2) represents a critical molecular link between ferroptosis and inflammation, with its
538 upregulation being closely associated with myocardial injury and inflammatory infiltration. Puerarin markedly suppresses PTGS2 mRNA expression, thereby
539 attenuating myocardial infarction, inflammatory responses, and myocardial injury in mice (Ding et al., 2023). HU Fajia et al. reported that puerarin pretreatment
540 attenuated cardiomyocyte ferroptosis and preserved mitochondrial function in both in vivo and in vitro models of ischemia-reperfusion (I/R) injury by downregulating
541 the protein expression of voltage-dependent anion channel 1 (VDAC1) [121]. Mechanistically, further studies showed that puerarin upregulated 14-3-3η expression,
542 thereby limiting intracellular iron accumulation, reducing malondialdehyde (MDA) and reactive oxygen species (ROS) levels, and preserving mitochondrial membrane
543 potential, ultimately suppressing ferroptosis [122].

544 Baicalin, a naturally occurring flavonoid glycoside, confers cardioprotection against myocardial ischemia-reperfusion injury (MIRI) by modulating the ACSL4-
545 mediated ferroptosis pathway. Experimental studies have demonstrated that baicalin, administered orally at 100 or 200 mg/kg for 6 consecutive days, markedly
546 attenuates ferroptosis in a rat model of myocardial ischemia-reperfusion injury (MIRI), as evidenced by reduced expression of pro-ferroptotic proteins, including
547 ACSL4, transferrin receptor 1 (TfR1) and nuclear NCOA4. Similarly, baicalin treatment suppresses the expression of these ferroptosis-associated proteins in H9c2
548 cardiomyocytes subjected to oxygen–glucose deprivation/reoxygenation (OGD/R), thereby mitigating ferroptotic cell death [123]. SLC6A14 functions as a pro-

549 ferroptotic factor. Baicalin suppresses SLC6A14 transcription by downregulating specificity protein 1 (SP1) and reducing SP1 binding to the SLC6A14 promoter,
550 thereby attenuating ferroptosis [124].

551 Vitexin is a naturally occurring bioactive flavonoid compound primarily derived from traditional medicinal plants, including hawthorn leaves [125]. Growing
552 experimental evidence indicates that vitexin confers cardioprotective effects against myocardial ischemia-reperfusion injury. In an isolated rat heart Langendorff
553 perfusion model, vitexin treatment at 50, 100, and 200 μmol/L significantly enhanced coronary flow, reduced myocardial pathological injury scores and downregulated
554 the expression of the pro-apoptotic protein Bax [126]. Moreover, accumulating evidence suggests that vitexin contributes to the maintenance of mitochondrial dynamics
555 homeostasis. In an H9c2 cardiomyocyte model of ischemia–reperfusion (I/R) injury, vitexin treatment significantly upregulated mitofusin 2 (MFN2) expression and
556 attenuated the recruitment of dynamin-related protein 1 (Drp1) to mitochondria, thereby limiting ischemia-induced excessive mitochondrial fission [127]. Although
557 direct experimental evidence linking vitexin-mediated ferroptosis inhibition to protection against myocardial ischemia-reperfusion injury remains lacking, studies in
558 renal tubular epithelial cells and rat models of diabetic kidney disease have demonstrated that vitexin suppresses ferroptosis by modulating the SLC7A11-GSH-GPX4
559 axis and associated ferroptosis-related markers. These findings raise the possibility that regulation of ferroptosis through the SLC7A11-GSH-GPX4 axis may represent
560 a potential mechanism underlying the cardioprotective effects of vitexin [128]. Therefore, inhibition of Epac1/Rap1- and Drp1-mediated excessive mitochondrial fission
561 by vitexin, together with its ability to reduce mitochondrial ROS production, may represent a novel potential mechanism for suppressing ferroptosis and mitigating

562 myocardial injury.

563 **6.2 | Polyphenols**

564 Resveratrol (Res), a naturally occurring polyphenol, has emerged as a potential regulator of ferroptosis through its effects on iron metabolism, antioxidant
565 defensesand ferritinophagy. In myocardial ischemia-reperfusion (I/R) injury, resveratrol attenuates ferroptotic processes by reducing intracellular Fe^{2+} levels and
566 transferrin receptor 1 (TfR1) expression, while enhancing the expression of the antioxidant proteins ferritin heavy chain 1 (FTH1) and glutathione peroxidase 4 (GPX4).
567 Mechanistically, resveratrol has been reported to suppress ferroptosis by modulating the interaction between ubiquitin-specific peptidase 19 (USP19) and Beclin1.
568 USP19 promotes Beclin1 deubiquitination and stabilization, thereby enhancing Beclin1-dependent autophagy, whereas resveratrol downregulates USP19 expression,
569 decreases Beclin1 stability, and consequently suppresses autophagic activity [129]. Another naturally occurring compound, cyanidin-3-O-glucoside (C3G), exhibits
570 effects similar to those of resveratrol. C3G suppresses USP19 and Beclin1 expression, thereby promoting K11-linked polyubiquitination of Beclin1 and reducing
571 autophagosome formation, which ultimately attenuates ferroptosis and confers protection against cardiomyocyte injury[130].

572 Piceatannol is a naturally occurring hydroxylated analog of resveratrol with potent antioxidant and anti-inflammatory properties. Nuclear factor erythroid 2-related
573 factor 2 (Nrf2) serves as a master transcriptional regulator of cellular responses to oxidative and electrophilic stress. Activation of Nrf2 promotes ferroportin 1 (FPN1)
574 transcription, thereby facilitating iron efflux and alleviating intracellular iron overload. In parallel, Nrf2 upregulates ferritin heavy chain 1 (FTH1) expression, enhancing

cellular iron storage and sequestration and consequently limiting ferroptosis [131]. Recent evidence suggests that piceatannol confers cardioprotection against myocardial ischemia-reperfusion (I/R) injury by modulating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway and maintaining iron homeostasis in cardiomyocytes, thereby attenuating I/R injury-induced ferroptosis [130].

