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MEDICINAL PLANTS AND FERROPTOSIS IN CANCER: EMERGING EVIDENCE AND THERAPEUTIC OPPORTUNITIES

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ABSTRACT

Ferroptosis is an iron-dependent type of regulated cell death characterized by excessive lipid peroxidation, loss of cellular antioxidant defenses, and buildup of redox-active iron. In contrast to apoptosis, ferroptosis is closely linked to iron metabolism, depletion of glutathione (GSH), inactivation of glutathione peroxidase 4 (GPX4), and oxidative damage to membrane lipids containing polyunsaturated fatty acids. Since malignant cells often show heightened iron requirements, altered lipid metabolism, and increased oxidative stress, ferroptosis has become a promising therapeutic vulnerability in cancer. Medicinal plants serve as a significant reservoir of structurally diverse compounds that can regulate these pathways. A growing body of experimental evidence shows that artemisinin and its derivatives, curcumin, quercetin, sulforaphane, and other phytochemicals can trigger ferroptotic cancer-cell death by altering iron homeostasis, ferritin degradation, system Xc− activity, GPX4, GSH metabolism, reactive oxygen species generation, and lipid peroxidation. Artemisinin derivatives can raise intracellular labile iron via ferritin degradation, thereby sensitizing tumor cells to ferroptosis. Curcumin has been demonstrated to induce ferroptosis in breast cancer models through iron accumulation, lipid peroxidation, and modulation of ferroptosis-associated signaling. Quercetin drives lysosomal ferritin degradation and iron-dependent lipid peroxidation, while sulforaphane can promote SLC7A11 degradation and ferroptosis in osteosarcoma. Despite these encouraging findings, the evidence remains largely preclinical. Poor bioavailability, chemical instability, absence of standardized botanical preparations, tumor selectivity, and inadequate clinical validation continue to be major obstacles. This review critically assesses the molecular link between medicinal plants and ferroptosis in cancer and explores opportunities for combination therapy, nanotechnology, and precision oncology.

Keywords: Ferroptosis, Medicinal plants, Phytochemicals, Cancer, Artemisinin, Curcumin, Quercetin, Sulforaphane, GPX4, SLC7A11, Lipid peroxidation, Iron metabolism.

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INTRODUCTION

Cancer cells display remarkable metabolic plasticity that enables them to endure hypoxia, nutrient deprivation, oxidative stress, and therapeutic pressure. Conventional anticancer therapies mainly target apoptosis, DNA damage, mitotic disruption, or specific oncogenic signaling pathways. Nevertheless, resistance to apoptosis and adaptation to therapeutic stress continue to be major drivers of treatment failure. As a result, alternative regulated cell-death mechanisms have gained increasing importance in cancer research. Ferroptosis is a distinct form of regulated cell death first formally described by Dixon

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et al. in 2012. This process differs morphologically and biochemically from apoptosis and necrosis and is primarily driven by iron-dependent lipid peroxidation **[1].** Later research established that ferroptosis is governed by interconnected networks involving intracellular iron, polyunsaturated fatty acids, glutathione metabolism, system Xc−, GPX4, and several lipid-antioxidant pathways **[2].** Cancer cells may be especially vulnerable to ferroptosis because malignant transformation is often accompanied by increased iron uptake, heightened metabolic activity, and elevated production of reactive oxygen species (ROS). At the same time, many tumors build strong antioxidant systems to withstand this oxidative environment. Disrupting this metabolic balance may therefore selectively kill cancer cells. Medicinal plants are especially attractive sources of ferroptosis-modulating agents because their secondary metabolites have diverse chemical structures and can interact with multiple cellular pathways. Experimental studies have identified several natural compounds able to induce or sensitize cancer cells to ferroptosis, including artemisinin derivatives, curcumin, quercetin, and sulforaphane **[3].** Notably, these compounds do not always work via the same mechanisms. Some raise intracellular iron levels, others weaken antioxidant defenses, and still others affect ferritinophagy, lysosomal activity or lipid metabolism. This review assesses the existing experimental evidence connecting medicinal plants and their bioactive components to ferroptosis in cancer, with special focus on original studies and their therapeutic implications.

Molecular Characteristics of Ferroptosis

Ferroptosis is essentially linked to the build-up of oxidized membrane lipids. Three interrelated processes are especially significant: iron dysregulation, breakdown of antioxidant defense and lipid peroxidation.

Iron Metabolism

Iron is needed for DNA synthesis, mitochondrial metabolism and many enzymatic reactions. Tumor cells frequently boost iron uptake by increasing transferrin receptor 1 expression and altering iron-storage proteins. As a result, cancer cells may hold an enlarged labile iron pool capable of taking part in redox reactions. The initial ferroptosis study showed that iron chelation blocked this type of cell death, confirming iron's essential role **[1].** Raising intracellular redox-active iron can thus heighten susceptibility to ferroptosis.

