

From Redox Vulnerability to Therapeutic Translation: Ferroptosis in Cancer Through Natural-Product Scaffolds, Resistance Biology, and Precision Targeting

Rema A. Ballg¹, Salah Neghmouche Nacer^{2*}

¹Department of Chemistry, Faculty of Sciences, Al-Ajaylat, University of Zawia Libya

²Laboratory of Applied Chemistry and Environment, Department of Chemistry, Faculty of Exact Sciences, University of El Oued, Algeria.

*Corresponding author: Dr. Salah Nacer, email: neghmouchenacer-salah@univ-eloued.dz

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Abstract

Ferroptosis has emerged as a therapeutically exploitable form of regulated cell death governed by iron metabolism, phospholipid peroxidation, and redox homeostasis. Its ability to eliminate metabolically adapted and therapy-resistant cancer cells has generated substantial interest; however, clinical translation remains limited by redundant antioxidant defenses, tumor metabolic plasticity, insufficient biomarkers, and the frequent disconnect between in vitro ferroptotic phenotypes and in vivo efficacy. Natural products offer structurally diverse and pharmacologically versatile scaffolds capable of targeting these vulnerabilities, yet the mechanistic evidence supporting many proposed ferroptosis modulators remains inconsistent. This review critically integrates the molecular architecture of ferroptosis with cancer redox vulnerability, resistance mechanisms, and natural-product pharmacology. Particular emphasis is placed on the SLC7A11–GSH–GPX4 axis and GPX4-independent defense systems, including FSP1–CoQ10, DHODH–CoQH2, and GCH1–BH4, together with iron homeostasis, ferritinophagy, lipid remodeling, and NRF2-dependent adaptation. Rather than cataloguing compounds, natural products are evaluated according to chemical class, molecular target, tumor context, and strength of ferroptosis-specific evidence. Combination strategies, tumor-micro environmental determinants, precision delivery, computational discovery, biomarkers, and translational barriers are also critically examined. Finally, we propose an evidence hierarchy and translational roadmap that distinguish biochemical association from pharmacological rescue, mechanistic confirmation, in vivo validation, and clinically relevant evidence. By linking natural-product chemical diversity to ferroptosis dependency and resistance biology, this review defines key experimental priorities for translating ferroptosis into a pharmacologically actionable strategy in oncology.

Keywords: Ferroptosis; cancer; natural products; lipid peroxidation; GPX4; FSP1; SLC7A11; oxidative stress; drug resistance; precision oncology.

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INTRODUCTION

Cancer cells survive under a persistent redox paradox. Oncogenic signaling, accelerated metabolism, mitochondrial dysfunction, and increased iron demand generate oxidative pressure that supports tumor progression while simultaneously creating a potentially lethal dependence on antioxidant defense. Ferroptosis exploits this vulnerability. Originally defined as an iron-dependent, non-apoptotic form of regulated

cell death¹, ferroptosis is now recognized as a process driven by catastrophic peroxidation of susceptible membrane phospholipids when cellular mechanisms preserving lipid redox homeostasis become insufficient²⁻⁴. Its dependence on iron availability, membrane lipid composition, and antioxidant capacity distinguishes ferroptosis from other regulated cell-death programs and creates opportunities to target metabolically adapted and therapy-resistant malignancies.

Ferroptosis sensitivity is determined by the balance between pro-ferroptotic metabolic pressure and a multilayered cytoprotective network. Iron accumulation and ferritin turnover expand the labile iron pool, whereas ACSL4- and LPCAT3-dependent incorporation of polyunsaturated fatty acids (PUFAs) into membrane phospholipids generates oxidation-prone substrates²⁻⁵. The system Xc⁻-GSH-GPX4 axis provides a central defense against this process, but it is not functionally isolated. FSP1-CoQ10, mitochondrial DHODH-CoQH₂, and GCH1-BH₄ constitute complementary antioxidant systems capable of suppressing lethal lipid peroxidation⁶⁻⁹. These discoveries have transformed ferroptosis from a predominantly GPX4-centered model into a compartmentalized and context-dependent network of metabolic liabilities and compensatory defenses.

Natural products provide a chemically diverse source of scaffolds capable of exploiting this network. Polyphenols, flavonoids, quinones, terpenoids, alkaloids, saponins, and other naturally derived compounds have been reported to perturb iron homeostasis, cysteine/GSH metabolism, GPX4 activity, lipid remodeling, mitochondrial function, and NRF2-dependent antioxidant signaling¹⁰⁻¹³. However, pharmacological pleiotropy represents a major interpretative challenge. Increased reactive oxygen species, malondialdehyde, or intracellular iron, together with GSH depletion or reduced GPX4 expression, may accompany ferroptosis but does not independently establish ferroptosis as the causal mechanism of cell death. Consequently, compounds currently described as natural “ferroptosis inducers” are supported by substantially different levels of mechanistic evidence.

This review therefore moves beyond a descriptive catalogue of natural ferroptosis modulators to establish an evidence-centered framework connecting chemical scaffold, cancer redox vulnerability, ferroptosis resistance, and therapeutic translation. Natural compounds are critically evaluated according to molecular target, tumor context, and strength of ferroptosis-specific validation, with explicit distinction between biochemical association, pharmacological rescue, mechanistic confirmation, in vivo efficacy, and clinically relevant evidence. Particular

attention is given to combination therapy, tumor-microenvironmental determinants, exposure and selectivity, precision delivery, biomarkers, and patient stratification. By integrating these dimensions, we identify the natural-product strategies with the strongest mechanistic and translational rationale for precision ferroptosis-based cancer therapy.

