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Review

Regulatory Effects of Plant-Derived Phenolic Compounds on Ferroptosis: A Novel Paradigm in Cancer Therapy

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Abstract

Ferroptosis is a recently identified, iron-dependent form of regulated cell death characterized by excessive lipid peroxidation and membrane damage, and it has emerged as a promising therapeutic target in cancer treatment. In recent years, increasing attention has been directed to plant-derived phenolic compounds due to their potent redox-modulating, metal-chelating, and signaling-regulatory properties. This review provides a comprehensive overview of the molecular mechanisms by which phenolic compounds regulate ferroptosis in cancer cells. Phenolics modulate ferroptosis through multiple pathways, including suppression of glutathione peroxidase 4 (GPX4), depletion of intracellular glutathione (GSH), disruption of iron homeostasis via ferritinophagy, and acceleration of lipid peroxidation mediated by acyl-CoA synthetase long-chain family member 4 (ACSL4) – and arachidonate lipoxygenase (ALOX)-dependent pathways. In addition, redox-sensitive signaling axes, particularly the nuclear factor erythroid 2-related factor 2 (NRF2) pathway, play a dual role by conferring cytoprotective effects in normal cells while promoting ferroptosis resistance in tumor cells. Recently, in silico, network pharmacology, and omics-based studies further reveal that phenolic compounds exert their effects via complex multi-target networks rather than single protein inhibition. Moreover, nanotechnological carrier systems significantly improve the bioavailability, tumor selectivity, and ferroptosis-inducing efficacy of phenolic compounds. Collectively, the available preclinical evidence highlights plant-derived phenolics as promising ferroptosis modulators and potential adjuvant agents in cancer therapy. Unlike previous reviews that focus primarily on either ferroptosis signaling or general anticancer effects of polyphenols, this review integrates molecular mechanisms, systems-level analyses, and delivery strategies to present a unified framework for phenolic-driven ferroptosis modulation in cancer.

Keywords: Cancer therapy, ferroptosis, lipid peroxidation, network pharmacology, phenolic compounds

1. Introduction

Cancer is the second leading cause of mortality worldwide after cardiovascular diseases, with millions of new cases diagnosed each year (1). Despite advances in conventional treatment strategies such as surgery, chemotherapy, and radiotherapy, tumor heterogeneity, multidrug resistance (MDR), therapy-associated systemic toxicity, and high recurrence rates significantly limit the overall efficacy of cancer treatment (2-4). Therefore, in recent years, the identification and therapeutic targeting of novel regulated cell death mechanisms independent of apoptosis have become a priority area in oncological research (5).

In this context, ferroptosis was defined in 2012 as an iron-dependent, lipid peroxidation-driven, non-apoptotic form of cell death, opening a new era in cancer biology (6,7). Ferroptosis is characterized by intracellular free iron accumulation, excessive production of reactive oxygen species (ROS), peroxidation of polyunsaturated fatty acids, and the collapse of antioxidant defense systems (7,8). In this process, glutathione peroxidase 4 (GPX4) and intracellular glutathione (GSH) levels play a central regulatory role. Inhibition of GPX4 activity or depletion of GSH irreversibly commits cells to ferroptotic death (9).

Due to their increased metabolic activity, elevated iron demand, and pronounced oxidative stress burden, cancer cells are considerably more susceptible to ferroptosis than normal cells (5). In aggressive tumor types such as hepatocellular carcinoma, pancreatic adenocarcinoma, triple-negative breast cancer, glioblastoma, and lung cancer, pharmacological modulation of ferroptosis pathways has been reported to yield significant antitumor effects (7,10). However, the identification of agents capable of selectively inducing ferroptosis while exhibiting minimal toxicity in healthy tissues remains a major unmet research need.

Natural products, particularly plant-derived secondary metabolites, occupy an important place in cancer chemoprevention and therapy owing to their multi-target mechanisms of action and low toxicity profiles (11-13). Among these compounds, plant phenolics represent a broad phytochemical class encompassing phenolic acids, flavonoids, stilbenes, and lignans (14,15). Traditionally recognized for their strong antioxidant properties, phenolic compounds have recently been shown to function not only as free radical scavengers but also as bioactive molecules capable of bidirectionally regulating cellular redox homeostasis (16-18).

An increasing number of molecular and cellular studies demonstrate that plant phenolics can regulate ferroptosis through direct or indirect mechanisms (17,19-21). Phenolic compounds influence ferroptosis via multiple pathways, including modulation of iron homeostasis (21), regulation of ferritin metabolism (22, 23), inhibition of GPX4 activity or suppression of GSH synthesis (24) and activation nonheme iron-based arachidonate lipoxygenase (ALOX)-dependent lipid peroxidation pathways (25). Moreover, activation of redox-sensitive signaling cascades such as nuclear factor erythroid 2-related factor 2 (NRF2) plays a central role in the bidirectional regulatory effects of phenolics on ferroptosis (26-28).

It has been reported that certain phenolic compounds such as resveratrol, quercetin, epigallocatechin gallate (EGCG), and curcumin increase intracellular free iron accumulation, suppress GPX4 activity, and trigger lipid ROS production in cancer cells, thereby inducing ferroptotic cell death (21,29-31). Morever, phenolic acids such as gallic acid, chlorogenic acid, and rosmarinic acid have been shown to reduce iron-mediated oxidative damage limit lipid peroxidation, and suppress ferroptosis by stabilizing the GSH-GPX4 axis in normal cells (33-35), This bidirectional regulatory effect clearly indicates that the phenolic-ferroptosis interaction is highly dependent on the type of compounds, dose, and cellular context.

The heightened susceptibility of cancer cells to ferroptosis, coupled with the ability of phenolics to protect healthy cells, highlights the exceptional therapeutic selectivity of these compounds. Indeed, preclinical studies have demonstrated that the combination of phenolic compounds with conventional chemotherapeutics can enhance therapeutic responses, suppress chemotherapy resistance, and potentiate ferroptosis-mediated cell death (36,37).

Nevertheless, the clinical translation of phenolic compounds is hindered by major limitations such as low bioavailability, rapid metabolism, limited tissue penetration, and unfavorable pharmacokinetic properties. To overcome these challenges, nanotechnological delivery systems based on polymeric nanoparticles, lipid-based carriers, chitosan, alginate, and liposomes have been developed in recent years, and these systems have been shown to significantly enhance the ferroptosis-modulating efficacy of phenolic compounds (38,39).

Collectively, these findings indicate that plant phenolics are not merely conventional antioxidant molecules, but rather multifunctional and selective natural anticancer agents capable of regulating ferroptosis through iron metabolism, lipid peroxidation, and antioxidant defense systems. When

the unique position of ferroptosis in cancer biology is combined with the pleiotropic redox-modulatory effects of phenolics, it becomes evident that these compounds may occupy a central role in next-generation ferroptosis-based therapeutic strategies.

In this review, the chemical classes of plant phenolics, the molecular mechanisms of ferroptosis, the cellular and molecular regulatory roles of phenolic-ferroptosis interactions, current preclinical evidence, and the clinical translation potential of nanotechnological carrier systems are comprehensively addressed from an integrated perspective. Thus, this work aims to elucidate how phenolic-based approaches targeting ferroptosis may establish a new paradigm in cancer therapy.

2. Ferroptosis

Ferroptosis is a regulated, iron-dependent, lipid peroxidation–driven and non-apoptotic form of cell death that was first described by Dixon et al. in 2012. Unlike apoptosis, necrosis, and autophagy, ferroptosis does not involve classical apoptotic hallmarks such as caspase activation, DNA fragmentation, or formation of apoptotic bodies (6,7). At the morphological level, ferroptotic cell death is characterized by mitochondrial shrinkage, loss of cristae, and increased density of the outer mitochondrial membrane, while nuclear integrity is largely preserved (40).

From a biochemical perspective, the fundamental determinants of ferroptosis can be summarized as intracellular Fe^{2+} accumulation, increased production of ROS, peroxidation of polyunsaturated fatty acids (PUFAs), and collapse of antioxidant defense systems (8). The complex molecular landscape of ferroptosis presents a vital frontier for medical research. Emergent data have identified innovative regulatory targets, paving the way for advanced pharmacological interventions to mitigate or harness this cell death pathway in various clinical contexts.

2.1. Central Regulators of Ferroptosis

2.1.1. Iron Homeostasis

Iron homeostasis is a tightly controlled cellular process that ensures sufficient iron availability for essential metabolic functions while preventing iron-induced oxidative damage. At the core of ferroptosis lies the expansion of the intracellular labile iron pool (LIP). Iron catalyzes the formation of highly reactive hydroxyl radicals (•OH) from hydrogen peroxide via the Fenton reaction, thereby initiating the lipid peroxidation cascade and cell death (41).

Multiple iron-regulatory pathways converge to modulate ferroptosis sensitivity. Enhanced iron uptake via the transferrin-transferrin receptor 1 (TFR1) axis increases intracellular iron loading, while endosomal ferrireductases such as six-transmembrane epithelial antigen of prostate 3 (STEAP3) facilitate the conversion of Fe^{3+} to the more reactive Fe^{2+} form (41). Simultaneously, impairment of iron storage mechanisms, particularly through the downregulation of ferritin heavy chain-1 (FTH1), limits iron sequestration and further enlarges the LIP. A critical contributor to this process is ferritinophagy, a selective form of autophagy mediated by nuclear receptor coactivator 4 (NCOA4), which promotes lysosomal degradation of ferritin and releases stored iron into the cytosol. Therefore, excessive activation of ferritinophagy causes intracellular iron overload, which further triggers oxidative stress and ferroptosis (42).

In addition to increased iron import and mobilization, ferroptosis is further reinforced by reduced iron export. Suppression of ferroportin-1 (FPN1), the sole known cellular iron efflux transporter, leads to intracellular iron retention and amplifies oxidative stress (43). Collectively, these alterations establish a pro-ferroptotic iron landscape characterized by sustained Fe^{2+} accumulation and heightened vulnerability to lipid peroxidation.

Notably, cancer cells exhibit profound alterations in iron metabolism, including elevated iron demand, increased TFR1 expression, and dysregulated ferritin dynamics, which render them particularly susceptible to ferroptosis (44). This iron-addicted phenotype creates a therapeutic window in which modulation of iron homeostasis can selectively induce ferroptotic death in malignant cells while sparing normal tissues. Consequently, targeting iron regulatory networks has emerged as a promising strategy for ferroptosis-based cancer therapies and for enhancing the efficacy of ferroptosis-inducing agents.

