www.ijarp.com ISSN 2456-9992 Page: 01-15

International Journal Advanced Research Publications

Review Article

Volume: 02
Issue: 11

FERROPTOSIS AS AN EMERGING THERAPEUTIC TARGET IN CANCER: MECHANISMS, MOLECULAR TARGETS AND THERAPEUTIC STRATEGIES- A REVIEW

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Article Received: 19 October 2026, Article Revised: 08 November 2026, Published on: 27 November 2026

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Doi: https://doi-doi.org/101555/ijarp.6755

ABSTRACT

Ferroptosis is a regulated form of cell death driven by iron-dependent phospholipid peroxidation and a failure of cellular lipid-antioxidant systems. It has attracted interest in cancer research because some malignant cells, including treatment-tolerant or metabolically adapted populations, rely strongly on antioxidant pathways to survive oxidative stress. This narrative review summarizes the molecular foundations of ferroptosis, its principal regulatory networks, and the opportunities and limitations of targeting this process in oncology. The review discusses iron uptake and storage, polyunsaturated phospholipid remodeling, the system Xc−–glutathione–glutathione peroxidase 4 (GPX4) axis, and alternative defenses involving ferroptosis suppressor protein 1 (FSP1), coenzyme Q10, dihydroorotate dehydrogenase (DHODH), and the GCH1–tetrahydrobiopterin pathway. Major targets and experimental agents are compared, including system Xc− inhibitors, GPX4 inhibitors, clinically used drugs reported to modulate ferroptosis, and selected natural products. Evidence across breast, lung, liver, colorectal, pancreatic, and brain tumors indicates that sensitivity is heterogeneous and is shaped by genotype, lipid composition, antioxidant capacity, iron handling, and the tumor microenvironment. Combination strategies with chemotherapy, radiotherapy, targeted therapy, and immunotherapy are mechanistically promising, but most ferroptosis-directed approaches remain preclinical. Key barriers include

limited compound selectivity, normal-tissue toxicity, uncertain pharmacodynamic biomarkers, compensatory resistance, and insufficient prospective clinical validation. The review concludes that successful translation will require better-defined ferroptosis biomarkers, tumor-selective delivery, rigorous mechanistic confirmation, and clinical studies that distinguish ferroptosis-dependent effects from other forms of drug-induced cell death.

KEYWORDS: Ferroptosis; Cancer therapy; Lipid peroxidation; GPX4; Iron metabolism; Therapeutic resistance.

INTRODUCTION

Cancer remains a major cause of morbidity and mortality, and treatment success is limited in many settings by tumor heterogeneity, metastatic spread, dose-limiting toxicity, and the evolution of treatment resistance. Surgery, radiotherapy, cytotoxic medicines, molecularly targeted agents, and immunotherapies have improved outcomes for multiple malignancies, yet no single approach controls every tumor. Many standard anticancer agents rely partly on apoptosis or other established cell-death programs, while tumor cells can adapt by altering survival signaling, DNA repair, metabolic flux, and antioxidant defenses. These limitations support continued investigation of regulated cell-death processes that may eliminate cancer cells with different vulnerabilities from those targeted by conventional treatment.[1-5]

Ferroptosis was named in 2012 as an iron-dependent, non-apoptotic cell-death process associated with oxidative damage and suppression by the small molecule ferrostatin-1. It is now understood as a regulated process in which iron-catalyzed reactions and enzymatic lipid oxidation overwhelm the capacity of cells to detoxify phospholipid hydroperoxides. The defining biochemical event is not simply an increase in total reactive oxygen species, but the accumulation of oxidized polyunsaturated fatty-acid-containing phospholipids within cellular membranes. Ferroptosis differs from apoptosis in its central reliance on lipid peroxidation and iron handling, although pathways can overlap in the same cell depending on the insult and context.[1-4]

The biological system controlling ferroptosis spans iron trafficking, membrane lipid composition, cystine and glutathione metabolism, and several parallel mechanisms that interrupt lipid-radical propagation. Glutathione peroxidase 4 (GPX4) is a key suppressor because it reduces phospholipid hydroperoxides; inhibition or loss of GPX4 can therefore reveal a lethal dependency in susceptible cancer cells. Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) support

the incorporation of oxidation-prone polyunsaturated fatty acids into membrane phospholipids, helping determine sensitivity. Cellular transferrin uptake, glutaminolysis, and labile iron pools also shape the threshold at which oxidative stress becomes lethal.[6-10]