FERROPTOSIS AS A REDOX VULNERABILITY IN CANCER

Ferroptosis is not synonymous with oxidative stress. It represents a regulated collapse of phospholipid redox homeostasis that occurs when redox-active iron, oxidation-prone membrane substrates, and insufficient antioxidant defense converge¹⁻⁴. Cancer cells frequently operate close to this threshold because oncogenic transformation increases iron demand, membrane biogenesis, mitochondrial activity, and oxidative metabolism while simultaneously selecting for reinforced antioxidant defenses. Ferroptotic vulnerability therefore emerges from the balance between these pro-oxidant pressures and the capacity of tumor cells to suppress lipid peroxide accumulation. The principal determinants of this balance are summarized in Figure 1 and Table 1.

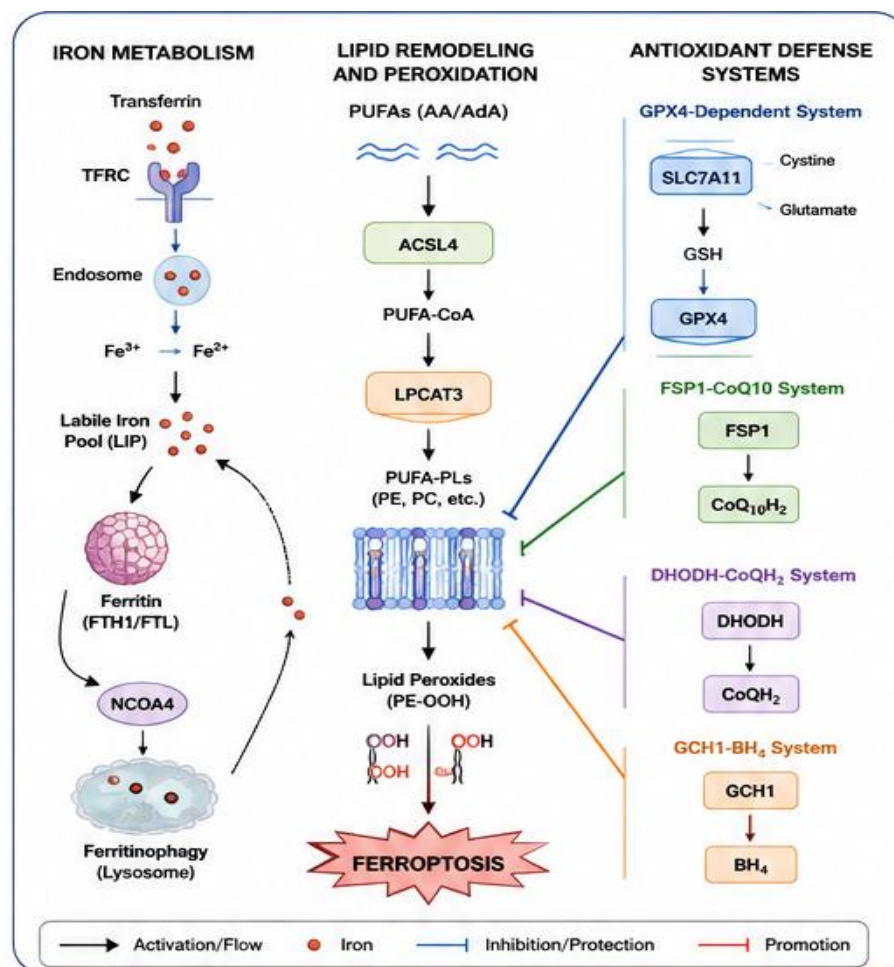
Defining Ferroptosis Beyond Oxidative Stress

General ROS accumulation is insufficient to define ferroptosis. Many cytotoxic insults increase ROS or deplete GSH without producing ferroptotic death. The defining biochemical lesion is the iron-dependent accumulation of oxidized membrane phospholipids to levels incompatible with membrane integrity²⁻⁴. Therefore, MDA, total ROS, Fe²⁺ accumulation, or decreased GPX4 should be interpreted as supportive observations unless combined with functional rescue by ferrostatin-1, liproxstatin-1, iron chelation, or genetic manipulation of core regulators.

This distinction is particularly important for natural products, many of which are redox-active and can simultaneously engage apoptosis, autophagy, necroptosis, or ferroptosis. A credible ferroptosis claim therefore requires orthogonal evidence. The evidence hierarchy proposed later in Figure 2 is designed to separate biochemical association from mechanism-specific causation.

Table 1. Core determinants of ferroptotic vulnerability in cancer.

