

Beyond Antioxidant Activity: Tocotrienols in Metabolic Dysfunction-Associated Steatotic Liver Disease—Linking Lipotoxicity, Insulin Resistance, Adipokines, Inflammation, and the Translational Gap

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Received: 10 Aug 2026; Accepted: 04 Sep 2026; Published: 16 Sep 2026

Citation: Loso Judijanto. Beyond Antioxidant Activity: Tocotrienols in Metabolic Dysfunction-Associated Steatotic Liver Disease—Linking Lipotoxicity, Insulin Resistance, Adipokines, Inflammation, and the Translational Gap. *Endocrinol Metab Nutr.* 2026; 5(2): 1-13.

ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a systemic metabolic disorder characterized by hepatic steatosis occurring in the context of cardiometabolic dysfunction and capable of progressing to metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma. Its pathogenesis involves adipose-tissue insulin resistance, excessive hepatic fatty-acid influx, de novo lipogenesis, lipotoxicity, mitochondrial and endoplasmic-reticulum stress, inflammation, dysregulated adipokines, hepatocyte death, and fibrogenesis. Tocotrienols, naturally occurring vitamin E isoforms abundant in palm oil and other botanical sources, have attracted interest because their biological activity extends beyond conventional antioxidant effects toward modulation of inflammatory, metabolic, and cell-signaling pathways. This qualitative literature review critically synthesizes evidence published predominantly from 2020–2026 concerning palm-derived tocotrienol-rich fractions and other defined tocotrienol preparations in MASLD. Human studies suggest improvements in fatty-liver indices, insulin resistance, aminotransferases, oxidative-stress markers, inflammatory cytokines, adiponectin, leptin, and cytokeratin-18. Nevertheless, most adult MASLD trials evaluated annatto-derived δ/γ -tocotrienol rather than palm-derived preparations, and clinically definitive evidence for MASH resolution or fibrosis regression remains lacking. The review argues that tocotrienols should be understood as potential multi-node metabolic modulators rather than merely antioxidants. Future trials require standardized source and isoform characterization, improved bioavailability, modern imaging and fibrosis endpoints, integration with contemporary standard-of-care therapies, longer follow-up, and precision-metabolic phenotyping before tocotrienols can be positioned as evidence-based adjunctive interventions for MASLD.

Keywords

Tocotrienol, Palm oil, Tocotrienol-rich fraction, MASLD, MASH, Hepatic lipotoxicity, Insulin resistance, Adiponectin, Inflammation, Liver fibrosis.

JEL Classification: I10; I12; I15; Q16; Q18.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as one of the dominant chronic liver disorders of the twenty-first century. The terminology introduced through a multisociety Delphi process replaced non-alcoholic fatty liver disease (NAFLD) with MASLD to emphasize the disease's close relationship with metabolic dysfunction and to reduce problems

associated with defining a disorder primarily by the absence of alcohol use. MASLD encompasses hepatic steatosis associated with at least one cardiometabolic risk factor, whereas metabolic dysfunction-associated steatohepatitis (MASH) denotes steatosis accompanied by inflammatory hepatocellular injury and varying degrees of fibrosis. The disease spectrum ultimately includes cirrhosis, liver failure and hepatocellular carcinoma [1-3].

The public-health importance of MASLD reflects its extraordinarily close relationship with the global epidemics of obesity, type 2 diabetes mellitus (T2DM), insulin resistance and metabolic syndrome. Meta-analytic estimates indicate that the global prevalence of NAFLD/MASLD has risen markedly over recent decades, with particularly high prevalence among people

with obesity and T2DM. In patients with T2DM, pooled estimates suggest that approximately two-thirds may have MASLD, while substantial proportions of biopsied patients have MASH or clinically significant fibrosis. These observations are clinically important because metabolic liver disease is not an isolated hepatic abnormality: it is associated with increased risk of cardiovascular disease, diabetes complications, malignancy, cirrhosis and liver-related mortality [4-8].

A major conceptual change in MASLD research is the recognition that hepatic triglyceride accumulation alone does not adequately explain disease progression. Some triglyceride storage may even represent an adaptive mechanism that temporarily buffers potentially toxic lipid intermediates. Progression toward MASH and fibrosis instead involves a complex interaction among adipose-tissue insulin resistance, increased free-fatty-acid delivery to the liver, hepatic de novo lipogenesis, impaired lipid disposal, accumulation of lipotoxic lipid species, mitochondrial dysfunction, oxidative stress, endoplasmic-reticulum stress, inflammatory signaling, altered adipokines and hepatocyte death. These processes stimulate Kupffer cells, recruit additional inflammatory cells and promote activation of hepatic stellate cells, ultimately increasing extracellular-matrix deposition and fibrosis [9-12]. Recent syntheses specifically place insulin resistance and lipotoxicity at the center of the MASLD-to-MASH transition, reinforcing the need to assess interventions across upstream metabolic and downstream inflammatory-fibrogenic nodes [13].

Fibrosis is particularly important because long-term outcomes are strongly related to fibrosis severity. A large meta-analysis of biopsy-confirmed disease demonstrated progressively increasing all-cause and liver-related mortality with increasing fibrosis stage. This evidentiary hierarchy means that reductions in aminotransferases, inflammatory biomarkers or hepatic steatosis should not automatically be interpreted as equivalent to clinically meaningful disease modification. Modern MASLD trials increasingly evaluate histological MASH resolution, fibrosis improvement, magnetic resonance imaging-derived proton-density fat fraction (MRI-PDFF), elastography and validated non-invasive fibrosis markers rather than relying only on aminotransferases or simple ultrasound [14-16].

Against this background, interest has increased in dietary bioactives capable of acting simultaneously on several pathogenic pathways. Tocotrienols represent one such class. Vitamin E consists of four tocopherol and four tocotrienol isoforms— α , β , γ and δ —sharing a chromanol ring but differing in their side chains. Tocotrienols contain an unsaturated isoprenoid side chain, a structural feature that affects membrane behavior, metabolism and biological activity. Palm oil is one of the most important natural sources of tocotrienols and contains α -, γ - and δ -tocotrienols within palm tocotrienol-rich fraction (TRF). Annatto, in contrast, provides preparations particularly enriched in δ - and γ -tocotrienol and contains little or no tocopherol [17-19].