System Xc− and Glutathione Metabolism

The cystine/glutamate antiporter system Xc− is composed mainly of SLC7A11 and SLC3A2. It transports cystine, which is needed for cysteine and later for glutathione synthesis. Glutathione is required for the activity of GPX4, an enzyme that turns toxic phospholipid hydroperoxides into relatively harmless lipid alcohols **[2].** Suppression of SLC7A11, depletion of GSH or inhibition of GPX4 thus encourages lipid-peroxide accumulation. This pathway is one of the most significant molecular vulnerabilities targeted by ferroptosis-inducing compounds.

Lipid Peroxidation

Polyunsaturated fatty acids integrated into membrane phospholipids are especially prone to oxidation. When lipid-peroxide formation surpasses the ability of GPX4 and other antioxidant systems to clear these products, membrane integrity becomes increasingly impaired. Therefore, a compound that both raises ROS or iron availability and weakens antioxidant defense may be especially effective at inducing ferroptosis.

Artemisinin and its Derivatives

Artemisinin is a sesquiterpene lactone derived from Artemisia annua. Although it is best known for its antimalarial action, its anticancer properties have drawn growing interest.A landmark original study by Chen et al. showed that artemisinin compounds can sensitize cancer cells to ferroptosis by regulating iron homeostasis **[3].** Dihydroartemisinin encouraged lysosomal degradation of ferritin, thus enlarging the cellular free-iron pool. It also affected iron-regulatory protein/iron-responsive element signaling. Notably, dihydroartemisinin boosted GPX4-inhibition-induced ferroptosis in several cancer models and raised ferroptotic sensitivity in a mouse xenograft model. These findings matter because they pinpoint iron homeostasis as a key mechanism by which a plant-derived compound can regulate ferroptosis. Artesunate offers further evidence. Eling et al. studied pancreatic ductal adenocarcinoma cells and discovered that artesunate triggered ROS- and lysosomal iron-dependent cell death **[4].** KRAS-driven pancreatic cancer cells were especially sensitive, while non-neoplastic pancreatic epithelial cells were comparatively resistant. Ferrostatin-1 blocked lipid peroxidation and cell death, supporting the involvement of ferroptosis rather than nonspecific cytotoxicity. These observations are especially pertinent to pancreatic cancer, where constitutively active KRAS drives therapeutic resistance. The emerging evidence therefore indicates that artemisinin derivatives may function as ferroptosis sensitizers, rather than merely conventional cytotoxic agents **[5].**

Curcumin and Ferroptosis

Curcumin is the main polyphenolic constituent of Curcuma longa and has been widely studied for its anti-inflammatory and anticancer properties. Even though curcumin is often labeled an antioxidant, its effects depend heavily on the surrounding context. Within cancer cells, it may act as a pro-oxidant and trigger oxidative types of cell death. Li et al. examined curcumin-induced ferroptosis in breast cancer cells,

reporting elevated intracellular iron, ROS, lipid peroxides and malondialdehyde alongside reduced GSH **[6].** Ferrostatin-1 and deferoxamine partially reversed curcumin-induced cell death, which supports a ferroptotic mechanism. The researchers also pinpointed heme oxygenase-1 (HO-1) as a key mediator of curcumin-induced ferroptosis. Cao et al. later showed that curcumin inhibited breast cancer growth via ferroptosis **[7].** In MDA-MB-453 and MCF-7 breast cancer cells, curcumin raised lipid ROS, malondialdehyde and intracellular Fe2+. The investigators pinpointed SLC1A5-mediated ferroptosis as a key mechanism and verified antitumor activity in a xenograft model. These results indicate that curcumin can influence multiple components of ferroptosis at once, such as iron accumulation, lipid oxidation and cellular antioxidant capacity. More recent work has extended this idea to rationally designed curcumin derivatives. In a 2025 study, Wu et al. synthesized 20 curcumin derivatives and pinpointed compound A4 as a potent ferroptosis inducer in breast cancer models **[5]**. A4 elevated ROS, Fe2+, lipid peroxidation and lowered GSH while suppressing GPX4 and SLC7A11. Gene-knockout experiments pointed to the p53/SLC7A11/GPX4 pathway. This marks an important advance, since chemically modifying natural compounds may surmount some limitations of the parent molecule while preserving its biological mechanism **[8, 9].**