Determinant	Key regulators	Principal function	Effect on ferroptosis	Cancer relevance
Iron uptake	TFRC, transferrin	Cellular iron acquisition	Promotes susceptibility	Often elevated in iron-demanding tumors
Labile iron pool	Fe ²⁺ , trafficking proteins	Redox-active iron supply	Promotes lipid radical formation	Potential targetable vulnerability
Iron storage	FTH1/FTL	Sequesters reactive iron	Restricts susceptibility	Buffers iron-mediated injury
Ferritinophagy	NCOA4	Ferritin degradation	Releases iron; promotes sensitivity	Potential vulnerability in resistant tumors
PUFA activation	ACSL4	AA/AdA → PUFA-CoA	Strongly increases sensitivity	Predictive/therapeutic candidate
PUFA incorporation	LPCAT3	PUFA incorporation into PLs	Expands oxidizable substrates	Associated with sensitivity
Lipid detoxification	GSH–GPX4	Reduces phospholipid hydroperoxides	Suppresses ferroptosis	Critical in resistant states

**Fig. 1 :** Molecular architecture of ferroptotic vulnerability in cancer.

Iron Dependency, Ferritinophagy, and the Labile Iron Pool

Iron supports respiration, DNA synthesis, and enzymatic catalysis but also creates oxidative risk. Transferrin receptor 1 (TFRC) drives iron uptake, while ferritin heavy and light chains sequester excess iron. NCOA4-mediated ferritinophagy mobilizes ferritin iron and expands the labile iron pool, increasing the availability of Fe²⁺ that promotes radical chemistry and lipid peroxide propagation^{14–16}. In cancer, altered TFRC, ferritin, ferroportin, and ferritinophagy can create an iron-addicted phenotype that is simultaneously growth-promoting and ferroptosis-permissive.

Importantly, total iron is less informative than the chemical and subcellular accessibility of redox-active iron. Tumor-selective strategies should therefore exploit abnormal iron trafficking or ferritin turnover rather than indiscriminately increase systemic iron, which risks normal-tissue toxicity.

Lipid Remodeling and Lethal Lipid Peroxidation

Ferroptosis also requires oxidation-prone membrane substrates. ACSL4 activates long-chain PUFAs such as arachidonic and adrenic acids, and LPCAT3 incorporates them into phospholipids. These PUFA-phospholipids are then susceptible to enzymatic and non-enzymatic peroxidation^{17–19}. ACSL4 loss markedly reduces ferroptosis sensitivity, establishing membrane composition as a determinant rather than a passive consequence of cell death.

Cancer cells can remodel this vulnerability. PUFA-enriched membranes favor ferroptosis, whereas monounsaturated fatty acid enrichment can reduce the pool of peroxidizable phospholipids. Thus, ferroptosis sensitivity is best viewed as an emergent property of iron availability, lipid architecture, and antioxidant capacity rather than a single-marker phenotype.

THE FERROPTOSIS DEFENSE NETWORK

Tumor-cell survival under ferroptotic stress is governed by a network of partially redundant antioxidant systems rather than a single protective pathway. The relative contribution of these defenses varies with tissue origin, oncogenic genotype, metabolic state, and microenvironmental conditions. This functional redundancy allows cancer cells to compensate for

disruption of individual pathways and represents a major mechanism of ferroptosis resistance and therapeutic failure.

SLC7A11–GSH–GPX4: the Canonical Axis

System Xc[−], principally composed of SLC7A11 and SLC3A2, imports cystine in exchange for glutamate. Intracellular cystine is reduced to cysteine, supporting glutathione (GSH) synthesis. GPX4 subsequently uses GSH to reduce phospholipid hydroperoxides and terminate lipid-peroxide chain reactions^{2–4, 20}. Consequently, inhibition of SLC7A11, cysteine/GSH depletion, or direct GPX4 inactivation can drive susceptible cancer cells beyond the ferroptotic threshold.

This axis is particularly relevant to natural-product pharmacology. Capsaicin, berberine, baicalin, tiliroside, erianin, and dihydroartemisinin have been reported to modulate components of the SLC7A11–GSH–GPX4 pathway and promote ferroptotic phenotypes in experimental cancer models^{21–29}. However, changes in SLC7A11, GSH, or GPX4 alone do not establish ferroptosis causality; mechanistic interpretation requires evidence of lipid peroxidation together with ferroptosis-specific rescue or genetic validation.

FSP1–CoQ10, DHODH–CoQH2, and GCH1–BH4

GPX4 is not the sole barrier to ferroptosis. FSP1 constitutes a major GPX4-independent defense by regenerating reduced coenzyme Q (CoQH2), a potent membrane-localized radical-trapping antioxidant⁶. FSP1 can therefore preserve membrane integrity when GPX4 activity is impaired and has emerged as an important determinant of ferroptosis resistance in cancer.

A spatially distinct defense operates within mitochondria, where DHODH maintains the reduced CoQ pool in the inner mitochondrial membrane and suppresses mitochondrial lipid peroxidation⁷. In parallel, GCH1-dependent tetrahydrobiopterin (BH4) metabolism protects membranes through radical-trapping activity and remodeling of lipid composition⁸. Together, these pathways establish compartment-specific layers of protection and explain why GPX4 abundance alone cannot reliably predict ferroptosis sensitivity. They also provide a mechanistic rationale for dual- or multi-pathway strategies designed to prevent compensatory antioxidant rescue.

NRF2 and Adaptive Redox Reprogramming

NRF2 functions as a broader transcriptional regulator of ferroptosis resistance by coordinating genes involved in GSH metabolism, iron sequestration, NADPH generation, detoxification, and cellular redox homeostasis^{30, 31}. Persistent NRF2 activation can therefore increase the ferroptotic threshold, facilitate metabolic adaptation, and contribute to resistance against anticancer therapy.

