

Beyond Steatosis: Palm-Derived Tocotrienols, Fibrosis, and Cardiometabolic Risk in Metabolic Dysfunction-Associated Steatotic Liver Disease—A Translational Review

Loso Judijanto

IPOSS Jakarta, Indonesia

Citation: Loso Judijanto. *Beyond Steatosis: Palm-Derived Tocotrienols, Fibrosis, and Cardiometabolic Risk in Metabolic Dysfunction-Associated Steatotic Liver Disease—A Translational Review*. *Ann Med Res Pub Health*. 2026;5(2):1-31.

Received Date: 10 September, 2026; **Accepted Date:** 21 September, 2026; **Published Date:** 24 September, 2026* **Corresponding author:** Loso Judijanto, IPOSS Jakarta, Indonesia

Copyright: © Loso Judijanto, Open Access 2026. This article, published in *Ann Med Res Pub Health* (AMRPH) (Attribution 4.0 International), as described by <http://creativecommons.org/licenses/by/4.0/>

ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly understood as a multisystem cardiometabolic disorder whose clinical consequences extend from hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, and chronic kidney disease. Tocotrienols, naturally occurring members of the vitamin E family and prominent bioactives in palm oil, have attracted interest because their biological actions intersect several mechanisms implicated in MASLD progression, including insulin resistance, lipotoxicity, oxidative stress, inflammatory signalling, mitochondrial dysfunction, and hepatocyte apoptosis. This qualitative literature review critically evaluates whether these mechanistic properties have translated into clinically meaningful disease modification. Human trials indicate that tocotrienol interventions can improve liver enzymes, indices of steatosis, insulin resistance, oxidative stress, inflammatory biomarkers, adipokines, and hepatocyte-apoptosis markers. However, current clinical evidence does not demonstrate histologically confirmed MASH resolution, reproducible fibrosis regression, prevention of cirrhosis, or reduction in liver-related and cardiovascular events. Interpretation is additionally complicated by differences between palm-derived tocotrienol-rich fractions, annatto-derived preparations, individual tocotrienol isomers, doses, and bioavailability. The review proposes an evidence hierarchy separating biochemical improvement from genuine disease modification and develops a translational roadmap incorporating source authentication, pharmacokinetic optimisation, phenotype-enriched recruitment, validated non-invasive fibrosis measurements, histological outcomes, and long-term cardiometabolic endpoints. Palm-derived tocotrienols should therefore be investigated as potential adjunctive metabolic interventions rather than regarded as established antifibrotic therapy.

Keywords: Metabolic dysfunction-associated steatotic liver disease; MASLD; Metabolic dysfunction-associated steatohepatitis; MASH; Tocotrienols; Palm oil; Tocotrienol-rich fraction; Liver fibrosis; Insulin resistance; Cardiometabolic risk

JEL Classification: I10; I12; I18; Q16; Q18

1. INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a conceptual and clinical transition from the former non-alcoholic fatty liver disease framework. The new nomenclature places metabolic dysfunction at the centre of disease definition and recognises steatotic liver disease as a heterogeneous spectrum rather than a diagnosis established principally through exclusion. Under the contemporary framework, MASLD is defined by hepatic steatosis together with at least one cardiometabolic risk factor, while its inflammatory and hepatocellular-injury phenotype is termed metabolic dysfunction-associated steatohepatitis (MASH). The disease continuum extends from relatively uncomplicated steatosis to MASH, progressive fibrosis, cirrhosis and hepatocellular carcinoma, although progression is neither inevitable nor biologically uniform among patients.^{1,2,3}

The scale of the problem is substantial. Meta-analytic evidence has estimated the worldwide prevalence of the former NAFLD construct at approximately one-third of adults, with prevalence rising considerably over recent decades as obesity, type 2 diabetes (T2D), sedentary behaviour and metabolic syndrome have become more common. Younossi et al.⁴ similarly documented a large and expanding global burden, indicating that steatotic liver disease is no longer appropriately conceptualised as a specialist hepatology problem affecting a small proportion of metabolically unhealthy individuals. Rather, it has become an important intersection among hepatology, diabetology, obesity medicine, cardiovascular medicine and public health.^{5,4}

The distinction between hepatic fat accumulation and fibrosis is fundamental to therapeutic evaluation. Steatosis is biologically important and may signal substantial metabolic dysfunction, but fibrosis stage provides much stronger information about future liver-related outcomes. Mortality analyses demonstrate a progressively increasing risk of all-cause and particularly liver-related mortality as fibrosis advances, while evidence from patients with established cirrhosis indicates that fibrosis regression can be associated with a lower incidence of liver-related complications. These observations mean that an intervention capable of reducing liver enzymes or hepatic fat should not automatically be described as disease modifying unless it can also demonstrate clinically consequential effects on inflammatory disease, fibrogenesis, fibrosis progression or subsequent clinical events.^{6,7,8}

MASLD is also a multisystem cardiometabolic disorder. Cardiovascular disease constitutes an important cause of morbidity and mortality, and longitudinal evidence associates steatotic liver disease with elevated risk of cardiovascular events and heart failure. A large body of observational evidence also links MASLD with incident

chronic kidney disease, while sarcopenia and adverse body-composition phenotypes may interact bidirectionally with metabolic dysfunction and liver fibrosis. These relationships are clinically important because an intervention that merely improves hepatic biochemical markers while leaving broader cardiometabolic risk unchanged would have a substantially different clinical value from one that alters both liver and systemic outcomes.^{9,10,11,12,13,14}

Against this background, vitamin E compounds have long attracted interest as potential interventions. Much of the traditional clinical literature has centred on α -tocopherol, whereas tocotrienols have received considerably less clinical attention. Tocotrienols share the chromanol ring of tocopherols but possess an unsaturated isoprenoid side chain, resulting in differences in membrane behaviour, metabolism, distribution and potentially biological activity. Palm oil represents an important natural source of tocotrienols and can yield tocotrienol-rich fractions (TRFs) containing α -, β -, γ - and δ -tocotrienol in differing proportions, commonly together with some tocopherol. Annatto, by contrast, can yield preparations particularly enriched in γ - and δ -tocotrienol. Treating these interventions as chemically and pharmacologically interchangeable risks obscuring potentially important source- and formulation-dependent effects.^{15,16}

The mechanistic rationale for studying tocotrienols in MASLD is nevertheless compelling. Experimental and clinical research suggests potential influences on oxidative stress, inflammatory signalling, insulin sensitivity, lipid metabolism, adipokine biology and cell-death pathways. These processes overlap considerably with contemporary models of MASLD progression, in which dysfunctional adipose tissue, increased free-fatty-acid delivery, de novo lipogenesis, lipotoxic lipid species, mitochondrial dysfunction, endoplasmic-reticulum stress, innate immune activation, hepatocyte injury and hepatic stellate-cell activation create interconnected drivers of inflammatory and fibrotic progression.^{17,18,19,20}

The central problem, however, is one of translation. Human tocotrienol trials have generated intriguing findings for liver enzymes, fatty liver indices, radiological steatosis, insulin resistance, inflammatory biomarkers, adipokines and cytokeratin-18. Yet such outcomes occupy an intermediate position in the chain from biological activity to clinical disease modification. They cannot establish that an intervention reverses fibrosis, prevents progression to cirrhosis, reduces hepatic decompensation, prevents hepatocellular carcinoma or lowers cardiovascular event rates. This distinction has become even more important because contemporary MASH drug trials increasingly use histological endpoints such as MASH resolution without worsening of fibrosis and improvement of at least one fibrosis stage without worsening of steatohepatitis.^{21,22,23}

This review therefore asks whether the biological promise of palm-derived tocotrienols can plausibly be translated into clinically meaningful modification of the MASLD continuum. It has four related aims: to map tocotrienol actions onto contemporary MASLD pathophysiology; to critically distinguish human evidence for biochemical and steatosis improvement from evidence relevant to inflammation and fibrosis; to examine the often-overlooked

problem of extrapolating evidence across palm TRF, annatto-derived tocotrienols and isolated isomers; and to propose a research roadmap capable of determining whether palm-derived tocotrienols could become rational adjunctive interventions in modern MASLD management.

2. LITERATURE REVIEW

2.1 From Metabolic Overload to Steatotic Liver Disease

MASLD emerges from the interaction of energy imbalance, adipose-tissue dysfunction, genetic susceptibility, insulin resistance, altered lipid handling and multiple organ-to-organ signals. In insulin-resistant adipose tissue, suppression of lipolysis becomes impaired, increasing delivery of free fatty acids to the liver. Hyperinsulinaemia and excess carbohydrate availability can simultaneously stimulate hepatic de novo lipogenesis. When lipid uptake and synthesis exceed the capacity for oxidation and export, triglycerides and more metabolically harmful lipid species accumulate within hepatocytes. Although triglyceride storage can initially represent an adaptive buffer, sustained metabolic overload promotes lipotoxicity, cellular stress and inflammatory signalling.^{17,19}

The liver is therefore not simply a passive storage organ for excess fat. Mitochondria initially adapt by increasing fatty-acid oxidation, but prolonged substrate overload can disturb electron transport, redox homeostasis and ATP production. Reactive oxygen species can increase through mitochondrial, microsomal and NADPH-oxidase pathways, while lipid peroxidation generates reactive products capable of damaging proteins, membranes and DNA. Oxidative injury interacts with endoplasmic-reticulum stress, impaired autophagy, altered organelle communication and cell-death pathways, creating conditions under which steatosis can evolve into inflammatory steatohepatitis.^{18,24} Contemporary mechanistic models reject an overly simplistic linear “two-hit” explanation. Multiple metabolic and cellular insults occur in parallel and reinforce one another. Lipotoxicity can induce mitochondrial and endoplasmic-reticulum stress, inflammasome activation, ferroptotic and apoptotic pathways, extracellular-vesicle signalling and activation of resident immune cells. Gut-derived metabolites and altered intestinal permeability may further influence hepatic inflammation through the portal circulation. Accordingly, MASLD progression reflects a dynamic network involving hepatocytes, Kupffer cells, recruited immune cells, liver sinusoidal endothelial cells, hepatic stellate cells, adipose tissue, skeletal muscle and the intestinal microbiome.^{20,25}

2.2 Inflammation, Hepatocyte Injury and the Transition to Fibrosis

Inflammation becomes clinically important when hepatic lipid accumulation is accompanied by hepatocyte ballooning, inflammatory-cell recruitment and persistent injury. Kupffer cells and recruited macrophages respond to damage-associated and pathogen-associated signals through pathways including Toll-like receptors and nuclear factor- κ B (NF- κ B). Cytokines and chemokines generated within this environment influence both hepatocyte survival and hepatic stellate-cell behaviour. The resulting inflammatory microenvironment can therefore link metabolic stress to extracellular-matrix deposition rather than functioning merely as an epiphenomenon of steatosis.²⁶