Ferroptosis is of interest in oncology for more than one reason. First, some cancer cells show high dependence on GPX4 or related lipid-peroxide defense systems, offering a potential way to attack cells that have become resistant to apoptosis-inducing agents. Second, oncogenic and tumor-suppressor signaling may alter ferroptosis sensitivity; for example, p53 can repress SLC7A11 under certain conditions, while NRF2-associated antioxidant programs can protect liver cancer cells from ferroptosis. Third, some treatments can modify ferroptosis sensitivity as one component of their broader pharmacology. These observations justify exploring ferroptosis as a vulnerability, but they do not establish that ferroptosis induction is the dominant mechanism of every implicated drug or that the strategy is clinically effective across tumor types.[11-13]

The purpose of this review is to connect molecular mechanisms with therapeutic opportunities and translational limitations. It covers ferroptosis biology, major antioxidant defense systems, relevant cancer models, experimental inducers, natural products, resistance, combination therapy, immune interactions, biomarkers, and future drug-development priorities. Particular attention is given to the difference between mechanistic plausibility, cell-based and animal evidence, and demonstrated clinical benefit. This distinction is important because many commonly discussed ferroptosis-inducing compounds remain research tools, and a cancer response reported in a laboratory model should not be interpreted as proof of a safe or effective treatment in patients. [3-5,14,15]

Overview and Discovery of Ferroptosis

The term ferroptosis was introduced to distinguish an iron-dependent non-apoptotic death phenotype from apoptosis, conventional necrosis, and autophagy-associated death. The original work used a small-molecule screen to identify erastin, which selectively killed RAS-transformed cells under the tested conditions, and identified ferrostatin-1 as a suppressor of the process. Subsequent work established GPX4 as a central regulator and showed that erastin-like agents can cause glutathione depletion while RSL3 directly inhibits GPX4. These studies supplied the conceptual and experimental basis for considering ferroptosis as a distinct regulated cell-death mechanism rather than a generic label for oxidative toxicity.[1,6,7]

Ferroptosis is commonly associated with relatively compact mitochondria with altered cristae and membrane density, but morphology alone is insufficient for diagnosis. Its most informative biochemical features are iron dependence, accumulation of oxidized membrane lipids, and suppression by chemically distinct ferroptosis inhibitors or by genetic restoration of protective pathways. It differs from apoptosis, which typically involves caspases and characteristic nuclear changes; necroptosis, which can involve RIPK1/RIPK3/MLKL signaling; and autophagy, which is primarily a degradative pathway rather than a single death mechanism. Cross-talk occurs, so mechanistic classification requires multiple assays rather than a single morphological or viability measurement. [2-5,15]

Table 1. Comparison of ferroptosis with selected cell-death mechanisms.

Feature	Ferroptosis	Apoptosis	Necroptosis	Autophagy-associated cell death
Core process	Iron-dependent phospholipid peroxidation; failure of lipid-radical defenses	Caspase-associated dismantling of the cell	Regulated necrotic process involving RIPK3/MLKL in canonical settings	Autophagy machinery contributes to cell demise in selected contexts
Common regulators	GPX4, system Xc−/GSH, FSP1, ACSL4, iron handling	BCL-2 family, initiator/executioner caspases	RIPK1, RIPK3, MLKL	ATG proteins and lysosomal/autophagic flux
Typical biochemical evidence	Oxidized phospholipids, lipid ROS; rescue by ferrostatin-	Caspase activation, PARP cleavage, DNA fragmentation	MLKL phosphorylation/translocation where canonical pathway applies	Altered autophagic flux; dependence on autophagy genes

Molecular Mechanisms and Regulation of Ferroptosis

A simplified sequence begins with an imbalance between the availability of oxidizable phospholipids and the capacity to neutralize lipid peroxides. Ferrous iron can support radical-generating reactions, while enzymatic processes and non-enzymatic chain reactions oxidize polyunsaturated fatty-acid (PUFA)-containing phospholipids. When lipid hydroperoxides accumulate beyond repair and detoxification capacity, membrane function is disrupted and ferroptotic death can follow. However, the exact lethal lipid species and execution events

vary with cell lineage, nutrient conditions, oxygen tension, and the inhibitor used; not every increase in lipid oxidation culminates in ferroptosis.[3-5,8,9]

Iron is required for multiple cellular functions, including mitochondrial metabolism and DNA synthesis, and is carefully controlled through transferrin-bound iron uptake, transferrin receptor 1 (TFRC), ferritin storage, ferroportin-mediated export, and intracellular trafficking. The labile iron pool is more immediately redox-active than ferritin-sequestered iron. Ferritinophagy, a selective lysosomal pathway involving nuclear receptor coactivator 4 (NCOA4), can release stored iron and increase susceptibility to lipid oxidation in some systems.[3,9,10,16]

Membrane substrate composition is a second determinant. ACSL4 activates long-chain PUFAs, including arachidonic and adrenic acid, for incorporation into phospholipids, while LPCAT3 transfers activated fatty acids into membrane phospholipids. These reactions can increase the pool of susceptible lipid substrates. Oxidation can then be driven by iron chemistry and, in certain contexts, lipoxygenases or other enzymatic pathways.[8,9,21]

