



Ferroptosis as a Master Regulator of Anthracycline-Induced Cardiotoxicity: Mechanistic Insights, Biomarkers, and Emerging Cardioprotective Strategies

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Abstract

Background: Anthracyclines, especially doxorubicin, are a key element of curative chemotherapy but are associated with dose-limiting and sometimes permanent cardiotoxicity. For decades, the prevailing theories have been oxidative stress and topoisomerase II β -mediated DNA damage, but neither fully explains cardiomyocyte sensitivity. Much of this injury occurs via ferroptosis, a type of iron-dependent programmed cell death involving lipid peroxidation. This discovery has changed the field and opened new therapeutic avenues. Doxorubicin forms redox-active complexes with intracellular iron, resulting in heme oxygenase-1-mediated free iron release, intercalates into mitochondrial DNA to interfere with heme synthesis, and downregulates glutathione peroxidase 4, causing mitochondrial lipid peroxidation and cardiomyocyte death. Iron chelation with dexrazoxane and ferroptosis inhibitors such as ferrostatin-1 and liproxstatin-1 ameliorated this injury in rodent models, but a landmark study showed that these inhibitors did not protect human induced pluripotent stem cell-derived cardiomyocytes, indicating a species-dependent translational gap. Statins and sodium-glucose co-transporter-2 inhibitors provide modest, mechanistically distinct cardioprotection in clinical cohorts. Troponin, natriuretic peptides, and growth differentiation factor-15 provide complementary, but imperfect, early detection. Ferroptosis as a shared injury pathway reinterprets anthracycline cardiotoxicity as a pharmacologically tractable process rather than an unavoidable trade-off, informing cardio-oncology risk stratification, biomarker-guided monitoring, and rational combination cardioprotective strategies. The priorities include closing the murine-to-human translational gap in the efficacy of ferroptosis inhibitors, developing clinically validated biomarkers, and testing iron-directed and systemic cardioprotective combination regimens in adequately powered, biomarker-stratified clinical trials.

Keywords: Ferroptosis; Doxorubicin; Cardiotoxicity; Lipid peroxidation; Iron chelation.

Introduction

Anthracyclines such as doxorubicin are among the most effective cytotoxic agents for breast cancer, lymphoma, sarcoma, and paediatric cancers, but they can cause irreversible heart failure years after treatment because of cumulative, dose-dependent cardiotoxicity. Despite decades of research into the mechanisms underlying doxorubicin-induced cardiomyocyte injury, including apoptosis, necroptosis, pyroptosis, and autophagy-dependent death (Christidi & Brunham, 2021), none of these mechanisms can fully explain the selective cardiac vulnerability observed in patients.

Ferroptosis, an iron-dependent type of programmed cell death marked by uncontrolled lipid peroxidation, emerged as a significant and independent participant in doxorubicin-induced cardiomyopathy. Inhibition of ferroptosis, but not of apoptosis or necroptosis, protected mice from lethal doxorubicin cardiotoxicity, an effect mediated mainly by heme oxygenase-1-dependent iron release (Fang et al., 2019). This finding connected anthracycline cardiotoxicity to a rapidly growing body of ferroptosis biology spanning neurodegeneration, ischaemia-reperfusion injury, and oncology (Dixon & Olzmann, 2024; Jiang et al., 2021).

Given the high mitochondrial density and oxygen demand of the heart, iron dysregulation is fundamental to cardiovascular pathophysiology, and recent comprehensive analyses have delineated the metabolic and molecular landscape connecting iron handling to ferroptotic cardiomyocyte loss across multiple cardiovascular disease states, including chemotherapy-induced cardiomyopathy (Fang et al., 2023).

This convergence of iron biology, lipid chemistry, and clinical cardio-oncology has generated much recent literature and scientific controversy, most notably regarding whether preclinical rodent findings on ferroptosis inhibition apply to human cardiomyocytes.

This review critically synthesizes the molecular and toxicological mechanisms of ferroptosis-driven anthracycline cardiotoxicity, evaluates the pharmacological strategies developed to counter it and examines the translational and clinical evidence, including biomarker-based monitoring and randomized cardioprotection trials that will determine whether this mechanistic insight can ultimately improve patient outcomes.