The distinction between these sources is critical. Some of the most

frequently cited adult fatty liver trials evaluated an annatto-derived preparation composed predominantly of δ -tocotrienol rather than palm-derived TRF. In a 24-week randomized placebo-controlled study, δ -tocotrienol improved fatty liver index (FLI), HOMA-IR, hs-CRP, malondialdehyde, ALT, AST and ultrasound-assessed steatosis. A subsequent 48-week trial comparing δ -tocotrienol with α -tocopherol reported improvements in steatosis-related and metabolic markers and more favorable changes in adiponectin, leptin, IL-6, TNF- α and cytokeratin-18 with δ -tocotrienol [20,21]. These findings are encouraging, but they cannot properly be described as direct clinical proof for palm-derived tocotrienols.

The central question is therefore not whether tocotrienols possess antioxidant activity, which is reasonably well established, but whether they modify the interconnected metabolic network that drives MASLD and whether these changes ultimately translate into clinically meaningful liver outcomes. This review critically evaluates experimental and clinical evidence regarding tocotrienols, with special emphasis on hepatic lipotoxicity, insulin resistance, adipose-liver communication, adipokines, mitochondrial dysfunction, oxidative stress, inflammation, hepatocyte injury and fibrosis. It additionally distinguishes palm-derived TRF from annatto-derived and other tocotrienol formulations and evaluates the evidence against contemporary standards for MASLD therapeutic development.

Literature Review: Conceptual and Theoretical Foundations

MASLD as a systemic metabolic disorder

MASLD is best understood as a hepatic component of systemic metabolic dysfunction rather than as an isolated disorder of intrahepatic fat storage. Visceral adiposity and adipose-tissue insulin resistance increase release of non-esterified fatty acids into the circulation. The liver consequently receives an increased lipid substrate burden while hyperinsulinemia and excessive carbohydrate intake stimulate hepatic de novo lipogenesis. Hepatic insulin resistance does not necessarily suppress lipogenesis; paradoxically, selective insulin resistance can coexist with persistent insulin-driven lipogenic signaling, contributing to continued triglyceride production even in metabolically insulin-resistant states [9,10].

This metabolic architecture helps explain the strong association between T2DM and progressive MASLD. Diabetes increases not only the likelihood of hepatic steatosis but also the probability of MASH and advanced fibrosis. Current guidelines therefore emphasize fibrosis case-finding among people with T2DM, obesity and other cardiometabolic risk factors. The liver participates in reciprocal inter-organ signaling through hepatokines, adipokines, myokines and inflammatory mediators; consequently, metabolic abnormalities in adipose tissue, skeletal muscle and the intestine can influence hepatic inflammation and fibrosis, while diseased liver can amplify systemic metabolic dysfunction [22-24]. A 2025 American Diabetes Association consensus report further emphasizes systematic fibrosis risk assessment in people with diabetes, underscoring the high-risk overlap between dysglycemia and progressive MASLD [25].

The gut–liver axis adds another level of complexity. Intestinal dysbiosis, altered barrier permeability, microbial metabolites, endotoxin exposure and bile-acid signaling can modify hepatic lipid handling and innate immune activation. These mechanisms do not imply that every patient has a microbiome-driven disease, but they reinforce the principle that MASLD results from multiple interacting biological “hits” rather than a single pathway. Personalized therapeutic responses may therefore depend upon metabolic phenotype, diet, genetic predisposition, microbiome composition and disease stage [26–28].

From Steatosis to Lipotoxicity

Hepatic triglyceride content is an important diagnostic feature, but triglyceride quantity is not synonymous with lipid toxicity. Free fatty acids, ceramides, diacylglycerols, free cholesterol and other lipid-derived metabolites may interfere with insulin signaling, mitochondrial function and membrane homeostasis. When lipid influx and synthesis exceed the liver’s capacity for oxidation, esterification and secretion, hepatocytes experience metabolic stress. The resulting lipotoxicity contributes to oxidative damage, ER stress, inflammasome activation and cell death [9,13].

De novo lipogenesis is particularly relevant because it is disproportionately elevated in metabolic fatty liver disease. Hyperinsulinemia and high carbohydrate availability activate transcriptional pathways involving SREBP-1c and ChREBP, increasing synthesis of fatty acids. Interventions that indirectly reduce insulin resistance or alter cellular energy sensing could therefore reduce hepatic substrate overload even without acting as direct inhibitors of lipogenesis. This concept is highly relevant when evaluating tocotrienols because experimental observations suggest effects on lipid regulation that extend beyond radical-scavenging activity.

Mitochondrial stress, oxidative injury and ER dysfunction

Mitochondria initially adapt to nutrient surplus by increasing β -oxidation and oxidative metabolism. Persistent overload can, however, impair electron transport, increase reactive oxygen species (ROS), alter mitochondrial dynamics and compromise ATP production. Oxidative stress can damage mitochondrial DNA, proteins and membrane lipids, reinforcing a cycle in which mitochondrial dysfunction generates additional oxidative injury. Whether mitochondrial impairment is an initiating mechanism or a consequence of metabolic overload probably varies across disease stages and phenotypes [29,30]. A recent redox-focused synthesis likewise emphasizes that antioxidant-system alterations vary across disease stage and interact with mitochondrial dysfunction, arguing against a simplistic oxidative-stress-only model [31].

ER stress provides a mechanistic bridge between lipid overload, inflammation and hepatocyte death. Excessive or abnormal lipid species disrupt membrane composition and protein folding, activating the unfolded-protein response. Adaptive ER responses may initially restore homeostasis, whereas persistent activation can promote inflammatory signaling, apoptosis and metabolic dysfunction. ER stress also interacts with mitochondrial stress

and autophagy, making it difficult to isolate a single pathway as causally dominant [12].

Inflammation and Inflammasome activation

The transition from uncomplicated steatosis to MASH involves activation of innate and adaptive immune pathways. NF- κ B signaling promotes transcription of pro-inflammatory mediators including TNF- α and IL-6. The NLRP3 inflammasome responds to metabolic and cellular danger signals and activates caspase-1-dependent inflammatory pathways, including maturation of IL-1 β and IL-18 and, under some conditions, pyroptotic cell death. Hepatocyte injury then releases damage-associated molecular signals capable of amplifying inflammatory and fibrogenic responses [11,32].