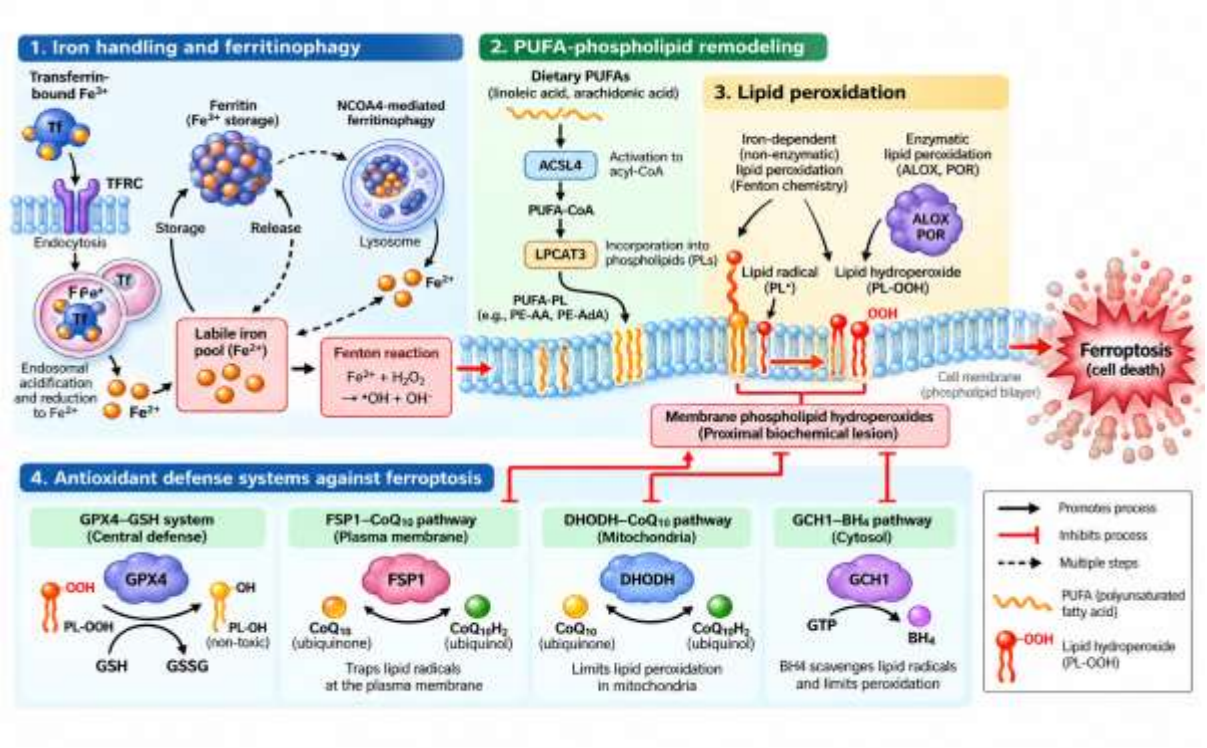

Figure 1. Molecular mechanism of ferroptosis.

Major Antioxidant Defense Systems

System Xc−, glutathione, and GPX4

System Xc− is a cystine/glutamate antiporter composed of the light-chain transporter xCT, encoded by SLC7A11, and the heavy-chain subunit SLC3A2. Imported cystine is reduced to cysteine, a substrate for glutathione (GSH) synthesis. GPX4 uses GSH to reduce phospholipid hydroperoxides to less reactive lipid alcohols. Inhibiting cystine uptake, blocking GSH synthesis, or directly inhibiting GPX4 can thus collapse the main lipid-peroxide defense system. GPX4 has been a prominent target because its genetic depletion or pharmacological inhibition can be lethal to selected cancer cells and treatment-resistant states. Nevertheless, complete GPX4 loss also causes severe injury in normal tissues, demonstrated by experimental models in which GPX4 inactivation produces acute renal failure. This finding is a central translational warning: cancer-cell dependence may create an opportunity, but systemic inhibition of an essential antioxidant enzyme may have a narrow therapeutic window. [12,19,22]

