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Beyond antioxidants: Context-selective reprogramming of ferroptosis by natural polyphenols in chronic disease intervention

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ABSTRACT: Chronic diseases, with a focus here on non-cancerous conditions including cardiovascular, metabolic, neurological, and musculoskeletal disorders, as well as other relevant conditions, share pathological characteristics, such as persistent oxidative stress, reduced metabolic flexibility, and progressive tissue degeneration. Ferroptosis, an iron-dependent cell death triggered by lipid peroxidation, is now recognized as a critical factor in these pathological processes. Natural polyphenols, derived from plant sources, exhibit antioxidant and anti-inflammatory properties and demonstrate potential in regulating ferroptosis-related signaling pathways. This review systematically explores the molecular crosstalk between ferroptosis and polyphenols across major chronic diseases, highlighting their therapeutic and translational potential. Specifically, it elucidates the regulatory role of polyphenols in iron homeostasis, the inhibition of lipid peroxidation, and the restoration of redox balance, thus uncovering novel opportunities for dietary or pharmacological interventions targeting ferroptosis. Elucidating this interaction underscores the therapeutic potential of natural polyphenols as an innovative strategy for the prevention and treatment of chronic diseases.

Keywords: Ferroptosis; Polyphenols; Chronic disease; Iron homeostasis; Lipid peroxidation

1. Introduction

The growing burden of chronic diseases (here referring specifically to non-cancerous conditions such as cardiovascular, metabolic, neurological, and musculoskeletal disorders) underscores the need for therapeutic strategies targeting shared molecular vulnerabilities [1]. While chronic conditions such as cardiovascular disease, neurodegenerative disorders, metabolic syndromes, and fibrotic diseases exhibit distinct clinical manifestations, they converge mechanistically through disrupted cellular homeostasis, redox imbalance, and progressive tissue injury [2]. Among the emerging forms of regulated cell death implicated in these shared pathological processes, the discovery of ferroptosis has established a novel paradigm fundamentally different from apoptosis and necrosis. This unique form of cellular demise is driven by an iron-dependent process that leads to excessive lipid peroxidation [3], and dysregulated ferroptosis is now recognized as a contributing pathogenic mechanism in many of these conditions.

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Concurrently, the biological roles of natural polyphenols are being re-evaluated. Historically regarded primarily as antioxidants, these structurally diverse plant-derived metabolites are now increasingly recognized as modulators of cellular signaling pathways [4], with effects that are inherently context-dependent and often evident at physiologically relevant concentrations [5]. Emerging evidence demonstrates that polyphenols directly modulate key ferroptosis regulators, including iron homeostasis, lipid peroxidation, and endogenous antioxidant defenses, through mechanisms that cannot be adequately explained by direct radical scavenging alone.

However, an integrated, mechanistically coherent framework that links the chemical diversity of polyphenols to their context-specific modulation of the ferroptosis network across diseases is still lacking. Existing reviews have largely focused on ferroptosis in isolated disease settings, such as renal disorders [6], diabetic cardiomyopathy [7], or on parallel therapeutic approaches, such as mesenchymal stem cell–derived extracellular vesicles [8]. By contrast, a comprehensive synthesis centered on natural polyphenols across chronic diseases, in which ferroptosis may exert distinct and context-dependent effects in different cell populations, remains lacking.

Accordingly, this review aims to systematically analyze the molecular crosstalk between natural polyphenols and ferroptosis across major chronic disease categories, integrating both pro- and anti-ferroptotic actions with their underlying structural determinants. Through this framework, we seek to clarify how context-dependent and cell type–selective modulation of ferroptosis underpins the therapeutic potential of polyphenols beyond a simplistic antioxidant paradigm.

2. The core machinery of ferroptosis

The term ferroptosis was introduced in 2012 by Stockwell [3], who discovered that two small-molecule compounds specifically triggered rat sarcoma (RAS)-mutant tumor cell death via a non-apoptotic mechanism [9]. Currently, ferroptosis is recognized as a distinct type of cell death characterized by iron dependence and lipid peroxidation [10]. Initially investigated as an anticancer strategy, this process aimed to trigger ferroptosis in malignant cells. However, the paradigm has considerably broadened. In chronic diseases, dysregulated ferroptosis is now known to contribute to tissue injury and disease progression [11]. Nowadays, growing evidence links ferroptosis to the development of neurodegenerative, cardiovascular, metabolic and fibrotic diseases [12].

At the mechanistic level, ferroptosis does not arise from a single linear cascade but instead reflects the collapse of an integrated regulatory network centered on iron metabolism, lipid remodeling, and redox homeostasis. Its susceptibility and execution are determined by a multilayered regulatory network composed of enzymes, transporters, and signaling molecules distributed across multiple subcellular compartments and membranes, including mitochondria, lysosomes, endoplasmic reticulum (ER), and plasma membrane [13]. This spatial and regulatory complexity underlies the pronounced context dependence of ferroptosis across different cell types and pathological conditions, providing a mechanistic basis for its bidirectional modulation by endogenous and exogenous factors. Consequently, a precise delineation of the core molecular

machinery governing ferroptosis within specific biological settings is essential for understanding how this process contributes to the development and progression of chronic diseases.

2.1 Iron homeostasis and ferroptosis

Cellular susceptibility to ferroptosis depends on iron homeostasis imbalance, which encompasses iron uptake, storage, and export processes [14]. Iron plays a key role in cellular metabolism and redox reactions, so even small changes in its levels can cause oxidative damage. Pharmacological agents such as erastin can induce ferroptosis, whereas the iron chelator deferoxamine (DFO) effectively inhibits it, highlighting the stringent dependence of ferroptosis on iron availability.

Ferritin safely stores Fe^{3+} and prevents deleterious redox cycling under normal physiological conditions. Ferroportin (FPN1) exports excessive Fe^{2+}, preventing its intracellular accumulation [15]. When these protective mechanisms fail, labile Fe^{2+} catalyzes the classic Fenton reaction, producing highly reactive hydroxyl radicals that initiate lipid peroxidation [16]:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^- \quad (1)$$

The Fenton reaction underscores the critical need to tightly regulate iron levels. Consequently, iron homeostasis is maintained at both the systemic and cellular levels through coordinated mechanisms. Systemically, dietary iron intake [17] entails the reduction of Fe^{3+} by duodenal cytochrome B (DcytB) and the subsequent absorption [18] of Fe^{2+} through the divalent metal transporter 1 (DMT1). At the same time, heme oxygenase-1 (HO-1) in macrophages recycles iron from old red blood cells [19]. At the cellular level, the transferrin receptor (TfR1/TFRC) governs iron uptake, ferritin (FTH1/FTL) manages storage, and FPN1 controls export. These pathways work together to maintain a tightly controlled labile iron pool (LIP) [20], thereby regulating key metabolic processes and mitigating oxidative stress. Systemic and cellular regulation of iron homeostasis is illustrated in **Figure 1**.

Beyond transcriptional and transporter-based control, intracellular iron availability is dynamically regulated by lysosome-dependent ferritinophagy. This process, mediated by nuclear receptor coactivator 4 (NCOA4), promotes the autophagic degradation of ferritin and releases redox-active Fe^{2+} into the cytosolic LIP [21]. Pathological conditions such as inflammation, mitochondrial dysfunction, or excessive NCOA4 activity can amplify ferritinophagy, leading to iron overload and heightened ferroptotic sensitivity [22]. Notably, lysosome-derived iron appears to exert a disproportionate influence on ferroptosis, as reflected by the preferential localization of ferroptosis inhibitors, including liproxstatin-1, at lysosomal membranes [23].

The ensuing elevation in reactive oxygen species (ROS) accelerates lipid peroxidation and initiates ferroptotic signaling cascades [24-26]. Genetic and pathological evidence supports this framework: the deletion of *Fth1* [27] exacerbates cardiomyopathic injury through ferroptosis activation, while aberrant HO-1 overexpression promotes pathological iron accumulation and oxidative stress. Collectively, these findings indicate that impaired iron sequestration and dysregulated ferritinophagy converge on the common outcome of expanding the labile iron pool beyond its buffering capacity, thereby establishing iron overload as a principal upstream determinant of susceptibility to ferroptosis [28].

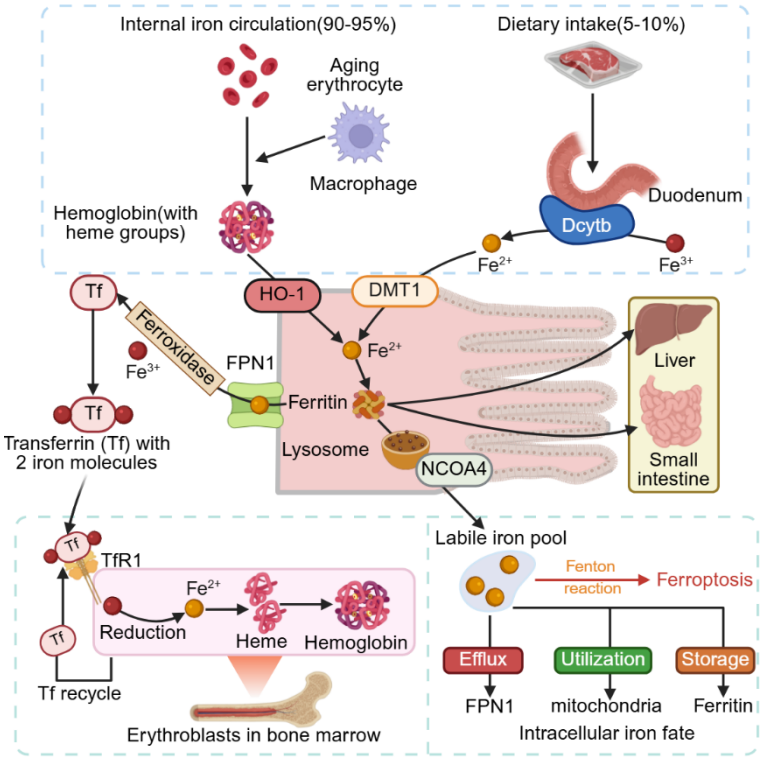

Figure 1. Systemic and cellular regulation of iron homeostasis and its connection to ferroptosis. Systemic iron homeostasis is primarily maintained through two mechanisms: dietary absorption and recycling of red blood cells. Dcytb lowers the amount of dietary Fe^{3+} in the duodenum, and Fe^{2+} is transported into enterocytes by DMT1. Alternatively, splenic and hepatic macrophages phagocytose senescent erythrocytes, during the degradation of heme by HO-1, thereby releasing Fe^{2+}. In both pathways, intracellular Fe^{2+} is either kept in ferritin or exported into the bloodstream through FPN1. When Fe^{2+} is exported, it is oxidized to Fe^{3+}, binds to Tf, and is delivered to the bone marrow to make hemoglobin in new red blood cells. Under physiological conditions, the labile iron pool supports mitochondrial utilization, storage, and efflux, whereas its pathological expansion catalyzes Fenton reactions that ultimately trigger ferroptosis.

2.2 Lipid metabolism and ferroptosis

The metabolism of fatty acids is mechanistically central to ferroptosis. Enzymes like acyl-CoA synthetase long-chain family member 4 (ACSL4) are necessary for the esterification of polyunsaturated fatty acids (PUFAs) and their subsequent incorporation into membrane phospholipids [29]. This remodeling process occurs predominantly at ER, which serves as a major intracellular platform for PUFA activation and phospholipid assembly [30]. The incorporation of PUFAs, especially those with multiple double bonds, into the phospholipid bilayer creates a pool of oxidizable substrates highly susceptible to lipid peroxidation [31]. The bis-allylic hydrogen atoms in PUFAs are particularly vulnerable to abstraction, and their peroxidation is a key step in initiating ferroptosis. By contrast, saturated fatty acids (SFAs) are largely resistant to peroxidation, while monounsaturated fatty acids (MUFAs) compete with PUFAs for membrane incorporation, thereby attenuating ferroptotic sensitivity. Thus, PUFAs remodeled by ACSL4 serve as the primary substrates for this process. This lipid peroxidation cascade unfolds through three distinct stages: initiation, propagation, and termination (**Figure 2**).

