Review Article *Open Access*

Journal of Biomedical Advancement Scientific Research

ISSN: 3069-0854

DOI: doi.org/10.63721/26JBASR0173

Palm Tocotrienols as Ferroptosis Suppressors: From Membrane Lipid Radical Trapping to Ischemia–Reperfusion and Acute Organ Injury—A Mechanistic and Translational Qualitative Review

Loso Judijanto

IPOSS Jakarta, Indonesia

Citation: *Hossain T, Akter R, Bashar MA, Robinson WC, Zimmerman LA (2026) Countering Early Marriage & Fertility: A Focus on Bangladesh's Rohingya Refugee Camps. J. of Bio Adv Sci Research, 2(5):01-16. WMJ/JBASR-173*

Abstract

Ferroptosis is an iron-dependent form of regulated cell death driven by uncontrolled phospholipid peroxidation and collapse of cellular lipid-antioxidant defenses. Its involvement in ischemia–reperfusion injury, acute kidney injury, myocardial injury, ischemic stroke, acute lung injury, sepsis, and other inflammatory disorders has created substantial interest in pharmacological ferroptosis suppression. Tocotrienols, naturally occurring members of the vitamin E family that are particularly abundant in palm-derived tocotrienol-rich fractions, possess an unsaturated isoprenoid side chain that distinguishes them structurally and functionally from tocopherols. A major advance emerged in 2026 when direct comparative experiments demonstrated that tocotrienols suppressed pharmacologically and genetically induced ferroptosis at substantially lower concentrations than tocopherols. This qualitative literature review integrates this new evidence with contemporary knowledge of GPX4, system Xc−, FSP1–CoQ10, GCH1–BH4, DHODH, iron metabolism, ACSL4/LPCAT3-mediated phospholipid remodeling, and mitochondrial redox biology. Particular attention is given to renal, cardiac, cerebral, pulmonary, and systemic acute injury. The review argues that tocotrienols should increasingly be considered membrane-level radical-trapping ferroptosis suppressors rather than merely nonspecific antioxidants. However, direct clinical evidence remains absent, and translation is constrained by bioavailability, tissue exposure, isoform differences, timing, formulation, and biomarker limitations. A further therapeutic paradox emerges because ferroptosis inhibition may protect acutely injured normal tissues while potentially opposing ferroptosis-based anticancer strategies. Carefully designed pharmacokinetic, biomarker, organ-specific, and early-phase clinical studies are therefore required before palm tocotrienols can be positioned as clinically validated ferroptosis-targeted interventions.

***Corresponding author**: Loso Judijanto, IPOSS Jakarta, Indonesia.

Submitted: 05.09.2026 **Accepted**: 15.08.2026 **Published**: 21.09.2026

Keywords: Tocotrienols, Palm Oil, Ferroptosis, Lipid Peroxidation, GPX4, Ischemia–Reperfusion Injury, Acute Kidney Injury, Myocardial Injury, Ischemic Stroke, Radical-Trapping Antioxidants

JEL Classification: I10; I12; O31; O32; Q16.

Introduction

Ferroptosis has transformed contemporary understanding of oxidative cell death. Rather than representing an undefined endpoint of excessive reactive oxygen species, ferroptosis is now recognized as a regulated cell-death program characterized by iron-dependent accumulation of oxidized phospholipids, failure of lipid peroxide detoxification, and ultimately destructive membrane damage. Its execution is therefore mechanistically distinct from classical apoptosis, necroptosis, and pyroptosis, although substantial biological cross-talk can occur among these pathways. Because ferroptosis depends strongly on the composition and redox state of cellular membranes, it provides a conceptual bridge between lipid biochemistry, membrane biophysics, metabolism, inflammation, and tissue injury (Du & Guo, 2022; Jiang et al., 2021; Stockwell, 2022; Tang et al., 2021; Zheng & Conrad, 2025).

This framework is particularly relevant to ischemia-reperfusion (I/R) injury. Restoration of blood flow is essential after ischemia, but reperfusion also introduces oxygen into a metabolically and redox-disturbed environment containing dysfunctional mitochondria, labile iron, damaged membranes, altered calcium homeostasis, and weakened endogenous antioxidant systems. These conditions provide many of the biochemical prerequisites for ferroptosis. Evidence increasingly implicates ferroptotic injury in renal tubular damage, myocardial reperfusion injury, ischemic stroke, acute lung injury, sepsis-associated organ dysfunction, traumatic brain injury, and other acute inflammatory states. Recent organ-level syntheses further indicate that ferroptosis is relevant across I/R injury of the kidney, heart, brain, liver, lung, and intestine, although the strength of causal evidence differs by organ and experimental model (Bayır et al., 2023; Fang et al., 2023; Huo et al., 2023; Luan et al., 2025; Zhou et al., 2022).

An important therapeutic implication follows from this biology. If lethal lipid-peroxidation chains can be interrupted before membrane injury becomes irreversible, cells that would otherwise be lost during acute injury might remain salvageable. Ferroptosis research has consequently expanded from characterization of cell death into the identification of endogenous and pharmacological defense systems. The canonical glutathione peroxidase 4 (GPX4) pathway is now understood to operate together with GPX4-independent systems such as ferroptosis suppressor protein 1 (FSP1)-coenzyme Q10 (CoQ10), GTP cyclohydrolase 1-tetrahydrobiopterin (GCH1-BH4), mitochondrial dihydroorotate dehydrogenase (DHODH)-CoQ, and phospholipid-remodeling mechanisms. These systems collectively reveal that cells have evolved several complementary ways to prevent catastrophic membrane oxidation (Chen et al., 2021; Kraft et al., 2020; Mao et al., 2021; Sun et al., 2021).

Vitamin E has long occupied an important position in membrane antioxidant biology. However, vitamin E is not a single compound. It comprises four tocopherol and four tocotrienol isoforms, differentiated by methylation of the chromanol ring and by the structure of the hydrophobic side chain. Tocopherols possess a saturated phytyl chain, whereas tocotrienols possess an unsaturated isoprenoid chain containing three double bonds. Palm oil represents an important dietary and industrial source of tocotrienols, particularly mixtures formulated as palm tocotrienol-rich fraction (TRF). Contemporary literature indicates that these structural differences influence absorption, metabolism, membrane behavior, and biological activity, making the treatment of all vitamin E analogues as interchangeable antioxidants increasingly untenable (Looi et al., 2025; Ranasinghe et al., 2022; Szewczyk et al., 2021; Wong et al., 2020).

The most important recent development occurred in January 2026. Yang et al. directly compared all major tocopherol and tocotrienol analogues across multiple ferroptosis models. Tocotrienols suppressed ferroptosis induced by GPX4 inhibition, system Xc− inhibition, glutathione depletion, and inducible genetic Gpx4 deletion at substantially lower concentrations

than tocopherols. In the Gpx4-deficient model, α-tocotrienol produced an EC_{50} of approximately 0.12 μM compared with about 2.0 μM for α-tocopherol. The results therefore extend beyond generic antioxidant assays and provide direct evidence that tocotrienols can behave as potent ferroptosis suppressors (Yang et al., 2026).

This evidence justifies a reconsideration of earlier tocotrienol literature. Tocotrienols have previously demonstrated antioxidant, anti-inflammatory, mitochondrial, neuroprotective, cardioprotective, and renoprotective effects. Yet many of those observations predated the contemporary ferroptosis framework or were not interpreted through it. For example, γ-tocotrienol improved mitochondrial respiration, ATP preservation, renal morphology, creatinine recovery, and survival in experimental renal ischemia. Such findings are not themselves proof of ferroptosis inhibition, because ferroptosis-specific rescue and molecular validation were not central endpoints. Nevertheless, they now create an important mechanistic convergence with the 2026 evidence (Nowak & Megyesi, 2021; Ramli et al., 2021).

Accordingly, the principal objective of this qualitative review is to determine how strongly contemporary evidence supports the concept of tocotrienols as membrane-level ferroptosis suppressors and whether this property provides a plausible translational framework for I/R and acute organ injury. The analysis distinguishes direct experimental evidence from mechanistic convergence and organ-protection evidence that did not directly measure ferroptosis. It also evaluates pharmacokinetic constraints, isoform differences, clinical biomarker gaps, treatment timing, and the therapeutic paradox created by cancer, where ferroptosis induction rather than suppression may sometimes be desirable.

