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From Membrane Antioxidants to Transplantable Grafts: Palm-Derived Tocotrienols, Hepatic Ischemia–Reperfusion and the Evidence Needed for Clinical Translation

Loso Judijanto

IPOSS Jakarta, Indonesia

***Corresponding author:** Loso Judijanto, IPOSS Jakarta, Indonesia. ORCID: https://orcid.org/0009-0007-7766-0647.

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Abstract

Background: Hepatic ischemia–reperfusion injury threatens graft viability and recovery after transplantation and complex liver surgery. Palm-derived tocotrienols have antioxidant and immunomodulatory properties, but their use in contemporary organ-preservation workflows remains unproven. **Objective:** To critically connect tocotrienol biology, hepatic ischemic injury and machine-perfusion technology while distinguishing demonstrated effects from translational hypotheses. **Method:** A qualitative literature review—not a systematic review—integrates peer-reviewed literature published in 2020–2026 on liver transplantation, injury pathways, tocotrienol pharmacology and ex situ preservation. **Findings:** Mitochondrial dysfunction, lipid peroxidation, sterile inflammation, sinusoidal injury and biliary vulnerability provide plausible targets. Randomized evidence supports selected machine-perfusion strategies, whereas tocotrienol studies largely concern non-surgical liver disease or experimental systems. The central missing evidence involves standardized isomer composition, perfusate compatibility, graft pharmacokinetics, multicellular safety and improved post-implantation outcomes. **Implications:** A gated program beginning with pharmaceutical characterization and culminating, only after successful organ-level testing, in controlled clinical trials offers a defensible translational pathway. Tocotrienols should currently be regarded as investigational candidates rather than established liver-preservation treatments.

Keywords: Palm-Derived Tocotrienols, Vitamin E, Hepatic Ischemia–Reperfusion Injury, Liver Transplantation, Graft Viability, Machine Perfusion, Mitochondrial Dysfunction, Ferroptosis, Sinusoidal Endothelium, Organ Preservation

JEL Classification: I10, I18, O31, O32, L65

Introduction

The surgical burden of hepatic ischemia–reperfusion injury

Hepatic ischemia–reperfusion injury (HIRI) is best understood as a time-dependent injury to an interconnected organ rather than a single episode of oxidant excess. During temporary inflow occlusion, partial hepatectomy, organ recovery, transport and implantation, oxygen delivery and energetic demand become uncoupled. Reoxygenation is indispensable to survival yet can rapidly intensify redox imbalance, inflammatory signalling, sinusoidal flow disturbances and cell death. In transplantation, these processes threaten hepatocytes, cholangiocytes, sinusoidal endothelial cells and the microvascular interface on which graft performance depends. In hepatic resection, similar processes superimpose on surgical stress and the requirement for functional regeneration of a reduced liver remnant. An intervention that changes a biochemical marker but fails to preserve these cellular compartments would be an incomplete form of hepatoprotection. Consequently, the relevant scientific question is whether a candidate therapy can improve organ-level recovery under the actual conditions of operative ischemia and reperfusion (Nemeth et al., 2021, Zhao, J. et al., 2025, Oliveira and Gonçalves, 2025b).

Contemporary transplantation creates both a sharper need for protective strategies and a stricter standard of proof. Wider use of donation-after-circulatory-death grafts and steatotic, older or otherwise extended-criteria donor organs makes ischemic vulnerability more heterogeneous. Cold preservation remains logistically valuable, but its inability to measure function during storage or address pre-existing graft injury motivates dynamic strategies. Crucially, hypothermic oxygenated perfusion has already demonstrated improved clinically relevant outcomes in randomized transplantation studies, whereas individual candidate drugs have not thereby inherited those benefits. A novel tocotrienol intervention would have to offer incremental advantage over an optimized preservation process, not merely outperform unprotected cells subjected to an artificial oxidative challenge. This contrast between mature perfusion evidence and exploratory molecular therapeutics organizes the present review (van Rijn et al., 2021, Parente et al., 2023, Tingle et al., 2023, Abbas et al., 2024, De Carlis et al., 2023).

Additional randomized evidence reinforces the clinical distinction between improved preservation and efficacy of an added drug. The multicentre HOPE ECD-DBD trial studied hypothermic oxygenated perfusion in extended-criteria grafts recovered after brain death, while a separate randomized trial in extended-criteria livers reported lower early allograft dysfunction with hypothermic oxygenated perfusion than with static cold storage (Czigany et al., 2021, Ravaioli et al., 2022). These findings widen the clinical basis for selecting an optimized perfusion control, they do not demonstrate a pharmacological effect of tocotrienols. Any future adjunct must show a reproducible additional effect beyond

preservation alone, with enough statistical precision to distinguish benefit from chance (Panayotova et al., 2024).

Rationale for investigating palm-derived tocotrienols

Tocotrienols are members of the vitamin E family with an unsaturated isoprenoid side chain, differentiating them from tocopherols and influencing interactions with lipids and biological membranes. Palm oil is a commercially important source of mixtures commonly termed tocotrienol-rich fractions (TRFs), nevertheless, commercial preparations vary in the proportions of alpha, gamma and delta tocotrienol, residual tocopherol, accompanying lipids and formulation ingredients. Reviews of palm-derived bioactives discuss antioxidant, anti-inflammatory and metabolic effects, while experimental research has reported activation of Nrf2-linked hepatoprotective signalling. Such findings provide biological plausibility for interrogating ischemic liver injury but do not show that a palm TRF is safe or efficacious in a perfused human graft. Source identity, analytical specification, isomer composition and route of administration therefore belong in the research hypothesis itself rather than in a supplementary product description (Zainal et al., 2022, Atia et al., 2021, Chin et al., 2023).

Clinical experience also imposes appropriate restraint. Trials in non-alcoholic fatty liver disease have reported changes in biochemical injury markers or steatosis-related endpoints after prolonged oral δ-tocotrienol exposure, but the exposure duration, patient physiology and disease mechanisms are not those of donor procurement or reperfusion. A wider meta-analysis found that tocotrienol supplementation did not consistently improve several inflammatory or oxidative-stress biomarkers across heterogeneous trials, and a review of palm TRF trials underscored mixed clinical evidence. One must therefore distinguish a possible effect in chronic metabolic liver injury from a meaningful reduction in early allograft dysfunction after transplantation. Preventing unsupported equivalence is not academic caution alone: it protects donor organs and recipients from the risks of poorly characterized adjunctive preservation agents (Pervez et al., 2022, Chin et al., 2023, Khor et al., 2021, Looi et al., 2025).