Hepatic stellate-cell activation is central to fibrogenesis. In a healthy liver, stellate cells remain relatively quiescent, but chronic injury transforms them toward activated, proliferative and matrix-producing phenotypes. Activated stellate cells increase production of collagens and other extracellular-matrix components while tissue remodelling becomes progressively abnormal. Fibrogenic signalling involves complex communication among injured hepatocytes, macrophages, stellate cells and endothelial cells rather than a single molecular switch. This complexity partly explains why compounds with apparently strong antioxidant effects may still fail to produce meaningful antifibrotic outcomes in humans.^{27,24}

Fibrosis should consequently be treated as a distinct therapeutic endpoint. Histological fibrosis regression is possible, but it requires changes in the balance among ongoing injury, extracellular-matrix synthesis, matrix degradation and cellular reprogramming. The clinical importance of this distinction is supported by evidence that fibrosis severity strongly predicts prognosis and that cirrhosis regression is associated with fewer subsequent liver-related events. An intervention that lowers alanine aminotransferase (ALT) may therefore be biologically active without having altered the fibrotic architecture that principally determines long-term liver-related risk.^{6,7,27}

2.3 Measuring What Matters in MASLD

Liver biopsy remains an important reference for diagnosing steatohepatitis and grading fibrosis in clinical trials, but its invasiveness, sampling variability and limited practicality constrain routine use. Contemporary care therefore increasingly employs sequential non-invasive tests (NITs), beginning with accessible blood-based approaches such as the fibrosis-4 index (FIB-4) and progressing where appropriate to vibration-controlled transient elastography (VCTE), enhanced liver fibrosis (ELF) testing, magnetic resonance elastography (MRE) or related modalities. Such tools are particularly important when identifying patients with clinically significant fibrosis who may benefit from targeted therapy.^{3,8,28} Recent reviews published after the transition to MASLD terminology further support stepwise combinations of serum scores and imaging-based NITs for identifying F2–F3 disease and for longitudinal risk assessment.^{29,30}

Imaging endpoints also require careful interpretation. Ultrasound can detect steatosis but has limited sensitivity at lower liver-fat concentrations and is not a direct measure of fibrosis. Magnetic resonance imaging-derived proton-density fat fraction (MRI-PDFF) provides more quantitative assessment of hepatic fat, while MRE can assess liver stiffness with substantially greater relevance to fibrotic disease. Serum approaches such as ELF and collagen-turnover markers add another dimension by capturing aspects of extracellular-matrix biology. Consequently, future tocotrienol research should not depend primarily on liver enzymes, fatty liver index or qualitative ultrasound grading if the objective is to demonstrate disease modification.^{31,32} Recent translational work also suggests that multi-protein biomarker panels may improve discrimination of fibrosis stages beyond conventional indices, although external validation and implementation studies remain necessary.³³

Composite tools can also enrich clinical-trial populations. The FibroScan-AST (FAST) score combines liver stiffness, controlled attenuation parameter and AST to identify patients more likely to have active steatohepatitis with significant fibrosis. Subsequent validation work has demonstrated the utility and limitations of FAST across heterogeneous populations. Such tools do not eliminate the need for carefully selected histological outcomes in proof-of-concept antifibrotic trials, but they can facilitate screening, risk stratification and longitudinal assessment.^{34,35}

2.4 Tocotrienols as Distinct Members of the Vitamin E Family

Vitamin E encompasses tocopherols and tocotrienols, each existing as α -, β -, γ - and δ -forms according to methyl-substitution patterns on the chromanol ring. Tocotrienols contain three double bonds in the side chain, distinguishing them structurally from tocopherols. This difference can alter membrane distribution, metabolism and interaction with molecular targets. Accordingly, evidence regarding α -tocopherol should not be assumed to apply quantitatively or qualitatively to tocotrienols, and evidence regarding one tocotrienol isomer should not automatically be generalised to another.¹⁵

Palm oil is an important dietary and industrial source of tocotrienols, and palm-derived TRF commonly contains a mixture of tocotrienol isomers plus a variable tocopherol fraction. Annatto preparations, in contrast, are generally characterised by greater enrichment in δ - and γ -tocotrienol and much lower α -tocopherol content. This compositional distinction has translational consequences because relative isomer exposure may influence biological effects, while α -tocopherol can affect vitamin E transport and metabolism. The umbrella term “tocotrienol supplementation” therefore conceals interventions that can differ materially in composition and pharmacokinetic behaviour.^{36,16} A recent systematic review of randomised controlled trials of palm-derived TRF likewise found a broad but heterogeneous clinical evidence base and emphasised the need to clarify optimal dose, formulation and treatment duration.³⁷

Bioavailability is an additional limitation. Tocotrienols are lipophilic, and absorption depends on gastrointestinal processing, dietary fat, formulation and subsequent lipoprotein transport. Human pharmacokinetic analyses suggest that annatto-derived δ -tocotrienol can achieve exposure profiles different from palm-derived TRF. Self-emulsifying delivery systems and related lipid-based technologies may improve solubilisation and intestinal absorption and may reduce dependence on concomitant dietary fat. Therefore, poor or variable exposure could contribute to heterogeneous intervention results and should be incorporated into trial design rather than treated as a secondary formulation issue.^{16,38}

2.5 Mechanistic Rationale for Tocotrienols in MASLD

The traditional description of tocotrienols as antioxidants is incomplete. Their phenolic chromanol structure permits free-radical scavenging, but experimental literature indicates potential modulation of inflammatory transcriptional pathways, lipid metabolism, cholesterol synthesis, cell-survival signalling and stress responses. Tocotrienols have been reported to suppress NF- κ B activation in various experimental systems, which is potentially relevant because NF- κ B-associated signalling participates in inflammatory responses arising from metabolic and cellular stress.³⁹

Experimental liver models provide more disease-specific evidence. Wong et al.⁴⁰ evaluated palm and annatto tocotrienols in rats exposed to a high-carbohydrate, high-fat diet. Tocotrienol treatment reduced indices of oxidative stress and inflammatory signalling, and the study identified suppression of Toll-like-receptor-related pathways as a possible mechanism. Importantly, palm tocotrienol at the higher tested dose reduced steatosis grade. Such findings support mechanistic congruence between tocotrienol actions and pathways implicated in metabolic liver injury, but they remain preclinical and cannot independently establish human antifibrotic efficacy.⁴⁰

Broader clinical evidence also requires caution. A meta-analysis of randomised trials examining inflammatory and oxidative-stress biomarkers found a significant reduction in C-reactive protein but did not demonstrate consistent effects on IL-6, TNF- α or malondialdehyde across all included studies. The CRP effect was strongly influenced by an individual δ -tocotrienol study. These findings illustrate why mechanistic narratives constructed solely from positive studies may overstate consistency across populations, sources, formulations and disease contexts.⁴¹

Evidence for lipid modification is similarly mixed. Zuo et al.⁴² found that tocotrienol supplementation did not consistently lower total cholesterol, LDL cholesterol or triglycerides across trials, although HDL cholesterol increased in pooled analyses and some dose-dependent subgroup findings were observed. Such results are relevant to MASLD because dyslipidaemia contributes to cardiovascular risk, but they do not support a simple claim that tocotrienols provide broad lipid-lowering efficacy. Any proposed cardiometabolic benefit should therefore be evaluated through phenotype-specific outcomes rather than presumed from biochemical mechanisms alone.⁴²

Clinical studies outside MASLD provide additional evidence of metabolic activity. In patients with T2D, δ -tocotrienol supplementation has been associated with improvements in fasting glucose, insulin resistance, glycated haemoglobin and selected inflammatory and oxidative biomarkers. Such findings make insulin-resistant MASLD an attractive phenotype for further investigation because metabolic improvements could theoretically reduce hepatic substrate overload. Nevertheless, metabolic biomarker improvement in T2D remains indirect evidence for preventing fibrosis or cardiovascular events among patients with MASH.⁴³

2.6 Vitamin E Evidence as a Precedent, Not a Substitute

The α -tocopherol literature is relevant because vitamin E has been investigated extensively in steatohepatitis, but it should be considered a clinical precedent rather than a surrogate for tocotrienol efficacy. Meta-analyses indicate that vitamin E can improve ALT, AST and several histological features in selected patients with NAFLD/NASH, although findings regarding fibrosis have varied according to included studies, duration, population and dose. More recent umbrella evidence has suggested possible improvements in pooled fibrosis scores under some conditions, but heterogeneity and the limitations of combining different trials require cautious interpretation.^{44,45}

Aminotransferase improvement likewise cannot be equated with reversal of progressive liver disease. Vogli et al.⁴⁶ confirmed effects of vitamin E on serum aminotransferases in pooled clinical data, but serum enzyme concentrations are indirect indicators of hepatocellular injury and can be normal even in patients with clinically important fibrosis. The distinction is particularly important when evaluating tocotrienols, because claims of superiority over α -tocopherol based on inflammatory biomarkers do not automatically demonstrate superiority in clinically consequential hepatic outcomes.⁴⁶

3. METHOD

This study employed a **qualitative literature review with critical and translational thematic synthesis**. It was explicitly not designed as a systematic literature review or meta-analysis. The purpose was therefore not exhaustive enumeration of every eligible study, statistical pooling of treatment effects, generation of a PRISMA flow diagram or formal certainty grading. Instead, the review sought to integrate mechanistic, pharmacokinetic, clinical and therapeutic literature in order to answer a translational question: whether the existing tocotrienol evidence base is sufficiently mature to support clinically meaningful disease modification across the MASLD–MASH–fibrosis continuum.

The literature base prioritised peer-reviewed journal articles published from January 2020 through September 2026. Targeted searches focused principally on PubMed/MEDLINE-indexed literature and publisher records using combinations of the terms “MASLD”, “NAFLD”, “MASH”, “NASH”, “tocotrienol”, “palm tocotrienol”, “tocotrienol-rich fraction”, “delta-tocotrienol”, “vitamin E”, “steatosis”, “fibrosis”, “insulin resistance”, “oxidative stress”, “inflammation”, “pharmacokinetics”, “cardiovascular disease”, “chronic kidney disease”, “non-invasive test”, “resmetirom”, “semaglutide”, “tirzepatide” and related concepts. Reference chaining from high-quality reviews and clinical guidelines was used to identify influential original trials and translational studies.

Evidence was prioritised hierarchically. Human randomised controlled trials and contemporary clinical-practice guidance were given greatest weight when assessing clinical efficacy. Meta-analyses and major reviews were used to contextualise heterogeneity and broader disease mechanisms. Experimental studies were included when they provided information directly relevant to mechanisms or palm-versus-annatto interpretation that could not be

inferred from human trials. This distinction was necessary because preclinical findings can establish biological plausibility but cannot independently demonstrate clinical disease modification.

For each tocotrienol study, interpretation considered the intervention source, isomer composition, dose, duration, comparator, population and endpoint. Particular attention was paid to avoiding “source drift”—the practice of describing evidence generated with annatto-derived δ -tocotrienol as if it represented direct evidence for a palm-derived TRF. Outcomes were organised into an evidence hierarchy comprising routine biochemical markers, metabolic and inflammatory surrogates, quantitative measures of steatosis, validated fibrosis-related NITs, histological MASH/fibrosis outcomes and hard clinical events.