Literature Review: Conceptual and Mechanistic Foundations

Ferroptosis as regulated membrane failure

The defining biochemical event in ferroptosis is not simply increased total cellular oxidative stress. Ferroptosis requires a lethal imbalance between production of oxidized membrane phospholipids and the capacity of the cell to detoxify or prevent them. Polyunsaturated fatty acids (PUFAs) are especially susceptible because bis-allylic hydrogen atoms can be abstracted, initiating self-propagating lipid-radical reactions. Once phospholipid hydroperoxides accumulate beyond the buffering capacity of cellular defenses, secondary radicals and electrophilic products amplify damage across membrane compartments, eventually producing permeability failure and cellular collapse (Jiang et al., 2021; Stockwell, 2022; Zheng & Conrad, 2025).

Iron is central because redox-active iron promotes radical chemistry and participates in enzymes that influence lipid oxidation. Cellular susceptibility is therefore shaped by transferrin-mediated iron uptake, ferritin storage, ferritinophagy, ferroportin-dependent export, mitochondrial iron utilization, and the size of the labile iron pool. Contemporary iron-biology research emphasizes that the same element required for respiration, DNA synthesis, and enzymatic function can become highly destructive when iron availability and redox control become uncoupled (Galy et al., 2024). Membrane composition is equally important. ACSL4 promotes formation of PUFA acyl-CoA species, while LPCAT3 contributes to their incorporation into membrane phospholipids. Pharmacological or genetic interference with LPCAT3 can remodel PUFA-containing phospholipids and alter ferroptosis sensitivity, demonstrating that membrane substrate availability is an active determinant rather than a passive consequence of oxidative stress. Oxidoreductases such as POR and CYB5R1 can further support lipid peroxidation by transferring reducing equivalents into oxygen-dependent redox reactions (Ai et al., 2021; Reed et al., 2022).

The system Xc⁻–GSH–GPX4 axis

The best-established ferroptosis-defense pathway centers on cystine uptake through system Xc⁻, glutathione synthesis, and GPX4. Cystine imported through the SLC7A11/SLC3A2 transporter system is reduced to cysteine and supports synthesis of glutathione (GSH). GPX4 uses GSH to reduce phospholipid hydroperoxides to less reactive lipid alcohols. Inhibition of cystine transport, depletion of GSH, direct pharmacological inhibition of GPX4, or genetic GPX4 loss can therefore drive ferroptosis under susceptible conditions (Du & Guo, 2022; Tang et al., 2021).

The biological significance of GPX4 extends beyond experimental cell models. Tissue-specific loss or impairment of GPX4 can produce profound biological consequences, and selenium availability influences GPX4 biology because GPX4 is a selenoprotein. The selenium–GPX4 axis has, for example, been shown to regulate ferroptosis susceptibility and survival in follicular helper T cells, illustrating that ferroptosis defense contributes not only to tissue injury but also to normal immune-cell homeostasis (Yao et al., 2021).

GPX4-Independent Defense Systems

The discovery of parallel antiferroptotic systems changed the field substantially. FSP1 reduces ubiquinone to ubiquinol at cellular membranes, creating a radical-trapping antioxidant system that can operate independently of GPX4. CoQ10 is therefore not only a mitochondrial electron carrier but also part of a wider lipid-defense network. The existence of FSP1-mediated protection explains why cells can display substantial differences in ferroptosis sensitivity even when GPX4 status is similar (Hadian, 2020).

A second system involves GCH1 and BH4. Kraft et al. demonstrated that GCH1/BH4 can counteract ferroptosis through both radical-trapping properties and remodeling of lipid metabolism. This is particularly important conceptually because it shows that small lipophilic or membrane-associated radical-trapping molecules can constitute biologically meaningful ferroptosis-defense mechanisms rather than merely reducing nonspecific oxidative markers (Kraft et al., 2020).

Mitochondria also contain ferroptosis-defense capacity. DHODH contributes to reduction of CoQ within the inner mitochondrial membrane and provides a defense pathway that can complement mitochondrial GPX4. This is relevant to ischemia and reperfusion because mitochondrial redox disruption, respiratory-chain injury, ATP depletion, and lipid oxidation are prominent features of many I/R syndromes (Mao et al., 2021).

Other pathways remove already oxidized phospholipids. iPLA2β can cleave oxidized fatty-acid tails from membrane phospholipids, thereby eliminating ferroptotic lipid signals, and this function can operate independently of GPX4. Such findings establish a broader principle: successful control of ferroptosis can occur through prevention of lipid oxidation, chemical quenching of lipid radicals, enzymatic reduction of hydroperoxides, or physical removal and remodeling of damaged phospholipids (Chen et al., 2021; Sun et al., 2021).

Endogenous radical-trapping lipids provide further evidence that membrane chemistry itself can determine ferroptosis sensitivity. The discovery that 7-dehydrocholesterol can act as an endogenous suppressor of ferroptosis demonstrates that lipid-phase radical interception is not merely pharmacological but can constitute an intrinsic biological defense strategy (Freitas et al., 2024).

Tocotrienols within the Vitamin E Family

Tocopherols and tocotrienols share a chromanol head group capable of donating hydrogen to lipid radicals, but their side chains differ substantially. Tocopherols have a saturated phytyl tail; tocotrienols have an unsaturated isoprenoid tail with three double bonds. These structural differences affect physical behavior in lipid environments, metabolic handling, and interactions with biological membranes. Tocotrienol isoforms include α-, β-, γ-, and δ-tocotrienol, paralleling the tocopherol family (Szewczyk et al., 2021).

Palm-derived TRF is particularly relevant because palm oil is naturally rich in tocotrienols and provides a practical source for human supplementation and pharmaceutical formulation. Contemporary randomized-trial literature demonstrates that palm TRF has been administered to humans across a variety of metabolic and inflammatory settings, establishing at least a foundation of human exposure and safety experience. However, these trials were not designed to test ferroptosis, and their outcomes cannot therefore be retrospectively reclassified as clinical antiferroptotic evidence (Ismail et al., 2020; Looi et al., 2025).

Meta-analytic evidence concerning inflammation and oxidative stress also requires careful interpretation. Tocotrienol supplementation has been evaluated against circulating inflammatory and oxidative biomarkers, but findings are heterogeneous. This matters because a reduction in CRP, malondialdehyde, or a general oxidative-stress marker is conceptually different from demonstrating suppression of ferroptosis.

Ferroptosis requires convergence between lipid-peroxidation biology, iron dependency, ferroptosis-specific regulators, and ideally rescue using validated ferroptosis inhibitors or genetic approaches (Khor et al., 2021).

Method

This article employed a qualitative literature-review design with a mechanistic and translational orientation. A qualitative narrative approach was selected because the evidence relevant to the research question is heterogeneous and spans molecular biochemistry, cell biology, animal models, human pharmacokinetics, randomized supplementation studies, organ-specific I/R research, and cancer biology. Such evidence cannot appropriately be reduced to a single pooled effect estimate. Narrative reviews can be rigorous when their purpose, literature-search logic, interpretive framework, and limitations are transparently stated (Sukhera, 2022).

Literature was identified through combinations of PubMed/MEDLINE, Scopus-oriented bibliographic searching, Web of Science-oriented searching, and publisher databases. Search concepts included "tocotrienol AND ferroptosis," "vitamin E AND ferroptosis," "tocotrienol AND lipid peroxidation," "tocotrienol AND ischemia reperfusion," "ferroptosis AND kidney," "ferroptosis AND myocardial ischemia," "ferroptosis AND stroke," "ferroptosis AND acute lung injury," "ferroptosis AND sepsis," and "ferroptosis AND cancer." Search breadth was intentionally larger than would be appropriate for a narrowly defined intervention meta-analysis because mechanistic evidence may occur across different tissues and experimental platforms (Heath et al., 2022).

