Diabetology & Metabolic Syndrome

REVIEW

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Antioxidant proteins can be potential targets in ameliorating ferroptosis in diabetic cardiomyopathy: a literature review

Yuting Lin[1], Shu Yang[2] and Jinjian Guo[1*]

Abstract

Diabetic cardiomyopathy (DCM) is one of the cardiovascular complications of diabetes mellitus, which is different from myocardial damage caused by coronary ischemia, hypertension, and valvular disease. DCM lacks distinct clinical manifestations in its early stages, and current therapeutic approaches primarily focus on symptomatic management. Emerging evidence indicates that even with optimized glycemic regulation, the pathophysiological progression of DCM remains unmitigated. Exploring the pathogenic mechanism of DCM is the focus and hotspot of current research. Ferroptosis, an iron-dependent form of regulatory cell death, is crucial in DCM myocardial damage. Dysfunctional antioxidant defense system, increased oxidative stress, and elevated reactive oxygen species are the key mechanisms of ferroptosis in DCM. Thus, this review innovatively takes antioxidant proteins as the entry point, and for the first time systematically summarizes the molecular mechanism of antioxidant proteins to improve DCM by regulating the ferroptosis pathway, and summarizes the therapeutic strategy of medications to enhance ferroptosis in DCM by targeting the expression of antioxidant proteins, to explore the potential targets to improve ferroptosis in DCM, to provide a new perspective for the study of delaying the progression of DCM.

Keywords Diabetic cardiomyopathy, Ferroptosis, Oxidative stress, Antioxidant proteins, Therapy

Introduction

By 2045, the global population affected by diabetes mellitus (DM) is projected to reach 784 million, cementing its status as one of the most widespread chronic diseases worldwide [1]. Of particular concern is diabetic cardiomyopathy (DCM), a cardiovascular complication affecting approximately 17% of diabetic patients and representing a leading etiology of heart failure and mortality in this population [2, 3]. Distinct from myocardial injury caused by coronary artery ischemia, hypertension, or valvular pathologies, DCM progresses insidiously, often remaining clinically silent during early stages. Diagnosis is typically delayed until advanced disease manifests as overt heart failure. Current therapeutic strategies prioritize glycemic control, lipid modulation, and heart failure management; however, multicenter randomized trials have demonstrated that even optimal glucose regulation fails to halt DCM progression [4]. This underscores the urgent need to elucidate the pathophysiological mechanisms underlying DCM and identify novel therapeutic targets.

Emerging evidence implicates ferroptosis plays an important role in the pathogenesis of DCM. Wang et al. [5] provided seminal evidence through in vitro and in vivo experiments, demonstrating elevated ferroptotic

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activity in DCM cardiomyocytes. Key findings included: (i) significantly increased malondialdehyde (MDA), a lipid peroxidation biomarker, (ii) downregulated expression of solute carrier family 7 member 11 (SLC7A11), (iii) depleted glutathione (GSH) and ferritin levels, and (iv) ultrastructural hallmarks of ferroptosis (e.g., mitochondrial cristae loss) in diabetic myocardial tissues. Notably, cardiomyocyte mortality in diabetic tissues was reported to be 85-fold higher than in non-diabetic counterparts [6]. Specifically, under hyperglycemic conditions, iron overload, impaired antioxidant defense systems, and excessive reactive oxygen species (ROS) production collectively contribute to the induction of ferroptosis in DCM [7].

This review systematically examines the mechanistic role of ferroptosis in DCM progression, with a focus on antioxidant proteins as potential therapeutic nodes. We further evaluate pharmacological strategies aimed at augmenting antioxidant protein expression to mitigate ferroptosis and ameliorate DCM-related cardiac dysfunction.

Ferroptosis pathogenesis in DCM

The concept of ferroptosis

Ferroptosis, first described by Dixon et al.. in 2012 as an iron-dependent form of regulated cell death [8], differs mechanistically from classical programmed cell death pathways such as apoptosis, autophagy, and necrosis. Morphologically, ferroptotic cells exhibit distinct necrotic features, including mitochondrial ultrastructural alterations (e.g., cristae loss, outer membrane rupture, and condensed matrix density), cytoplasmic shrinkage, and preserved nuclear architecture without hallmark apoptotic changes such as plasma membrane blebbing or apoptotic body formation [9]. Biochemically, ferroptosis manifests GSH depletion, glutathione peroxidase 4 (GPX4) inactivation, and an increase in divalent iron ions (Fe^{2+}) and lipid peroxidation [10]. These pathognomonic features underscore ferroptosis as a pivotal contributor to diverse disease pathologies, positioning its modulation as a promising therapeutic frontier.

Central to ferroptotic cascades are four interdependent drivers: (i) dysfunction of the system Xc^--GSH-GPX4 antioxidant axis, (ii) intracellular iron overload, (iii) uncontrolled lipid peroxidation, and (iv) mitochondrial metabolic derangements. The interplay of these mechanisms will be systematically analyzed in subsequent sections.

System Xc^--GSH-GPX4

Ferroptosis fundamentally arises from the pathological accumulation of lipid hydroperoxides, driven by the collapse of cellular antioxidant defenses-particularly the inactivation of the system Xc^--GSH-GPX4 axis [10]. This antioxidant machinery comprises the cystine/glutamate antiporter system Xc^-, a heterodimeric complex formed by SLC7A11 and solute carrier family 3 member 2 (SLC3A2), embedded within the phospholipid bilayer. Functionally, system Xc^- mediates a 1:1 exchange of intracellular glutamate for extracellular cystine. The imported cystine undergoes reduction to cysteine, a rate-limiting substrate for GSH biosynthesis [11].

Central to this antioxidant network is GPX4, formerly termed phospholipid hydroperoxide glutathione peroxidase (PHGPX), which exists as three splice variants-mitochondrial (mGPX4), cytoplasmic (cGPX4), and nuclear (nGPX4)-derived from a single gene through alternative transcriptional initiation and splicing [12, 13]. GPX4 catalyzes the GSH-dependent reduction of phospholipid hydroperoxides (PLOOH) to non-reactive phospholipid alcohols (PLOH), concomitantly generating oxidized glutathione (GSSG). This enzymatic activity is indispensable for neutralizing lipid ROS and maintaining redox equilibrium. Conversely, when GPX4 expression was reduced, ROS was significantly elevated in vivo, which in turn induced lipid peroxidation of phospholipid-containing cell membranes and the production of MDA, thereby triggering the ferroptosis program [14–17]. Notably, GPX4 activity is strictly GSH-dependent; intracellular GSH depletion directly impairs its detoxification capacity, thereby exacerbating lipid peroxidation cascades [18].

