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Review Article




# Palm-Derived Tocotrienols as Ferroptosis Modulators in Ischemia–Reperfusion Injury: Linking Phospholipid Peroxidation to Multi-Organ Protection—A Review

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## Abstract

*Ischemia–reperfusion injury (IRI) is an important determinant of tissue loss following restoration of blood flow in ischemic stroke, myocardial infarction, acute kidney injury, organ transplantation, hepatic surgery, intestinal ischemia, and pulmonary transplantation. Ferroptosis has emerged as a mechanistically important component of IRI because reperfusion simultaneously increases reactive oxygen species, redox-active iron, mitochondrial stress, and oxidation of polyunsaturated membrane phospholipids while weakening endogenous antioxidant defenses. Palm-derived tocotrienols are compelling candidates for intervention because their membrane-associated antioxidant chemistry is accompanied by effects on inflammation, mitochondrial function, lipid metabolism, and redox signaling. Recent experimental evidence further demonstrates that tocotrienols can directly suppress ferroptosis more effectively than corresponding tocopherols in pharmacological and genetic models. This qualitative literature review integrates contemporary evidence on ferroptosis across cerebral, myocardial, renal, hepatic, intestinal, and pulmonary IRI with current tocotrienol biology. The synthesis supports a dual-layer hypothesis whereby tocotrienols may directly terminate phospholipid radical propagation while indirectly strengthening cellular antiferroptotic resilience. Nevertheless, direct evidence involving standardized palm tocotrienol-rich fractions in organ-specific IRI remains limited, and human proof-of-mechanism studies are absent. Future work should differentiate tocotrienol isoforms, employ validated ferroptosis endpoints, define post-ischemic therapeutic windows, establish tissue pharmacokinetics, and test compatibility with contemporary reperfusion therapies.*

## Introduction

Ischemia–reperfusion injury (IRI) represents one of the major paradoxes of contemporary acute-care medicine. Rapid restoration of blood flow is indispensable for rescuing ischemic tissue, yet reperfusion itself can produce a second wave of cellular and microvascular injury. This phenomenon is relevant to acute ischemic stroke treated with intravenous thrombolysis or mechanical thrombectomy, acute myocardial infarction treated with percutaneous coronary intervention, kidney and liver transplantation, acute kidney injury, hepatic resection, intestinal ischemia, lung transplantation, and several forms of circulatory shock. Reperfusion-associated injury arises from the interaction of reactive oxygen species (ROS), mitochondrial dysfunction, calcium overload, endothelial activation, sterile inflammation, microvascular obstruction, metabolic disorganization, and several forms of regulated cell death. Within this complex network, ferroptosis has emerged as a particularly compelling mechanism because its defining biochemical event—iron-dependent phospholipid peroxidation—closely matches the oxidative and metabolic conditions generated during ischemia followed by sudden reoxygenation [1-3].

Ferroptosis differs fundamentally from apoptosis and other historically recognized modes of regulated cell death. Rather than being defined primarily by caspase activation or characteristic nuclear fragmentation, ferroptosis is driven by the accumulation of oxidized membrane phospholipids in the presence of redox-active iron. Cellular susceptibility is determined by the balance between processes that create ferroptotic substrates—including iron accumulation and polyunsaturated fatty-acid-containing phospholipids—and defense systems that terminate lipid oxidation. The latter include the system Xc−–glutathione–glutathione peroxidase 4 (SLC7A11–GSH–GPX4) axis and several GPX4-independent networks, including ferroptosis suppressor protein 1 (FSP1)–coenzyme Q, dihydroorotate dehydrogenase (DHODH)–coenzyme Q, and

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the GTP cyclohydrolase 1–tetrahydrobiopterin pathway [4-7].

Ischemia creates a cellular environment in which those protective systems are placed under extreme pressure. ATP depletion disrupts ion homeostasis and mitochondrial metabolism, while cysteine and GSH availability may decline. Upon reperfusion, an abrupt increase in oxygen availability enables rapid ROS formation at a time when antioxidant capacity remains compromised. Iron redistribution and ferritin degradation can increase the labile iron pool, whereas ACSL4-dependent remodeling enriches membranes with polyunsaturated phospholipids susceptible to radical attack. The combination of iron, oxidizable lipid substrate, ROS generation, and weakened peroxide-removal capacity creates a biologically plausible setting for ferroptotic execution [1-3].

This emerging mechanistic framework is highly relevant to tocotrienols. Tocotrienols constitute one branch of the vitamin E family and share a chromanol antioxidant head group with tocopherols but contain an unsaturated isoprenoid side chain. Palm oil is a particularly important natural source of α-, γ-, and δ-tocotrienols and is widely used to prepare tocotrienol-rich fractions (TRFs). Tocotrienols have frequently been described as lipid-soluble antioxidants, but contemporary research demonstrates a broader pharmacological profile involving inflammatory signaling, endothelial biology, mitochondrial function, lipid metabolism, HMG-CoA reductase regulation, and cellular stress responses [8-10].

Evidence that tocotrienols can reduce tissue injury in cerebral and myocardial ischemia–reperfusion models predates the current focus on ferroptosis. A systematic review by Ramli et al [11] found beneficial effects on structural, functional, biochemical, oxidative, inflammatory, and apoptotic outcomes across preclinical brain and cardiac I/R studies. However, most of the underlying experiments did not incorporate the molecular criteria now used to establish ferroptosis. Consequently, reduced oxidative stress in an older tocotrienol study cannot automatically be reclassified as evidence of ferroptosis suppression. Instead, those earlier observations should be regarded as bridging evidence that now requires reinterpretation with contemporary ferroptosis-specific methodology [11].

A major development occurred with the publication by Yang et al [12], who directly compared tocotrienols and tocopherols in pharmacological and genetic ferroptosis models. Tocotrienols suppressed ferroptosis induced by GPX4 inhibition, inhibition of system Xc−, glutathione synthesis blockade, and inducible genetic Gpx4 deletion, and several tocotrienol analogues acted at substantially lower concentrations than corresponding tocopherols. The activity across multiple ferroptosis-inducing mechanisms is particularly important because it is consistent with downstream interception of phospholipid radical propagation rather than dependence on one specific upstream receptor or signaling pathway [12].

Additional 2026 studies broaden the biological context without yet proving efficacy in I/Yao et al [13] identified transferrin receptor-related ferroptosis biology in sepsis and investigated regulatory effects of γ-tocotrienol, while Brzóska et al [14] reported that γ-tocotrienol modified radiation-associated lipid-peroxidation products and iron-related signatures in non-human primates. These studies are not ischemia–reperfusion experiments, but they strengthen the concept that tocotrienols can interact with iron-dependent lipid-peroxidation pathways in vivo and therefore justify direct investigation in organ-specific IRI [13,14].

Human translation remains a separate problem. Meta-analytic evidence from clinical supplementation studies indicates heterogeneous effects of tocotrienols on systemic oxidative-stress and inflammatory biomarkers, and pharmacokinetic studies demonstrate substantial variation in oral exposure among formulations and isoforms. More recent formulation research continues to identify low aqueous solubility, intestinal absorption barriers, rapid elimination, and relatively weak interaction with α-tocopherol transfer protein as factors limiting predictable systemic exposure [15-18].

The central question addressed in this qualitative literature review is therefore not whether tocotrienols are broadly "antioxidant," but whether inhibition of ferroptotic phospholipid damage provides a mechanistically coherent explanation for at least part of their previously observed cytoprotection in I/R. The review integrates current evidence across cerebral, myocardial, renal, hepatic, intestinal, and pulmonary IRI, differentiates direct tocotrienol–ferroptosis evidence from indirect mechanistic inference, and develops a translational roadmap for evaluating purified tocotrienol isoforms and standardized palm TRF as potential adjuncts to reperfusion therapy.

## Literature Review: Conceptual and Theoretical Foundations

### Ferroptosis as a Lipid-Centered Form of Regulated Cell Death

Ferroptosis is best understood as a failure of the cellular systems that maintain membrane lipid redox homeostasis. Polyunsaturated fatty acids incorporated into membrane phospholipids contain bis-allylic hydrogen atoms that are especially susceptible to radical abstraction. Once phospholipid radicals form, molecular oxygen can generate phospholipid peroxyl radicals capable of propagating a chain reaction to neighboring lipids. If this process is not terminated, phospholipid hydroperoxides accumulate and ultimately compromise membrane organization, permeability, ion transport, and organelle integrity [1,2,7].