Priority was given to peer-reviewed journal literature published from 2020 through 2026. Primary mechanistic studies were emphasized when evaluating direct causal claims, while high-quality contemporary reviews were used to integrate organ-specific ferroptosis biology and tocotrienol pharmacology. The synthesis followed thematic analysis principles in which mechanistically related findings were grouped, compared, and progressively integrated into higher-order themes rather than simply summarized study by study (Purssell & Gould, 2021).

Four evidence categories were used. Tier I consisted of direct studies in which tocotrienols were administered in experimentally validated ferroptosis models. Tier II comprised tocotrienol studies demonstrating protection against acute organ injury without direct ferroptosis validation. Tier III consisted of organ-specific ferroptosis literature without tocotrienol treatment. Tier IV included mechanistic evidence concerning membrane lipid oxidation, GPX4, FSP1, CoQ10, BH4, DHODH, iron regulation, phospholipid remodeling, and radical-trapping antioxidants. This hierarchy was used to avoid converting mechanistic compatibility into evidence of causality.This article is therefore a qualitative literature review rather than a systematic review or meta-analysis. No PRISMA flow diagram is presented, no pooled effect size was calculated, and absence of formal meta-analytic weighting should be considered when interpreting conclusions.

Results: Thematic Findings

Direct Evidence that Tocotrienols Suppress Ferroptosis

The 2026 study by Yang et al. represents the pivotal direct evidence. The investigators compared naturally occurring vitamin E analogues in several distinct ferroptosis models. Tocotrienols protected cells against ferroptosis caused by pharmacological GPX4 inhibition, system Xc− inhibition, and inhibition of glutathione synthesis, as well as against ferroptosis triggered by inducible genetic deletion of Gpx4. This multi-model design is important because protection against one chemical inducer could potentially result from an off-target interaction, whereas activity across upstream transporter inhibition, antioxidant depletion, direct GPX4 disruption, and genetic GPX4 loss is more consistent with a downstream ability to interrupt the common lipid-peroxidation execution pathway (Yang et al., 2026).

Tocotrienols also demonstrated greater potency than their tocopherol counterparts. The difference was particularly striking in the genetic GPX4-loss model, where α-tocotrienol achieved a reported EC_{50} near 0.12 μM compared with approximately 2.0 μM for α-tocopherol. The experiments further showed superior suppression of lipid peroxidation by tocotrienols. Importantly, conventional antioxidant assays did not fully predict ferroptosis-inhibitory activity, supporting the principle that chemical antioxidant capacity

measured in a simple solution is not equivalent to protection of living cellular membranes from ferroptotic lipid-radical propagation (Yang et al., 2026).

As shown in Figure 1, the central molecular argument can be represented as a mechanistic map in which ferroptosis emerges when membrane lipid oxidation overwhelms several parallel defense systems. The figure positions tocotrienols primarily at the lipid-radical propagation stage, where they are proposed to interrupt membrane chain reactions rather than act as proven direct activators of GPX4, FSP1, GCH1, or DHODH.

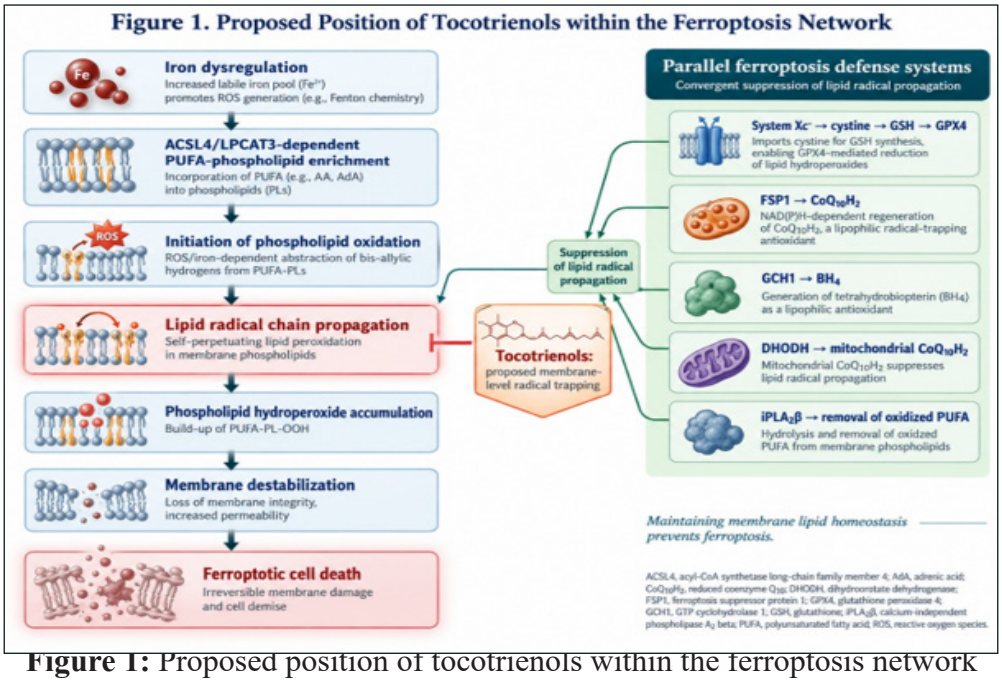

Figure 1: Proposed position of tocotrienols within the ferroptosis network

The figure emphasizes an important distinction. Current evidence directly supports the ability of tocotrienols to suppress ferroptosis and lipid peroxidation, but it does not establish that tocotrienols directly activate GPX4, FSP1, GCH1, or DHODH. Their strongest mechanistic placement is therefore downstream or parallel to these enzymatic systems, where their lipophilic chromanol structure can intercept propagating lipid radicals within membranes. This interpretation is consistent with the general biology of radical-trapping antioxidant systems and with ferroptosis suppression by endogenous membrane-active molecules (Freitas et al., 2024; Kraft et al., 2020; Yang et al., 2026).

Why Tocotrienols may Outperform Tocopherols

The unsaturated side chain of tocotrienols provides the most obvious structural basis for their distinct behavior, although the precise biophysical explanation of superior ferroptosis suppression remains incompletely established. The unsaturated isoprenoid tail may alter mobility, membrane distribution, orientation, interaction with lipid domains, and intracellular trafficking relative to the saturated tocopherol tail. These effects could allow tocotrienols to reach or redistribute within oxidizing membrane regions more efficiently. Contemporary tocotrienol reviews support substantial biological differences among tocopherols and tocotrienols, while the 2026 comparative ferroptosis study demonstrates that these differences have functional consequences for ferroptotic death (Ranasinghe et al., 2022; Szewczyk et al., 2021; Wong et al., 2020; Yang et al., 2026).

Figure 2 illustrates that the ferroptosis hypothesis depends not only on the chromanol antioxidant head group shared by vitamin E molecules but also on how the tocotrienol side chain may influence membrane

localization and radical interception. The side-by-side comparison therefore frames the proposed biophysical advantage of tocotrienols as a testable hypothesis rather than an established molecular mechanism.