Alternative ferroptosis-defense pathways

Ferroptosis suppressor protein 1 (FSP1), formerly associated with apoptosis-inducing factor mitochondria-associated 2 (AIFM2), can reduce coenzyme Q10 (CoQ10) to its radical-trapping form at cellular membranes. Mitochondrial dihydroorotate dehydrogenase (DHODH) links pyrimidine biosynthesis with CoQ reduction and mitochondrial membrane protection. Research has shown that DHODH can provide a ferroptosis defense in certain cancer contexts, particularly when mitochondrial GPX4 activity is limited. This creates a possible vulnerability in tumors that rely on the DHODH-linked pathway, but the rationale is not universal because mitochondrial dependence varies between lineages and metabolic states. The clinical significance of DHODH inhibition as a ferroptosis strategy remains investigational and must be separated from its established or unrelated effects on pyrimidine metabolism.[22,24,25]

Major Molecular Targets for Cancer Therapy

A practical target map distinguishes pro-ferroptotic factors from protective factors. GPX4, SLC7A11, FSP1, and NRF2-associated antioxidant outputs generally suppress ferroptosis; their inhibition can increase susceptibility when the tumor relies on them. ACSL4, LPCAT3, and certain iron-mobilizing processes can support lipid-peroxidation sensitivity, although their biological functions extend beyond ferroptosis. TFRC can increase iron uptake, while

ferritin storage and ferroportin export buffer or reduce redox-active iron. NCOA4-mediated ferritinophagy is context-dependent because it can supply iron for ferroptosis or support tumor metabolism. This framework discourages treating every ferroptosis-associated gene as a simple drug target. [24-25]

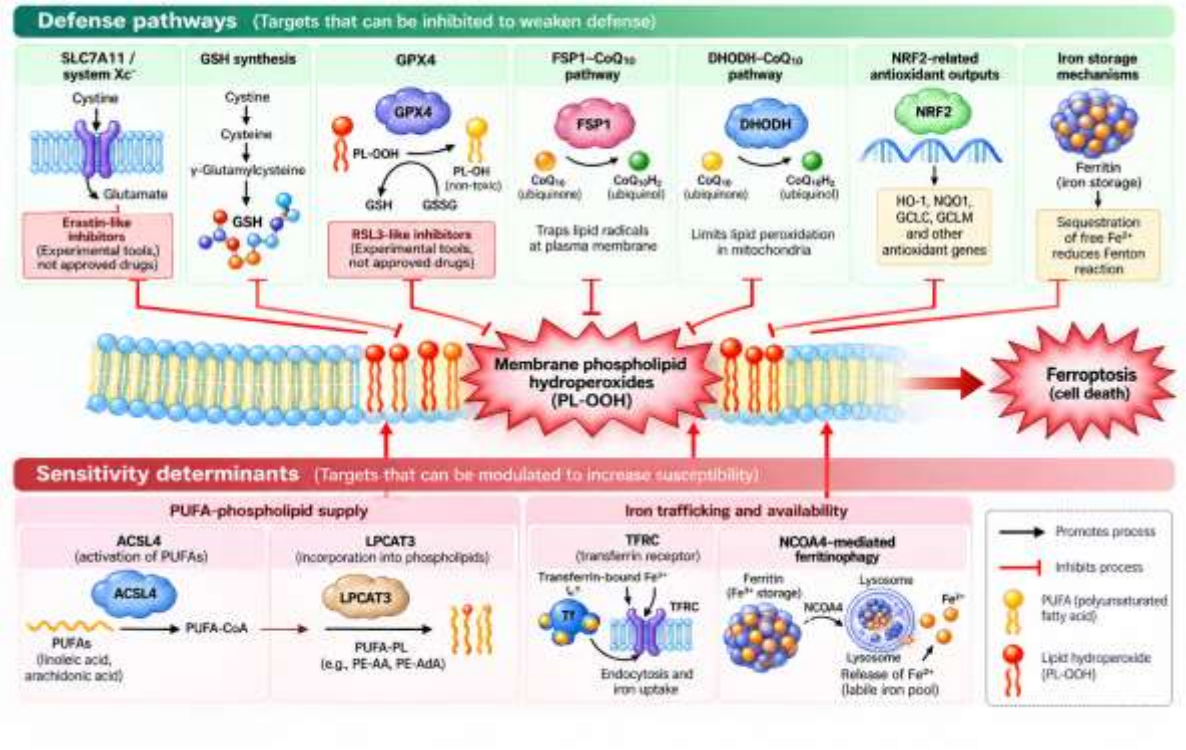

Figure 2. Major molecular targets and therapeutic intervention points.