Initiation: This is the rate-limiting first step that starts the entire lipid peroxidation cascade. It occurs when a sufficient ROS, most notably the hydroxyl radical (·OH), attacks a stable PUFA on a phospholipid molecule, PUFA-containing phospholipid (PUFA-PL). The hydroxyl radical abstracts a hydrogen atom from

a susceptible carbon (typically a bis-allylic position) on the lipid chain. This initial abstraction event is critical as it overcomes the stability of the non-radical lipid, resulting in the formation of the first lipid alkyl radical (PL·). This highly unstable, carbon-centered PL· then enters the propagation phase. The initiation reaction is represented as:

$$\mathrm{PUFA-PL} + \mathrm{HO}\cdot \rightarrow \mathrm{PL}\cdot + \mathrm{H_2O} \quad (2)$$

Propagation: This phase constitutes the core, self-perpetuating cycle of lipid peroxidation, responsible for the rapid amplification of oxidative damage from a single initiating event. This destructive cycle is driven by a two-step chain reaction. It begins with the extremely rapid, diffusion-limited reaction between a PL· and molecular oxygen (O_2). This addition converts the initial carbon-centered radical into a highly reactive, oxygen-centered lipid peroxyl radical (PLOO·). Subsequently, this newly formed peroxyl radical drives the rate-limiting, chain-propagating step by attacking an adjacent, stable PUFA-PL. This crucial step has a dual outcome: it generates a lipid hydroperoxide (PUFA-PL-OOH), a primary and relatively stable product of lipid peroxidation, while simultaneously regenerating a new PL·. The regeneration of this PL· is the key to the amplification cascade, as it is immediately available to react with another molecule of oxygen, thereby perpetuating the destructive cycle and propagating the oxidative damage to numerous neighboring lipid molecules. This two-step propagation cycle is represented by the following formula:

$$\mathrm{PL}\cdot + \mathrm{O_2} \rightarrow \mathrm{PLOO}\cdot \quad (3)$$

$$\mathrm{PLOO}\cdot + \mathrm{PUFA-PL} \rightarrow \mathrm{PL}\cdot + \mathrm{PUFA-PL-OOH} \quad (4)$$

Termination: This phase concludes the chain reaction by consuming free radicals, thus stopping the propagation of oxidative damage. Termination occurs when two radical species collide and combine to form stable, non-radical products. The pathway shown describes a primary termination mechanism, often referred to as the Russell mechanism, where two lipid peroxyl radicals interact. This complex interaction leads to a disproportionation reaction, extinguishing both radicals. The process results in the formation of a lipid ketone (PL=O) and a lipid alcohol (PLOH), both of which are stable non-radical molecules. This reaction also characteristically produces O_2, often in its excited singlet state. As no new free radicals are generated, the chain reaction is effectively broken. This termination pathway is represented by the following formula:

$$\mathrm{PLOO}\cdot + \mathrm{PLOO}\cdot \rightarrow \mathrm{PL=O} + \mathrm{PLOH} + \mathrm{O_2} \quad (5)$$

In addition to the non-enzymatic initiation by ROS, as shown in the initiation stage, enzymatic pathways are critical drivers of this process. In parallel to ACSL4-mediated esterification, enzymes such as arachidonate 15-lipoxygenase (ALOX15) can further catalyze the direct oxidation of PUFAs to generate PUFA-PL-OOH [32]. The ER and mitochondria function as complementary hubs in lipid peroxidation: the ER serves as the primary platform for ACSL4-dependent PUFA esterification and lipoxygenase-driven oxidation, whereas mitochondria may contribute indirectly by serving as a source of ROS that can fuel Fe^{2+}-dependent autoxidative reactions [33].

The primary effectors of ferroptosis are the PUFA-PL-OOH and the PLOO· generated during propagation [34]. Their accumulation destabilizes membrane integrity by altering fluidity and permeability.

These hydroperoxides can also directly damage macromolecules, such as proteins embedded in phospholipid bilayers, disrupting essential cellular functions. Furthermore, their degradation by-products, such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) [35], are themselves highly reactive electrophiles that can further damage vital proteins and nucleic acids, exacerbating oxidative stress. Collectively, the progressive buildup of lipid peroxidation products culminates in mitochondrial dysfunction, bioenergetic failure, and redox imbalance, thereby amplifying oxidative stress and reinforcing ferroptosis progression [36].

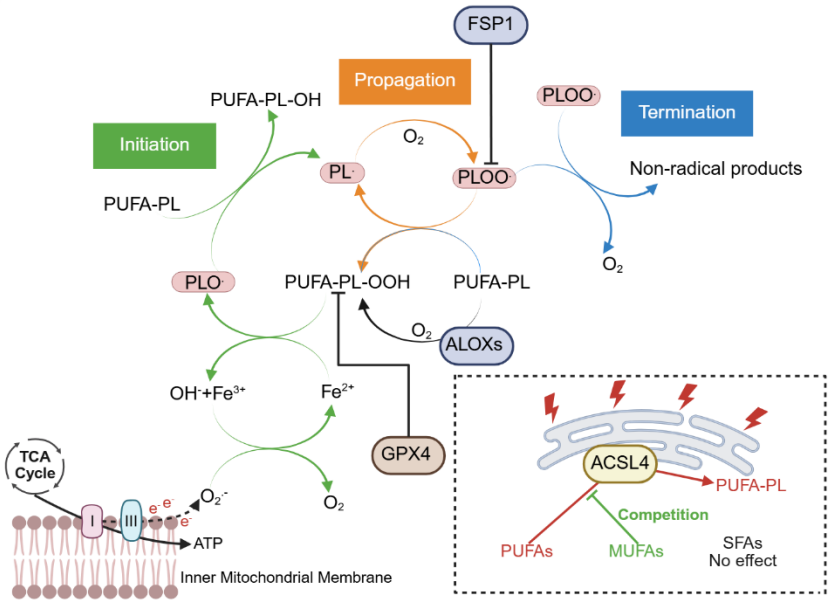

Figure 2. Lipid peroxidation pathway in ferroptosis. This figure illustrates the key steps of lipid peroxidation leading to ferroptosis. The initiation stage (green) starts when hydroxyl radicals (·OH), which are generated by Fenton reactions with the involvement of the labile iron pool, attack the bis-allylic sites of membrane phospholipids containing polyunsaturated fatty acids (PUFA-PLs) to produce a phospholipid radical (PL·). This radical then goes through the propagation cycle (orange), where it first reacts with O_2 to generate a phospholipid peroxyl radical (PLOO·). This highly reactive PLOO· then abstracts a hydrogen atom from a nearby PUFA-PL, making a phospholipid hydroperoxide (PL-OOH) and a new PL· radical to keep the chain reaction going. The accumulation of PL-OOH, in conjunction with iron capable of altering its oxidation state, instigates membrane instability, precipitates organelle dysfunction, and ultimately culminates in ferroptosis. The chain is broken during the termination stage (blue), where two PLOO· interact via the Russell mechanism. This disproportionation reaction consumes the radicals and forms stable, non-radical products, effectively terminating the propagation of oxidative damage. The inset (bottom right) illustrates the substrate activation process at the endoplasmic reticulum (ER). The enzyme ACSL4 catalyzes the incorporation of polyunsaturated fatty acids (PUFAs) into membrane phospholipids (PUFA-PL), creating the necessary substrates for lipid peroxidation. This process is competitively inhibited by monounsaturated fatty acids (MUFAs), which limit PUFA incorporation, whereas saturated fatty acids (SFAs) have no effect on this pathway.

2.3 Antioxidant defense systems

Ferroptosis results from the failure of cellular antioxidant defense systems when confronted with excessive iron-induced oxidative stress [37]. This defense is coordinated by multiple, parallel, and partially independent systems. The canonical system Xc^--GSH-GPX4 signal pathway represents the primary line of defense, with glutathione peroxidase 4 (GPX4) [38] as its central enzymatic effector. Using glutathione (GSH) as a cofactor, GPX4 detoxifies phospholipid hydroperoxides, thereby directly blocking the execution of ferroptosis [39]. As a result, the depletion of GSH by erastin or the direct inhibition of GPX4 activity by RAS-selective-lethal-3 (RSL3) promotes the accumulation of lipid peroxides, culminating in ferroptotic cell death [40].

Ferroptosis suppressor protein 1 (FSP1) functions primarily as a NAD(P)H-dependent oxidoreductase that regenerates coenzyme Q_{10} (CoQ10) rather than directly reducing lipid hydroperoxides [41]. The GSH-independent FSP1-CoQ10-NAD(P)H axis constitutes a parallel, major defense system. It continuously regenerates the reduced form of coenzyme Q_{10} ($CoQ_{10}H_2$, ubiquinol) from its oxidized form (CoQ10, ubiquinone) [42]. The reduced CoQ_{10} then acts as a potent radical-trapping antioxidant that arrests the propagation phase of lipid peroxidation by scavenging PLOO·. Recent studies show that GPX4 and FSP1 systems are largely non-redundant, meaning that they offer two separate layers of protection. These systems cooperate to suppress ferroptosis by neutralizing distinct oxidative threats [43].

Nuclear factor erythroid 2-related factor 2 (NRF2) functions as the master regulator of this entire antioxidant response. As a transcription factor, it typically promotes the expression of protective genes involved in iron homeostasis (like FTH1 and FPN1) and antioxidant defense (like GPX4) [44]. However, the role of NRF2 is context-dependent and can be dualistic. Under conditions of compromised iron storage capacity (e.g., insufficient ferritin), NRF2 activation may paradoxically exacerbate ferroptotic sensitivity by upregulating HO-1, leading to increased free Fe^{2+} release from heme degradation [45].

Consistent with this principle, antioxidant activity per se does not necessarily equate to ferroptosis inhibition. The biological outcome depends on the specific redox reaction pathways engaged, their interaction with iron metabolism, and their influence on lipid peroxidation dynamics. Thus, ferroptosis-relevant antioxidant effects are mechanistically separable from generalized antioxidant capacity. Natural polyphenols exemplify this context-dependent behavior. Owing to their chemically diverse redox mechanisms and iron-interacting properties, polyphenols may either suppress or facilitate lipid peroxidation depending on molecular structure and cellular microenvironment. This inherent bidirectional potential underscores that polyphenols cannot be simplistically categorized as ferroptosis inhibitors or inducers. Therefore, evaluating their net effect necessitates a structure- and mechanism-oriented framework in the future.

3. Natural polyphenols: bioactive signaling modulators

Natural polyphenols are a structurally diverse group of secondary metabolites synthesized by plants in response to environmental stressors such as UV radiation, herbivory, and pathogenic invasion [46, 47]. Abundant in the human diet, they are found in fruits, vegetables, tea, and red wine [48]. Their consumption has long been associated with a reduced risk of chronic diseases. This review therefore reframes polyphenols not as passive dietary antioxidants, but as bioactive signaling modulators capable of reshaping the ferroptosis regulatory network. This framework explores their capacity to coordinate iron chelation, counteract lipid peroxidation, and activate endogenous antioxidant defenses.

3.1 Classification and chemical structures

Natural polyphenols constitute a vast library of secondary metabolites, unified by the presence of hydroxylated aromatic rings but distinguished by their heterogeneous carbon skeletons [49]. As outlined in

Table 1, these compounds are systematically classified into three primary categories based on their structural features: flavonoids, non-flavonoids, and a diverse group of other polyphenols [50].

Flavonoids share a characteristic C6-C3-C6 backbone comprising two aromatic rings linked by a three-carbon heterocyclic ring [51]. Variations in the saturation of the C-ring and the substitution patterns of the B-ring divide this category into six major subclasses: flavonols (e.g., quercetin), flavones (e.g., baicalein), isoflavones (e.g., puerarin), flavanones (e.g., naringenin), anthocyanidins (e.g., cyanidin), and flavan-3-ols (e.g., epigallocatechin-3-gallate, EGCG). Non-flavonoids encompass a broader range of skeletal structures. This category includes phenolic acids, divided into hydroxybenzoic acids (C6-C1) and hydroxycinnamic acids (C6-C3); stilbenes with a C6-C2-C6 skeleton (e.g., resveratrol); and lignans formed by oxidative dimerization of phenylpropanoids. Additionally, it includes coumarins and tannins, which are high-molecular-weight polymers formed by the esterification of phenolic units. Finally, representative members of other polyphenols, such as curcumin and salvianolic acid B, exhibit unique structural configurations essential for their biological activity.

Structure-activity relationship (SAR) analyses further underscore the positional specificity of these hydroxyl groups. Studies on the anti-inflammatory activity of flavonoids indicate that hydroxyl moieties at the C-5 and C-4′ positions enhance biological activity, whereas substitutions at the C-6, C-7, C-8, and C-3′ positions may attenuate efficacy [52].

However, biological potency is not a simple function of hydroxyl group count. A striking illustration of this principle is the metabolic transformation of quercetin: although its metabolite, quercetin Diels-Alder anti-dimer (QDAD), containing seven phenolic hydroxyls compared to quercetin with five phenolic hydroxyls, exhibits superior activity. This discrepancy stems from an ortho-quinone moiety within the QDAD structure, which resists further oxidation and thus diminishes its antioxidant capacity despite the higher hydroxyl count [53]. This case exemplifies that anti-ferroptotic activity is governed by specific structural configurations rather than hydroxyl abundance alone [54]. These distinct configurations, in turn, dictate the unique redox chemical behaviors analyzed in the following section.