2.1.2. Lipid Peroxidation

The execution phase of ferroptosis is governed by the iron-dependent oxidative degradation of PUFAs within membrane phospholipids. Due to their bis-allylic hydrogen atoms, PUFAs are highly susceptible to radical-mediated peroxidation, rendering cellular membranes particularly vulnerable under conditions of redox imbalance. Lipidomics studies have identified phosphatidylethanolamine (PE) species containing arachidonic acid (AA) and adrenic acid (AdA) as the most critical lipid substrates driving ferroptotic cell death (45).

Chain reactions of lipid peroxidation initiated by free radicals and Fe^{2+} cause irreversible damage to the cell membrane, disrupt membrane integrity, and trigger cell death (6). Toxic aldehydes generated as a result of lipid peroxide decomposition, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), further exacerbate cellular dysfunction by forming covalent adducts with proteins and DNA (16).

Enzymatic incorporation of these PUFAs into membrane phospholipids by ACSL4 and lysophosphatidylcholine acyltransferase 3 (LPCAT3) further sensitizes cells to ferroptosis (46).

Ferroptosis is a highly regulated ROS-dependent type of cell death, derived from free iron overload. Lipid peroxidation is initiated when Fe^{2+} catalyzes the formation of highly reactive oxygen species, which abstract hydrogen atoms from PUFA-containing phospholipids, generating lipid radicals (7). These radicals rapidly react with molecular oxygen to form lipid peroxyl radicals, thereby propagating self-amplifying chain reactions across the membrane bilayer. The uncontrolled accumulation of lipid hydroperoxides leads to irreversible membrane damage, increased membrane permeability, and loss of membrane integrity, ultimately culminating in ferroptotic cell death (47).

Beyond membrane disruption, the decomposition of lipid hydroperoxides yields highly reactive secondary products, including electrophilic aldehydes such as 4-hydroxynonenal (4-HNE) and MDA (48). These toxic products exacerbate cellular dysfunction by forming covalent adducts with proteins, lipids, and nucleic acids, thereby impairing enzyme activity, altering signaling pathways, and inducing genomic instability (47). The accumulation of such lipid-derived aldehydes represents a point of no return in ferroptosis, reinforcing oxidative damage and amplifying cell death signaling.

Under physiological conditions, lipid peroxidation is tightly controlled by antioxidant defense systems, most notably the GPX4 pathway, which detoxifies phospholipid hydroperoxides using reduced GSH. However, impairment of GPX4 activity or depletion of GSH results in unchecked lipid peroxide accumulation, establishing lipid peroxidation as the central lethal event in ferroptosis (9,24,41).

2.1.3. GSH–GPX4 Antioxidant System

The most critical regulatory mechanism of ferroptosis is the GSH-GPX4 system. GPX4 reduces phospholipid hydroperoxides to non-toxic lipid alcohols and thereby suppresses lipid peroxidation (5). Intracellular GSH serves as an essential cofactor for GPX4 and ensures the continuity of this enzymatic antioxidant defense line. The regulation of ferroptosis through iron homeostasis, lipid peroxidation, and the GSH-GPX4 axis is schematically illustrated in Fig 1.

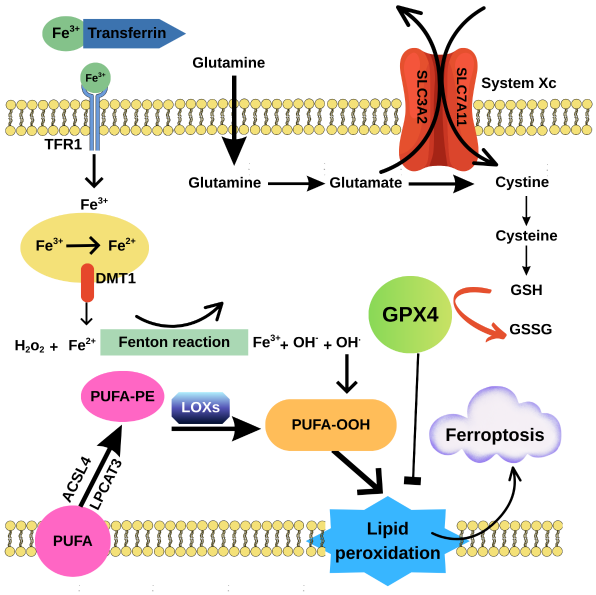

Figure 1. Schematic representation of the molecular regulation of ferroptosis mediated by iron homeostasis, the Fenton reaction, the GSH-GPX4 axis, and lipid peroxidation. TFR1, transferrin receptor 1; DMT1, divalent metal transporter 1; GPX4, glutathione peroxidase 4; LOXs, lipoxygenases; PUFAs, polyunsaturated fatty acids; PE, phosphatidylethanolamine; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; GSH, glutathione; GSSG, glutathione disulfide.

In physiological conditions, cellular iron uptake is primarily mediated by transferrin-bound ferric iron (Fe^{3+}), which enters the cell through TFR1. Within endosomes, Fe^{3+} is reduced to Fe^{2+} and transported into the cytosol via divalent metal transporter 1 (DMT1), thereby increasing the labile iron pool (40,42). Abnormal distribution and excess intracellular Fe^{2+} catalyzes the Fenton reaction with hydrogen peroxide (H_2O_2), generating highly reactive hydroxyl radicals (•OH), which initiate lipid peroxidation cascades (47).

Polyunsaturated fatty acids (PUFA's) are esterified into membrane phospholipids through the coordinated action of ACSL4 and LPCAT3, generating PUFA-containing phosphatidylethanolamine (PUFA-PE) (45). These PUFA-PE species serve as preferred substrates for lipid peroxidation. Iron-dependent LOXs further catalyze the oxidation of PUFA-PE, producing phospholipid hydroperoxides (PUFA-OOH) (49).

Concurrently, glutamine metabolism contributes to ferroptosis sensitivity by fueling glutamate production (6). Glutamate is exported in exchange for cystine via the cystine/glutamate antiporter System Xc^-, composed of SLC7A11 and SLC3A2 subunits. Inhibition or downregulation of System Xc^- leads to reduced cystine uptake, limiting intracellular cysteine availability and consequently impairing GSH synthesis (50). Depletion of GSH or direct inhibition of GPX4 results in uncontrolled accumulation of lipid peroxides (7,8,51).

2.1.4. ACSL4 – and ALOX-Dependent Ferroptosis Pathway

The biosynthesis of lipid substrates involved in ferroptosis is primarily regulated by ACSL4. ACSL4 catalyzes the esterification of AA and AdA into membrane phospholipids, thereby increasing the susceptibility of the cell membrane to ferroptosis (7,49).

The enzymatic arm of lipid peroxidation is mainly mediated by ALOXs. ALOXs, a family of enzymes, produce oxygen lipids from PUFAs, including ALOXE3, ALOX5, ALOX12, ALOX12B, ALOX15, and ALOX15B (52). ALOX12 and ALOX15 are particularly known to mediate p53-induced ferroptosis in cancer cells after an alternative stimuli (52,53). These enzymes directly oxidize PUFA-containing phospholipids, thereby accelerating lipid hydroperoxide formation and promoting the progression of ferroptosis. Inhibition of the ACSL4-ALOX axis confers a strong cytoprotective effect against ferroptosis (40).

2.1.5. NRF2 and Other Redox-Sensitive Signaling Pathways

Nrf2 is a significant transcription factor involved in regulating the intracellular antioxidant stress response and maintaining the stability of the intracellular environment. NRF2 regulates the transcriptional activation of genes involved in GSH synthesis, iron transport, heme regulation, GPX4 expression, and antioxidant enzyme systems, thereby forming a protective shield against ferroptosis (28,54).

While NRF2 mitigates ferroptosis by upregulating downstream antioxidant genes, this protective mechanism paradoxically supports the survival of both healthy and malignant cells. Over the past decade, extensive research has demonstrated that NRF2 activation in neoplastic tissues facilitates tumor progression and metastasis while simultaneously conferring resistance to conventional chemotherapy and radiotherapy (55).

In addition, the p53, mTOR, AMPK, and Hippo signaling pathways have been shown to indirectly modulate ferroptosis through their effects on System Xc^-, lipid metabolism, and intracellular GSH levels (40,56). These findings indicate that ferroptosis is not controlled by a single pathway but rather by a multilayered molecular network.

3. The Role and Mechanisms of Plant-Derived Phenolic Compounds as Ferroptosis Inducers in Cancer

Plant-derived phenolic compounds represent a broad class of phytochemicals synthesized as secondary metabolites and characterized by the presence of one or more hydroxylated aromatic rings. These compounds play central roles in plant defense mechanisms, ultraviolet protection, pigmentation, and resistance to pathogens (9,10). The chemical diversity of phenolics is extensive, and they are mainly classified into phenolic acids, flavonoids, stilbenes, and lignans. Structural differences among these compounds critically determine their bioavailability, intracellular targets, and biological activities (8).

Beyond their ecological functions, phenolic compounds have garnered significant attention in human health due to their potent antioxidant and iron-chelating properties. In the context of ferroptosis, phenolic compounds act as multi-targeted inhibitors. Their structural hydroxyl groups facilitate the scavenging of lipid peroxyl radicals, thereby interrupting the lethal chain reactions that compromise membrane integrity (29-31). Furthermore, many phenolics possess the capacity to sequester intracellular labile iron, preventing the Fenton chemistry-driven generation of hydroxyl radicals (21).

One of the most remarkable features of phenolic compounds in the regulation of ferroptosis is their ability to exert both antioxidant and pro-oxidant effects depending on the dose and the cellular microenvironment (Fig 2). At low concentrations, phenolics protect cells against oxidative damage through their free radical-scavenging and metal-chelating properties; however, at high concentrations or within the acidic and iron-rich microenvironment of cancer cells, they may shift toward a pro-oxidant mode of action (16). This bidirectional behavior enables phenolic compounds to suppress ferroptosis in healthy cells while inducing ferroptosis in cancer cells. From a therapeutic perspective, this unique characteristic endows phenolics with selective anticancer potential (5).