Iron acts as a catalyst and regulator of this process. Transferrin receptor-mediated uptake, ferritin storage, ferroportin-dependent export, lysosomal iron release, and NCOA4-mediated ferritinophagy collectively influence the size of the labile iron pool. Ferrous iron can participate in Fenton-type chemistry and may contribute to the generation of radicals capable of initiating or amplifying lipid peroxidation. Consequently, ferroptosis is not simply a consequence of "high ROS"; it results from the specific convergence of redox-active iron, oxidizable lipid substrate, and insufficient lipid-peroxide detoxification [1,19,20].

Lipid remodeling is equally important. ACSL4 activates long-chain polyunsaturated fatty acids for incorporation into phospholipids, thereby increasing the abundance of ferroptosis-susceptible membrane species. This explains why changes in ACSL4 frequently accompany I/R-related ferroptosis in the myocardium, kidney, liver, brain, and other tissues. Conversely, biological systems that alter fatty-acid composition or prevent formation of oxidizable phospholipids can reduce ferroptosis even without directly changing iron concentration [2,21,22].

### Canonical and Non-Canonical Ferroptosis Defense Systems

The best-characterized protective network is the SLC7A11–GSH–GPX4 pathway. SLC7A11 forms part of system Xc− and supports import of cystine in exchange for glutamate.

Intracellular reduction of cystine to cysteine provides substrate for GSH synthesis, and GPX4 uses reducing equivalents from GSH to convert phospholipid hydroperoxides into less reactive lipid alcohols. Inhibition of SLC7A11, GSH synthesis, or GPX4 can therefore produce a common outcome: uncontrolled phospholipid oxidation [1,12].

GPX4 is not the only ferroptosis defense. FSP1 regenerates reduced coenzyme Q at cellular membranes and thereby provides a parallel radical-trapping system. Mitochondrial DHODH can also maintain reduced coenzyme Q pools, generating a mitochondrial ferroptosis-defense mechanism that becomes especially important under particular metabolic conditions. In addition, GCH1-mediated tetrahydrobiopterin production regulates lipid remodeling and radical chemistry. These parallel mechanisms explain why ferroptosis susceptibility cannot always be predicted solely from GPX4 abundance and why compounds acting as membrane radical traps may remain active when GPX4 function is compromised [4-6].

This point is central to the tocotrienol hypothesis. If tocotrienols primarily terminate lipid radical chains through direct chemical action in membranes, they could potentially compensate for incomplete GPX4 activity without necessarily restoring GPX4 expression. Conversely, if tocotrienol treatment also activates NRF2 or indirectly maintains cysteine/GSH homeostasis, it could produce a second layer of protection by increasing endogenous resistance to lipid peroxide accumulation. These mechanisms are complementary rather than mutually exclusive.

## Why Reperfusion Favors Ferroptosis

The ischemic phase initiates ATP depletion, intracellular acidosis, mitochondrial electron-transport disruption, calcium accumulation, membrane depolarization, and consumption of reducing equivalents. Reperfusion restores oxygen but does so before metabolic and antioxidant systems have fully recovered. Mitochondrial electron leakage, NADPH oxidase activity, xanthine oxidase, activated leukocytes, and damaged endothelium can all contribute to the reperfusion ROS burst. Meanwhile, iron handling may remain dysregulated and PUFA-containing membranes remain vulnerable to oxidation [3].

The temporal dimension is important. Ferroptotic signaling does not necessarily occur at the same rate in every organ. Iron mobilization, GPX4 depletion, lipid remodeling, inflammatory recruitment, and mitochondrial damage can have different kinetics in cerebral, myocardial, renal, hepatic, intestinal, or pulmonary I/R. Consequently, an intervention that is effective when given before ischemia may lose efficacy if administered several hours after reperfusion. This issue is especially important for translating tocotrienols from preventive experimental models into emergency clinical therapy.

The interaction among these processes is summarized in Figure 1, which depicts ischemia-induced ATP depletion, GSH stress, and mitochondrial dysfunction followed by reperfusion-associated ROS generation, $Fe^{2+}$ mobilization, ACSL4-dependent enrichment of oxidizable phospholipids, lipid hydroperoxide accumulation, and ferroptotic membrane injury.

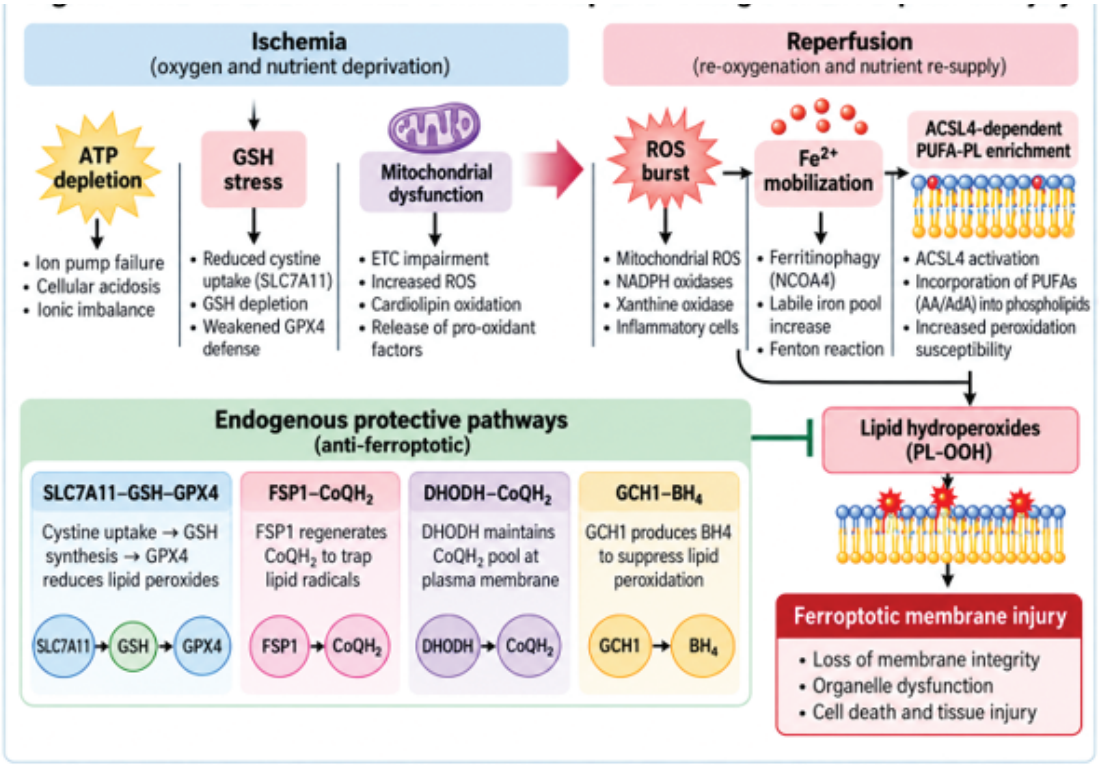



***Figure 1.*** *Mechanistic architecture of ferroptosis during ischemia–reperfusion injury.*

*The conceptual value of Figure 1 lies in distinguishing ferroptosis from generic oxidative stress. ROS formation is necessary but not sufficient to establish ferroptosis; the decisive transition occurs when iron-dependent phospholipid oxidation exceeds the capacity of membrane-protective systems. This distinction is essential when interpreting tocotrienol studies because reduction of total ROS or MDA alone cannot conclusively demonstrate inhibition of ferroptosis.*

The figure simultaneously presents the principal endogenous counter-regulatory systems—SLC7A11–GSH–GPX4, FSP1–$CoQH_2$, DHODH–$CoQH_2$, and GCH1–BH4—to emphasize that ferroptosis reflects the net balance between lipid peroxide generation and detoxification.