Thus, ferroptosis can be triggered by GPX4 inactivation/depletion, system Xc^- inhibition, and decreasing GSH levels, which is the first indication that SLC7A11 has an anti-ferroptosis impact in the heart, as selective overexpression of SLC7A11 in cardiomyocytes could raise cellular GSH levels and inhibite ferritin H deficiency-mediated cardiac ferroptosis [19]. Furthermore, the knockdown of SLC7A11 exacerbated cardiac hypertrophy and cardiac dysfunction in mice, both of which could be reversed by inhibiting ferroptosis [20]. In DCM models, diminished SLC7A11 and GSH levels correlate with diastolic impairment, reversible via ferroptosis inhibitors [5]. Zang et al.. further demonstrated that DCM progression associates with myocardial iron deposition, GPX4 downregulation, cardiac fibrosis, and cardiomyocyte death [21]. Collectively, these findings implicate hyperglycemia-induced dysregulation of the system Xc^--GSH-GPX4 axis as a central driver of ferroptosis in DCM pathogenesis.

Iron overload

Iron, as an essential trace element, plays indispensable roles in diverse physiological processes, including oxygen transport, mitochondrial respiration, and enzymatic catalysis. Dietary trivalent iron (Fe^{3+}) undergoes duodenal reduction to ferrous iron (Fe^{2+}) via duodenal

cytochrome B (DCYTB), followed by systemic distribution through a coordinated transport network: (i) apical absorption via divalent metal transporter 1 (DMT1), (ii) basolateral export through ferroportin 1 (FPN1) coupled with hephaestin (HEPH)-mediated reoxidation, and (iii) circulation as transferrin (TF)-bound complexes for cellular delivery [22–24]. Disruption of iron homeostasis-encompassing uptake, trafficking, storage, and redox cycling-profoundly modulates cellular susceptibility to ferroptosis [25], an iron-dependent programmed death pathway [8]. Excess iron can induce and promote ferroptosis by generating ROS and regulating lipid peroxidation. ROS are easily produced by the Fenton reaction between free Fe^{2+} and lipid peroxidation when there is an excess of Fe^{2+} in the cell [8]. In the meantime, Fe^{2+} and Fe^{3+} are also crucial catalytic cofactors that stimulate ferroptosis, encourage lipid peroxidation, and boost the generation of free radicals such as alkoxy radical (RO) and peroxy radical (RO2) [26]. Furthermore, aberrant iron storage and release by iron-regulated proteins 1 (IRP1) and 2 (IRP2), as well as ferritin degradation and the ensuing autophagy, can raise intracellular levels of unstable iron, produce ROS, and increase vulnerability to ferroptosis [27].

Experimental evidence highlights the cardiotoxic consequences of iron dysregulation. Murine models fed iron-enriched diets exhibit myocardial iron deposition, characteristic ferroptotic ultrastructural changes, and systolic impairment [19]. Iron excess has been shown to cause insulin resistance in cardiomyocytes [28], which in turn causes lipid peroxidation and ROS overproduction [29, 30], ultimately leading to heart failure [31]. The pathophysiology of DCM is largely influenced by insulin resistance, which suggests that iron overload is a significant contributing factor [32]. Several animal models of DCM show lower cardiac function, increased ROS levels, and iron accumulation in cardiomyocytes [5, 21, 33]. These findings collectively implicate iron-driven oxidative cascades as central mediators of ferroptotic cardiomyocyte loss in DCM progression.

Lipid peroxidation

Lipid peroxidation is the process by which unsaturated fatty acids are oxidized by ROS through enzymatic or non-enzymatic reactions to form lipid peroxides, which play a driving role in the development of ferroptosis. Polyunsaturated fatty acids (PUFA) are very sensitive to oxidation due to their unstable double bonds [34]. Therefore, polyunsaturated fatty acids are more likely to induce ferroptosis than monounsaturated fatty acids. Acyl-CoA synthetase long-chain family member 4 (ACSL4) is a key determinant of ferroptosis susceptibility [35]. ACSL4 catalyzes the addition of Coenzyme A (CoA) to the long-chain polyunsaturated bonds of arachidonic acid, which promotes the esterification of PUFA with phospholipids. ACSL4 catalyzes the esterification of binding of long-chain PUFA (LC-PUFA) and adrenergic acid to CoA to form Polyunsaturated Fatty Acid-Coenzyme A (PUFA-CoA), thereby facilitating the entry of LC-PUFA into lipids and membranes [36]. Upon ACSL4 activation, lysophosphatidylcholine acyltransferase 3 (LPCAT3) participates in ferroptosis signaling by inserting acyl groups into lysophospholipids. Interestingly, ferroptosis can also occur in an ACSL4-independent manner. On the one hand, lipoxygenases (LOXs) are key enzymes in the production of lipid peroxides. On the other hand, iron promotes non-enzymatic lipid autoxidation via the Fenton reaction [37, 38].

Both systemic and cellular damage result from the long-term buildup of glucose-induced peroxides in cardiomyocytes, which causes ferroptosis [39]. In addition, during the onset of DCM, the energy metabolism of cardiomyocytes shifts from glycogenolysis to fatty acid oxidation, leading to increased intracellular lipid accumulation and lipotoxicity [40]. One of the most obvious signs of cardiac stress is lipid peroxidation, which exacerbates myocardial damage in DCM and causes ferroptosis by rupturing cell membranes [41]. Thus, lipid peroxide elimination may lessen cardiomyocyte damage in DCM. Research has shown that medications that inhibit ferroptosis and lower the generation of lipid peroxides can significantly enhance the function of DCM endothelial cells [42].

Mitochondrial dysfunction

Cardiomyocytes, as high-energy-demanding cells, critically depend on mitochondrial integrity to sustain contractile function and bioenergetic homeostasis. The etiology and progression of DCM have been linked to mitochondrial dysfunction. Ferroptosis and lipid peroxidation also depend on mitochondrial ROS generation. The eukaryotic mitochondrial outer membrane contains a voltage-dependent nonion channel (VDAC), an anion-regulating membrane protein. The mitochondrial membrane is composed of an outer membrane (OMM) and an inner membrane (IMM). When microtubule proteins are present, the ferroptosis activator erastin activates the VDAC, triggering mitochondrial regulatory imbalance, ROS production, membrane potential hyperpolarization, and oxidative stress, all of which ultimately result in cellular ferroptosis [43]. Furthermore, erastin induces mitochondrial membrane potential (MMP) depolarization and opening of the mitochondrial permeability transition pore (mPTP), which cause mitochondrial swelling, functional collapse, and activation of both apoptotic and necrotic processes [44]. Ferroptosis is further exacerbated by mitochondrial malfunction, which in turn causes a disturbance in mitochondrial iron homeostasis.