Role of Ferroptosis in Different Cancers

Breast cancer studies suggest that ferroptosis sensitivity can vary with hormone-receptor status, oncogenic signaling, mesenchymal plasticity, lipid composition, and antioxidant activity. A notable concept is that therapy-resistant or mesenchymal-like cancer-cell states can become dependent on GPX4-mediated lipid-peroxide defense. This creates a potential opportunity to target selected drug-tolerant populations that evade other therapies. However, breast cancer comprises diverse molecular subtypes and treatment histories; no single GPX4 or ACSL4 measurement is sufficient to assume sensitivity in an individual tumor, and patient-level predictive evidence remains limited. [8,24]

In lung adenocarcinoma, studies of ACSL4 and LPCAT3 have linked lipid remodeling to ferroptosis sensitivity and shown that regulatory interactions involving YAP, ZEB, and EP300 may influence LPCAT3 expression. In liver cancer, sorafenib-associated iron-dependent death and NRF2-mediated defense have been studied extensively, but sorafenib is

a multikinase inhibitor whose antitumor effects cannot be attributed solely to ferroptosis. Colorectal cancer models have reported ferroptosis-related effects for compounds such as baicalein and β-lapachone. These findings are useful proof-of-concept examples, but they differ in model design, compound exposure, mechanistic controls, and the relative contribution of other death pathways.[22,25]

Ferroptosis-Inducing Agents and Therapeutic Compounds

Clinically used drugs have also been reported to induce or sensitize cells to ferroptosis under particular experimental conditions. Sorafenib, a multikinase inhibitor used in certain cancers, has been associated with iron-dependent death in hepatocellular carcinoma models, but its activity is multifactorial and its clinical benefits should not be attributed exclusively to ferroptosis. Other agents, including some chemotherapies, targeted agents, and radiation, may influence lipid oxidation or antioxidant defense indirectly. These effects need compound-specific validation because oxidative stress is widespread in drug pharmacology and does not by itself identify ferroptosis as the cause of tumor-cell death.[24]

Ferroptosis evaluation should use orthogonal evidence. Useful approaches include lipid-reactive probes, measurements of oxidized phospholipid species, iron chelation, rescue with ferrostatin-1 or liproxstatin-1, genetic manipulation of GPX4/SLC7A11/ACSL4, and comparison with apoptosis or necroptosis inhibitors. No single assay is definitive: fluorescent lipid probes are affected by experimental conditions, total reactive oxygen species measurements are nonspecific, and rescue agents may have off-target effects. Compound claims are strongest when the mechanism is demonstrated in the same disease model and exposure range used to support the therapeutic interpretation.[1-5]

Table 2. Representative compounds and the level of evidence for ferroptosis modulation.

Compound / class	Proposed intervention	Representative model or finding	Evidence level and limitations
Erastin and derivatives	System Xc− inhibition; cystine depletion	Foundational cancer-cell studies; sensitizes selected RAS-transformed models	Primarily experimental; drug-like properties and selectivity limit clinical use
RSL3 and related GPX4 inhibitors	Direct GPX4 inhibition	GPX4-dependent cancer cells; selected xenograft evidence	Research tools; systemic GPX4 inhibition raises normal-tissue safety

Compound / class	Proposed intervention	Representative model or finding	Evidence level and limitations
			concerns
Sulfasalazine / system Xc− interference	Can reduce cystine transport in some settings	Investigated in cell and clinical contexts for other indications	Ferroptosis is not necessarily its dominant mechanism; exposure and specificity vary
Sorafenib	Multikinase inhibition with reported ferroptosis-related effects	Iron-dependent death reported in hepatocellular carcinoma models	Approved for cancer indications, but clinical efficacy is multifactorial
β-Lapachone	Reported xCT/GPX4 modulation and NCOA4-mediated ferritinophagy	Colorectal cancer models; JNK pathway implicated	Preclinical and potentially multi-mechanistic; not an established ferroptosis therapy

Natural Products and Ferroptosis Modulation

Natural products provide chemically diverse starting points for ferroptosis research, but their effects are often concentration-dependent and may include antioxidant, pro-oxidant, cytostatic, and apoptosis-related activities. Artemisinin and derivatives such as dihydroartemisinin can interact with iron metabolism and increase sensitivity to ferroptosis in experimental systems. In a mechanistic study, dihydroartemisinin promoted lysosomal ferritin degradation and increased the labile iron pool, thereby sensitizing cells to GPX4 inhibition. This is a useful example of a natural-product-derived compound acting as a sensitizer rather than a selective GPX4 inhibitor. The result should not be generalized to every cancer model or interpreted as proof of anticancer efficacy in patients.[18,22]

Table 3. Selected natural products reported to modulate ferroptosis in cancer.