Salvianolic acid B (Sal B), a major water-soluble phenolic compound derived from Salvia miltiorrhiza (Danshen), exhibits potent antioxidant, anti-inflammatory and anti-fibrotic activities. The catechol moieties within its chemical structure enable Sal B to directly scavenge reactive oxygen species (ROS) and chelate transition metal ions [132]. Growing evidence indicates that salvianolic acid B (Sal B) exerts potent anti-ferroptotic effects in a variety of pathological models. In myocardial ischemia-reperfusion injury (MIRI), Sal B attenuates the ubiquitin–proteasome-dependent degradation of GPX4, thereby maintaining GPX4 protein stability and enhancing the reduction of phospholipid hydroperoxides, which ultimately limits ferroptosis [133].

6.3 | Alkaloids

Tetramethylpyrazine (TMP), a major bioactive alkaloid derived from Ligusticum chuanxiong, has demonstrated significant cardioprotective properties. Excessive reactive oxygen species (ROS) generation represents an early initiating event in reperfusion injury and a crucial upstream driver of ferroptosis. In the context of myocardial ischemia-reperfusion injury (MIRI), TMP protects against myocardial damage through multiple mechanisms, including direct ROS scavenging to attenuate lipid peroxidation, mitigation of calcium overload and restoration of intracellular calcium homeostasis, inhibition of apoptosis, regulation of inflammatory responses

and improvement of endothelial function [134]. In a mouse model of ischemia-reperfusion (I/R) injury, treatment with tetramethylpyrazine (TMP) reversed the decrease in GPX4 expression and reduced intracellular Fe^{2+} levels in cardiomyocytes, thereby alleviating iron accumulation[135]. Moreover, tetramethylpyrazine (TMP) directly interacts with myosin light chain 2 (MLC2) and enhances its expression, thereby inhibiting Myl2-mediated activation of the NLRP3 signaling pathway and consequently attenuating inflammatory responses and pyroptosis [136]. However, the precise molecular pathways through which ferroptosis regulation alleviates myocardial ischemia-reperfusion injury remain largely unclear and warrant further investigation.

6.4 | Saponins

Astragaloside IV (AS-IV), a major bioactive component of Astragalus membranaceus, has demonstrated potent cardioprotective effects. Mechanistically, AS-IV activates nuclear factor erythroid 2-related factor 2 (Nrf2), facilitating its dissociation from Kelch-like ECH-associated protein 1 (Keap1) and subsequent translocation into the nucleus. Nuclear Nrf2 then forms complexes with small Maf proteins and binds to antioxidant response elements (AREs) in the promoters of downstream antioxidant genes, such as heme oxygenase-1 (HO-1), thereby enhancing ROS-scavenging capacity in myocardial tissue [137]. Moreover, in models of myocardial ischemia-reperfusion injury (MIRI), AS-IV attenuates NOX4 expression, thereby limiting ROS production and oxidative stress and ultimately suppressing ferroptosis [138].

Salidroside, a major bioactive constituent derived from the traditional Tibetan medicinal herb Rhodiola, is chemically characterized as p-hydroxyphenethyl-β-D-

glucoside. Extensive pharmacological studies have demonstrated that salidroside exerts diverse biological effects, including potent antioxidant, anti-inflammatory and anti-apoptotic activities, together with immunomodulatory and cardioprotective properties [139]. p38 MAPK, a key member of the MAPK family, functions as a stress-responsive protein kinase that is activated under ischemic or hypoxic conditions and consequently contributes to a range of pathological processes, including apoptosis, inflammation and myocardial ultrastructural injury. Experimental evidence has demonstrated that, in a rat model of exhaustive swimming exercise, salidroside markedly decreased p38 MAPK phosphorylation in myocardial tissue, reduced MDA levels and enhanced SOD activity. In addition, salidroside dose-dependently decreased serum levels of the cardiac injury biomarkers creatine kinase (CK), creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH) [140]. In 2024 , Yang B demonstrated in both an H9c2 cardiomyocyte hypoxia/reoxygenation model and a rat model of myocardial ischemia/reperfusion injury that salidroside pretreatment conferred cardioprotective effects comparable to those of the ferroptosis inhibitor ferrostatin-1 and the mitochondrial ROS scavenger MitoTEMPO. Salidroside pretreatment attenuated Fe^{2+} accumulation and redox imbalance while preserving mitochondrial energy metabolism and overall mitochondrial function. Importantly, these findings provided the first direct evidence linking the cardioprotective effects of salidroside to the suppression of ferroptosis and the regulation of mitochondrial ROS [141]. However, Yang proved that knockdown of AMPKα2 substantially attenuated the anti-ferroptotic and cardioprotective effects of salidroside, suggesting that the mitochondrial-AMPKα2 axis plays a critical role in mediating the protective effects of salidroside against myocardial injury.

6.5 | Terpenoids

Dihydrotanshinone I (DHT), a lipophilic diterpenoid isolated from the roots of Salvia miltiorrhiza, possesses notable cardioprotective properties. Emerging evidence suggests that its cardioprotective effects are closely associated with its antioxidant and anti-apoptotic activities. Oxidative stress represents a key pathological mechanism contributing to myocardial ischemia–reperfusion injury. Nrf2 functions as a master transcriptional regulator of the cellular antioxidant defense system and, upon activation, binds to antioxidant response elements (AREs) to induce the expression of a wide range of cytoprotective genes, including phase II detoxification enzymes such as NAD(P)H:quinone oxidoreductase 1 (NQO1) and glutathione S-transferases (GSTs), antioxidant enzymes such as heme oxygenase-1 (HO-1) and peroxiredoxins, and proteins involved in glutathione biosynthesis and metabolism [142]. Dihydrotanshinone I (DHT) has been identified as a potent inducer of nuclear factor erythroid 2-related factor 2 (Nrf2), with its cardioprotective effects being largely dependent on Nrf2 activity. Mechanistically, DHT activates protein kinase C-δ (PKC-δ) signaling, promoting phosphorylation of Nrf2 at Ser40. This phosphorylation facilitates Nrf2 conformational rearrangement and dissociation from Kelch-like ECH-associated protein 1 (Keap1), thereby limiting Nrf2 ubiquitination and subsequent proteasomal degradation. Consequently, Nrf2 accumulates and efficiently translocates to the nucleus, where it activates the transcription of downstream cytoprotective genes [143].