Emerging evidence delineates the critical role of mitochondrial dysfunction in driving ferroptosis through iron overload mechanisms. Experimental studies demonstrate that iron overload triggers cardiomyocyte ferroptosis via mitochondrial ROS overproduction and iron accumulation, ultimately culminating in coordinated cardiac dysfunction and mitochondrial impairment [45]. Reduced mitochondrial membrane potential, downregulation of the expression of important antioxidant defense enzymes (superoxide dismutase [SOD2] and glutathione peroxidase 1 [GPX1]), and markedly elevated mitochondrial ROS levels are the main symptoms of abnormal mitochondrial ferroptosis in the heart of diabetic mice [46]. Notably, emerging evidence suggests that impaired mitochondrial autophagy in DCM leads to the accumulation of dysfunctional mitochondria, exacerbating intracellular oxidative stress and thereby driving myocardial injury and DCM progression [47, 48]. Collectively, it is clear that ferroptosis in DCM is significantly influenced by mitochondrial dysfunction. (Fig. 1)

Antioxidant proteins in ferroptosis and DCM

In the complex pathogenesis of DCM, ferroptosis, as a form of regulated cell death driven by iron-dependent lipid peroxidation, has emerged as a critical driver of myocardial injury and fibrosis. Recent studies have revealed that oxidative stress and dysregulated iron metabolism are central triggers of ferroptosis in DCM. Antioxidant proteins, by regulating redox homeostasis, mitochondrial function, and iron metabolism networks, play pivotal roles in suppressing ferroptosis. The nuclear transcription factor erythroid-2-related factor 2 (Nrf2),