Natural product	Reported mechanism	Cancer evidence described in the literature	Interpretive caution
Artemisinin / dihydroartemisinin	Iron-homeostasis disruption, lysosomal ferritin degradation, increased sensitivity to GPX4 inhibition	Experimental cancer-cell systems and mouse xenograft sensitization models	Multiple anticancer mechanisms; not a validated ferroptosis-directed cancer treatment
Baicalein	Reported inhibition of JAK2/STAT3 signaling with reduced GPX4 expression	Colorectal cancer cells and xenograft model	Preclinical study; pharmacokinetics and patient benefit unestablished

Natural product	Reported mechanism	Cancer evidence described in the literature	Interpretive caution
β-Lapachone	Reported xCT/GPX4 changes and NCOA4-mediated ferritinophagy involving JNK	Colorectal cancer cell models	Likely multiple mechanisms; no established clinical ferroptosis indication

Ferroptosis and Cancer Treatment Resistance

Ferroptosis can also intersect with resistance to targeted agents, chemotherapy, and radiotherapy by altering antioxidant signaling, iron handling, or membrane lipid composition. Resistance may arise through increased SLC7A11, GPX4, FSP1, NRF2-associated defenses, or changes in PUFA metabolism; other tumors may reduce sensitivity through iron sequestration or metabolic rewiring. A combination that initially sensitizes cells can still select for adaptive clones. Longitudinal sampling and functional testing are therefore needed to determine whether ferroptosis sensitivity is a stable tumor trait, an inducible state, or a transient response to treatment stress.[14,16]

Combination Therapeutic Strategies

Combining a ferroptosis-inducing strategy with chemotherapy or radiotherapy may increase the burden of lipid oxidative damage beyond the tumor cell's antioxidant capacity. Mechanistically, DNA damage, metabolic stress, and lipid peroxidation can converge, allowing a combination to affect more than one survival pathway. However, interaction is dependent on dose, sequence, oxygen and nutrient state, and treatment-specific changes in lipid metabolism. Apparent synergy based solely on cell viability curves does not prove ferroptosis-mediated synergy; pathway rescue and appropriate controls are needed to establish causal involvem ent.[3,16-20]

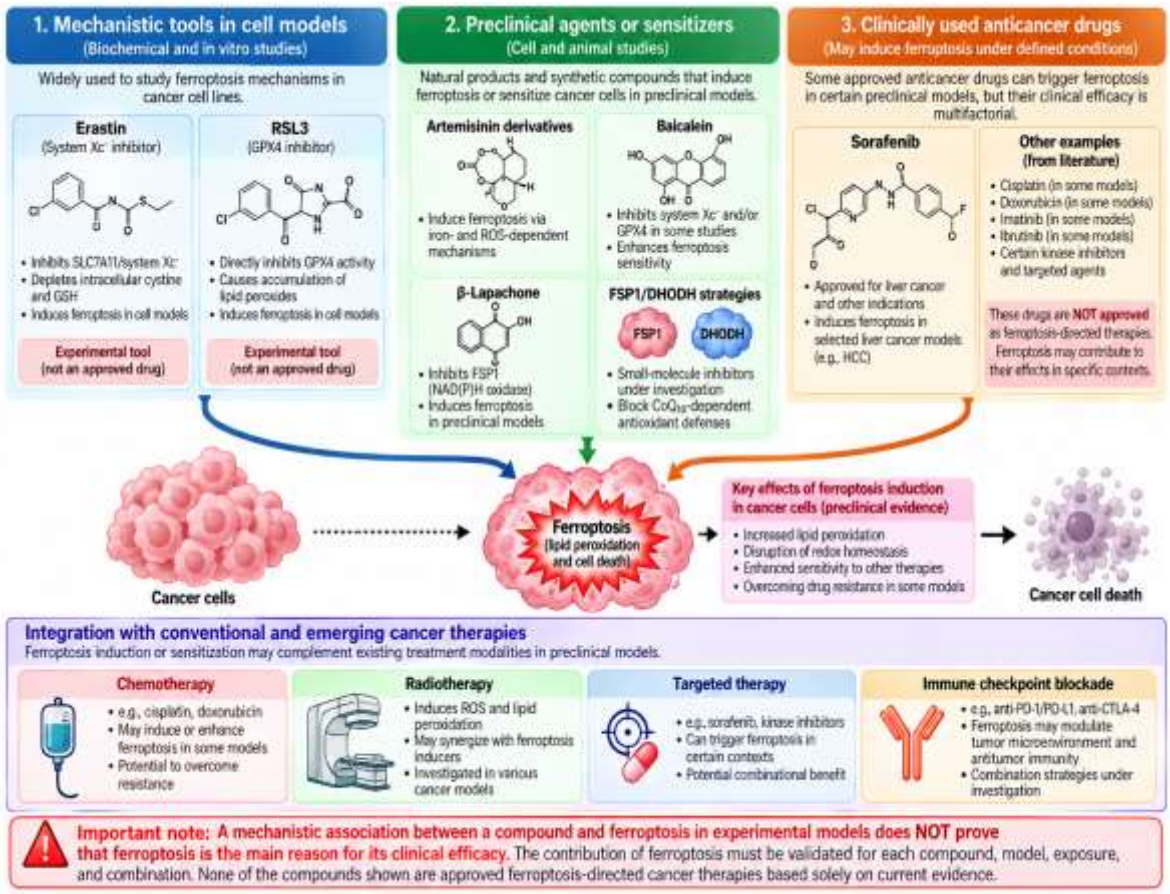

Figure 3. Therapeutic strategies for inducing ferroptosis in cancer.