Purpose, scope and contribution

This article evaluates tocotrienols through a three-part lens: biologically plausible targets, clinically relevant delivery environments and evidence required before translation. It asks which injury pathways are directly supported by tocotrienol experiments, which pathways are established in hepatic ischemia–reperfusion without tocotrienol-specific proof, and where a mechanistic bridge remains merely conjectural. We also examine ex situ machine perfusion as a potential experimental dosing platform rather than an implicit endorsement of clinical exposure. The emphasis is on liver transplantation, but lessons extend cautiously to hepatic resection and vascular-control procedures. The intended contribution is an evidence-calibrated roadmap with explicit go/no-go gates for identity, pharmacokinetics, organ-level safety and surgical efficacy. It is not a recommendation for patients or transplant teams to supplement tocotrienols during routine perioperative care (Huwyler et al., 2025, Nguyen et al., 2025, Parente et al., 2024, Schlegel et al., 2023).

Literature review: biological and technological foundations

The sequence from ischemic energetics to sterile inflammation

Ischemia restricts oxygen-dependent oxidative phosphorylation while ATP demand persists. Ionic gradients fail, calcium handling deteriorates and mitochondria become vulnerable to structural and metabolic perturbations. Reintroduction of oxygen does not simply return mitochondria to their pre-ischemic state: changes in respiratory-chain activity and cellular reducing equivalents can accompany bursts of reactive oxygen species. In parallel, injured parenchymal and non-parenchymal cells release endogenous danger signals that activate innate immunity. Kupffer cells, infiltrating monocytes and neutrophils participate in tissue injury, clearance and subsequent resolution, with their effects changing over time. Recent human transplant tissue investigations and mechanistic studies underscore that myeloid-cell state matters, making binary suppression of inflammation a potentially misleading therapeutic objective. The same pathway might worsen early injury yet contribute to tissue repair later (Zhao, J. et al., 2025, Wang et al., 2024, Zhao, Q.-H. et al., 2025, Oliveira and Gonçalves, 2025b).

The liver microcirculation is a second organizing principle. Sinusoidal endothelial cells regulate perfusion, leukocyte traffic, endothelial permeability and exchange between circulating blood and hepatocytes. Ischemia–reperfusion can promote endothelial swelling, glycocalyx disturbance, altered rheology and local flow heterogeneity, macrovascular patency therefore does not guarantee functional sinusoidal oxygen delivery. Experimental work targeting endothelial stress pathways supports the relevance of this compartment, but it does not establish that every antioxidant will distribute adequately into the sinusoidal wall or maintain its protective actions at physiological perfusion pressures. Where tocotrienol delivery is proposed, distribution across sinusoidal endothelium and uptake by hepatocytes and cholangiocytes should be measured separately. A reduction in bulk homogenate oxidation may obscure persisting microvascular injury, especially in fatty grafts with compressed or distorted sinusoids (Nemeth et al., 2021, Yinzhi et al., 2024, Yang, D.-J. et al., 2024, Yin et al., 2025).

Inflammatory signalling and regulated cell death

NF-κB signalling links cellular stress and innate immune activation to inflammatory gene expression, while inflammasome pathways such as NLRP3 participate in processing downstream inflammatory mediators under appropriate activating conditions. Apoptosis, necrotic injury and iron-dependent lipid-peroxidation-associated ferroptosis can coexist in ischemic liver tissue. Their relative contribution depends on the ischemia model, oxygenation, iron handling, metabolic state and assessment time. Recent HIRI research provides an increasingly detailed map of MAPK signalling, cell-death pathways and mitochondrial stress, but identifying a pathway in a liver-injury model does not establish causality for a particular tocotrienol formulation. Mechanistic attribution requires compound-specific experiments with pharmacological and genetic controls, dose–response testing and direct target engagement in the relevant tissue compartment (Guo et al., 2024, Wang et al., 2024, Singh et al., 2024, Hu et al., 2024).

Ferroptosis offers a particularly revealing example. Its defining biology involves iron-dependent phospholipid oxidation and impaired defence against the propagation of lipid radicals, frequently investigated through GPX4 and related antioxidant systems. Tocotrienols can plausibly alter lipid-phase oxidative chemistry because of their membrane-associated antioxidant properties, but experiments on unrelated cell types cannot be substituted for direct evidence of GPX4 preservation, labile-iron changes or ferroptosis rescue in liver grafts. In the liver, lipid-peroxidation markers also arise from processes that are not uniquely ferroptotic. A credible experiment must combine biochemical markers with orthogonal perturbations, morphology, cell-specific measurements and comparative controls such as validated ferroptosis inhibitors. It must also test whether manipulation of ferroptosis leaves apoptosis, inflammation or reparative cellular signalling unaffected. The hypothesis is

compelling, but the evidentiary line between plausibility and demonstrated therapeutic effect must remain visible (Guo et al., 2024, Atia et al., 2021, Yang, S. et al., 2022, Dallner et al., 2021).

Contemporary syntheses of programmed cell death emphasize that liver ischemia–reperfusion may involve apoptosis, necroptosis, ferroptosis and inflammatory forms of cell death in overlapping temporal and cellular compartments. These mechanisms should not be collapsed into a single pathway merely because they share reactive oxygen intermediates or damage markers (Luo et al., 2024). For a tocotrienol candidate, the decisive experiment is therefore not a fall in a generic oxidative biomarker, but concordant target engagement, cell-type-specific rescue and improved physiological function (Guo et al., 2024).

Tocotrienol identity, exposure and biological activity

A palm-derived TRF is not equivalent to purified δ-tocotrienol, γ-tocotrienol or α-tocopherol. Different preparations may vary in purity, oxidative status, esterification, carrier oils and accompanying tocopherols. These characteristics influence dispersion, assay recovery, stability and potential distribution within perfusate and graft tissue. Chronic oral clinical data cannot simply determine an ex situ concentration: oral dosing involves intestinal absorption, lipoprotein transport, tissue redistribution and metabolism, whereas machine perfusion exposes organs to an engineered circulating medium with different protein, lipid and oxygen-carrier composition. Translational studies must document concentration in the preparation, total and free perfusate concentrations, tissue accumulation, washout kinetics and whether the administered species remain chemically intact throughout circulation. Analytical uncertainty could otherwise create a false negative through non-delivery or a false positive because an unmeasured vehicle affects the graft (Zainal et al., 2022, Looi et al., 2025, Goon et al., 2021, Li et al., 2022).

Reported tocotrienol biology is also heterogeneous rather than uniformly protective. Experimental liver work has implicated Nrf2 nuclear translocation, whereas studies in immune cells have examined γ-tocotrienol effects on IL-6/JAK/STAT3-related differentiation. Research in muscle progenitors and metabolic mouse models demonstrates antioxidative or metabolic actions in non-hepatic settings, but these systems differ substantially from cold-preserved donor livers. Clinical data in fatty liver disease, paediatric metabolic risk and other chronic disorders expand the plausibility envelope while introducing more uncertainty about effect size and transferability. Accordingly, this review treats observations as evidence tiers: direct human transplant evidence, direct experimental hepatic ischemia evidence, non-ischemic hepatic tocotrienol evidence and non-hepatic mechanistic analogy. The final tier can identify experiments but cannot support clinical claims (Atia et al., 2021, Al-Baiaty et al., 2021, Zhao et al., 2022, Yang, S. et al., 2022, Dallner et al., 2021).