The biological interest in tocotrienols arises partly from their reported capacity to modulate NF- κ B-related signaling. A systematic review of experimental evidence found that tocotrienols can influence multiple regulators of NF- κ B activation, although the available studies span diverse disease models and formulations and should not automatically be interpreted as MASLD-specific clinical evidence [33].

Adipokines and adipose–liver crosstalk

Adipose tissue functions as an endocrine organ. Adiponectin promotes insulin sensitivity, fatty-acid oxidation and anti-inflammatory signaling and is commonly reduced in obesity and insulin-resistant states. Leptin regulates appetite and energy balance but is frequently elevated in obesity as leptin resistance develops. Chronically increased leptin may also participate in immune and fibrogenic signaling. These adipokines operate together with TNF- α , IL-6 and other mediators, creating an endocrine network through which dysfunctional adipose tissue can influence hepatic metabolism and fibrosis [23].

This framework is particularly relevant to tocotrienol research because the 48-week δ -tocotrienol study reported increases in adiponectin and reductions in leptin alongside lower inflammatory biomarkers. Rather than interpreting these findings independently, they can be conceptualized as potential evidence of improved adipose–liver communication [21].

Tocotrienol Biology and Source-Specific Considerations

Tocotrienols are not interchangeable with tocopherols

Tocopherols and tocotrienols share antioxidant chromanol chemistry but differ structurally in their hydrophobic side chains. This difference affects membrane distribution and pharmacokinetics. Tocotrienols have often shown biological activity at concentrations that cannot be explained solely by classical chain-breaking antioxidant chemistry, with reported actions involving cellular signaling, inflammatory regulation, lipid metabolism and gene expression [17,19].

The term “vitamin E” is therefore too broad when interpreting therapeutic studies. α -Tocopherol cannot be assumed to have the same biological effects as δ -tocotrienol, and findings from purified

δ -tocotrienol cannot automatically be transferred to mixed palm TRF. This is especially important because α -tocopherol has a higher affinity for hepatic α -tocopherol transfer protein, whereas tocotrienols are cleared more rapidly and show lower and more variable circulating exposure [34,35].

Palm-derived TRF versus annatto-derived tocotrienols

Palm-derived TRF typically contains mixed tocotrienol isoforms and tocopherol, whereas annatto products are generally dominated by δ - and γ -tocotrienol. Composition therefore changes the proportion of biologically active isoforms delivered and potentially alters pharmacokinetic interactions. Clinical reviews of palm TRF document considerable heterogeneity in dose, duration, underlying health conditions and study endpoints, which complicates attempts to define an optimal formulation or therapeutic exposure [18,36].

A critical implication follows: evidence should be classified according to intervention provenance. The adult fatty liver trials by Pervez and colleagues used an annatto-derived tocotrienol preparation. These studies provide direct clinical evidence for tocotrienol-class activity in fatty liver but only indirect support for a hypothesis involving palm TRF. Conversely, palm-specific liver evidence includes experimental research such as Goon et al. [37], in which palm TRF administered with palm-kernel oil reduced liver steatosis and NAFLD activity-related outcomes in mice fed a high-fat diet, and pediatric work evaluating TRF in obese children with NAFLD [38].

Figure 1 illustrates why the intervention should not be conceptualized as “vitamin E” alone. The biological effect observed in a clinical trial reflects the combined influence of

botanical source, isoform mixture, formulation, dose, absorption and host metabolic phenotype, so source attribution is essential when interpreting efficacy.

The figure emphasizes a central methodological principle: source and formulation constitute part of the biological intervention itself. Pooling palm TRF, annatto δ -tocotrienol and purified tocotrienols under a single “vitamin E” category may obscure genuine differences in efficacy. Future studies should therefore report quantitative isoform composition, excipients, carrier oil, timing relative to meals and circulating tocotrienol concentrations.

Method

This study employed a critical qualitative literature review design. It was not designed as a systematic literature review or meta-analysis. The qualitative approach was selected because the literature relevant to tocotrienols and MASLD is heterogeneous in biological scale, ranging from molecular and animal experiments to randomized clinical trials, pharmacokinetic studies, systematic reviews, guidelines and contemporary therapeutic trials. The objective was therefore interpretive integration rather than quantitative pooling.

Literature considered for the review was identified principally through PubMed/MEDLINE, Scopus, Web of Science and major publisher databases. Search concepts combined disease terms—“MASLD”, “MASH”, “NAFLD”, “NASH”, and “metabolic fatty liver”—with intervention terms including “tocotrienol,” “tocotrienol-rich fraction,” “palm tocotrienol,” “palm vitamin E”, “delta-tocotrienol” and “annatto tocotrienol”. Mechanistic terms included “insulin resistance”, “lipotoxicity”, “de novo lipogenesis”,