Molecular and Cellular Mechanisms

Mechanistically and morphologically, ferroptosis differs from apoptosis and necroptosis in that it does not involve caspase activation or the membrane pores formation typical of necroptotic cell death. Instead, it is characterized by iron-catalyzed peroxidation of phospholipids containing polyunsaturated fatty acids within cellular membranes. Sensitivity to this process is regulated by three interconnected nodes: the labile iron supply, the glutathione-GPX4 antioxidant axis, and the enzyme system that produces peroxidisable membrane lipids (Figure 1) (L. Yu et al., 2023).

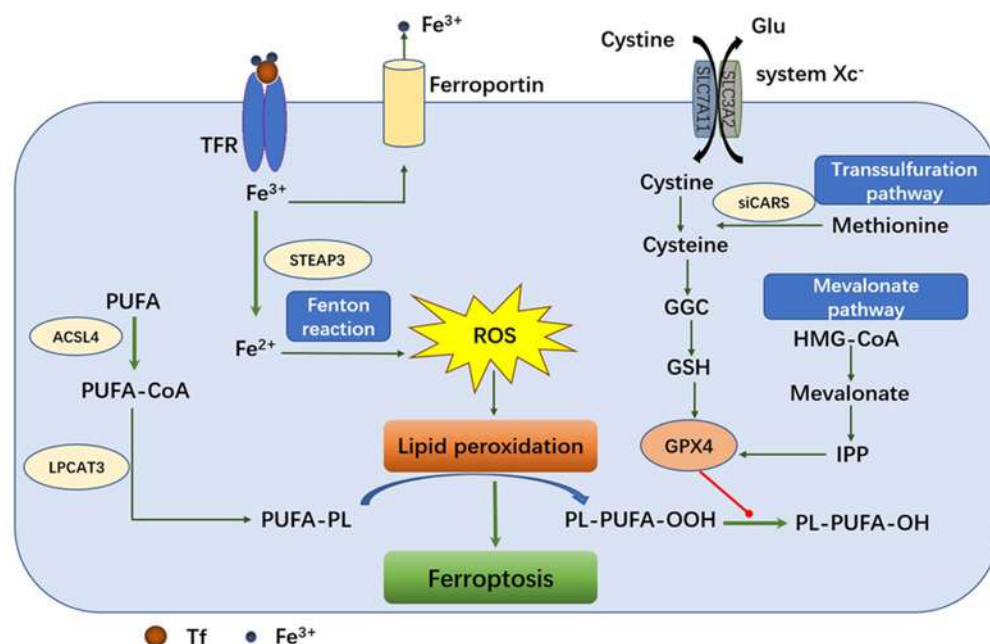


Figure 1. The mechanism of the ferroptosis pathway. The main metabolic processes of ferroptosis can be divided broadly into three categories: iron metabolism, the GSH/GPX4 pathway, and lipid peroxidation. Transferrin transports iron into cells via transferrin-receptor-1-mediated endocytosis. Fe^{2+} promotes accumulation of lipid peroxides through the Fenton reaction and lipid oxidation. System xc^- delivers cystine in exchange for glutamate in a 1:1 ratio; once inside the cell, cystine is reduced to cysteine, which is used to synthesis glutathione (GSH) under the catalytic action of glutamate-cysteine ligase and glutathione synthetase. GPX4 reduces toxic lipid peroxides (PL-OOH) to non-toxic lipid alcohols (PL-OH) using glutathione as a reducing cofactor. Cells can also acquire cysteine via the reverse transsulfuration pathway. A related GSH/GPX4-associated pathway is the mevalonate pathway, in which 3-hydroxy-3-methylglutaryl-coenzyme A is converted to mevalonate. Long-chain fatty acid-CoA ligase 4 (ACSL4) and lysophospholipid acyltransferase 5/3 (LPCAT3) promote the incorporation of polyunsaturated fatty acids (PUFAs) into phospholipids to form PUFA-containing phospholipids, which are subsequently oxidized to lipid peroxides by reactive oxygen species (L. Yu et al., 2023).

Intracellular Fe^{2+} in a labile state, derived from ferritinophagy and transferrin-mediated uptake, catalyses the Fenton reaction, generating hydroxyl radicals that initiate chain reactions of lipid peroxidation (Fang et al., 2023; Jiang et al., 2021). This pro-oxidant pathway is normally counteracted by the cystine/glutamate antiporter system xc^- (SLC7A11), which imports cystine for glutathione biosynthesis. Glutathione serves as an essential cofactor for glutathione peroxidase 4 (GPX4), the principal enzyme responsible for reducing toxic lipid hydroperoxides to non-toxic lipid alcohols (Dixon & Olzmann, 2024; Jiang et al., 2021).