Quercetin-induced Ferroptosis

Quercetin is a flavonoid found widely in fruits, vegetables and medicinal plants. Its biological effects encompass antioxidant, anti-inflammatory and anticancer activities. Wang et al. supplied especially strong mechanistic evidence connecting quercetin with ferroptosis **[10].** The investigators showed that quercetin activated lysosomal function via transcription factor EB, leading to ferritin degradation and release of free iron. Greater iron availability combined with ROS generation caused lipid peroxidation and ferroptotic cell death. Crucially, blocking lysosomal activity prevented these effects. This study matters because it shows that ferroptosis can be triggered indirectly through lysosome-dependent ferritin degradation. The mechanism differs somewhat from classical system Xc− inhibition. Instead of mainly blocking cystine uptake, quercetin modifies intracellular iron availability and lysosomal biology. Such findings highlight the mechanistic diversity of natural ferroptosis modulators. Quercetin thus represents a possible lead compound for cancers marked by altered iron metabolism. Nevertheless, its poor systemic bioavailability remains a major hurdle for therapeutic translation **[11].**

Sulforaphane as a Ferroptosis-inducing Phytochemical

Sulforaphane is an isothiocyanate that comes mainly from cruciferous vegetables, especially broccoli and broccoli sprouts. It has been widely investigated for its chemopreventive and anticancer effects. A recent primary study by Zou et al. showed that sulforaphane triggers ferroptosis in osteosarcoma **[12].** The researchers noted elevated ROS and lipid peroxidation along with depletion of GSH. In terms of mechanism, sulforaphane enhanced the interaction between p62 and SLC7A11, promoting lysosomal degradation of SLC7A11 and thus impairing the cystine-GSH antioxidant system. Ferrostatin-1 reversed the cytotoxic effects, which supports a ferroptotic mechanism. Importantly, the investigators confirmed antitumor efficacy in both subcutaneous and intratibial osteosarcoma mouse models. This study offers especially compelling evidence, as it connects a dietary phytochemical to a specific molecular mechanism—p62/SLC7A11 regulation—and confirms the effect in vivo **[13-15].**

Other Medicinal-plant-derived Ferroptosis Modulators

The compounds described above are only a portion of the natural products currently being studied for ferroptosis modulation. Experimental studies and recent reviews have identified further candidates, such as resveratrol, celastrol, tanshinones, ginkgetin, capsaicin and several compounds obtained from traditional medicinal plants **[16, 17].** However, the strength of the evidence differs considerably. Certain compounds have been examined only in cultured cancer cells, whereas others have advanced to animal models. Consequently, natural products should not be labeled ferroptosis inducers merely because they raise ROS. A convincing demonstration of ferroptosis should ideally involve multiple complementary criteria, such as lipid ROS accumulation, iron dependence, GSH depletion, GPX4/SLC7A11 changes and rescue by pharmacological ferroptosis inhibitors. This distinction matters for preserving scientific rigor in natural-product research **[18].**

Ferroptosis and Chemotherapy Resistance

An important therapeutic opportunity lies in using ferroptosis to overcome resistance to apoptosis-based chemotherapy. Cancer cells that escape apoptosis may still carry vulnerabilities linked to iron metabolism and oxidative stress. As a result, combining ferroptosis-inducing natural compounds with conventional anticancer drugs could potentially enhance therapeutic efficacy. Artemisinin derivatives are especially appealing in this setting because they can sensitize cells to ferroptosis via increased intracellular iron **[3].** Curcumin derivatives may likewise offer opportunities for combination therapy **[8].** Recent experimental work

with engineered curcumin derivatives indicates that simultaneous modulation of p53, SLC7A11 and GPX4 can generate substantial ferroptotic stress in breast cancer models. Combination treatment is also being explored using natural compounds on their own. A 2025 study of resveratrol and curcumin in breast cancer cells reported synergistic effects on cell viability and modulation of ferroptosis-associated genes, though these findings remain preclinical and need validation in animal and clinical models. Thus, natural products may be valuable as ferroptosis sensitizers rather than necessarily serving as standalone anticancer agents **[18].**

Medicinal Plants, Ferroptosis and Precision Cancer Therapy

Not every cancer is equally sensitive to ferroptosis. Tumor genotype, iron metabolism, lipid composition and antioxidant capacity all affect ferroptotic susceptibility. For instance, KRAS-driven pancreatic cancer showed particular sensitivity to artesunate in the study by Eling et al**. [4].** Likewise, SLC7A11 and GPX4 expression can determine whether a tumor is able to resist lipid-peroxide accumulation. This implies that future clinical application should shift toward biomarker-guided ferroptosis therapy. Potential biomarkers include: GPX4 expression; SLC7A11/system Xc− activity; intracellular iron and ferritin levels; lipid-peroxidation signatures; ACSL4 expression; NRF2 pathway activity; and tumor lipid composition. A precision approach could identify tumors with high ferroptotic vulnerability and then choose suitable natural compounds or derivatives **[19].**