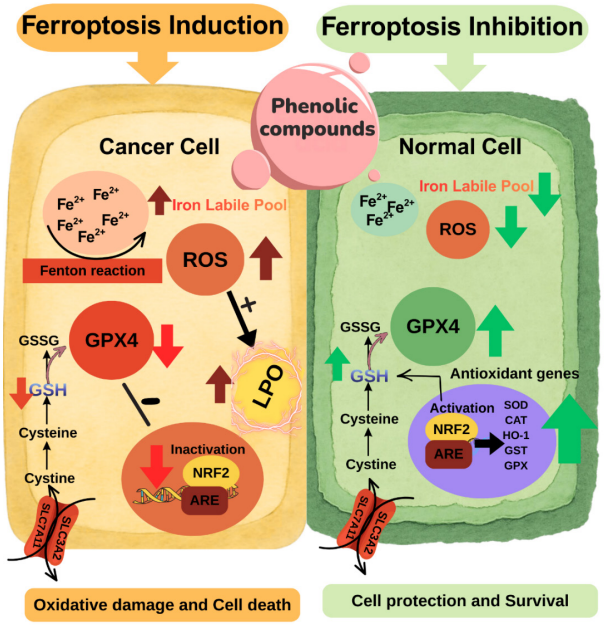

Figure 2. Dual role of phenolic compounds in the regulation of ferroptosis in cancer and normal cells. Phenolic acids (e.g., gallic acid, rosmarinic acid, quercetin) exert context-dependent effects on ferroptosis by differentially modulating iron metabolism, redox homeostasis, and lipid peroxidation pathways. In cancer cells, henolic compounds promote ferroptosis through expansion of the labile iron pool, enhancement of Fenton reaction-driven ROS generation, suppression of GPX4 activity, depletion of GSH, and inactivation of the NRF2/ARE antioxidant axis, leading to excessive LPO, oxidative damage, and cell death. In contrast,, phenolic compounds inhibit ferroptosis by limiting iron-dependent ROS production, activating NRF2/ARE signaling, upregulating antioxidant genes in normal cells (e.g., HO-1, SLC7A11, GPX4), restoring GSH homeostasis, and preventing lipid peroxidation, thereby promoting cellular protection and survival. ARE, antioxidant response element; CAT, catalase; GSH, Glutathione; GSSG, glutathione disulfide; GPX4, glutathione peroxidase 4; HO-1, heme oxygenase 1; LPO, lipid peroxidation; NRF2, Nuclear factor erythroid – 2; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; SOD, superoxide dismutases; SLC3A2, solute carrier family 3 member 2.

3.1. Phenolic Acids

Phenolic acids are phenolic compounds that contain at least one hydroxyl group and a carboxylic acid function attached to a benzene ring. They are low-molecular-weight compounds derived primarily from the shikimate pathway and are subdivided into two main groups according to their carbon skeleton: Hydroxybenzoic acids (e.g., gallic, vanillic, syringic and protocatechuic acids) and hydroxycinnamic acids (e.g., caffeic, ferulic, sinapic, p-coumaric and chlorogenic acids) (14,15). Phenolic acids are widely distributed in cereals, fruits, vegetables, coffee, and medicinal plants and are well known for their strong antioxidant activities. However, recent studies have demonstrated that phenolic acids such as gallic acid, ferulic acid, caffeic acid, and chlorogenic acid not only act as antioxidants but also modulate ferroptosis by increasing iron uptake and ROS generation, and decreasing the GSH/GPX4 levels in cancer (Table 1).

Table 1. Experimental evidence of phenolic acids inducing ferroptosis in cancer models

Phenolic compound	Cancer cell line/model	Key ferroptosis markers	Main outcome	Reference
Gallic acid	HepG2	↓SLC7A11, and GPX4	**Inhibition of Wnt/β-catenin/SLC7A11/GPX4**	(57)
Gallic acid	HCT116 and Caco-2	↑Fe^{2+}, lipid ROS, MDA, ATF4 and TFR1 ↓SLC7A11, GPX4 and SIGMAR1	Growth inhibition of colon cancer cells by inducing ferroptosis	(58)
Gallic acid	HeLa, SH-SY5Y, and H446 cell	↑Fe^{2+}, lipid ROS	GA-induced cytotoxicity	(59)
Gallic acid	NSCLC (A549 and H1299)	↑ROS, MDA, ACSL4 ↓NRF2, SLC7A11, and GPX4	Enhancing NSCLC radiosensitivity by promoting ferroptosis	(60)
Chlorogenic acid	HepG2	↑Fe^{2+}, lipid ROS, MDA, PTGS2, ACSL4, and LPCAT3 ↓GPX4, GSH	Induction of ferroptosis through the PTGS2/AKR1C3/GPX4 axis	(64)
Rosmarinic acid	DLD-1 and LoVo cells	↑NCOA4 ↓SLC7A11, GPX4	Induction of apoptosis and ferroptosis pathway in cisplatin-induced cytotoxicity of CRC cells	(66)
Rosmarinic acid	MDA-MB-231	↑Fe^{2+}, ROS	Ferroptotic and apoptotic cell death via mitochondrial dysfunction and reduced mitochondrial activity	(67)
Rosmarinic acid	HCT-116	↑Fe^{2+}, ROS, MDA, AKR1C3, ACSL4, and LPCAT3 ↓GSH	Triggering ferroptosis via mitochondrial dysfunction and modulation of lipid metabolic pathways	(68)
Ferulic acid	TE-4 and EC-1	↑Fe^{2+}, ROS, MDA, ↓SLC7A11, GPX4, SOD, GSH	Ferroptosis by inhibiting SLC7A11 and GPX4 axis.	(72)
CAPE	MDA-MB 231	↑ROS, MDA ↓GSH	Ferroptosis via HO-1 induction	(74)
Para-coumaric acid (p-CA)	H460 and A549	↑Fe^{2+}, ROS, MDA ↓NRF2 GPX4, xCT, GSH	Induction of erroptosis through the GPX4, xCT, and NRF2 signaling pathways	(75)

ACSL4, acyl-CoA synthetase long-chain family member 4; ATF4, activated transcription factor 4; CAPE, caffeic acid phenethyl ester; GSH, glutathione; GPX4, glutathione peroxidase 4; HO-1, heme oxygenase 1; LPCAT3, lysophosphatidylcholine acyltransferase 3; MDA, malondialdehyde; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid – 2; PTGS2, prostaglandin-endoperoxide synthase 2; ROS, reactive oxygen species; SIGMAR1, sigma-1 receptor; SLC7A11, solute carrier family 7 member 11; SOD superoxide dismutases; TFR1, transferrin receptor 1.

3.1.1. Gallic acid

Gallic acid is a widely distributed phenolic acid belonging to the hydroxybenzoic acid derivatives and it is found in grapes, tea, fruit peels, and many medicinal plants. Its antioxidant, anti-inflammatory, and cytoprotective properties have long been recognized. A recent investigation highlights the dual role of gallic acid (GA) in the regulation of ferroptosis, revealing that its biological effect is fundamentally determined by the cellular context. In malignant settings, GA has been identified as a potent inducer of ferroptosis. For example, in hepatocellular carcinoma (HCC) cells, GA triggers ferroptotic cell death by suppressing the Wnt/β-catenin signaling pathway, which subsequently leads to the downregulation of the cystine/glutamate antiporter SLC7A11 and the primary antioxidant enzyme GPX4 (57). Similarly, Hong et al. (2021) demonstrated that GA treatment significantly restricts the proliferation of colon cancer cells by inhibiting expression of ferroptosis-related proteins SLC7A11 and GPX4 (58). This mechanism leads to catastrophic accumulation of lipid peroxides and iron-dependent ROS, effectively bypassing conventional apoptotic resistance in tumor cells.

Beyond inducing ferroptosis, GA has been reported to exhibit a pleiotropic effect by simultaneously activating three different death mechanisms: apoptosis, necroptosis, and ferroptosis (59). This multifaceted approach allows for the elimination of malignant cells, even in the presence of single-path resistance, because GA disrupts mitochondrial integrity, activates caspases, and facilitates iron-dependent lipid peroxidation. Furthermore, GA may enhance the sensitivity of non-small cell lung cancer (NSCLC) cells to radiotherapy

by disrupting the NRF2-mediated antioxidant defense system, promoting iron accumulation and lipid peroxidation (60).

In contrast, GA functions as a ferroptosis inhibitor and cytoprotective agent in normal physiological contexts and non-cancerous injury models. Due to its strong radical scavenging and iron chelation properties, GA has been shown to protect healthy tissues (e.g., in traumatic brain injury or diabetic cardiomyopathy models) by neutralizing lipid peroxyl radicals and, binding unstable Fe^{2+} ions through their phenolic hydroxyl groups (33,61). By maintaining membrane integrity and preventing the initiation of the Fenton reaction, GA mitigates oxidative damage in normal cells. This differential activity-selectively promoting ferroptosis in neoplastic tissues while acting as a scaffold for cellular survival in healthy cells-highlights GA's therapeutic potential as a selective modulator in redox-based medicine.

3.1.2. Chlorogenic Acid

Chlorogenic acid (CGA) is an ester of caffeic acid and quinic acid and is abundantly found in coffee, apples, pears, and numerous medicinal plants. Traditionally, CGA has been characterized as a robust inhibitor of ferroptosis, primarily valued for its ability to mitigate iron-dependent oxidative stress in healthy tissues through the NRF2/GPX4 signaling axis (35,62,63). However, a recent study by Wu et al. (2025) has challenged this singular perspective, demonstrating that CGA can selectively function as a potent ferroptosis inducer within the context of HCC (64). According to Wu et al., CGA triggers ferroptotic cell destruction in HCC by regulating the reprogramming of arachidonic acid metabolism. This process occurs via the PTGS2/AKR1C3/GPX4 transport pathway, leading to disruption of the cell's antioxidant defense and subsequent lipid peroxidation. This important finding demonstrates that the role of CGA in ferroptosis is highly environment-dependent: while maintaining redox homeostasis and supressing lipid peroxidation in healthy organ models, it can be used to register overcoming cell death resistance in malignant tissues. By targeting the PTGS2/AKR1C3/GPX4 pathway, this research provides novel mechanistic insights into how CGA can serve as a dual-function therapeutic agent; acting as a scaffold for cytoprotection under normal conditions while effectively promoting ferroptotic abnormalities in cancer (64).

However, it should be noted that CGA concentrations used in in vitro studies often exceed plasma levels achievable through diet or conventional administration, due to its limited bioavailability and rapid metabolism. Therefore, while these findings provide valuable mechanistic information on CGA-mediated ferroptosis modulation, improved application strategies may be needed to translate these effects into physiologically and clinically relevant settings.