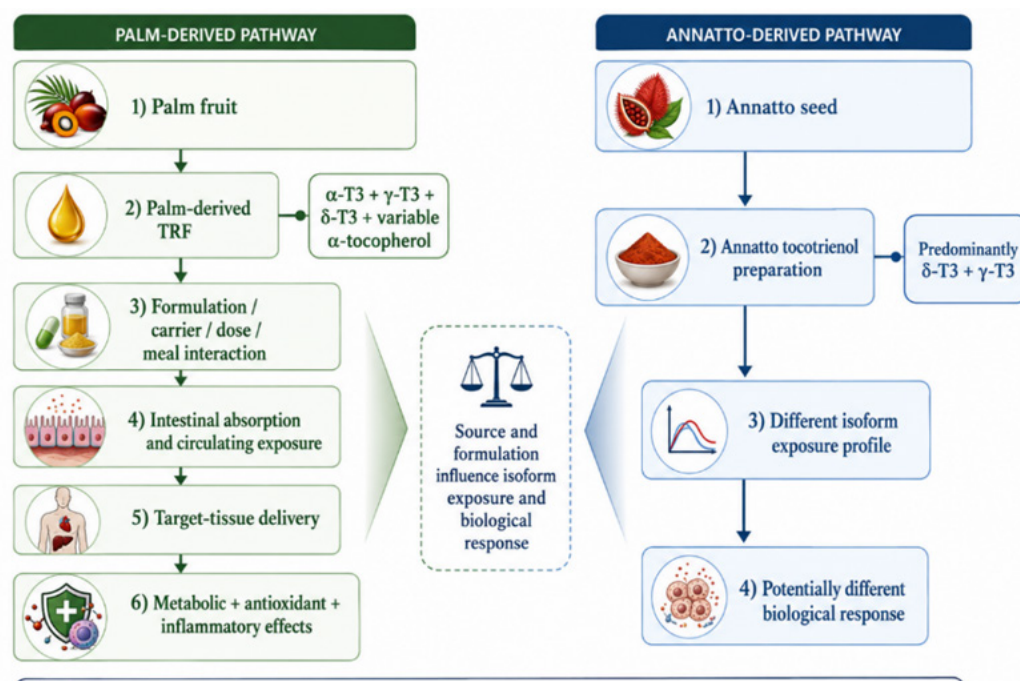


Figure 1: Source-to-effect framework for tocotrienol interventions.

Source: Author’s synthesis based on refs [17,18,35,36].

“oxidative stress”, “mitochondrial dysfunction”, “endoplasmic reticulum stress”, “NF- κ B”, “inflammation”, “adiponectin”, “leptin”, “microRNA”, “apoptosis”, “cytokeratin-18” and “fibrosis”.

The principal temporal window was January 2020 through August 2026. Preference was given to peer-reviewed journal articles, randomized trials, recent meta-analyses, contemporary mechanistic reviews, clinical-practice guidelines and high-impact MASLD therapeutic trials. Earlier studies were not required to construct the central argument because a sufficiently large body of contemporary literature was available.

The synthesis followed an evidence hierarchy. Molecular and animal findings were treated as mechanistic support but were not considered proof of clinical efficacy. Human biochemical outcomes such as ALT, AST, hs-CRP and malondialdehyde were interpreted as markers of biological activity. HOMA-IR and FLI were treated as clinically useful but indirect surrogate measures. Imaging outcomes were assigned higher evidentiary value when quantitative methods were used, whereas histological MASH resolution, fibrosis improvement and clinically meaningful liver outcomes represented the strongest level of disease-modifying evidence.

The literature was organized deductively around eight thematic domains: hepatic lipid metabolism and lipotoxicity; insulin resistance; adipose–liver crosstalk; oxidative stress; mitochondrial and ER dysfunction; inflammatory signaling; hepatocyte injury and fibrosis; and source/formulation-dependent translation. An inductive component was also used to incorporate emerging themes, particularly microRNAs, pharmacokinetic limitations and precision-metabolic phenotyping. This structure allowed apparently conflicting findings to be interpreted as consequences of different formulations, populations, endpoints or biological contexts rather than forcing a binary positive-versus-negative conclusion.

Results: Thematic Findings

Scope and limitations of direct clinical evidence

A recent systematic review identified only a limited number of direct tocotrienol studies related to fatty liver, comprising predominantly animal experiments and a small number of human trials. This is important because the broader tocotrienol literature in diabetes, cardiovascular disease and inflammation is substantially larger than the evidence specific to MASLD [39].

The most influential adult study randomized 71 patients with NAFLD to δ -tocotrienol 300 mg twice daily or placebo for 24 weeks. Compared with placebo, δ -tocotrienol reduced FLI, HOMA-IR, hs-CRP, malondialdehyde, ALT and AST and was associated with greater improvement in ultrasound-assessed steatosis [20]. These findings provide evidence that tocotrienol exposure can simultaneously influence hepatic, metabolic, inflammatory and oxidative-stress markers. They do not, however, establish histological MASH resolution or fibrosis regression

because neither endpoint was directly measured.

The subsequent active-controlled trial compared δ -tocotrienol with α -tocopherol over 48 weeks. Both interventions were associated with improvement in selected hepatic and metabolic indices, but δ -tocotrienol showed stronger changes in body weight, adiponectin, leptin, IL-6, TNF- α and cytokeratin-18. This pattern supports a hypothesis that tocotrienol acts through several interacting pathways and may exert effects distinct from conventional α -tocopherol [21].

A related microRNA analysis reported altered expression of circulating miRNAs after tocotrienol intervention, adding a potential regulatory layer to the observed metabolic effects. However, circulating miRNAs in MASLD are themselves influenced by hepatic injury, obesity, insulin resistance and treatment response, and their interpretation as causal mediators remains premature. Contemporary reviews identify miR-122, miR-34a, miR-21 and miR-192 among the better-studied MASLD-associated candidates, but none currently provides a stand-alone validated therapeutic-response endpoint [40–42].

Tocotrienols and Insulin Resistance

Insulin resistance may represent one of the most important mechanistic bridges between tocotrienol supplementation and improved hepatic phenotype. In insulin-resistant adipose tissue, impaired suppression of lipolysis increases fatty-acid delivery to the liver. Simultaneously, hyperinsulinemia and glucose availability support hepatic DNL. Reducing systemic insulin resistance could therefore decrease hepatic substrate pressure even without directly targeting hepatocyte lipid synthesis.

The HOMA-IR improvement reported in the δ -tocotrienol NAFLD trial is consistent with evidence from metabolic populations. In T2DM, Mahjabeen et al. [43] reported improvements in glucose, insulin, HOMA-IR and HbA1c together with reductions in inflammatory and oxidative markers after δ -tocotrienol supplementation. A randomized trial in prediabetes also reported improved glycemic-control indices [44]. Meta-analysis of TRF trials in T2DM found a modest pooled reduction in HbA1c but no consistent effect on blood pressure or hs-CRP, demonstrating that metabolic effects are neither universal nor uniform across preparations and populations [45].

These findings support but do not prove a causal pathway from tocotrienol exposure to insulin sensitization to reduced hepatic steatosis. Changes in body weight, diet or other metabolic parameters could contribute to observed effects. Future MASLD trials should therefore incorporate more sophisticated assessments such as fasting insulin, oral-glucose-tolerance-derived indices, continuous glucose monitoring and, in mechanistic subsets, clamp-based or tracer-based assessment of hepatic and peripheral insulin sensitivity.