Machine perfusion as a distinct biological intervention

Machine perfusion should not be treated as a single technology. Hypothermic oxygenated perfusion limits metabolic demand while offering oxygen-supported mitochondrial recovery. Normothermic machine perfusion (NMP) maintains substantial metabolic activity, enabling functional testing and potential therapeutic exposure. Normothermic regional perfusion restores circulation in situ in carefully governed donation-after-circulatory-death pathways and carries different procedural and ethical constraints from ex situ perfusion. Each modality changes the biophysical environment of any co-administered tocotrienol: temperature affects solubility and uptake, flow influences distribution, and perfusate constituents influence binding and oxidative stability. A compound compatible with warm, oxygenated circulation may be unsuitable for a cold acellular circuit. Clinical trials of one perfusion modality cannot validate tocotrienol exposure in another (van Rijn et al., 2021, Chapman et al., 2023, Mastrovangelis et al., 2024, Steinberg et al., 2023, De Carlis et al., 2023).

The field has already progressed from passive storage to dynamic assessment and, experimentally, organ repair. Viability evaluation during NMP usually considers lactate trends, perfusate acid–base status, transaminase release, vascular flows and bile production, cholangiocyte assessment may require bile pH, bicarbonate or glucose interpretation. None is a perfect stand-alone proxy for future graft survival, and steatotic grafts may require longer observation with attention to trends. Long-term ex situ perfusion opens a conceptual window for targeted intervention, but extended circulation adds risks of contamination, red-cell injury, edema, oxygenation instability and deterioration of the perfusion medium. Tocotrienol research should exploit perfusion as a controlled experimental platform without confusing an attractive delivery opportunity with an accepted clinical therapy (Huwyler et al., 2025, Groen et al., 2024, Patrono et al., 2023, Quintini et al., 2022, Schlegel et al., 2023).

Extended machine perfusion has attracted interest as an experimental platform for detailed graft assessment and intervention development. A human liver was transplanted following three days of ex situ normothermic preservation in a landmark report, illustrating technical feasibility but providing only a single-case observation, not evidence that prolonged treatment is generally safe or that tocotrienols are effective (Clavien et al., 2022). This distinction matters because longer exposure may increase opportunity for both tissue delivery and vehicle-related complications, including perfusate instability and cumulative graft exposure. Protocols involving lipophilic agents must first demonstrate stability and reproducible kinetics within the specific perfusion circuit rather than extrapolate from oral supplementation.

Method: qualitative literature review

Review design and epistemic position

This work uses a qualitative literature review (QLR), not a systematic literature review and not a quantitative meta-analysis. Its purpose is conceptual integration across surgical trials, transplant physiology, experimental cell-death biology, bioactive compound pharmacology and organ-preservation technology. Rather than estimating a pooled treatment effect, the review builds an explanatory framework around causal plausibility, transferability and requirements for prospective testing. The unit of synthesis is the strength of a mechanism–intervention–outcome link. High-quality clinical evidence about machine perfusion is interpreted as contextual evidence for a platform, it is not counted as a tocotrienol trial. Similarly, mechanistic evidence about hepatic injury is not attributed to tocotrienols unless the experiment itself tested a specified tocotrienol preparation. This approach avoids the methodological error of treating separate bodies of evidence as though their intersection had already been demonstrated (Parente et al., 2023, Tingle et al., 2023, Zainal et al., 2022, Khor et al., 2021).

Literature identification, selection and interpretation

The preliminary evidence base prioritised peer-reviewed journal publications from 2020 through 11 October 2026, including controlled transplant studies, clinical observational cohorts, mechanistic studies, pharmacology investigations and authoritative reviews. Searches were structured around combinations of liver ischemia–reperfusion, transplantation, hepatectomy, sinusoidal

endothelium, mitochondria, ferroptosis, NLRP3, tocotrienol, tocotrienol-rich fraction, preservation and machine perfusion. Reference chaining and thematic relevance supported the interpretive process. Inclusion emphasized direct relevance to the review's causal questions, excluded materials included promotional claims, unverified journal records and conclusions requiring inference beyond the underlying data. Because this is QLR, no PRISMA flow diagram, exhaustive search claim, numerical study-selection denominator or pooled estimate is asserted. References constitute a transparent, dated working knowledge base rather than a claim of complete capture of every eligible paper (Nguyen et al., 2025, Parente et al., 2024, Zhao, J. et al., 2025, Chin et al., 2023).

Analytical matrix and evidence calibration

Five analytical dimensions structure the synthesis: biological target, evidence provenance, exposure feasibility, graft-specific vulnerability and outcome relevance. For each candidate pathway, the guiding questions are whether it operates in hepatic ischemia, whether a tocotrienol intervention has directly modified it, whether the candidate can reach the relevant compartment and whether the response predicts a clinical endpoint. Evidence is classified as A when it comes from clinical liver transplantation studies, B when it derives from mechanistic or ex situ liver ischemia experiments, C when it comes from tocotrienol studies outside surgical ischemia, and D when it is hypothesis-level extrapolation. These are interpretive labels rather than validated grading scores. Conflicting findings are retained to prevent selective optimistic synthesis, especially when molecular findings and clinically meaningful outcomes diverge (Chapman et al., 2023, Parente et al., 2023, Looi et al., 2025, Khor et al., 2021).

Limitations of the interpretive method

The method can identify conceptual gaps and design useful experiments but cannot supply a pooled estimate for tocotrienol efficacy, a prespecified systematic risk-of-bias assessment or a clinical practice recommendation. Publishing patterns, unreported negative experiments and different definitions of early allograft dysfunction may distort a purely narrative synthesis. Preclinical models also differ in liver ischemia duration, warm versus cold exposure, donor metabolic phenotype and immune status. We therefore anchor stronger statements to randomized perfusion outcomes and make tentative language explicit where mechanistic translation is indirect. The review's proposed pathway and trial sequence should be tested, revised and potentially rejected as new evidence emerges. Its value rests on exposing uncertainties rather than concealing them (Tingle et al., 2023, Wehrle et al., 2024, Guo et al., 2024, Oliveira and Gonçalves, 2025b).

Results: thematic findings

Theme one—clinically established preservation gains do not establish adjunct-drug efficacy

The clearest positive evidence in the surgical landscape concerns perfusion technology itself. In a multicentre randomized trial involving donor livers after circulatory death, hypothermic oxygenated perfusion reduced symptomatic nonanastomotic biliary strictures at six months from 18% to 6% compared with static cold storage. Early allograft dysfunction was also lower in the perfusion group, although the trial did not establish an effect for a tocotrienol or any specific antioxidant additive. Subsequent comparative syntheses generally support clinically meaningful benefits for oxygenated hypothermic techniques in suitable graft populations. These studies demonstrate the standard against which additional organ-protective substances should be judged. Future tocotrienol research must assess whether a compound adds benefit to the same baseline platform, including whether it protects the biliary compartment rather than only reducing circulating transaminases (van Rijn et al., 2021, Parente et al., 2023, Tingle et al., 2023).