Table 1. Structural Classification and sources of polyphenols with ferroptosis-regulating activity

Main class	Subclass	Carbon skeleton	Compounds (CAS No.)	Representative ferroptosis-regulatory pathways	Common natural sources
Flavonoids	**Flavonols**	3-Hydroxyflavone (C_6-C_3-C_6)	Quercetin (117-39-5) Kaempferol (520-18-3) Myricetin (529-44-2) Icariin (489-32-7)	↑NRF2/HO-1, ↑GPX4/SLC7A11, ↓ACSL4, Fe^{2+} chelation	Onions, kale, berries, tea
	Flavones	2-Phenyl-1-benzopyran-4-one	Baicalein (491-67-8) Baicalin (21967-41-9) Luteolin (491-70-3) Wogonoside (51059-44-0) Diosmin (520-27-4)	↑NRF2/HO-1, ↑GPX4/SLC7A11, ↓ACSL4, Lipid peroxidation inhibition	*Scutellaria baicalensis*, celery, chamomile
	Isoflavones	3-Phenylchromen-4-one	Puerarin (3681-99-0) Calycosin (20575-57-9)	↑NRF2/GPX4/SLC7A11, ↑GSH, ↓ACSL4, lipid ROS reduction	Soybean, legume
	Flavanones	Saturated 2,3-position (C_6-C_3-C_6)	Hesperetin (520-33-2) Naringenin (480-41-1) Liquiritin (551-15-5) Liquiritigenin (578-86-9)	Lipid metabolic reprogramming, ferroptosis resistance via PPARα/SCD1/FADS2	Citrus fruits

	Anthocyanidins	Flavylium cation	Cyanidin (528-58-5) Delphinidin (528-53-0)	↑GPX4/FSP1-mediated lipid peroxide detoxification	Berries, red grape skin
	Flavan-3-ols	2-Phenyl-3,4-dihydro-2H-chromene-3-ol	Catechin (154-23-4) EGCG (989-51-5)	↑GPX4, Fe^{2+} chelation, mitochondrial ROS suppression	Green tea, grapes, cocoa
Non-flavonoids	**Hydroxybenzoic acids**	C_6-C_1 phenolic acid	Gallic acid (149-91-7) Protocatechuic acid (99-50-3)	↑GPX4/NRF2 signaling, ↓Fe^{2+} accumulation, mitochondrial ROS reduction	Tea, berries, gallnuts
	Hydroxycinnamic acids	C_6-C_3 phenylpropanoid	Caffeic acid (331-39-5) Ferulic acid (1135-24-6) p-Coumaric acid (501-98-4) Chlorogenic acid (327-97-9) Caffeic acid phenethyl ester (104594-70-9)	↑NRF2/HO-1/GPX4/SLC7A11, ↓ACSL4, Mitochondrial protection	Coffee, fruits, grains
	Lignans	C_6-C_3-C_3-C_6 dimer	Schisandrin A (61281-38-7) Schisandrin B (61281-37-6)	↑NRF2/GPX4, ↓Lipid peroxidation Mitochondrial quality control	*Schisandra chinensis*, flaxseed
	Stilbenes	C_6-C_2-C_6 stilbene skeleton	Resveratrol (501-36-0) Pterostilbene (537-42-8) Isorhapontigenin (1006-29-7) Polydatin (65914-17-2)	↑SIRT1/NRF2, ↑GPX4/SLC7A11, ↓ACSL4, Mitochondrial and lipid protection	Grapes, berries, peanuts
	Coumarins	Benzopyrone (C_6-C_3)	Umbelliferone (93-35-6) Esculetin (305-01-1) Scopoletin (92-61-5)	↑NRF2/HO-1, ↑GPX4/SLC7A11, ↓Lipid peroxidation	*Fraxinus*, tonka bean
	Tannins	Polymeric esters of gallic acid/flavan-3-ols	Proanthocyanidins (mixture) Ellagic acid (476-66-4) Tannic acid (1401-55-4)	↑GPX4, Fe^{2+} chelation, lipid ROS scavenging	Oak bark, pomegranate, tea
Other polyphenols	--	Variable	Curcumin (458-37-7) Myricanol (23094-10-4) Echinacoside (82854-37-3) Paeonol (552-41-0) Salvianolic acid B (121521-90-2) Urolithin A (1143-70-0) Glabridin (59870-68-7) Dihydromyricetin (27200-12-0)	↑NRF2/GPX4/SLC7A11, ↓ACSL4, Mitochondrial protection, lipid peroxidation inhibition, cell-context-dependent dual regulation	*Curcuma longa*, gut microbiota metabolites, *Salvia miltiorrhiza*, *Paeonia lactiflora*, *Myrica rubra*, *Glycyrrhiza glabra*

3.2 Polyphenols as redox-active chemical entities

As redox-active chemical entities, polyphenols exert their biological effects through a complex interplay between quantum chemical properties and environmental context. A fundamental distinction exists based on structural complexity: while some simple phenolics have been reported to form iron complexes that could potentially enhance the Fenton reaction, many structurally complex dietary polyphenols act as inhibitors of iron-driven lipid peroxidation under physiological conditions, through distinct redox-chemical mechanisms [55].

The inhibitory mechanism hinges on the dual capacity of these molecules to chelate iron and scavenge radicals. Molecules possessing catechol or pyrogallol moieties, exemplified by the B-ring of quercetin and the galloyl group of EGCG, efficiently chelate labile iron species, particularly redox-active Fe^{2+}, thereby attenuating Fenton chemistry and downstream lipid peroxidation [54, 56]. Simultaneously, they neutralize PLOO· [57]. Unlike synthetic inhibitors such as ferrostatin-1 (Fer-1), which are often described as relying on electron transfer (ET) from aromatic nitrogen atoms, dietary polyphenols predominantly quench lipid-derived radicals via hydrogen atom transfer (HAT)-favored pathways, particularly in lipid-rich environments. Quantum chemical calculations on representative flavonoid classes reveal that the 4′-hydroxyl

(4′-OH) group often exhibits a relatively low bond dissociation enthalpy (BDE), identifying it as a preferred hydrogen donor site under radical-scavenging conditions (**Figure 3**). This mechanism explains the high potency of flavonoids like luteolin and baicalein, where the resultant phenoxyl radical is stabilized through extensive resonance delocalization across the π-conjugated flavonoid scaffold, potentially undergoing radical–radical coupling or further stabilization reactions that contribute to the termination of lipid radical propagation [58, 59].

However, this redox chemistry exhibits an inherent duality. The same catechol and galloyl moieties responsible for iron sequestration can also exhibit pro-oxidant behavior in environments characterized by excessive or dysregulated transition metal availability [60]. Under conditions of pathological iron overload, these structural groups may facilitate the reduction of Fe^{3+} to redox-active Fe^{2+} via auto-oxidation, generating semiquinone radicals and potentially fueling the Fenton reaction instead of suppressing it [61]. This structure-based duality defines polyphenols as adaptive redox regulators: acting as radical scavengers in physiological contexts while capable of amplifying oxidative stress in iron-rich pathological states.

However, structural modifications introduce functional trade-offs between these chelation and scavenging capabilities. Generally, galloyl moieties exhibit superior iron-binding capacity compared to simple catechol groups, and the presence of carboxylate groups is often associated with optimal iron complexation [62, 63]. Conversely, methoxy substitutions (e.g., in ferulic acid) enhance radical scavenging stability but inhibit iron chelation; similarly, the C-3 hydroxyl group in gallic acid stabilizes the ring for scavenging but reduces chelation efficiency [64]. Thus, the net ferroptosis-regulatory profile of a given polyphenol is defined by a precise molecular balance between iron-chelating pharmacophores, context-dependent hydrogen-donating sites (particularly 4′-OH), and the redox stability of its metabolic intermediates.

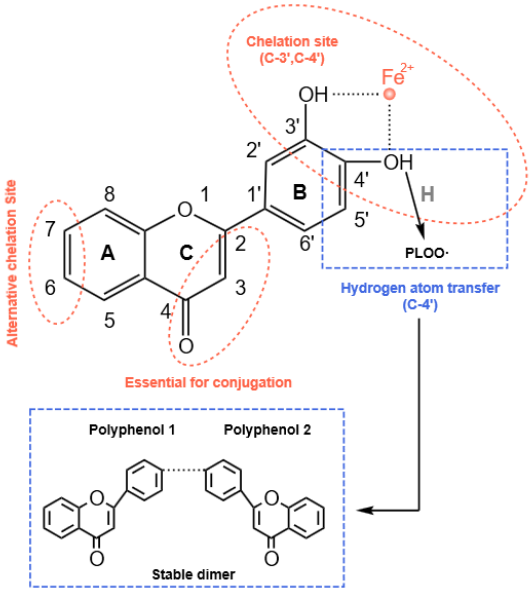

Figure 3. Structural basis of ferroptosis inhibition by flavonoids. The B-ring catechol moiety serves as the primary site for sequestering labile iron to prevent Fenton reaction initiation, while the C-4' hydroxyl group neutralizes lipid peroxyl radicals via hydrogen atom transfer. Resonance stabilization, facilitated by the C2=C3 double bond and C4-keto group, supports the termination of lipid peroxidation chains through the formation of stable polyphenol dimers. The chemical structures in this figure were drawn using KingDraw.

3.3 Polyphenols as signaling network modulators

The conceptual shift from viewing polyphenols as "chemical antioxidants" to "network regulators" is driven by an improved understanding of the bioavailability paradox and the principle of hormesis [65]. Typical physiological concentrations in circulation, frequently in the nanomolar to low micromolar range (often lower than 10 μM), are generally insufficient to support sustained, direct stoichiometric quenching of ROS [66].

Advances in molecular profiling and omics technologies have revealed that polyphenols primarily function as indirect regulators of redox signaling, operating at nanomolar to low micromolar concentrations to activate adaptive cellular defense programs. This regulatory capacity aligns with the principle of hormesis, which describes a biphasic dose-response whereby low-level stress induces adaptive benefits, whereas higher exposures may elicit detrimental effects [67], and this principle is central to the paradigm. At physiological doses, polyphenols can induce mild electrophilic or redox-sensitive stress signals that modulate key signaling nodes [68] such as NRF2, sirtuin1 (SIRT1), and 5'-AMP-activated protein kinase (AMPK), thereby augmenting endogenous antioxidant and metabolic resilience.

The bioavailability paradox further supports this regulatory paradigm. After ingestion, polyphenols undergo extensive phase II conjugation [69] (glucuronidation, sulfation, methylation) and microbial metabolism, resulting in derivatives that exhibit altered, and in some contexts enhanced, signaling potency [70]. These metabolites circulate systemically and modulate ferroptosis-related signaling pathways often inaccessible to their parent compounds.

This framework is especially pertinent to ferroptosis, which itself signifies a breakdown of adaptive redox regulation. Rather than merely mitigating oxidative stress, polyphenols thus act as adaptive molecular rheostats that fine-tune the ferroptosis network, restoring its dynamic balance. The maturation of this field is reflected in a chronological progression of discoveries, tracing the trajectory from foundational structural characterizations to the contemporary identification of molecular targets implicated in ferroptosis regulation (**Figure 4**).

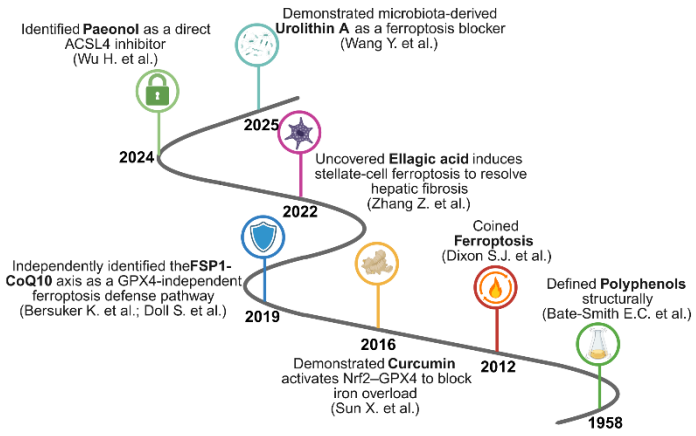

Figure 4. Timeline of key milestones linking polyphenol biology and ferroptosis research. Key events are arranged from the structural definition of polyphenols in 1958 to recent findings in which natural polyphenols and microbiota-derived metabolites modulate ferroptosis through signaling pathways related to iron metabolism, lipid remodeling, and antioxidant defense.

4. Polyphenol intervention across the ferroptosis axis: Mechanisms and therapeutic implications in chronic diseases

In contrast to oncological settings, where therapeutic strategies frequently aim to induce ferroptosis to eradicate malignant cells, a major therapeutic objective in chronic diseases is to attenuate excessive or maladaptive ferroptosis while preserving physiological iron metabolism and redox homeostasis. Within this framework, dietary and phytochemical polyphenols constitute a biocompatible and nutritionally sustainable class of ferroptosis modulators and offer potential translational advantages over synthetic ferroptosis inhibitors.

Chronic diseases are intrinsically systemic disorders and arise from the convergence of metabolic dysregulation, persistent inflammation, and, in many cases, microbiota-associated metabolic perturbations. Polyphenols are well positioned to operate at this intersection by functioning as redox modulators, metabolic adaptogens, and substrates for microbial transformation. Rather than acting as uniform suppressors of ferroptosis, polyphenols display pronounced context-dependent regulatory behavior. They can mitigate ferroptotic injury in vulnerable parenchymal cells, including neurons, cardiomyocytes, and myocytes. Under specific pathological conditions, however, they may facilitate ferroptosis in activated fibroblasts or stellate cells, thereby contributing to tissue remodeling processes that may favor the re-establishment of homeostatic balance.