This pathway is particularly complex in natural-product research because phytochemicals can exert context-dependent and apparently opposing effects. NRF2 activation may protect normal tissues from oxidative injury, whereas suppression of NRF2-dependent defenses in tumor cells can increase ferroptotic vulnerability. Consequently, NRF2 modulation should not be classified as intrinsically pro- or anti-ferroptotic without considering cell type, exposure, metabolic context, and downstream functional evidence.

Collectively, SLC7A11–GSH–GPX4, FSP1–CoQ10, DHODH–CoQH2, GCH1–BH4, and NRF2 should be viewed as an interconnected ferroptosis-resistance network rather than isolated pathways. Their context-dependent redundancy creates a major obstacle to single-target therapy but simultaneously exposes opportunities for rational combination strategies that disable both canonical and compensatory defenses.

CANCER-SPECIFIC FERROPTOSIS VULNERABILITIES

Ferroptosis sensitivity is determined less by tumor identity than by the metabolic and redox state of individual cancer cells. Tumors characterized by increased iron uptake, elevated TFRC expression, expanded labile iron pools, PUFA-enriched membranes, or active ACSL4/LPCAT3-dependent lipid remodeling may exist close to the ferroptotic threshold^{3,4,31}. This vulnerability can become particularly pronounced in mesenchymal, dedifferentiated, drug-tolerant, and persister cell states, which frequently develop increased dependence on GPX4, FSP1, or related antioxidant defenses for survival. Conversely, NRF2 activation, efficient CoQ-dependent radical trapping, altered lipid metabolism, and microenvironment-driven metabolic adaptation can shift cells away from this threshold and promote ferroptosis resistance.

Importantly, ferroptotic vulnerability is dynamic rather than fixed. Therapeutic pressure can reprogram iron metabolism, membrane composition, and antioxidant dependencies, potentially creating ferroptosis-sensitive states in cancer populations that have escaped apoptosis or survived conventional treatment. Ferroptosis induction may therefore provide a strategy for targeting residual, therapy-resistant cell populations rather than merely reproducing the cytotoxic effects of existing treatments.

This state dependence has major implications for precision oncology. Tumor histology or expression of a single ferroptosis-associated protein is unlikely to provide sufficient predictive power. Instead, patient stratification should integrate functional and molecular determinants of ferroptotic liability, including labile iron availability, PUFA-phospholipid composition, ACSL4 activity, GPX4/FSP1 dependency, and NRF2-mediated redox adaptation. Ultimately, multidimensional vulnerability signatures coupled with functional ferroptosis testing may provide a more reliable framework for identifying tumors most likely to respond to ferroptosis-directed therapies.

NATURAL PRODUCTS AS CHEMICAL PROBES AND THERAPEUTIC SCAFFOLDS

Natural products occupy a distinctive position in ferroptosis research because their structural diversity encompasses redox-active phenols and quinones, electrophilic terpenoids, alkaloids, glycosides, and lipid-interacting scaffolds capable of perturbing multiple components of ferroptotic control. This chemical diversity makes them valuable both as potential therapeutic leads and as chemical probes for exposing latent ferroptosis dependencies. However, their frequent pleiotropy also complicates target attribution and increases the risk of interpreting nonspecific oxidative injury as mechanism-defined ferroptosis. Representative natural products with reported ferroptosis-modulating activity in cancer are summarized in Table 2.

Flavonoids illustrate this mechanistic diversity particularly well. Baicalin, quercetin, and tiliroside have been associated with modulation of ferritin turnover, NRF2 signaling, SLC7A11/GPX4 activity, and cellular iron homeostasis^{24–27, 32–35}. Quercetin is especially relevant to the iron arm of ferroptosis because lysosomal regulation and ferritinophagy

can increase the availability of redox-active iron. Quinones and related aromatic redox scaffolds may instead amplify oxidative pressure through redox cycling or disruption of antioxidant defenses, although such activity should not by itself be considered evidence of ferroptosis.

Terpenoids and sesquiterpenes provide another mechanistically important group. Andrographolide and artemisinin derivatives have been reported to integrate mitochondrial dysfunction, iron-dependent oxidative chemistry, and modulation of SLC7A11/GPX4-centered defenses^{36–42}. Dihydroartemisinin is particularly attractive because its iron-responsive endoperoxide chemistry provides a plausible chemical connection between abnormal tumor iron metabolism and ferroptotic vulnerability. Nevertheless, the relative contribution of ferroptosis versus other regulated death programs remains dependent on tumor context and exposure conditions.

Alkaloids further broaden this chemical space. Berberine and evodiamine have been linked to suppression of system Xc[−]/GSH/GPX4 signaling, increased lipid oxidative stress, and ferroptosis-associated antitumor responses^{22, 43, 44}. Erianin provides an especially instructive example of context-dependent polypharmacology: different cancer models have connected its activity to GPX4 degradation, NRF2 suppression, autophagy-associated ferroptosis, and regulation of JAK2/STAT3/SLC7A11 signaling^{45–49}. Rather than weakening its therapeutic relevance, these observations illustrate how a natural scaffold may converge on ferroptosis through distinct upstream mechanisms in different cellular states.

Importantly, the same compound can behave as an antioxidant, pro-oxidant, or ferroptosis sensitizer depending on concentration, iron availability, metabolism, subcellular localization, membrane partitioning, and the basal redox state of the target cell. Binary classification of phytochemicals as simply “antioxidants” or “pro-oxidants” is therefore mechanistically inadequate. Structure–activity relationships should instead integrate phenolic redox potential, quinone-forming capacity, electrophilicity, metal coordination, lipophilicity, membrane localization, metabolic activation, and engagement of defined ferroptosis-regulatory proteins.