Evidence for normothermic perfusion is informative but not uniform. A randomized United States trial reported early allograft dysfunction in 20.6% of NMP recipients compared with 23.7% of static-storage recipients, a difference that did not reach statistical significance, while exploratory analyses suggested larger effects in higher-risk organs. Other observational experience describes improved logistics, graft assessment and expanded opportunities to use otherwise declined livers, but such cohorts are exposed to selection and practice effects. These observations show why a proof-of-concept tocotrienol study should not be evaluated by comparison with historical static-storage controls alone. Appropriate control groups need to include the perfusion process, the matched tocotrienol vehicle and, when possible, a relevant reference intervention. The incremental treatment effect must be isolated from preservation-induced benefit (Chapman et al., 2023, Yamamoto et al., 2023, Quintini et al., 2022, Canizares et al., 2024).

Recent randomized trials have not delivered a uniform advantage across every platform and donor group. In the United States PILOT non-inferiority trial, portable hypothermic oxygenated machine perfusion met its prespecified non-inferiority criterion compared with static cold storage, while observed numerical differences in several secondary biliary outcomes did not achieve statistical significance (Panayotova et al., 2024). Together with the HOPE ECD-DBD and extended-criteria randomized studies, these findings argue for specifying donor characteristics, platform, endpoint definitions and comparator conditions before studying any added antioxidant (Czigany et al., 2021, Ravaioli et al., 2022).

Theme two—mitochondrial and redox pathways provide the strongest preliminary rationale

Early mitochondrial stress connects ischemia with tissue-wide consequences. Mitochondrial dysfunction reduces the capacity to restore ATP and may contribute to reactive oxygen species generation during reperfusion. In experimental HIRI studies, modulation of autophagy, cellular stress pathways and oxidative defences has altered liver injury, lending credence to upstream mitochondrial intervention. Tocotrienol-related evidence of hepatic Nrf2 activation is relevant because an appropriately timed endogenous antioxidant response could influence injury tolerance. Nevertheless, a chronic or non-ischemic mouse experiment does not demonstrate beneficial mitochondrial effects at the moment of human graft reperfusion. A rigorous program should quantify ATP recovery, oxygen consumption, respiratory reserve, membrane potential and cellular injury across hepatocytes and non-parenchymal compartments, with blinded analysis of the relative change over matched vehicle controls (Zhao, J. et al., 2025, Wang et al., 2025, Pan et al., 2024, Atia et al., 2021).

An important conceptual distinction is between suppressing oxidant biomarkers and preserving function. A lower malondialdehyde concentration or altered Nrf2 expression may not mean improved oxygen uptake, bile composition or vascular flow. It could also reflect differences in tissue viability, assay interference or sample timing. Plasma biomarker meta-analysis in mixed tocotrienol clinical studies has not yielded uniformly favorable changes in inflammatory and oxidative endpoints, cautioning against simplistic assumptions of universally reproducible antioxidant effects. For liver graft experiments, complementary readouts should assess mitochondrial performance, lipid oxidation, organ microcirculation, histological necrosis and post-implantation function. The causal claim becomes stronger only when compound

exposure, pathway engagement and an independent physiological improvement appear in the same model (Atia et al., 2021, Li et al., 2022, Khor et al., 2021, Oliveira and Gonçalves, 2025b).

This measurement challenge also bears on translational interpretation. Established injury pathways have been demonstrated using multiple pharmacological and genetic approaches, but the literature on programmed cell death in hepatic ischemia does not establish that a tocotrienol can selectively prevent ferroptosis while preserving other adaptive responses (Luo et al., 2024). Ex vivo work should therefore include orthogonal biomarkers and, when feasible, positive-control rescue compounds, coupled to viability readouts that cannot be explained solely by chemical interference with an assay (Guo et al., 2024).

Theme three—ferroptosis is plausible but compound-specific hepatic evidence remains necessary

Ferroptotic signalling is attractive because ischemic membranes are exposed to iron-dependent lipid oxidation. Contemporary research identifies ferroptosis as a candidate contributor to HIRI, and the broader pharmacology of tocotrienols gives a reasonable basis for asking whether lipid-phase antioxidants could alter this process. However, demonstrating suppression of a lipid oxidation signal is not equivalent to proving prevention of ferroptotic death. Relevant experiments should quantify labile iron, GPX4, oxidized phospholipid species, system xc− activity or appropriate surrogates, and rescue by mechanistically distinct inhibitors. They should identify the cell compartment responsible for a signal, test adverse effects on hepatocyte recovery and include pure-isomer versus defined-mixture comparisons. Until those data are available, anti-ferroptotic protection in transplantable human liver grafts remains a research hypothesis (Guo et al., 2024, Zainal et al., 2022, Dallner et al., 2021).

The timing of ferroptotic and non-ferroptotic injury is also decisive. A treatment active only after substantial membrane destruction is unlikely to reverse necrotic tissue loss. Conversely, aggressive redox suppression before reperfusion might interfere with physiologic signalling that coordinates defence and repair. Research should therefore compare pre-ischemic, end-ischemic, during-perfusion and immediately post-reperfusion exposure windows rather than combining them. Dose and time interactions may matter more than whether a tested compound is labelled an antioxidant. Because circulating perfusate permits timed delivery and removal, ex situ models can differentiate a prophylactic exposure from a rescue intervention with better experimental control than chronic oral administration. These considerations turn a general claim about reactive oxygen species into an experimentally discriminating translational question (Guo et al., 2024, Zheng et al., 2025, Ishikawa et al., 2025, Schlegel et al., 2023).

Theme four—sterile inflammation is multicellular and cannot be reduced to NF-kappa-B alone

Inflammatory activation after reperfusion emerges from interactions among hepatocytes, sinusoidal endothelium, resident macrophages and infiltrating leukocytes. Experimental findings implicating NF-κB, MAPK and myeloid CD38 demonstrate that the cellular source of a signal is vital for interpreting intervention effects. Similarly, studies of complement and endothelial inflammatory pathways show how vascular and immune functions intersect. Gamma-tocotrienol has altered IL-6/JAK/STAT3-related immune differentiation in an unrelated context, yet these observations do not show that a palm TRF safely limits innate immune activation in liver transplantation. A candidate anti-inflammatory effect could improve acute injury while also interfering with clearance of damaged cells or adaptive tissue repair. Distinguishing harmful amplification from useful resolution should therefore be a primary research endpoint (Wang et al., 2024, Hu et al., 2024, Zhao, Q.-H. et al., 2025, Oliveira and Gonçalves, 2025a, Zhao et al., 2022).