When GPX4 activity is insufficient relative to the rate of lipid peroxide formation, peroxidised phospholipids accumulate in cell membranes, compromising membrane integrity. The lipid substrates available for peroxidation are themselves under enzymatic control: acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) catalyze the esterification of polyunsaturated fatty acids into membrane phospholipids, generating the polyunsaturated-fatty-acid-containing phosphatidylethanolamine species that are the preferred substrates for lipoxygenase-mediated and non-enzymatic oxidation (Fang et al., 2023; Jiang et al., 2021).

This lipidomic specificity explains the increased susceptibility of terminally differentiated cardiomyocytes to ferroptotic damage, given their high mitochondrial content and membrane composition rich in

polyunsaturated fatty acids (Dixon & Olzmann, 2024; Fang et al., 2019). The Nrf2-HMOX1 (heme oxygenase-1) axis constitutes a critical regulatory node: Nrf2 activation generally upregulates genes involved in antioxidant and glutathione biosynthesis to protect against oxidative injury, yet excessive or dysregulated HO-1 induction can paradoxically increase the labile iron pool through heme degradation, illustrating a context-dependent duality that is especially relevant to anthracycline exposure (Fang et al., 2019).

Toxicological Mechanisms

Doxorubicin triggers the ferroptotic pathway through several convergent, drug-specific mechanisms rather than through non-specific oxidative damage alone (Figure 2) (Tadokoro et al., 2020). The quinone moiety of doxorubicin forms redox-active complexes with intracellular $\text{Fe}^{2+}/\text{Fe}^{3+}$, driving continuous redox cycling and reactive-oxygen-species production independent of classical Fenton chemistry with free iron alone (L. Yu et al., 2023). In addition, doxorubicin-induced, Nrf2-dependent overexpression of HO-1 degrades heme and releases free iron, particularly within mitochondria, the primary site of subsequent lipid peroxidation (Fang et al., 2019).

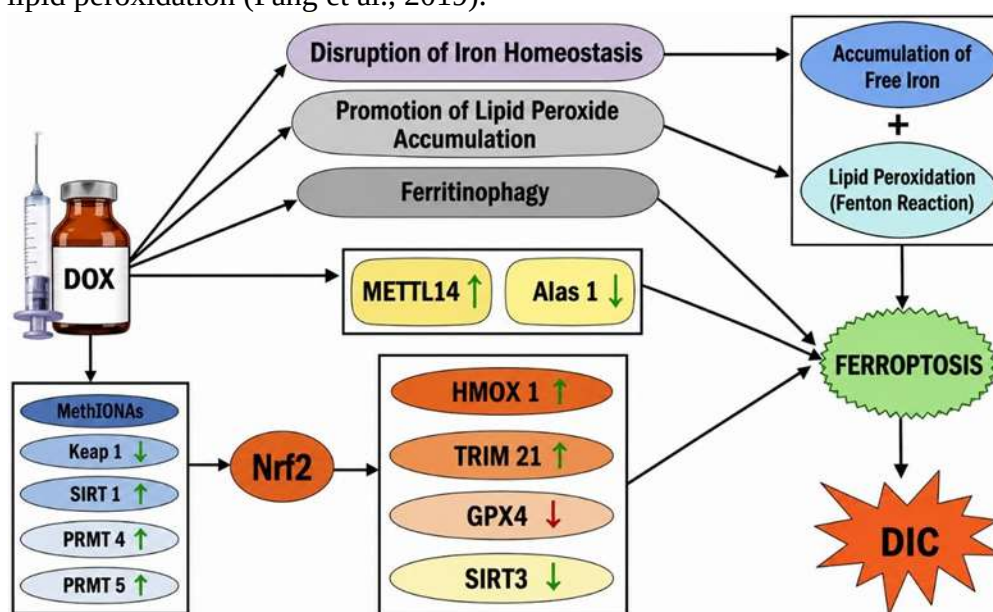


Figure 2. Doxorubicin-induced ferroptotic cascade in the cardiomyocyte, integrating doxorubicin- Fe^{2+} redox cycling, HO-1-mediated heme degradation, mitochondrial DNA intercalation with disruption of ALAS1-dependent heme synthesis, GPX4 downregulation, and resultant mitochondrial lipid peroxidation culminating in ferroptotic cardiomyocyte death (Tadokoro et al., 2020).