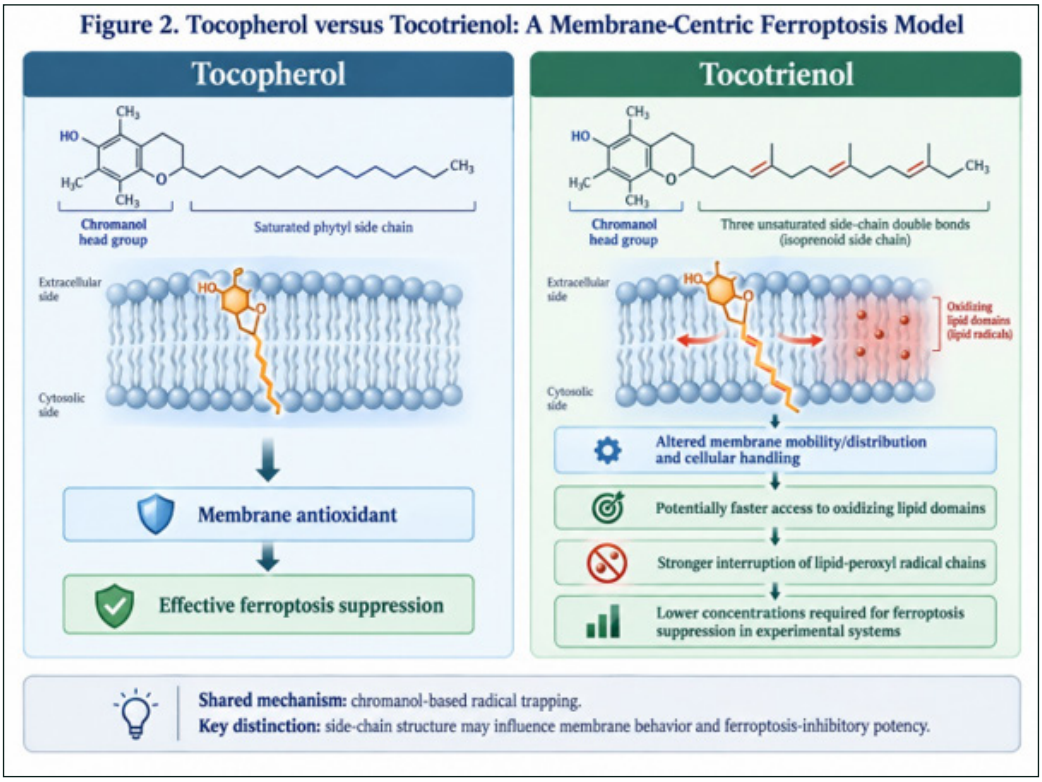

Figure 2: Tocopherol versus tocotrienol: a membrane-centric ferroptosis model

Figure 2 should be interpreted as a hypothesis-generating model rather than definitive proof of the exact physical mechanism. The common chromanol ring provides radical-trapping capacity in both vitamin E families. The distinguishing observation is that tocotrienols suppress ferroptosis at lower concentrations than tocopherols under the tested cellular conditions. Further molecular-dynamics, lipidomic, fluorescence-localization, and membrane-kinetic experiments are required to determine whether improved ferroptosis suppression arises predominantly from bilayer distribution, intracellular uptake, recycling kinetics, subcellular localization, radical reaction rates, or a combination of these factors.

Renal Ischemia–Reperfusion and Acute Kidney Injury

The kidney is arguably the strongest initial organ system for translational investigation. Renal tubular epithelial cells have high metabolic demands, abundant mitochondria, and substantial exposure to oxidative and iron-related disturbances during ischemia and reperfusion. Contemporary nephrology literature increasingly regards ferroptosis as an important mechanism in AKI, particularly in tubular injury, and potentially in maladaptive progression from AKI to chronic kidney disease. Broader organ-level reviews likewise identify the kidney as one of the best-developed I/R models for testing ferroptosis-directed interventions (Bayır et al., 2023; Guo et al., 2023; Liu et al., 2023; Luan et al., 2025).

Mechanistically, ischemia disrupts mitochondrial ATP production and ionic homeostasis, while reperfusion promotes oxidative reactions in a tissue with disturbed iron and lipid metabolism. GPX4-dependent defenses, iron handling, phospholipid peroxidation, and ferroptosis-sensitive tubular populations therefore intersect within renal I/R pathology. The possibility that blocking ferroptotic amplification might preserve viable tubular epithelium has prompted considerable interest in ferroptosis inhibitors as experimental renoprotective agents

(Bayır et al., 2023).

Tocotrienol evidence provides an intriguing but incomplete bridge. Nowak and Megyesi showed that γ-tocotrienol administered before bilateral renal ischemia preserved mitochondrial respiration, respiratory-chain activities, ATP synthase function, and tissue ATP, while improving renal morphology, plasma creatinine recovery, tubular regeneration, and survival. These findings predate direct experimental proof that tocotrienols are potent ferroptosis suppressors and therefore were not structured around ferroptosis-specific endpoints (Nowak & Megyesi, 2021).

It is nevertheless plausible that radical-trapping suppression of membrane lipid peroxidation contributed to this renal protection. The appropriate scientific conclusion is not that γ-tocotrienol has already been proven to prevent ferroptotic AKI, but that established renal I/R protection now converges with independent evidence that tocotrienols can suppress ferroptosis. A decisive next experiment would reproduce renal I/R injury while simultaneously measuring oxidized phosphatidylethanolamine species, labile iron, ACSL4, GPX4 status, 4-HNE, and rescue patterns with ferroptosis-specific interventions.

Myocardial Ischemia–Reperfusion Injury

Myocardial reperfusion injury is another compelling context because cardiomyocytes contain abundant mitochondria and highly active lipid metabolism. Restoration of coronary blood flow saves myocardium but can also produce oxidative bursts, calcium dysregulation, mitochondrial injury, inflammation, and multiple forms of regulated cell death. Contemporary cardiovascular reviews increasingly integrate ferroptosis into this pathophysiology, emphasizing iron overload, phospholipid oxidation, GPX4 depletion, mitochondrial dysfunction, and interactions with inflammatory signaling (Fang et al., 2023; Laukaitiene et al., 2023; Zhang et al., 2024).

The translational attractiveness of tocotrienols lies in their membrane activity and earlier experimental cardioprotective literature. A systematic review of tocotrienols in cerebral and myocardial I/R models found improvements across structural, functional, biochemical, oxidative, inflammatory, and apoptotic outcomes. Yet these studies predominantly interpreted tocotrienols through antioxidative, anti-inflammatory, and anti-apoptotic mechanisms rather than ferroptosis (Ramli et al., 2021).

This distinction matters. Myocardial infarction is a clinical emergency in which pretreatment is usually impossible. Many nutraceutical organ-protection experiments administer agents before ischemia, demonstrating biological capacity but not clinical rescue feasibility. Future cardiac studies must therefore determine whether tocotrienols remain effective when administered at reperfusion or after ischemia has begun, whether cardioprotective concentrations can be reached rapidly enough, and whether intravenous or nanoparticle formulations are required.

Cerebral Ischemia and Neurological Injury

The brain is highly vulnerable to ferroptosis because neuronal membranes are enriched in oxidation-prone PUFAs, iron is tightly regulated but regionally abundant, and neuronal function depends heavily on mitochondrial metabolism. Ischemic stroke produces glutamate dysregulation, excitotoxicity, blood–brain barrier disruption, iron redistribution, inflammatory activation, mitochondrial stress, and depletion of antioxidant capacity. These features interact strongly with the ferroptotic machinery (Guo et al., 2023; Hu et al., 2024; Liu et al., 2024; Tian et al., 2024).

Tocotrienol neuroprotection has been explored for many years, including in cerebral I/R models. Systematic evaluation of palm oil and palm TRF has identified substantial preclinical neuroprotective evidence, while the I/R-specific literature reports reductions in oxidative injury, inflammatory signaling, and structural damage (Ismail et al., 2020; Ramli et al., 2021). Once again, these observations are consistent with but do not prove ferroptosis suppression.

The concept may also extend beyond stroke. Ferroptosis has been implicated in traumatic brain injury, where secondary damage includes iron accumulation, lipid peroxidation, mitochondrial injury, and inflammatory amplification (Geng et al., 2021; Pang et al., 2022). The neurological application nevertheless presents major pharmacokinetic challenges, including blood–brain barrier penetration, optimal isoform selection, timing, and the need to distinguish neuron, astrocyte, oligodendrocyte, microglial, endothelial, and immune-

cell responses.

Acute Lung Injury, Sepsis, and Systemic Injury

Acute lung injury and acute respiratory distress syndrome provide another potential ferroptosis-sensitive context. Evidence links altered iron handling, depleted antioxidant defenses, ACSL4-related lipid remodeling, oxidative epithelial injury, and inflammatory signaling with pulmonary ferroptosis. Reviews of acute lung injury increasingly identify ferroptosis as a potential therapeutic target, although causal importance may differ according to infectious, toxic, ventilator-associated, or inflammatory etiology (Liu et al., 2022; Yu & Sun, 2023).

Sepsis creates an even more complex environment. Ferroptosis has been implicated in sepsis-associated damage to the kidney, heart, lung, liver, and brain, but suppression of ferroptosis cannot be considered independently of host defense. The immune response to infection depends on tightly controlled redox signals and regulated cell-death processes, and excessive antioxidant or antiferroptotic activity could theoretically alter microbial clearance or immune function. Reviews nevertheless identify pharmacological ferroptosis inhibition as an emerging strategy for reducing sepsis-associated organ damage (Huang et al., 2023; Huo et al., 2023).