Research focused only on serum cytokines would miss much of this complexity. Human explant or discarded-graft experiments can examine cell-resolved expression, spatial immune distribution, endothelial adhesion, neutrophil retention and Kupffer-cell phenotypes during standardized perfusion. Whole-organ RNA or proteomic profiles may detect pathways but require validation at the protein and functional levels, including careful attention to perioperative immunosuppressive drugs. Suppression of inflammatory transcripts without improved lactate handling, perfusion dynamics or later graft performance would not alone be persuasive. Experimental evidence about peptides targeting inflammation illustrates how a proposed therapeutic signal still requires organ-level survival and functional testing. A tocotrienol intervention should meet the same standard while preserving the distinction between immune modulation and generic antioxidant activity (Ishikawa et al., 2025, Zhao, Q.-H. et al., 2025, Yang, D.-J. et al., 2024, Yin et al., 2025).

Theme five—sinusoidal injury and bile-duct vulnerability shape clinically meaningful endpoints

Successful transplantation requires function beyond the hepatocyte. Endothelial swelling and microcirculatory impairment can lead to uneven tissue oxygenation even when large vessels remain patent. Cholangiocytes and their microvascular supply have a distinct ischemic vulnerability, especially in donor livers after circulatory death. The hypothermic perfusion randomized evidence regarding biliary strictures makes this compartment central to adjunctive therapy development. A tocotrienol formulation that improves aminotransferases but worsens bile-duct secretion, viscosity or perfusion would be unacceptable. Consequently, organ-level testing must include sinusoidal flow distribution, endothelial permeability, biliary epithelial integrity and bile chemistry, as well as hepatocyte bioenergetics. There is no robust basis for assuming identical tocotrienol uptake across these compartments (van Rijn et al., 2021, Nemeth et al., 2021, Yinzhi et al., 2024, Yang, D.-J. et al., 2024).

A related finding concerns the challenge of clinical viability criteria. During NMP, lactate clearance, bile output, bile pH and bicarbonate response can inform graft acceptance, but measurement conditions and thresholds vary. A candidate antioxidant may influence an assay result or metabolite concentration without altering genuine graft viability, conversely, favorable biochemical markers may coexist with subsequent ischemic cholangiopathy. For any tocotrienol intervention, the baseline feasibility of viability assessment must therefore be preserved. Perfusate analytical assays should be checked for chemical interference, and investigators should predefine criteria for drug-related changes in lactate, pH, oxygen consumption and bile composition. Endpoints need to remain interpretable to transplant clinicians who must make a high-stakes accept-or-decline decision (Groen et al., 2024, Patrono et al., 2023, Steinberg et al., 2023, Wehrle et al., 2024).

Theme six—steatotic and extended-criteria grafts could benefit differently, or be harmed

Steatotic donor livers represent an especially relevant but challenging test population. Lipid accumulation can coexist with mitochondrial dysfunction, altered membrane susceptibility, microvascular compression and heightened vulnerability to ischemia. It is tempting to reason that a lipid-associated bioactive compound should preferentially protect such grafts, but that inference ignores altered distribution, metabolism and potential accumulation of lipophilic compounds in a fatty organ. Studies of steatotic donor grafts highlight the need for individualized

viability assessment, with selected normothermically perfused grafts showing successful transplantation but also cases of primary nonfunction when metabolic testing was suboptimal. The possibility of a benefit therefore competes with an equally important possibility of poor delivery or toxicity in the very grafts thought most likely to benefit (Patrono et al., 2023, Abbas et al., 2024, Li et al., 2025, Gou et al., 2025).

Heterogeneity extends beyond steatosis to older donors, donation-after-circulatory-death organs, differing warm ischemia exposure and recipients with metabolic or renal vulnerability. These factors influence baseline risk and may modify any adjunct effect. A tocotrienol study that combines all donor groups without stratification could conceal a clinically important interaction or produce a spurious average effect. The design should prospectively stratify models by steatosis grade and ischemic exposure and later incorporate donor age, preservation duration and recipient risk. Feasible human experiments should start with discarded or research-consented organs and proceed only after repeatable improvements with a predefined safety margin. The endpoint is not simply salvaging an organ that would otherwise be discarded, but producing predictable post-implantation outcomes without unreasonable risk (Richards et al., 2023, Camagni et al., 2023, Robinson et al., 2024, De Carlis et al., 2023).

Theme seven—route of administration is a defining translational uncertainty

Palm tocotrienols are lipophilic compounds, so direct addition to aqueous perfusate should not be presumed to produce homogeneous exposure. Formulation vehicles, emulsifiers, carrier lipids or delivery particles may change membrane behavior, hemolysis, vascular resistance or perfusate oxygenation. Hypothermic and normothermic media have different composition and physical properties, any delivery system must be stable across the intended temperature and flow conditions. Before efficacy testing, investigators should document particle size where appropriate, dispersibility, compound recovery, container adsorption, free fraction, chemical oxidation and washout. The vehicle requires its own randomized control because changes attributed to tocotrienols could be caused by the solvent or carrier. Research on topical delivery and other tissues illustrates the value of formulation engineering but does not establish compatibility with a perfused transplant organ (Huwyler et al., 2025, Nguyen et al., 2025, Nair et al., 2022, Schlegel et al., 2023).

Ex situ perfusion offers an unusual chance to perform exposure–response science under controlled conditions. Investigators can sample the circulating medium serially, measure tissue accumulation by region and compare concentrations entering and leaving the hepatic circulation. However, repeated organ sampling must be reconciled with tissue integrity, and uptake cannot be equated with safety. Potential drug interactions with immunosuppressants, antibiotics or oxygen-carrier components need separate testing. Chronic oral trial data—including studies in fatty liver disease and kidney disease—cannot supply a validated graft-perfusion dose. Instead, concentrations should be selected using formulation stability, organ exposure data, concentration–response curves and toxicology thresholds. Only after this groundwork can a biologic effect be interpreted as a plausible therapeutic dose rather than an arbitrary nominal amount added to a circuit (Looi et al., 2025, Trugilho et al., 2025, Pervez et al., 2022, Chin et al., 2023).

Discussion and analysis

A causal chain rather than an antioxidant narrative

The core synthesis is a sequence of increasingly demanding claims: a particular palm-derived molecule is analytically identifiable, its formulation remains stable in a selected perfusion environment, the active species reaches the appropriate liver compartment, relevant injury pathways change, organ-level function improves, and post-transplant patient-centred outcomes improve without offsetting harms. Every arrow in this chain requires its own evidence. The existing research strongly supports several early steps for the biology of HIRI and the clinical benefit of defined perfusion modalities, but it does not complete this chain for tocotrienol-supplemented liver perfusion. Importantly, improvements at one level cannot be treated as proof of the next: reduced lipid peroxidation is not graft rescue, and an attractive animal model is not a transplant trial. Figure 1 formalizes this evidence boundary as a proposed testable causal architecture (Zhao, J. et al., 2025, Zainal et al., 2022, Schlegel et al., 2023, Oliveira and Gonçalves, 2025b).