A more recently discovered mechanism is that doxorubicin intercalates directly into mitochondrial DNA, inhibiting transcription of ALAS1, the rate-limiting enzyme in mitochondrial heme biosynthesis. This disruption paradoxically promotes ferroptosis by altering mitochondrial iron handling and heme availability, linking the well-characterised DNA-intercalating pharmacology of doxorubicin directly to the ferroptotic injury pathway rather than to genotoxic effects alone (Abe et al., 2022). Doxorubicin treatment also directly downregulates GPX4 expression in cardiomyocytes, an effect not seen at comparable concentrations in malignant cell lines, suggesting a cell-type-specific susceptibility with possible therapeutic implications for preserving antitumour efficacy while protecting the myocardium (Tadokoro et al., 2020).

Oxidative stress arising from these mechanisms independently initiates mitochondrial iron overload, creating a feed-forward process that exacerbates ferroptotic damage once initiated (Chen et al., 2023).

The relative contribution of ferroptosis compared with other regulated cell death pathways implicated in doxorubicin-induced cardiotoxicity including topoisomerase II β -mediated transcriptional dysregulation, calcium-handling abnormalities, and pyroptotic and autophagic cell death (Christidi & Brunham, 2021) remains a central, unresolved toxicological question. Ferroptosis has been repeatedly identified as the dominant, non-redundant pathway in vivo in murine genetic and pharmacological studies (Fang et al., 2019; Tadokoro et al., 2020).

However, a key 2025 study using both H9c2 cells and human induced pluripotent stem cell-derived cardiomyocytes showed that the ferroptosis-specific inhibitors ferrostatin-1 and liproxstatin-1, although fully protective against the direct ferroptosis inducer RSL3, did not prevent doxorubicin-induced cell death or restore normal electrophysiological function, and under certain conditions even slightly worsened cardiomyocyte dysfunction (Cha et al., 2026).

Pharmacological Interventions

Iron chelation is the most clinically advanced pharmacological approach, reflecting the iron-dependent nature of ferroptosis. Dexrazoxane, a cyclic derivative of an EDTA-related compound, chelates intracellular ferrous iron, thereby inhibiting Fenton chemistry. More than two decades after its original mechanistic rationale was proposed, dexrazoxane remains the only cardioprotective agent approved by the United States Food and Drug Administration for anthracycline-induced cardiotoxicity. Direct comparison with ferroptosis-specific inhibition has shown that the cardioprotective action of dexrazoxane is mediated primarily by inhibition of ferroptosis rather than simply by prevention of topoisomerase-mediated DNA damage (Fang et al., 2019). However, the use of dexrazoxane is limited by ongoing concerns in paediatric and adult oncology regarding reduced antitumour efficacy and an increased risk of secondary haematological malignancies, restricting it to high cumulative-dose settings (Prabhune et al., 2025).

This clinical limitation has stimulated the development of novel synthetic and natural iron-chelating strategies designed to selectively capture ferrous iron with an improved safety profile, such as engineered nanochelator platforms and plant-derived chelating agents; although these strategies show promise in preclinical efficacy studies, they remain limited to rodent and in-vitro models and lack clinical validation. In parallel, direct pharmacological inhibition of lipid peroxidation has been widely explored: the radical-trapping antioxidants ferrostatin-1 and liproxstatin-1 prevent doxorubicin-induced ferroptosis and death in mouse models (Fang et al., 2019; Tadokoro et al., 2020), and the related compound ethoxyquin shows similar efficacy as a radical-trapping antioxidant in mouse models of doxorubicin cardiotoxicity (Tadokoro et al., 2022).

However, as noted above, the inability of these agents to protect human induced pluripotent stem cell-derived cardiomyocytes represents a significant and unresolved translational limitation for this entire drug class (Cha et al., 2026).

A further pharmacological approach targets the Nrf2-GPX4 antioxidant pathway upstream of lipid peroxidation. Resveratrol activates the p62-Nrf2 signalling axis in cardiomyocytes, protecting against doxorubicin-induced ferroptosis (W. Yu et al., 2022).