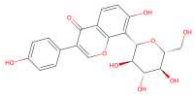
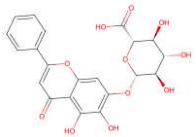
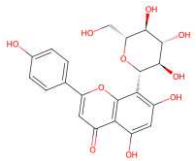
Obacunone, a limonoid triterpenoid isolated from Dictamnus dasycarpus, exerts anti-inflammatory activity by targeting macrophage migration inhibitory factor (MIF) and stabilizing mitogen-activated protein kinase phosphatase-1 (MKP-1) mRNA. In turn, it suppresses the p38 MAPK–AP-1 signaling axis, thereby attenuating the production of pro-inflammatory mediators such as nitric oxide (NO), interleukin-6 (IL-6, and interleukin-1β (IL-1β) [144]. Nrf2 serves as a master regulator of the

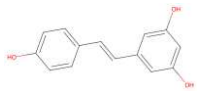
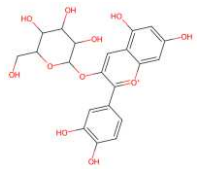
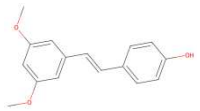
627 cellular antioxidant defense system and represents a key endogenous barrier against ferroptosis. Obacunone promotes Nrf2 protein stability by inhibiting Keap1-mediated
628 ubiquitination and subsequent proteasomal degradation of Nrf2 [145]. In an LPS-induced acute lung injury model, obacunone intervention markedly decreased ROS
629 generation, Fe^{2+} accumulation and inflammatory cytokine levels, while enhancing the expression of key anti-ferroptotic proteins, including glutathione peroxidase 4
630 (GPX4) and solute carrier family 7 member 11 (SLC7A11) [146].

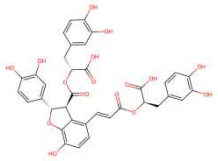
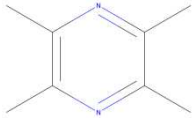
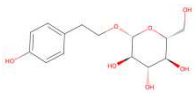
631 **6.6 | Polysaccharides**

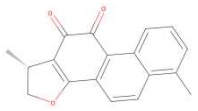
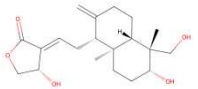
632 Polysaccharides from Gastrodia elata are important bioactive constituents of this medicinal plant. In experimental models of cerebral ischemia-reperfusion injury,
633 Gastrodia elata-derived neutral polysaccharides activate the Nrf2/HO-1 signaling pathway, thereby markedly increasing GPX4 expression and reducing ROS generation,
634 MDA accumulation and Fe^{2+} levels, ultimately attenuating neuronal ferroptosis (Zhang et al., 2024). Pharmacological inhibition of Nrf2 with brusatol markedly
635 attenuated the anti-ferroptotic and anti-inflammatory effects of Gastrodia elata neutral polysaccharides, highlighting the critical role of the Nrf2/HO-1 signaling pathway
636 in mediating their protective effects. Fucoidan, a sulfated polysaccharide, has likewise demonstrated cardioprotective properties by suppressing doxorubicin-induced
637 cardiomyocyte ferroptosis and cardiotoxicity through activation of the Nrf2/GPX4 signaling axis [147].

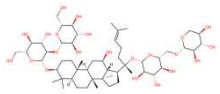
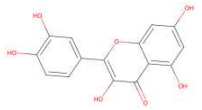
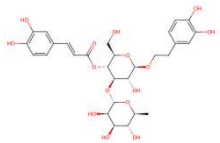
TABLE 1 Natural monomers and bioactive ingredients targeting ferroptosis-related pathways in myocardial ischemia-reperfusion injury.

Monomer	Ingredient	Target/Pathway	Effects	Chemical structure	Ref
Puerarin	Pueraria-derived isoflavone	GPX4; FTH1; PTGS2; VDAC1; 14-3-3η	Upregulates GPX4 and FTH1; suppresses PTGS2 and VDAC1; reduces Fe^{2+}, ROS, MDA, and 4-HNE; stabilizes mitochondrial membrane potential; inhibits ferroptosis and alleviates MIRI.		Chen et al., 2026; Wang et al., 2022; Ding et al., 2023; Hu et al., 2024; Qiao et al., 2025
Baicalin	Scutellaria-derived flavone glycoside	ACSL4; TfR1; NCOA4; SP1/SLC6A14	Downregulates ACSL4, TfR1, and NCOA4; inhibits SP1-mediated SLC6A14 transcription; suppresses iron-dependent lipid peroxidation and protects against MIRI.		Fan et al., 2021; Sun et al., 2025
Vitexin	Hawthorn leaf-derived flavone C-glycoside	MFN2/Drp1; Epac1/Rap1; SLC7A11/GSH/GPX4	Improves coronary flow and mitochondrial dynamics and reduces mitochondrial fragmentation and ROS. Its anti-ferroptotic action in MIRI remains		Xue et al., 2020; Dong et al., 2011; Yang et al., 2021; Zhang et al., 2023

			a mechanistic hypothesis because direct MIRI evidence is limited.		
Resveratrol	Natural stilbene polyphenol	USP19/Beclin1; TfR1; FTH1; GPX4	Reduces Fe^{2+} and TfR1; increases FTH1 and GPX4; inhibits USP19-mediated Beclin1 stabilization and autophagy-associated ferroptosis in myocardial I/R models.		Li et al., 2022
Cyanidin-3-glucoside	Natural anthocyanin glycoside	USP19/Beclin1; K11-linked ubiquitination	Inhibits USP19 and Beclin1; promotes K11-linked ubiquitination of Beclin1; reduces autophagosome formation and ferroptosis and protects cardiomyocytes.		Shan et al., 2021
Pterostilbene	Dimethoxylated stilbene polyphenol	Nrf2/FPN1/FTH1	Activates Nrf2-dependent iron regulation; promotes FPN1 and FTH1 expression; reduces intracellular iron overload; inhibits ferroptosis and protects		Tang and Kang, 2024; Zhu et al., 2024

			cardiomyocytes during I/R.		
Salvianolic acid B	Salvia miltiorrhiza-derived phenolic acid	GPX4 ubiquitin-proteasome degradation	Reduces ubiquitin-proteasome-dependent GPX4 degradation; maintains GPX4 protein abundance; clears phospholipid hydroperoxides and blocks ferroptosis in MIRI.		Wang et al., 2016; Xu et al., 2023
Tetramethylpyrazine	Ligusticum chuanxiong-derived alkaloid	GPX4; Fe^{2+}; Myl2/NLRP3	Scavenges ROS; suppresses lipid peroxidation and iron accumulation; reverses GPX4 reduction; reduces calcium overload, inflammation, and pyroptosis; protects against MIRI.		Qian et al., 2014; Lu et al., 2025; Li et al., 2025
Salidroside	Rhodiola-derived phenylethanoid glycoside	p38 MAPK; mitochondrial ROS/AMPKα2	Reduces p38 MAPK phosphorylation, Fe^{2+} accumulation, and redox imbalance; preserves mitochondrial energy metabolism and function; inhibits ferroptosis and myocardial injury.		Zhang et al., 2021; Wang et al., 2013; Yang et al., 2024