### Tocotrienol Structure and Palm-Derived Preparations

Vitamin E comprises tocopherol and tocotrienol families, each containing α-, β-, γ-, and δ-analogues. Tocotrienols possess an unsaturated side chain with three double bonds, whereas tocopherols contain a saturated phytyl chain. Although both groups possess the chromanol head group responsible for radical-scavenging chemistry, side-chain differences affect membrane behavior, distribution, metabolism, and potentially biological potency [8,10].

Palm-derived vitamin E commonly contains α-tocopherol together with substantial proportions of α-, γ-, and δ-tocotrienol. Accordingly, "palm tocotrienol" should not be used as though it denotes one pharmaceutical entity. Purified α-tocotrienol may differ biologically from γ- or δ-tocotrienol, and a mixed palm TRF may display pharmacodynamic interactions not observed with a purified compound. This distinction is particularly important now that direct ferroptosis comparisons indicate non-equivalent potencies among vitamin E analogues [12].

Tocotrienols also exert non-antioxidant effects. Reviews of palm-derived tocotrienols describe modulation of inflammatory pathways, HMG-CoA reductase and mevalonate metabolism, endothelial biology, cell signaling, mitochondrial function, and oxidative-response pathways. These additional actions are relevant because ferroptosis in I/R does not occur in biochemical isolation; inflammatory cytokines, mitochondrial dysfunction, metabolic substrate availability, and endothelial injury can all alter the threshold for ferroptotic death [8-10].

### Pharmacokinetic and Formulation Constraints

The physical characteristics that make tocotrienols attractive as lipid-phase antioxidants also complicate oral delivery. Tocotrienols are poorly water soluble, depend on lipid digestion and intestinal transport for absorption, and have relatively rapid elimination compared with α-tocopherol. Human studies demonstrate substantial differences among isoforms, doses, fed conditions, and formulations. Palm TRF and annatto-derived products do not necessarily produce equivalent systemic exposures, making formulation an important determinant of biological interpretation [16].

Self-emulsifying and other lipid-based delivery systems have therefore been investigated to improve solubilization and intestinal uptake. Mohamad [17] reviewed strategies based on self-emulsifying systems, whereas Ooi et al [18] emphasized saturable intestinal transport, rapid elimination, and the need to combine physicochemical formulation improvements with strategies that address biological absorption barriers. These issues have direct implications for acute I/R, where the clinically relevant question is not whether oral supplementation eventually increases plasma tocotrienols but whether therapeutic concentrations can reach the ischemic organ rapidly enough to interrupt lipid-peroxidation cascades [17,18].

## Methods

### Review Design

This article was designed as a qualitative literature review rather than a systematic literature review or meta-analysis. Its primary purpose was conceptual integration across several partially disconnected fields: contemporary ferroptosis biology, organ-specific I/R research, tocotrienol pharmacology, and translational pharmacokinetics. The review therefore emphasized mechanistic coherence, convergence and divergence among studies, and identification of research gaps rather than exhaustive article enumeration or pooled quantitative effect estimation.

### Literature Identification

Literature was identified iteratively from PubMed/MEDLINE, Scopus, Web of Science, publisher databases, and citation chaining. Priority was given to peer-reviewed articles published from 2020 through September 2026. Search concepts included combinations of "tocotrienol," "palm tocotrienol," "tocotrienol-rich fraction," "alpha-tocotrienol," "gamma-tocotrienol," "delta-tocotrienol," "ferroptosis," "GPX4," "SLC7A11," "ACSL4," "lipid peroxidation," "ferritinophagy," "NCOA4," "ischemia reperfusion," "hypoxia reoxygenation," "stroke," "myocardial," "renal," "hepatic," "intestinal," "lung," and "transplantation."

Because the objective was qualitative synthesis, the search process remained iterative. New molecular themes identified during reading—such as ferritinophagy, FSP1, DHODH, and formulation-dependent tocotrienol bioavailability—were used to identify additional literature needed to clarify the emerging framework. This approach differs from an SLR because literature discovery and interpretation occurred recursively rather than through a prospectively fixed search-and-screening protocol.

### Evidence Categories

Four evidence categories were distinguished to prevent causal overinterpretation. Tier A comprised direct studies in which tocotrienols were tested against validated ferroptosis induction or ferroptosis-related molecular pathways. Tier B comprised tocotrienol studies in I/R that demonstrated structural, functional, oxidative, inflammatory, or apoptotic protection without explicitly establishing ferroptosis. Tier C comprised studies demonstrating mechanistic roles for ferroptosis in organ-specific I/R but not involving tocotrienols. Tier D comprised translational research on tocotrienol pharmacokinetics, formulation, systemic biomarkers, and human exposure.

The distinction is important because strong evidence in Tier A and Tier C creates a mechanistically compelling bridge but does not automatically constitute direct proof that tocotrienols suppress ferroptosis during a particular organ-specific I/R event. Claims were therefore formulated according to the level of evidence available rather than by assuming that all tocotrienol antioxidant activity represents ferroptosis inhibition.

### Thematic Analysis

Articles were interpreted according to organ system, experimental design, ferroptosis markers, iron-handling pathways, phospholipid-peroxidation outcomes, mitochondrial changes, inflammatory signals, treatment timing, tocotrienol isoform or preparation, and functional outcomes. Particular weight was placed on experiments that used multiple ferroptosis-related endpoints rather than generic markers of oxidative stress alone. Studies using genetic manipulation, validated inhibitors such as ferrostatin-1 or liproxstatin-1, mitochondrial ultrastructure, lipid ROS measurements, GPX4/SLC7A11/ACSL4 analysis, and iron-related markers were considered especially informative.

## Results: Thematic Findings

### A Shared Ferroptotic Signature Across Organ I/R

A consistent theme across organ systems is that I/R shifts the balance toward ferroptotic lipid damage through three interdependent processes: increased iron availability, increased susceptibility of membrane phospholipids to oxidation, and insufficient lipid-peroxide detoxification. Frequently reported signatures include increased $Fe^{2+}$ or iron deposition, ACSL4 expression, lipid ROS, MDA or 4-HNE, accompanied by decreases in GSH, SLC7A11, or GPX4. Mitochondrial shrinkage, dense membranes, altered cristae, and membrane-potential disruption are also described in many experimental systems. Nevertheless, no single biomarker is specific enough to establish ferroptosis independently, making multi-marker validation essential [2,3,23]. A recent systematic review and meta-analysis of abdominal-organ I/R models likewise found broadly protective effects of pharmacological ferroptosis inhibition in kidney, liver, and intestinal injury, although the evidence base remained overwhelmingly preclinical and study quality was variable [23].

An equally important observation is that the relative contribution of these mechanisms differs across organs and disease states. Ferritinophagy is particularly prominent in several cerebral, renal, intestinal, and metabolically compromised myocardial models, whereas NRF2-related antioxidant signaling is highly visible in cerebral, myocardial, hepatic, and pulmonary research. These differences suggest that tocotrienol efficacy may depend on local metabolic and iron-handling environments rather than representing a uniform systemic antioxidant effect.

### Cerebral Ischemia–Reperfusion Injury

The brain is intrinsically vulnerable to ferroptosis because it combines high oxygen utilization, abundant polyunsaturated lipid content, substantial iron demand, and limited tolerance for membrane oxidative injury. Contemporary stroke literature increasingly implicates ferroptosis in neurons, glia, microvascular structures, and inflammatory responses following cerebral ischemia and reperfusion [24].