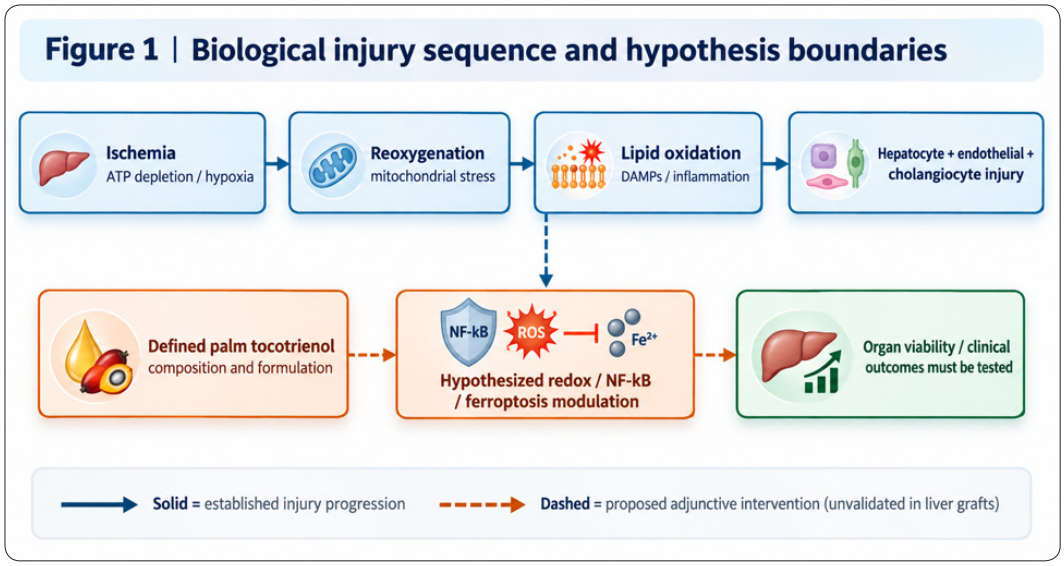


Figure 1: Integrated ischemia–reperfusion sequence and hypothesized tocotrienol interventions. Dashed elements indicate unvalidated graft-level links.

Figure 1 should be read from left to right. The upper route depicts ischemia-driven energetic failure, reperfusion stress, microvascular

disturbance and innate immune activation, its downstream outputs include liver and bile-duct injury. The lower route depicts hypothetical points at which a chemically defined tocotrienol formulation might alter redox, inflammatory or membrane-associated processes. Dashed arrows in the figure mark proposed mechanisms for which direct graft-level evidence remains insufficient. The clinical outcome box is deliberately separated from the molecular pathway box: a future study must measure both rather than infer that modulation of a signal guarantees better graft survival. This distinction provides a practical safeguard against the recurring translational failure of interventions that affect plausible injury mechanisms without improving clinically relevant outcomes (van Rijn et al., 2021, Guo et al., 2024, Atia et al., 2021, Khor et al., 2021).

The preservation platform determines the therapy question

The most defensible first use of tocotrienols is as an investigational adjunct in an experimentally controlled perfusion circuit. NMP permits active metabolism and serial functional measurements, whereas hypothermic oxygenated perfusion offers a different strategy centred on mitochondrial recovery under limited metabolic demand. They should not be treated as interchangeable dosing environments. Preclinical studies should choose one platform, match the vehicle to the platform and define target tissue exposure before comparing efficacy. Expanding immediately into multiple preservation modes would make negative results uninterpretable and complicate attribution of adverse effects. Figure 2 translates this logic into a platform-specific exposure and safety pathway, emphasizing that the opportunity to dose is not itself evidence that dosing is beneficial (Chapman et al., 2023, Brüggenwirth et al., 2024, Huwyler et al., 2025, Groen et al., 2024, Schlegel et al., 2023).

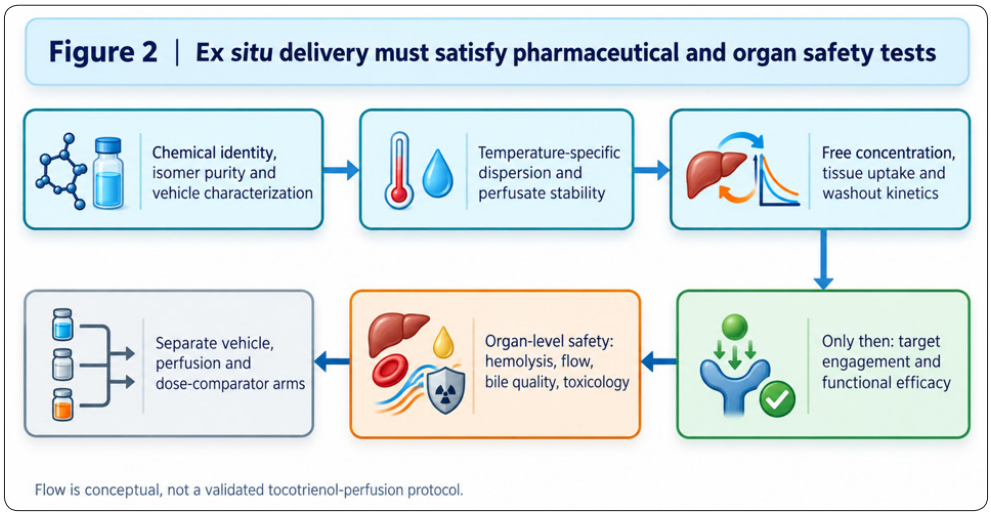


Figure 2: Proposed compatibility and exposure assessment for tocotrienols during ex situ machine perfusion, all elements require validation.

The left portion of Figure 2 places compound characterization ahead of contact with the organ. Its central path describes perfusate and organ pharmacokinetics, including a reference vehicle arm and measurements of flow, hemolysis and chemical stability. The right path connects biological target engagement to hepatocellular, cholangiocellular and vascular function. A toxicity or assay-interference signal triggers a stop gate before any effectiveness claim. This arrangement is not a claim that a particular emulsion or encapsulation technology is validated, it is a minimum experimental logic by which any proposed formulation should be evaluated. An advantage of this approach is that negative results still supply information about whether failure reflects absent delivery, lack of molecular effect or genuine organ injury (Huwyler et al., 2025, Nguyen et al., 2025, Parente et al., 2024, Nair et al., 2022).

A staged research program with explicit go/no-go decisions

The first stage should address pharmaceutical identity and physical compatibility. Researchers must specify the palm source and extraction method, quantify each tocotrienol isomer and contaminating tocopherols, document impurities and storage conditions, and verify assay specificity. Stability experiments should reproduce perfusate composition, light exposure, oxygenation, circulation time and temperature. The second stage should assess dose and toxicity in primary human hepatic cell systems, liver sinusoidal endothelial cells and cholangiocytes, using matched vehicles. Cellular models should include hypoxia–reoxygenation and metabolically stressed conditions, but no single monoculture may be treated as representative of transplantation. Only formulations that remain stable and non-toxic while demonstrating reproducible target engagement would proceed to ex situ liver evaluation (Nemeth et al., 2021, Yinzhi et al., 2024, Zainal et al., 2022, Atia et al., 2021).