Dihydrotanshinone I	Salvia miltiorrhiza-derived diterpenoid	PKC-δ/Nrf2/ARE	Promotes Nrf2 Ser40 phosphorylation and nuclear translocation; activates antioxidant gene transcription; reduces oxidative stress and may suppress ferroptosis-related myocardial injury.		Done and Traustadóttir, 2016; Zeng et al., 2021
Obacunone	Dictamnus-derived limonoid triterpenoid	MIF/MKP-1/p38 MAPK/AP-1; Keap1/Nrf2; SLC7A11/GPX4	Reduces inflammatory mediators, ROS, and Fe^{2+}; stabilizes Nrf2 and upregulates SLC7A11 and GPX4. Anti-ferroptotic evidence is mainly derived from non-cardiac models.		Gao et al., 2018; Li et al., 2022; Ou and Zhang, 2025
Andrographolide	Andrographis paniculata-derived diterpene lactone	TLR4/Keap1/Nrf2	Suppresses TLR4-mediated inflammation and activates Nrf2 antioxidant signaling; inhibits ferroptosis in LPS-induced acute lung injury models.		Li et al., 2024

Ginsenoside Rb3	Panax-derived dammarane-type saponin	NLRP3/NF-κB/GPX4	Reduces iron and MDA; improves the GSH/GSSG ratio; decreases TNF-α, IL-1β, and IL-6; suppresses ferroptosis and inflammation in cerebral I/R models.		Tian et al., 2024
Quercetin	Natural flavonol	EGFR	Binds EGFR and may inhibit ferroptosis and inflammatory signaling; evidence in the uploaded text is primarily related to endothelial protection rather than direct MIRI validation.		Reference not specified in the source text
Verbascoside	Natural phenylethanoid glycoside	Ferroptosis-related oxidative stress pathway	Acts as a ferroptosis inhibitor and alleviates ovalbumin- or house-dust-mite-induced allergic airway inflammation; direct MIRI evidence is unavailable.		Reference not specified in the source text

Note: Evidence derived from non-cardiac or non-MIRI models is explicitly identified in the Effects column. Chemical structures were rendered from PubChem canonical/isomeric SMILES records. Polysaccharides and multicomponent saponin preparations do not have a single defined molecular structure.

Abbreviations: ACSL4, acyl-CoA synthetase long-chain family member 4; ARE, antioxidant response element; FTH1, ferritin heavy chain 1; GPX4, glutathione peroxidase 4; GSH, glutathione; I/R, ischemia/reperfusion; MDA, malondialdehyde; MIRI, myocardial ischemia-reperfusion injury; NCOA4, nuclear receptor coactivator 4; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; TfR1, transferrin receptor 1; VDAC1, voltage-dependent anion channel 1; 4-HNE, 4-hydroxynonenal.

7 | Clinical Pharmacological Therapy

At present, therapeutic strategies targeting ferroptosis in clinical settings primarily focus on its inhibition. Increasing evidence indicates that several widely used conventional pharmacological agents can exert anti-inflammatory and other beneficial effects, at least in part, through modulation of ferroptosis.(Table 2)

7.1 | Dexmedetomid

Dexmedetomidine (Dex) is a highly selective α_2-adrenergic receptor agonist widely used in perioperative and critical care settings. Increasing evidence suggests that Dex is a promising pharmacological modulator of ferroptosis and that its cardioprotective effects in myocardial ischemia-reperfusion injury (MIRI) are closely associated with ferroptosis suppression. In an isolated rat heart Langendorff perfusion model and an H9c2 cardiomyocyte hypoxia/reoxygenation model, Dex treatment markedly reduced myocardial infarct size and improved cardiac function. Restoration of the fluorescence signal of the fatty acid analog C11-BODIPY 581/591, together

with a reduction in Fe^{2+} levels detected using the Phen Green SK probe, demonstrated that Dex markedly attenuates reoxygenation-induced intracellular Fe^{2+} accumulation and lipid peroxidation in cardiomyocytes [148]. Furthermore, Dex markedly upregulated the expression of Nrf2, SLC7A11 and GPX4, whereas inhibition of Nrf2 using ML385 significantly diminished its protective effects. These findings suggest that Nrf2 acts as a critical downstream mediator through which Dex exerts its cardioprotective effects against ferroptosis [149]. Glycogen synthase kinase-3β (GSK-3β) is a constitutively active kinase that negatively regulates Nrf2 signaling by directly phosphorylating specific serine residues on Nrf2, thereby promoting its nuclear export and subsequent proteasomal degradation [150]. Therefore, suppression of GSK-3β activity represents an important strategy for enhancing Nrf2 activation. AMP-activated protein kinase (AMPK), a key cellular energy sensor, is capable of phosphorylating and inhibiting GSK-3β upon activation, thereby promoting Nrf2 signaling [151]. Dexmedetomidine (Dex) activates the AMPK/GSK-3β/Nrf2 signaling axis, facilitating Nrf2 nuclear translocation and enhancing the expression of downstream cytoprotective proteins, including heme oxygenase-1 (HO-1), SLC7A11 and GPX4, thereby attenuating myocardial ischemia–reperfusion injury-induced ferroptosis. Moreover, Yu P et al. reported that Dex administered during reperfusion alleviated IRI-induced myocardial injury and mitochondrial dysfunction, at least in part, through activation of the SLC7A11/GPX4 axis and regulation of ferritin heavy chain (FTH) and cyclooxygenase-2 (COX-2) expression [152].