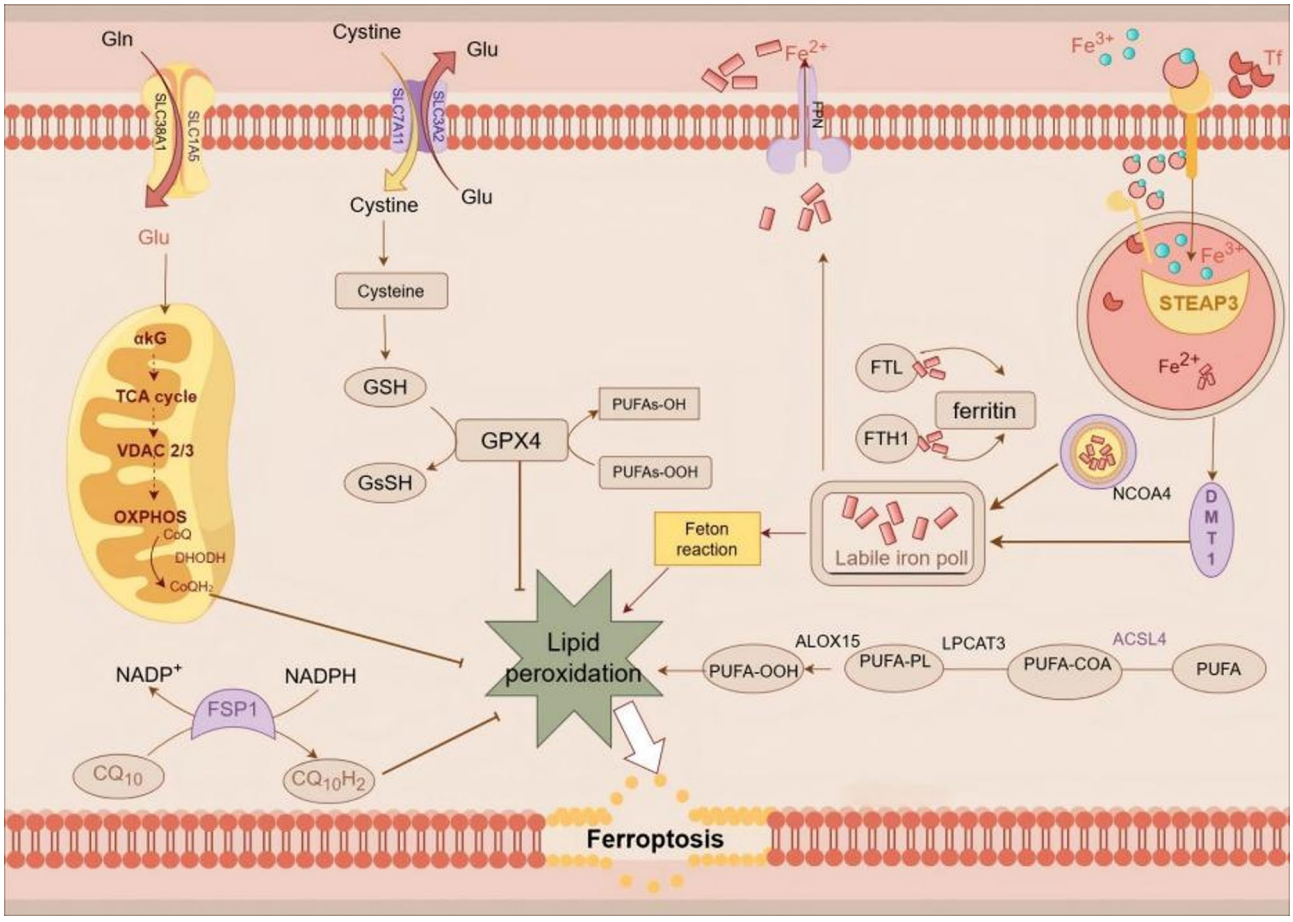

Fig. 1 Ferroptosis mechanism. ACSL4, Acyl-CoA Synthetase Long Chain Family Member 4; ALOX15, Arachidonate 15-Lipoxygenase; CQ10, Coenzyme Q10; CQ10H2, Coenzyme Q10H2; DMT1, Divalent Metal Transporter 1; DHODH, Dihydroorotate Dehydrogenase; FSP1, Ferroptosis Suppressor Protein1; FTL, Ferritin Light Chain; FTH1, Ferritin Heavy Chain 1; Glu, Glutamic Acid; Gln, Glutamine; GSH, Glutathione; GSSH, Glutathione Sulfide; GPX4, Glutathione Peroxidase 4; LPCAT3,Lysophosphatidylcholine Acyltransferase 3; $NADP^+$, Nicotinamide Adenine Dinucleotide Phosphate - Oxidized Form; NADPH, Nicotinamide Adenine Dinucleotide Phosphate - Reduced Form; NCOA4, Nuclear Receptor Coactivator 4; OXPHOS, Oxidative Phosphorylation; PUFA, Polyunsaturated Fatty Acid; PUFA-CoA, Polyunsaturated Fatty Acid-Coenzyme A; PUFA-PL, Polyunsaturated Fatty Acid-Phospholipid; PUFA-OOH, Polyunsaturated Fatty Acid Hydroperoxide; PUFAs-OH, Polyunsaturated Fatty Acids; PUFAs-OOH, Polyunsaturated Fatty Acids Hydroperoxides; STEAP3, Six-transmembrane Epithelial Antigen of the Prostate 3; TAC cycle, Tricarboxylic Acid Cycle; α-kG, α-Ketoglutarate; VDAC, Voltage Dependent Anion Channel. The figure was created by Figdraw. ⊥, suppress;↓, activate

the sirtuin family, ferritin, GPX4, and ferroptosis suppressor protein 1 (FSP1) are core antioxidant proteins that ameliorate ferroptosis in DCM cardiomyocytes through mechanisms such as activation of endogenous antioxidant pathways, regulation of iron homeostasis, or inhibition of lipid peroxidation. Collectively, these proteins establish a multilayered antioxidant defense network and offer promising therapeutic strategies for targeting ferroptosis in DCM. The following sections will comprehensively dissect the functions and regulatory roles of these antioxidant proteins in ferroptosis associated with DCM.

NRF2

Nrf2 is key to the cellular antioxidant response and can increase the transcription of downstream antioxidant genes by binding to antioxidant response elements to orchestrate redox homeostasis [49]. It has been identified as the most significant endogenous antioxidant stress route capable of increasing the expression of several genes encoding antioxidant proteins [50, 51]. By controlling lipid metabolism, mitochondrial activity, and GSH homeostasis, Nrf2 may play a role in manipulating ferroptosis [52].

Ferroptosis in DCM is ameliorated by activating Nrf2 [53, 54]. Wang et al.. demonstrated that sulforaphane upregulates myocardial ferritin expression via Nrf2 activation, effectively suppressing advanced glycation end products (AGEs)-induced ferroptosis in DCM. These findings suggest sulforaphane's therapeutic potential for DCM management [5]. Activation of Nrf2/GPX4 and Nrf2/HO-1 pathways could inhibit ferroptosis and thereby alleviate high glucose-induced cardiomyocyte injury [40, 55, 56]. At the molecular level, inhibition of Nrf2-regulated GPX4 transcription and abnormalities in the Nrf2-regulated iron metabolism gene network may contribute to glycolipotoxicity, and oxidative stress in cardiomyocytes, ultimately triggering ferroptosis and accelerating DCM [21].

The antioxidant enzyme heme oxygenase1 (HO-1) is controlled by Nrf2, a significant stress-induced protein that breaks down hemoglobin into carbon monoxide, biliverdin, and divalent iron ions. It then reduces these byproducts to bilirubin, which has anti-inflammatory, anti-apoptotic, and antithrombotic properties [57]. The classical Nrf2/HO-1 pathway has been investigated in numerous disease models, and Nrf2 activation is crucial for HO-1 expression [58]. In DCM, Nrf2/HO-1 activation reduces myocardial fibrosis and cardiac enlargement, suppresses ferroptosis, and exerts an antioxidant stress effect [40, 59].

Sirtuin protein family

Sirtuin1 (Sirt1), a member of the sirtuin protein family, is a NAD^+-dependent deacetylase involved in protein deacetylation (removal of post-translational acetylation modifications) in a variety of pathways [60, 61] and is crucial for antioxidant and mitochondrial energy metabolism in the heart and other organs [62]. Numerous studies have established that Sirt1 knockdown causes insulin resistance, which detrimentally affects insulin secretion and tissue-specific insulin sensitivity [63]. There are cardioprotective benefits to Sirt1 stimulation [64]. Sirt1 has been linked to cardiac function and myocardial development. Adult mice with Sirt1 knockdown had enlarged ventricles and mitochondrial dysfunction [65]. By controlling several downstream variables, Sirt1 may have an impact on heart function. Sirt1 regulates the activity of Forkhead box O proteins (FOXOs), inhibits DCM cardiomyocyte injury, and ameliorates DCM cardiac dysfunction [66, 67]. Sirt1 ameliorates DCM by regulating Nrf2 expression and attenuating oxidative stress and inflammation in DCM [68]. Activation of the Sirt1/PGC-1α pathway inhibits high glucose-induced oxidative stress and mitochondrial damage, exerting a protective effect on DCM cardiomyocytes [69–71]. Sirt1 also decreases p53 protein expression, which in turn upregulates SLC7A11 and GPX4 expression, inhibiting ferroptosis in DCM to protect cardiomyocytes and improve cardiac function [72].

Sirtuin3 (Sirt3) is mainly found in the mitochondrial matrix and plays an important role in the regulation of mitochondrial metabolism, including energy production, lipid metabolism, resistance to oxidative damage, and balance of acetylation modifications [73, 74]. It has been demonstrated that Sirt3 has protective properties in the heart that attenuate damage, fibrosis, and hypertrophy [75]. Previous experimental studies showed that overexpression of Sirt3 led to reduced ROS generation and improved cardiac function in a diabetic mouse model [76]. Recent breakthroughs implicate Sirt3 might be crucial for ferroptosis, and its inactivation greatly increased GPX4-mediated ROS stress and ferroptosis [77]. Activating Sirt3 may also help treat ferroptosis in several disorders. In DCM, Sirt3 is thought to mitigate ventricular hypertrophy and fibrosis, inhibit ferroptosis, and protect the heart from oxidative stress and mitochondrial damage [78]. Baicalin ameliorates DCM by modulating Sirt3 levels, restoring mitochondrial integrity, reducing ROS accumulation, and suppressing cardiomyocyte ferroptosis [79]. Collectively, Sirt1 and Sirt3 coordinately suppress ferroptosis through oxidative stress mitigation and mitochondrial functional restoration in DCM pathogenesis.