Similarly, the steroidal saponin dioscin activates the Nrf2-GPX4 signalling pathway and protects against chronic doxorubicin cardiotoxicity in murine models. This distinction is important, because most studies of ferroptosis-related cardiotoxicity have focused on acute rather than chronic, cumulative-dose exposure models that are more representative of standard clinical regimens (Liu et al., 2024).

Beyond agents that directly influence the ferroptotic pathway, randomized clinical trials have evaluated two classes of systemically acting drugs with distinct cardiovascular effects. The STOP-CA trial demonstrated that atorvastatin significantly reduced the decline in left ventricular ejection fraction in patients receiving anthracycline-based chemotherapy for lymphoma (Neilan et al., 2023), consistent with the earlier PREVENT trial, which assessed statin therapy for the prevention of early cardiac dysfunction in patients at increased risk of cardiotoxicity (Thavendiranathan et al., 2023).

However, the overall evidence on statins remains sufficiently heterogeneous that the 2022 European Society of Cardiology cardio-oncology guidelines assign only a conditional (Class IIa) recommendation to statin-based cardioprotection (Lyon et al., 2022)

Sodium-glucose co-transporter-2 (SGLT2) inhibitors, by contrast, have an expanding but predominantly observational evidence base: retrospective cohort studies have linked SGLT2 inhibitor use with improved cardiac outcomes both in patients with pre-existing cardiac dysfunction who are treated with anthracyclines and in patients with type 2 diabetes receiving anthracycline chemotherapy (Abdel-Qadir et al., 2023; Avula et al., 2024; Gongora et al., 2022). Pharmacological intervention points along the ferroptotic cascade in anthracycline cardiotoxicity illustrated in figure 3 (Cha et al., 2026; Fang et al., 2019; Gongora et al., 2022; Neilan et al., 2023; Prabhune et al., 2025; Thavendiranathan et al., 2023),

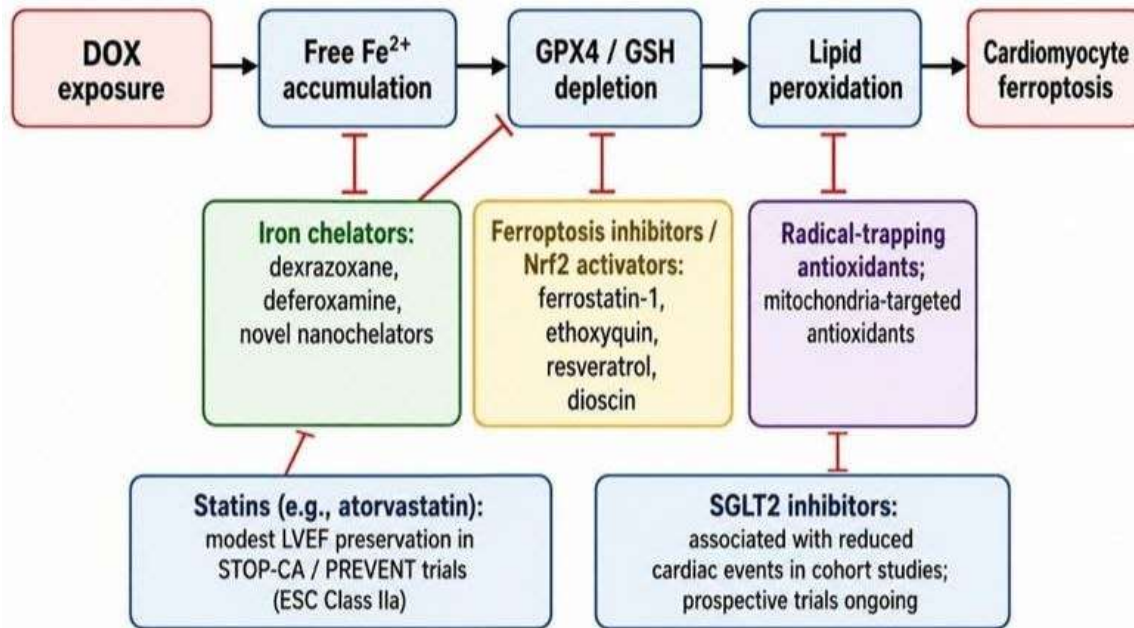


Figure 3. Pharmacological intervention points along the ferroptotic cascade in anthracycline cardiotoxicity, integrating iron chelation, direct ferroptosis/lipid-peroxidation inhibition, Nrf2-directed antioxidant activation, and systemically acting cardioprotective agents evaluated in randomised trials. Original schematic prepared by the author synthesising mechanistic and clinical-trial data reported in references (Cha et al., 2026; Fang et al., 2019; Gongora et al., 2022; Neilan et al., 2023; Prabhune et al., 2025; Thavendiranathan et al., 2023).