7.2 | Propofol

Propofol, or 2,6-diisopropylphenol, is one of the most widely used intravenous anesthetic agents in clinical practice. Its distinctive chemical structure, featuring

an aromatic ring with a phenolic hydroxyl group, confers both sedative–hypnotic and antioxidant properties. Early electron spin resonance spectroscopy studies demonstrated that propofol reacts with free radicals to generate relatively stable phenoxyl radicals, thereby exerting potent free radical-scavenging activity comparable to that of the endogenous antioxidant α-tocopherol (vitamin E) [153]. Early experimental and clinical studies have demonstrated that propofol protects against ischemia-reperfusion injury by alleviating mechanical dysfunction and metabolic disturbances and by suppressing myocardial accumulation of malondialdehyde (MDA), a terminal product of lipid peroxidation. Moreover, in patients undergoing coronary artery bypass grafting (CABG), propofol has been shown to markedly reduce myocardial lipid peroxidation [154,155]. Ferroptosis is an iron-dependent form of regulated cell death characterized by the lethal accumulation of lipid peroxides and has emerged as a critical pathological process contributing to myocardial ischemia-reperfusion (I/R) injury. As a pivotal tumor suppressor, p53 can transcriptionally repress SLC7A11 expression in response to specific stress stimuli, thereby limiting cystine uptake, disrupting cellular redox homeostasis and ultimately promoting ferroptosis [156]. Sheng et al. reported that propofol attenuates myocardial ischemia-reperfusion (I/R) injury, at least in part, by suppressing ferroptosis through activation of the AKT/p53 signaling pathway. In H9c2 cardiomyocytes, erastin-induced ferroptosis was significantly attenuated by 1 h of propofol pretreatment, as evidenced by increased cell viability and reduced intracellular reactive oxygen species (ROS) levels. Moreover, propofol upregulated the expression of ferroptosis-associated antioxidant proteins, including ferritin heavy chain 1 (FTH1), xCT (SLC7A11) and glutathione peroxidase 4 (GPX4), supporting its anti-ferroptotic activity. Consistently, in an isolated rat heart I/R model, propofol pretreatment (I/R + P) markedly reduced myocardial pathological injury, myocardial iron accumulation, and

679 p53 protein expression, while enhancing the expression of antioxidant proteins. Further studies using the AKT inhibitor MK2206 and AKT-specific siRNA showed that
680 inhibition or knockdown of AKT markedly attenuated the protective effects of propofol, thereby providing strong evidence for a critical role of the AKT/p53 signaling
681 axis in mediating its anti-ferroptotic effects [157]. Another study demonstrated that myocardial ischemia-reperfusion (I/R) injury markedly increased SLC16A13
682 expression, whereas SLC16A13 overexpression inhibited AMPK phosphorylation, resulting in suppression of the downstream GPX4-dependent antioxidant defense
683 and consequent exacerbation of iron accumulation and lipid peroxidation in cardiomyocytes. Notably, propofol pretreatment downregulated SLC16A13 expression and
684 restored AMPK/GPX4 signaling, thereby alleviating ferroptosis and improving cardiac function [158].

685 **7.3 | Etomidate**

686 Etomidate is a commonly used intravenous anesthetic agent characterized by minimal cardiovascular effects and favorable hemodynamic stability. During
687 ischemia-reperfusion, disruption of cardiomyocyte membrane integrity leads to the release of intracellular creatine kinase (CK) and lactate dehydrogenase (LDH) into
688 the circulation, accompanied by impaired cardiac contractile and diastolic function. In a rat model of myocardial ischemia-reperfusion injury (MIRI), administration of
689 etomidate during reperfusion was found to attenuate cardiac dysfunction and myocardial injury, while reducing serum CK and LDH levels and the secretion of pro-
690 inflammatory cytokines [159]. In a cellular model, erastin treatment abolished the protective effects of etomidate against hypoxia/reoxygenation (H/R)-induced
691 cardiomyocyte injury, suggesting that the cardioprotective effects of etomidate against myocardial ischemia-reperfusion injury (MIRI) are closely associated with its

anti-ferroptotic activity. As a key downstream antioxidant axis of Nrf2, the Nrf2/HO-1 signaling pathway exerts cytoprotective effects, with HO-1 and its metabolites, including bilirubin and carbon monoxide (CO), contributing to antioxidant and anti-inflammatory defense [160]. In a rat model of myocardial ischemia-reperfusion injury (MIRI), etomidate treatment markedly increased the protein expression of Nrf2 and HO-1 in myocardial tissue and facilitated Nrf2 nuclear translocation, thereby strengthening antioxidant defenses and suppressing ferroptosis.

7.4 | Dapagliflozin

Dapagliflozin is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor that, in addition to its glucose-lowering effects, exerts cardioprotective effects that are largely independent of glycemic control [161]. Experimental evidence indicates that dapagliflozin exerts anti-ferroptotic effects, at least in part, by inhibiting MAPK signaling and thereby preserving the SLC7A11-GSH-GPX4 antioxidant axis. In both in vivo and in vitro models, dapagliflozin decreased the levels of cardiac injury biomarkers, including cardiac troponin T (cTnT) and B-type natriuretic peptide (BNP), attenuated reperfusion-induced arrhythmias and improved H9c2 cardiomyocyte viability. Notably, dapagliflozin also reversed hypoxia/reoxygenation-induced downregulation of SLC7A11 and GPX4 and restored intracellular glutathione (GSH) levels [162]. Prostaglandin-endoperoxide synthase 2 (PTGS2) is a key enzyme involved in lipid peroxidation, and its transcriptional upregulation is commonly regarded as a molecular marker of ferroptosis. In an LPS-induced model of septic cardiomyopathy, dapagliflozin markedly suppressed PTGS2 mRNA expression, thereby reducing the conversion of lipid substrates, including arachidonic acid, into downstream lipid peroxidation products and consequently attenuating ferroptotic cell death

[163]. NCOA4 functions as a selective cargo receptor for ferritinophagy, facilitating the delivery of ferritin, including FTH1, to lysosomes for degradation and subsequent release of labile iron. Dysregulated ferritinophagy during ischemia-reperfusion may increase the intracellular labile iron pool, thereby enhancing Fenton chemistry and promoting ferroptosis. Emerging evidence suggests that dapagliflozin may preserve cellular iron homeostasis, at least in part, by modulating EGFR/NHE1/NCOA4-mediated ferritinophagy [164]. Using both in vivo and in vitro models, researchers demonstrated that dapagliflozin ameliorated myocardial injury, oxidative stress, and mitochondrial structural and functional abnormalities. Pharmacological inhibition of EGFR signaling or autophagy using AG and bafilomycin A1 (Baf) revealed that erastin (ERA) did not significantly influence NCOA4-mediated ferritinophagy. Conversely, activation of EGFR by NSC counteracted these protective effects, suggesting that dapagliflozin promotes cardioprotection by modulating NCOA4-mediated ferritinophagy through an EGFR-dependent mitochondrial regulatory mechanism.