This bidirectional regulatory capacity is rooted in the integration of their intrinsic chemical reactivity, such as radical scavenging and iron chelation, with their ability to influence transcriptional programs, metabolic fluxes, and mitochondrial function that collectively determine cellular susceptibility to ferroptosis. Additionally, compounds such as quercetin, curcumin, and resveratrol act as mild mitochondrial stressors, eliciting hormetic adaptive responses associated with improved bioenergetic function, further enhancing cellular resilience against ferroptosis [71]. The following sections synthesize contemporary evidence across major chronic non-cancerous disease systems and illustrate how distinct classes of natural polyphenols recalibrate ferroptosis-associated signaling networks to alleviate oxidative stress, metabolic dysfunction, and iron-mediated tissue injury.

4.1 Neurological disorders

Ferroptotic imbalance within the central nervous system (CNS) represents a pivotal intersection of iron dysregulation, mitochondrial dysfunction, and neuronal cell death [72]. Indeed, high oxygen consumption in brain, coupled with its enrichment in PUFAs, renders it exceptionally vulnerable to iron-catalyzed lipid peroxidation [73]. This inherent vulnerability establishes ferroptosis as a key driver of neurodegenerative progression [74, 75]. In conditions like Alzheimer's disease (AD) and Parkinson's disease (PD), neuronal ferroptosis is not an isolated event; it signifies the failure of integrated redox and metabolic defense mechanisms that regulate iron homeostasis and glutathione concentrations [76].

Consequently, targeting signaling pathways for regulating ferroptosis has emerged as a promising therapeutic strategy. In this context, natural polyphenols, with their multi-target modulatory capacity, have

shown considerable promise in rectifying these dysregulated pathways. Existing studies indicate that ferroptosis inhibitors can ameliorate disease progression and severity [77]. For example, iron chelators such as DFO are widely used to control ferroptosis in AD and PD [78]. Other inhibitors act by modulating lipid peroxidation. For instance, pioglitazone [79] has been confirmed to inhibit ACSL4; notably, long-term use of pioglitazone has been associated with a lower incidence of dementia in type 2 diabetes mellitus (T2DM) patients. Building on this pharmacological precedent, natural polyphenols are now emerging as critical modulators of ferroptosis in neurological diseases. These findings possess significant mechanistic and translational relevance for neurological disorders and provide a mechanistic rationale for their potential prevention and treatment (**Figure 5**).

A hallmark of ferroptosis in dopaminergic neurodegeneration is the accumulation of labile iron and ROS in the substantia nigra region. The green tea catechin EGCG [80] illustrates the capacity of polyphenols to restore iron homeostasis and impede ferroptosis. In a *PINK1*-mutant *Drosophila* model with PD, EGCG mitigated behavioral deficits and protected against dopaminergic neuron degeneration by down-regulating the iron importer malvolio (Mvl), the *Drosophila* homolog of mammalian iron transporter DMT1, and up-regulating ferritin expression to sequester surplus iron. This dual mechanism lowered intracellular free Fe^{2+} levels and arrested lipid peroxidation, with comparable efficacy to the ferroptosis inhibitor Fer-1 [81]. Similarly, liquiritin [82], a flavonoid extracted from Chaihu-Shugan-San, activates the PPARα/SCD1/FADS2 signaling axis to facilitate lipid remodeling and avert ferroptotic membrane damage in MPP^+-treated MES23.5 cells, thereby establishing a connection between polyunsaturated fatty acid metabolism and ferroptosis resistance. These results demonstrate that polyphenols safeguard against neuronal ferroptosis via dual mechanisms: diminishing iron accumulation and reprogramming lipid homeostasis—two interrelated signaling pathways that significantly affect neuronal vulnerability in PD. In addition to dopaminergic injury, phenylethanoid glycosides like acteoside and salidroside have strong neuroprotective effects by stabilizing the NRF2-GPX4 antioxidant axis and resolving mitochondrial dysfunction [83]. Acteoside directly inhibits ferroptosis by down-regulating ACSL4, a pro-ferroptotic lipid acyltransferase, thereby averting salsolinol-induced neurotoxicity [84] in SH-SY5Y cells. Simultaneously, acteoside partially restores mitochondrial integrity through NRF2-mediated mitophagy, diminishes lipid peroxide accumulation, and rescues dopaminergic neurons in MPTP-induced PD model [85]. Salidroside, a substance derived from *Rhodiola rosea*, safeguards against ferroptosis in both PD and AD models. In MPTP-induced PD mice, it activates the NRF2/GPX4 signaling pathway to safeguard dopaminergic neurons [86]. This NRF2-dependent mechanism is also present in AD models, wherein salidroside diminishes iron accumulation and lipid peroxidation by activating the NRF2/GPX4 signaling axis [87] in SAMP8 mice and the NRF2/HO-1 signaling pathway [88] in amyloid-β (Aβ)-induced models, thereby protecting neurons from injury.

Ferroptotic signatures are increasingly recognized in AD, along with the more well-known Aβ and Tau pathology. In the brains of patients with AD, there are higher levels of ACSL4, NCOA4, and iron transporters like DMT1, but lower levels of GPX4 and the cystine/glutamate antiporter system Xc^- [89, 90].

Tetrahydroxystilbene glycoside (TSG) [91] activates the Keap1/NRF2/ARE signaling axis, increases GSH synthesis and GPX4 activity, and decreases DMT1 and NCOA4 levels, thereby contributing to the reduction of both iron accumulation and lipid peroxidation in APP/PS1 mice. Forsythoside A [92] demonstrates synergistic anti-ferroptotic and anti-inflammatory properties: it enhances NRF2/GPX4 signaling while inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, leading to decreased lipid peroxidation and pro-inflammatory cytokine production, thereby improving cognitive function and diminishing Aβ accumulation. Eriodictyol [93] diminishes Aβ aggregation and Tau phosphorylation while counteracting ferroptosis-associated molecular features in APP/PS1 mice via vitamin D receptor (VDR)-mediated activation of the NRF2/HO-1 signaling pathway. In a mechanistically distinct instance, tannic acid (TA) [94], a polyphenol enriched in catechol and galloyl moieties, counteracts Aβ-induced ferroptosis through a structure-dependent mechanism. Its multiple catechol and galloyl groups confer high-affinity chelation toward ferric iron, while the polyphenolic scaffold and spatial conformation of TA enable direct binding to the allosteric activation pocket of GPX4. Specifically, TA interacts with acidic residues including Asp21 and Asp23, together with hydrophobic contacts involving Val98, Phe100, and Met102, thereby promoting GPX4 catalytic activity toward lipid hydroperoxides through an allosteric interaction. This finding supports a structure–activity relationship in which defined polyphenol architectures translate into direct enzymatic activation rather than nonspecific antioxidant effects.

Recent parallel advances suggest that ferroptosis encompasses not only classical neurodegenerative disorders but also neurovascular and metabolic encephalopathies. In vascular dementia (VaD), chronic cerebral hypoperfusion leads to neuronal ferroptosis, which can be alleviated by anthocyanins [95] through the dual activation of FSP1 and GPX4/SLC7A11 signaling pathways, thereby inhibiting lipid peroxidation and restoring mitochondrial integrity. In a similar way, gastrodin [96], a neuroactive phenolic glycoside, enhances this protective mechanism through the NRF2/Keap1-GPX4 signaling pathway, to reduce the level of Fe^{2+} and MDA and increase the level of GSH in hippocampal neurons. The synchronized re-establishment of FSP1- and GPX4-mediated defense mechanisms indicates that polyphenols can restore ferroptosis checkpoints that are generally disrupted during ischemic-hypoxic stress. In diabetic cognitive dysfunction (DCD), elevated glucose levels trigger neuronal ferroptosis by up-regulating ACSL4 and down-regulating GPX4 effects, while dihydromyricetin [97] mitigates these effects by inhibiting the JNK-mediated inflammatory cascade. Quercetin [98] attenuates hippocampal neuron ferroptosis in diabetic rats by directly binding to Kelch-like ECH-associated protein 1 (Keap1). This interaction is structurally stabilized through the formation of four hydrogen bonds, which disrupt Keap1-mediated ubiquitination and degradation of NRF2, thereby facilitating NRF2 nuclear translocation and activation of the downstream HO-1–associated antioxidant response that limits iron accumulation and lipid peroxidation. Additionally, resveratrol [99] inhibits miR-9-3p, which is an upstream regulatory mechanism, to enhance SLC7A11 expression, thereby leading to reduced lipid peroxidation in hippocampus and improved cognitive function, and to suppress insulin resistance in T2DM mice. These findings highlight that ferroptotic signaling

constitutes a vital connection between metabolic dysregulation and neuronal dysfunction, establishing polyphenols as multi-node modulators capable of disrupting this pathological axis.

Collectively, the evidence consolidated in this section consolidates the role of natural polyphenols as important regulators of ferroptosis in the nervous system. They orchestrate a multi-faceted defense by concurrently targeting the core pillars of this iron-dependent cell death: chelating labile iron, reprogramming lipid metabolism to reduce peroxidation susceptibility, and effectively activating endogenous antioxidant pathways, with the NRF2-GPX4 signaling axis emerging as a central node. The consistent efficacy of diverse polyphenol classes across a spectrum of neurodegenerative models validates targeting signaling pathways of ferroptosis as a unified and mechanistically coherent neuroprotective strategy. This body of evidence confirms the paradigm shift: polyphenols function not merely as antioxidants, but as sophisticated redox-network modulators capable of re-establishing neuronal homeostasis.

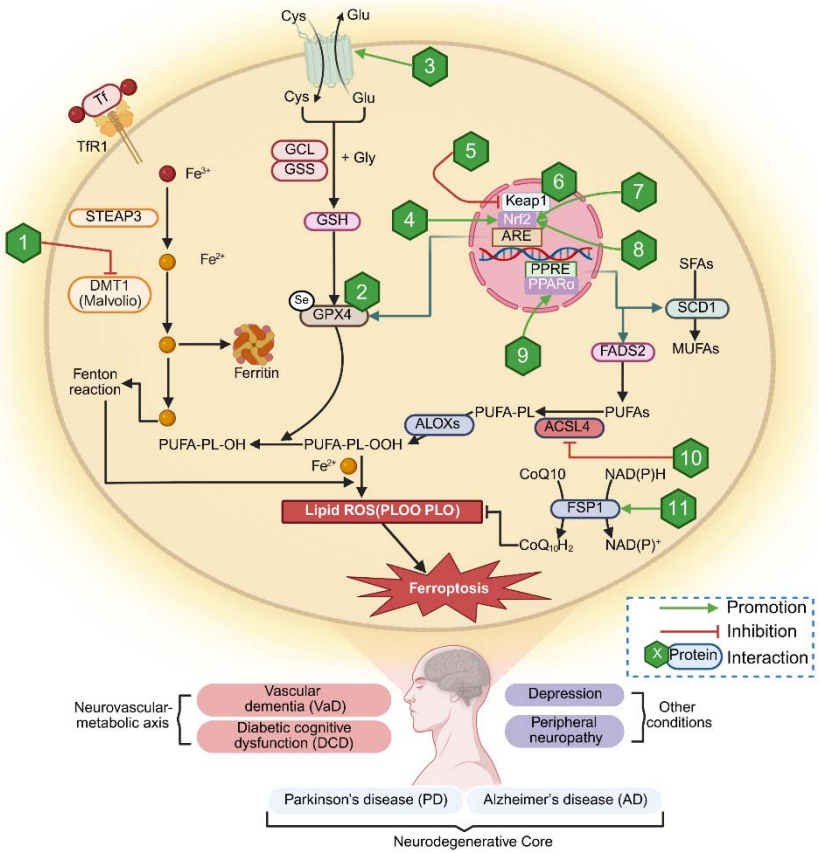

Figure 5. Polyphenols exert neuroprotection by modulating the signaling network of ferroptosis. Schematic diagram illustrating multi-target mechanisms by which natural polyphenols, including EGCG (1), tannic acid (2), resveratrol (3), forsythoside A (4), tetrahydroxy stilbene glycoside (5), quercetin (6), salidroside (7), eriodictyol (8), liquiritin (9), acteoside (10), and anthocyanins (11), mitigate ferroptosis in neurodegenerative diseases. These compounds intervene at critical checkpoints of iron homeostasis (e.g., TfR1, DMT1, NCOA4, HO-1), lipid metabolism (e.g., ACSL4, ALOXs, FADS2), and antioxidant defense. Polyphenols boost the expression of GPX4, GCL, GSS, and HO-1 by activating the NRF2-ARE signaling pathway. They also modulate the FSP1-CoQ10 axis and encourage mitochondriogenesis. These coordinated actions stabilize the redox and metabolic network, inhibiting ROS-induced lipid peroxidation and presenting therapeutic potential for conditions such as AD, PD, VaD, DCD, and depression.

4.2 Metabolic diseases

In metabolic organs such as the liver and kidney, the convergence of excessive nutrient flow and dysregulated metal homeostasis creates a highly permissive environment for iron-dependent lipid

peroxidation and mitochondrial dysfunction. This pathological nexus is now recognized as an important contributor to ferroptotic susceptibility in metabolic-associated steatotic liver disease (MASLD) and diabetic kidney disease (DKD). Ferroptosis in these tissues represents a form of redox collapse distinct from apoptosis, one deeply intertwined with energy metabolism, fatty acid profiles, and cellular detoxification capacity. Natural polyphenols are emerging as effective modulators at this interface. This section will examine the mechanisms by which polyphenols recalibrate these interconnected pathways—targeting redox equilibrium, lipid homeostasis, and mitochondrial function—to augment metabolic resilience against chronic oxidative stress.