Table 4: Combination strategies: rationale and limitations.

Combination approach	Scientific rationale	Potential benefit	Key limitation to address
Chemotherapy + ferroptosis sensitizer	Increase oxidative/lipid stress or weaken adaptive defense	May address heterogeneous death-pathway dependence	Overlapping toxicity; prove ferroptosis contribution in the chosen model
Radiotherapy + ferroptosis strategy	Radiation can alter ROS burden and cellular stress responses	Possible sensitization of selected radioresistant states	Normal-tissue oxidative injury and schedule dependence
Targeted agent + GPX4/system Xc− intervention	Exploit a metabolic state created by oncogenic pathway inhibition	Could suppress escape states or persisters	Adaptive resistance and variable lipid composition
FSP1 or DHODH cotargeting + GPX4 inhibition	Block parallel lipid-peroxide defense systems	May overcome single-pathway compensation	Safety window and pathway redundancy need in vivo validation.

Translational Challenges and Safety Concerns

The main translational barrier is selectivity. Lipid-peroxide defense is not unique to malignant cells, and normal organs with high oxidative or metabolic demands may be vulnerable to strong ferroptosis induction. Experimental GPX4 loss has caused severe tissue injury, underscoring that the therapeutic window cannot be assumed from tumor-cell killing in vitro. Tumor-targeted delivery, local administration, antibody or ligand-guided carriers, and schedule optimization are possible approaches, but each adds manufacturing, distribution, and regulatory complexity and must demonstrate improved safety rather than merely higher tumor exposure.[7,16,17]

Emerging Therapeutic Strategies and Future Perspectives

Drug delivery may improve the therapeutic index if an inducer can be concentrated in a tumor, released in a defined microenvironment, or directed toward cells expressing an appropriate marker. Nanocarriers, prodrugs, tumor-activated linkers, and local delivery are plausible approaches, but they must be tested for reproducible manufacture, cargo stability, biodistribution, clearance, and off-target accumulation. Biomarker-guided selection could be paired with patient-derived organoids or other functional models to test whether a tumor responds to the intended mechanism. These strategies remain developmental and should not be described as clinically validated without prospective patient data.[16-19]

CONCLUSION

Ferroptosis has emerged as an important area of cancer research because it links iron metabolism, membrane lipid composition, oxidative stress, and antioxidant defense into a regulated cell-death process. The system Xc−–glutathione–GPX4 axis is a major protective pathway, while FSP1–CoQ10, DHODH, and GCH1–BH4 provide alternative layers of protection. Regulators such as ACSL4, LPCAT3, NRF2, transferrin receptor 1, ferritin, and NCOA4 influence sensitivity by changing the balance between oxidizable lipids, redox-active iron, and cellular defense capacity. These networks create opportunities to investigate tumors that depend on lipid-peroxide defense, including selected treatment-resistant or metabolically adapted cancer states. Experimental inducers and sensitizers have demonstrated activity in cell-based and animal models, and selected natural products have provided useful mechanistic leads. However, many agents remain research tools, and drugs that influence ferroptosis may also act through other pharmacological mechanisms. Tumor responses are

not uniform across cancer types, and the same iron or oxidative processes that make malignant cells vulnerable can damage normal tissues.

The absence of validated predictive biomarkers, limited selectivity, adaptive resistance, uncertain pharmacokinetics, and a shortage of prospective clinical evidence remain major barriers. Progress toward clinical use will require more selective compounds, tumor-directed delivery, validated pharmacodynamic measurements, robust models that reflect human tumor heterogeneity, and careful evaluation of combinations with chemotherapy, radiotherapy, targeted treatment, and immunotherapy. Researchers should use convergent mechanistic assays to confirm ferroptosis rather than infer it from reactive oxygen species or loss of viability alone. Ultimately, ferroptosis should be developed as a biomarker-guided and context-dependent strategy, not as a universal solution for cancer. Its clinical value will depend on showing that a defined patient group can obtain meaningful benefit at exposures that are acceptably safe for normal tissues.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to **Ms. Apeksha D. Thite** Assistant Professor, Department of Pharmaceutical Quality Assurance for their valuable guidance, constructive suggestions, and continuous support throughout the preparation of this review article. The authors also gratefully acknowledge **Dr. Tushar Shelke** Principal, for providing the necessary institutional support, encouragement, and facilities required for the completion of this work. The authors sincerely appreciate their valuable contributions and support.