The thematic synthesis was organised around five analytical domains: mechanistic congruence with MASLD pathogenesis; source and formulation fidelity; strength of human efficacy evidence; evidence for fibrosis modification and systemic cardiometabolic benefit; and requirements for future clinical translation. This approach permits simultaneous consideration of positive biological signals and evidential limitations without treating absence of definitive fibrosis data as evidence of biological inactivity.

4. RESULTS: THEMATIC FINDINGS

4.1 Theme 1: Tocotrienols Intersect Multiple Drivers of MASLD

The first thematic finding is strong mechanistic congruence. MASLD progression involves insulin resistance, excess hepatic fatty-acid exposure, lipotoxicity, mitochondrial and endoplasmic-reticulum stress, reactive oxygen species, inflammatory signalling, hepatocyte death and activation of fibrogenic cell populations. Tocotrienols potentially intersect several of these processes rather than acting through a single pathway. This multi-target profile is attractive because MASLD itself is a network disease in which monofunctional suppression of one downstream mediator may be insufficient.^{17,20,24}

Insulin resistance represents one plausible intervention point. Improvement in systemic insulin sensitivity could reduce adipose lipolysis, lower free-fatty-acid flux to the liver and attenuate hyperinsulinaemia-driven hepatic lipogenesis. Clinical δ -tocotrienol data in T2D and NAFLD show reductions in measures such as HOMA-IR, supporting metabolic activity in insulin-resistant populations. Whether such changes are sufficiently large and durable to alter hepatic fibrosis, however, remains unknown.^{43,21}

Oxidative and inflammatory signalling forms another plausible axis. Tocotrienols can reduce lipid-peroxidation-related markers and modulate inflammatory pathways in experimental settings, including NF- κ B- and Toll-like-receptor-associated signalling. In MASLD, these pathways are relevant because persistent hepatocyte stress promotes inflammatory-cell activation and communication with hepatic stellate cells. Nevertheless, the inconsistent pooled effects of tocotrienols on IL-6, TNF- α , and malondialdehyde show that pathway plausibility cannot be translated automatically into reproducible systemic biomarker effects in humans.^{40,39,41}

Figure 1 positions tocotrienols within the disease process rather than treating them as generic antioxidants. Their theoretical attractiveness arises from the possibility of simultaneously influencing metabolic overload, oxidative stress, inflammatory signalling and hepatocyte injury, all of which occur upstream of or alongside hepatic fibrogenesis.

Figure 1. Mapping Proposed Tocotrienol-Sensitive Pathways Across the MASLD Continuum

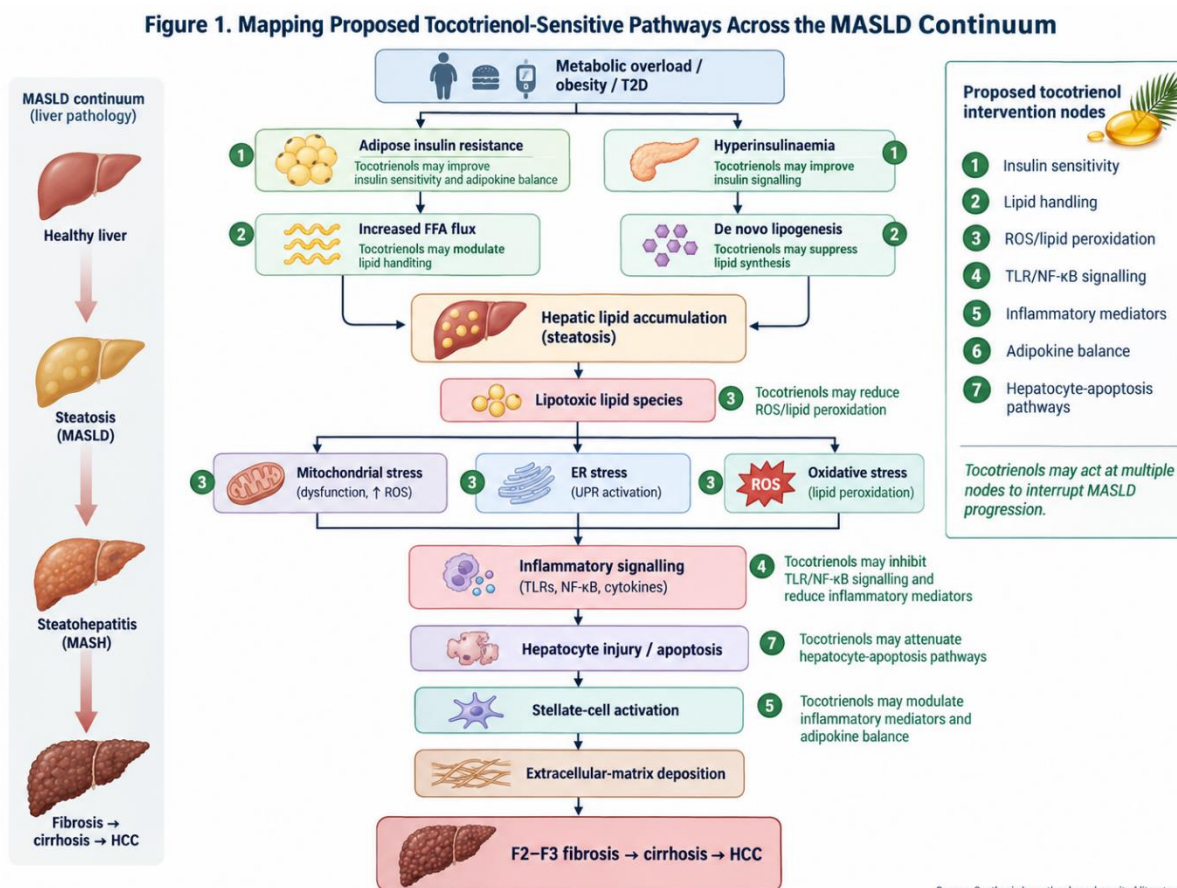


Figure 1 also identifies the core translational limitation. Evidence for tocotrienol effects is strongest around the upper and middle parts of the pathway—insulin resistance, oxidative stress, inflammation and steatosis—whereas direct evidence becomes progressively weaker toward stellate-cell deactivation, matrix remodelling, fibrosis regression and prevention of cirrhosis. Mechanistic breadth therefore increases biological plausibility but does not remove the requirement for fibrosis-specific clinical evidence.

4.2 Theme 2: “Tocotrienol” Is Not a Single Intervention

A second major theme is intervention heterogeneity. The literature frequently discusses “tocotrienols” as though all preparations delivered an equivalent active ingredient. In reality, a palm-derived TRF may contain multiple

tocotrienol isomers and some tocopherol, whereas annatto products may be particularly rich in δ - and γ -tocotrienol. Trials using isolated or highly enriched δ -tocotrienol therefore test a different exposure from trials using palm TRF. This distinction becomes particularly important when a positive δ -tocotrienol study is subsequently cited to support broad claims for “palm-derived tocotrienols”.^{36,16}

Pharmacokinetic evidence reinforces this concern. Comparative literature suggests differences in systemic exposure between annatto-derived tocotrienols and palm TRF. Absorption is also influenced by formulation and meal conditions, while self-emulsifying systems may improve bioavailability. It follows that two trials nominally administering the same milligram amount of “tocotrienol” may produce meaningfully different plasma exposures. Future clinical work therefore needs batch-level compositional reporting and, ideally, measured pharmacokinetic exposure rather than dose alone.^{16,38}

This issue can be termed the **source/formulation fidelity problem**. It has three dimensions: botanical source, compositional identity, and systemic exposure. If these are not reported, apparently inconsistent findings may result from pharmacological heterogeneity rather than from absence of biological activity. Conversely, apparent consistency across studies cannot be interpreted as proof that all tocotrienol preparations are interchangeable.

Figure 2 illustrates that direct clinical evidence obtained with annatto-derived or isolated δ -tocotrienol should not be relabelled as direct evidence for palm TRF. Instead, it should be treated as supportive evidence for the tocotrienol class whose transferability requires pharmacological justification.

Figure 2. The Source/Formulation Fidelity Problem

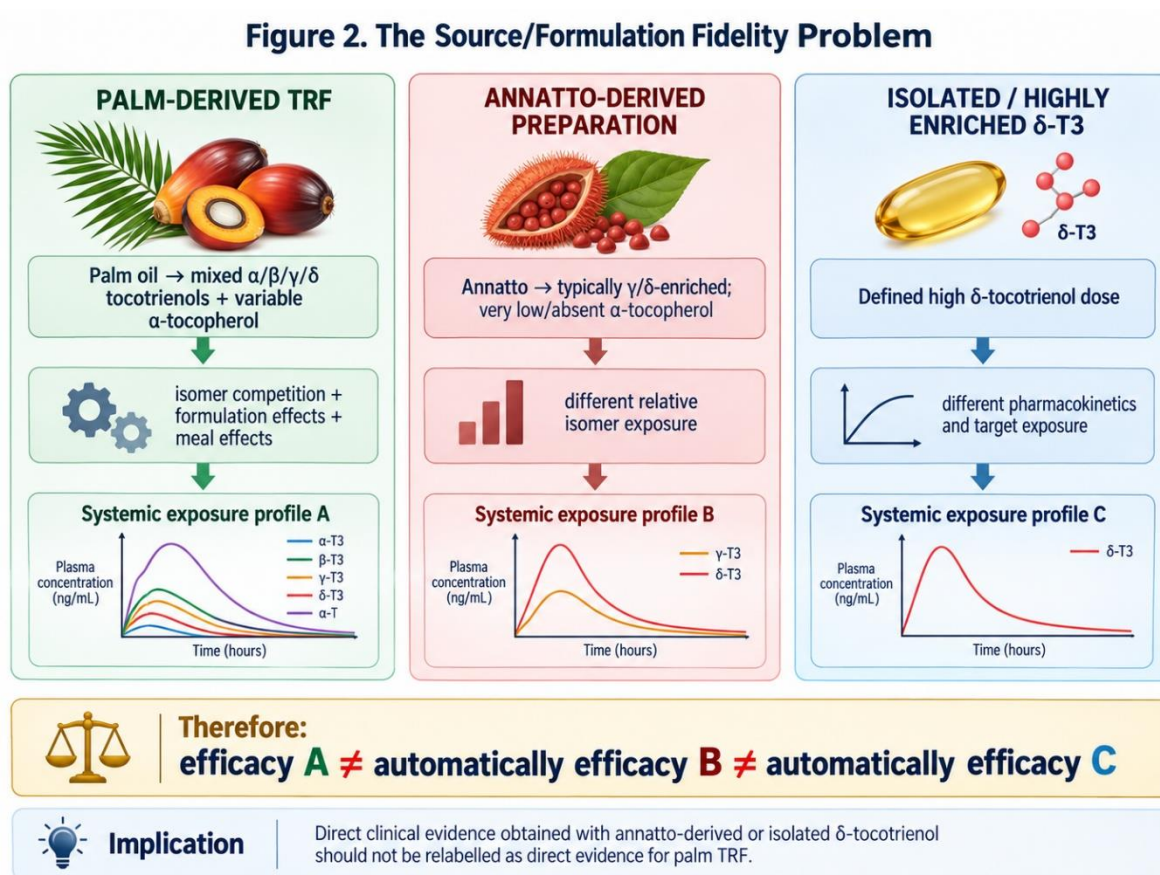


Figure 2 explains that the distinction has practical implications for future manuscripts and trials. Product authentication should report botanical source, individual tocotrienol concentrations, tocopherol content, excipients, dose per isomer, administration with or without food and, where feasible, plasma exposure. Without such information, the field risks making efficacy claims at the level of a chemical family when the actual evidence applies only to a specific formulation.