7.5 | Melatonin

Melatonin is a potent free radical scavenger and endogenous antioxidant. Recent studies have demonstrated that melatonin modulates ferroptosis through multiple signaling pathways, thereby exerting protective effects against myocardial ischemia–reperfusion injury (MIRI). Notably, a 2025 study in a rat model of MIRI showed that melatonin inhibits ferroptosis by regulating the ATF3/GPX4 signaling axis. Mechanistically, melatonin suppresses ATF3 expression, which in turn enhances GPX4 expression, ultimately reducing ferroptotic cell death in cardiomyocytes and alleviating MIRI [165]. Another study reported that melatonin may attenuate ferroptosis

by inhibiting the ataxia-telangiectasia mutated (ATM)/p53 signaling pathway, thereby suppressing lipid peroxidation and protecting cardiomyocytes from ferroptotic injury [166]. Furthermore, melatonin promotes mitochondrial fusion and mitophagy through activation of the AMPK/OPA1 signaling pathway, thereby preserving mitochondrial homeostasis and attenuating oxidative stress and apoptotic cell death in cardiomyocytes [167].

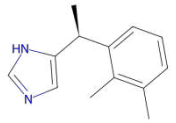
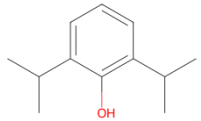
7.6 | Metformin

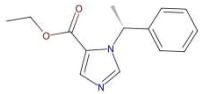
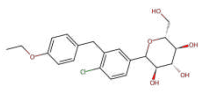
Metformin is a first-line oral pharmacological agent for the treatment of type 2 diabetes mellitus (T2DM), primarily by inhibiting hepatic gluconeogenesis and improving peripheral insulin sensitivity. Increasing evidence has highlighted the role of metformin in modulating ferroptosis in cancer. In breast cancer, metformin inhibits the UFMylation of solute carrier family 7 member 11 (SLC7A11), thereby destabilizing the SLC7A11 protein and reducing its expression [168]. miR-324-3p directly binds to the 3′-untranslated region (3′-UTR) of GPX4 and suppresses its expression. Metformin has been reported to upregulate miR-324-3p expression, thereby modulating GPX4-mediated lipid peroxidation [169]. Accumulating clinical and preclinical evidence indicates that the cardiovascular protective effects of metformin extend beyond its glucose-lowering activity. During myocardial ischemia-reperfusion injury (MIRI), oxidative stress serves as a major driver of ferroptotic cell death. NADPH oxidase 4 (NOX4), a member of the NADPH oxidase family, is a major source of reactive oxygen species (ROS) in cardiomyocytes [170]. In 2023, Wu et al. reported that metformin increased AMPKα expression while suppressing NOX4 expression in cardiac tissues. Knockdown of AMPKα using siRNA eliminated the protective effects of metformin against OGD/R-induced ferroptotic injury in H9c2 cardiomyocytes, suggesting that the AMPKα/NOX4 signaling axis is a key mediator

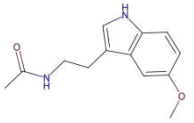
of the cardioprotective and anti-ferroptotic actions of metformin [171]. Recent evidence indicates that metformin promotes the cytoplasmic-to-nuclear translocation of Nur77, enabling Nur77 to bind to the promoter of IDH1 and directly enhance its transcription. Isocitrate dehydrogenase 1 (IDH1) is a key cytosolic metabolic enzyme that catalyzes the conversion of isocitrate to α-ketoglutarate, thereby contributing to the maintenance of intracellular redox homeostasis. Consequently, upregulation of IDH1 may enhance cellular antioxidant capacity and preserve redox balance [172]. Pharmacological inhibition of IDH1 with the catalytic-site inhibitor compound 2 (AGI-5198) completely abolished the anti-ferroptotic protective effect of metformin, providing evidence that IDH1 catalytic activity is required for this protection. Collectively, these findings suggest that metformin suppresses myocardial ischemia-reperfusion injury-induced ferroptosis, at least in part, through the Nur77–IDH1 signaling axis [173]. Interestingly, the effects of metformin on ferroptosis exhibit considerable context dependence, with metformin exerting either pro-ferroptotic or anti-ferroptotic effects in different disease settings. In hepatocellular carcinoma, for example, metformin has been shown to promote ferroptosis, thereby suppressing tumor cell proliferation [174]. In clinical practice, the risk of lactic acidosis associated with metformin should be evaluated according to renal function and hemodynamic status. Dose escalation should not be undertaken solely to achieve anti-ferroptotic effects, given the potential safety concerns.

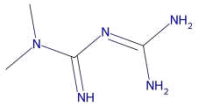
Table 2. Clinically used drugs that modulate ferroptosis in myocardial ischaemia–reperfusion injury

Monomer	Ingredient	Target/Pathway	Effects	Chemical structure	Ref

Dexmedetomidine	Highly selective α_2-adrenergic receptor agonist; perioperative and intensive-care sedative	AMPK/GSK-3β/Nrf2; Nrf2/SLC7A11/GPX4; FTH/COX-2	Decreases Fe^{2+} accumulation and lipid peroxidation; promotes Nrf2 nuclear translocation and restores SLC7A11/GPX4-dependent antioxidant defence; preserves mitochondrial function, reduces infarct size and improves cardiac function in preclinical I/R models.		Salazar et al., 2006; Choi et al., 2010; Yu et al., 2022; Z. Wang et al., 2022; M. Wang et al., 2024
Propofol	2,6-Diisopropylphenol; intravenous general anaesthetic with free-radical-scavenging activity	AKT/p53; FTH1/xCT/GPX4; SLC16A13/AMPK/GPX4	Scavenges lipid radicals and reduces ROS, myocardial iron and lipid peroxidation; restores FTH1, xCT and GPX4; suppresses SLC16A13 and reactivates AMPK/GPX4 signalling,		Murphy et al., 1992; Kokita et al., 1998; Sayin et al., 2002;