A further distinction is required between ferroptosis association and ferroptosis causation. Increased ROS, MDA, intracellular Fe²⁺, GSH depletion, or reduced GPX4 expression provides supportive evidence but cannot independently establish ferroptotic death. Strong mechanistic claims should incorporate lipid-specific peroxidation measurements, rescue by ferrostatin-1 or liproxstatin-1, iron-chelator sensitivity, and, ideally, genetic manipulation of relevant regulators. Applying this evidence hierarchy is particularly important for natural products because many simultaneously activate apoptosis, autophagy, mitochondrial dysfunction, and other stress-response pathways.

FROM CHEMICAL STRUCTURE TO FERROPTOTIC ACTIVITY

A medicinal-chemistry view is essential for translation. Phenolic hydroxyl groups can support radical scavenging at low exposure yet undergo oxidation or redox cycling under different conditions. Quinone and naphthoquinone motifs can participate in electron transfer and electrophilic reactions, while lipophilic scaffolds may preferentially partition into membranes where ferroptotic lipid oxidation occurs. Metal-binding motifs may alter the labile iron pool, whereas electrophilic centers can modify cysteine- or selenocysteine-containing proteins.

For each candidate, three questions should be prioritized: is the proposed molecular target directly engaged; is the exposure required for ferroptosis pharmacologically achievable; and does structural modification preserve tumor selectivity while improving solubility, metabolic stability, and distribution? Natural-product optimization should therefore move beyond potency in cell culture toward target engagement, exposure-response relationships, and structure-informed selectivity.

HOW STRONG IS THE EVIDENCE FOR NATURAL-PRODUCT-INDUCED FERROPTOSIS?

The rapid expansion of ferroptosis research has produced uneven standards of mechanistic evidence. For natural products in particular, ROS accumulation or GPX4 suppression is frequently interpreted as ferroptosis despite the potential involvement of other death pathways. We therefore propose a five-tier evidence hierarchy (Fig. 2) that

Table 2. Representative natural products reported to modulate ferroptosis in cancer.

Compound	Chemical class	Cancer context	Reported target/pathway	Principal ferroptosis evidence	Refs.
Baicalin	Flavonoid	Bladder, oral, osteosarcoma, gastric	FTH1; NRF2/xCT/GPX4	Lipid ROS and iron/GSH alterations; inhibitor rescue in selected models	[24–26]
Quercetin	Flavonoid	Breast, gastric and other models	TFEB/ferritinophagy; NRF2/GPX4	Lipid peroxidation, lysosomal iron mobilization and rescue evidence	[32–34]
Tiliroside	Flavonoid glycoside	Pancreatic, HCC, TNBC	Calpain-2; TBK1; iron homeostasis	Iron dysregulation, lipid ROS and ferroptosis sensitization	[27,35]
Capsaicin	Phenolic amide	Glioblastoma, NSCLC	ACSL4/GPX4; SLC7A11/GPX4	Lipid redox imbalance with ferroptosis-compatible rescue	[21,23]
Berberine	Alkaloid	Nasopharyngeal carcinoma	System Xc ⁻ /GSH/GPX4	Suppression of antioxidant defenses and ferroptosis-associated antitumor activity	[22]
Andrographolide	Diterpenoid	Multiple myeloma, NSCLC	p38/NRF2/HO-1; mitochondrial pathways	Lipid oxidative stress and mitochondrial dysfunction	[36,37]
Dihydroartemisinin	Sesquiterpene endoperoxide	Glioma, HCC, lung, head and neck cancers	GPX4; PEBP1/15-LO; CHAC1; SLC7A11	Multiple rescue and mechanistic studies; translational evidence emerging	[38–42]
Evodiamine	Alkaloid	Bladder, prostate	GPX4; HIF1A-associated signaling	GPX4 suppression and ferroptosis-associated phenotypes	[43,44]
Erianin	Dibenzyl compound	CRC, bladder, HCC, renal/lung CSC models	GPX4 degradation; NRF2; JAK2/STAT3/SLC7A11	Mechanistic, pharmacological-rescue and in vivo evidence across several models	[45–49]

separates association from causation. The corresponding experimental requirements and strength of interpretation for each tier are summarized in Table 3.

Tier 1 comprises associative biomarkers, including increased ROS, MDA/4-HNE, Fe²⁺, or GSH depletion. Tier 2 adds pathway-compatible alterations such as SLC7A11/GPX4 suppression or ACSL4 activation. Tier 3 requires functional rescue by ferrostatin-1, lipoxstatin-1, and/or iron chelation. Tier 4 establishes mechanistic causality through genetic perturbation, direct target engagement, or pathway epistasis. Tier 5 provides the highest confidence through in vivo exposure–

response relationships, patient-derived models, biomarkers, or clinical evidence.

This hierarchy prevents mechanistic overstatement: a compound that merely increases ROS and decreases GPX4 is not equivalent to one whose lethality is rescued by ferroptosis inhibitors, genetically validated, and reproduced in patient-derived models at pharmacologically achievable exposure. Table 3 therefore provides a practical framework for grading ferroptosis claims and distinguishing supportive observations from mechanistic and translational evidence.