4.3 Theme 3: Human Evidence Supports Biological Activity but Is Surrogate-Dominant

The most informative post-2020 adult clinical evidence comes from randomised studies of δ -tocotrienol. Pervez et al.²¹ randomised patients with NAFLD to δ -tocotrienol 300 mg twice daily or placebo for 24 weeks. The intervention produced statistically significant reductions in fatty liver index, HOMA-IR, hs-CRP, malondialdehyde, ALT and AST, while ultrasound-based hepatic steatosis also improved relative to placebo. These findings establish biological and metabolic activity but do not directly establish improvement in MASH or fibrosis because biopsy-based inflammatory and fibrotic endpoints were not evaluated.²¹

A subsequent 48-week active-controlled trial compared δ -tocotrienol with α -tocopherol. Both groups improved fatty liver index, liver-to-spleen attenuation ratio, HOMA-IR and malondialdehyde. The δ -tocotrienol group showed greater reductions in body weight, IL-6, TNF- α , leptin and cytokeratin-18 and a greater increase in adiponectin. The CK-18 result is particularly interesting because it provides a closer connection with hepatocyte injury and apoptosis than routine aminotransferases alone. Nevertheless, neither CK-18 nor CT-based steatosis constitutes proof of histological fibrosis regression.²²

Pediatric evidence adds a different formulation context. Al-Baiaty et al.⁴⁷ evaluated a tocotrienol-rich fraction in obese children with NAFLD. The study is valuable because it expands the evidence base beyond adult δ -tocotrienol preparations and illustrates that TRF can be clinically studied. Yet differences in age, disease duration, fibrosis prevalence, and intervention composition substantially limit extrapolation from obese children to adults with established F2–F3 MASH.

The overall tocotrienol literature therefore supports a conclusion of **activity without demonstrated disease modification**. Chin et al.³⁶, reviewing human and preclinical evidence, concluded that tocotrienols may improve several NAFLD-related outcomes while also emphasising heterogeneity in disease severity, duration and intervention type. This is a more defensible interpretation than either extreme position—that tocotrienols are already proven liver therapeutics or that positive biomarker findings are clinically meaningless. The evidence instead occupies an intermediate translational state.³⁶

Table 1 consolidates the principal contemporary human studies that inform the translational assessment of tocotrienols in metabolic liver disease, including adult NAFLD trials, a paediatric TRF study and a trial in T2D.^{21,22,47,43} The comparison shows that the most consistent signals concern steatosis, insulin resistance, inflammatory or oxidative biomarkers, whereas direct histological evidence for fibrosis modification remains unavailable.

Table 1. Key Contemporary Human Tocotrienol Evidence Relevant to MASLD

Study	Population	Intervention	Duration	Important findings	Main translational limitation
Pervez et al. ²¹	Adults with NAFLD	δ -T3 300 mg twice daily vs placebo	24 weeks	Improved FLI, HOMA-IR, hs-CRP, MDA, ALT, AST and ultrasound steatosis	No biopsy-defined MASH/fibrosis outcome; δ -T3 source should not be equated with palm TRF
Pervez et al. ²²	Adults with NAFLD	δ -T3 vs α -tocopherol	48 weeks	Both improved steatosis and HOMA-IR; δ -T3 had greater effects on several inflammatory/adipokine/CK-18 outcomes	Active comparator; no histological fibrosis endpoint

Study	Population	Intervention	Duration	Important findings	Main translational limitation
Al-Baiaty et al. ⁴⁷	Obese children with NAFLD	Tocotrienol-rich fraction	Clinical trial	Supports feasibility and potential hepatic benefit	Paediatric phenotype; small evidence base; cannot establish adult antifibrotic efficacy
Mahjabeen et al. ⁴³	Adults with T2D	δ-T3 vs placebo	24 weeks	Improved glycaemic, inflammatory and oxidative measures	Indirect evidence for MASLD; no liver fibrosis outcome

Source: Synthesis by the author from the cited studies.

As [Table 1](#) indicates, the available human evidence is sufficient to justify additional clinical investigation but not to support an antifibrotic efficacy claim. The central evidentiary gap is the absence of trials designed around validated fibrosis measures or paired histological outcomes in appropriately phenotyped adults with MASH.

4.4 Theme 4: The Critical Gap Lies Between Surrogate Improvement and Fibrosis Modification

The strongest case for caution emerges when outcomes are ranked according to clinical meaning. ALT and AST provide useful information about hepatocellular injury but can fluctuate substantially and correlate imperfectly with histological disease. Fatty liver index combines metabolic and biochemical variables and is useful for estimating steatosis probability but cannot directly measure hepatic inflammatory activity or fibrosis. Ultrasound and CT can provide stronger anatomical evidence for steatosis yet still do not answer whether extracellular-matrix deposition has changed.

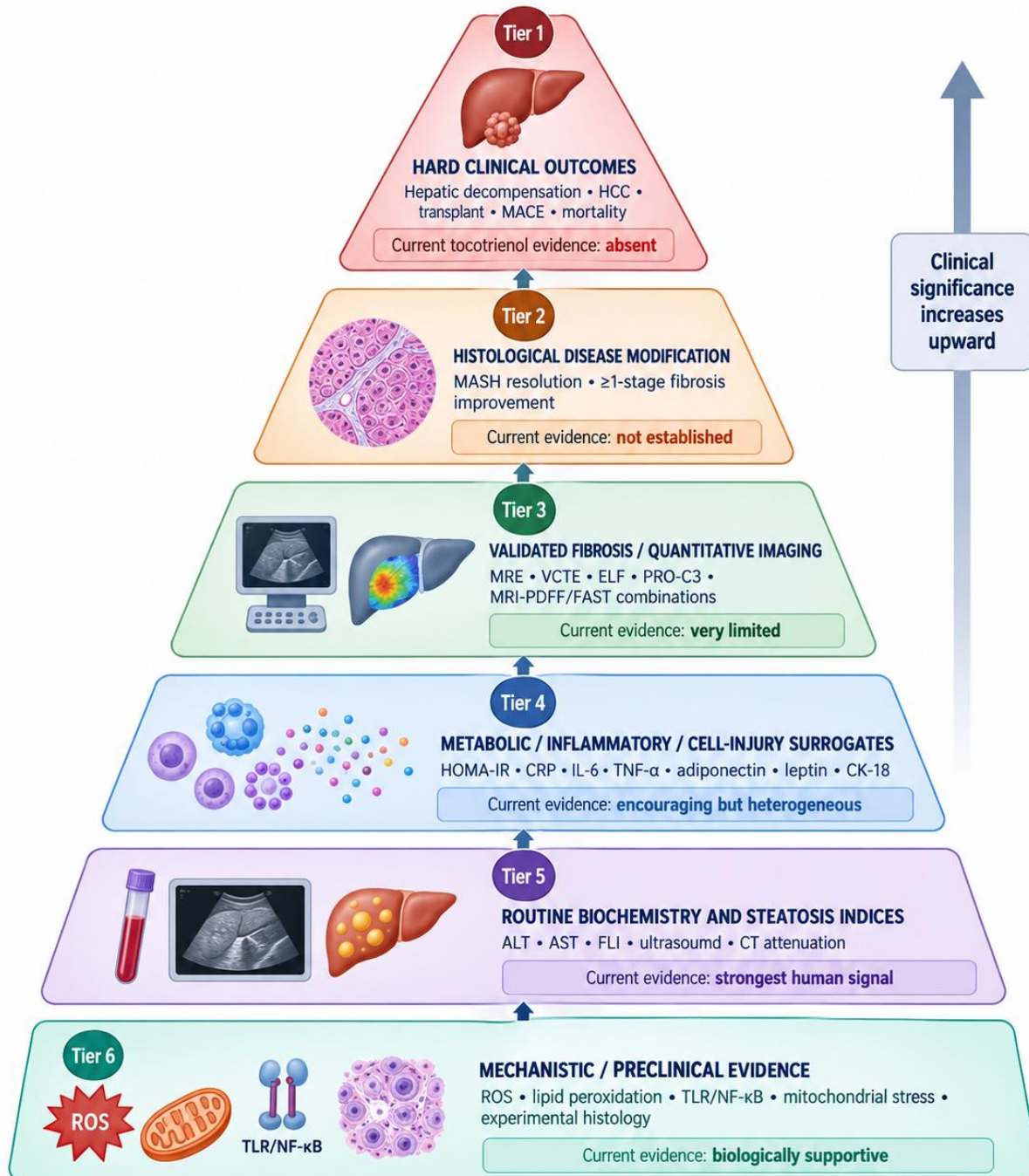
Inflammatory biomarkers such as hs-CRP, IL-6 and TNF-α are conceptually closer to disease mechanisms, while CK-18 provides information about hepatocyte death. Nevertheless, circulating biomarkers remain indirect. Their improvement may accompany reduced metabolic stress without producing the structural changes required to reverse established fibrotic disease. This distinction is particularly important in F2–F3 MASH, where reduction of liver fat might be necessary but insufficient for a clinically important antifibrotic effect.^{26,32}

By contrast, contemporary MASH trials have established a much more demanding evidentiary framework. Clinically important histological endpoints typically include resolution of MASH without worsening of fibrosis and improvement of at least one fibrosis stage without worsening of MASH. Long-term confirmation ultimately requires assessment of progression to cirrhosis, hepatic decompensation, transplantation, liver-related mortality and other meaningful clinical events. Compared with this framework, the tocotrienol evidence remains concentrated at biochemical, metabolic and steatosis levels.

[Figure 3](#) shows that the apparent strength of a nutraceutical evidence base can change dramatically depending on where efficacy is defined. Tocotrienols appear promising when success means improvement in biochemical and metabolic markers, but the evidence becomes progressively less complete when success is redefined as fibrosis regression or prevention of clinical events.

Figure 3. Tocotrienol Evidence Ladder: From Biological Activity to Disease Modification

Figure 3. Tocotrienol Evidence Ladder: From Biological Activity to Disease Modification



Source: Synthesis by author based on cited literature.

Figure 3 explains that the ladder does not imply that lower-tier outcomes are unimportant. Rather, lower tiers should be interpreted as evidence-generating stages that justify progression to stronger endpoints. A rational research programme would therefore use metabolic and mechanistic responses to identify responsive phenotypes and adequate doses before proceeding to fibrosis-focused trials.