			thereby attenuating myocardial I/R injury.		S. Li et al.,
			Clinical CABG studies support reduced		2022; Sun et
			lipid peroxidation but do not establish		al., 2024; Su
			ferroptosis-specific efficacy.		et al., 2025
			Promotes Nrf2 nuclear translocation and		
			HO-1 expression; reduces CK, LDH and		
	Imidazole-derived		pro-inflammatory cytokine release;		Zhang et al.,
Etomidate	intravenous anaesthetic	Nrf2/HO-1; ferroptosis-	improves cardiac systolic and diastolic		2020; Lv et
	with relative	dependent protection	function. Loss of protection after erastin		al., 2021
	haemodynamic stability		treatment supports a ferroptosis-related		
			mechanism in preclinical MIRI models.		
	Sodium–glucose	MAPK/SLC7A11/GSH/GPX4;	Restores GSH, SLC7A11 and GPX4;		Li, 2021; W.
Dapagliflozin	cotransporter 2 inhibitor	PTGS2; EGFR/NHE1/NCOA4-	decreases PTGS2-related lipid		Chen et al.,

	used for diabetes and cardiorenal disease	mediated ferritinophagy	peroxidation; limits NCOA4-mediated ferritinophagy and labile iron accumulation; improves myocardial injury markers, mitochondrial structure/function and reperfusion arrhythmia in experimental models.		2023; K. Hu et al., 2024; Yu et al., 2026
Melatonin	Endogenous indoleamine and clinically used chronobiotic with antioxidant activity	ATF3/GPX4; ATM/p53; AMPK/OPA1	Downregulates ATF3 and restores GPX4; inhibits ATM/p53-associated lipid peroxidation; activates AMPK/OPA1 to improve mitochondrial fusion, mitophagy and redox homeostasis, thereby reducing cardiomyocyte ferroptosis and myocardial I/R injury in preclinical		Y. Zhang et al., 2019; He et al., 2025; Wang et al., 2025

			studies.		
Metformin	Biguanide glucose-lowering agent widely used in type 2 diabetes	AMPKα/NOX4; Nur77/IDH1; context-dependent SLC7A11/GPX4 regulation	Activates AMPKα and suppresses NOX4-derived ROS; promotes Nur77 nuclear translocation and IDH1 transcription to maintain redox balance; reduces iron accumulation, lipid peroxidation and MIRI-associated ferroptosis. Its ferroptosis effect is disease-context dependent; renal function and haemodynamic status must be considered because of lactic-acidosis risk.		J. Yang et al., 2021; Hou et al., 2021; Szekeres et al., 2021; Murnan et al., 2023; Wu et al., 2023; Wu et al., 2025; J. Sun et al., 2025

Note: The anti-ferroptotic effects listed are predominantly supported by cellular, isolated-heart and animal studies; clinical use of a drug does not imply that ferroptosis inhibition is an established

clinical indication. Chemical structures were redrawn from PubChem canonical/isomeric SMILES (CIDs 5311068, 4943, 667484, 9887712, 896 and 4091).

Abbreviations: AMPK, AMP-activated protein kinase; CABG, coronary artery bypass grafting; COX-2, cyclooxygenase-2; FTH1, ferritin heavy chain 1; GPX4, glutathione peroxidase 4; GSH, glutathione; HO-1, haem oxygenase-1; I/R, ischaemia/reperfusion; MIRI, myocardial ischaemia–reperfusion injury; NCOA4, nuclear receptor coactivator 4; Nrf2, nuclear factor erythroid 2-related factor 2; PTGS2, prostaglandin-endoperoxide synthase 2; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; xCT, cystine/glutamate antiporter light chain.

8 | Interactions between Anti-inflammatory Agents and Ferroptosis Inhibitors

Emerging evidence indicates a reciprocal relationship between inflammation and ferroptosis, with several anti-inflammatory drugs exhibiting ferroptosis-suppressive effects in vitro and conventional ferroptosis inhibitors attenuating inflammatory mediator release. In a dextran sulfate sodium (DSS)-induced mouse model of ulcerative colitis, the classical anti-inflammatory drug celecoxib increased intracellular glutathione (GSH) levels, reduced malondialdehyde (MDA) accumulation and enhanced the expression of GPX4 and xCT, thereby alleviating ferroptotic features[175]. Dimethyl fumarate (DMF), an anti-inflammatory agent approved for the treatment of multiple sclerosis, alleviates ferroptosis in a sepsis-induced acute lung injury model by suppressing STING-mediated autophagic degradation of GPX4, thereby limiting ROS accumulation and oxidative damage [176]. In a model of cerebral ischemia–reperfusion injury (CIRI), minocycline suppressed ferroptosis by downregulating heme oxygenase-1 (HO-1), thereby limiting the intracellular labile iron pool and lipid peroxidation while preserving mitochondrial structure and

function. The potential of ferroptosis inhibitors to modulate inflammatory diseases has also been supported by several studies. In nonalcoholic steatohepatitis (NASH), liproxstatin-1, a potent ferroptosis inhibitor, attenuates hepatic lipid peroxidation and consequently reduces the severity of inflammatory responses, while also limiting subsequent immune cell infiltration and inflammatory activation [177]. In an LPS-induced acute lung injury (ALI) model, treatment with the ferroptosis inhibitor ferrostatin-1 (Fer-1) significantly reduced neutrophil infiltration and protein levels in bronchoalveolar lavage fluid (BALF), thereby alleviating pulmonary inflammation and improving the survival rate of ALI mice[178]. However, the effects of anti-inflammatory agents on ferroptosis are not uniformly inhibitory. Dexamethasone, for example, increases cellular susceptibility to ferroptosis through glucocorticoid receptor activation and subsequent upregulation of dipeptidyl peptidase-like 1 (DPEP1), which promotes intracellular GSH depletion [179]. In CRC models, aspirin inhibits AKT/mTOR signaling in PIK3CA-mutant CRC cells, leading to downregulation of sterol regulatory element-binding protein 1 (SREBP-1) and stearoyl-CoA desaturase 1 (SCD1). Consequently, aspirin suppresses de novo synthesis of monounsaturated fatty acids while increasing the cellular availability of oxidation-sensitive polyunsaturated fatty acids (PUFAs), thereby potentially enhancing susceptibility to lipid peroxidation [180].