Hepatic lipid metabolism and lipotoxicity

Evidence that tocotrienols may influence lipid metabolism is

biologically plausible but remains less clinically established than the antioxidant literature. Tocotrienols have been associated experimentally with changes in lipid synthesis, cholesterol metabolism and cellular signaling. Palm TRF prevented or attenuated steatotic changes in a high-fat-diet mouse model, but the intervention also involved palm-kernel oil as a carrier and cannot be translated directly into a human therapeutic effect [37].

The distinction between steatosis and lipotoxicity is fundamental. A therapy could reduce total liver triglyceride while having limited impact on toxic ceramides, diacylglycerols, free cholesterol or oxidative lipid products. Conversely, improved sequestration of lipid into relatively inert triglyceride droplets could theoretically reduce toxic stress without producing a dramatic fall in total liver fat. Future trials should therefore combine quantitative imaging with lipidomic measurements when testing the hypothesis that tocotrienols modify hepatic lipotoxicity.

Figure 2 summarizes the metabolic cascade that potentially connects tocotrienol activity with MASLD while deliberately separating biologically plausible pathways from clinically proven effects. The diagram also makes clear that proposed tocotrienol actions occur at several interconnected nodes and should not be interpreted as evidence that any single pathway has been clinically established as causal.

This representation highlights why a single-marker interpretation is inadequate. An observed decline in malondialdehyde may reflect lower oxidative stress but does not establish an antifibrotic effect.

Similarly, an improvement in HOMA-IR may reduce upstream metabolic pressure but does not prove reversal of MASH. The clinically meaningful question is whether simultaneous modest effects across several nodes ultimately alter the trajectory of disease.

Oxidative stress and mitochondrial function

Tocotrienols have traditionally been discussed primarily as antioxidants. Their unsaturated side chain may facilitate distribution within lipid membranes, while the chromanol structure can interrupt lipid-peroxidation reactions. In MASLD, such activity is biologically relevant because oxidative injury accompanies mitochondrial overload and lipotoxicity. Nevertheless, oxidative stress is embedded in a feedback network: mitochondrial dysfunction generates ROS, while ROS further impair mitochondrial proteins, membranes and DNA [29].

The clinical evidence is inconsistent when viewed across all populations. Khor et al. [46] found that tocotrienol supplementation did not consistently lower IL-6, TNF- α or malondialdehyde across randomized trials, although selected subgroups and formulations showed more favorable results. Similarly, broader analyses of tocotrienol interventions have emphasized substantial heterogeneity. This finding argues against portraying tocotrienols as universally potent systemic antioxidants in humans. Instead, response may depend upon dose, baseline oxidative burden, formulation and disease phenotype.

The importance of bioavailability reinforces this interpretation.

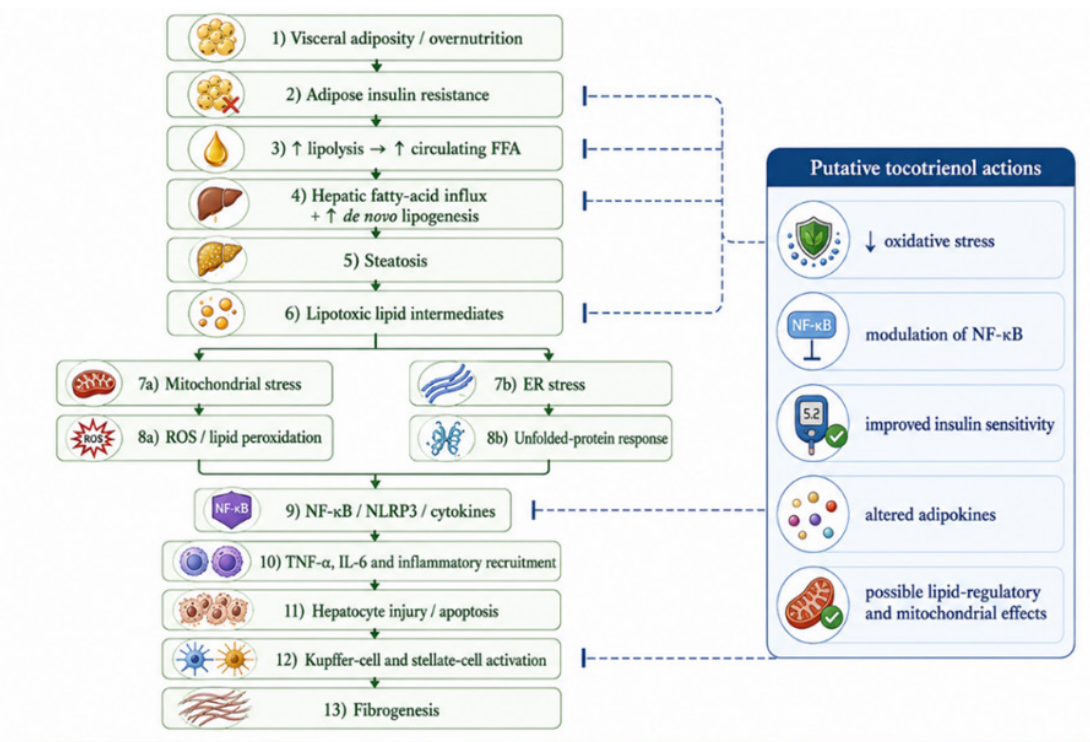


Figure 2: MASLD pathogenic network and proposed tocotrienol intervention nodes.

Source: Author's synthesis based on refs [9,18,20,21,29,32,33].

Tocotrienols have relatively poor and variable oral exposure because of low aqueous solubility, rapid elimination and weaker binding to α -tocopherol transfer protein. Absorption is also saturable and affected by formulation. Modern delivery strategies—including self-emulsifying formulations, nanoemulsions and other lipid-based systems—may therefore be essential if consistent tissue exposure is required for therapeutic effects [34,35].

Inflammatory signaling and adipokines

The inflammatory findings from the 48-week δ -tocotrienol study are among the most conceptually interesting observations in the human fatty liver literature because reductions in TNF- α and IL-6 occurred alongside favorable changes in adiponectin and leptin. This supports the possibility that the effect is not limited to direct antioxidant activity within hepatocytes but involves systemic metabolic signaling [21].