4.5 Theme 5: Cardiometabolic Benefits Are Plausible but Unproven at the Event Level

MASLD is tightly integrated with T2D, obesity, atherogenic dyslipidaemia and hypertension. Tocotrienol-related improvements in insulin resistance and some inflammatory markers could therefore be clinically valuable even if direct antifibrotic efficacy proves modest. For example, improved glycaemic control could decrease hepatic lipogenesis and free-fatty-acid exposure over time, potentially reducing recurrent metabolic injury to the liver. This creates a rationale for testing tocotrienols in metabolically active MASLD rather than only in patients selected by liver enzymes.⁴³

However, evidence linking tocotrienol supplementation to cardiovascular-event prevention remains insufficient. MASLD itself is associated with cardiovascular disease, and cardiovascular outcomes often dominate prognosis before decompensated liver disease develops. A compound proposed as a cardiometabolic adjunct should therefore ideally demonstrate improvements in validated risk factors and, eventually, clinical outcomes rather than relying on assumptions derived from antioxidant activity.^{9,13}

Renal outcomes deserve similar attention. Longitudinal evidence suggests that steatotic liver disease is associated with incident CKD independently of several traditional risk factors. It is biologically plausible that improved insulin sensitivity, inflammation and metabolic control could influence kidney risk, but there are currently no robust data showing that tocotrienol therapy prevents CKD progression specifically in MASLD. Kidney function and albuminuria should therefore be prespecified secondary outcomes in sufficiently long future trials.¹⁰

Skeletal muscle is another increasingly important component of the MASLD phenotype. Sarcopenia is associated with adverse metabolic health and appears more frequent among patients with advanced steatotic liver disease. Therapies that produce weight loss without consideration of lean mass may also alter the balance between metabolic benefit and frailty risk. Future tocotrienol research should consequently record body composition and physical function, especially if tocotrienols are tested alongside potent weight-reducing incretin therapies.¹²

4.6 Theme 6: Safety and Bioavailability Are Part of Efficacy

Existing human tocotrienol studies have generally reported acceptable tolerability over the studied periods, which supports further clinical development. Yet safety evidence derived from relatively small trials cannot establish long-term safety in advanced MASH, older adults, patients with CKD or people receiving multiple cardiometabolic

medications. Interactions with antithrombotic therapy, lipid-lowering agents, incretin-based therapy and emerging liver-directed treatments require formal evaluation rather than inference from nutraceutical use.

Bioavailability deserves equal attention because an inadequately absorbed compound can appear pharmacodynamically weak even when its molecular target is valid. Conversely, a highly bioavailable formulation might create exposures not comparable with historical dietary supplementation. Palm TRF development should therefore integrate pharmaceutical principles—standardised composition, stability, fed-versus-fasted administration, exposure assessment and dose ranging—before proceeding to expensive histological trials.^{16,38}

5. DISCUSSION AND ANALYSIS

5.1 Tocotrienols Occupy an Intermediate Translational Zone

The central synthesis of this review is that tocotrienols occupy an intermediate rather than an early or mature translational position in MASLD. They are beyond a purely hypothetical intervention because human trials have shown measurable effects on clinically relevant biological processes. Yet they remain short of established disease-modifying therapy because the outcomes that most strongly determine prognosis—fibrosis progression, cirrhosis, liver-related events and cardiovascular outcomes—have not been adequately tested.

This distinction helps reconcile seemingly conflicting interpretations of the literature. A favourable interpretation is justified when the question is whether tocotrienols display biological activity in metabolically unhealthy humans. A sceptical interpretation becomes justified when the claim escalates to proven antifibrotic efficacy. Both assessments can be simultaneously correct because they concern different levels of evidence.

The relevant question is therefore not whether tocotrienols “work” in an undifferentiated sense. It is **what they have been shown to change, in which population, with which preparation, and at what level of clinical significance**. This framework is more informative than a binary efficacy judgement and is particularly appropriate for nutraceutical-derived interventions whose evidence bases often span cell models, animals, biomarkers and relatively small human trials.

5.2 Why Steatosis Reduction Is Not Equivalent to Fibrosis Regression

The biological distinction between steatosis and fibrosis explains why surrogate improvement cannot be treated as proof of long-term benefit. Hepatic triglyceride content can change relatively quickly when caloric balance, insulin sensitivity or lipid flux changes. Fibrotic tissue, by contrast, reflects cumulative extracellular-matrix deposition, cross-linking, cellular activation and remodelling. Although fibrosis can regress, reversal requires changes beyond simply reducing lipid storage.²⁷

This distinction is visible across the modern MASLD therapeutic literature. Some drugs markedly reduce liver fat but show weaker fibrosis effects, whereas others influence fibrosis despite more modest changes in steatosis. Pemafibrate, for example, did not significantly improve its primary MRI-PDFF endpoint in a phase 2 study but produced signals in MRE-derived liver stiffness and other secondary parameters. This illustrates that liver fat and fibrosis-related outcomes can diverge and reinforces the need to measure both directly.⁴⁸

For tocotrienols, the current situation is almost the reverse problem: improvements in FLI, imaging-derived steatosis and metabolic biomarkers provide a promising basis for further study, but fibrosis-focused assessment has not caught up. Future work should therefore resist simply reproducing earlier trials with larger sample sizes while retaining the same surrogate endpoints. Accordingly, the next generation of trials should address a qualitatively different question centred on fibrosis and clinically meaningful disease modification.

5.3 Modern MASH Therapy Has Raised the Evidentiary Benchmark

The contemporary therapeutic landscape provides a useful benchmark. In the MAESTRO-NASH phase 3 trial, the thyroid-hormone-receptor- β agonist resmetirom was evaluated using co-primary histological outcomes involving steatohepatitis resolution and fibrosis improvement. These data led to a major shift in MASH management and established a clinically relevant precedent for liver-directed treatment in non-cirrhotic patients with moderate-to-advanced fibrosis.^{23,49}

Incretin-based therapies have simultaneously changed the metabolic side of treatment. Earlier phase 2 semaglutide data showed a strong signal for NASH resolution but did not establish a statistically significant fibrosis endpoint. The subsequent phase 3 ESSENCE programme demonstrated both MASH resolution and fibrosis improvement and materially altered the standard against which future adjunctive interventions must be judged.^{50,51,52}

Other agents reinforce the same trend. Tirzepatide has shown important histological effects in MASH with fibrosis, while the glucagon/GLP-1 receptor agonist survodutide has produced promising phase 2 histological findings. Lanifibranor, a pan-PPAR agonist, has generated evidence across steatohepatitis and fibrosis-related outcomes, and the FGF21 analogue pegozafermin has demonstrated antifibrotic and steatohepatitis-related activity in patients with F2–F3 disease. The obeticholic acid REGENERATE programme further illustrates both the possibility of fibrosis improvement and the complexity of balancing efficacy, safety and regulatory considerations.^{53,54,55,56,57}

The implication for tocotrienols is not that a naturally derived intervention must immediately reproduce the development programme of a pharmaceutical agent. Rather, the field should adopt the same conceptual discipline in defining meaningful outcomes. Claims should progress from “improves liver enzymes” to “reduces steatosis,” then

to “reduces inflammatory hepatocyte injury,” and only subsequently to “modifies fibrosis” when direct evidence supports that statement.

5.4 Reinterpreting the Tocotrienol Trials

Viewed through this framework, the 2020 δ -tocotrienol trial represents a useful proof-of-concept metabolic liver study. It showed that intervention can influence several linked outcomes over 24 weeks: FLI, insulin resistance, oxidative stress, inflammation, aminotransferases and ultrasound steatosis. The consistency across these domains reduces the likelihood that the intervention affected only an isolated laboratory variable. At the same time, the absence of histological or validated fibrosis endpoints prevents conclusions about progressive MASH.²¹

The 2022 active-controlled trial advanced the field because it extended treatment to 48 weeks and included CT assessment, inflammatory mediators, adipokines and CK-18. Greater improvement in several inflammatory and apoptosis-related measures with δ -tocotrienol than α -tocopherol is mechanistically interesting. Nevertheless, neither reduction in CK-18 nor improved liver-to-spleen attenuation demonstrates collagen regression. The appropriate interpretation is therefore stronger evidence for anti-inflammatory and hepatocyte-injury modulation, not proof of antifibrotic superiority.²²

The pediatric TRF trial provides additional breadth but a different phenotype. Childhood metabolic liver disease may be more reversible, shorter in duration and less fibrotically advanced than adult MASH. Positive pediatric findings consequently strengthen the argument that TRF has biological activity but cannot close the adult fibrosis evidence gap.⁴⁷

5.5 Palm-Specific Evidence Requires Palm-Specific Trials

An especially important conclusion is that a manuscript centred on palm-derived tocotrienols must distinguish between **class evidence** and **product-specific evidence**. Annatto δ -tocotrienol trials provide class-level support that tocotrienols can exert metabolic and hepatic effects in humans. They do not, however, prove that a palm TRF containing a different isomer distribution and tocopherol content will produce identical exposure or efficacy.

This is not a semantic technicality. Sharif et al.¹⁶ reported pharmacokinetic differences between annatto-based tocotrienols and palm TRF, while formulation research shows that oral exposure can be altered substantially by delivery systems. Thus, future palm-focused trials should not merely adopt doses from annatto studies on a milligram-for-milligram basis. They should determine whether the selected formulation achieves biologically relevant circulating concentrations of the intended isomers.^{16,38}

For the palm sector, this requirement may actually create an opportunity. A well-characterised pharmaceutical-grade palm TRF could be developed as a reproducible intervention rather than marketed simply as a generic natural vitamin E mixture. Such a development pathway would require quality control, stability specifications, compositional fingerprinting, pharmacokinetics, dose-response work and rigorous clinical endpoints. It would thereby move the discussion from commodity origin toward evidence-based precision formulation. This need for standardisation is consistent with the 2025 synthesis of palm-TRF randomised trials, which identified formulation, dose and duration as continuing determinants of interpretability.³⁷

5.6 Which MASLD Phenotypes Are Most Plausible Targets?

Patient selection is likely to determine whether future trials succeed. Early MASLD dominated by obesity, hyperinsulinaemia and elevated triglyceride flux may be particularly biologically responsive to an intervention affecting oxidative and metabolic pathways. In such populations, MRI-PDFF and metabolic endpoints could detect relatively rapid responses, although fibrosis event rates would be low. These studies would be appropriate for dose finding and mechanistic validation.