The third stage should exploit research-consented discarded human livers or validated large-animal transplantation models. Randomized paired-organ designs are ideal where biologically and logistically possible, although true pairing may be rare for human liver studies. At minimum, groups require an optimized perfusion-only control, an identical vehicle control and one or more prospectively selected exposure levels. Blinding should cover outcome assessment and histopathology, with sample size justified by organ-level endpoints rather than convenient availability. Prespecified stop criteria include deteriorating flow, hemolysis, unstable pH, bile-duct injury, tissue accumulation above toxicology limits or impaired lactate handling. A staged design discourages cherry-picking isolated molecular effects while ignoring physiological harm (Groen et al., 2024, Patrono et al., 2023, Steinberg et al., 2023, Wehrle et al., 2024, Abbas et al., 2024).

The fourth stage would require a clinically representative implantation model demonstrating not only improved ex situ biomarkers but also reduced postoperative dysfunction and acceptable longer-term biliary outcomes. Ultimately, randomized human trials could evaluate an investigational, standardized

tocotrienol formulation only when regulatory approval, safety testing and independent monitoring support that transition. Such trials should compare optimized preservation plus tocotrienol with optimized preservation plus matched vehicle, rather than substituting historical controls or comparing fundamentally different devices. Stratification by steatosis, donation pathway and ischemia exposure would be important. Figure 3 depicts this progression as a series of evidence gates designed to stop advancement after credible safety signals or null mechanistic results. At present, the literature does not justify bypassing the earlier gates (van Rijn et al., 2021, Chapman et al., 2023, Parente et al., 2023, Tingle et al., 2023, Canizares et al., 2024).

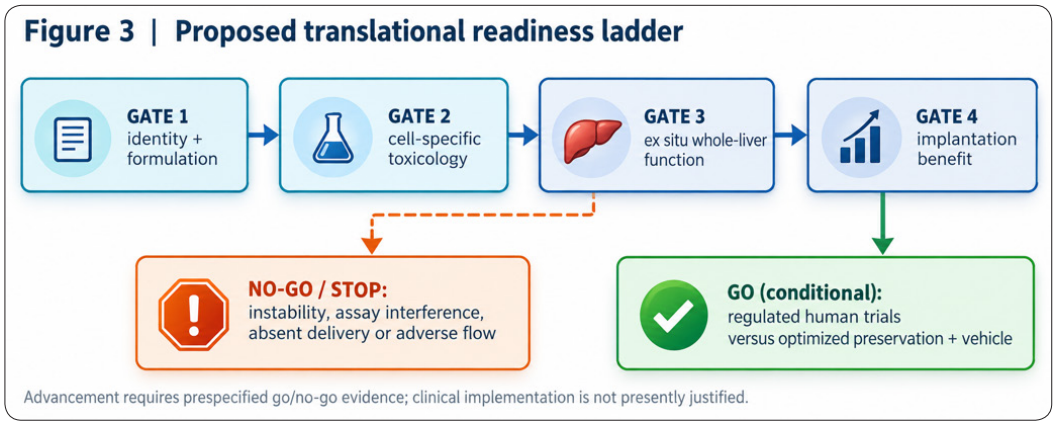


Figure 3: Sequential research gates from formulation characterization to possible clinical evaluation, a conceptual roadmap, not a treatment protocol.

Figure 3 presents four sequential translational gates: chemical identity and formulation, cell-specific toxicology, ex situ whole-liver function, and demonstrable benefit after implantation. Progression requires prespecified criteria at each gate, including control of analytical interference, haemolysis, vascular resistance, biliary integrity and dose-dependent tissue accumulation. The orange 'stop' condition represents an independent veto: instability, absent delivery or adverse flow should terminate advancement rather than lead automatically to clinical trials. The green clinical-trial pathway is conditional on favourable evidence across the preceding gates, regulatory authorization and a comparison with optimized preservation plus a matched vehicle. The figure is a decision framework, not a validated intervention protocol (Panayotova et al., 2024, Clavien et al., 2022, Groen et al., 2024).

Endpoint hierarchy and avoidance of surrogate traps

An adequate endpoint hierarchy begins with feasibility and safety: formulation integrity, organ hemodynamics, hemolysis, perfusate compatibility, drug concentration and bile-duct harm. Mechanistic endpoints then evaluate mitochondrial recovery, oxidative phospholipid injury, immune activation, sinusoidal integrity and histological cell death. Organ viability endpoints include lactate trajectories, bile production and composition, glucose handling and standardized flow measurements. Clinical endpoints, if human use eventually becomes justified, should include early allograft dysfunction by a prospectively specified definition, primary nonfunction, biliary strictures, postreperfusion syndrome, renal complications, graft survival and serious adverse events. Peak transaminase alone should not serve as an adequate primary outcome for a practice-changing trial. Discordance among surrogate measures should be regarded as a result requiring interpretation rather than hidden in a composite (van Rijn et al., 2021, Chapman et al., 2023, Groen et al., 2024, Wehrle et al., 2024, Robinson et al., 2024).

Potential renal effects deserve special attention because recipients of liver transplants may be vulnerable to hemodynamic instability and kidney injury. Although tocotrienols have been examined in non-transplant clinical populations, such experience does not establish perioperative renal safety or interactions with calcineurin inhibitors. Other safety issues include fat-emulsion-related microcirculatory effects, altered coagulation, oxidative degradation products and unforeseen effects on innate immune function. Even if a preparation does not enter the recipient intentionally, graft retention could result in systemic transfer after reperfusion. Testing should therefore include both circuit pharmacokinetics and the recipient-facing exposure scenario. Adverse endpoints must be collected as actively as oxidative biomarkers, because a small biochemical improvement could be outweighed by rare but serious graft injury (Nemeth et al., 2021, Looi et al., 2025, Trugilho et al., 2025, Khor et al., 2021).

Donor–recipient matching and interpretive heterogeneity

Future investigation should not assume that tocotrienol responsiveness is constant across the donor pool. Steatotic livers differ in metabolic flexibility, membrane composition and microvascular resistance, circulatory-death organs face distinctive warm ischemic insults, and recipient physiology determines how much marginal graft function can be tolerated. Studies of high-risk organs and normothermic regional perfusion illustrate how procurement context changes outcomes and viability judgments. A personalized hypothesis might predict that a specified preparation benefits only a subgroup with high lipid-peroxidation signals but adequate residual mitochondrial capacity. However, such stratification must be prespecified and externally validated, not constructed post hoc from favorable responders. Negative findings in well-functioning grafts and safety signals in steatotic grafts are equally informative for translational decisions (Richards et al., 2023, Camagni et al., 2023, Campo-Cañaveral de la Cruz et al., 2023, Mastrovangelis et al., 2024, Li et al., 2025).