Adiponectin deserves particular attention because it promotes fatty-acid oxidation and insulin sensitivity and can inhibit inflammatory and fibrogenic signaling. An increase in adiponectin could therefore theoretically improve several MASLD pathways simultaneously. Conversely, elevated leptin in obesity may contribute to inflammation and fibrosis in addition to signaling energy stores. A treatment that increases adiponectin while reducing pathologically elevated leptin could represent endocrine remodeling of the adipose–liver axis.

However, cytokine measurements are highly variable and sensitive to baseline phenotype, assay methods and concurrent changes in weight or glucose control. Tocotrienol meta-analysis outside MASLD demonstrates that anti-inflammatory effects are not consistently reproduced across studies [46]. The most appropriate conclusion is therefore that adipokine and cytokine changes represent promising mechanistic signals requiring replication rather than definitive proof of systemic anti-inflammatory efficacy.

Hepatocyte injury, CK-18 and fibrosis

ALT and AST are useful clinical markers but are imperfect indicators of disease severity. Patients with advanced fibrosis may have only modestly elevated or even normal aminotransferases. Cytokeratin-18 fragments provide a closer connection with hepatocyte apoptosis and have been investigated as non-invasive biomarkers of steatohepatitis, yet CK-18 also lacks sufficient accuracy to replace comprehensive staging [3].

The reduction in CK-18 reported after δ -tocotrienol is therefore intriguing because it may indicate less hepatocyte cell death. It should not, however, be equated with histological reversal of MASH or fibrosis. This distinction becomes particularly important when tocotrienol results are compared with contemporary drug trials.

Fibrosis is the decisive translational gap. Current tocotrienol studies have not convincingly demonstrated ≥ 1 -stage histological fibrosis improvement without worsening of steatohepatitis, nor have they demonstrated reduced progression to cirrhosis or liver-

related clinical events. Given the strong relationship between fibrosis stage and mortality, absence of such evidence substantially limits therapeutic claims [14].

Discussion and Critical Analysis

From antioxidant supplement to multi-node metabolic modulator

The central synthesis of this review is that tocotrienols should no longer be conceptualized solely as antioxidants. The clinical pattern—improvements in HOMA-IR, inflammatory biomarkers, adipokines, oxidative-stress markers and hepatocyte-injury measures—is more consistent with a multi-node biological effect. Mechanistically, tocotrienols may alter redox signaling, NF- κ B activity, lipid metabolism, insulin sensitivity and inflammatory pathways simultaneously [18,19,33].

This does not necessarily mean that tocotrienols directly target every pathway. Improvements may propagate through the metabolic network. For example, greater insulin sensitivity could reduce adipose lipolysis, thereby decreasing hepatic fatty-acid delivery, which could reduce mitochondrial overload and ROS formation and subsequently lower inflammatory signaling. Conversely, primary reduction of inflammatory signaling might improve insulin action. The causal direction cannot be established from current biomarker trials.

The strongest conceptual contribution of tocotrienol research may therefore lie in its compatibility with the modern view of MASLD as a systems-metabolism disorder. A compound does not need to be a powerful agonist or inhibitor of a single hepatic target if modest effects across several upstream metabolic pathways produce a clinically meaningful combined effect. The problem is that this hypothesis has not yet been tested against sufficiently rigorous liver endpoints.

Biomarker improvement is not equivalent to disease modification

A central methodological weakness of the existing tocotrienol literature is reliance on surrogate markers. FLI incorporates body mass index, waist circumference, triglycerides and γ -glutamyl transferase and can therefore improve because of changes in systemic metabolism without necessarily documenting a proportional change in liver histology. HOMA-IR provides information about insulin resistance but is not liver specific. ALT and AST can improve without fibrosis regression. Contemporary biomarker reviews similarly emphasize that individual serum-based scores are most informative within staged diagnostic pathways rather than as stand-alone proxies for histological disease activity or fibrosis [47].

The evidentiary standard in MASLD has changed rapidly. Resmetirom was evaluated in a large phase III trial using histological endpoints including resolution of steatohepatitis and fibrosis improvement [47,48]. Tirzepatide and survodutide have also been tested in biopsy-defined MASH with fibrosis using histological outcomes [49,50]. Semaglutide's phase III program

similarly evaluates MASH resolution without fibrosis worsening and fibrosis improvement without worsening of MASH [51].

Earlier therapeutic development provides the same lesson. Semaglutide phase II demonstrated substantial NASH-resolution activity but did not initially show significant fibrosis improvement, illustrating why steatohepatitis resolution and fibrosis response must be treated as separate therapeutic outcomes [52]. Lanifibranor and the FGF21 analogue pegozafermin have likewise been assessed with histological endpoints rather than reliance on serum enzymes alone [53,54].

Figure 3 provides an evidence-translation ladder showing where the tocotrienol literature currently sits relative to modern MASLD therapeutic development. Its purpose is to distinguish substantial mechanistic and biomarker evidence from the higher-order imaging, histological, fibrosis and clinical-outcome evidence that remains insufficient or absent.

This hierarchy explains why the conclusion of a critical review should differ from the conclusion of a promotional nutraceutical review. The existing studies support biological activity; they do not yet support classification of tocotrienols as proven MASH-modifying or antifibrotic therapy.

Importance of source-specific interpretation

A review explicitly involving palm oil must resist the temptation to use the strongest annatto data without qualification. Palm-derived TRF is biologically distinctive because it contains a mixture of

isoforms and frequently α -tocopherol. Differences in absorption, metabolism and target-tissue exposure could theoretically amplify, attenuate or qualitatively change effects relative to purified δ -tocotrienol.

The palm-specific evidence base nevertheless provides an important foundation. Palm TRF is biologically active across multiple clinical contexts, and a contemporary systematic review of randomized trials concluded that palm TRF has evidence of effects on lipid peroxidation, inflammation and selected health outcomes, while emphasizing uncertainty regarding optimal dose, formulation and intervention duration [36].

The pediatric NAFLD trial adds direct palm-TRF-related clinical relevance. Although limited by small sample size and pediatric specificity, the study incorporated FibroScan and LiverFAST alongside biochemical outcomes, pointing toward a more modern approach to liver phenotyping than some earlier adult studies [38].