Ferritin

Ferritin light chain (FTL) and ferritin heavy chain 1 (FTH1) are two of the 24 hollow circular subunits that make up ferritin, a widely distributed iron storage protein. By chelating redox-activated iron and functioning as an antioxidant, ferritin plays a crucial role in cells [80]. Paradoxically, ferritinophagy (selective autophagy of ferritin) liberates stored iron into the labile iron pool (LIP), creating a pro-oxidant milieu that accelerates lipid peroxidation and ferroptosis initiation [81]. The iron oxidase activity of the H-chain sequesters excess cytoplasmic iron, resulting in antioxidant and cytoprotective functions [82]. FTH1 is likewise controlled by the upstream gene Nrf2, and its specific deletion results in aberrant cardiac iron regulation, elevated oxidative stress, and increased vulnerability to tissue damage caused by iron overload [19, 83]. In DCM animals and cells, FTH1 expression is downregulated. By controlling FTH1, maintaining cardiac iron homeostasis, and enhancing the system Xc^-/GSH/GPX4 axis in DCM, canagliflozin prevents ferroptosis and reduces myocardial oxidative stress [84]. Similarly, reduced levels of FTH1, SLC7A11, and antioxidant capacity were detected in DCM models in vivo and in vitro, and knockdown of ubiquitin-specific protease 24 (USP24) resulted in increased levels of SLC7A11 and FTH1, improved antioxidant capacity and cell viability, and inhibition of ferroptosis [85]. Fibroblast Growth Factor 21 (FGF21) binds to FTL and FTH1, preventing their excessive degradation via proteasomal and lysosomal autophagy pathways in DCM. This mechanism suppresses ferroptosis and ameliorates DCM progression [86, 87].

GPX4

As delineated in preceding sections, ferroptosis is caused by an imbalance in the system Xc^--GSH-GPX4 antioxidant defense system. GPX4, an antioxidant protein in this system, can also be a direct therapeutic target. Elevated expression of GPX4 can function as a significant antioxidant force and neutralize lipid peroxidation while preserving the flexibility of cell membranes [88]. In mice fed by a high-sugar, high-fat diet, GPX4 reduces heart injury, and its absence is linked to mitochondrial lipid peroxidation, which can result in ventricular hypertrophy [89]. Pharmacological modulation of GPX4 demonstrates therapeutic promise in DCM: Curcumin attenuates cardiac fibrosis via Nrf2-mediated GPX4 upregulation, while Schisandra chinensis ethanol extract coordinately elevates GPX4, HO-1, and Nrf2 expression to suppress ferroptotic injury [39, 90]. By controlling FTH1, canagliflozin improves cardiomyocyte damage, lowers oxidative stress, suppresses ferroptosis, stimulates GPX4 expression in DCM, maintains cardiac iron homeostasis, and reduces collagen deposition [84].

Notably, multiple upstream regulators-including Sirt1, Sirt3, Nrf2, and FTH1-functionally converge on GPX4 as a downstream effector, establishing it as a central integration node for antioxidant defense and ferroptosis suppression in DCM pathogenesis.

FSP1

FSP1, also known as flavoprotein apoptosis factor mitochondria-associated 2 (AIFM2), was originally identified as a downstream target of the *p53* tumor suppressor gene [91]. By taking part in a redox pathway that depends on the substrate ubiquitinone of Coenzyme Q10 (COQ10), FSP1 has been demonstrated to efficiently prevent iron toxicity in GPX4 knockout cells [92]. Specifically, in this process, FSP1 was able to convert COQ10 to Coenzyme Q10H2 (COQ10H2) and consume Nicotinamide Adenine Dinucleotide Phosphate Hydrogen(NADPH). COQ10H2 then acted to sequester lipid peroxides at the cell membrane, converting PLOOH to PLOH, which prevented excessive accumulation of ROS and thus inhibited cellular hypertrophy [93]. FSP1 and COQ10 together form a ferroptosis pathway parallel to the GPX4 pathway [94]. It has been demonstrated that DCM myocardial fibrosis results from the inhibition of FSP1 levels caused by activation of the FoxO1/DDAH1/ADMA pathway [95]. Zhang et al. [96]. demonstrated that Toll-like receptor 6 (TLR6) deficiency protects cardiomyocytes in DCM against ferroptosis and fibrosis through attenuation of oxidative stress and suppression of inflammatory signaling pathways, potentially via modulation of FSP1 expression and activity. In DCM rats, higher levels of FSP1 and less endothelial-mesenchymal transition (EndMT) and myocardial fibrosis were found compared to those treated with Irbesartan [97]. All of the aforementioned data might implicate a relationship between improved myocardial fibrosis in DCM and raised FSP1 expression levels, but further research is required to ascertain whether or not FSP1 expression has a direct impact on DCM. (Fig. 2)

Potential interventions for ferroptosis in DCM

Based on the aforementioned pathways leading to ferroptosis, targeting antioxidant proteins and antioxidant defense system may help ameliorate myocardial injury and ferroptosis in DCM. It has been demonstrated that pharmacological agents may exert protective effects against ferroptosis and mitigate myocardial injury in DCM through augmentation of antioxidant defense mechanisms. Vitamin E is not only an inhibitor of ferroptosis but also an endogenous antioxidant defense factor that plays an important role in DCM. Hamblin et al.. found increased expression of myocardial oxidative stress markers and reduced cardiac function in DCM rats. However, vitamin E supplementation resulted in reduced