Acute pancreatitis provides a related inflammatory model in which ferroptosis has been linked with iron disturbance, lipid-peroxidation pathways, systemic inflammation, and multiorgan complications. The broader implication is that ferroptosis suppression may eventually be relevant beyond classical vascular I/R, although each disease requires independent validation rather than extrapolation from one organ to another (Li et al., 2022).

Figure 3 summarizes the translational evidence ladder from direct cellular evidence to human therapy. It shows that the evidence becomes progressively more inferential as translation moves from mechanistic models to organ protection and clinical application.

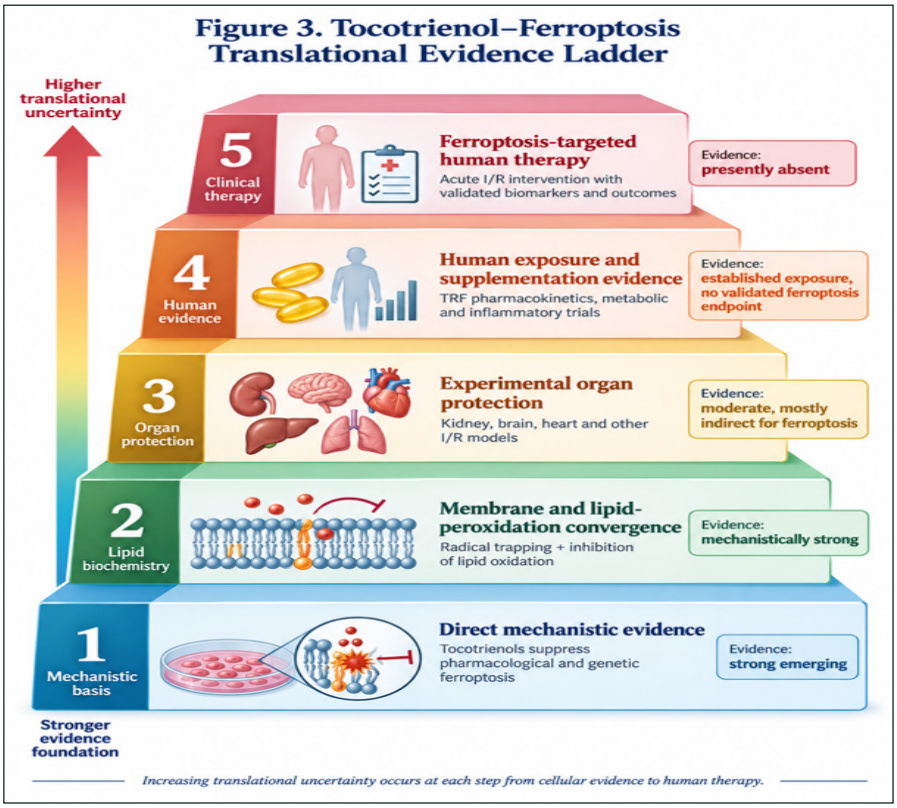

Figure 3: Tocotrienol–ferroptosis translational evidence ladder

This evidence ladder prevents an important category error. Demonstration that tocotrienols suppress ferroptosis

in controlled cellular systems is not equivalent to demonstration that an orally administered palm TRF prevents ferroptotic cell loss in human myocardial infarction, stroke, or AKI. Each transition introduces new uncertainty involving formulation, absorption, plasma binding, tissue penetration, metabolism, time to therapeutic exposure, and disease-specific biology.4.7 Pharmacokinetics and bioavailability as translational bottlenecks.

The pharmacokinetic question may determine whether the elegant cellular biology becomes clinically useful. Tocotrienols are lipid-soluble molecules whose absorption depends on gastrointestinal conditions, food intake, formulation, transport, and metabolism. Human pharmacokinetic studies demonstrate measurable systemic exposure but also substantial variation among tocotrienol preparations and isoforms. Palm TRF and annatto-derived preparations differ in composition, and plasma kinetics cannot automatically predict concentrations in kidney cortex, myocardium, ischemic brain, or pulmonary tissue (Sharif et al., 2023).

The 2026 ferroptosis study is encouraging because effective concentrations were in the low-micromolar to submicromolar range for some tocotrienols. Nevertheless, direct comparison between nominal culture-medium concentrations and human tissue concentrations is inappropriate. Protein binding, lipoprotein carriage, intracellular accumulation, metabolites, membrane partitioning, and local vascular delivery can alter effective exposure substantially (Sharif et al., 2023; Yang et al., 2026).

Human intervention evidence provides useful safety and feasibility information but not ferroptosis validation. Trials involving TRF in metabolic disorders have examined glycemic parameters, inflammation, hepatic outcomes, and other endpoints. Systematic reviews in type 2 diabetes and non-alcoholic fatty liver disease show that tocotrienols can be administered clinically, but therapeutic effects vary across endpoints and study designs (Chin et al., 2023; Phang et al., 2023).

The comprehensive review of randomized trials of palm TRF likewise found a broad human evidence base but emphasized heterogeneity in dose, formulation, duration, and outcome measures. These limitations become particularly important for ferroptosis because acute organ injury may require rapid achievement of a protective membrane concentration rather than chronic modest supplementation (Looi et al., 2025).

Discussion and Analysis

From "antioxidant" to ferroptosis suppressor

The most important conceptual contribution of this review is the argument that tocotrienols should no longer be discussed exclusively using the broad label "antioxidants." That term is chemically correct but biologically imprecise. Antioxidant effects measured in solution-based assays do not necessarily predict the ability to prevent iron-dependent phospholipid oxidation within intact cells. Ferroptosis research has made this distinction especially important because survival depends on where an antioxidant operates, what radicals it intercepts, whether it reaches vulnerable membrane compartments, and whether it can function when GPX4-dependent detoxification collapses.

The 2026 study satisfies an important threshold because tocotrienols suppressed death after several different upstream disturbances, including genetic GPX4 loss. This suggests activity at or downstream of the common lipid-peroxidation execution pathway. In this respect, tocotrienols conceptually resemble radical-trapping defense molecules that prevent propagation of lethal phospholipid oxidation. They should not, however, be described as proven direct activators of GPX4, FSP1, GCH1, or DHODH unless future experiments establish such interactions (Kraft et al., 2020; Mao et al., 2021; Yang et al., 2026).

The membrane-centric interpretation also provides a plausible explanation for apparently overlapping tocotrienol actions. Protection of mitochondrial function, reduction of inflammatory amplification, attenuation of secondary oxidative stress, and decreased necrotic injury may not represent completely independent effects. If tocotrienols prevent the initiating spread of phospholipid oxidation, downstream preservation of organelle function and reduced release of damage-associated molecular patterns could produce secondary anti-inflammatory and metabolic benefits.

Reinterpreting earlier organ-protection literature

The temptation to reinterpret every earlier tocotrienol study as ferroptosis evidence should be resisted.

Biomarkers such as MDA, ROS, 4-HNE, GSH, inflammatory cytokines, mitochondrial membrane potential, apoptosis markers, and tissue histology are not uniquely diagnostic of ferroptosis. Many cell-death and stress pathways produce overlapping changes.

A more scientifically defensible approach is convergence analysis. Earlier tocotrienol experiments demonstrate that the compounds can protect organs exposed to ischemia, oxidative injury, or inflammation. Contemporary ferroptosis studies independently demonstrate that ferroptosis contributes to those same injuries. Direct 2026 evidence then establishes that tocotrienols can suppress ferroptosis in controlled models. Together these three evidence streams create a mechanistically coherent hypothesis, but only future experiments combining them in a single causal design can demonstrate that ferroptosis inhibition is responsible for a defined proportion of organ protection.

For kidney I/R, such a study could compare γ-tocotrienol with ferrostatin-like controls, use pharmacological and genetic modulation of GPX4 or ACSL4, quantify oxidized phosphatidylethanolamines through lipidomics, and determine whether the protective effect of tocotrienol disappears when ferroptotic lipid oxidation is experimentally uncoupled. Similar designs could be adapted to myocardium and brain.