Longer perfusion time may create opportunities for drug delivery and mechanistic observation, but it can also expose a graft to new sources of physiological stress. Experimental systems increasingly contemplate multiday organ maintenance and repair, yet this should not be conflated with proven safe long-term drug supplementation. Tocotrienol concentration might decline through container adsorption or metabolism, or local accumulation might rise despite stable perfusate concentrations. Serial spatial sampling and compartmental analyses would help detect such mismatches. The wider expansion of machine-perfusion use and variation in reported outcomes reinforce the importance of multicentre protocols, common adverse-event definitions and reproducible assays. Experimental innovation should not be allowed to erode

clinical viability criteria already needed for transplantation decisions (Brüggenwirth et al., 2024, Huwyler et al., 2025, Nguyen et al., 2025, Parente et al., 2024, Robinson et al., 2024).

The feasibility of an extended experimental dosing window should not be mistaken for proof of clinical scalability. The report of three-day normothermic preservation before a successful transplant provides a valuable demonstration that continuous organ assessment may be achievable in an intensively managed system, but its design cannot resolve population-level safety, optimal duration or drug-added efficacy (Clavien et al., 2022). A credible multicentre programme should test whether gains persist across device types and perfusate formulations and should prospectively measure interactions between compound exposure, baseline steatosis and preservation duration.

Interpreting the broader tocotrienol literature without overclaiming

The tocotrienol evidence base supports a credible reason to investigate, not an inference of perioperative efficacy. A clinical trial comparing δ-tocotrienol with α-tocopherol in fatty liver disease addresses chronic metabolic injury, studies of tocotrienol-enriched diets in mice document systemic metabolic responses, and reports from other tissues illuminate immune or redox modulation under different conditions. Evidence syntheses, meanwhile, reveal variation by preparation, population and outcome, including inconsistent effects on several inflammatory markers. These differences mean that neither the phrase vitamin E nor the phrase palm-derived antioxidant describes a single pharmacological intervention. Investigators should preregister a specific molecular preparation and intended biological mechanism, resist substituting a different isomer after results emerge and distinguish product-source claims from compound-specific causal evidence (Zainal et al., 2022, Looi et al., 2025, Goon et al., 2021, Li et al., 2022, Pervez et al., 2022, Khor et al., 2021).

Indirect evidence still has a constructive role. Studies of tocotrienols in paediatric fatty liver risk, wound repair, immune differentiation, muscle stem cells and metabolic complications illustrate potential routes for future experimentation, such as improving formulation or probing tissue-specific pathways. Their inferential status should, however, be stated precisely: they show that a pathway can respond to a tocotrienol in a defined non-transplant context, not that graft viability will improve. The same principle applies to emerging HIRI studies involving alternate pharmacological targets, gene regulation and endothelial pathways. These studies advance the mechanistic map and supply comparators but are not evidence of tocotrienol target engagement. The review thus proposes a productive division of labor between molecular discovery and surgical validation (Zheng et al., 2025, Wang et al., 2025, Al-Baiaty et al., 2021, Nair et al., 2022, Zhao et al., 2022, Yang, S. et al., 2022, Dallner et al., 2021).

Negative results, reproducibility and responsible translation

A translational program should be designed to learn from failure. If a compound changes neither tissue exposure nor target engagement, the principal problem is delivery or stability, not lack of clinical benefit. If exposure is adequate but injury pathways remain unchanged, the molecular rationale may not generalize to the selected organ context. If molecular endpoints improve but graft function does not, surrogate validity is in doubt. If injury increases, development should pause even when selected antioxidant biomarkers improve. Reporting these distinct outcomes prevents the recurrent practice of treating any favorable isolated signal as therapeutic success. It also reduces pressure to move prematurely from rodent biology into organs destined for transplantation. Reproducibility across laboratories and blinded analysis must precede clinical claims (Wehrle et al., 2024, Guo et al., 2024, Atia et al., 2021, Khor et al., 2021).

Ethically, the fact that a donor liver is outside the body does not make experimental exposure risk-free. Research use requires legally valid consent and governance, meticulous tracking of retained compounds, separation from clinical graft allocation decisions and an explicit plan for which organs will never be implanted. If clinical transplantation is later contemplated, an independent safety committee should judge device–drug compatibility, unexpected recipient exposure and stopping rules. These requirements are not obstacles to innovation, they are intrinsic to trustworthy translational science where a biological intervention affects both a donor organ and a highly vulnerable recipient. A conceptually plausible, commercially available supplement cannot substitute for pharmaceutical-grade characterization and organ-specific toxicology. The correct near-term conclusion is experimental prioritization, not routine perioperative administration (Huwyler et al., 2025, Nguyen et al., 2025, Parente et al., 2024, Schlegel et al., 2023).

Integrative answer to the research questions

The available evidence offers three answers. First, mitochondrial and lipid oxidation stress, sterile inflammation, endothelial dysfunction and regulated cell death are defensible biological targets in HIRI, but most tocotrienol-target connections remain indirect. Second, NMP and selected hypothermic approaches supply technically plausible environments for controlled investigation, provided compatibility and pharmacokinetics are demonstrated in the chosen circuit. Third, translation requires substantial evidence beyond molecular rescue: regional delivery, safety across liver compartments, reproducible organ function, implantation outcomes and eventually human trials against optimized preservation controls. No source examined in this qualitative synthesis warrants presenting palm-derived tocotrienols as a clinically proven adjunct to liver transplantation. The strongest contribution of the present framework is a disciplined order of questions that can convert mechanistic plausibility into a falsifiable research program (van Rijn et al., 2021, Parente et al., 2023, Zhao, J. et al., 2025, Zainal et al., 2022, Schlegel et al., 2023, Oliveira and Gonçalves, 2025b).

Conclusion and future directions

The interface between palm-derived tocotrienols and hepatic surgery is scientifically intriguing because ischemia–reperfusion involves processes that lipid-associated bioactives might plausibly modify. Yet liver graft protection is a multicellular and organ-level outcome, not an antioxidant assay. Contemporary transplantation literature establishes that optimized oxygenated preservation can improve selected graft outcomes, while tocotrienol literature supplies largely non-surgical biological and clinical observations. Their intersection remains an evidence gap rather than a verified therapeutic opportunity. Any claim of clinical benefit would currently outrun the available direct evidence.

The most responsible next step is a staged preclinical programme beginning with chemical characterization, isomer-specific purity, perfusate compatibility and exposure measurement. Work should then advance to cell-compartment injury models, rigorous ex situ human-liver or large-animal experiments and implantation-based confirmation only if safety and functional benefit are reproducible. Research should prioritize steatotic and other vulnerable grafts without assuming that they will respond favorably. Common viability definitions, bile-duct protection, vascular injury, renal effects and long-term graft performance must remain visible in the endpoint hierarchy.

Future studies should compare defined tocotrienol formulations, not vague labels such as vitamin E, differentiate direct biological effects from formulation artifacts, and report null or harmful findings transparently. A properly controlled perfusion study can determine whether tocotrienols offer incremental benefit over modern preservation without exposing patients prematurely. Until such evidence exists, palm-derived tocotrienols should be described as investigational candidates for liver-graft preservation research, not clinical prevention or treatment for hepatic ischemia–reperfusion injury.

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