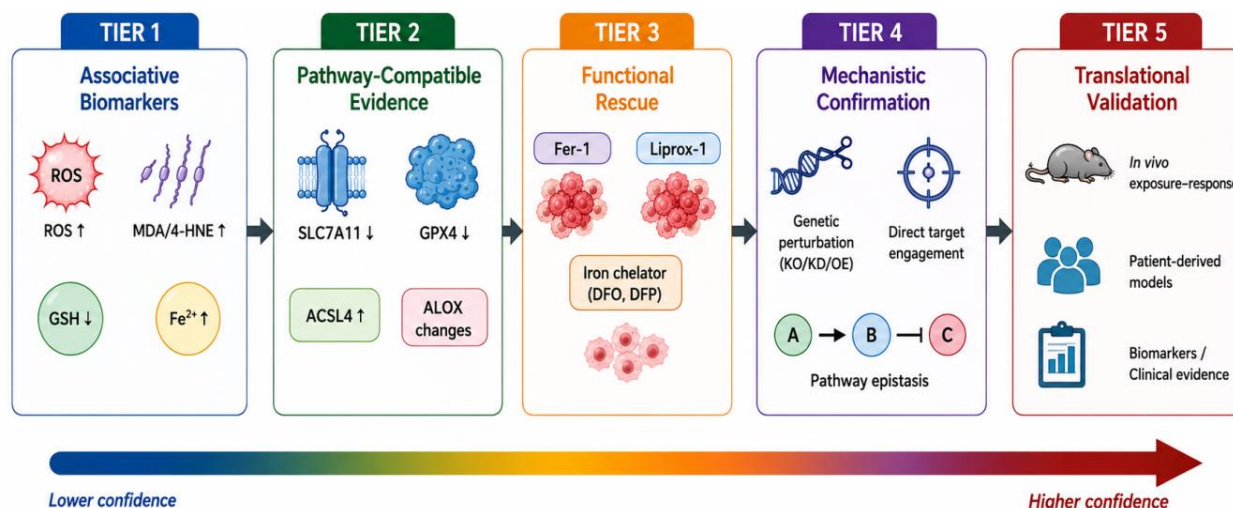


Fig. 2: Evidence hierarchy for natural-product-induced ferroptosis.

Table 3. Minimum evidence standards for ferroptosis claims.

Tier	Evidence level	Key criteria	Interpretation
1	Associative	ROS↑, MDA/4-HNE↑, GSH↓, Fe ²⁺ ↑	Suggestive only
2	Pathway-compatible	GPX4/SLC7A11↓, ACSL4/ALOX alterations	Compatible with ferroptosis
3	Functional rescue	Ferostatin-1/liproxstatin-1 or iron chelator rescues death	Strong pharmacological evidence
4	Mechanistic confirmation	Genetic perturbation, target engagement, epistasis	Causal pathway evidence
5	Translational validation	In vivo exposure-response, patient-derived models, biomarkers	Highest translational confidence

FERROPTOSIS AND THERAPEUTIC RESISTANCE

Therapy resistance can create a ferroptotic liability. Drug-tolerant and resistant cancer cells frequently rewire lipid metabolism and become increasingly dependent on GPX4, FSP1, NRF2, and related antioxidant defenses. Targeting these dependencies may therefore eliminate populations that escape conventional therapy. Natural products can exploit this vulnerability: baicalin has been linked to enhanced 5-fluorouracil activity, tiliroside to sorafenib sensitization, and ginkgetin to improved cisplatin response through ferroptosis-associated mechanisms ^{26, 35, 50}.

However, greater cytotoxicity is not evidence of resistance reversal. Robust combination studies must demonstrate quantitative synergy, ferroptosis-specific rescue, and mechanistic validation. The therapeutic opportunity is therefore

not simply to induce more oxidative damage, but to selectively eliminate ferroptosis-dependent resistant cancer states.

COMBINATION STRATEGIES AND THERAPEUTIC APPLICATIONS

Ferroptosis can intersect with chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Radiation generates oxidative stress and can increase lipid peroxidation, potentially lowering the ferroptotic threshold. Targeted therapies may create metabolic states that expose ferroptosis dependencies.

Immunotherapy is more complex: ferroptotic tumor cells may alter antigenicity and inflammatory signaling, but ferroptosis of activated immune cells can be detrimental. Therefore, the objective is not maximal systemic ferroptosis but spatially and temporally controlled ferroptosis in malignant cells.

Natural products are well suited to combination design when they target a complementary ferroptosis-defense node. Rational combinations might pair GPX4/SLC7A11 suppression with FSP1 or NRF2 inhibition, increase tumor iron accessibility while blocking lipid peroxide detoxification, or use a natural scaffold to sensitize tumors to standard therapy. Table 4 summarizes representative translational strategies.

TUMOR MICROENVIRONMENT AND THE FERROPTOSIS PARADOX

The tumor microenvironment can profoundly reshape ferroptosis. Hypoxia, acidity, nutrient availability, lipid transfer, stromal interactions, and immune-cell metabolism alter both pro-ferroptotic substrates and antioxidant capacity. Extracellular

lipids can change membrane composition, while cysteine availability and redox metabolites influence system Xc⁻ dependence. Macrophages, fibroblasts, and lymphocytes may either support or constrain ferroptosis in neighboring tumor cells.