3.1.3. Rosmarinic Acid

Rosmarinic acid (RA) is a naturally occurring polyphenolic compound found in many plants (e.g., *Rosmarinus officinalis*, *Melissa officinalis*, and *Salvia* species with known antioxidant, anti-inflammatory, and anticancer properties (65). As a plant-derived polyphenolic compound, RA has emerged as a context-dependent regulator of ferroptosis, exhibiting opposing effects in cancerous and non-cancerous cells.

In various cancer models, RA has been shown to promote ferroptotic cell death by disrupting redox homeostasis through downregulation of key antioxidant systems such as GPX4 and SLC7A11, glutathione depletion, intracellular Fe^{2+} accumulation, and increased lipid peroxidation, ultimately making tumor cells susceptible to oxidative damage and chemotherapeutic agents (66-68). In colorectal cancer cell lines (DLD-1, LoVo), RA combined with cisplatin enhances cell death by promoting both apoptosis and ferroptosis. This is evidenced by downregulation of GPX4 and SLC7A11, key antioxidant regulators, and reversal of RA's effects by ferroptosis inhibitors (66).

In contrast, in normal or non-malignant cells exposed to pathological stress (e.g., ischemia-reperfusion injury, liver or kidney damage, and inflammatory conditions), RA functions predominantly as a ferroptosis inhibitor by activating cytoprotective signaling pathways, particularly the NRF2/HO-1 axis, preserving GPX4 activity, and suppressing iron-induced lipid peroxidation (69-71). Liu et al (2025)

reported that RA suppresses ferroptosis and protects neurons via activation of the NRF2 antioxidant pathway and inhibition of KEAP1, reducing oxidative injury cerebral ischemia-reperfusion injury (69). NRF2 protects cells against ferroptosis by transcriptionally activating genes involved in GSH synthesis, GPX4 expression, ferritin production, and antioxidant enzyme systems (26). In recent study, researhers found that RA mitigates acetaminophen-induced liver injury by enhancing antioxidant defense (NRF2/HO-1) and maintaining GPX4 and GSH levels, thereby preventing lipid peroxidation and ferroptosis in hepatocytes (70). This dual behavior highlights the redox-adaptive nature of RA, where its pro-oxidant, ferroptosis-inducing effects primarily manifest in the metabolically and oxidatively sensitive tumor microenvironment, while its antioxidant and ferroptosis-suppressive properties are dominant in normal tissues. This contextual selective regulation positions RA as a promising candidate for ferroptosis-based cancer therapy with a potentially favorable safety profile for non-malignant cells.

3.1.4. Ferulic acid

Ferulic Acid (FA), a ubiquitous dietary phenolic acid found in the cell walls of cereal grains, fruits, and vegetables, has long been celebrated for its potent antioxidant properties. However, recent pharmacological insights have repositioned FA as a context-dependent modulator of ferroptosis.

Emerging evidence indicates that FA can function as a pro-ferroptotic agent in malignant cells by amplifying oxidative stress, increasing intracellular reactive oxygen species and iron accumulation, and promoting lipid peroxidation while simultaneously suppressing key antioxidant defense systems. In esophageal squamous cell carcinoma (ESCC), FA treatment reduced cell viability, increased ROS and iron levels, elevated MDA, and downregulation of the SLC7A11/GPX4 axis; notably, these effects were partially reversed by ferroptosis inhibitors, like deferoxamine, suggesting FA's potential as a pro-ferroptotic anticancer agent (72). Conversely, in non-cancer contexts such as sepsis-induced acute lung injury and oxidative hepatocyte damage, FA mitigated ferroptosis by activating the NRF2/HO-1 antioxidant pathway, increasing GPX4 and GSH, reducing lipid peroxidation and iron overload, and preserving cellular function (73). These findings underscore FA as a compelling candidate for selective ferroptosis-based anticancer investigations with minimal toxicity to healthy cells.

3.2. Flavonoids

Flavonoids, a diverse class of plant secondary metabolites characterized by a polyphenolic a C6-C3-C6 skeleton, represent a cornerstone of natural product research due to their widespread presence in medicinal plants, fruits, and vegetables (76). Based on their chemical structures, flavonoids are classified into **flavonols** (quercetin, kaempferol, myricetin and fisetin), **flavones** (luteolin, apigenin), **flavanones** (naringenin, hesperetin), **flavanols** (catechin, epicatechin), **isoflavones** (genistein, daidzein), and **anthocyanins** (cyanidin, delphinidin) revealing further structural diversity arising from glycosylation and acylation at various hydroxyl and methyl sites (77).

Due to their redox-active chemical structures, flavonoids can modulate key molecular determinants of ferroptosis, including iron homeostasis, ROS formation, lipid peroxidation, and antioxidant defense systems (Table 2). Recent evidence suggests that flavonoids can act as both inducers and inhibitors of ferroptosis, depending on the context. In cancer cells, some flavonoids promote ferroptotic cell death by increasing intracellular unstable iron, enhancing ROS production, suppressing the SLC7A11/GSH/GPX4 axis, and remodeling PUFA-containing phospholipids, thus making tumor cells susceptible to ferroptosis-based therapeutic strategies (31,32). Conversely, in normal or non-malignant cells, flavonoids frequently exert ferroptosis-suppressing effects by activating cytoprotective pathways such as NRF2/ARE signaling, maintaining GPX4 activity, and limiting iron-induced lipid peroxidation (19,24). This dual, cell-context-dependent regulation highlights flavonoids as critical modulators of ferroptosis, emphasizing their potential to selectively target cancer cells while protecting normal tissues from oxidative damage.

3.2.1. Quercetin

Quercetin (QUE), one of the most abundant members of the flavonol subclass, is well known for its strong

antioxidant, anti-inflammatory, and anticancer properties (78). Recent studies have also demonstrated that quercetin promotes ferroptosis by increasing ROS, iron accumulation, and lipid peroxidation while suppressing ferroptosis regulators such as GPX4 and SLC7A11, leading to cancer cell death in lung cancer, glioblastoma, and colon cancer cell lines in association with increased ferroptosis markers.

In gastric cancer cells, QUE has been shown to increase lipid peroxidation and intracellular iron content, inhibit SLC1A5 expression, disrupt NRF2 nuclear translocation, and downregulate the NRF2/xCT/GPX4 axis, thereby triggering ferroptotic cell death and suppressing tumor progression (31). Zhu et al (2024) demonstrated that in oral squamous cell carcinoma models, QUE induced ferroptosis by suppressing SLC7A11, lowering GSH levels, and increasing ROS production in a mTOR/S6KP70-dependent manner (79). Additionally, QUE has been shown to induce ferritinophagy in breast and hepatic cancer cells by facilitating the transport of Transcription Factor EB (TFEB) to the nucleus, an event that triggers lysosomal degradation of ferritin, increasing free iron concentration, promoting ROS and lipid peroxidation, and highlighting its capacity to trigger ferroptosis (30,80). These reports are also corroborated by the results of studies on HEC-1-A endometrial cancer cells. Li et al (2022) showed that in endometrial carcinoma cells, QUE suppressed cell proliferation and migration by inducing ferroptosis (81). Collectively, these findings support quercetin as a pro-ferroptotic flavonoid in cancer models, acting through multiple molecular mechanisms that converge on iron dysregulation, antioxidant inhibition (e.g., GPX4, SLC7A11), and increased oxidative lipid damage.

Table 2. Experimental evidence of flavanoids inducing ferroptosis in cancer models

Phenolic compound	Cancer cell line / model	Key ferroptosis markers	Main outcome	Reference (s)
Quercetin	MCF-7, MDA-MB-231	↑ROS, MDA, Fe^{2+}	Induction of ferroptosis inducing TFEB-mediated ferritinophagy	(30)
Quercetin	AGS, MKN-45 cells	↑ROS, Fe^{2+} ↓NRF2 GPX4, SLC7A11, GSH	Induction of ferroptotic cell death	(31)
Quercetin	Oral squamous cell carcinoma	↑ROS, LPO ↓SLC7A11, GSH, GPX4	Ferroptosis via mTOR/S6KP70-dependent manner	(79)
Quercetin	HepG2 cells	↑ROS, Fe^{2+}, LPO ↓GPX4	TFEB-mediated ferroptosis and Bid-involved apoptosis	(80)
Quercetin	HEC-1-A	↑ROS, Fe^{2+}, TFR-1 ↓GPX4, xCT, ACO1 and FLC	Induction of ferroptotic cell death	(81)
Luteolin	HCT116, SW480, MC38/CT26 cells; colon cancer xenograft model	↑Lipid-ROS, ↓GPX4, GSH	Ferroptotic cell death	(82,83)
Luteolin	DU145 and PC-3 cells; prostate cancer xenograft model	↑ROS, MDA, Fe^{2+} ↓SLC7A11, GPX4, FTH1, and FTL1	Ferritinophagy-induced ferroptosis	(84)
Luteolin	Renal cell carcinoma cells	↑ROS, Fe^{2+}, MDA ↓GSH	Induction of ferroptosis	(85)
Luteolin	U87MG	↑ lipid-ROS ↓GSH	NRF2/xCT/GPX4-mediated ferroptosis	(86)
Naringenin	HOS, U2OS, and MG63; subcutaneous tumor model	↑ROS, Fe^{2+}, LPO ↓GPX4	Induction of STAT3-MGST2 signaling pathway	(87)
Naringenin	HepG2, Hep3B and SNU182 cells; liver cancer xenograft model	↑ROS, Fe^{2+}, MDA ↓GSH	Increasing the efficacy of ferroptosis inducers by attenuating aerobic glycolysis	(88)
Hesperetin	T24 (HTB-4) and 5637 (HTB-9)	↑ROS ↓GPX4	Promotion of apoptosis and ferroptosis	(89)
EGCG	A549 and H1299	↑ROS, MDA, Fe^{2+}, ACSL4 ↓SLC7A11, GPX4	Inhibition of GPX4/SLC7A11	(32)

ACO1, anti-aconitase 1; ACSL4, acyl-CoA synthetase long-chain family member 4; FTL1, ferritin light chain; FTH1, ferritin heavy chain 1; GSH, glutathione; GPX4, glutathione peroxidase 4; MDA, malondialdehyde; MGST2, microsomal glutathione S-transferase 2; NRF2, nuclear factor erythroid – 2; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; TFR-1, transferrin receptor 1

3.2.2. Luteolin

Luteolin (3′,4′,5,7-tetrahydroxyflavone) is a naturally occurring flavonoid found in many fruits, vegetables, and medicinal herbs. While traditionally recognized for its antioxidant and anti-inflammatory properties, accumulated evidence indicates that luteolin can act as a potent ferroptosis inducer in various cancer types through multiple molecular mechanisms, including enhancement of ROS generation, disruption of iron homeostasis, activation of ferritinophagy, GPX4 suppression, and increased lipid peroxidation (Fig 3).