Timing may be as important as dose

Timing represents one of the most important unresolved translational questions. Many experimental antioxidant and nutraceutical studies demonstrate benefit when compounds are administered before an ischemic insult. Such pretreatment models are relevant to predictable I/R states including transplantation, cardiopulmonary bypass, major vascular surgery, or selected procedures involving temporary ischemia. They are much less directly applicable to spontaneous myocardial infarction, stroke, sepsis, or unexpected AKI.

Ferroptosis itself is temporally dynamic. Early biochemical disturbances may remain reversible, while later widespread membrane peroxidation may cross a threshold beyond which radical trapping cannot restore viability. The effective therapeutic window for tocotrienols must therefore be defined relative to ischemia onset, reperfusion, and established tissue damage. A clinically useful acute ferroptosis suppressor would ideally work when administered at or shortly before reperfusion rather than requiring days of prior dietary supplementation.

This timing problem interacts with formulation. Oral tocotrienols may be reasonable for chronic risk modification or predictable procedures, but rapid rescue after acute vascular occlusion may require formulations capable of achieving target-tissue exposure within minutes. Nanoparticles, emulsions, liposomes, or parenteral formulations could theoretically address this problem, but their pharmacokinetics and safety would require independent development (Ranasinghe et al., 2022).

The normal-tissue protection versus cancer paradox

The same mechanism that makes ferroptosis suppression attractive in I/R injury creates a major therapeutic paradox in oncology. Ferroptosis is increasingly being exploited as a vulnerability in malignant cells, especially tumors that are resistant to apoptosis-based therapies, have altered lipid metabolism, accumulate iron, or depend strongly on GPX4/FSP1-mediated defenses. Current cancer research therefore seeks not only ferroptosis inhibitors but also ferroptosis inducers, with growing interest in exploiting ferroptosis vulnerability in therapy-resistant states (Lei et al., 2022, 2024; Nakamura & Conrad, 2024; Yapici et al., 2024).

The tumor microenvironment further complicates the issue because ferroptosis can influence immune cells as well as malignant cells. Depending on cellular context, ferroptotic signals may support antitumor immunity, promote immunosuppressive conditions, or damage immune populations needed for tumor control. Contemporary literature therefore describes ferroptosis as a double-edged process rather than a universally desirable therapeutic endpoint (Dang et al., 2022; Qi & Peng, 2023).

Figure 4 captures the principal clinical paradox: an intervention cannot be labeled beneficial merely because it suppresses ferroptosis, because the desirability of that effect depends on which cells are protected. The figure therefore contrasts normal-tissue rescue during acute injury with the possibility that systemic ferroptosis suppression

could undermine treatments designed to exploit ferroptosis vulnerability in malignant cells.

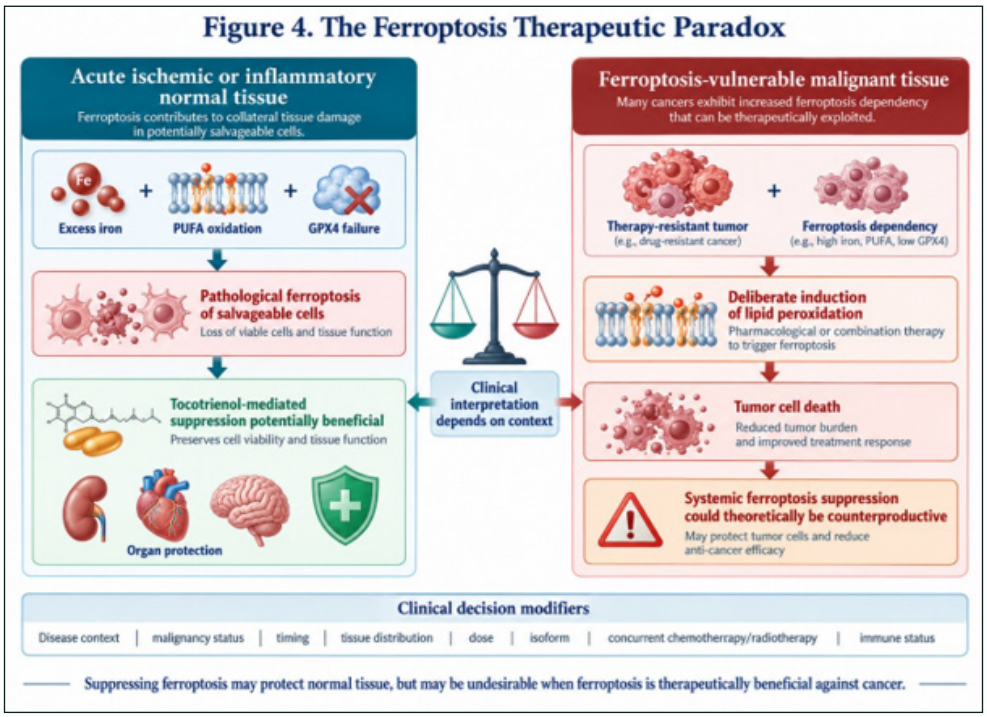

Figure 4: The ferroptosis therapeutic paradox

The paradox does not mean that tocotrienols are contraindicated in all patients with cancer. Tocotrienols themselves have been studied for anticancer effects through multiple mechanisms, including isoform-dependent actions investigated in preclinical and emerging clinical contexts, and ferroptosis is only one component of tumor biology (Ranasinghe et al., 2022; Wong et al., 2020; Younes et al., 2024). Rather, Figure 4 demonstrates why systemic anti-ferroptotic effects should be evaluated explicitly when tocotrienols are combined with therapies that rely on lipid peroxidation or ferroptosis induction. Cell type, dose, timing, tumor genotype, pharmacological partner, and tissue exposure could determine whether the net effect is protective or detrimental.

Ferroptosis Suppression and Immune Defense

A related concern involves immunity. Ferroptosis regulation is involved in immune-cell survival, differentiation, and function, and recent immunology syntheses emphasize that immune cells can both undergo and actively shape ferroptotic processes. The selenium-GPX4 axis, for example, influences follicular helper T-cell survival and humoral responses, while broader immune effects vary according to cell type and disease context (Bell et al., 2024; Yao et al., 2021). Ferroptosis can also alter inflammatory signaling and immune-cell behavior within cancer and infection. Consequently, systemic ferroptosis suppression during sepsis or acute infection should not automatically be assumed to improve outcomes.

This issue argues for targeted rather than indiscriminate ferroptosis control. An ideal intervention would protect vulnerable parenchymal cells during a defined window of acute injury without chronically suppressing physiologically useful lipid-redox signaling, antimicrobial defense, or tumor-suppressive ferroptosis.

Biomarkers: the Major Clinical Translation Gap

A major obstacle is the absence of a universally validated clinical biomarker that directly quantifies ferroptosis in human organs. Increased MDA, 4-HNE, oxidized lipids, ferritin, or altered GPX4 may support a ferroptotic interpretation but are not independently specific. Contemporary reviews therefore recommend multimodal interpretation because candidate markers of lipid peroxidation can also arise in non-ferroptotic oxidative states

and physiological contexts (Chen et al., 2024). The strongest experimental evidence usually combines lipid peroxidation, iron dependency, characteristic molecular changes, and rescue by ferroptosis-specific inhibitors or genetic intervention.

For clinical trials, a multimarker strategy may therefore be necessary. Candidate approaches include targeted oxidized phospholipid lipidomics, circulating or tissue 4-HNE adducts, GPX4 and ACSL4 signatures, iron-related markers, CoQ redox state, tissue-specific injury biomarkers, and pharmacodynamic demonstration that tocotrienol exposure modifies a ferroptosis-consistent signature. Such strategies should be prospectively validated against organ-specific injury outcomes because no single currently proposed biomarker provides sufficient specificity for ferroptotic cell death in vivo (Chen et al., 2024). Discovery work must first determine which markers correlate most strongly with actual ferroptotic tissue loss rather than general oxidative stress.

Isoforms and formulation should not be treated as minor details

The vitamin E family contains eight molecules, and the available evidence indicates that their biological effects cannot be assumed identical. α-, γ-, and δ-tocotrienols differ in metabolism and biological activity. Palm TRF additionally contains mixtures of tocotrienols and tocopherols whose composition varies by preparation. A purified tocotrienol used in cellular ferroptosis studies is therefore not pharmacologically identical to a commercially available palm TRF.