Patients with T2D-associated MASLD are another attractive group. T2D is associated with a higher likelihood of clinically important fibrosis, and δ -tocotrienol already has human evidence for effects on glycaemic and inflammatory variables. Enriching trials for insulin-resistant participants could therefore increase mechanistic alignment. However, participants would commonly receive statins, metformin, SGLT2 inhibitors, GLP-1 receptor agonists or other therapies, creating both interaction questions and a higher evidentiary bar for demonstrating incremental benefit.^{43,2}

F2–F3 MASH is the most important phenotype for proving antifibrotic activity but also the most challenging. Patients have enough fibrosis to permit meaningful improvement to be measured, yet intervention periods generally need to be substantially longer than those required to change ALT or HOMA-IR. A definitive palm-TRF trial in this population should therefore incorporate validated NITs and histological endpoints and should probably last at least 48–72 weeks.

Advanced cirrhosis should not be the first target population. Once portal hypertension, substantial architectural distortion and decompensation risk are present, the probability that a modest metabolic intervention alone will reverse disease is lower, safety becomes more complex and event-driven trials become much larger. Current MASH guidelines similarly distinguish non-cirrhotic fibrotic disease from cirrhosis when recommending targeted pharmacotherapy.³

5.7 Tocotrienols Should Be Positioned as Adjunctive Therapy

The rapidly evolving treatment landscape makes an “alternative medicine versus pharmaceutical therapy” framing increasingly obsolete. The more plausible future role for tocotrienols is adjunctive. A palm-derived intervention might complement weight reduction and metabolic therapy by targeting oxidative, inflammatory or lipid-associated pathways that remain active despite standard treatment.

This approach also creates a more rigorous question: does adding a standardised tocotrienol preparation produce incremental benefit beyond contemporary care? For patients with obesity or T2D, background therapy may already include potent incretin-based drugs capable of inducing substantial weight loss and improving MASH histology. In F2–F3 disease, liver-directed resmetirom may also be used in appropriate patients. Tocotrienols will therefore need to demonstrate added value rather than merely outperform an untreated historical control.^{23,51,52}

Potential combination strategies should initially focus on pharmacodynamic complementarity and safety rather than assuming synergy. For example, an intervention affecting oxidative and inflammatory stress could theoretically complement weight-loss-driven reductions in substrate delivery. However, the combination of resmetirom and semaglutide itself continues to require further evidence, demonstrating how premature it would be to assume benefits from untested combinations involving tocotrienols.

6. PROPOSED TRANSLATIONAL ROADMAP

A rational development programme should proceed through sequential stages rather than immediately launching a large histology trial. The first stage should establish a pharmaceutical-quality palm-derived product. Each batch should quantify individual tocotrienol isomers, tocopherol content, oxidation status and relevant excipients. Stability under intended storage conditions should be established, because deterioration of a lipid-soluble formulation could alter both exposure and biological activity.

The second stage should be pharmacokinetic and dose-ranging work. Fed and fasted exposure should be characterised, and formulation strategies such as self-emulsifying delivery should be considered if they meaningfully reduce variability. Plasma concentrations of individual isomers should be measured rather than relying only on administered milligrams. Pharmacodynamic biomarkers can then be related to exposure, permitting a rational selection of doses for efficacy trials.^{16,38}

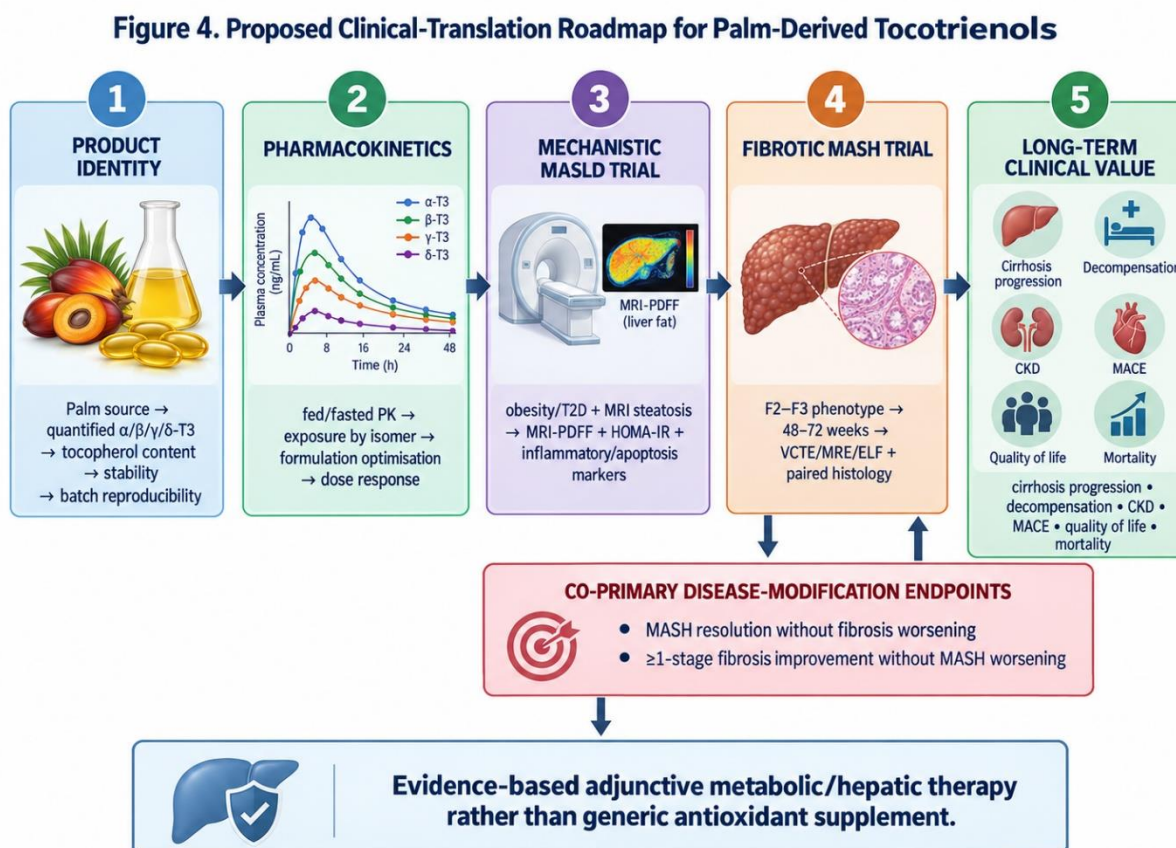
The third stage should involve a mechanistic MASLD trial enriched for metabolic activity. Adults with MRI-confirmed steatosis, obesity and/or T2D could be randomised to standardised palm TRF or placebo on top of standard care. Primary outcomes could include MRI-PDFF and HOMA-IR, with secondary measurements of ALT,

AST, hs-CRP, CK-18, adiponectin, leptin and lipid-related biomarkers. Such a study would determine whether direct palm-specific evidence reproduces signals seen with δ -tocotrienol preparations.

Only after adequate exposure and mechanistic activity are demonstrated should development move to an F2–F3 MASH study. In that setting, the key questions should become fibrosis improvement and MASH resolution rather than changes in enzymes. Baseline and longitudinal VCTE, ELF, and preferably MRE should complement histological assessment. Biomarker panels can be retained for mechanistic interpretation but should no longer function as the principal evidence for efficacy.

Figure 4 illustrates that the proposed roadmap deliberately places product characterisation and pharmacokinetic validation before expensive efficacy testing. This ordering addresses a recurrent weakness in nutraceutical research, where heterogeneous formulations are often moved directly into clinical studies without proving equivalent systemic exposure.

Figure 4. Proposed Clinical-Translation Roadmap for Palm-Derived Tocotrienols



Source: Synthesis by author based on cited literature.

Figure 4 shows that the pathway also prevents premature use of the term “antifibrotic.” Mechanistic and steatosis trials can establish biological activity and determine which patients respond, whereas F2–F3 trials are required to test genuine liver disease modification. Long-term event studies would then determine whether any histological benefit translates into outcomes meaningful to patients and healthcare systems.

7. A PROPOSED ENDPOINT MATRIX FOR FUTURE TRIALS

Table 2 translates the evidence hierarchy developed in this review into a practical endpoint framework for future palm-tocotrienol trials. It separates pharmacokinetic and mechanistic outcomes from quantitative steatosis, fibrosis, histological and hard clinical endpoints so that claims of efficacy remain proportional to the level of evidence obtained.

Table 2. Recommended Outcome Hierarchy for Palm-Tocotrienol Development in MASLD

Domain	Candidate endpoints	Interpretation
Product/PK	Individual isomer concentrations; AUC; Cmax; Tmax	Confirms exposure and comparability
Metabolic	Weight, waist, HOMA-IR, HbA1c, fasting insulin, triglycerides, ApoB	Establishes systemic metabolic response
Hepatocellular injury	ALT, AST, GGT, CK-18	Supportive but not disease-modification evidence
Inflammation	hs-CRP, IL-6, TNF-α, adiponectin, leptin	Mechanistic support
Steatosis	MRI-PDFF; controlled attenuation parameter	Quantitative liver-fat response
Fibrosis NITs	FIB-4, ELF, VCTE, MRE, PRO-C3	Intermediate fibrosis-related evidence
Histology	MASH resolution; ≥1-stage fibrosis improvement	Core disease-modification evidence
Liver outcomes	Progression to cirrhosis, decompensation, HCC, transplantation	Clinical benefit
Systemic outcomes	MACE, incident/progressive CKD, T2D control, physical function	Multisystem clinical value

Source: Synthesis by the author based on the cited literature.

Table 2 provides a framework for interpreting both existing and future findings. Importantly, the value of an outcome depends on the question being asked. ALT is entirely appropriate for detecting hepatocellular biochemical response but insufficient for establishing fibrosis regression; similarly, MRI-PDFF is a powerful quantitative measure of steatosis but does not substitute for fibrosis assessment.

8. BROADER CARDIOMETABOLIC AND CLINICAL IMPLICATIONS

The multisystem character of MASLD means that liver-centred drug development should not overlook cardiovascular and renal disease. Meta-analytic data demonstrate associations between NAFLD/MASLD and cardiovascular events, heart failure and CKD, while fibrosis severity identifies patients at especially high clinical risk. Consequently, an intervention's overall clinical value could theoretically derive from a combination of hepatic and systemic effects rather than from fibrosis alone.^{9,10,11,14}

This perspective may favour tocotrienols conceptually because their proposed biological effects extend beyond the liver. However, it also raises the required standard of evidence. Improving CRP or HOMA-IR does not demonstrate prevention of myocardial infarction or CKD, just as reducing ALT does not prove fibrosis regression. Cardiometabolic claims should therefore follow the same evidence hierarchy proposed for liver disease.

Hepatocellular carcinoma further illustrates the importance of long-term disease modification. MASLD-related HCC can arise in the context of cirrhosis and, in some patients, before cirrhosis becomes clinically recognised. Metabolic dysfunction, inflammation and fibrogenesis interact with carcinogenic pathways over years. No currently available tocotrienol trial provides evidence that supplementation prevents MASLD-associated HCC, and such a claim would substantially exceed available data.⁵⁸

The most defensible near-term clinical concept is consequently risk-factor modification rather than event prevention. If palm-derived tocotrienols reproducibly improve insulin sensitivity, liver fat, hepatocyte injury or inflammatory activity on top of evidence-based care, they could become relevant adjuncts for selected patients. Demonstrating that role would already represent a meaningful translational achievement without requiring premature claims of cirrhosis, cancer or cardiovascular prevention.