A logical next step is therefore not another small uncontrolled or biomarker-only trial. The appropriate study would directly evaluate a chemically standardized palm TRF against placebo in a well-characterized MASLD population using quantitative imaging, validated fibrosis markers and predefined mechanistic endpoints.

Tocotrienols within contemporary MASLD management

Lifestyle modification remains foundational. Dietary quality, energy balance, weight reduction and physical activity can improve liver fat and cardiometabolic risk, although sustained adherence

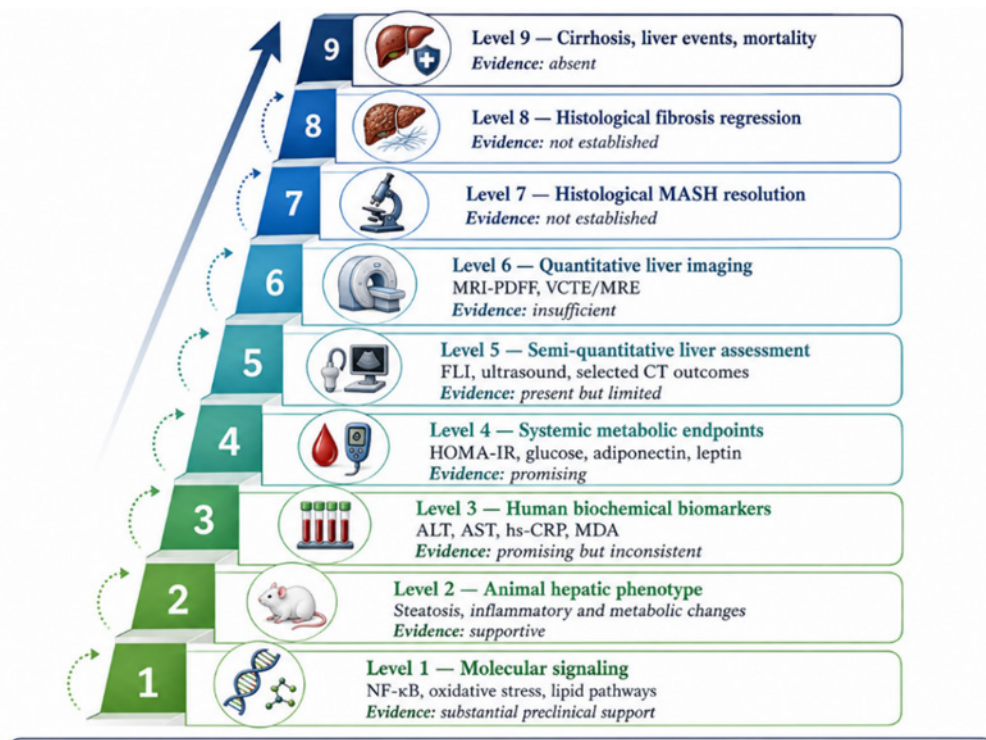


Figure 3: Evidence translation ladder for tocotrienols in MASLD.

Source: Author's synthesis.

remains challenging. Mediterranean-style dietary patterns, lower consumption of ultra-processed foods and structured exercise are widely supported as components of management [55-58]. Evidence regarding long-term hard clinical outcomes from specific lifestyle interventions remains less complete, but lifestyle modification remains standard care because of its broad metabolic benefits [59].

The therapeutic landscape increasingly includes agents originally developed for obesity and diabetes. GLP-1 receptor agonists reduce body weight, visceral adiposity and liver fat and have demonstrated increasingly strong evidence in MASH. Tirzepatide adds combined GIP/GLP-1 activity and has produced substantial MASH-resolution signals. SGLT2 inhibitors improve glycemic and cardiometabolic outcomes and may reduce liver fat and some non-invasive fibrosis-related measures, particularly in patients with T2DM, although direct histological evidence remains less robust than for several emerging MASH-directed drugs [60,61].

Tocotrienols should therefore not be positioned as alternatives to proven cardiometabolic therapy. Their most plausible future role is adjunctive. An adjunct could theoretically address residual oxidative, inflammatory or metabolic stress while patients continue evidence-based obesity, diabetes, lipid and liver-directed therapies. At present, however, no robust clinical evidence establishes synergy between tocotrienols and GLP-1 receptor agonists, SGLT2 inhibitors, resmetirom or other contemporary treatments. Such synergy is a research question, not a therapeutic claim.

Precision nutrition and responder heterogeneity

The heterogeneity of tocotrienol trials may reflect more than methodological inconsistency. Biological responsiveness may differ according to baseline insulin resistance, obesity phenotype, diabetes duration, liver-fat burden, fibrosis stage, diet and baseline oxidative status. For example, metabolic benefits might be most visible in patients with pronounced oxidative or inflammatory abnormalities, whereas participants with advanced fibrosis may require direct antifibrotic interventions in addition to metabolic modulation.

Pharmacokinetic heterogeneity may be equally important. Poor and saturable oral absorption means that administered dose does not necessarily predict systemic exposure. Future studies should measure plasma tocotrienol isoforms, allowing exposure-response analysis rather than merely dose-response analysis. This strategy could identify apparent “nonresponders” who simply failed to achieve biologically relevant exposure [35].

Metabolic and molecular phenotyping could provide another layer. Lipidomics may identify changes in ceramides, diacylglycerols and oxidized lipid species; metabolomics may reveal changes in β -oxidation or amino-acid pathways; and transcriptomic or microRNA analyses could identify regulatory signatures. Such approaches would allow the field to determine whether tocotrienol responders share a recognizable metabolic phenotype.

Priorities for next-generation clinical trial design

Future clinical development should begin with chemically standardized palm TRF. Investigators should specify the concentrations of α -, β -, γ - and δ -tocotrienol and α -tocopherol, the carrier system, the timing of ingestion and plasma exposure. Different formulations should not be considered interchangeable merely because they contain an equivalent total milligram dose.

Participants should have well-characterized MASLD. A pragmatic early-phase trial could enroll adults with MRI-confirmed steatosis and elevated cardiometabolic risk, followed by stratification according to diabetes status and fibrosis risk. A more advanced MASH trial would ideally require evidence of at-risk disease, such as biopsy-confirmed MASH with F2–F3 fibrosis or a rigorously validated non-invasive equivalent.