REFERENCES

1. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149(5):1060-1072. doi:10.1016/j.cell.2012.03.042. PMID:22632970.
2. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ. 2018;25:486-541. doi:10.1038/s41418-017-0012-4.
3. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. Nat Rev Mol Cell Biol. 2021;22:266-282. doi:10.1038/s41580-020-00324-8.
4. Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. Cell. 2017;171(2):273-285. doi:10.1016/j.cell.2017.09.021.

5. Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. Cell Res. 2021;31:107-125. doi:10.1038/s41422-020-00441-1.
6. Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, et al. Regulation of ferroptotic cancer cell death by GPX4. Cell. 2014;156(1-2):317-331. doi:10.1016/j.cell.2013.12.010. PMID:24439385.
7. Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. Nat Cell Biol. 2014;16:1180-1191. doi:10.1038/ncb3064.
8. Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol. 2017;13(1):91-98. doi:10.1038/nchembio.2239.
9. Kagan VE, Mao G, Qu F, Angeli JPF, Doll S, Croix CS, et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol. 2017;13:81-90. doi:10.1038/nchembio.2238.
10. Gao M, Monian P, Quadri N, Ramasamy R, Jiang X. Glutaminolysis and transferrin regulate ferroptosis. Mol Cell. 2015;59(2):298-308. doi:10.1016/j.molcel.2015.06.011. PMID:26166707.
11. Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, et al. Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 2015;520:57-62. doi:10.1038/nature14344.
12. Sun X, Ou Z, Chen R, Niu X, Chen D, Kang R, et al. Activation of the p62-Keap1-NRF2 pathway protects against ferroptosis in hepatocellular carcinoma cells. Hepatology. 2016;63(1):173-184. doi:10.1002/hep.28251.
13. Shimada K, Skoulia D, Warwick L, Gopal S, Foletto V, Jiao Y, et al. Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis. Nat Chem Biol. 2016;12:497-503. doi:10.1038/nchembio.2079.
14. Viswanathan VS, Ryan MJ, Dhruv HD, Gill S, Eichhoff OM, Seashore-Ludlow B, et al. Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway. Nature. 2017;547:453-457. doi:10.1038/nature23007.
15. Hangauer MJ, Viswanathan VS, Ryan MJ, Bole D, Eaton JK, Matov A, et al. Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition. Nature. 2017;551:247-250. doi:10.1038/nature24297.
16. Diao J, Jia Y, Dai E, Liu J, Kang R, Tang D, et al. Ferroptotic therapy in cancer: benefits, side effects, and risks. Mol Cancer. 2024;23:89. doi:10.1186/s12943-024-01999-9.

17. Wahida A, Conrad M. Decoding ferroptosis for cancer therapy. Nat Rev Cancer. 2025;25:910-924. doi:10.1038/s41568-025-00864-1.
18. Dai Z, Liu J, Zeng L, Shi K, Peng X, Jin Z, et al. Targeting ferroptosis in cancer therapy: mechanisms, strategies, and clinical applications. Cell Investig. 2025;1(4):100049. doi:10.1016/j.clnves.2025.100049.
19. Stockwell BR. Ferroptosis turns 10: emerging mechanisms, physiological functions, and therapeutic applications. Cell. 2022;185(14):2401-2421. doi:10.1016/j.cell.2022.06.003. PMID:35803244.
20. Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, et al. Ferroptosis: process and function. Cell Death Differ. 2016;23:369-379. doi:10.1038/cdd.2015.158.
21. Cui J, Wang Y, Tian X, Miao Y, Ma L, Zhang C, et al. LPCAT3 is transcriptionally regulated by YAP/ZEB/EP300 and collaborates with ACSL4 and YAP to determine ferroptosis sensitivity. Antioxid Redox Signal. 2023;39(7-9):491-511. doi:10.1089/ars.2023.0237.
22. Mao C, Liu X, Zhang Y, Lei G, Yan Y, Lee H, et al. DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. Nature. 2021;593:586-590. doi:10.1038/s41586-021-03539-7.
23. Conrad M, Sato H. The oxidative stress-inducible cystine/glutamate antiporter, system xc−: cystine supplier and beyond. Amino Acids. 2012;42:231-246. doi:10.1007/s00726-011-0867-5.
24. Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, et al. The CoQ oxidoreductase FSP1 acts in parallel to GPX4 to inhibit ferroptosis. Nature. 2019;575:688-692. doi:10.1038/s41586-019-1705-2.
25. Doll S, Freitas FP, Shah R, Aldrovandi M, Ingold I, Goya Grocin A, et al. FSP1 is a glutathione-independent ferroptosis suppressor. Nature. 2019;575:693-698. doi:10.1038/s41586-019-1707-0.