In fatty liver disorders, the excessive accumulation of free fatty acids and heightened mitochondrial ROS production trigger a self-amplifying cycle of lipid peroxidation and hepatocellular damage. Polyphenols have shown promise in disrupting this pathological cycle by restoring the balance between antioxidants and lipid metabolism. Protocatechuic acid (PCA), a principal metabolite of anthocyanins and catechins, mitigates hepatic lipotoxicity in both high-fat diet (HFD)-fed and palmitate-induced models by activating the NRF2 signaling pathway, thereby restoring redox homeostasis and inhibiting iron accumulation. Studies in both wild-type and NRF2-knockout mice demonstrate that PCA [100] restores tricarboxylic acid (TCA) cycle flux and diminishes lipid peroxide formation, supporting a central role of NRF2-dependent transcription in mediating its hepatoprotective effects. EGCG [101] inhibits hepatic ferroptotic damage by targeting mitochondrial-derived ROS, decreasing lipid accumulation, and normalizing the expression of GPX4 and ACSL4 in HFD-fed mice and steatotic L-02 cells. Quercetin [102], a prevalent flavonoid found in fruits and vegetables, enhances this protective network by reducing mitochondrial oxidative bursts and preventing mtROS-induced lipid peroxidation, thereby maintaining GPX4 expression and alleviating hepatic iron overload. These findings collectively elucidate a convergent mechanism through which polyphenols target the mitochondria-lipid-antioxidant axis in hepatic steatosis, thereby effectively mitigating oxidative stress and averting the onset of ferroptosis.

A comparable metabolic interaction is evident in progressive hepatic conditions like MASLD, wherein chronic inflammation, glucose dysregulation, and lipid accumulation lead to sustained ferroptotic stress [103]. Proanthocyanidins [104], intricate polyphenols extracted from grape seeds, provide dual protective benefits by enhancing glucose homeostasis and inhibiting ferroptosis through the coordinated regulation of GPX4 and ACSL4, in conjunction with iron-regulatory proteins. This is associated with an attenuated increase in liver enzymes and an improvement in histopathological steatosis. Echinacoside [105], a caffeic acid glycoside, enhances the Nrf2/HO-1/SLC7A11-GPX4 signaling pathway, while down-regulating ACSL4, effectively inhibiting lipid peroxidation and restoring mitochondrial integrity in diabetic *db/db* mice and oleic acid-exposed hepatocytes. In addition to traditional lipotoxic models, curcumin, in the context of hepatolenticular degeneration (HLD), a disorder characterized by copper overload and associated with abnormal homeostasis of iron, exhibits the ability to chelate excessive copper and activate the Nrf2/HO-1/GPX4 signaling axis [106], thus averting oxidative collapse caused by dual metal accumulation.

The consistency of these results across various hepatic models indicates that polyphenols function not only as radical scavengers but also as metabolic re-programmers, capable of reconfiguring redox-sensitive transcriptional networks, thus safeguarding hepatocytes from surpassing the ferroptotic threshold. Metabolic overload leads to systemic insulin resistance and hyperglycemia, while ferroptotic mechanisms are emerging as important drivers of organ damage in people with diabetes, especially in the liver. Gegen Qinlian Decoction (GQD), a traditional Chinese medicinal formulation consisting of puerarin, baicalin, berberine, and liquiritin, exemplifies a polyphenol-rich therapeutic agent. In an HFD/STZ-induced T2DM mouse model, GQD [107] restored hepatic function, reduced ROS accumulation, and increased GPX4 expression via NRF2 activation, thereby effectively inhibiting hepatic ferroptosis and enhancing structural integrity of mitochondria. These findings bolster the overarching hypothesis that polyphenol combinations may synergistically enhance cellular defenses against ferroptosis through complementary antioxidant and metabolic regulatory mechanisms.

This nexus of metabolic stress and ferroptosis is also critically implicated in the progression of diabetic nephropathy (DN) and DKD. Chronic hyperglycemia induces lipid peroxidation, mitochondrial dysfunction, and iron overload in renal tubular epithelial cells, which are pathological features analogous to ferroptotic signatures observed in the liver [108]. Quercetin [109, 110] mitigates renal ferroptosis by up-regulating GPX4, FTH1, and SLC7A11, down-regulating TfR1, and activating the NRF2/HO-1 signaling pathway, thereby reducing tubular oxidative injury in diabetic mice and high glucose-stimulated HK-2 cells. Glabridin [111], an isoflavan derived from licorice, provides synergistic protective effects by up-regulating GPX4/SLC7A11, enhancing the activities of GSH and superoxide dismutase (SOD), and inhibiting VEGF/Akt/ERK signaling, thereby mitigating renal oxidative stress and functional deterioration. Umbelliferone [112], a coumarin compound, reinforces this protective framework by activating the NRF2/HO-1 signaling axis, down-regulating ACSL4, and up-regulating GPX4. These effects are negated upon NRF2 silencing, highlighting the essential function of NRF2 in inhibiting ferroptosis. Recent findings emphasize mitochondrial regulation as a vital ferroptotic checkpoint in DN. Caffeic acid phenethyl ester (CAPE) [113] protects tubular epithelial cells from ferroptosis in diabetic kidney disease by restoring PINK1-mediated mitophagy. CAPE exhibits directly interact with and stabilize the PINK1 protein through structure-dependent interactions, in which phenolic hydroxyl groups on its side chain form hydrogen bonds with residues including Val256, Phe257, Phe291, and Leu293, while aromatic ring–mediated hydrophobic and π–π interactions further reinforce binding. This stabilization limits proteolytic degradation of PINK1, sustains mitophagic flux, preserves mitochondrial membrane potential, and indirectly constrains ferroptotic progression by limiting mitochondrial oxidative stress and iron accumulation. Similarly, Schisandrin A [114], derived from *Schisandra chinensis*, activates the AdipoR1/AMPK signaling pathway to alleviate ROS-induced mitochondrial damage and inhibit NLRP3 inflammasome activation, consequently attenuating both ferroptosis and pyroptosis in diabetic glomeruli. Calycosin [115], an isoflavonoid derived from *Astragalus membranaceus*, reinforces the therapeutic targeting of ferroptosis in DKD by restoring

intracellular GSH levels and GPX4 expression, while concurrently inhibiting lipid ROS accumulation and NCOA4-mediated ferritinophagy, thus preventing iron overload and subsequent cell apoptosis. Together, these natural polyphenolic compounds exhibit consistent nephroprotective effects by maintaining mitochondrial health, enhancing antioxidant defenses, coordinating autophagic clearance with redox balance, and reducing iron-dependent lipid peroxidation.

In essence, the findings in this section position natural polyphenols as metabolic adaptogens that enhance hepatic and renal resilience (**Figure 6**). In conditions of nutrient excess and diabetic stress, they transcend the role of simple inhibitors. Instead, they recalibrate the critical nexus of nutrient metabolism and ferroptosis. This is achieved through a dual-pronged strategy: they concurrently upregulate cytoprotective transcription factors (e.g., NRF2) to fortify the GPX4/SLC7A11 axis, and directly inhibit key pro-ferroptotic factors such as ACSL4. This recurring profile of action, observed across diverse molecular classes, highlights their capacity to reprogram metabolic pathways, rendering hepatocytes and renal cells inherently less susceptible to iron-dependent lipid peroxidation.

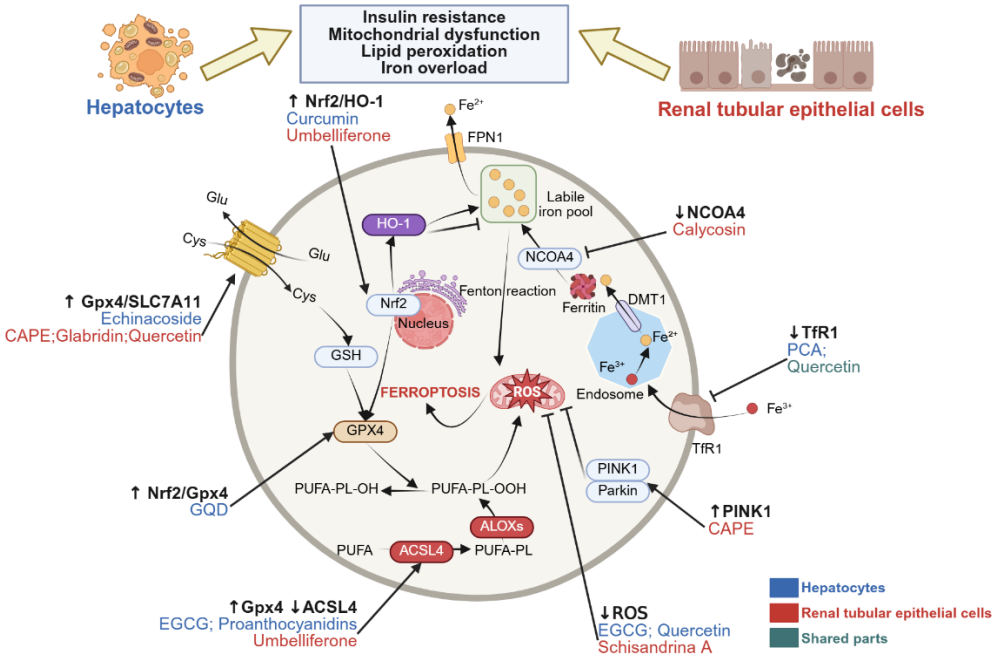

Figure 6. Polyphenols modulate shared ferroptotic pathways in hepatocytes and renal tubular epithelial cells under metabolic stress. This figure shows how natural polyphenols affect ferroptosis in hepatocytes (blue) and renal tubular epithelial cells (yellow) through shared (purple) and tissue-specific mechanisms. In the presence of insulin resistance, mitochondrial dysfunction, lipid peroxidation, and iron overload, both cell types experience ferroptotic injury, marked by the accumulation of ROS and disrupted lipid-iron homeostasis. Polyphenols like CAPE, glabridin, quercetin, echinacoside, and umbelliferone strengthen the shared NRF2-GPX4-SLC7A11 antioxidant axis (purple) to fight oxidative stress. On the other hand, EGCG, proanthocyanidins, and schisandrin A inhibit ROS formation. Curcumin and umbelliferone act on hepatocytes by inducing HO-1 and increasing iron efflux through FPN1. Calycosin protects renal tubular epithelial cells by inhibiting NCOA4, PCA and quercetin inhibit TfR1, and CAPE activates PINK1 to keep mitochondrial quality control. These pathways work together to terminate the ACSL4-ALOXs-PUFA-PL lipid peroxidation loop, which restoring redox balance and inhibiting ferroptosis in the liver and kidneys.

4.3 Cardiovascular diseases

Cardiomyocyte death represents a critical determinant in the pathophysiology of cardiovascular diseases. As terminally differentiated cells, lost cardiomyocytes are irreplaceable, leading to permanent

structural abnormalities, gradual functional decline, and heightened risk of heart failure [116]. In this context, ferroptosis is increasingly recognized as a non-apoptotic cell death pathway that directly contributes to myocardial and vascular injury. This iron-dependent mechanism, previously regarded as uncontrolled oxidative stress, links lipid peroxidation and mitochondrial deterioration to endothelial dysfunction and cardiac remodeling [117, 118]. Therefore, inhibiting this specific cascade represents a novel therapeutic avenue for preserving cardiovascular integrity [119, 120]. Natural polyphenols offer a compelling, multi-pronged counter-strategy at this cardiometabolic nexus. This section will explore their capacity to preserve endothelial function and bolster mitochondrial quality control, thereby neutralizing the oxidative-metabolic cascade that leads to cardiometabolic diseases.

Atherosclerosis (AS) is the vascular disease that best exemplifies ferroptosis as a common pathogenic driver. Atherosclerotic plaques exhibit signatures of ferroptotic stress in macrophages, endothelial cells, and vascular smooth muscle cells (VSMCs), including lipid peroxide accumulation, iron overload, and GPX4 depletion. Resveratrol [121], a polyphenol, has been shown to arrest these processes by targeting mitogen-activated protein kinase 1 (MAPK1), which is a key regulator in the redox-inflammation-ferroptosis axis. Combined bioinformatics analysis, machine learning prediction, and validation in ApoE$^{-/-}$ mice show that resveratrol is associated with reduced oxidative markers in the blood and decreased plaque burden in the aorta while restoring iron balance by inhibiting MAPK1.

Likewise, catechin [122], a flavanol present in green tea, inhibits ox-LDL-induced ferroptosis in VSMCs by reestablishing the NRF2/SLC7A11/GPX4 signaling pathway, lowering intracellular Fe^{2+} and ROS levels, and preserving mitochondrial ultrastructure, thereby stabilizing plaques and preventing foam cell formation. Ferulic acid [123] further strengthens this framework by modulating the HIF-1α/GPX4/Bcl-2 signaling pathway in macrophages. This simultaneously inhibits ferroptosis and apoptosis while improving mitochondrial function and lipid metabolism. Endothelial dysfunction, the initial marker of atherogenesis, also demonstrates ferroptotic features. Quercetin [124], long recognized for its vascular protective properties, mitigates postmenopausal atherosclerosis in ovariectomized ApoE$^{-/-}$ mice by facilitating KEAP1 ubiquitination, triggering NRF2 nuclear translocation, and reinstating GPX4 activity. Quercetin inhibits endothelial lipid peroxidation and iron deposition while mitigating the oxidative susceptibility linked to estrogen withdrawal. EGCG [125] also slows down the aging of blood vessels by activating the SIRT1/NRF2/GPX4/HO-1 signaling pathway, enhancing autophagic flux, and preventing ferroptosis in aged endothelial cells.