NCOA4-mediated ferritinophagy provides one mechanistic route linking ischemia to iron accumulation. Li et al [19] demonstrated that NCOA4-related ferritin degradation contributes to cerebral ischemia-induced ferroptosis. Conversely, Yang et al [25] reported that RXRγ reduced neuronal ferroptosis by transcriptionally promoting GPX4 expression. Together, these findings illustrate complementary upstream and downstream mechanisms: one increases the iron

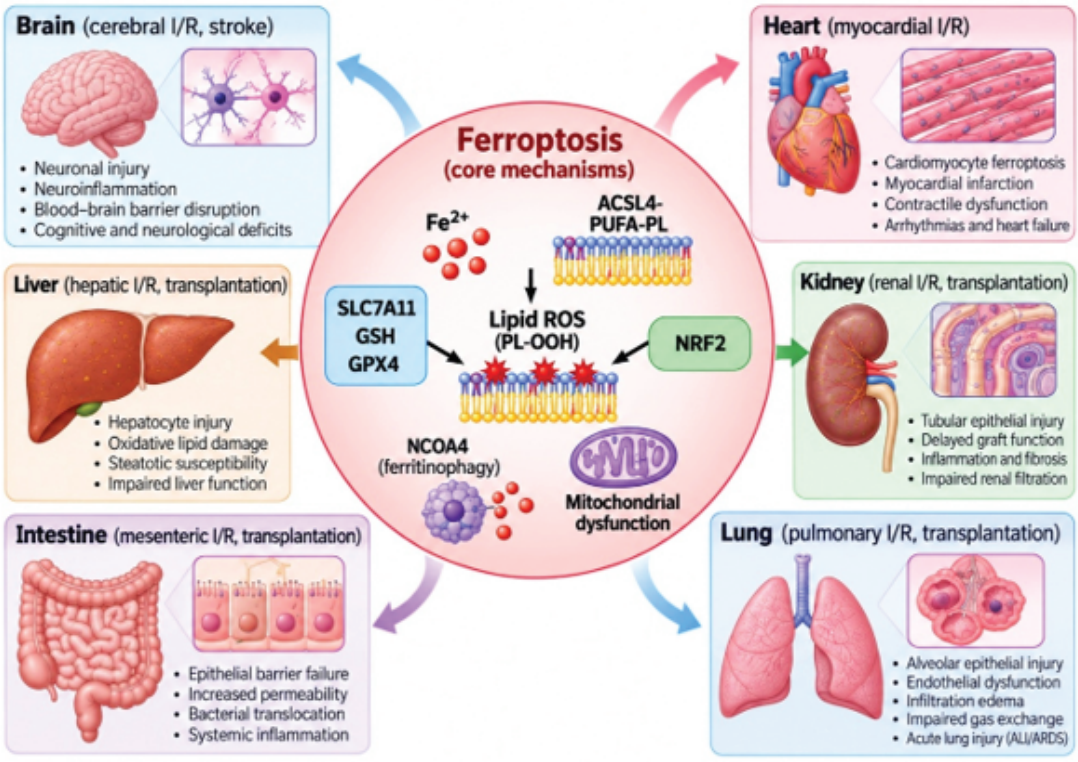



***Figure 2.*** *Multi-organ map of ferroptosis in ischemia–reperfusion injury.*

*The figure emphasizes that multi-organ ferroptosis is not identical across tissues. Instead, shared biochemical machinery is embedded in organ-specific contexts. Neuronal injury is shaped by high PUFA content and neuro-inflammation, cardiomyocyte injury by extreme energetic demand, renal injury by tubular metabolism, hepatic injury by lipid and iron handling, intestinal injury by barrier disruption, and pulmonary injury by epithelial, endothelial, and inflammatory interactions.*

substrate that drives oxidation, while the other strengthens enzymatic detoxification of lipid hydroperoxides [19,25].

NRF2-linked pathways are another recurring neuroprotective theme. β-Caryophyllene reduced cerebral I/R-associated ferroptosis in association with NRF2/HO-1 activation, while pentoxifylline was reported to protect through an NRF2/SLC7A11/GPX4 mechanism. Baicalein similarly reduced cerebral I/R injury through regulation of GPX4/ACSL4/ACSL3, demonstrating that lipid composition and peroxide detoxification can be simultaneously manipulated [26-28].

Inflammatory and ferroptotic processes also intersect. Wang et al [29] demonstrated that NLRP3 inflammasome deficiency reduced cerebral infarction, $Fe^{2+}$ accumulation, MDA, and inflammatory signaling while increasing GSH and GPX4-related protection. Such findings show why a compound with both lipid-radical-scavenging and anti-inflammatory effects could theoretically generate broader protection than a highly selective inhibitor acting at only one point in the cascade [29]. More recent work also demonstrates simultaneous modulation of ferroptosis and pyroptosis through the SLC7A11/GPX4/ACSL4 and caspase-1/GSDMD axes, reinforcing the view that regulated death programs interact during cerebral reperfusion injury [30].

The relevance to tocotrienols is therefore substantial but not yet definitive. Earlier tocotrienol studies in cerebral I/R reported reductions in oxidative injury and improvements in neurological or structural outcomes, but most did not employ modern ferroptosis endpoints. Their results should therefore be viewed as Tier B evidence requiring prospective validation through measurements of iron, ACSL4, GPX4, oxidized phospholipid species, and ferroptosis-specific rescue experiments [11].

## Myocardial Ischemia–Reperfusion Injury

The myocardium provides another strong model because reperfusion generates rapid mitochondrial ROS production and oxidative membrane damage in cells with exceptionally high energetic demand. Reviews of myocardial ferroptosis describe convergence of iron accumulation, ACSL4-dependent lipid remodeling, GPX4 impairment, mitochondrial dysfunction, and inflammatory amplification [31-33].

Several experiments provide functional mechanistic support. Mei et al [21] demonstrated that Shenmai injection reduced $Fe^{2+}$ accumulation, ACSL4 expression, infarct injury, and mitochondrial abnormalities while activating NRF2/GPX4-related signaling. Gossypol acetic acid similarly attenuated cardiac I/R injury through an antiferroptotic mechanism involving reduced lipid peroxidation and increased GPX4 activity [34].

Metabolic status modifies the response. Huang et al [35] showed that nobiletin reduced ferroptosis-associated injury in diabetic myocardial I/R, with involvement of ACSL4 and NCOA4-related pathways. This is important because diabetes changes lipid handling, oxidative stress, mitochondrial function, and iron biology, potentially increasing dependence on ferroptotic mechanisms. Chen et al [36] further highlighted the role of the SLC7A11/GSH/GPX4 axis in myocardial I/R, while Hu et al [37] linked PPAR-α activation to reduced ferroptosis and mitochondrial injury.

Collectively, these studies establish a strong Tier C rationale for testing tocotrienols directly in myocardial ferroptosis. Earlier cardioprotective tocotrienol studies already provide evidence of reduced oxidative injury and improved cardiac outcomes, but direct causal linkage to ferroptosis remains incomplete. A contemporary experiment should therefore compare palm TRF and purified isoforms with ferrostatin-1 or liproxstatin-1, quantify oxidized phospholipids and myocardial tocotrienol concentrations, and determine whether protection persists when GPX4 signaling is experimentally impaired [11].

## Renal Ischemia–Reperfusion Injury

The proximal renal tubule is particularly susceptible to I/R because of high mitochondrial density, dependence on oxidative metabolism, and limited tolerance of prolonged oxygen deprivation. Ferroptosis has consequently emerged as a major regulated-cell-death mechanism in experimental acute kidney injury.

Ferritinophagy provides an important link between autophagy and ferroptosis in renal tissue. Sui et al [20] demonstrated that CIRBP promotes ferroptosis through interaction with ELAVL1 and activation of ferritinophagy during renal I/R. This mechanism illustrates how autophagic degradation of ferritin can transform a nominally protective recycling process into a source of redox-active iron.

ACSL4 is another significant renal target. Tao et al [38] reported that dexmedetomidine reduced renal I/R-associated ferroptosis and inflammation through suppression of ACSL4-related signaling. Shi et al [22] similarly demonstrated that miR-20a-5p protects against kidney I/R by targeting ACSL4-dependent ferroptosis, including in a transplantation-relevant context. These studies reinforce the importance of membrane lipid composition in renal susceptibility.

Other renal pathways broaden the mechanistic landscape. Pan et al [39] linked USP14 inhibition with reduced ROS-dependent ferroptosis; Du et al [40] demonstrated protection by cyanidin-3-glucoside through an AMPK-related pathway; Wang et al [41] found that carnosine attenuated renal I/R through GPX4-associated ferroptosis inhibition; and Feng et al [42] identified a TLR4/NOX4-associated mechanism through which lysine-specific demethylase 1 aggravated oxidative stress and ferroptosis. Zhao et al [43] further demonstrated that selenium-binding protein 1 supports renal tubular resistance to ferroptosis through maintenance of GPX4. More recent nanozyme research further showed that combined ferrous-ion chelation and ROS scavenging can reduce renal iron overload, lipid peroxidation, and ACSL4-associated ferroptosis in mice, illustrating the potential value of simultaneously targeting iron chemistry and membrane oxidation [44].