9. RESEARCH GAPS

Several gaps emerge from the synthesis. First, there is a **direct palm-evidence gap**. Much of the most compelling recent adult clinical evidence involves δ -tocotrienol interventions whose composition should not be presumed equivalent to palm TRF. Dedicated adult trials using authenticated palm-derived formulations are therefore necessary.

Second, there is a **fibrosis endpoint gap**. Existing clinical studies have focused on steatosis, enzymes and mechanistic biomarkers. Future studies need MRE, VCTE, ELF or similar validated fibrosis tools and, for definitive proof, histological fibrosis endpoints.

Third, there is a **dose–exposure gap**. Milligram dose alone does not establish systemic exposure, particularly for poorly water-soluble lipid-derived bioactives. Pharmacokinetic characterisation should become routine.

Fourth, there is a **phenotype gap**. Existing studies provide limited information on whether effects differ by T2D status, baseline fibrosis, sex, age, genetic risk, obesity severity or metabolic phenotype. Precision recruitment may prove more successful than treating MASLD as a uniform disorder.

Fifth, there is a **background-therapy gap**. The therapeutic environment has changed substantially since earlier tocotrienol trials. Future studies must determine incremental efficacy on top of contemporary obesity, diabetes, lipid and MASH treatments.

Finally, there is an **outcome-duration gap**. Twenty-four or forty-eight weeks may be sufficient to detect changes in enzymes and steatosis but may be inadequate to characterise durable fibrosis regression or clinical events. Longer follow-up will be necessary if the field intends to move from nutraceutical biomarker research toward disease-modification claims.

10. CONCLUSION

Palm-derived tocotrienols have a biologically credible rationale for investigation in MASLD because their proposed actions intersect insulin resistance, lipid dysregulation, oxidative stress, inflammatory signalling and hepatocyte injury. Contemporary human tocotrienol studies provide evidence of biological activity and show that improvements in hepatic and metabolic surrogate markers are achievable.

The existing evidence, however, does not justify describing palm-derived tocotrienols as established antifibrotic or disease-modifying therapy. Direct adult evidence specifically attributable to authenticated palm TRF remains limited, and much of the strongest recent clinical evidence has been generated with δ -tocotrienol preparations that should not automatically be treated as pharmacologically interchangeable with palm-derived mixtures.

The next stage of research should therefore move beyond repeating studies of aminotransferases and qualitative steatosis. Product authentication, isomer-specific pharmacokinetics, quantitative MRI, validated fibrosis NITs and appropriately selected F2–F3 MASH populations are necessary to determine whether metabolic and anti-inflammatory activity can progress to histological disease modification.

Tocotrienols are consequently best positioned as candidate adjunctive metabolic interventions rather than generic antioxidant supplements. Their future clinical significance will depend not on demonstrating that they can change another biomarker, but on establishing whether a defined palm-derived formulation can modify the biological and structural processes that determine long-term liver and cardiometabolic outcomes.

REFERENCES

1. Rinella, M. E., Lazarus, J. V., Ratziu, V., Francque, S. M., Sanyal, A. J., Kanwal, F., Romero, D. et al.. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* **78**, 1966–1986 (2023). <https://doi.org/10.1097/HEP.0000000000000520>
2. Rinella, M. E., Neuschwander-Tetri, B. A., Siddiqui, M. S., Abdelmalek, M. F., Caldwell, S., Barb, D., Kleiner, D. E. & Loomba, R.. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* **77**, 1797–1835 (2023). <https://doi.org/10.1097/HEP.0000000000000323>
3. EASL-EASD-EASO. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J. Hepatol.* **81**, 492–542 (2024). <https://doi.org/10.1016/j.jhep.2024.04.031>
4. Younossi, Z. M., Golabi, P., Paik, J. M., Henry, A., Van Dongen, C. & Henry, L.. The global epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: a systematic review. *Hepatology* **77**, 1335–1347 (2023). <https://doi.org/10.1097/HEP.0000000000000004>
5. Riazi, K., Azhari, H., Charette, J. H., Underwood, F. E., King, J. A., Ehteshami Afshar, E., Swain, M. G., Congly, S. E., Kaplan, G. G. & Shaheen, A.-A.. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol. Hepatol.* **7**, 851–861 (2022). [https://doi.org/10.1016/S2468-1253\(22\)00165-0](https://doi.org/10.1016/S2468-1253(22)00165-0)
6. Ng, C. H., Lim, W. H., Lim, G. E. H., Tan, D. J. H., Syn, N., Muthiah, M. D., Huang, D. Q. & Loomba, R.. Mortality outcomes by fibrosis stage in nonalcoholic fatty liver disease: A systematic review and meta-analysis. *Clin. Gastroenterol. Hepatol.* **21**, 931–939.e5 (2023). <https://doi.org/10.1016/j.cgh.2022.04.014>
7. Sanyal, A. J., Anstee, Q. M., Trauner, M., Lawitz, E. J., Abdelmalek, M. F., Ding, D., Han, L. et al.. Cirrhosis regression is associated with improved clinical outcomes in patients with nonalcoholic steatohepatitis. *Hepatology* **75**, 1235–1246 (2022). <https://doi.org/10.1002/hep.32204>
8. Tamaki, N., Kurosaki, M., Huang, D. Q. & Loomba, R.. Noninvasive assessment of liver fibrosis and its clinical significance in nonalcoholic fatty liver disease. *Hepatol. Res.* **52**, 497–507 (2022). <https://doi.org/10.1111/hepr.13764>
9. Mantovani, A., Csermely, A., Petracca, G., Beatrice, G., Corey, K. E., Simon, T. G., Byrne, C. D. & Targher, G.. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. *Lancet Gastroenterol. Hepatol.* **6**, 903–913 (2021). [https://doi.org/10.1016/S2468-1253\(21\)00308-3](https://doi.org/10.1016/S2468-1253(21)00308-3)
10. Mantovani, A., Petracca, G., Beatrice, G., Csermely, A., Lonardo, A., Schattenberg, J. M., Tilg, H., Byrne, C. D. & Targher, G.. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. *Gut* **71**, 156–162 (2022). <https://doi.org/10.1136/gutjnl-2020-323082>

11. Salah, H. M., Pandey, A., Van Spall, H. G. C., Michos, E. D., McGarrah, R. W. & Fudim, M.. Meta-analysis of nonalcoholic fatty liver disease and incident heart failure. *Am. J. Cardiol.* **171**, 180–181 (2022). <https://doi.org/10.1016/j.amjcard.2022.02.012>
12. Malik, A., Javaid, S., Malik, M. I. & Qureshi, S.. Relationship between sarcopenia and metabolic dysfunction-associated steatotic liver disease (MASLD): A systematic review and meta-analysis. *Ann. Hepatol.* **29**, 101544 (2024). <https://doi.org/10.1016/j.aohep.2024.101544>
13. Zheng, H., Sechi, L. A., Navarese, E. P., Casu, G. & Vidili, G.. Metabolic dysfunction-associated steatotic liver disease and cardiovascular risk: a comprehensive review. *Cardiovasc. Diabetol.* **23**, 346 (2024). <https://doi.org/10.1186/s12933-024-02434-5>
14. Jain, P., Jain, A., Deshmukh, R., Samal, P., Satapathy, T. & Ajazuddin. Metabolic dysfunction-associated steatotic liver disease (MASLD): Exploring systemic impacts and innovative therapies. *Clin. Res. Hepatol. Gastroenterol.* **49**, 102584 (2025). <https://doi.org/10.1016/j.clinre.2025.102584>
15. Szweczyk, K., Chojnacka, A. & Górnicka, M.. Tocopherols and tocotrienols—bioactive dietary compounds; what is certain, what is doubt?. *Int. J. Mol. Sci.* **22**, 6222 (2021). <https://doi.org/10.3390/ijms22126222>
16. Sharif, M., Khan, D. A., Farhat, K., Noor, M., Khan, M. A. & Rafique, S.. Pharmacokinetics and bioavailability of tocotrienols in healthy human volunteers: a systematic review. *Journal of the Pakistan Medical Association* **73**, 603–610 (2023). <https://doi.org/10.47391/JPMA.6008>
17. Pafili, K. & Roden, M.. Nonalcoholic fatty liver disease from pathogenesis to treatment concepts in humans. *Mol. Metab.* **50**, 101122 (2021). <https://doi.org/10.1016/j.molmet.2020.101122>
18. Chen, Z., Tian, R., She, Z., Cai, J. & Li, H.. Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease. *Free Radic. Biol. Med.* **152**, 116–141 (2020). <https://doi.org/10.1016/j.freeradbiomed.2020.02.025>
19. Bansal, M. B. & Bansal, S. K.. Pathogenesis of MASLD and MASH—role of insulin resistance and lipotoxicity. *Aliment. Pharmacol. Ther.* **59**, S10–S22 (2024). <https://doi.org/10.1111/apt.17930>
20. Li, Y., Yang, P., Ye, J., Xu, Q., Wu, J. & Wang, Y.. Updated mechanisms of MASLD pathogenesis. *Lipids Health Dis.* **23**, 117 (2024). <https://doi.org/10.1186/s12944-024-02108-x>
21. Pervez, M. A., Khan, D. A., Slehria, A. U. R. & Ijaz, A.. Delta-tocotrienol supplementation improves biochemical markers of hepatocellular injury and steatosis in patients with nonalcoholic fatty liver disease: A randomized, placebo-controlled trial. *Complement. Ther. Med.* **52**, 102494 (2020). <https://doi.org/10.1016/j.ctim.2020.102494>
22. Pervez, M. A., Khan, D. A., Mirza, S. A., Slehria, A. U. R., Nisar, U. & Aamir, M.. Comparison of delta-tocotrienol and alpha-tocopherol effects on hepatic steatosis and inflammatory biomarkers in patients with non-alcoholic fatty liver disease: A randomized double-blind active-controlled trial. *Complement. Ther. Med.* **70**, 102866 (2022). <https://doi.org/10.1016/j.ctim.2022.102866>