These findings collectively illustrate that polyphenols maintain vascular youthfulness by the coordinated regulation of redox homeostasis, mitochondrial quality control, and inhibition of ferroptosis processes, which are especially vital in age- or estrogen-deficient vasculature. Innovative drug-delivery systems and hybrid formulations further enhance the vascular protective effects of polyphenols. For example, a macrophage-targeted resveratrol-pitavastatin nanocomplex significantly reduced hyperhomocysteinaemia-induced atherosclerosis by simultaneously activating GPX4/SLC7A11 and FSP1

signaling pathways [126]. This nanotherapeutic enhanced resveratrol accumulation in atherosclerotic plaques, prolonged its systemic retention, and remodeled macrophage metabolism to prevent ferroptotic collapse. These approaches demonstrate how using nanocarriers to deliver polyphenols can overcome natural bioavailability problems and allow for cell-type-specific modulation of ferroptosis in different vascular microenvironments.

Ferroptosis has emerged as a significant factor in cardiac pathologies, where ongoing oxidative and metabolic stress leads to progressive myocardial remodeling and ultimately heart failure. Pterostilbene (PTS), a methylated derivative of resveratrol, safeguards cardiomyocytes from angiotensin II (Ang II)-induced ferroptosis by stimulating the SIRT1/GSK-3β/GPX4 signaling pathway. In mice with transverse aortic constriction, PTS improved mitochondrial morphology, increased GSH level, and reduced cardiac fibrosis and remodeling. Significantly, these protective effects were nullified following the knockdown of either SIRT1 or GPX4, thereby validating the critical function of this pathway in facilitating anti-ferroptotic responses [127]. Similarly, resveratrol arrests cardiac ferroptosis and slows down the progression of heart failure by activating the SIRT1/p53/SLC7A11 signaling axis, which inhibits p53 acetylation, maintains SLC7A11 expression, and sustains the GPX4-GSH antioxidant system [128].

These findings collectively elucidate a conserved molecular mechanism facilitating polyphenol-mediated cardioprotection: SIRT1 functions as a pivotal regulator of ferroptosis, integrating NAD^+ metabolism with redox homeostasis and mitochondrial integrity. Moreover, polyphenol-rich extracts derived from traditional herbal formulation have exhibited modulatory effects on ferroptosis in models with metabolic cardiomyopathy. The Ling-Gui-Zhu-Gan decoction, abundant with liquiritin [129] and associated flavonoids, alleviates heart failure by regulating PLIN5-mediated lipid peroxidation, restoring mitochondrial ultrastructure, and reversing gene expression profiles associated with ferroptosis through the down-regulation of ACSL4 and CD36 and the up-regulation of GPX4 and FPN1. These results demonstrate that polyphenolic compounds can simultaneously modulate ferroptosis and lipid metabolism, reinforcing the concept that ferroptotic sensitivity is contingent upon the metabolic context and intricately associated with lipid droplet dynamics. In a complementary model of atrial fibrosis, Schisandrin B [130] mitigates Ang II-induced ferroptosis through the activation of SIRT1, thereby reinstating the levels of SLC7A11, GPX4, and FTH1, while diminishing Fe^{2+} accumulation and pro-inflammatory cytokine production.

Polyphenols modulate ferroptosis in microvascular injury and diabetic cardiomyopathy (DCM), which are marked by initial mitochondrial dysfunction and lipid peroxidation. Isorhapontigenin (ISO), a resveratrol analog, mitigates cardiac microvascular injury in *db/db* mice by modulating the PRDX2/MFN2/ACSL4 signaling pathway, restoring mitochondrial dynamics, and inhibiting mitochondria-associated ferroptosis. ISO [131] prevents MFN2-mediated mitochondrial fragmentation and inhibits the translocation of ACSL4 to mitochondria, revealing a spatial link between organelle dynamics and susceptibility to ferroptosis. This mechanistic insight bolsters a developing paradigm: ferroptosis in the diabetic heart is not merely a result of cytosolic redox imbalance, but also signifies mitochondria-centric metabolic failure that can be effectively

addressed by polyphenols. Moreover, polyphenol-mediated regulation of ferroptosis plays a role in vascular adaptation in cases of hypertension and endothelial injury. Kaempferol, a prevalent flavanol, mitigates ferroptosis in endothelial cells by up-regulating GPX4 and SLC7A11, decreasing lipid peroxidation, and reestablishing cell viability under RSL3-induced stress [132]. Kaempferol [133] protects cardiovascular cells by directly targeting ATF4, a key transcription factor in ER stress. Its flavonol scaffold contains multiple phenolic hydroxyl groups that form hydrogen bonds with Gly81, Arg296, and Arg300 on ATF4, while hydrophobic contacts with Trp84, Tyr295, and Met85 further stabilize the interaction. This structure-dependent binding inhibits ATF4 transcriptional activity, preventing downstream activation of ACSL4 and its cofactor lysophosphatidylcholine acyltransferase 3 (LPCAT3), thereby suppressing PUFA esterification and lipid peroxidation. Consequently, pro-ferroptotic lipid mediators such as 12-HETE and 15-HETE are reduced, while the GSH/GPX4 antioxidant axis is maintained.

In summary, the cardiovascular evidence suggests a convergent protective mechanism centered on the SIRT1-ferroptosis axis (**Figure 7**). Polyphenols, particularly stilbenoids like resveratrol and pterostilbene, function as potent SIRT1 activators. This activation initiates a protective cascade by modulating key downstream effectors, including p53 and GSK-3β. Consequently, the GPX4/SLC7A11 defense system is safeguarded, and mitochondrial integrity is preserved. Thus, the SIRT1-ferroptosis axis emerges as a central regulatory hub, integrating diverse protective effects—from plaque stabilization via NRF2 activation to metabolic cardiomyopathy alleviation via lipid metabolism modulation. The recurring theme is that polyphenols impart contextual resilience, reducing the susceptibility of cardiomyocytes and vascular cells to ferroptotic insults during pressure overload, metabolic stress, or age-related decline. This action is fundamental to preserving the functional and structural integrity of the heart and vasculature.

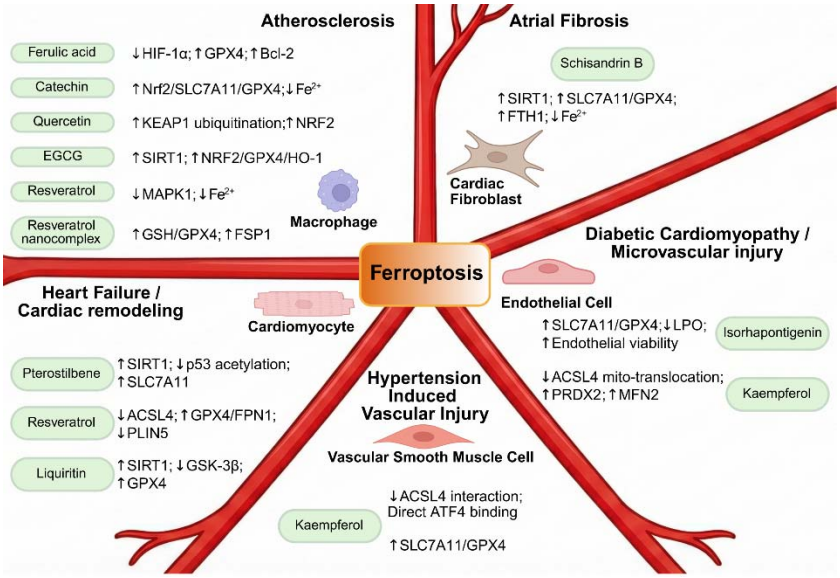

Figure 7. Polyphenol-mediated modulation of ferroptosis in cardiovascular diseases. This figure outlines the cardioprotective mechanisms through which polyphenols alleviate ferroptosis-induced pathologies, encompassing atherosclerosis, atrial fibrosis, vascular endothelial injury, diabetic cardiomyopathy, and heart failure. Substances like resveratrol, catechin, quercetin, ferulic acid, and EGCG stimulate NRF2/SLC7A11/GPX4 or SIRT1/NRF2/HO-1 signaling, thereby reducing oxidative stress, iron overload, and lipid peroxidation. Others, such as schisandrin B, kaempferol, isorhapontigenin, and liquiritin, regulate ferritinophagy, ACSL4, or mitochondrial pathways to maintain the integrity of the endothelium and myocardium. Collectively, these interventions inhibit ferroptosis, which protects the heart and blood vessels from damage caused by oxidative metabolism.

4.4 Musculoskeletal disorders

Musculoskeletal tissues face a unique pathological challenge where biomechanical stress and metabolic dysregulation converge. Ferroptosis has emerged as a key integrator of these insults, translating mechanical overload and inflammatory signals into iron-dependent lipid peroxidation, which in turn undermines extracellular matrix integrity and tissue function. This section will explore how natural polyphenols function as mechano-protectants—modulators that decouple mechanical stress from ferroptotic execution. We will examine their capacity to reinforce redox defenses and metabolic flexibility, thereby preserving tissue integrity under chronic biomechanical and oxidative load.

Skeletal muscle is one of the most metabolically active tissues in the body, and its high mitochondrial density makes it especially vulnerable to ferroptotic stress during redox imbalance. Gallic acid (GA), a prevalent plant polyphenol, helps protect against exercise-induced muscle injury by alleviating mitochondrial oxidative stress and preventing ferroptosis. In murine overtraining models, GA [134] markedly diminished serum concentrations of LDH, TNF-α, and MDA, concurrently restoring ATP synthesis and mitochondrial membrane potential. At the same time, it arrested the accumulation of Fe^{2+} and prevented the loss of GPX4. This dual protective effect on mitochondrial function and ferroptosis regulation elucidates a mechanistic connection between metabolic exhaustion and iron-dependent cell damage in exercise-induced myopathy. Likewise, in muscle atrophy associated with chronic kidney disease (CKD), caffeic acid offers protective effects by diminishing oxidative stress and inflammatory catabolism via the inhibition of the TLR4/MYD88/NF-κB signaling pathway. Caffeic acid [135] mitigated muscle wasting in 5/6 nephrectomized rats by decreasing muscle iron overload and reinstating GPX4 expression.

The intervertebral disc degeneration (IVDD), although avascular and metabolically constrained, is particularly vulnerable to ferroptotic stress. Gallic acid [136] mitigates disc degeneration by reestablishing the redox equilibrium between p53 and NRF2, consequently inhibiting extracellular matrix degradation and lipid peroxidation in nucleus pulposus (NP) cells. Resveratrol [137] also slows down the degeneration of discs by reinforcing ferroptosis regulatory checkpoints in NP cells. It induces GPX4/SLC7A11 signaling pathway while suppressing the expression of pro-inflammatory mediators interleukin-1 beta (IL-1β) and interleukin-6 (IL-6).

In osteoarthritis (OA), chondrocyte ferroptosis serves as a principal mechanism driving cartilage degradation and extracellular matrix depletion. An increasing body of evidence demonstrates that diverse polyphenols can effectively disrupt this pathological process through multiple initiating pathways that ultimately converge on the inhibition of ferroptosis and inflammation. Baicalein [138], a flavonoid from *Scutellaria baicalensis*, activates the AMPK/NRF2/HO-1 signaling pathway, which stabilizes NRF2, promotes the breakdown of Keap1, and stops the buildup of lipid ROS in chondrocytes. Urolithin A (UA) [139], a metabolite of ellagitannins derived from gut microbiota, mitigates IL-1β-induced ferroptosis and inflammatory responses by modulating the AMPK/mTOR/HIF-1α signaling axis, resulting in decreased levels of MDA, Fe^{2+}, and NF-κB activation, while restoring GPX4 and ferritin expression. Curcumin [140]

counteracts erastin-induced chondrocyte ferroptosis by up-regulating NRF2, which in turn enhances the expression of SLC7A11, GPX4, and FTH1; however, *Nrf2* knockdown negates this protective effect. Nanocarrier-based delivery strategies have been developed to overcome the poor bioavailability of polyphenols. For instance, curcumin-loaded biomimetic nanosponges [141] synergistically mitigate chondrocyte ferroptosis and inflammation by significantly reducing levels of Fe^{2+}, ACSL4, and MDA while upregulating GPX4 and SLC7A11. EGCG-selenium nanodrugs [142] also boost GPX4 activity and stop Fe^{2+} from building up, which helps protect cartilage from damage in OA models. Paeonol, recognized as a selective inhibitor of ACSL4, directly interacts with this pro-ferroptotic enzyme and inhibits IL-1β/FAC-induced lipid peroxidation, iron deposition, and extracellular matrix degradation in both *in vitro* and destabilized medial meniscus (DMM)-induced osteoarthritis models [143]. Icariin [144], a prenylated flavonoid from epimedium, also protects cartilage from oxidative and inflammatory damage by reactivating the SLC7A11/GPX4 signaling pathway and restoring collagen II and GPX4 expression.