These data make the kidney an attractive translational model for tocotrienols. In transplantation, the timing of ischemia and reperfusion is known, meaning that the donor organ can potentially be exposed to an intervention during preservation, machine perfusion, or immediately before reperfusion. This design partly overcomes the timing limitations encountered in spontaneous myocardial infarction or stroke. Moreover, kidney tissue, urine, preservation fluid, and post-transplant functional outcomes provide multiple opportunities for mechanistic biomarker assessment.

## Hepatic Ischemia–Reperfusion Injury

The liver integrates lipid metabolism, iron storage, antioxidant defense, and inflammatory signaling, making it particularly relevant to ferroptosis. Hepatic I/R occurs in liver transplantation, hepatic resection, trauma, shock, and vascular occlusion. Contemporary research demonstrates that GPX4-

related defense, NRF2 signaling, lipid substrate availability, and mitochondrial integrity all contribute to hepatic ferroptotic vulnerability. A transplantation-focused review published in 2025 similarly identified ferroptosis inhibition as a promising strategy for limiting I/R injury in marginal and steatotic liver grafts while emphasizing the continuing lack of clinically validated ferroptosis-directed therapies [45].

Guo et al [46] demonstrated that hepatocyte-specific TMEM16A deficiency reduced hepatic I/R injury through suppression of GPX4-related ferroptosis. Ye et al [47] showed that MCTR1 protected against hepatic I/R by promoting NRF2 expression and inhibiting ferroptosis. Together, these experiments support the concept that both membrane and transcriptional mechanisms regulate ferroptotic injury.

A particularly important observation concerns steatotic liver. Rokop et al [48] found that exacerbated I/R injury in fatty livers was associated with lipid-peroxidation stress and ferroptosis. Steatosis provides an expanded lipid substrate environment and is clinically relevant because fatty donor organs are increasingly encountered in transplantation. A membrane-active radical-trapping compound might therefore have especially strong theoretical value in steatotic grafts, although direct testing is required before this possibility can be considered established.

Pharmacological evidence also supports the tractability of hepatic ferroptosis. Ma et al [49] reported that ticlopidine reduced liver necrosis, transaminase release, tissue iron, lipid-peroxidation products, and ferroptotic mitochondrial injury in experimental hepatic I/R. Collectively, these results suggest that liver transplantation and elective hepatic surgery could provide controlled clinical environments for early testing of tocotrienol-based antiferroptotic strategies.

## Intestinal Ischemia–Reperfusion Injury

Intestinal I/R is clinically dangerous because epithelial and endothelial barrier disruption can convert a localized ischemic event into systemic inflammation, bacterial translocation, and remote-organ injury. Ferroptosis has been demonstrated in intestinal epithelial and endothelial compartments and appears to interact closely with ferritinophagy, mitochondrial injury, and inflammatory signaling.

Feng et al [50] reported that an apigenin derivative prevented endothelial ferroptosis and attenuated intestinal I/R through pathways involving HO-1 and MAO-B. Wang et al [51] showed that corilagin disrupted the NCOA4–ferritin interaction, thereby suppressing ferritinophagy-mediated ferroptosis. These findings demonstrate that intestinal ferroptosis can be attenuated both by modifying redox defense and by limiting iron release from ferritin.

More recent work expands the range of regulatory pathways. Hou et al [52] reported that naringenin alleviated intestinal I/R-associated ferroptosis through the YAP/STAT3 axis, while Fan et al [53] demonstrated protection by methane saline through NRF2/HO-1 signaling. Although the interventions differ markedly, their convergence on iron-dependent lipid injury reinforces the notion that ferroptosis constitutes a recurring downstream component of intestinal reperfusion pathology.

These findings also have implications for systemic protection. Intestinal barrier failure can initiate distant pulmonary and hepatic injury, raising the possibility that inhibition of intestinal ferroptosis may reduce secondary organ dysfunction even when the therapeutic compound does not accumulate strongly in every distant organ.

## Pulmonary Ischemia–Reperfusion Injury and Remote Lung Injury

Pulmonary I/R occurs during lung transplantation, pulmonary vascular procedures, and cardiopulmonary resuscitation and can also arise indirectly after ischemia in other organs. Experimental evidence implicates ferroptosis in pulmonary epithelial and endothelial injury and in the recruitment of inflammatory cells.

Wang et al [54] demonstrated that salidroside postconditioning reduced lung I/R-associated ferroptosis by activating the NRF2/SLC7A11 pathway. Importantly, the study linked ferroptotic cells with macrophage recruitment, providing a direct example of interaction between regulated lipid death and inflammatory amplification. Zhang et al [55] similarly showed that β-aminoisobutyric acid activated AMPK/NRF2 signaling, increased SLC7A11 and GPX4-related defenses, and reduced pulmonary ferroptosis.

Additional work has identified HIF-related pathways. Lu et al [56] found that hydroxycitric acid attenuated lung I/R-associated oxidative stress and ferroptosis through HIF-1α-related mechanisms. In a remote-organ model, Zhongyin et al [57] demonstrated that isoliquiritin apioside reduced acute lung injury caused by intestinal I/R by suppressing HIF-1α-mediated ferroptosis. The latter finding is especially relevant to the concept of multi-organ protection because it suggests that ferroptosis can participate not only in primary ischemic injury but also in secondary injury propagated through systemic responses.

## Direct Evidence Linking Tocotrienols to Ferroptosis

Until recently, the mechanistic connection between tocotrienols and ferroptosis was largely inferential. Tocotrienols clearly inhibited lipid oxidation in numerous biological settings, but direct comparisons using contemporary ferroptosis models were sparse. Yang et al [12] materially changed this evidence base by examining all major vitamin E analogues in multiple ferroptosis paradigms.

The study showed that tocotrienols inhibited ferroptosis produced by direct GPX4 inhibition, system Xc− inhibition, inhibition of glutathione synthesis, and inducible genetic GPX4 loss. Notably, α-tocotrienol acted at substantially lower concentrations than α-tocopherol in the Gpx4-knockout model. This broad activity is important because protection persisted across upstream perturbations that converged on lipid-peroxidation-mediated death, strengthening the hypothesis that tocotrienols act as highly efficient membrane-associated radical-trapping antioxidants [12].

Yao et al [13] added a complementary ferroptosis-related perspective in sepsis by identifying TFRC as a target connected to ferroptosis and investigating γ-tocotrienol as a regulatory intervention. This work suggests that tocotrienol effects may extend beyond terminal lipid radical chemistry toward iron-handling networks, although the disease context is sepsis rather than I/R.

Brzóska et al [14] provided another in-vivo bridge by studying γ-tocotrienol in irradiated non-human primates. Treatment was associated with attenuation of several secondary lipid-peroxidation products and changes consistent with reduced ferroptosis-related oxidative injury. Because irradiation and reperfusion differ substantially, the study should not be used as direct evidence for I/R efficacy; nevertheless, it is important because it demonstrates in vivo modulation of lipid-peroxidation