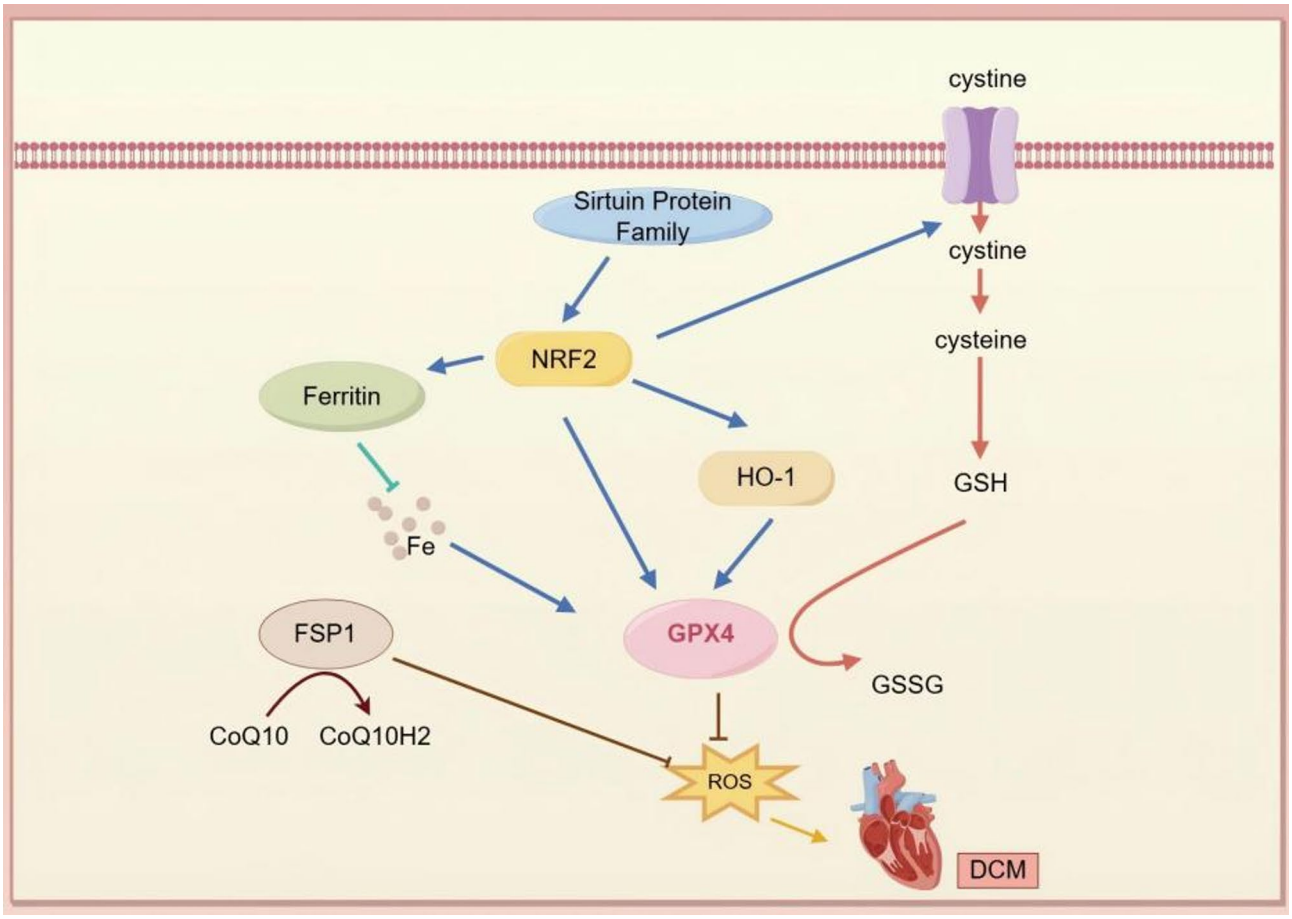

Fig. 2 The role of antioxidant proteins in ferroptosis in DCM. CoQ10, Coenzyme Q10; CoQ10H2, Coenzyme Q10H2; DCM, Diabetic Cardiomyopathy; FSP1, ferroptosis suppressor protein1; GSH, Glutathione; GSSH, Glutathione Sulfide; GPX4, Glutathione Peroxidase 4; HO-1, Heme Oxygenase-1; Nrf2, Nuclear Factor Erythroid 2-related Factor 2; ROS, Reactive Oxygen Species. The figure was created by Figdraw. ⊥, suppress;↓, activate

myocardial oxidative stress, enhanced hemodynamics, and improved cardiac function [98]. Vitamin E demonstrates potent anti-ferroptotic activity in vitro [99], with concomitant protective effects observed in genetically engineered GPX4-deficient murine models where it rescues ferroptosis-associated cellular damage [34].

Dexmedetomidine is a highly selective α2-adrenergic agonist primarily used for sedation [100] with a variety of pharmacological properties, including cardioprotection and anti-inflammation [101]. In rats, dexmedetomidine has been demonstrated to reduce myocardial ischemia-reperfusion injury by activating the SLC7A11/GPX4 axis and inhibiting ferroptosis through the AMPK/GSK-3β/Nrf2 axis [102] or by altering the expression of ferroptosis-related proteins [103], such as SLC7A11, GPX4, FTH1, and cyclooxygenase-2. Dexmedetomidine has been demonstrated to improve autophagy dysfunction and reduce cardiac dysfunction in diabetic mice [104]. According to recent data, dexmedetomidine reduces ROS levels, prevents ferroptosis, and alleviates cardiomyocyte damage via the Nrf2/GPX4 pathway, all of which help to improve DCM [55].

Canagliflozin is a new oral hypoglycemic drug that belongs to the sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and has been shown to lower cardiovascular risk in both diabetic and non-diabetic patients [105]. Canagliflozin may raise GPX4, FTH1, and GSH levels, activate the system Xc^-/GSH/GPX4 axis, mitigate heart damage, and decrease collagen fiber deposition and myocardial fiber rupture in DCM mice, according to both in vitro and in vivo studies [84]. Irbesartan is a blocker of the angiotensin II receptor that has antihypertensive properties. In DCM rats, higher levels of FSP1, less EndMT, and myocardial fibrosis were found compared to those treated with irbesartan [97]. However, more research is needed to determine whether higher FSP1 following irbesartan therapy is causally linked to DCM. (Table 1)

Furthermore, by activating antioxidant proteins, herbal medicines and compounds have been shown in multiple studies to improve ferroptosis and cardiomyocyte

Table 1 Targets of antioxidant action of Western medications for the treatment of ferroptosis in DCM

Western medications	Target of action	Reference
Vitamin E	GPX4,endogenous antioxidant defense factor	[34]
Dexmedetomidine	GPX4,FTH1,Nrf2	[55, 102, 103]
Canagliflozin	GPX4, FTH1	[84]
Irbesartan	FSP1	[97]