MRI-PDFF could provide a quantitative liver-fat endpoint, while VCTE or magnetic resonance elastography would assess liver stiffness. Serum fibrosis panels and FIB-4 could complement imaging, but should not substitute for higher-quality fibrosis assessment when antifibrotic claims are contemplated. Histology remains important in advanced development when regulators or scientific objectives require demonstration of MASH resolution or fibrosis improvement. A recent meta-analysis comparing FIB-4, vibration-controlled transient elastography, shear-wave elastography and magnetic resonance elastography found modality- and threshold-dependent differences in diagnostic performance, supporting multimodal rather than single-test assessment in clinical-trial design [62].

Figure 4 proposes a next-generation trial architecture intended to close the gap between tocotrienol biochemistry and modern MASLD therapeutics. The framework integrates intervention standardization, metabolic and liver phenotyping, mechanistic measurements and clinically relevant longitudinal endpoints within contemporary standard-of-care management.

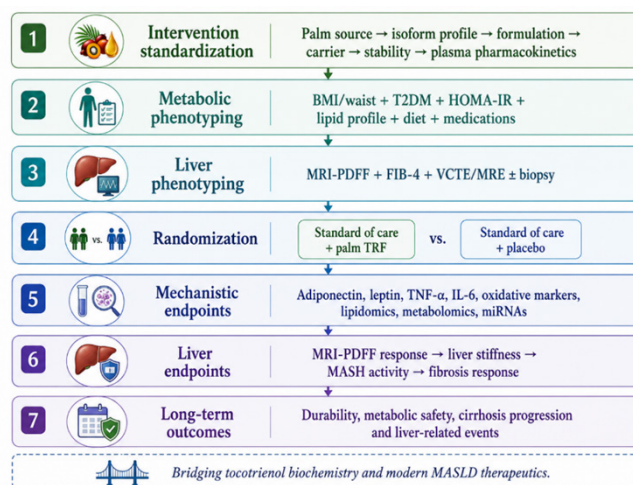


Figure 4: Proposed next-generation palm-TRF trial architecture.

Source: Author’s synthesis.

The design should also preserve contemporary standard-of-care therapy. Ethical and clinically meaningful evaluation no longer requires studying nutraceuticals in isolation. The relevant translational question is whether tocotrienols deliver incremental benefit on top of lifestyle and appropriate metabolic treatment.

Broader Implications for Palm-Derived Nutraceutical Development

The tocotrienol–MASLD literature has implications beyond a single disease. Palm oil is frequently discussed primarily in terms of its fatty-acid composition, whereas its minor components include tocotrienols and other potentially bioactive compounds. Developing standardized high-value palm-derived nutraceuticals could diversify downstream utilization of palm biomass and move part of the value proposition from bulk lipid supply toward evidence-based functional ingredients.

Such development nevertheless requires an explicit separation between agricultural origin and clinical efficacy. The fact that a compound is naturally derived from palm oil does not establish health benefit. Likewise, favorable evidence for a purified tocotrienol isoform from annatto cannot be used as proof that palm oil consumption itself treats MASLD. Whole palm oil, palm TRF and purified tocotrienol are nutritionally and pharmacologically distinct exposures.

This distinction is particularly important for scientific credibility. Overstated claims could undermine otherwise legitimate research into palm-derived bioactives. A stronger translational strategy is to characterize palm TRF as a defined pharmaconutritional ingredient, determine its isoform-specific pharmacokinetics, evaluate therapeutic concentrations and test it under controlled conditions.

From an innovation perspective, improved delivery technology may be necessary. Tocotrienol bioavailability remains a major bottleneck. Nanoformulations and lipid-based delivery systems may improve absorption, but they also alter the intervention and require separate safety, stability and manufacturing evaluation [34,35]. Consequently, future palm-tocotrienol innovation should integrate nutritional science, pharmaceutical formulation, metabolomics and hepatology rather than remain confined to conventional supplement research.

Conclusion

MASLD is an increasingly prevalent metabolic liver disease arising from the interaction of obesity, insulin resistance, altered lipid metabolism, adipose dysfunction, mitochondrial and ER stress, inflammation and progressive fibrogenesis. Its modern conceptualization requires therapeutic research to move beyond the narrow objective of lowering hepatic fat or aminotransferases toward prevention of MASH progression, fibrosis, cirrhosis and liver-related events.

Tocotrienols are biologically plausible candidates for adjunctive

metabolic intervention because their actions appear to extend beyond conventional antioxidant chemistry. Current experimental and clinical evidence suggests possible effects on insulin resistance, hepatic steatosis, oxidative stress, inflammatory signaling, adiponectin, leptin and hepatocyte injury. The adult δ -tocotrienol trials are particularly important because simultaneous improvements across several of these domains support a multi-node metabolic hypothesis rather than a purely antioxidant mechanism.

The evidence nevertheless has significant limitations. The best-known adult fatty liver trials evaluated annatto-derived δ/γ -tocotrienol rather than palm-derived TRF. Direct palm-specific human evidence remains comparatively limited, and clinical studies are generally too small or insufficiently equipped with modern liver endpoints to establish MASH resolution or fibrosis regression. Improvements in FLI, ALT, AST, HOMA-IR, hs-CRP, malondialdehyde, adipokines or CK-18 should therefore be interpreted as evidence of biological activity rather than definitive disease modification.

Future research should focus on standardized palm-derived formulations with clearly quantified tocotrienol isoforms and demonstrated systemic exposure. Trials should integrate contemporary MASLD phenotyping using MRI-PDFF, VCTE or MRE, validated fibrosis biomarkers and, where justified, histological endpoints. Longer follow-up is needed to assess durability and fibrosis-related outcomes. Multi-omics approaches could identify biological responders and clarify whether tocotrienols directly modify hepatic lipid toxicity or produce secondary benefits through improved systemic metabolism.

Most importantly, tocotrienols should be investigated as potential adjuncts to lifestyle intervention and contemporary cardiometabolic therapy rather than substitutes for established treatment. The scientific opportunity is substantial precisely because mechanistic plausibility currently exceeds clinical-outcome evidence. Closing that gap through rigorous source-specific trials would determine whether palm-derived tocotrienols can progress from promising nutraceutical bioactives to credible components of precision metabolic care for MASLD.

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