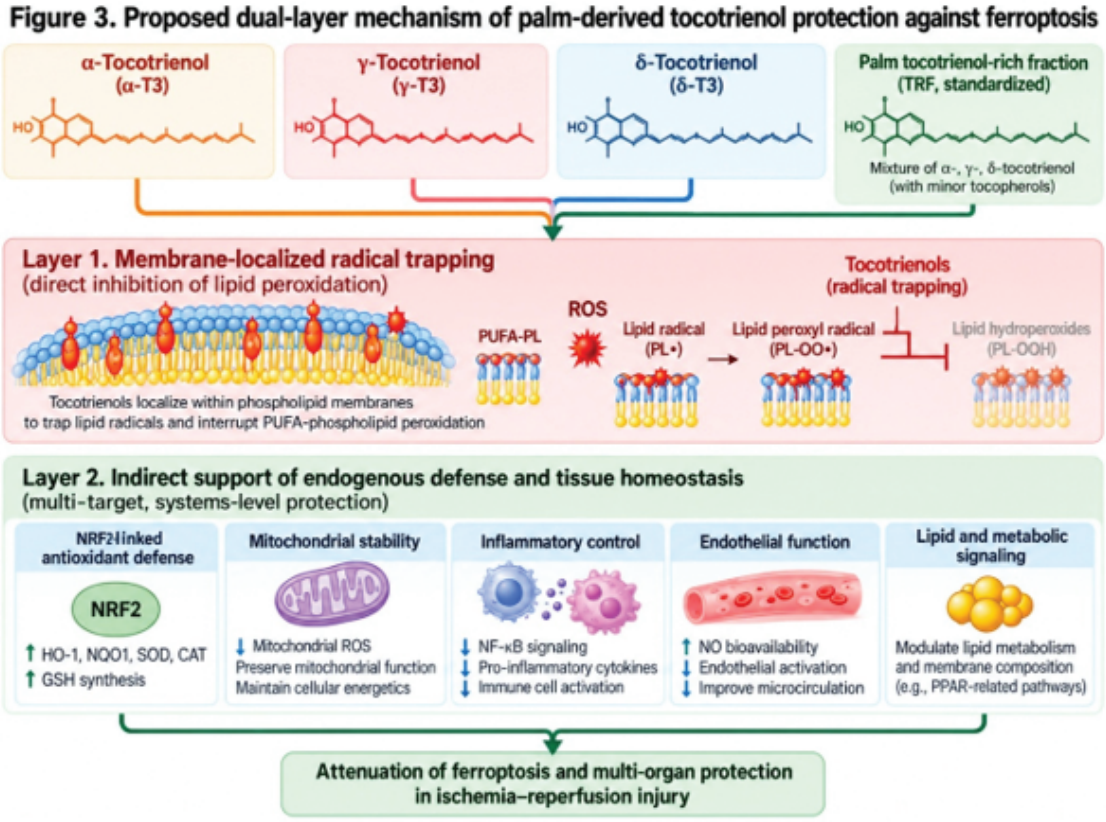



***Figure 3.*** *Proposed dual-layer mechanism of palm-derived tocotrienol protection against ferroptosis.*

*Layer 1 provides the most direct connection to ferroptosis because tocotrienols can potentially terminate PUFA-phospholipid radical propagation even when upstream stress persists. Layer 2 may increase the cellular threshold for ferroptosis through NRF2-related antioxidant defense, mitochondrial stabilization, inflammatory control, endothelial support, and modulation of lipid or mevalonate metabolism. Importantly, Figure 3 should be interpreted as a mechanistic hypothesis rather than as established clinical proof.*

chemistry by γ-tocotrienol in a large-animal model.

The potential relationship between these direct findings and earlier tocotrienol I/R observations is summarized in Figure 3. The figure proposes a two-layer model: direct membrane-localized radical trapping as the first layer, and indirect support of endogenous redox, mitochondrial, inflammatory, endothelial, and metabolic homeostasis as the second.

## Tocotrienol Isoforms Cannot Be Treated as Interchangeable

An important theme emerging from the literature is that α-, γ-, and δ-tocotrienols should not automatically be pooled into a single pharmacological category. Differences in methyl substitution on the chromanol ring influence antioxidant characteristics, metabolism, protein interactions, and biological potency. Moreover, a standardized palm TRF contains several isoforms and usually some tocopherol, creating a different exposure from purified γ- or δ-tocotrienol [8,9,12].

This distinction has practical consequences for study design. A positive result with purified α-tocotrienol does not establish efficacy for commercial palm TRF, and a null result from a poorly absorbed mixture cannot invalidate the potential of another isoform or formulation. Future research should therefore provide full compositional analysis, purity, dose, route, formulation, plasma exposure, and tissue exposure rather than reporting simply "tocotrienol treatment."

## Cross-Talk with Apoptosis, Autophagy, Pyroptosis, and Inflammation

Ferroptosis occurs within a wider regulated-cell-death network. Ferritinophagy is one of the clearest examples of cross-talk because autophagic ferritin degradation can increase labile iron and accelerate lipid oxidation. NCOA4-dependent pathways identified in cerebral, renal, intestinal, and myocardial models therefore connect autophagic machinery directly with ferroptotic execution [19,20,35,51].

Inflammatory signaling is also bidirectional. Ferroptotic cells can release oxidized lipids and damage-associated mediators that activate surrounding immune cells, whereas inflammatory pathways can alter cellular iron handling, ROS production, and antioxidant defenses. The NLRP3 cerebral I/R study and the salidroside lung I/R model provide examples of this ferroptosis–inflammation interaction [29,54].

For tocotrienols, such cross-talk complicates mechanistic attribution but may simultaneously increase therapeutic relevance. A compound capable of suppressing membrane lipid oxidation while also moderating inflammatory and mitochondrial amplification could theoretically provide

broader cytoprotection than an agent acting exclusively on one molecular target. However, this pleiotropy means that reduction of ferroptosis markers after tocotrienol treatment would still require causal experiments to determine whether ferroptosis inhibition is a primary effect, a secondary consequence, or one component of a broader protective response.

## Discussion and Analysis

### Reinterpreting Tocotrienols Through Ferroptosis Biology

The principal conceptual contribution of this review is the reframing of tocotrienol cytoprotection from a nonspecific antioxidant narrative toward a more precise lipid-peroxidation and ferroptosis framework. Generic oxidative stress encompasses numerous reactive species, compartments, and molecular targets. Ferroptosis is more specific: iron-catalyzed oxidation of membrane phospholipids progresses beyond the capacity of endogenous radical-control systems and produces lethal membrane dysfunction.

This distinction improves interpretation of previous I/R studies. Reduction of ROS, MDA, inflammatory cytokines, or apoptosis after tocotrienol treatment is important but does not independently establish ferroptosis. Conversely, the recent observation that tocotrienols suppress ferroptosis after pharmacological or genetic disruption of GPX4-related systems creates a credible mechanistic bridge that did not exist when many early tocotrienol I/R experiments were performed [11,12].

The most defensible synthesis is therefore not that earlier tocotrienol experiments "proved" ferroptosis inhibition, but that ferroptosis now provides a testable explanation for part of the protective phenotype previously attributed broadly to antioxidant effects. This distinction strengthens rather than weakens the novelty of the proposed research agenda because it identifies specific molecular experiments needed to convert retrospective plausibility into prospective causal evidence.

### The Proposed Dual-Layer Mechanism

The first layer of the proposed model is direct membrane radical trapping. Tocotrienols can donate a hydrogen atom from the chromanol group to lipid peroxyl radicals, interrupting chain propagation. Their unsaturated side chains influence membrane localization and mobility, potentially contributing to efficient access to oxidizing lipid domains. In a ferroptotic context, this mechanism is attractive because it operates near the final common execution stage—phospholipid radical propagation—rather than requiring correction of every upstream defect.

The second layer comprises indirect reinforcement of cellular resistance. Tocotrienol research has identified effects on inflammatory pathways, redox-responsive signaling, endothelial function, HMG-CoA reductase, and mitochondrial biology. These actions could indirectly preserve cysteine/GSH availability, support NRF2-regulated defenses, reduce mitochondrial ROS formation, decrease inflammatory radical generation, or alter membrane lipid composition. The magnitude and relative importance of these mechanisms are likely to vary by isoform, organ, metabolic condition, and formulation [8-10].

Crucially, the dual-layer model does not require direct interaction between tocotrienols and GPX4. The findings of Yang et al [12] demonstrate activity even when GPX4 is experimentally lost, supporting a mechanism downstream or parallel to GPX4. Future studies should therefore avoid assuming that any increase in GPX4 after tocotrienol treatment proves the principal mechanism of action. GPX4 preservation may be beneficial but could coexist with a more fundamental membrane radical-trapping effect.

### Why a Multi-Organ Hypothesis Is Biologically Plausible

The case for multi-organ relevance rests on biochemical convergence. Brain, heart, kidney, liver, intestine, and lung I/R models all demonstrate combinations of iron dysregulation, PUFA-phospholipid oxidation, GPX4/SLC7A11 impairment, ACSL4 activation, ferritinophagy, mitochondrial injury, and inflammatory amplification. A compound acting at membrane lipid-radical propagation could theoretically provide protection even if the organ-specific upstream triggers differ.