However, the specific contribution of ferroptosis suppression, as opposed to the general metabolic and haemodynamic effects of SGLT2 inhibitors (Hlail & Al-Shawi, 2025) has not been directly confirmed in this setting. The principal pharmacological agents discussed in this review are summarised in Table 1, together with their proposed mechanisms, evidential status, and major limitations.

Table 1. Pharmacological agents and mechanisms proposed for cardioprotection against ferroptosis-driven anthracycline cardiotoxicity, with corresponding evidence level and key limitations.

Agent / class	Proposed mechanism	Level of evidence	Key limitation
Dexrazoxane	Iron chelation; prevents Fe ²⁺ -dependent Fenton chemistry and suppresses ferroptosis	Only FDA-approved cardioprotectant; randomised paediatric and adult	Concerns over reduced antitumour efficacy and secondary

Agent / class	Proposed mechanism	Level of evidence	Key limitation
		evidence (Cha et al., 2026; Fang et al., 2019)	malignancy risk restrict use (Prabhune et al., 2025)
Novel iron chelators / nanochelators	Selective ferrous iron capture with reduced off-target chelation	Preclinical (rodent, in vitro) (Prabhune et al., 2025)	Not yet clinically validated; delivery and specificity remain unresolved
Ferrostatin-1 / liproxstatin-1	Radical-trapping antioxidants blocking lipid peroxidation	Robust in murine and rodent cardiomyocyte models (Fang et al., 2019; L. Yu et al., 2023)	Failed to prevent doxorubicin-induced death in human iPSC-cardiomyocytes (Cha et al., 2026)
Ethoxyquin	Radical-trapping antioxidant	Effective in murine doxorubicin cardiotoxicity models (Tadokoro et al., 2022)	Human translational data lacking
Resveratrol / dioscin (Nrf2 activators)	Upregulate Nrf2-GPX4 antioxidant response	Preclinical rodent and cardiomyocyte studies (Liu et al., 2024; W. Yu et al., 2022)	Bioavailability and dosing standardisation remain unresolved for clinical use
Statins (atorvastatin)	Pleiotropic antioxidant/anti-inflammatory effects; possible ferroptosis-modulating activity	Randomised trials (STOP-CA, PREVENT) (Neilan et al., 2023; Thavendiranathan et al., 2023)	Modest, inconsistent effect on LVEF preservation; ESC Class IIa (conflicting evidence) (Lyon et al., 2022)
SGLT2 inhibitors	Proposed reduction of oxidative stress and improved cardiac metabolic efficiency	Observational cohorts and post hoc analyses (Abdel-Qadir et al., 2023; Avula et al., 2024; Gongora et al., 2022)	Prospective randomised trials in cardio-oncology still ongoing

Experimental and Clinical Evidence

Table 2 summarises the principal experimental studies that established, and subsequently qualified, the role of ferroptosis in doxorubicin-induced cardiotoxicity, from the original 2019 discovery through the 2025 report of translational limitations in human cardiomyocytes.

Table 2 Key experimental studies establishing and qualifying the role of ferroptosis in doxorubicin-induced cardiotoxicity.