This issue is especially relevant because α-tocopherol handling is strongly influenced by α-tocopherol transfer protein and can affect the disposition of other vitamin E analogues. Human pharmacokinetic evidence confirms substantial variation in tocotrienol bioavailability, while clinical TRF studies show heterogeneous dosing and formulation strategies (Looi et al., 2025; Sharif et al., 2023).

Future experiments should therefore report exact isoform composition, dose, formulation, fed/fasted administration, plasma pharmacokinetics, tissue accumulation where feasible, and concentrations of relevant metabolites. The field should avoid using the terms “vitamin E,” “tocotrienol,” and “palm TRF” interchangeably.

A translational Research Roadmap

The immediate research priority is replication of the 2026 ferroptosis observations across independent laboratories, human primary cells, organoids, and disease-relevant cell types. Renal tubular epithelial cells, cardiomyocytes, neurons, brain endothelial cells, pulmonary epithelial cells, and selected immune-cell populations should be evaluated. Comparative experiments should include tocopherols, α-, γ-, and δ-tocotrienols, clinically relevant TRFs, and established ferroptosis inhibitors.

The second priority is causal organ-level validation. Acute kidney I/R may provide the strongest first model because tocotrienol renoprotection and ferroptosis biology are both comparatively well developed. Cardiac and cerebral reperfusion should follow, with strict attention to post-insult treatment rather than prophylaxis alone. Cross-organ reviews published in the current literature reinforce the need to test whether apparently shared ferroptotic pathways behave similarly enough across tissues to support a common therapeutic strategy (Luan et al., 2025).

Third, pharmacokinetic/pharmacodynamic work must establish whether ferroptosis-suppressing concentrations can be achieved in relevant human tissues. Existing human supplementation literature demonstrates exposure but was not designed around acute target engagement. Dedicated studies should measure plasma and tissue tocotrienol isoforms, metabolites, lipidomic signatures, and temporal relationships between exposure and ferroptosis-relevant biomarkers.

Fourth, clinical development should initially focus on situations where treatment timing is predictable. Organ transplantation, cardiac surgery, vascular procedures, and other planned I/R events may provide more practical early translational models than spontaneous stroke or myocardial infarction. Tocotrienols could be administered before and during the insult, creating an opportunity to test target engagement and organ-protection endpoints under controlled conditions.

Finally, oncology interactions require explicit safety assessment. Trials should document active or previous malignancy and concurrent therapies, especially

treatments that may depend partly on oxidative lipid injury or ferroptosis. The therapeutic objective should be context-specific suppression of pathological ferroptosis rather than indiscriminate lifelong inhibition of ferroptotic signaling.

Conclusion

The ferroptosis field provides a substantially new intellectual framework for understanding tocotrienol biology. Tocotrienols have historically been categorized broadly as antioxidant, anti-inflammatory, neuroprotective, cardioprotective, or metabolic nutraceuticals. Direct comparative evidence published in 2026 now demonstrates that tocotrienols can suppress experimentally induced ferroptosis more potently than tocopherols across pharmacological and genetic models. This finding warrants a shift from the nonspecific language of antioxidant activity toward investigation of tocotrienols as membrane-level radical-trapping regulators of ferroptotic cell death.

The strongest translational opportunities arise in pathological states where ferroptosis contributes to loss of otherwise salvageable cells, particularly renal, myocardial, and cerebral ischemia–reperfusion injury. Acute lung injury, sepsis-associated organ dysfunction, traumatic brain injury, and other inflammatory injuries may provide additional applications. Existing tocotrienol studies demonstrating mitochondrial, renal, cardiac, and neurological protection increase biological plausibility but should not be misrepresented as direct ferroptosis evidence.

Major translational barriers remain. Human tissue concentrations required for ferroptosis suppression are uncertain; bioavailability differs across formulations and isoforms; optimal treatment timing is unknown; validated human ferroptosis biomarkers are lacking; and oral supplementation may not achieve rapid enough exposure for emergency reperfusion therapy. Palm TRF also cannot automatically be treated as pharmacologically equivalent to purified tocotrienol isoforms.

The therapeutic paradox of ferroptosis must remain central to future development. Suppression may protect normal tissues during ischemia and inflammation, whereas ferroptosis induction is increasingly being pursued to kill therapy-resistant malignant cells. Tocotrienol therapy must therefore ultimately be defined by disease context, tissue targeting, timing, dose, isoform, and concurrent therapies.

The most defensible contemporary conclusion is therefore that tocotrienols have progressed from plausible lipid antioxidants to experimentally demonstrated ferroptosis suppressors, but they have not yet progressed to clinically validated ferroptosis-targeted therapeutics. Closing that gap will require mechanistically rigorous organ studies, quantitative pharmacokinetics, ferroptosis-specific biomarkers, and carefully staged human trials.

References

1. Ai Y, Yan B, Wang X (2021) The oxidoreductases POR and CYB5R1 catalyze lipid peroxidation to execute ferroptosis. Molecular & Cellular Oncology 8: 1881393.
2. Bayır H, Dixon SJ, Tyurina YY, Kellum JA, Kagan VE (2023) Ferroptotic mechanisms and therapeutic targeting of iron metabolism and lipid peroxidation in the kidney. Nature Reviews Nephrology 19: 315-336.
3. Bell HN, Stockwell BR, Zou W (2024) Ironing out the role of ferroptosis in immunity. Immunity 57: 941-956.
4. Chen D, Chu B, Yang X, Liu Z, Jin Y, et al. (2021) iPLA2β-mediated lipid detoxification controls p53-driven ferroptosis independent of GPX4. Nature Communications 12: 3644.
5. Chen F, Kang R, Tang D, Liu J (2024) Ferroptosis: Principles and significance in health and disease. Journal of Hematology & Oncology 17: 41.
6. Chin KY, Ekeuku SO, Chew DCH, Trias A (2023) Tocotrienol in the management of nonalcoholic fatty liver disease: A systematic review. Nutrients 15: 834.
7. Dang Q, Sun Z, Wang Y, Wang L, Liu Z, et al. (2022) Ferroptosis: A double-edged sword mediating immune tolerance of cancer. Cell Death & Disease 13: 925.
8. Du Y, Guo Z (2022) Recent progress in ferroptosis: Inducers and inhibitors. Cell Death Discovery 8: 501.
9. Fang X, Ardehali H, Min J, Wang F (2023) The molecular and metabolic landscape of iron and ferroptosis in cardiovascular disease. Nature Reviews Cardiology 20: 7-23.
10. Freitas FP, Alborzinia H, Ferreira dos Santos A, Nepachalovich P, Pedrera L, et al. (2024) 7-Dehydrocholesterol is an endogenous suppressor of ferroptosis. Nature 626: 401-410.