Yet biochemical convergence should not be confused with uniform pharmacological response. The brain has unique barriers to drug distribution; the liver is a primary metabolic and lipid-processing organ; the kidney can accumulate and excrete metabolites; and the heart requires exceptionally rapid drug delivery during acute reperfusion. Tissue concentrations, isoform metabolism, receptor-independent membrane distribution, lipid composition, basal iron content, and expression of endogenous ferroptosis-defense systems will all influence efficacy.

Comorbidities can further modify the response. Steatotic liver contains more lipid substrate for peroxidation, whereas diabetic myocardium has altered substrate utilization, mitochondrial function, and oxidative stress. Aging, chronic kidney disease, dyslipidemia, or systemic inflammation could similarly alter the balance between ferroptosis drivers and defense systems. This means that future tocotrienol studies should deliberately incorporate clinically relevant metabolic states rather than relying exclusively on young healthy animals [35,48].

### The Therapeutic-Window Problem

The largest obstacle to translating many antioxidant I/R studies is treatment timing. Pretreatment before experimental ischemia is mechanistically informative but unrealistic for an unpredictable stroke or myocardial infarction. Even treatment at the exact moment of experimentally controlled reperfusion may overestimate clinical feasibility because human drug preparation, administration, absorption, distribution, and reperfusion timing are variable.

Future tocotrienol experiments should therefore explicitly compare chronic pretreatment, acute pre-ischemic administration, dosing immediately before reperfusion, administration at reperfusion, and delayed post-reperfusion rescue. The clinically most informative question is whether effective lipid-peroxidation suppression remains achievable after the ischemic event has already begun.

Predictable I/R settings offer advantages. Liver resection, cardiopulmonary bypass, and organ transplantation permit planned drug exposure. In transplantation, tocotrienols could theoretically be administered to donors, recipients, preservation solutions, or machine-perfusion circuits. These settings may therefore provide more realistic first opportunities for proof-of-mechanism research than spontaneous vascular occlusion.

### Pharmacokinetics as a Mechanistic Variable

Pharmacokinetics should be treated as part of the biological hypothesis rather than as a downstream development issue. Tocotrienol efficacy in cultured cells cannot be translated meaningfully unless comparable free or membrane-associated

concentrations are achieved in the target tissue. Oral exposure is affected by formulation, food intake, intestinal transport, isoform, competition among vitamin E analogues, and elimination kinetics [16-18].

The 2026 review by Ooi et al [18] emphasizes continuing challenges in oral delivery, including poor and variable bioavailability, low aqueous solubility, chemical instability, rapid elimination, and saturable intestinal absorption. These constraints become especially important in acute I/R because the therapeutic window may be measured in minutes to hours rather than days.

Tissue pharmacokinetics are therefore essential. Brain studies should quantify cerebral concentrations; myocardial experiments should measure cardiomyocyte or ventricular tissue exposure; kidney and liver transplantation studies should quantify graft levels; and lung studies should determine pulmonary distribution. Isoform-specific analytical methods are necessary because a total "vitamin E" measurement can conceal major differences in the concentrations of α-, γ-, and δ-tocotrienol.

## Appropriate Biomarkers for Tocotrienol–Ferroptosis Research

One of the strongest recommendations from this review is that future studies should avoid labeling an effect "antiferroptotic" based solely on lower ROS or MDA. Those measures indicate oxidative injury but lack specificity. A convincing study should use multiple orthogonal domains.

First, iron biology should be assessed through labile $Fe^{2+}$, ferritin, transferrin receptor, ferroportin, or NCOA4 as appropriate. Second, lipid peroxidation should be evaluated through lipid ROS probes, 4-HNE, oxidized phospholipid lipidomics, or related endpoints. Third, ferroptosis machinery should include GPX4, SLC7A11, ACSL4, FSP1, or relevant regulatory proteins. Fourth, causal rescue evidence should be provided through ferrostatin-1, liproxstatin-1, iron chelation, genetic manipulation, or comparable mechanistic tools [2].

Transmission electron microscopy can provide supportive evidence through characteristic mitochondrial changes, but morphology alone cannot establish ferroptosis. Similarly, PTGS2 expression is sometimes used as an associated marker but is not sufficient by itself. The strongest studies combine biochemical, pharmacological, genetic, lipidomic, and functional evidence.

## Comparison of Individual Tocotrienols with Palm TRF

Future experimental programs should include at least four intervention arms: purified α-tocotrienol, γ-tocotrienol, δ-tocotrienol, and a chemically standardized palm TRF. A tocopherol comparator would further determine whether observed protection reflects general vitamin E chemistry or a tocotrienol-specific advantage.

The standardized TRF should be fully characterized for tocotrienol and tocopherol content, oxidation state, vehicle, and batch variability. Plasma and tissue exposure should be measured for individual isoforms rather than inferred from administered dose. This is especially important because a mixed preparation could contain one highly active isoform at a subtherapeutic tissue concentration while another isoform dominates plasma measurements.

Dose-response studies should distinguish pharmacodynamic potency from pharmacokinetic exposure. A nominally higher oral dose does not necessarily produce proportionally higher tissue concentrations because tocotrienol intestinal absorption can be saturable. Formulation improvements should therefore be evaluated according to tissue exposure and ferroptosis biomarker modulation, not merely total administered dose.

## Interaction with Contemporary Reperfusion Therapy

Any clinical use of tocotrienols should be conceptualized as an adjunct to reperfusion rather than as a replacement for it. Thrombolysis, thrombectomy, primary PCI, and surgical or transplant reperfusion remain essential because ferroptosis inhibition cannot rescue tissue that remains indefinitely deprived of blood flow.

This principle has implications for experimental models. Stroke studies should incorporate transient vascular occlusion followed by reperfusion rather than permanent ischemia alone. Myocardial studies should model coronary reopening. Transplant experiments should reproduce cold and warm ischemic intervals as well as reperfusion. Only then can investigators determine whether tocotrienols interact positively, neutrally, or negatively with standard reperfusion strategies.

Drug interactions also require investigation. Effects on platelet biology, anticoagulation, vascular signaling, cytochrome-mediated metabolism, or immunosuppressive therapy could be clinically relevant in myocardial infarction and transplantation. A biologically promising antioxidant cannot be advanced without establishing compatibility with standard treatment regimens.

## Translation to Clinical Endpoints

A major limitation of many mechanistic studies is reliance on biochemical surrogate outcomes. Ultimately, organ protection must be demonstrated using endpoints that matter clinically. For ischemic stroke, these include infarct volume, neurological deficit, disability, hemorrhagic transformation, and recovery. For myocardial infarction, relevant outcomes include infarct size, microvascular obstruction, ventricular function, arrhythmia, and remodeling.

In renal I/R and transplantation, serum creatinine alone is insufficient; delayed graft function, dialysis requirement, urine biomarkers, tissue injury, and long-term graft function are important. Hepatic studies should incorporate aminotransferase release, early allograft dysfunction, bile production, histological necrosis, and graft survival. Pulmonary research should assess oxygenation, lung compliance, edema, inflammatory infiltration, and transplant function.

The challenge is to link these outcomes to mechanistic target engagement. A clinical trial showing improved organ function but no evidence of reduced ferroptotic lipid injury would support efficacy but not necessarily the proposed mechanism. Conversely, a biomarker change without functional benefit would demonstrate biological activity but uncertain therapeutic value.

## Proposed Experimental Research Program

A rational preclinical sequence should begin with head-to-head comparison of individual tocotrienol isoforms and standardized palm TRF in hypoxia/reoxygenation or oxygen-glucose-deprivation/reoxygenation models. Ferroptosis should be induced through several independent routes, including GPX4 inhibition, system $Xc^-$ inhibition, GSH depletion, and iron loading. This design would test whether the broad antiferroptotic profile reported by Yang et al [12] can be

reproduced in organ-specific cells.

The next phase should evaluate at least two organs with distinct pharmacological barriers—for example brain and kidney or myocardium and liver. Tissue pharmacokinetics should be measured simultaneously with ferroptosis biomarkers. Tocotrienols should be administered at several clinically relevant time points, including delayed post-reperfusion treatment.