FSP1, Ferroptosis Suppressor Protein1; FTH1, Ferritin Heavy Chain 1; GPX4, Glutathione Peroxidase 4; Nrf2, Nuclear Factor Erythroid 2-related Factor 2

damage in DCM. 6-Gingerol activates the Nrf2/HO-1 signaling, upregulating GPX4 expression, while suppressing the secretion of inflammatory factors, thereby reducing cardiomyocyte hypertrophy and interstitial fibrosis in DCM models [56]. Phloridzin prevents cardiomyocyte hypertrophy and fibrosis in DCM, considerably raises left ventricular ejection fraction, and decreases ferroptosis by controlling the Nrf2/GPX4 axis to combat oxidative stress [106]. Astragaloside IV reduces expression levels of CD36 and ferroptosis-related factors, increases GPX4 levels, improves myocardial injury and cardiac contractile function, and attenuates myocardial lipid deposition in DCM rats [107]. Sulforaphane activates the Nrf2 pathway to inhibit cardiomyocyte ferroptosis in DCM mice by upregulating ferritin and SLC7A11 levels [5]. Curcumin promotes the nuclear translocation of Nrf2, increases the expression of oxidative scavengers such as HO-1, preserves GPX4 levels, and inhibits ferroptosis in DCM cardiomyocytes [40]. Salidroside increases SLC7A11, GPX4, and ferritin levels and exerts a regulatory effect on iron metabolism in DCM mice [108]. Rutin, a natural Nrf2-activating phytochemical, demonstrates multimodal therapeutic effects in DCM murine models. Mechanistically, it enhances glucose-lipid metabolic homeostasis while augmenting antioxidant defenses through coordinated upregulation of ferritin, GPX4, and GSH/GSSG ratio. These actions collectively attenuate oxidative stress-mediated myocardial injury, suppressed fibrotic remodeling, and improved systolic function, thereby effectively halting DCM progression

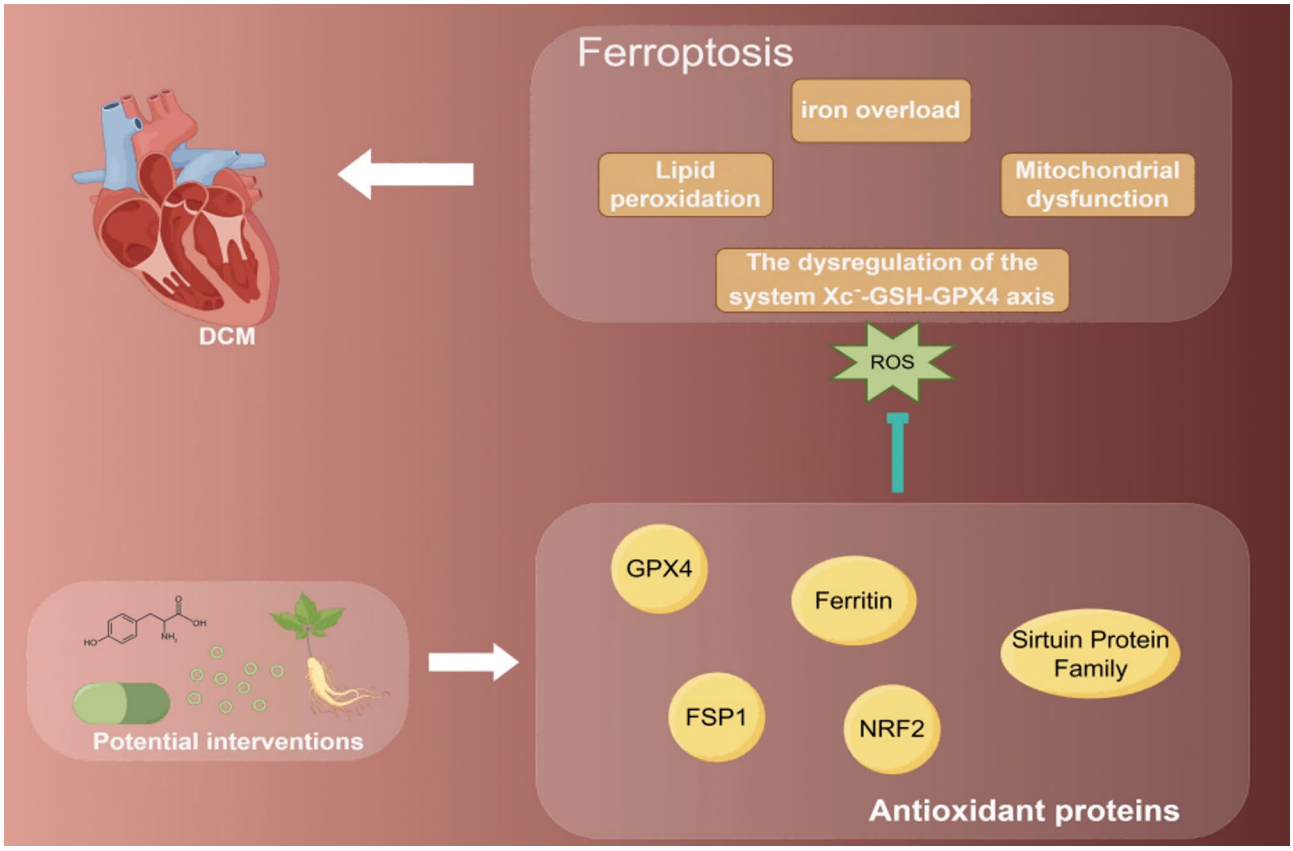

Fig. 3 Targeting antioxidant proteins ameliorates ferroptosis in DCM. DCM, Diabetic Cardiomyopathy; FSP1, ferroptosis suppressor protein1; GPX4, Glutathione Peroxidase 4; Nrf2, Nuclear Factor Erythroid 2-related Factor 2; ROS, Reactive Oxygen Species. The figure was created by Figdraw. ⊥, suppress;↓, activate

Table 2 Targets of antioxidant effects of active ingredients and complexes of traditional Chinese medicines for the treatment of ferroptosis in DCM

Chinese Medicine Active Ingredients and Compound Formulas	Target of action	Reference
6-Gingerol	Nrf2,GPX4	[56]
Phloridzin	Nrf2,GPX4	[106]
Astragaloside IV	GPX4	[107]
Sulforaphane	Nrf2	[5]
Curcumin	Nrf2,HO-1,GPX4	[40]
Salidroside	GPX4,Ferritin	[108]
Rutin	Nrf2,Ferritin, GPX4	[109]
Berberine	Nrf2	[110]
Britanin	Nrf2,GPX4	[112]
Schisandrin B	Nrf2,HO-1, GPX4	[90]
Irisin	Sirt1,GPX4	[72]
Resveratrol	Sirt1,Nrf2	[113]
Baicalin	Sirt3	[79]
Erzhi Pill	GPX4	[114]