11. Galy B, Conrad M, Muckenthaler M (2024) Mechanisms controlling cellular and systemic iron homeostasis. Nature Reviews Molecular Cell Biology 25: 133-155.
12. Geng ZW, Guo ZL, Guo RB, Ye RD, Zhu WS, et al. (2021) Ferroptosis and traumatic brain injury. Brain Research Bulletin 172: 212-219.
13. Guo J, Tuo QZ, Lei P (2023) Iron, ferroptosis, and ischemic stroke. Journal of Neurochemistry 165: 487-520.
14. Guo R, Duan J, Pan S, Cheng F, Qiao Y, et al. (2023) The road from AKI to CKD: Molecular mechanisms and therapeutic targets of ferroptosis. Cell Death & Disease 14: 426.
15. Hadian K (2020) Ferroptosis suppressor protein 1 (FSP1) and coenzyme Q10 cooperatively suppress ferroptosis. Biochemistry 59: 637-638.
16. Heath A, Levay P, Tuvey D (2022) Literature searching methods or guidance and their application to public health topics: A narrative review. Health Information & Libraries Journal 39: 6-21.
17. Hu X, Bao Y, Li M, Zhang W, Chen C (2024) The role of ferroptosis and its mechanism in ischemic stroke. Experimental Neurology 372: 114630.
18. Huang Q, Ding Y, Fang C, Wang H, Kong L (2023) The emerging role of ferroptosis in sepsis, opportunity or challenge? Infection and Drug Resistance 16: 5551-5562.
19. Huo L, Liu C, Yuan Y, Liu X, Cao Q (2023) Pharmacological inhibition of ferroptosis as a therapeutic target for sepsis-associated organ damage. European Journal of Medicinal Chemistry 257: 115438.
20. Ismail M, Alsalahi A, Imam MU, Ooi DJ, Khaza'ai H, et al. (2020) Safety and neuroprotective efficacy of palm oil and tocotrienol-rich fraction from palm oil: A systematic review. Nutrients 12: 521.
21. Jiang X, Stockwell BR, Conrad M (2021) Ferroptosis: Mechanisms, biology and role in disease. Nature Reviews Molecular Cell Biology 22: 266-282.
22. Khor BH, Tiong HC, Tan SC, Wong SK, Chin KY, et al. (2021) Effects of tocotrienols supplementation on markers of inflammation and oxidative stress: A systematic review and meta-analysis of randomized controlled trials. PLOS ONE 16: e0255205.
23. Kraft VA N, Bezjian CT, Pfeiffer S, Ringelstetter L, Müller C, et al. (2020) GTP cyclohydrolase 1/ tetrahydrobiopterin counteract ferroptosis through lipid remodeling. ACS Central Science 6: 41-53.
24. Laukaitiene, J., Gujyte, G., & Kadusevicius, E. (2023). Cardiomyocyte damage: Ferroptosis relation to ischemia-reperfusion injury and future treatment options. International Journal of Molecular Sciences 24: 12846.
25. Lei G, Zhuang L, Gan B (2022) Targeting ferroptosis as a vulnerability in cancer. Nature Reviews Cancer 22: 381-396.
26. Lei G, Zhuang L, Gan B (2024) The roles of ferroptosis in cancer: Tumor suppression, tumor microenvironment, and therapeutic interventions. Cancer Cell 42: 513-534.
27. Li H, Lin Y, Zhang L, Zhao J, Li P (2022) Ferroptosis and its emerging roles in acute pancreatitis. Chinese Medical Journal 135: 2026-2034.
28. Liu X, Zhang J, Xie W (2022) The role of ferroptosis in acute lung injury. Molecular and Cellular Biochemistry 477: 1453-1461.
29. 29. Liu J, Han X, Zhou J, Leng Y (2023) Molecular mechanisms of ferroptosis and their involvement in acute kidney injury. Journal of Inflammation Research 16: 4941-4951.
30. Liu C, Wang G, Han W, Tian Q, Li M (2024) Ferroptosis: A potential therapeutic target for stroke. Neural Regeneration Research 19: 988-997.
31. Looi AD, Palanisamy UD, Moorthy M, Radhakrishnan AK (2025) Health benefits of palm tocotrienol-rich fraction: A systematic review of randomized controlled trials. Nutrition Reviews 83: 307-328.
32. Luan X, Chen P, Miao L, Yuan X, Yu C, et al. (2025) Ferroptosis in organ ischemia-reperfusion injuries: Recent advancements and strategies. Molecular and Cellular Biochemistry 480: 19-41.
33. Mao C, Liu X, Zhang Y, Lei G, Yan Y, et al. (2021) DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. Nature 593: 586-590.
34. Nakamura T, Conrad M (2024) Exploiting ferroptosis vulnerabilities in cancer. Nature Cell Biology 26: 1407-1419.
35. Nowak G, Megyesi J (2021) γ-Tocotrienol protects against mitochondrial dysfunction, energy deficits, morphological damage, and decreases in renal functions after renal ischemia. International Journal of Molecular Sciences 22: 12674.
36. Pang Q, Zheng L, Ren Z, Xu H, Guo H, et al. (2022) Mechanism of ferroptosis and its relationships with other types of programmed cell death: Insights for potential therapeutic benefits in traumatic brain

injury. Oxidative Medicine and Cellular Longevity 1274550.
37. Phang SCW, Ahmad B, Abdul Kadir K, Palanisamy UDM (2023) Effects of tocotrienol-rich fraction supplementation in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Advances in Nutrition 14: 1159-1169.
38. Purssell E, Gould D (2021) Undertaking qualitative reviews in nursing and education—A method of thematic analysis for students and clinicians. International Journal of Nursing Studies Advances 3: 100036.
39. Qi D, Peng M (2023) Ferroptosis-mediated immune responses in cancer. Frontiers in Immunology 14: 1188365.
40. Ramli FF, Ali A, Ibrahim NI (2021) Protective effects of tocotrienols in cerebral and myocardial ischemia-reperfusion injury: A systematic review. Applied Sciences 11: 7994.
41. Ranasinghe R, Mathai M, Zulli A (2022) Revisiting the therapeutic potential of tocotrienol. BioFactors 48: 813-856.
42. Reed A, Ichu TA, Milosevich N, Melillo B, Schafroth MA,et al. (2022) LPCAT3 inhibitors remodel the polyunsaturated phospholipid content of human cells and protect from ferroptosis. ACS Chemical Biology 17: 1607-1618.
43. Sharif M, Khan DA, Farhat K, Noor M, Khan MA, et al. (2023) Pharmacokinetics and bioavailability of tocotrienols in healthy human volunteers: A systematic review. Journal of the Pakistan Medical Association 73: 603-610.
44. Stockwell BR (2022) Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. Cell 185: 2401-2421.
45. Sukhera J (2022) Narrative reviews: Flexible, rigorous, and practical. Journal of Graduate Medical Education 14: 414-417.
46. Sun WY, Tyurin VA, Mikulska-Ruminska K, Shrivastava IH, Anthonymuthu TS, et al. (2021) Phospholipase iPLA2β averts ferroptosis by eliminating a redox lipid death signal. Nature Chemical Biology 17: 465-476.
47. Szewczyk K, Chojnacka A, Górnicka M (2021) Tocopherols and tocotrienols—Bioactive dietary compounds; what is certain, what is doubt? International Journal of Molecular Sciences 22: 6222.
48. Tang D, Chen X, Kang R, Kroemer G (2021) Ferroptosis: Molecular mechanisms and health implications. Cell Research 31: 107-125.
49. Tian X, Li X, Pan M, Yang LZ, Li Y, et al. (2024) Progress of ferroptosis in ischemic stroke and therapeutic targets. Cellular and Molecular Neurobiology 44: 25.
50. Wong SK, Kamisah Y, Mohamed N, Muhammad N, Masbah N, et al. (2020) Potential role of tocotrienols on non-communicable diseases: A review of current evidence. Nutrients 12: 259.
51. Yang H, Ito J, Maejima T, Kimura S, Ino H, et al. (2026) Tocotrienols exhibit superior ferroptosis inhibition over tocopherols. Scientific Reports 16: 4497.
52. Yao Y, Chen Z, Zhang H, Chen C, Zeng M, et al. (2021) Selenium-GPX4 axis protects follicular helper T cells from ferroptosis. Nature Immunology 22: 1127-1139.
53. Yapici FI, Bebber CM, von Karstedt S (2024) A guide to ferroptosis in cancer. Molecular Oncology 18: 1378-1396.
54. Younes M, Loubnane G, Sleiman C, Rizk S (2024) Tocotrienol isoforms: The molecular mechanisms underlying their effects in cancer therapy and their implementation in clinical trials. Journal of Integrative Medicine 22: 1-11.
55. Yu T, Sun S (2023) Role and mechanism of ferroptosis in acute lung injury. Cell Cycle 22: 2119-2129.
56. Zhang CH, Yan YJ, Luo Q (2024) The molecular mechanisms and potential drug targets of ferroptosis in myocardial ischemia-reperfusion injury. Life Sciences 340: 122439.
57. Zheng J, Conrad M (2025) Ferroptosis: When metabolism meets cell death. Physiological Reviews 105: 651-706.
58. Zhou L, Han S, Guo J, Qiu T, Zhou J, et al. (2022) Ferroptosis—A new dawn in the treatment of organ ischemia-reperfusion injury. Cells 11: 3653.