Experimental system	Key mechanistic finding	Interpretation / significance
Murine doxorubicin and ischaemia-reperfusion cardiomyopathy models	First demonstration that ferroptosis, not apoptosis/necroptosis, mediates doxorubicin cardiomyopathy; HO-1 upregulation drives heme degradation and iron release	Established ferroptosis as a bona fide, targetable mechanism of anthracycline cardiotoxicity
Mouse hearts and cardiomyocytes vs. cancer cell lines	Doxorubicin downregulates GPX4 and induces mitochondria-dependent lipid peroxidation selectively in cardiomyocytes, not in malignant cells	Suggests a cardiomyocyte-selective vulnerability exploitable for cardioprotection without compromising antitumour efficacy
Murine cardiomyocytes	Doxorubicin intercalates into mitochondrial DNA, disrupting ALAS1-dependent heme synthesis and promoting ferroptosis	Links doxorubicin's DNA-intercalating pharmacology directly to ferroptotic, rather than purely genotoxic, injury
Cellular oxidative stress model	Oxidative stress independently induces mitochondrial iron overload and ferroptotic cell death	Reinforces a self-amplifying loop between oxidative stress and iron dysregulation
Chronic doxorubicin cardiotoxicity mouse model	Dioscin activates the Nrf2-GPX4 axis and attenuates chronic cardiac ferroptosis	Supports natural-compound Nrf2 activation as a cardioprotective strategy in chronic dosing regimens
H9c2 cells and human iPSC-derived cardiomyocytes	Ferrostatin-1 and liproxstatin-1 rescued RSL3-induced ferroptosis but failed to prevent doxorubicin-induced cardiomyocyte death or electrophysiological dysfunction	Challenges the generalisability of murine ferroptosis-inhibitor data to human cardiomyocytes; a critical translational caveat

Alongside these mechanistic findings, biomarker-driven surveillance has also advanced considerably in clinical settings, although no ferroptosis-specific biomarker has yet been validated for clinical use. In a prospective analysis of cardiac and non-cardiac biomarkers in patients receiving anthracycline chemotherapy, high-sensitivity cardiac troponin T and growth differentiation factor-15 (GDF-15) were

significantly elevated from baseline to the end of chemotherapy and remained elevated three to six months after chemotherapy completion (Dean et al., 2023).

Soluble ST2 also showed significant changes over time, whereas several markers of oxidative stress and inflammation, such as myeloperoxidase, declined over time, illustrating the difficulty of interpreting biomarker trajectories in this setting (Hlail & Al-Shawi, 2026; Tian et al., 2024). GDF-15 has emerged as a promising biomarker candidate for cardiotoxicity risk in HER2-targeted neoadjuvant regimens, correlating with natriuretic peptide levels and other cardiovascular risk factors; however, its association with confirmed cardiotoxicity events in that cohort did not reach statistical significance, underscoring the need for larger validation studies.

Although a ferroptosis-specific assay has not yet been validated, these circulating biomarkers, combined with cardiac troponin and natriuretic peptide criteria, have now been incorporated into the formal definition of cancer therapy-related cardiac dysfunction in the 2022 European Society of Cardiology cardio-oncology guidelines (Lyon et al., 2022), reflecting their integration into routine risk stratification. Table 3 summarizes the principal biomarkers used in this setting.

Table 3. Circulating biomarkers used for monitoring anthracycline-induced cardiotoxicity in clinical cardio-oncology practice.

Biomarker	Biological category	Clinical relevance in anthracycline cardiotoxicity
High-sensitivity cardiac troponin (cTnT/cTnI)	Myocardial injury marker	Rises significantly after anthracycline exposure; incorporated into ESC 2022 cardio-oncology risk criteria (>99th percentile upper reference limit) (Hlail & Al-Shawi, 2025; Lyon et al., 2022)
NT-proBNP / BNP	Ventricular wall stress marker	Elevation (NT-proBNP ≥ 125 ng/L) forms part of the ESC biomarker-based definition of cancer therapy-related cardiac dysfunction (Lyon et al., 2022)
Growth differentiation factor-15 (GDF-15)	Stress-responsive cytokine	Increases significantly with anthracycline exposure and correlates with cardiotoxicity risk in HER2-targeted regimens (Hlail & Al-Shawi, 2025; Tian et al., 2024)
Soluble ST2 (sST2)	Cardiac fibrosis / remodelling marker	Shows significant interval change following anthracycline chemotherapy in prospective biomarker cohorts (Hlail & Al-Shawi, 2025)
Myeloperoxidase (MPO), 8-OHdG	Oxidative stress / inflammation markers	Reflect systemic oxidative stress accompanying anthracycline exposure, though changes were paradoxically decreased in one cohort, illustrating biomarker complexity (Hlail & Al-Shawi, 2025)

Current Challenges and Limitations

Several major challenges temper enthusiasm for rapid translation of ferroptosis-based cardioprotection to the bedside. Despite strong efficacy in rodent models and immortalised cell lines, the failure of ferrostatin-1 and liproxstatin-1 to protect human induced pluripotent stem cell-derived cardiomyocytes suggests that species-specific differences in iron metabolism, lipid composition, or compensatory cell-death

mechanisms may limit the direct applicability of preclinical ferroptosis research. This discrepancy is not yet well understood mechanistically and, in our view, represents the most important open question in the field.