Causal validation should manipulate major ferroptosis regulators. GPX4 knockdown or inhibition could determine whether protection remains effective despite enzymatic lipid-peroxide detoxification failure. ACSL4 manipulation could assess dependence on PUFA-phospholipid remodeling. NCOA4 manipulation could determine whether ferritinophagy modifies tocotrienol efficacy. NRF2 inhibition could distinguish direct radical trapping from transcriptionally mediated antioxidant effects.

The most convincing evidence would show that tocotrienol exposure reduces oxidized phospholipid species and organ injury; that the effect resembles a validated ferroptosis inhibitor; that tissue concentration correlates with mechanistic effect; and that clinically realistic post-ischemic administration remains effective. Such a design would link target engagement, pharmacological exposure, and functional tissue protection rather than relying on any single biochemical surrogate.

The proposed sequence is summarized in Figure 4, which progresses from standardized chemistry and isoform comparison through in vitro validation, organ-specific I/R models, tissue pharmacokinetics, therapeutic-window studies, combination with reperfusion therapy, proof-of-mechanism biomarker studies, and finally early-phase clinical trials. This staged progression is intended to prevent premature clinical extrapolation before organ-specific target engagement and dosing feasibility have been demonstrated.

## A Roadmap for Human Proof-of-Concept Studies

The first human step should be acute pharmacokinetic and safety studies using a formulation capable of producing predictable exposure. These studies should determine whether potentially antiferroptotic concentrations are achievable within clinically relevant time frames and whether individual isoforms reach the intended compartment.

Transplantation may be an attractive initial clinical platform because timing is controlled and tissue or perfusate samples can be collected. In kidney transplantation, candidate endpoints include delayed graft function, early creatinine kinetics, urinary tubular-injury biomarkers, lipidomics, iron-related biomarkers, and—when clinically available—biopsy GPX4/ACSL4 or oxidized lipid measurements. Liver transplantation could incorporate early allograft dysfunction, tissue lipid peroxidation, graft steatosis, aminotransferases, and perfusate analyses.

Stroke and myocardial infarction would represent more demanding translational environments. Tocotrienol therapy would need rapid administration compatible with thrombolysis, thrombectomy, or PCI. Imaging endpoints could provide organ-specific information: diffusion and perfusion imaging in stroke, or cardiac magnetic resonance assessment of infarct size and microvascular obstruction after myocardial infarction.

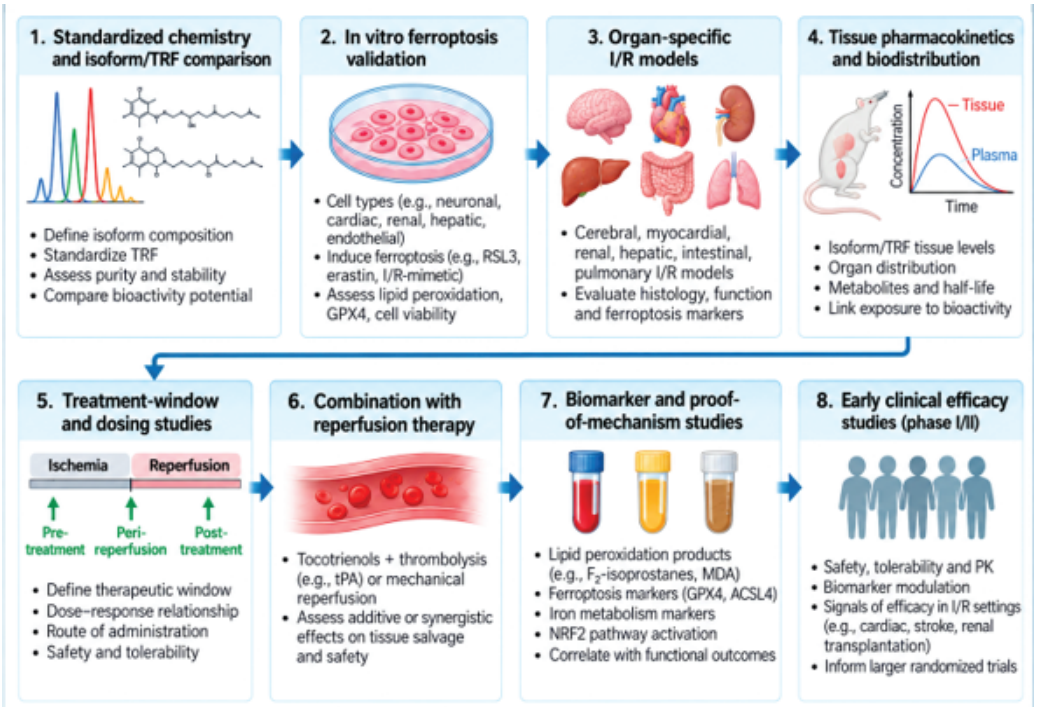



***Figure 4.*** *Translational roadmap for palm-derived tocotrienols as antiferroptotic adjuncts in ischemia–reperfusion injury.*

*Figure 4 deliberately places human efficacy studies at the end rather than immediately after general antioxidant experiments. The principal missing bridge is evidence that pharmacologically achievable tocotrienol concentrations suppress validated ferroptosis pathways in target organs under realistic reperfusion conditions.*

Biomarker analyses should accompany, not replace, established clinical functional outcomes.

### Research Gaps

ASeveral research gaps emerge clearly from the synthesis. First, there remains a shortage of direct experiments combining palm-derived tocotrienols, ischemia–reperfusion, and validated ferroptosis endpoints in the same model. Second, individual tocotrienol isoforms and mixed TRF formulations are frequently treated as pharmacologically equivalent when they are not. Third, pretreatment dominates many experimental designs despite limited relevance to unpredictable clinical ischemia.

Fourth, tissue pharmacokinetics are rarely integrated with mechanistic endpoints. Fifth, few studies establish that reduction of oxidative stress specifically reflects ferroptosis inhibition rather than generalized antioxidant action. Sixth, the interaction between tocotrienols and standard reperfusion therapies is largely unexplored. Seventh, human trials rarely use organ-specific ferroptosis-related biomarkers. Finally, large-animal models remain underused despite their value for dosing, pharmacokinetic, and translational studies.

## Conclusion and Recommendations

SFerroptosis provides a compelling contemporary framework for understanding an important component of ischemia–reperfusion injury. Across the brain, heart, kidney, liver, intestine, and lung, different upstream triggers repeatedly converge on iron dysregulation, oxidizable membrane phospholipids, impaired lipid-peroxide detoxification, mitochondrial dysfunction, and inflammatory amplification. This convergence makes lipid-phase radical control an attractive therapeutic target.

Palm-derived tocotrienols are mechanistically relevant because their antioxidant chemistry is located precisely within the lipid environment in which ferroptotic damage is executed. Their wider effects on inflammation, mitochondrial function, endothelial biology, and metabolism may provide an additional layer of cellular protection. Recent direct evidence demonstrating strong ferroptosis suppression by tocotrienols substantially strengthens this hypothesis and differentiates the current framework from earlier descriptions of tocotrienols as nonspecific antioxidants.

Nevertheless, the evidence remains incomplete. Direct antiferroptotic activity in cell-based or non-I/R systems does not establish that standardized palm TRF can prevent organ-specific reperfusion injury in humans. Critical unanswered questions concern isoform-specific potency, tissue exposure, post-ischemic therapeutic windows, dose–response relationships, organ-specific pharmacokinetics, interaction with reperfusion therapy, and validation using rigorous ferroptosis criteria.

Future work should therefore compare purified α-, γ-, and δ-tocotrienol with standardized palm TRF; quantify tissue concentrations; use lipidomics, iron measurements, GPX4/SLC7A11/ACSL4 and ferritinophagy-related markers; employ pharmacological and genetic validation; test treatment after ischemia has begun; and prioritize functional organ outcomes. Transplantation and planned surgical ischemia may provide particularly useful early clinical settings because treatment timing and tissue sampling are more controllable.

If these research requirements are met, ferroptosis could provide the mechanistic bridge that connects the established lipid-protective chemistry of palm-derived tocotrienols with a new generation of adjunctive strategies for reducing reperfusion injury. At present, that possibility should be regarded as a strong and experimentally testable translational hypothesis rather than established clinical therapy.

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