A central paradox is that ferroptosis is not uniformly beneficial. Ferroptotic injury to antitumor immune cells can compromise immunity, whereas ferroptotic tumor cells can generate signals with context-dependent inflammatory or immunosuppressive effects. Precision targeting is therefore essential. Tumor-selective delivery, biomarker-guided patient selection, and careful assessment of immune consequences should be integrated into preclinical development.

Table 4. Rational combination strategies involving ferroptosis.

Strategy	Rationale	Natural-product example/context	Key validation need
Chemotherapy + ferroptosis sensitizer	Eliminate resistant populations	Baicalin + 5-FU; ginkgetin + cisplatin	Quantitative synergy + ferroptosis rescue
Targeted therapy + ferroptosis	Exploit adaptive redox dependence	Tiliroside + sorafenib	Target-specific sensitization in vivo
Radiotherapy + ferroptosis	Amplify lipid oxidative injury	Redox-active natural scaffolds	Normal-tissue protection and timing
Immunotherapy + ferroptosis	Potentially enhance tumor immunogenicity	DHA-associated immunogenic death	Immune-cell ferroptosis must be excluded
Dual defense inhibition	Prevent compensatory rescue	GPX4/SLC7A11 plus FSP1/NRF2 targeting	Tumor selectivity and toxicity

DELIVERY SYSTEMS AND PRECISION FORMULATION

Many natural products suffer from poor aqueous solubility, rapid metabolism, low oral bioavailability, and broad tissue distribution. Nanoparticles, liposomes, polymeric carriers, prodrugs, and tumor-responsive delivery systems can increase local exposure and reduce systemic toxicity. For ferroptosis, delivery systems can be designed to co-deliver a natural-product scaffold with iron-modulating agents, GPX4/FSP1 inhibitors, or conventional anticancer drugs.

However, nanodelivery should not be treated as a universal solution. Carrier composition can itself alter oxidative stress, iron chemistry, or immune responses. Pharmacokinetic studies must therefore separate effects of the active compound from the delivery platform and establish whether intratumoral concentrations are sufficient to

reproduce the ferroptosis mechanism observed in vitro.

COMPUTATIONAL AND AI-ASSISTED DISCOVERY

Network pharmacology, molecular docking, molecular dynamics, QSAR, transcriptomic signatures, and machine learning can prioritize natural products and predict ferroptosis-related targets. These tools are particularly useful for multi-target compounds and for integrating chemical structure with tumor-specific dependencies. Candidate targets include GPX4, SLC7A11, FSP1, DHODH, ACSL4, NCOA4, NRF2, and regulators of iron or lipid metabolism.

Prediction, however, is not validation. Docking scores should not be interpreted as proof of binding, and network overlap should not be equated with mechanism. Computational claims should be followed by biophysical or biochemical target engagement, perturbation studies, rescue

experiments, and exposure-aware in vivo testing. The most productive role of AI is therefore hypothesis prioritization and chemical optimization rather than replacement of mechanistic pharmacology.

BIOMARKERS FOR FERROPTOSIS-GUIDED CANCER THERAPY

Candidate biomarkers include GPX4, SLC7A11, ACSL4, FSP1, TFRC, ferritin, NCOA4, 4-HNE, oxidized phospholipids, labile iron, and ferroptosis-related transcriptomic signatures. No single marker is sufficient because ferroptosis is a network state. A clinically useful biomarker panel should capture substrate availability, iron accessibility, antioxidant defense, and evidence of lipid oxidation.

Dynamic biomarkers may be particularly valuable. Changes in oxidized phospholipids or ferroptosis-defense proteins before and after therapy could indicate target engagement, while baseline multi-omic signatures may identify susceptible tumors. Standardization of sample handling, assay platforms, and thresholds is necessary before ferroptosis biomarkers can guide clinical decisions.

TRANSLATIONAL BARRIERS

The largest gap between promising cell-culture studies and clinical therapy is pharmacological realism. Many natural products induce ferroptosis only at micromolar concentrations that may not be achievable in human tumors. Poor solubility, extensive metabolism, protein binding, and rapid clearance can further reduce active exposure. Studies should therefore report free drug concentrations, relevant metabolites, pharmacokinetics, and tumor exposure whenever possible.

Selectivity is equally important. Ferroptosis contributes to tissue injury in several non-malignant contexts, so systemic induction could damage vulnerable organs. Tumor-selective delivery and dependency-based patient selection are preferable to indiscriminate pro-oxidant therapy. Additional barriers include tumor heterogeneity, compensatory antioxidant pathways, inconsistent ferroptosis definitions, limited patient-derived validation, and lack of standardized biomarkers. These issues are summarized in Table 5.

Table 5. Major barriers to clinical translation and proposed solutions.