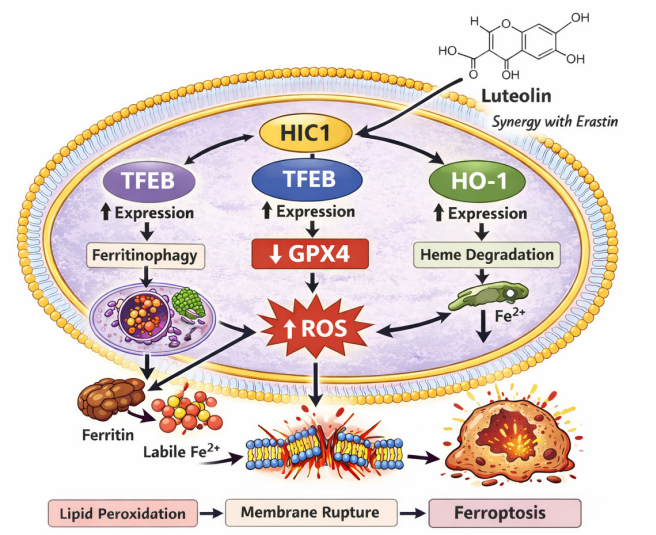

Figure 3. Luteolin-induced ferroptosis in cancer cells through multiple molecular mechanisms. Luteolin induces ferroptotic cell death through the coordinated regulation of antioxidant defense, iron metabolism, and lipid peroxidation pathways. Luteolin exhibits synergistic activity with ferroptosis triggers such as erastin, further intensifying ferroptotic signaling. HIC1, hypermethylated cancer 1; TFEB, transcription factor EB; GPX4, glutathione peroxidase 4; HO-1, heme oxygenase 1; ROS, reactive oxygen species.

Zheng et al. (2023) demonstrated that luteolin exhibits a potent ferroptosis-inducing effect in colon cancer cells primarily through transcriptional repression of GPX4. Mechanistically, luteolin activated the tumor suppressor hypermethylated cancer 1 (HIC1), which directly inhibits GPX4 expression, leading to excessive lipid hydroperoxide accumulation and ferroptotic cell death. Specifically, luteolin showed synergistic therapeutic efficacy with the ferroptosis-inducing erastin, significantly enhancing lipid peroxidation and ferroptosis-related cytotoxicity (82). Consistent with these findings, Cao et al. (2025) reported that luteolin induces GPX4-dependent ferroptosis in colon cancer models and simultaneously enhances antitumor immune activation. Luteolin treatment led to increased lipid peroxidation, disruption of membrane integrity, and upregulation of ferroptosis markers; suggesting that luteolin-induced ferroptosis may also contribute to immunogenic cell death, thereby enhancing antitumor immune responses (83).

In addition to GPX4 inhibition, luteolin promotes ferroptosis by altering intracellular iron metabolism. Fu et al. (2024) demonstrated that luteolin facilitates nuclear translocation of transcription factor EB (TFEB) in prostate cancer cells, leading to activation of the autophagy-lysosome pathway and increased ferritinophagy (84). Ferritin degradation increases the intracellular unstable Fe^{2+} pool, accelerating the formation of reactive oxygen species driven by Fenton chemistry and lipid peroxidation, ultimately triggering ferroptosis. Furthermore, Han et al. (2022) identified heme oxygenase-1 (HO-1) as a critical mediator of luteolin-induced ferroptosis in clear cell renal cell carcinoma (85). Luteolin-mediated upregulation of HO-1 promotes heme degradation, expanding the unstable iron pool and intensifying lipid peroxidation. The combined effects of iron loading and impaired antioxidant defenses make cancer cells highly susceptible to ferroptotic cell death.

Very recent evidence further supports the role of luteolin as a ferroptosis-inducing agent through the modulation of the NRF2/xCT/GPX4 signaling axis, a central pathway governing cellular redox homeostasis and ferroptosis resistance (Table 2). Luteolin has been shown to inhibit tumor growth by suppressing NRF2 activity, leading to downregulation of xCT (SLC7A11) and subsequent intracellular GSH depletion. in glioblastoma cells. Decreased GSH availability compromises GPX4 enzymatic activity, limiting the detoxification of lipid hydroperoxides and promoting excessive ROS accumulation (86). The resulting oxidative imbalance facilitates lipid peroxidation and makes glioblastoma cells susceptible to ferroptotic cell death. These findings demonstrate that luteolin disrupts ferroptosis defense mechanisms not only through transcriptional repression of GPX4 via

HIC1, but also by weakening the NRF2-driven antioxidant network, thus strengthening its role as a multi-target regulator of ferroptosis. Collectively, these studies demonstrate that luteolin triggers ferroptosis through multiple interconnected mechanisms, including GPX4 suppression, ferritinophagy-mediated iron release, HO-1-induced iron accumulation, and sustained lipid peroxidation. Thanks to its ability to target multiple ferroptosis regulatory axes simultaneously, luteolin, especially in combination with known ferroptosis inducers, emerges as a promising natural compound for ferroptosis-based anticancer strategies.

3.2.3. Naringenin and Hesperetin

Natural flavonoids such as naringenin and hesperetin have recently attracted significant attention as modulators of ferroptosis. Naringenin has been shown to exhibit ferroptosis-promoting effects through multiple signaling mechanisms in the context of cancer. In osteosarcoma cells, naringenin treatment significantly reduced cell viability and increased ferroptotic markers, including increased ROS, Fe^{2+} accumulation, and MDA levels; this indicates increased lipid peroxidation consistent with ferroptosis induction (87). Naringenin reduces the expression of MGST2, a gene normally involved in antioxidant defenses; this is associated with decreased GPX4 expression, thus reducing cellular antioxidant capacity and making cells susceptible to ferroptosis.

On the other hand, naringenin has been reported to enhance the efficacy of classical ferroptosis inducers by modulating cancer cell metabolism. In liver cancer cells, naringenin reduces aerobic glycolysis by activating the AMPK-PGC1α signaling axis and shifts cellular metabolism toward increased oxidative stress (88). This metabolic reprogramming lowers the threshold for ferroptosis induction by classical inducers, suggesting that naringenin may synergistically enhance ferroptosis through both metabolic effects and direct signaling pathway regulation.

Compared to naringenin, evidence regarding the direct role of hesperetin in ferroptosis is less extensive but emerging. Network pharmacology and molecular docking studies in bladder cancer cells show that hesperetin not only inhibits proliferation and migration via the PI3K/AKT pathway but also promotes cell death with features consistent with ferroptosis, such as ROS accumulation and decreased GPX4 expression (89). The role of PI3K/AKT signaling is important, as inhibition of this pathway has been associated with susceptibility to ferroptotic triggers in multiple cancer models.

In conclusion, these studies highlight that naringenin and hesperetin primarily influence ferroptosis through modulation of cellular redox balance, suppression of antioxidant defenses, and metabolic stress pathways. While naringenin's ability to inhibit the STAT3-MGST2 axis and enhance AMPK-mediated metabolic reprogramming clearly activates ferroptotic mechanisms, hesperetin's role appears to focus on PI3K/AKT signaling modulation and associated oxidative stress amplification, further supported by the emerging ferroptosis-inducing delivery systems. These flavonoids, alone or in combination with established ferroptosis inducers, stand out as promising natural compounds for ferroptosis-based anti-cancer strategies.

3.2.4. Epigallocatechin Gallate

Epigallocatechin-3-gallate (EGCG) is an important catechin found predominantly in green tea and also naturally occurring in various plant-based foods such as apples, blackberries, and carob. EGCG has been widely reported for its antioxidant, anti-inflammatory, and anticancer properties; however, its role in regulating ferroptosis has only recently begun to emerge. A recent study by Wang et al. (2024) reported that EGCG induced ferroptosis in non-small cell lung cancer (NSCLC). The authors demonstrate that EGCG inhibited the proliferation and survival of tumor cells through the downregulation of tsRNA-13502, a transfer RNA-derived small RNA involved in redox homeostasis. EGCG treatment was shown to activate ferroptotic cell disruption, leading to significant changes in ferroptosis-related markers, including increased lipid peroxidation and iron-dependent oxidative stress (32).

Suppression of tsRNA-13502 by EGCG disrupted cellular antioxidant defense systems, thereby enhancing susceptibility to ferroptosis. Although the precise downstream targets of tsRNA-13502 remain to be fully elucidated, its modulation was associated

with dysregulation of key ferroptosis regulators, suggesting that non-coding RNA–mediated control represents a novel layer of ferroptosis regulation by natural polyphenols. Importantly, restoration of tsRNA-13502 expression partially rescued cells from EGCG-induced ferroptotic damage, confirming the functional relevance of this pathway.

3.3. Stilbenes

Stilbenes represent a narrower group of phenolic compounds characterized by a C6–C2–C6 backbone consisting of two aromatic rings linked by an ethylene bridge. The most well-known member of this group is resveratrol, which is abundant in various plant sources, particularly grapes, peanuts, and red wine (11).

3.3.1. Resveratrol

In addition to its antioxidant, anti-inflammatory, and anticancer effects, resveratrol has attracted considerable attention in recent years for its ferroptosis-inducing effects, particularly in breast, colon, prostate, and liver cancer cells (29). Experimental studies have revealed that resveratrol increases intracellular labile iron levels, suppresses GPX4 activity, and accelerates lipid peroxidation, ultimately leading to ferroptotic cell death (90-98). These properties place stilbenes among the most promising natural compounds in ferroptosis-based anticancer strategies.

A review of the literature reveals that resveratrol exhibits a potent ferroptosis-inducing effect in a wide range of cancer types through multifaceted molecular mechanisms (Table 3). Resveratrol primarily promotes ferroptotic cell death by downregulating GPX4 and system Xc^- (xCT), leading to impaired glutathione metabolism and uncontrolled lipid peroxidation (91,93,95). In triple-negative breast cancer, resveratrol induces ferroptosis via NEDD4L-mediated ubiquitination and proteasomal degradation of GPX4, highlighting a post-translational regulatory mechanism (91). Similarly, in bladder cancer organoids and acute myeloid leukemia cells, resveratrol increases intracellular ROS accumulation and suppresses GPX4-dependent antioxidant defenses in a ROS-dependent manner (93, 95).