FSP1, Ferroptosis Suppressor Protein1; FTH1, Ferritin Heavy Chain 1; GPX4, Glutathione Peroxidase 4; HO-1, Heme Oxygenase-1; Nrf2, Nuclear Factor Erythroid 2-related Factor 2; Sirt1,Silent Information Regulator 1; Sirt3,Silent Information Regulator 3

[109]. Berberine, a cardiomyocyte protector, increases cell viability and MMP by inhibiting Nrf2 [110] or reducing ROS generation and lipid peroxidation [111] and has a good inhibitory effect on ferroptosis. Britanin can prevent ferroptosis in cardiomyocytes by upregulating GPX4 and activating the AMPK/GSK3β/Nrf2 signaling pathway [112]. Schisandrin B attenuated myocardial injury in DCM mice through enhancing myocardial GSH levels and activating the Nrf2 signaling pathway, as evidenced by upregulated Nrf2 and its downstream antioxidant enzymes HO-1 and GPX4, which collectively inhibited ferroptosis [90]. Irisin increased Sirt1 expression by activating the Sirt1-p53-SLC7A11/GPX4 pathway and decreased p53 acetylation, which reduces p53 protein expression by increasing degradation. This cascade subsequently upregulates SLC7A11 and GPX4 expression, thereby inhibiting ferroptosis and improving cardiac function in DCM [72]. Resveratrol inhibits ferroptosis by reversing the DCM-induced reduction in Sirt1 protein levels, thereby modulating the Nrf2 gene to alleviate apoptosis and impaired cardiomyocyte function due to high glucose [113]. Baicalin improves DCM by modulating Sirt3 levels, restoring mitochondrial integrity, lowering ROS accumulation, and suppressing ferroptosis in cardiomyocytes [79]. Erzhi Pill (EZP) is a traditional Chinese herbal compound that has kidney tonifying and liver nourishing properties. In a mechanistic study of EZP in the treatment of DCM, it was discovered that EZP effectively reduced the levels of SOD, GPX4, and ROS in cardiac tissue, inhibited oxidative stress, and improved myocardial injury [114]. (Table 2)

After experiments in vivo and in vitro, there has been a gradual clinical translation into clinical studies for the treatment of disease through the enhancement of the endogenous antioxidant response. The BEACON trial was a Phase 3, randomized, double-blind, parallel-group, international, multicenter trial designed to assess the effects of bardoxolone methyl, an activator of the Nrf2 pathway, in diabetic kidney disease; however, the trial was prematurely terminated due to an increase in cardiovascular events in the bardoxolone methyl group [115]. A subsequent phase 2 clinical study conducted in Japan, the TSUBAKI study, demonstrated for the first time a direct improvement in GFR with bardoxolone methyl using inulin clearance [116]. Another phase 3 clinical study, the AYAME study, also evaluating the efficacy of bardoxolone methyl in the treatment of diabetic kidney disease, had the primary and key secondary endpoints of a decrease in eGFR of ≥30% duration or end-stage renal disease, and results published in 2023 indicate that the study met its study endpoints without significant safety concerns [117]. Notably, this series of clinical trials in diabetic nephropathy has demonstrated the feasibility of modulating antioxidant pathways such as Nrf2. Although these trials have focused on renal outcomes, their success in improving markers of oxidative stress suggests their potential cross-applicability to DCM. Future studies should explore similar interventions in DCM-specific trials, leveraging insights from parallel fields.

Conclusions

Accumulating evidence underscores the pivotal role of ferroptosis in the pathogenesis and progression of DCM. The dysregulation of the system Xc^--GSH-GPX4 axis, iron overload, enhanced lipid peroxidation, and mitochondrial dysfunction collectively precipitate cellular damage. Oxidative stress markers such as MDA and inducible nitric oxide synthase (iNOS) have been established as prognostic indicators of myocardial injury [118, 119]. Central to this process is the oxidative

stress-induced collapse of antioxidant defenses, which perpetuates ferroptosis and DCM. Key regulatory nodes include Nrf2, the sirtuin family (Sirt1/Sirt3), ferritin, GPX4, and FSP1, all of which represent promising therapeutic targets to mitigate ferroptosis-mediated myocardial injury. Pharmacological interventions such as vitamin E, dexmedetomidine, canagliflozin, and irbesartan demonstrate cardioprotective effects by enhancing antioxidant capacity and attenuating cardiac fibrosis in preclinical DCM models. Notably, some herbal extracts and chemicals, such as 6-gingerol, phloridzin, astragaloside IV, and EZP, et al. have been found capable of lowering oxidative stress, preventing ferroptosis, and improving cardiac fibrosis in DCM. These findings provide a mechanistic foundation for developing targeted strategies against DCM. (Fig. 3)

Despite these advances, critical challenges persist. Current knowledge predominantly derives from in vitro and animal studies, and there is heterogeneity of findings across different animal model studies. Variations in genetic background (e.g., db/db versus STZ-induced diabetic mice) and experimental protocols (e.g., dietary composition and glucose monitoring methods) may explain the differences in results across studies. In addition, interspecies differences in iron metabolism pathways (e.g., expression of human versus rodent iron transport proteins) need to be taken with caution when extrapolating results to the clinical setting. There are currently insufficient clinical trials and observations to treat DCM by targeting ferroptosis. Thus, the pathogenic pathways and mechanisms associated with both in the vast and complex regulatory system of the human body are not yet known [10]. Furthermore, the absence of ferroptosis-specific biomarkers has long been impeding the development of clinical applications targeted at ferroptosis in such a quickly developing field. To bridge bridge the gap between preclinical discovery and clinical application, future research should prioritize: (i)Identification of ferroptosis-specific biomarkers (e.g., lipid peroxidation-derived aldehydes or iron-regulatory proteins) for early diagnosis and therapeutic monitoring; (ii)Development of patient-derived induced pluripotent stem cell cardiomyocyte models to recapitulate DCM pathophysiology; (iii)Initiation of phase I clinical trials combining ferroptosis inhibitors with standard DCM therapies. In conclusion, the absence of validated biomarkers and human trials remains a major barrier to clinical translation. Urgent efforts are needed to elucidate ferroptosis pathways in human DCM and validate therapeutic efficacy in population-based studies. Only through such rigorous approaches can we advance from preclinical promise to clinically effective ferroptosis-targeted interventions.

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YTL: design, conceptualization, writing original draft. SY: provide help and advice on writing articles.JJG: provided guidance on the design and implementation of the article, data collection and article writing. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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