Barrier	Why it matters	Recommended solution
Poor bioavailability	In vitro concentrations may be unachievable	PK-guided optimization, prodrugs, formulation
Pleiotropy / off-target oxidation	Mechanism may be misassigned	Direct target engagement and rescue studies
Tumor heterogeneity	Ferroptosis dependency varies	Functional biomarkers and patient stratification
Compensatory defenses	Single-node inhibition may fail	Combination/dual-pathway strategies
Normal-tissue ferroptosis	Systemic toxicity risk	Tumor-selective delivery and therapeutic windows
Weak biomarkers	Difficult to prove target engagement clinically	Standardized lipid oxidation and defense panels
Model limitations	Cell culture may not reflect tumors	Organoids, PDX, immune-competent and patient-derived models

FUTURE PERSPECTIVES

The next phase of ferroptosis research should be defined by precision rather than by the number of compounds reported to increase lipid ROS. High-priority directions include direct inhibitors of context-specific defense systems such as FSP1, dual-pathway strategies that prevent compensatory rescue, tumor-selective delivery, patient-derived functional testing, and biomarker-

guided stratification. Natural products can contribute both as drug leads and as mechanistic probes, but their development requires modern medicinal chemistry, exposure-aware pharmacology, and rigorous target validation.

A practical translational sequence is shown in Figure 3: scaffold identification should be followed by target mapping, ferroptosis-specific rescue, genetic or biochemical validation, in vivo

exposure-response testing, patient-derived confirmation, and biomarker-guided clinical development. This sequence can reduce false-positive mechanistic claims and prioritize candidates with genuine therapeutic potential.

CONCLUSION

Ferroptosis exposes a fundamental vulnerability in cancer: the dependence of rapidly adapting tumor cells on systems that restrain iron-driven phospholipid oxidation. Natural products provide chemically diverse scaffolds capable of perturbing this balance, but chemical diversity alone does not guarantee translational value. The field now requires stronger discrimination between oxidative stress and ferroptotic causation, between pathway

association and direct target engagement, and between in vitro potency and achievable tumor exposure.

An evidence-centered approach—integrating pharmacological rescue, mechanistic validation, in vivo relevance, pharmacokinetics, biomarkers, and tumor selectivity—can transform natural-product ferroptosis research from a catalogue of promising observations into a disciplined drug-discovery strategy. The most credible future therapies will likely combine tumor-specific ferroptosis dependencies with optimized natural-product scaffolds, rational combination partners, and precision delivery. Such integration offers a realistic path toward translating ferroptosis biology into clinically actionable oncology.

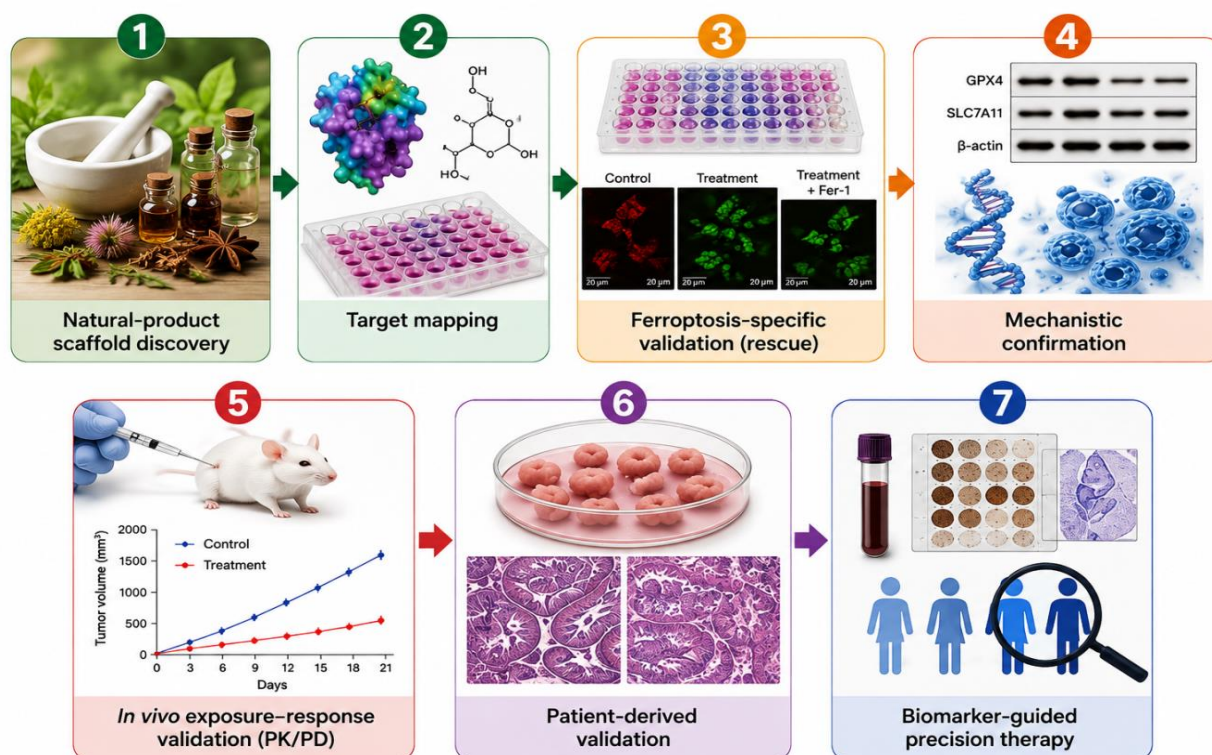


Fig. 3: Translational roadmap from natural-product scaffold discovery to biomarker-guided precision ferroptosis therapy.

Author Contributions

Rema Amara Abdalla Ballg: Writing – original draft, literature review, investigation, data curation, and manuscript preparation. Salah Neghmouche Nacer: Conceptualization, methodology, supervision, validation, critical review, writing – review & editing, and final approval of the manuscript.

Conflict of interest

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