Resveratrol modulates ferroptosis not only by directly targeting GPX4, but also through iron metabolism, mitochondrial signaling, and oncogenic pathways. By increasing iron ion accumulation and lipid peroxidation, it sensitizes cancer cells to ferroptosis inducers such as sulfasalazine and cisplatin (96,97). Resveratrol also regulates ferroptosis by inducing autophagy-ferroptosis cross-interaction via EGFR/PI3K/AKT/GPX4, HMMR, and DHODH-mediated mitochondrial pathways and the USP36-SOD2 axis (92,94,98). Specifically, resveratrol has been shown to reshape the tumor microenvironment by increasing $CD8^+$ T cell cytotoxicity through ferroptosis regulation, further supporting its therapeutic importance (94).

In contrast, emerging studies highlight that resveratrol may also play a context-dependent protective role against ferroptosis, particularly in nonmalignant tissues or under conditions of excessive oxidative stress. This dual behavior largely stems from differences in basal ROS levels, iron availability, and antioxidant capacity between normal and cancer cells. In malignant cells, which typically exhibit high basal ROS levels and increased reliance on GPX4-mediated detoxification of lipid peroxides, resveratrol-induced disruption of redox balance and iron homeostasis can exceed cellular defense thresholds, thus promoting ferroptosis. Conversely, in non-malignant cells with lower basal oxidative stress, resveratrol, through its antioxidant capacity and iron chelation properties, maintains redox homeostasis and limits ferroptotic damage by activating antioxidant and cytoprotective pathways, including NRF2 signaling. In conclusion, these findings position resveratrol as a bidirectional ferroptosis regulator that can selectively induce ferroptotic cell death in cancer cells while maintaining normal tissue integrity (90).

3.4. Lignans

Lignans, found in seeds (especially flaxseed), whole grains, and various fruits and vegetables, are a class of plant-derived phenolic compounds formed through the dimerization of phenylpropanoid units. Some lignans, such as enterolactone and enterodiol, are converted by the gut microbiota into more biologically active metabolites. They have been extensively studied for

their antioxidant, anti-inflammatory, and anticancer activities. However, research linking lignans to ferroptosis regulation is extremely limited (Table 3). To date, only a few studies have begun to explore this link, with myrislignan emerging as the best-characterized example (99).

A recent study by Zhou et al. (2023) demonstrated that myrislignan, a naturally occurring lignan and a known NF-κB pathway inhibitor, effectively induced ferroptosis in glioblastoma cells. In this study, myrislignan treatment led to classic signs of ferroptotic cell death, including increased lipid peroxidation, disruption of redox homeostasis, and increased susceptibility to iron-dependent oxidative stress. Mechanistically, these effects were linked to the regulation of epithelial-mesenchymal transition (EMT) through the modulation of the transcription factor Slug (SNAI2), a key EMT driver. Specifically, myrislignan caused downregulation of Slug by suppressing NF-κB signaling, which in turn affected the expression of ferroptosis-related genes and increased susceptibility to ferroptotic triggers (99). While the precise downstream influencers linking key ferroptosis pathways such as Slug and GPX4, the system Xc^- (xCT), or iron metabolism are not fully defined, the study highlights a novel interaction between EMT regulation and ferroptosis susceptibility. EMT is increasingly recognized as a determinant of tumor cell plasticity and treatment resistance, and its modulation by myrislignan suggests that lignans may exert ferroptosis-promoting effects through indirect regulation of transcriptional networks governing redox balance and cell fate decisions.

Since the limited information in the literature, it is currently premature to generalize ferroptosis-regulating effects to all lignans. Further research is needed to elucidate whether other lignan subclasses share this capacity and to identify relevant molecular targets and signaling pathways, including their effects on GPX4 activity, iron homeostasis, and lipid peroxidation cascades.

Table 3. Experimental evidence of stilbenes, lignans, andother phenolic compounds inducing ferroptosis in cancer models

Phenolic compound	Cancer cell line/ model	Key ferroptosis markers	Main outcome	Reference (s)
Resveratrol	MDA-MB-231, SUM159, 4T1	↑ROS, Fe^{2+}, Lipid ROS, MDA ↓GPX4, GSH	Ferroptotic cell death through NEDD4L-mediated GPX4 ubiquitination and degradation	(91)
Oxyresveratrol	MDA-MB-231	↑ROS, Fe^{2+}, Lipid ROS, MDA ↓GPX4	Ferroptosis through suppression of the EGFR/PI3K/AKT/GPX4 signalling axis	(92)
Resveratrol	T24 and UM-UC-3	↑ROS, Fe^{2}, Lipid ROS, ↓GPX4, xCT	Induction of ferroptosis	(93)
Resveratrol	H520	↑ROS, MDA, ACSL4, ↓GSH, SOD, SLC7A11, GPX4	Promotion of ferroptosis through SLC7A11-HMMR interaction	(94)
Resveratrol	AML-193 and OCI-AML-3	↑ROS, Fe^{2}, ↓GPX4	Ferroptotic cell death through Hsa-miR-335-5p/NFS1/ GPX4 pathway	(95)
Resveratrol	Melanoma cell lines	↑ROS, Fe^{2+}, Lipid ROS ↓GSH	Enhancement of sulfasalazine-induced ferroptosis	(96)
Resveratrol	PANC1 and BxPC-3	↑ROS, MDA, ↓SLC7A11, GPX4	Increasing cisplatin sensitivity by modulating dihydroorotatede hydrogenase-mediated ferroptosis	(97)
Resveratrol	MKN-45, MKN-1, SNU-5, AGS; gastric cancer xenograft model	↑ROS, Fe^{2}, MDA, ACSL4 ↓FTH1, GSH, GPX4	Induction of autophagy and ferroptosis by inhibiting USP36–SOD2 axis	(98)
Myrislignan	U87 and U251; intracranial xenograft model	↑ROS, MDA ↓SLC7A11, GSH	Ferroptosis via Slug-SLC7A11 pathway	(99)
Curcumin	A549 and H1299; LLC-bearing mice	↑ROS, Fe^{2}, MDA, ACSL4 ↓SLC7A11, GSH, GPX4	Induction of autophagy and ferroptosis	(21)
Curcumin	MNNG/HOS and MG-63	↓NRF2, SLC7A11, HO-1, GPX4	Induction of ferroptosis regulating the NRF2/GPX4 signaling	(28)
Curcumin	HCT-8	↑ROS, Fe^{2}, MDA ↓GSH, SLC7A11, GPX4,	Ferroptosis via PI3K/Akt/mTOR signaling	(100)

Curcumin	HepG2 cells; Hepa1-6 xenograft mouse model	↑ROS, Fe^{2}, MDA, KEAP1 ↓P62, NRF2	Induction of ferroptosis through modulation of the P62-KEAP1-NRF2-signaling pathway	(101)
Curcumin	HepG2 and SMMC7721	↑Fe^{2}, MDA, ACSL4, PTGS2 ↓GSH, GPX4, SLC7A11	Ferroptotic death via upregulation of ACSL4	(102)
Curcumin	MCF-7, MDA-MB-453; Breast cancer xenograft model (BALB/c nude mice)	↑Lipid ROS, Fe^{2+}, ACSL4, SLC1A5 ↓GPX4, FTL	Promotion of SLC1A5-mediated ferroptosis	(103)
Curcumin	MB-MDA-231	↑ROS, Lipid ROS, Fe^{2+}, HO-1 ↓GSH, FHC	Ferroptotic death by increasing HO-1 expression	(104)
Curcumin analogue, EF24	U2os and Saos-2	↑ROS, Fe^{2}, MDA, HO-1 ↓GPX4	Ferroptotic death by increasing HO-1 expression	(105)
Curcumin	FTC-133, and FTC-238; tissue samples	↑ROS, Fe^{2}, MDA, HO-1 ↓GPX4, GSH	Induction of ferroptosis via HO-1 upregulation	(106)
Curcumin	AGS and HGC-27	↑Fe^{2}, MDA, ACSL4, GSH ↓GPX4, SLC7A11	Autophagy-mediated ferroptosis by inhibiting the PI3K/AKT/mTOR signaling pathway	(107)
Curcumin derivative NL01	Anglne and HO8910PM; ovarian cancer xenograft model	↑Lipid ROS, Fe^{2+} ↓GPX4, SLC11A2	Ferroptosis via HCAR1/MCT1 signaling pathway	(108)
Curcumin	LK-2 and H1650 cells; NSCLC tissue samples; xenograft tumor model	↑MDA, LDH, Fe^{2+}, ACSL4, TFR-1 ↓SOD, GSH, GPX4, SLC7A11	Induction of ferroptosis through the DMRT3/SLC7A11 axis	(109)

ACSL4, acyl-CoA synthetase long-chain family member 4; DMRT3, Doublesex and Mab-3 related Transcription Factor 3; FTH1, ferritin heavy chain 1; FTL1, ferritin light chain; GSH, glutathione; GPX4, glutathione peroxidase 4; HCAR1, hydroxycarboxylic acid receptor 1; HO-1, heme oxygenase 1; KEAP1, Kelch-like ECH-associated protein 1; MCT1, monocarboxylate transporter; MDA, malondialdehyde; NRF2, nuclear factor erythroid – 2; PTGS2, prostaglandin-endoperoxide synthase 2; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; SLC11A2, solute carrier family 11 member 2; TFR-1, transferrin receptor 1

4. Other Phenolic Compounds As Ferroptosis Inducer

4.1. Curcumin

Curcumin is a polyphenolic compound isolated from the rhizomes of *Curcuma longa* and exhibits a broad spectrum of biological activities. Recent literature indicates that curcumin triggers ferroptotic cell death in cancer cells, and that this occurs through a wide range of mechanisms (Table 3). These mechanisms include suppression of the antioxidant system, increased lipid peroxidation, modulation of signaling pathways (PI3K/Akt/mTOR, NRF2), and processes associated with autophagy (21,28). These activities of curcumin reinforce the emerging importance of ferroptosis in anticancer therapy.

A decrease in GSH levels and suppression of GPX4 activity are necessary to trigger ferroptosis. Curcumin administration significantly reduced GSH, SLC7A11, and GPX4 levels in HCT-8 colorectal cancer cells, while increasing intracellular Fe^{2+}, ROS, and lipid peroxidation product levels which supports ferroptotic cell death. Ferroptosis inhibitors such as Ferrostatin-1 can reverse these effects, suggesting that ferroptosis is part of curcumin's antiproliferative effect (100).