23. Harrison, S. A., Bedossa, P., Guy, C. D., Schattenberg, J. M., Loomba, R., Taub, R., Labriola, D. et al.. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N. Engl. J. Med.* **390**, 497–509 (2024). <https://doi.org/10.1056/NEJMoa2309000>
24. Sharma, S., Le Guillou, D. & Chen, J. Y.. Cellular stress in the pathogenesis of nonalcoholic steatohepatitis and liver fibrosis. *Nature Reviews Gastroenterology & Hepatology* **20**, 662–678 (2023). <https://doi.org/10.1038/s41575-023-00832-w>
25. Maher, S., Rajapakse, J., El-Omar, E. & Zekry, A.. Role of the gut microbiome in metabolic dysfunction-associated steatotic liver disease. *Semin. Liver Dis.* **44**, 457–473 (2024). <https://doi.org/10.1055/a-2438-4383>
26. Lee, Y. A. & Friedman, S. L.. Inflammatory and fibrotic mechanisms in NAFLD—implications for new treatment strategies. *J. Intern. Med.* **291**, 11–31 (2022). <https://doi.org/10.1111/joim.13380>
27. Friedman, S. L. & Pinzani, M.. Hepatic fibrosis 2022: Unmet needs and a blueprint for the future. *Hepatology* **75**, 473–488 (2022). <https://doi.org/10.1002/hep.32285>
28. Sanyal, A. J., Castera, L. & Wong, V. W.-S.. Noninvasive assessment of liver fibrosis in NAFLD. *Clin. Gastroenterol. Hepatol.* **21**, 2026–2039 (2023). <https://doi.org/10.1016/j.cgh.2023.03.042>
29. Tincopa, M. A. & Loomba, R.. Noninvasive Tests to Assess Fibrosis and Disease Severity in Metabolic Dysfunction-Associated Steatotic Liver Disease. *Semin. Liver Dis.* **44**, 287–299 (2024). <https://doi.org/10.1055/s-0044-1788277>
30. Feng, G., Wong, V. W.-S., Targher, G., Byrne, C. D. & Zheng, M.-H.. Non-invasive tests of fibrosis in the management of MASLD: revolutionising diagnosis, progression and regression monitoring. *Gut* **74**, 1741–1750 (2025). <https://doi.org/10.1136/gutjnl-2025-335542>
31. Yu, J. H., Lee, H. A. & Kim, S. U.. Noninvasive imaging biomarkers for liver fibrosis in nonalcoholic fatty liver disease: current and future. *Clin. Mol. Hepatol.* **29**, S136–S149 (2023). <https://doi.org/10.3350/cmh.2022.0436>
32. Reinson, T., Buchanan, R. M. & Byrne, C. D.. Noninvasive serum biomarkers for liver fibrosis in NAFLD: current and future. *Clin. Mol. Hepatol.* **29**, S157–S170 (2023). <https://doi.org/10.3350/cmh.2022.0348>
33. Verschuren, L., Mak, A. L., van Koppen, A. et al.. Development of a novel non-invasive biomarker panel for hepatic fibrosis in MASLD. *Nat. Commun.* **15**, 4564 (2024). <https://doi.org/10.1038/s41467-024-48956-0>
34. Newsome, P. N., Sasso, M., Deeks, J. J., Paredes, A., Boursier, J., Chan, W.-K., Yilmaz, Y. et al.. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol. Hepatol.* **5**, 362–373 (2020). [https://doi.org/10.1016/S2468-1253\(19\)30383-8](https://doi.org/10.1016/S2468-1253(19)30383-8)
35. Ravaioli, F., Dajti, E., Mantovani, A., Newsome, P. N., Targher, G. & Colecchia, A.. Diagnostic accuracy of FibroScan-AST score for the non-invasive identification of patients with fibrotic non-alcoholic

- steatohepatitis: a systematic review and meta-analysis. *Gut* **72**, 1399–1409 (2023). <https://doi.org/10.1136/gutjnl-2022-328689>
36. Chin, K.-Y., Ekeuku, S. O., Chew, D. C. H. & Trias, A.. Tocotrienol in the management of nonalcoholic fatty liver disease: A systematic review. *Nutrients* **15**, 834 (2023). <https://doi.org/10.3390/nu15040834>
37. Looi, A. D., Palanisamy, U. D., Moorthy, M. & Radhakrishnan, A. K.. Health Benefits of Palm Tocotrienol-Rich Fraction: A Systematic Review of Randomized Controlled Trials. *Nutr. Rev.* **83**, 307–328 (2025). <https://doi.org/10.1093/nutrit/nuae061>
38. Mohamad, N.-V.. Strategies to enhance the solubility and bioavailability of tocotrienols using self-emulsifying drug delivery system. *Pharmaceuticals* **16**, 1403 (2023). <https://doi.org/10.3390/ph16101403>
39. Abdul Nasir, N. A., Sadikan, M. Z. & Agarwal, R.. Modulation of NFκB signalling pathway by tocotrienol: A systematic review. *Asia Pac. J. Clin. Nutr.* **30**, 537–555 (2021). [https://doi.org/10.6133/apjcn.202109_30\(3\).0020](https://doi.org/10.6133/apjcn.202109_30(3).0020)
40. Wong, S. K., Chin, K.-Y., Ahmad, F. & Ima-Nirwana, S.. Regulation of inflammatory response and oxidative stress by tocotrienol in a rat model of non-alcoholic fatty liver disease. *J. Funct. Foods* **74**, 104209 (2020). <https://doi.org/10.1016/j.jff.2020.104209>
41. Khor, B.-H., Tiong, H.-C., Tan, S. C., Wong, S. K., Chin, K.-Y., Karupaiah, T., Ima-Nirwana, S. & Abdul Gafar, A. H.. Effects of tocotrienols supplementation on markers of inflammation and oxidative stress: A systematic review and meta-analysis of randomized controlled trials. *PLoS ONE* **16**, e0255205 (2021). <https://doi.org/10.1371/journal.pone.0255205>
42. Zuo, S., Wang, G., Han, Q., Xiao, H., Santos, H. O., Rodriguez, D. A., Khani, V. & Tang, J.. The effects of tocotrienol supplementation on lipid profile: A meta-analysis of randomized controlled trials. *Complement. Ther. Med.* **52**, 102450 (2020). <https://doi.org/10.1016/j.ctim.2020.102450>
43. Mahjabeen, W., Khan, D. A., Mirza, S. A. & Pervez, M. A.. Effects of delta-tocotrienol supplementation on glycemic control, oxidative stress, inflammatory biomarkers and miRNA expression in type 2 diabetes mellitus: A randomized control trial. *Phytother. Res.* **35**, 3968–3976 (2021). <https://doi.org/10.1002/ptr.7113>
44. Vadarlis, A., Antza, C., Bakaloudi, D. R. et al.. Systematic review with meta-analysis: The effect of vitamin E supplementation in adult patients with non-alcoholic fatty liver disease. *J. Gastroenterol. Hepatol.* **36**, 311–319 (2021). <https://doi.org/10.1111/jgh.15221>
45. Wang, M. Y., Prabakar, K., Găman, M.-A. & Zhang, J. L.. Vitamin E supplementation in the treatment of nonalcoholic fatty liver disease: Evidence from an umbrella review of meta-analysis on randomized controlled trials. *J. Dig. Dis.* **24**, 380–389 (2023). <https://doi.org/10.1111/1751-2980.13210>
46. Vogli, S., Naska, A., Marinos, G., Kasdagli, M.-I. & Orfanos, P.. The effect of vitamin E supplementation on serum aminotransferases in non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Nutrients* **15**, 3733 (2023). <https://doi.org/10.3390/nu15173733>

47. Al-Baiaty, F. D. R., Ishak, S., Mohd Zaki, F., Masra, F., Abdul Aziz, D. A., Wan Md Zin, W. N., Hing, E. Y., Kuthubul Zaman, A. S., Abdul Wahab, N., Muhammad Nawawi, K. N., Hamid, Z., Raja Ali, R. A. & Mohd Mokhtar, N.. Assessing the efficacy of tocotrienol-rich fraction vitamin E in obese children with non-alcoholic fatty liver disease: a single-blind, randomized clinical trial. *BMC Pediatr.* **24**, 529 (2024). <https://doi.org/10.1186/s12887-024-04993-8>
48. Nakajima, A., Eguchi, Y., Yoneda, M., Imajo, K., Tamaki, N., Suganami, H., Nojima, T. et al.. Randomised clinical trial: Pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator, versus placebo in patients with non-alcoholic fatty liver disease. *Aliment. Pharmacol. Ther.* **54**, 1263–1277 (2021). <https://doi.org/10.1111/apt.16596>
49. Suvarna, R., Shetty, S. & Pappachan, J. M.. Efficacy and safety of resmetirom, a selective thyroid hormone receptor- β agonist, in the treatment of metabolic dysfunction-associated steatotic liver disease: a systematic review and meta-analysis. *Sci. Rep.* **14**, 19790 (2024). <https://doi.org/10.1038/s41598-024-70242-8>
50. Newsome, P. N., Buchholtz, K., Cusi, K., Linder, M., Okanoue, T., Ratzl, V., Sanyal, A. J. et al.. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N. Engl. J. Med.* **384**, 1113–1124 (2021). <https://doi.org/10.1056/NEJMoa2028395>
51. Sanyal, A. J., Newsome, P. N., Kliers, I., Østergaard, L. H., Long, M. T., Kjær, M. S., Cali, A. M. G. et al.. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N. Engl. J. Med.* **392**, 2089–2099 (2025). <https://doi.org/10.1056/NEJMoa2413258>
52. Bansal, M. B., Patton, H., Morgan, T. R., Carr, R. M., Dranoff, J. A. & Allen, A. M.. Semaglutide therapy for metabolic dysfunction-associated steatohepatitis: November 2025 updates to AASLD Practice Guidance. *Hepatology* **83**, 1326–1340 (2026). <https://doi.org/10.1097/HEP.0000000000001608>
53. Loomba, R., Hartman, M. L., Lawitz, E. J., Vuppalanchi, R., Boursier, J., Bugianesi, E., Yoneda, M. et al.. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N. Engl. J. Med.* **391**, 299–310 (2024). <https://doi.org/10.1056/NEJMoa2401943>
54. Sanyal, A. J., Bedossa, P., Fraessdorf, M., Neff, G. W., Lawitz, E., Bugianesi, E., Anstee, Q. M. et al.. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N. Engl. J. Med.* **391**, 311–319 (2024). <https://doi.org/10.1056/NEJMoa2401755>
55. Francque, S. M., Bedossa, P., Ratzl, V., Anstee, Q. M., Bugianesi, E., Sanyal, A. J., Loomba, R., Harrison, S. A. et al.. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. *N. Engl. J. Med.* **385**, 1547–1558 (2021). <https://doi.org/10.1056/NEJMoa2036205>
56. Loomba, R., Sanyal, A. J., Kowdley, K. V., Bhatt, D. L., Alkhouri, N., Frias, J. P., Bedossa, P. et al.. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. *N. Engl. J. Med.* **389**, 998–1008 (2023). <https://doi.org/10.1056/NEJMoa2304286>
57. Sanyal, A. J. et al.. Results from a new efficacy and safety analysis of the REGENERATE trial of obeticholic acid for treatment of pre-cirrhotic fibrosis due to non-alcoholic steatohepatitis. *J. Hepatol.* **79**, 1110–1120 (2023). <https://doi.org/10.1016/j.jhep.2023.07.014>

58. Polyzos, S. A., Chrysavgis, L., Vachliotis, I. D., Chartampilas, E. & Cholongitas, E.. Nonalcoholic fatty liver disease and hepatocellular carcinoma: Insights in epidemiology, pathogenesis, imaging, prevention and therapy. *Semin. Cancer Biol.* **93**, 20–35 (2023). <https://doi.org/10.1016/j.semcancer.2023.04.010>