9 | Discussion

Acute myocardial infarction (AMI) is one of the cardiovascular diseases that poses a major threat to human health [181]. Timely restoration of blood flow to the ischemic myocardium is the cornerstone of current clinical management. At present, reperfusion of the ischemic myocardium is primarily achieved through thrombolytic therapy, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), with the aim of restoring myocardial perfusion, limiting cardiomyocyte death, reducing infarct size, and ultimately lowering mortality [182]. However, reperfusion itself may paradoxically induce myocardial ischemia-reperfusion injury (MIRI), leading to metabolic derangements and structural damage in the myocardium, cardiomyocyte death and impairment of endothelial and microvascular function. These pathological changes can, in turn, precipitate severe arrhythmias and increase the risk of sudden cardiac death [183]. Although timely reperfusion through interventional procedures and thrombolytic therapy has substantially improved the survival of critically ill patients with myocardial ischemia, the incidence of post-reperfusion complications associated with myocardial ischemia-reperfusion injury (MIRI) continues to pose a major challenge, thereby limiting the overall clinical benefit of reperfusion therapy. MIRI is a complex pathological network arising from the interplay among oxidative stress, dysregulated iron metabolism, mitochondrial dysfunction, inflammatory responses and multiple forms of regulated cell death. Notably, ferroptosis is not only an important execution mechanism of cardiomyocyte injury during the early phase of reperfusion but can also initiate sterile inflammation through the release of damage-associated molecular patterns (DAMPs) and oxidized lipid mediators. Conversely, inflammatory signaling can increase cardiomyocyte susceptibility to ferroptosis by perturbing iron homeostasis, remodeling lipid metabolism, and compromising antioxidant defenses. Therefore, targeting oxidative stress alone is

779 unlikely to be sufficient to effectively mitigate MIRI, whereas disrupting the ferroptosis–inflammation positive-feedback loop may represent a promising therapeutic
780 strategy and identify a potential target for intervention.

781 This review highlights the pronounced multitarget characteristics of natural bioactive compounds and clinically used drugs in the treatment of myocardial
782 ischemia-reperfusion injury (MIRI). However, it remains unclear to what extent their cardioprotective effects are genuinely attributable to ferroptosis inhibition rather
783 than to broader antioxidant, anti-inflammatory, anti-apoptotic, or hemodynamic effects. Moreover, the actions of these agents are highly dependent on the cellular
784 context and disease setting. For example, moderate activation of heme oxygenase-1 (HO-1) may exert antioxidant and anti-inflammatory effects through the
785 generation of bilirubin and carbon monoxide, whereas excessive HO-1 activation may increase the labile iron pool by accelerating heme degradation and releasing
786 Fe^{2+}. Similarly, metformin suppresses ferroptosis in models of myocardial ischemia-reperfusion injury through the AMPKα/NOX4 or Nur77/IDH1 axes, yet
787 promotes ferroptosis in hepatocellular carcinoma models. Likewise, not all anti-inflammatory agents necessarily suppress ferroptosis; under certain conditions,
788 dexamethasone and related agents may increase cellular susceptibility to ferroptosis by depleting glutathione (GSH). Therefore, alterations in individual molecular
789 markers should not be interpreted in isolation as definitive evidence of ferroptosis modulation. For instance, increased Nrf2 or HO-1 expression and reduced
790 inflammatory cytokine levels do not necessarily establish ferroptosis inhibition, whereas decreased GPX4 expression, increased ACSL4 expression, elevated
791 malondialdehyde levels, or iron accumulation alone are insufficient to confirm ferroptotic cell death. A rigorous assessment should integrate multiple complementary

792 parameters, including lipid peroxidation, the labile iron pool, mitochondrial ultrastructural changes, and GPX4 activity or function, together with pharmacological
793 rescue or validation using established ferroptosis inhibitors or inducers, such as ferrostatin-1 (Fer-1), liproxstatin-1 (Lip-1), erastin, or RSL3, to establish a causal
794 relationship between ferroptosis and the observed phenotype.

795 Current experimental evidence is derived predominantly from H9c2 cells, primary cardiomyocytes and rodent models, with most studies employing ischemic
796 preconditioning or pretreatment paradigms. However, these experimental designs differ substantially from the clinical scenario of patients with acute myocardial
797 infarction, in whom therapeutic interventions are typically initiated only after hospital admission and reperfusion by percutaneous coronary intervention (PCI).
798 Moreover, existing animal studies frequently use young, healthy animals of a single sex, whereas patients with acute myocardial infarction often present with
799 advanced age and multiple comorbidities, including diabetes mellitus, obesity, chronic kidney disease, and long-term medication use. These factors may substantially
800 influence iron metabolism, lipid composition, inflammatory status, and drug responsiveness, thereby limiting the generalizability of preclinical findings.Natural
801 bioactive compounds also face important translational challenges, including low bioavailability, a potential mismatch between experimentally effective doses and
802 clinically achievable exposures, insufficiently characterized pharmacokinetic profiles, and difficulties in standardizing formulation quality. Therefore, future clinical
803 studies should prioritize drug-repurposing strategies involving agents with well-established safety profiles and approved clinical indications, while focusing on
804 therapeutic windows that are feasible during the peri-reperfusion period. Early-phase clinical trials could incorporate cardiac magnetic resonance (CMR)-derived

infarct size, myocardial salvage index, microvascular obstruction, and intramyocardial hemorrhage as mechanistic endpoints, together with conventional assessments of myocardial injury biomarkers, cardiac function, and long-term heart failure outcomes. Patient stratification based on ferroptosis- and inflammation-related biomarkers may be more effective than indiscriminate treatment of all patients with myocardial infarction and could facilitate the identification of populations most likely to derive clinical benefit.Although targeting the ferroptosis–inflammation positive-feedback loop represents a promising therapeutic avenue for mitigating myocardial ischemia–reperfusion injury (MIRI), its clinical relevance remains to be established through rigorous causal validation, standardized assessment frameworks, and carefully designed translational and clinical studies.

Author Contributions

Min Zhang: Investigation;Conceptualization; Methodology; Visualization; Writing-Original Draft; Writing-Review & Editing Xuli Ji: Investigation; Methodology; Resources;Software; Supervision; Validation. Luyao Wan: Investigation; Project Administration; Resources; Software; Validation. Bingfu Wang: Conceptualization; Methodology; Resources; Discussion. Liyang Deng：Conceptualization; Methodology; Resources. Zuoying Xing: Investigation; Project Administration; Resources; Software; Supervision. Genhao Fan:Conceptualization; Methodology; Funding Acquisition; Software; Supervision. Yongxia Wang:Conceptualization; Methodology; Funding Acquisition; Software; Supervision

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Data Availability Statement

No datasets were generated or analyzed in the study described in this manuscript.

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