Collectively, these findings establish polyphenols as essential "mechano-protectants" in musculoskeletal health, maintaining mechano-chemical homeostasis (**Figure 8**). They function precisely at the critical interface where mechanical stress converges with metabolic distress to drive ferroptosis, thereby preserving tissue integrity. This protective capacity has been reported across skeletal muscle, intervertebral discs, osteoarthritic cartilage and notably extends to symptom management in fibromyalgia, where polyphenol-rich diets have shown promise in alleviating pain [145]. Polyphenols decouple biomechanical insults from iron-dependent lipid peroxidation and extracellular matrix breakdown. This conclusively establishes their function as guardians of musculoskeletal resilience, safeguarding tissue structure and function against the composite stresses of oxidative, inflammatory, and biomechanical failure.

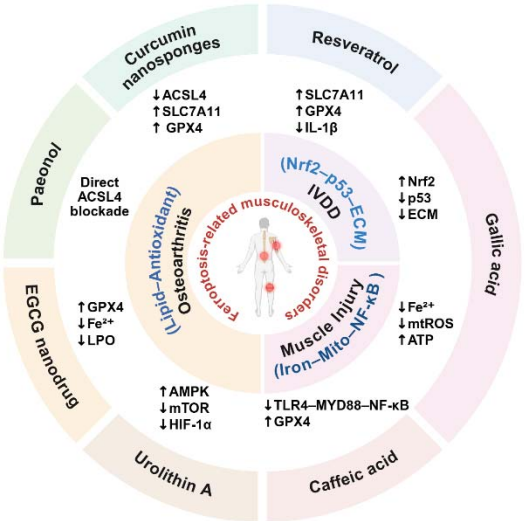

Figure 8. Protective mechanisms of natural polyphenols against musculoskeletal disorders. Natural polyphenols mitigate degeneration related to ferroptosis in musculoskeletal disorders, including osteoarthritis (OA), muscle injury, and intervertebral disc degeneration (IVDD). Several polyphenol compounds enhance the core anti-ferroptotic defense: resveratrol, curcumin nanosponges, and caffeic acid boost the SLC7A11/GPX4 signaling axis. EGCG nanodrugs and gallic acid reduce key ferroptosis drivers such as iron (Fe^{2+}) overload, mitochondrial ROS (mtROS), and lipid peroxidation. Concurrently, ferroptosis is inhibited through other key pathways, such as direct ACSL4 blockade by paeonol and modulation of the AMPK/mTOR/HIF-1α signaling pathway by urolithin A. This multi-target strategy protects chondrocytes and muscle cells from structural degeneration and redox imbalance. Overall, these polyphenols restore redox homeostasis and protect tissue integrity by inhibiting ferroptotic damage in musculoskeletal systems.

4.5 Fibrotic diseases

In organ-specific chronic disorders like renal fibrosis and hepatic stellate cell activation, ferroptosis manifests as a context-dependent redox pathology. This pathology is marked by iron accumulation and lipid peroxidation, which collectively drive pathological tissue remodeling. These conditions illustrate the dichotomous role of ferroptosis: it is detrimental to parenchymal cells but potentially restorative, when selectively activated in fibrotic or hyperproliferative cellular environments. Natural polyphenols are uniquely positioned to modulate this dichotomy. They can either suppress ferroptosis in parenchymal cells or selectively enhance it in activated fibroblasts and stromal cells, reflecting their context-dependent modulation of redox activity and potential therapeutic selectivity (**Table 2**).

Renal fibrosis signifies the final stage of diverse kidney injuries and is intricately linked to prolonged oxidative stress, mitochondrial dysfunction, and ferroptosis in tubular epithelial cells. Numerous polyphenols specifically target this pathological pathway. Baicalein [146] mitigates unilateral ureteral obstruction (UUO)-induced renal interstitial fibrosis by simultaneously down-regulating profibrotic markers such as TGF-β1 and α-SMA, while reestablishing essential ferroptosis regulatory proteins including SLC7A11, GPX4, and FTH1. These dual antifibrotic and anti-ferroptotic effects indicate that the inhibition of ferroptosis synergizes with the inhibition of canonical TGF-β signaling to stop the deposition of extracellular matrix. Diosmin [147], a glycosylated flavonoid, protects renal tubular cells by directly binding the PAS-B domain of HIF-1α. Its glycosylated flavonoid scaffold forms high-affinity interactions that stabilize HIF-1α and prevent its nuclear translocation. This structure-dependent binding blocks transcriptional activation of FABP4, reducing lipid uptake and metabolism, thereby decreasing ACSL4-mediated lipid peroxidation, labile iron accumulation, and MDA levels, while enhancing GPX4 and SOD2 expression. Functionally, this cascade mitigates tubular damage, collagen deposition, and fibrosis in UUO mice, revealing a clear link between the glycosylated flavonoid structure of Diosmin and its anti-ferroptotic, anti-fibrotic activity. Along with these effects, myricanol [148] activates mitochondrial transcription factor A (TFAM) and zinc and ring finger 1 (ZNRF1), which helps keep mitochondria healthy and controls iron transport by increasing lipocalin-2 levels. These effects collectively contribute to the mitigation of tubular ferroptosis and renal fibrosis. In a hyperuricemia-induced fibrosis model, a mixture of chlorogenic acid [149], p-coumaric acid, luteolin, myricetin, and kaempferol from hazel leaves alleviates oxidative and mitochondrial stress and inhibits ferroptosis by activating the NRF2/GPX4 signaling pathway, demonstrating synergistic multi-component protection against CKD.

Simultaneously, diverse renal pathologies exhibit context-dependent engagement of ferroptosis. Luteolin [150], a flavonoid, binds the ligand-binding domain of NR4A1 via its C-5, C-7, C-3′, and C-4′ hydroxyls forming 2–4 hydrogen bonds and hydrophobic contacts, inhibiting NR4A1 transcriptional repression of Slc7a11, thereby enhancing cystine uptake and GPX4 activity, reducing lipid peroxidation and ferroptotic tubular injury. Quercetin [151] safeguards against ochratoxin A (OTA)-induced nephrotoxicity by

reinstating GPX4 expression and attenuating ACSL4 and HO-1 levels, thereby effectively reversing the ferroptotic signature in kidneys exposed to the toxin.

In the liver, ferroptosis plays a contradictory and context-dependent role: its inhibition safeguards hepatocytes from apoptosis, while its activation specifically eradicates activated hepatic stellate cells (HSCs) [152], consequently diminishing fibrotic scarring. This duality renders hepatic fibrosis a suitable model for exploring the context-dependent effects of polyphenols in influencing ferroptosis. Salvianolic acid B (Sal B), a phenolic compound from *Salvia miltiorrhiza*, reduces CCl_4-induced hepatic fibrosis by targeting extracellular matrix protein 1 (Ecm1) and improving its interaction with SLC7A11 to stabilize cystine uptake and inhibit ferroptosis in hepatocytes. *Ecm1* knockdown negates the protective effect of Sal B, establishing Ecm1 as an essential mediator of its anti-ferroptotic activity [153].

In contrast, wogonoside, a flavonoid derived from *Scutellaria*, elicits an opposing yet equally advantageous effect by selectively inducing ferroptosis in activated HSCs through the SOCS1/p53/SLC7A11 signaling pathway. Wogonoside [154] selectively induces ferroptosis in HSCs by down-regulating SLC7A11 and GPX4 and promoting mitochondrial condensation, while sparing hepatocytes, leading to decreased expression of α-SMA and collagen I. Ellagic acid [155] also promotes ferroptosis in HSCs by inhibiting the formation of the VAMP2-dependent SNARE complex. This inhibits the trafficking of FPN1, which causes intracellular iron retention and increasing lipid peroxidation. Schisandrin B engages an immunomodulatory mechanism by polarizing $Ly6C^+$ macrophages through the Wnt signaling pathway. This induces GPX4-dependent ferroptosis in HSCs and promotes fibrotic resolution [156].

In summary, this section crystallizes the most sophisticated aspect of polyphenols in disease modulation: their ability to act as dual-function regulators of ferroptosis within the intricate tissue ecosystem of fibrosis. The data from renal and hepatic models demonstrate that certain polyphenols can concurrently inhibit ferroptosis in functional parenchymal cells such as hepatocytes and tubular epithelial cells, while facilitating its execution in activated pro-fibrotic cells such as hepatic stellate cells. This cell-context-dependent duality, exemplified by salvianolic acid B's protection of hepatocytes and wogonoside's induction of ferroptosis in HSCs, is rooted in their ability to dynamically recalibrate disparate signaling pathways, such as ECM1/SLC7A11 for protection and SOCS1/p53 for potentiation. This selectivity is dictated by the distinct redox and metabolic states of different cell types. This conclusively establishes polyphenols not as mere antioxidants, but as advanced, cell-type-specific redox rheostats that utilize the hormetic principle to dismantle the fibrotic cascade at its core, suggesting a potential therapeutic strategy to mitigate fibrosis while supporting tissue function.

Table 2. Polyphenol-mediated ferroptosis modulation in fibrotic diseases

Disease	Polyphenol	Modulatory role	Pathological mechanism	Ferroptosis-related mechanism	*In vivo* model	*In vitro* model
Renal interstitial fibrosis	Baicalein	Inhibitor	↓ TGF-β1, α-SMA, ROS &	↑ SLC7A11, GPX4 & FTH1	UUO-induced renal fibrosis	Erastin-induced ferroptosis in

			MDA; ↑ SOD, GSH		(rat)	MPC-5 renal cells
Calcium oxalate-induced nephrolithiasis	Luteolin	Inhibitor	↓ Renal fibrosis, lipid peroxidation & mitochondrial injury	↑ NR4A1-SlC7A11-GPX4; Binding NR4A1	Glyoxylate (100 mg/kg, 12 d)-induced mouse model	HK-2 cells (CaO_X-induced injury)
OTA-induced nephrotoxicity	Quercetin	Inhibitor	↓ BUN, CRE, TNFα, Il6, lipid peroxidation	↓ ACSL4, HO-1; ↑ GPX4	C57BL/6 mice exposed to OTA	NA
UUO-induced renal fibrosis	Diosmin	Inhibitor	↓ Collagen deposition	↓ MDA, ACSL4; ↑ GPX4	UUO-induced renal fibrosis	HK-2 cells stimulated with TGF-β1
CKD model	Myricanol	Inhibitor	↓ Mitochondrial injury and fibrosis markers	↑ TFAM	UUO-induced renal fibrosis; *Tfam*-deficient mice	HK-2 cells stimulated with TGF-β1
Hyperuricemia-induced renal fibrosis	Hazel leaf polyphenols (chlorogenic acid, p-coumaric acid, luteolin, myricetin, kaempferol)	Inhibitor	↓ UA, BUN, CRE; ↓ Oxidative stress & fibrosis; mitochondrial injury	↑ NRF2-GPX4 axis	Yeast extract + adenine + oteracil potassium-induced hyperuricemia model (C57BL/6 mice)	NA
Liver fibrosis	Salvianolic acid B	Inhibitor	↓ Inflammation and HSCs activation	↑ Ecm1; strengthening Ecm1-SLC7A11 interaction	CCl_4-induced hepatic fibrosis (WT & hepatocyte-specific *Ecm1* knockout mice)	LO2 epatocytes ± Erastin/CCl_4 (*Ecm1* knockdown)
Liver fibrosis	Schisandrin B	Activator	↓ Collagen deposition, α-SMA; Regulation $Ly6C^+$ macrophage polarization	Induction of GPX4-dependent ferroptosis in HSCs	CCl_4-induced hepatic fibrosis (mouse)	$Ly6C^+$ macrophage-HSC co-culture
Liver fibrosis	Wogonoside	Activator	↓ α-SMA; Mitochondrial condensation; ↓ ECM	↑ SOCS1, p53; ↓ SLC7A11, GPX4 & GSH	CCl_4-induced hepatic fibrosis (mouse)	HSC-T6 cells
Liver fibrosis	Ellagic acid	Activator	↓ Fibrosis; ↑ lipid peroxidation & Fe^{2+} retention	Promoting VAMP2 degradation; blocking FPN translocation	CCl_4-induced hepatic fibrosis (mouse)	LX-2 cells

5. Translational considerations for polyphenols and ferroptosis

There is substantial preclinical evidence demonstrating that polyphenols play a central role in regulating ferroptosis, yet their clinical applications remain limited. Translating this potential into effective therapies is obstructed by a series of challenges, ranging from the intrinsic instability of the compounds to the intricate complexity of human pathophysiology. Overcoming these challenges is essential to advance the field and realize the therapeutic promise of polyphenols.