In a recent investigation done with liver cancer cells it was found that curcumin triggers the ferroptotic process by suppressing P62-KEAP1-NRF2 signaling (101). In this mechanism, downregulation of NRF2 leads to a decrease in antioxidant response elements (AREs) and thus a weakening of the cellular anti-ferroptosis protective response. Similarly, Jiang et al (2024) demonstrated that curcumin increased lipid peroxidation by increasing ACSL4 levels in hepatocellular carcinoma cells HepG2 and SMMC7721, and weakened antioxidant capacity by lowering intracellular GSH levels

through downregulating the expression of GPX and SLC7A11 (102). In addition to these findings, curcumin and synthetic analogues have been shown to suppress tumorigenesis in breast (103,104), osteosarcoma (105) and follicular thyroid cancer (106) by specifically inducing ferroptosis through the modulation of HO-1 and the inhibition of SLC7A11.

In addition to the mechanisms mentioned above, curcumin initiates the ferroptotic process, particularly in gastric and lung cancer cells, by triggering autophagy activation. Inhibition of the PI3K/Akt/mTOR signaling pathway increases the levels of autophagy markers (ATG5, Beclin-1, LC3B), which, along with the increase in ferroptotic markers, facilitates cell death. This process can be partially inhibited by ferrostatin-1 or other autophagy inhibitors (107,21).

Further studies have revealed that the mechanism by which the curcumin derivative NL01 contributes to ferroptosis is related to lactate metabolism (108). Approximately 13 times more potent than curcumin, NL01 can reduce lactate uptake from the extracellular environment by decreasing HCAR1 (hydroxycarboxylic acid receptor 1)/MCT1 (monocarboxylic acid transporter protein 1) expression, and improve energy metabolism by activating the AMPK/SREBP1 pathway in ovarian cancer cells, thereby reducing glucose uptake and lactate production.

Curcumin's effect on ferroptosis is important because it offers a potential therapeutic target as a cell death pathway other than classical apoptosis/necrosis (109). Ferroptosis is considered an additional death mechanism, particularly in chemotherapy-resistant tumors. The effect of curcumin and its derivatives on this process may have the potential for a synergistic effect in combination therapies. Accumulated evidence shows that curcumin plays a role in cancer not only as a ferroptosis-inducing agent but also as a potent chemosensitizer that enhances the efficacy of chemotherapeutic drugs (110-112). Curcumin weakens the resistance mechanisms developed by tumor cells against chemotherapy by increasing ROS accumulation, causing cell cycle arrest, and disrupting redox balance. In this respect, curcumin stands out as a promising adjuvant strategy that simultaneously enhances chemotherapy efficacy through ferroptosis-based cell death. However, since the bioavailability of the bioactive compound is poor, research continues on solutions such as nanoformulations, drug delivery systems, and derivative development strategies for clinical applications.

5. Mechanistic Insights from Network Pharmacology, Molecular Docking, and Systems Biology Approaches

Recent advances in systems biology and computational pharmacology have significantly expanded our understanding of the way how the plant-derived phenolic compounds regulate ferroptosis in multiple cancer types (113, 114). Evidence from network pharmacology, molecular docking, virtual screening, ADMET profiling, and transcriptomic analyses consistently demonstrate that phenolic compounds modulate ferroptosis through multiple target and multiple pathway mechanisms rather than single-gene regulation.

Ming et al. (2024) demonstrated that curcumin induced dose-dependent ferroptotic cell death in colorectal cancer cells through the regulation of the p53/SLC7A11/GSH/GPX4 signaling axis. This study highlights GPX4 and SLC7A11 as core ferroptosis-related targets using an integrated network pharmacology and molecular docking strategy (113). In parallel, a very recently published study revealed that a newly synthesized curcumin derivative (Compound 4d) strongly binds to the active site of GPX4 in MCF-7 cells, inducing SLC7A11/GPX4 axis-mediated ferroptosis (115). In another study, network pharmacology and molecular docking analyses have shown that curcumin's ferroptosis-inducing activity against esophageal squamous cell carcinoma targets CHEK1 and CDK6 proteins (116). These findings suggest that curcumin is capable of simultaneously targeting multiple nodes within the ferroptosis regulatory network, thereby reinforcing its role as a multi-target ferroptosis modülatör in cancer therapy.

Furthermore, transcriptomic and multidimensional data-driven studies have increasingly highlighting ferroptosis as a key outcome of curcumin-mediated

anticancer activity. Firouzjaei et al (2023) systematically investigated the effect of curcumin on ferroptosis-related gene expression in colorectal cancer using integrated *in silico* analyses and *in vitro* validation, revealing significant transcriptional modulation of genes involved in iron metabolism, lipid metabolism, and antioxidant defense, including MYC, IL1-ß Caveolin 1 and SLC1A5 (117). Li et al. (2020) demonstrated that curcumin treatment in breast cancer cells elicits a ferroptosis-associated gene expression signature, prominently characterized by the upregulation of HMOX1/HO-1, linking oxidative stress responses, iron metabolism, and lipid peroxidation to ferroptotic cell death (118). Consistent with these findings, EF24, a synthetic curcumin analog, was shown to induce ferroptosis in osteosarcoma cells through transcriptional activation of HMOX1, further supporting HO-1 as a recurrent ferroptosis-associated molecular feature of curcumin-based compounds rather than a single direct target (105). In colorectal cancer, transcriptome-guided pathway analyses revealed that combined treatment with curcumin and Andrographis activates ferroptosis-related gene networks through coordinated suppression of antioxidant defense mechanisms, including GPX4 and ferroptosis suppressor protein-1 (FSP1), highlighting ferroptosis as an emergent outcome of large-scale transcriptional modulation (119). Moreover, a curcumin synthetic derivative, NL01, was reported to induce ferroptosis in ovarian cancer cells via modulation of the HCAR1/MCT1 signaling axis, a mechanism supported by gene expression changes associated with metabolic reprogramming and redox imbalance (108). These studies underscore the value of transcriptomic approaches in uncovering ferroptosis as a systems-level response to curcumin and its derivatives, revealing consistent ferroptosis-associated gene signatures across different cancer types and compound variants.

In another study employing molecular docking approaches, hydroxytyrosol, a phenolic compound derived from olives, was shown to exhibit strong binding affinities toward several key ferroptosis-related proteins, including NRF2, NAD(P)H quinone oxidoreductase 1 (NQO1), PTGS2, AKR1C3, and thioredoxin reductase 1 (TrxR1), in colorectal cancer cells (120). These targets are critically involved in redox regulation, lipid peroxidation, and antioxidant defense, underscoring the potential role of hydroxytyrosol in modulating ferroptosis-associated pathways. Similarly, Hong et al. (2021) applied virtual screening and molecular docking strategies to evaluate the therapeutic potential of GA in colorectal cancer. Their analyses revealed that GA displays high binding affinity toward several prognostically relevant proteins, including GPX4, TP53, TFRC, and AURKA, all of which are implicated in ferroptosis regulation and cancer progression. Beyond these predicted static interactions, the study suggested that GA actively contributes to ferroptosis induction by perturbing iron metabolism and disrupting ROS homeostasis, thereby reinforcing the functional relevance of the docking-based predictions (58). Similarly, oxyresveratrol emerged as a novel ferroptosis inducer in breast cancer by targeting the EGFR/PI3K/AKT/GPX4 signaling axis, with molecular docking analyses confirming stable binding to GPX4 and upstream signaling proteins (121).

Flavonoids constitute a prominent class of phenolic ferroptosis modulators with diverse molecular targets. 4,4′-Dimethoxychalcone was reported to induce ferroptosis in cancer cells by synergistically activating the Keap1/NRF2/HMOX1 pathway while simultaneously inhibiting ferrochelatase (FECH), thereby increasing intracellular labile iron levels and promoting lipid peroxidation. These findings were supported by molecular docking and mechanistic pathway analyses, illustrating how iron metabolism and antioxidant signaling converge in ferroptosis execution (122). Consistently, baicalin induced ferroptosis in osteosarcoma cells via a novel NRF2/xCT/GPX4 regulatory axis, where inhibition of cystine uptake and GPX4 activity disrupted redox homeostasis (123). Comparable mechanisms were observed for nobiletin, which triggered ferroptosis in melanoma cells through a GSK3β-mediated Keap1/NRF2/HO-1 signaling cascade, reinforcing the central role of NRF2-dependent antioxidant responses in ferroptosis resistance (124). Similarly, luteolin was demonstrated to trigger ferroptosis in clear cell renal cell carcinoma by promoting

HO-1-dependent increases in the labile iron pool and lipid peroxidation, thereby linking flavonoid-mediated iron dysregulation to ferroptotic cell death (125). Finally, hesperetin was identified via network pharmacology and docking analyses to promote bladder cancer cell death through modulation of the PI3K/AKT pathway, indirectly sensitizing cells to ferroptosis-associated oxidative stress (89).

Consequently, these findings demonstrate that phenolic compounds regulate ferroptosis through integrated redox modulation, iron metabolism dysregulation, and signaling pathway interference, as revealed by multi-layered computational and experimental approaches. The convergence of network pharmacology, molecular docking, ADMET analysis, and systems-level validation highlights phenolic compounds as promising multi-target agents for ferroptosis-based cancer therapy and provides a robust framework for future translational and clinical investigations.

6. Phenolic Compound Integrated Nanomaterials as Ferroptosis-Inducing Platforms for Cancer Treatment

Despite the potent regulatory effects of phenolic compounds on ferroptosis, their clinical translation of phenolic compounds in cancer therapy is often limited by pharmacokinetic barriers such as poor aqueous solubility, rapid metabolism, restricted tissue penetration, insufficient systemic distribution and low bioavailability (126). To overcome these limitations, recent studies have focused on integrating phenolic compounds into nanostructured delivery systems, which markedly improve their stability, tumor accumulation, and therapeutic efficacy while enabling ferroptosis-based anticancer strategies. Nanocarrier systems improve intracellular delivery of phenolics, provide controlled-release profiles, and contribute to overcoming multiple drug-resistance mechanisms. Moreover, tumor microenvironmental features such as acidic pH, elevated ROS levels, and abnormal vasculature facilitate both passive (EPR effect) and active targeting of nanoparticles, thereby enhancing the selectivity of ferroptosis-based therapies. These nano-enabled platforms include metal-polyphenol networks, polymeric nanoparticles, lipid-based nanocarriers, biomimetic systems, and inorganic nanocomposites (127).