Nanotechnology as an Opportunity

Poor bioavailability represents a significant constraint for numerous phytochemicals. Curcumin and quercetin undergo rapid metabolism and show only limited systemic exposure. Nanotechnology might be able to address these constraints. Nanoformulations can enhance solubility, shield compounds from degradation, boost cellular uptake and improve tumor accumulation. More sophisticated systems might pair a phytochemical with iron delivery, GPX4 inhibition or tumor-targeting ligands. For instance, recent experimental studies have investigated curcumin-containing nanoparticles that integrate chemotherapy, photothermal therapy and ferroptosis. In a triple-negative breast cancer model, curcumin nanoparticles coated with tannic acid/Fe(III) raised intracellular Fe2+, ROS and lipid peroxidation while reducing GSH, thus generating ferroptotic effects. Even though such approaches are still experimental, they illustrate how compounds from medicinal plants can be combined with contemporary drug-delivery technologies **[14, 18].**

LIMITATIONS AND RESEARCH GAPS

Despite considerable advances, several notable limitations stand in the way of immediate clinical translation. First, most studies are still conducted in vitro or in animals. Effective concentrations achieved in cell culture might not be attainable in human tumors. Second, phytochemical preparations differ depending on plant species, cultivar, geographical origin, extraction method and storage conditions. Standardization is therefore essential. Third, many studies rely on isolated compounds instead of standardized whole-plant extracts. Although isolated compounds make mechanistic studies easier, they may not reflect the pharmacological activity of traditional preparations **[6].** Fourth, some studies detect ferroptosis mainly through ROS or MDA measurements. These parameters by themselves are inadequate, since oxidative stress can occur alongside various forms of cell death. Future research should employ multiple ferroptosis-specific endpoints along with suitable rescue experiments. Fifth, tumor selectivity continues to be a major obstacle. Ferroptosis is not pathological only to cancer cells; excessive ferroptosis can also cause tissue injury. Consequently, selective activation within tumors is crucial. Finally, human evidence is still very scarce. Currently, the strongest evidence for medicinal-plant-derived ferroptosis originates from experimental cancer biology rather than clinical oncology **[2, 5].**

FUTURE PERSPECTIVES

Future research should aim to integrate natural-product pharmacology, molecular oncology, ferroptosis biology and advanced drug delivery. First, systematic screening of medicinal-plant libraries could uncover additional ferroptosis-inducing compounds. High-throughput lipidomics and transcriptomics may assist in establishing molecular fingerprints linked to ferroptotic sensitivity. Second, network pharmacology and molecular docking can be employed to identify possible targets, but computational predictions need validation through gene knockdown, overexpression and pharmacological rescue experiments. Third, research should move beyond conventional cancer cell lines toward three-dimensional organoids, patient-derived xenografts and genetically characterized models. Fourth, combination strategies merit special attention. Natural ferroptosis modulators might be combined with chemotherapy, radiotherapy, immune checkpoint inhibitors or molecularly targeted therapies. Finally, nanotechnology could help tackle problems of bioavailability and tumor selectivity. Nevertheless, nanoparticle safety, biodistribution and long-term toxicity need careful assessment.

CONCLUSION

Ferroptosis has become a key therapeutic vulnerability in cancer, and medicinal plants offer a valuable reservoir of molecules able to regulate this process. At present, the experimental evidence is especially convincing for artemisinin derivatives, curcumin, quercetin and sulforaphane. Artemisinin derivatives mainly affect ferroptosis via iron homeostasis and the degradation of ferritin. Curcumin is able to boost iron buildup, lipid peroxidation and oxidative stress, while also acting on ferroptosis-related pathways including SLC1A5, HO-1, SLC7A11 and GPX4. Quercetin encourages the lysosomal breakdown of ferritin along with iron-dependent lipid peroxidation. Sulforaphane is capable of promoting lysosomal degradation of SLC7A11 via p62, thus weakening the GSH-dependent antioxidant system. The way these mechanisms converge indicates that medicinal plants might offer both direct ferroptosis inducers and ferroptosis sensitizers. Even so, the evidence available today is still mostly preclinical. Poor bioavailability, inconsistency in botanical preparations, insufficient standardization and a lack of human studies are key obstacles to translation. Future research should thus focus on standardized phytochemicals, molecular biomarkers, combination therapy, advanced delivery systems and clinically relevant experimental models. Combining traditional knowledge of medicinal plants with contemporary ferroptosis biology could eventually yield new approaches for overcoming cancer progression and therapeutic resistance.

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