5.1 Bioavailability and metabolism

Polyphenols face significant physicochemical hurdles in reaching their target sites, primarily due to their intrinsic instability upon exposure to environmental factors, limited intestinal absorption, and poor permeability across the blood-brain barrier (BBB) [157]. Due to their chemical instability and sensitivity to light, oxygen, and pH, they are difficult to store and formulate effectively [158]. Furthermore, physical properties such as molecular weight and polarity, alongside sensory characteristics like bitterness, can negatively impact patient compliance [159]. Intestinal absorption is strictly regulated and often relies on epithelial transporters such as glucose transporters or monocarboxylate transporters (MCTs), which are easily saturated, thereby limiting uptake [160]. Anthocyanins [64] typically exhibit low bioavailability unless enhanced by binding to dietary fibers. Crossing the BBB remains a specific hurdle, with only minute quantities of compounds like resveratrol typically detectable in brain tissue [161].

Upon ingestion, polyphenols undergo substantial phase II metabolism—such as glucuronidation and sulfation—in the liver and intestinal epithelium [162]. Subsequently, gut microbiota transform many of these compounds into a diverse array of metabolites [163], meaning bioactive molecules circulating in the bloodstream are often a complex mixture of derivatives rather than the parent compounds [164]. Given the uniqueness of each individual's gut microbiome, the resulting metabolic profile and response to polyphenols are highly variable [165]. The pro-oxidant, lipid peroxide- and iron-rich microenvironment of ongoing ferroptosis may alter polyphenol stability and metabolism, potentially altering pharmacokinetics in disease contexts. This reciprocal interaction is critical yet underexplored for translating preclinical efficacy.

There is abundant literature using *in vitro* or animal models to study the effects of dietary supplements on gut microbiota, human studies remain relatively limited [166]. More long-term intervention studies are needed to verify these benefits and quantify optimal dosage ranges in a human context [167]. Therefore, the direct translation of pre-clinical efficacy to humans requires cautious interpretation and underscores the necessity for more long-term human intervention studies to verify benefits and define optimal dosing.

Elimination pathways subsequently clear these metabolites from the body. While the primary excretion route is renal [168], biliary excretion plays a crucial role for hydrophobic compounds such as curcumin [169]. Of particular concern, polyphenols can modulate the activity of cytochrome P450 enzymes, leading to altered metabolism of concomitant medications and increasing the risk of adverse drug-nutrient interactions [170, 171]. High doses of polyphenols are associated with possible hepatotoxicity, indicating the need to balance efficacy and safety [172]. Thus, understanding the delicate balance between therapeutic efficacy and metabolic toxicity is a prerequisite for clinical application [173].

5.2 Mechanistic and model limitations

Translational efforts are further hampered by the inherent limitations of conventional research models. While *in vitro* systems are valuable for mechanistic screening, they often lack the metabolic and cellular complexity of whole organisms, may overestimate efficacy relative to complex biological systems [150]. A prime example of this discrepancy involves the cystine/glutamate antiporter (system Xc^-). In cell cultures [174], cysteine is predominantly present as oxidized cystine, making cells highly dependent on system Xc^- for

uptake. However, in human plasma, cysteine exists in reduced forms accessible via neutral amino acid transporters, rendering systemic SLC7A11 inhibition less effective *in vivo* than *in vitro*. Similarly, genetic models like *Gpx4* systemic knockout mice [175] are embryonic lethal, whereas *Slc7a11*-deficient mice [176] exhibit normal lifespans, highlighting compensatory mechanisms absent in isolated cells.

Furthermore, distinguishing ferroptosis from other forms of regulated cell death (e.g., autophagy or apoptosis) remains challenging due to shared signaling nodes [177]. This overlap complicates the identification of whether ferroptosis is the primary driver of disease progression or merely a bystander. To address this complexity, omics technologies have driven a shift toward high-throughput detection and data generation. Techniques such as transcriptomics, phenomics, metagenomics, metabolomics, and proteomics provide unprecedented insights into precision medicine by comprehensively revealing the molecular composition of biological systems [178]. These technologies allow for the systematic, unbiased identification of metabolites and genes, avoiding the limitations of pre-set targets.

Coupled with artificial intelligence and machine learning for analyzing multi-omics datasets [179], these computational approaches enable the prediction of novel molecular interactions and the identification of clinically relevant biomarkers [180]. Recent advances in computational toxicology, exemplified by platforms such as the ToxDP2 database [181], further demonstrate how in silico models can be leveraged to screen structure–toxicity relationships of dietary polyphenols prior to clinical investigation.

However, it is important to recognize that these data-driven and computational tools, while powerful, primarily generate probabilistic associations rather than definitive therapeutic conclusions. At present, it remains scientifically inappropriate to extrapolate disease-specific efficacy solely from polyphenol structural motifs, as structure–activity relationships derived from isolated systems may not consistently apply across tissues or disease contexts. Future structure–activity investigations should therefore adopt a pathway-oriented rather than disease-oriented framework, focusing on how specific chemical features bias polyphenols toward distinct ferroptosis-regulatory nodes. A related and often overlooked challenge is the systematic bias in published evidence. The literature predominantly reports positive findings, while null or negative results on polyphenol efficacy in modulating ferroptosis are underrepresented [182]. This evidentiary skew is compounded by the historical context of the field. As Lesjak [77] notes, the novelty of "ferroptosis" as a defined concept implies that many earlier *in vivo* studies documenting polyphenol-mediated reductions in oxidative stress may have in fact captured ferroptosis inhibition, indicating that the pool of preclinical data supporting this link may be larger than a simple keyword search would suggest.

Ultimately, the successful translation of these integrative approaches depends on strict adherence to rigorous experimental guidelines [183], which remain essential for ensuring reproducibility, biological relevance, and clinical credibility in this highly complex field.

5.3 Translational gaps and synergistic strategies

To bridge this translational gap, future research should be directed toward three strategic pillars: precision medicine, advanced delivery systems [184], and synergistic combination therapies. This involves

stratifying patients based on gut microbiome profiles to ensure the metabolic activation of polyphenols. Equally important is the implementation of context-dependent dosing strategies based on the principle of hormesis [4]. A "low-dose, long-term" approach is likely optimal for chronic conditions like neurodegeneration to enhance cellular defense via NRF2 activation, whereas a “short-term, high-dose” strategy might be required to selectively induce ferroptosis in pathological cells, such as activated stellate cells in fibrosis. However, defining these therapeutic windows remains challenging due to the lack of real-time monitoring tools. Future efforts must validate stable surrogate markers detectable in biofluids—such as specific lipid peroxidation byproducts or ferroptosis-associated proteins in exosomes—to quantify the pharmacodynamic effects of polyphenols in patients.

Parallel to precision medicine, nanotechnology provides a critical strategy to overcome the intrinsic bioavailability and stability limitations of polyphenols. Recent bioengineering innovations—ranging from macrophage-targeted nanocomplexes [126] and biomimetic nanosponges [141] to dual-functional nanodrugs [142] —have successfully achieved cell-specific delivery and controlled release. Notably, natural polymers like chitosan have gained attention due to their biocompatibility and biodegradability. Positively charged chitosan-polyphenol conjugates [185] have been shown to enhance adhesion to the gastrointestinal mucosa, thereby prolonging retention time and improving absorption. These nanocarriers not only protect the active compounds from physiological degradation but also facilitate their accumulation in specific microenvironments characterized by inflammation or iron overload, thereby enhancing the local therapeutic index.

Synergistic application of polyphenols represents another promising yet underexplored translational avenue in non-cancerous diseases. While combination strategies aimed at ferroptosis modulation are well established in oncology [186], their adaptation to chronic disorders—where the therapeutic goal is tissue preservation rather than cell elimination—remains in its infancy. Polyphenols can synergize with standard pharmacological agents, metabolic cofactors, or other natural compounds to achieve multi-target regulation at lower individual doses [187]. For instance, Quercetin [188] combined with rosuvastatin exerts superior inhibition of renal tubular ferroptosis in diabetic nephropathy compared to monotherapy by simultaneously targeting lipid metabolism and iron transport. Similarly, the combination of propofol and salvianolic acid A [189, 190] attenuated cardiac ischemia-reperfusion injury via the CD36/AMPK signaling pathway. Additionally, the herbal pair luteolin and astragaloside IV [191] promoted neural repair following spinal cord injury via synergistic antioxidant effects. Integrating polyphenols into multi-target regimens thus represents a feasible strategy to enhance efficacy, improve safety profile, and reduce the economic burden of long-term management.

5.4 Polyphenols and exercise in ferroptosis regulation

Emerging evidence reveals a convergent role for polyphenols and regular physical exercise in regulating ferroptosis. Exercise stimulates the release of exerkines [192]—such as irisin, BDNF, and FGF21—that act as systemic mediators, optimizing iron metabolism, lipid peroxidation, and redox

homeostasis to prevent excessive ferroptosis. Polyphenols, including quercetin [193], resveratrol and hesperidin [194], complement these effects by directly scavenging reactive oxygen species, modulating key ferroptosis regulators such as GPX4 and SLC7A11, and enhancing mitochondrial biogenesis through AMPK/SIRT1/PGC-1α signaling. Together, these interventions may contribute to an environment in which oxidative stress is mitigated without impairing adaptive cellular responses.

In specific organ contexts, the interplay between polyphenols and exercise reveals notable translational potential. In the liver, irisin [195] released during exercise protects hepatocytes from ferroptotic damage and inflammation by activating the NRF2/GPX4 signaling pathway, an effect that can be further supported by dietary polyphenols. Skeletal muscle exhibits fiber-type dependent regulation, with lifelong aerobic exercise upregulating GPX4, SLC7A11, and ferritin heavy chain (FTH) to reduce age-related ferroptosis, while polyphenol supplementation [196] enhances mitochondrial biogenesis, improves muscle function, and attenuates inflammatory signaling. In polycystic ovary syndrome, aerobic exercise combined with irisin [197] suppresses granulosa cell ferroptosis via the NCOA4-FTH signaling axis, restoring ovarian function under hyperandrogenic stress. Similarly, in the central nervous system, exercise modulates ferroptosis by balancing iron homeostasis and oxidative stress [198], a process that may be reinforced by polyphenol intake to support neuroprotection and mitochondrial integrity in aging-related neurodegenerative conditions [199].

Taken together, the current evidence positions the combination of polyphenols and regular physical activity as a promising, non-pharmacological strategy to modulate ferroptosis across multiple tissues in chronic diseases. Rather than acting merely as antioxidants, polyphenols complement exercise-induced systemic signals, such as exerkines, to fine-tune iron metabolism, lipid peroxidation, and redox homeostasis, thereby preserving cellular resilience while preventing pathological ferroptosis. Future investigations should aim to delineate these mechanistic interactions more precisely, explore optimal combinatorial regimens, and expand translational studies beyond preclinical models, ultimately laying a conceptual foundation for lifestyle-based interventions that leverage ferroptosis regulation to mitigate chronic disease progression.

6. Conclusion

This review delineates a paradigm in which ferroptosis functions not merely as a novel cell death pathway, but as a central signaling nexus that integrates metabolic dysregulation, oxidative stress, and inflammatory cascades across a range of non-cancerous chronic diseases [9]. In addition to establishing its pathological significance, our synthesis articulates a complex framework for comprehending natural polyphenols, potentially reclassifying them from general antioxidants to context-sensitive network modulators, whose therapeutic significance resides in dynamically recalibrating the cellular redox environment, rather than simply neutralizing free radicals.

The recurrent involvement of shared pathways, such as iron homeostasis, lipid peroxidation, and the NRF2-GPX4 signaling axis, across diverse diseases confirms that polyphenols engage a core ferroptosis network. The present synthesis advances the key insight that their disease-specific therapeutic effects stem not from unrelated mechanisms, but from the selective and prioritized modulation of this network within

distinct pathological contexts. In neurodegeneration, the modulation is biased toward iron chelation and neuronal membrane stabilization. In metabolic diseases, it focuses on countering lipotoxicity and mitochondrial dysfunction. In the cardiovascular system, network activity converges on the SIRT1 signaling pathway to preserve post-mitotic cells. Notably, in fibrosis, polyphenols appear to exert cell-type-selective effects, potentially inhibiting ferroptosis in parenchymal cells while promoting it in fibrogenic cells. Thus, natural polyphenols emerge as precise modulators capable of fine-tuning a fundamental cell death pathway. This capacity for context-selective modulation provides the mechanistic rationale for their targeted application within the framework of precision redox medicine.

The strongest evidence supporting this concept lies in the disease-specific functional roles of polyphenols, as highlighted in this article: they stabilize redox networks in the nervous system, act as metabolic adaptogens in the liver and kidneys, protect cardiovascular health, and, most interestingly, act as dual-purpose rheostats that resolve fibrosis by regulating ferroptosis in specific cell types. This functional versatility, rooted in hormesis, demonstrates a level of context-discriminatory precision that is largely unattainable by conventional single-target drugs. The relationship between polyphenols and ferroptosis offers a system-level explanation for the well-documented health benefits of plant-rich diets and herbal medicine. This insight transforms the field from a descriptive catalog of observed effects into a predictive science of redox-based interventions. Therefore, by reconceptualizing polyphenols from generic antioxidants to context-selective precision modulators of ferroptosis, this article not only provides a foundational rationale for their targeted therapeutic development but also integrates their action into the emerging paradigm of precision redox medicine, offering a novel framework for chronic disease intervention.

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Declaration of competing interest

The authors declare that they have no competing interests.

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