Among these approaches, metal-phenolic coordinated nanomaterials have emerged as particularly effective ferroptosis inducers due to their intrinsic iron content and redox activity (Table 4). Metal-polyphenol coordination assemblies formed through supramolecular interactions between Fe^{2+}/Fe^{3+} ions and phenolic ligands generate stable nanostructures capable of catalyzing Fenton reactions and amplifying lipid peroxidation. Yu et al. (2022) developed a Fe(II)–polyphenol coordinated nanomedicine that combined photoacoustic imaging guidance with mild hyperthermia, thereby enhancing iron-catalyzed lipid peroxidation and inducing ferroptotic cell death in breast cancer models. The nanoformulation exhibited potent anticancer efficacy by inducing ROS production and inhibiting the expression of GPX4 in both *in vitro* and *in vivo* settings. (128). Similarly, self-assembled Fe-phenolic acid networks were shown to synergize with ferroptosis pathways, resulting in significant tumor suppression through iron-dependent ROS accumulation and GPX4 inactivation (129). Furthermore, Qing et al. (2025) reported a supramolecular nanocomposite (bm–Cur–NC) formed via the coordination of bisdemethylcurcumin with Cu(II) exhibiting high aqueous stability and mitochondrial affinity. Specifically, this nanomedical product represents the first system capable of depleting intracellular glutathione (GSH) through three synergistic mechanisms: suppression of GSH biosynthesis via SLC7A11 downregulation, Cu(II)-mediated GSH redox depletion, and Michael addition reactions with a polyphenolic framework. The resulting redox imbalance leads to lipid peroxidation and mitochondrial dysfunction, triggering ferroptosis in drug-resistant cancer cells. bm–Cur–NC demonstrated strong antitumor activity both *in vitro* and *in vivo*, with ferroptosis identified as the dominant mode of cell death, and exhibited broad cytotoxic activity in multiple drug-resistant cancer models (130). In line with this polyphenol-metal coordination strategy, Wang et al. (2024) developed an EGCG-based supramolecular nanocomplex using Fe(III) instead of Cu(II) as the catalytic metal center. In contrast to the Cu-mediated GSH depletion dominant mechanism reported by Qing et al., the FeE@PEG nanocomplex primarily generates excess hydroxyl radicals (•OH) using H_2O_2-sensitive cleavage and Fe(III)-driven Fenton reactions. Simultaneously, EGCG enhances

Table 4. Nanomaterials integrated with phenolic compounds that trigger ferroptosis in cancer treatment.

Phenolic compound	Nanomaterial structure	Nanosystem	Cancer model	Ferroptosis-related mechanism	Reference
Gallic acid	Fe(II)-polyphenol coordinated nanoparticles co-loaded with Sorafenib	Fe-GA@BSA-SRF	Breast cancer cells and xenograft breast cancer model	Fe(II)-catalyzed Fenton reaction, lipid peroxidation, hyperthermia-enhanced ferroptosis	(128)
Rosmarinic acid	Self-assembled Fe-phenolic acid network	Fe-RA	Hepatoma-22 (H22) cells and xenograft tumor model	Iron overload, ROS amplification, GPX4 suppression	(129)
Curcumin	Polyphenol-metal supramolecular nanocomplex	bm–Cur–NC	Cisplatin-resistant HCC (HepG2/DDP) cells; HCC mouse model	Activation of ferroptosis via iron-dependent lipid peroxidation	(130)
Catechins (green tea)	Self-assembled metal-phenolic nanocomplex	FeE@PEG	SKOV3 ovarian cancer cells and xenograft mouse model	Tumor-specific ferroptosis via iron redox cycling and ROS generation	(131)
Curcumin	Cancer cell membrane-camouflaged nanoparticles	MSN-CUR@CM	SGC7901 and MGC803 gastric cancer cells; mouse xenograft tumor model	Lipid ROS accumulation, iron dysregulation, ferroptosis induction	(132)
Curcumin	Curcumin – polydopamine nanoparticles	Cur–PDA NPs	PC-12 cells	Iron chelation and redox modulation (ferroptosis regulation)	(133)
Resveratrol	Nanoliposomes co-loaded with rapamycin	Rapa/Res liposomes	HCT116 colorectal cancer cells; CRC mouse model	Lipid peroxidation, antioxidant system inhibition, apoptosis–ferroptosis crosstalk	(134)
Resveratrol	Biomimetic nano-delivery system	RSV-NPs@RBCm	HT29 and HCT116 CRC cells; CRC mouse model	Iron metabolism modulation, ferroptosis induction	(29)
Gallic acid	Iron oxide nanoparticles	IONP–GA/PAA	glioblastoma (U87MG and U373MG); neuroblastoma (IMR32); fibrosarcoma (HT1080)	Iron overload, ROS-mediated lipid peroxidation	(135)
Apigenin	Fe_2O_3/Fe_3O_4@$mSiO_2$ nanocomposites	API-Fe2O3/Fe3O4@mSiO2-	A549 lung cancer cells	Iron accumulation, oxidative stress, ferroptotic cell death	(136)
Apigenin	Iron–apigenin nanocomplex	FeAPG	4T1, MDA-MB-231 breast cancer cells; xenograft tumor model	Photothermal-enhanced ferroptosis and immune activation	(137)
Hesperetin	Targeted nanocomposites	HFPN	4T1, MDA-MB-231 and BT-549 breast cancer cells; subcutaneous tumor model	AURKA targeting, ferroptosis induction, radiosensitization	(138)
Gallic acid	Ultrasound-responsive nanoparticles	GA-Fe@BSA@PTX	B16F10 melanoma cells	Iron accumulation, oxidative stress, ultimately leading to mitochondrial damage, lipid peroxidation, and apoptosis	(139)

ferroptotic stress by promoting H_2O_2 production via auto-oxidation and depleting intracellular GSH, leading to significant lipid peroxidation and ferroptosis in chemotherapy-resistant ovarian cancer models (131). These findings highlight how metal selection critically determines the ferroptotic pathway activated by polyphenol-based nanomedical drugs.

Polymeric (e.g., PLGA, chitosan, PEG-modified systems) and hybrid nanocarriers incorporating phenolic compounds further enhance ferroptosis-mediated anticancer effects by improving intracellular delivery and controlled release. Curcumin-loaded nanoparticles camouflaged with cancer cell membranes represent a biomimetic polymer-based system that enhances tumor targeting and immune evasion while triggering ferroptosis in gastric cancer via excessive lipid peroxidation and iron dysregulation (132). In contrast, curcumin-polydopamine nanoparticles have been reported to chelate iron and modulate oxidative stress, highlighting that the ferroptotic outcome of phenolic

nanoformulations strongly depends on nanocarrier composition and iron availability (133).

Lipid-based nanocarriers, particularly nanoliposomes, have also been successfully employed to co-deliver phenolic compounds and synergistic agents. Nanoliposomal encapsulation of resveratrol in combination with rapamycin significantly enhanced both apoptotic and ferroptotic cell death in colorectal cancer by promoting lipid ROS accumulation and impairing antioxidant defenses (134). Biomimetic resveratrol-loaded nano-delivery systems have further demonstrated tumor-specific ferroptosis induction through modulation of iron metabolism and membrane lipid peroxidation (29).

In addition to organic nanocarriers, inorganic and magnetic nanocomposites incorporating GA provide multifunctional ferroptosis-based therapeutic platforms. Iron oxide nanoparticles and Fe-based nanocomposites inherently promote ferroptosis through iron overload and ROS generation (135). Apigenin-loaded $Fe_2O_3/Fe_3O_4@mSiO_2$ magnetic nanocomposites significantly enhanced intracellular iron accumulation and oxidative stress, leading to ferroptotic cell death in lung cancer cells (136). Moreover, multifunctional iron-apigenin nanocomplexes integrating photothermal therapy have been shown to amplify ferroptosis while simultaneously activating antitumor immune responses in triple-negative breast cancer (137).

These studies demonstrate that phenolic compound-integrated nanomaterials not only overcome the pharmacokinetic limitations of free phenolics but also actively participate in ferroptosis induction through iron delivery, redox modulation, and lipid peroxidation amplification. The rational design of nanocarrier composition (metal-coordinated, polymeric, lipid-based, or inorganic) plays a decisive role in dictating ferroptotic sensitivity and therapeutic outcomes, highlighting the promise of nanotechnology-enabled phenolic compounds as next-generation anticancer agents.

Beyond polyphenol-metal redox nanocomplexes, emerging nanotherapy platforms incorporate additional physical or procedural triggers to further learn ferroptotic cell destruction. Guo et al. developed a hesperetin-based nanocomposite that enhances radiotherapy in triple-negative breast cancer by inducing AURKA-dependent ferroptosis (138). In parallel, Wang et al. designed an ultrasound-resistant nanocatalyst capable of simultaneously activating ferroptosis and apoptosis, leading to effective suppression of metastatic uveal melanoma (139). These approaches highlight the expanding design of ferroptosis-inducing nanomedical applications that integrate redox regulation with radiotherapy or sonodynamic activation.

7. Future Perspective

Future studies should focus on improving the translational potential of ferroptosis-targeting strategies by addressing key challenges such as bioavailability, pharmacokinetics, and tissue-specific delivery of ferroptosis modulators. In addition, the identification of reliable ferroptosis-related biomarkers will be critical for patient stratification and therapeutic monitoring in clinical settings. Combining ferroptosis-modulating agents with conventional therapies, such as chemotherapy or radiotherapy, may also represent a promising approach to enhance treatment efficacy and overcome therapeutic resistance, ultimately facilitating the transition of ferroptosis-based interventions from preclinical research to clinical application.

8. Conclusion

This review comprehensively examines the regulatory effects of plant-derived phenolic compounds on ferroptosis by integrating molecular mechanisms, preclinical anticancer evidence, in silico and system-level network pharmacology analyses, nanotechnological delivery strategies, and clinical translation considerations. Collectively, these interconnected layers form a unified framework explaining how phenolic compounds can modulate ferroptosis in a context-dependent manner, exhibiting stimulatory or inhibitory effects depending on cellular redox status, iron metabolism, and disease context, thereby providing high therapeutic selectivity. Within this framework, the phenolic-ferroptosis axis emerges as an innovative anticancer strategy with high potential for overcoming drug resistance, reducing off-target toxicity, and supporting the development of

personalized therapeutic approaches. However, safe and effective clinical translation of this information will require rigorously designed, mechanism-oriented, and large-scale clinical trials.

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