Second, dexrazoxane, the only iron-chelating agent approved for clinical use, remains underused because of ongoing, unresolved concerns regarding the risk of secondary malignancies and possible reductions in antitumour efficacy, which restrict its recommended use to selected high-risk pediatric and adult populations rather than more widespread prophylactic use (Prabhune et al., 2025).

Third, circulating biomarkers such as troponin, natriuretic peptides, and GDF-15 are statistically significantly altered following anthracycline exposure but are not specific to ferroptosis as a mechanism. Moreover, their predictive capacity for cardiotoxicity risk at the individual-patient level, as opposed to the group level, remains insufficient, with at least one candidate biomarker failing to reach significance for predicting confirmed cardiotoxicity events in a dedicated validation cohort (Dean et al., 2023; Tian et al., 2024). Statin-based cardioprotection carries only a conditional (Class IIa) recommendation, reflecting clinical evidence that remains sufficiently inconsistent between trials, whereas the promising evidence for SGLT2 inhibitors requires confirmation in adequately powered, prospective randomized trials rather than retrospective cohort studies. Finally, most mechanistic studies to date have focused on acute, high-dose doxorubicin exposure, whereas clinical cardiotoxicity generally arises from cumulative, fractionated dosing regimens; the sparse literature addressing chronic exposure suggests that ferroptotic mechanisms remain relevant in this context, but considerably more mechanistic and interventional data on chronic dosing are needed.

Future Perspectives

Addressing the murine-to-human translational gap in the efficacy of ferroptosis inhibitors should be a research priority. This could be achieved by systematically comparing iron metabolism, GPX4 expression dynamics, and lipidomic profiles across rodent and human cardiomyocyte models, and by evaluating complementary or combinatorial interventions in human induced pluripotent stem cell-derived systems before further extrapolating from rodent to human studies (Cha et al., 2026). A major advance for the field would be the development of a clinically validated, ferroptosis-specific biomarker, likely derived from circulating oxidised phospholipid species or iron-regulating proteins, moving beyond the current non-specific damage markers such as troponin and GDF-15 (Dean et al., 2023; Tian et al., 2024).

Continued preclinical development of novel iron-chelating nanomedicines and Nrf2-targeted natural compounds is needed, with a specific focus on achieving the selectivity that dexrazoxane has not attained, thereby enabling broader prophylactic use without the secondary-malignancy risks that currently limit its application (Liu et al., 2024; Prabhune et al., 2025). Future, adequately powered randomized trials of SGLT2 inhibitors in cardio-oncology populations many of which are already underway will be essential to raise this promising but currently observational body of evidence to the level of clinical validation achieved by statin trials such as STOP-CA and PREVENT (Abdel-Qadir et al., 2023; Avula et al., 2024; Gongora et al., 2022; Neilan et al., 2023; Thavendiranathan et al., 2023). Combination strategies that pair iron-targeted therapies with systemically acting cardioprotective agents, guided by biomarker-based risk stratification consistent with the 2022 European Society of Cardiology guidelines, constitute a feasible and mechanistically sound approach to reducing the clinical impact of anthracycline cardiotoxicity while preserving antitumour efficacy.

Conclusion

Ferroptosis is emerging as a major, mechanistically distinct contributor to anthracycline-induced cardiotoxicity, driven by iron-dependent lipid peroxidation arising from doxorubicin-iron redox cycling, HO-1-mediated heme degradation, intercalation into mitochondrial DNA, and GPX4 down regulation. This mechanistic clarity has yielded one approved drug, dexrazoxane, and an expanding array of iron-

chelating, antioxidant, and systemically acting cardioprotective candidates. Recent evidence that ferroptosis inhibitors effective in rodent models fail to rescue human cardiomyocytes serves as a stark warning against premature clinical extrapolation. Continued mechanistic, biomarker, and clinical-trial research, particularly work that directly addresses this species-specific translational gap, is essential before ferroptosis-targeted cardioprotection can be confidently incorporated into standard cardio-oncology care.

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Disclosure of Conflict of Interest

Conflict of interest: none declared.

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