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Palm-Derived Tocotrienols in Metabolic Dysfunction-Associated Steatotic Liver Disease: From Lipotoxicity and Insulin Resistance to Adipokine Remodeling, Inflammation, and Clinical Translation

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a highly prevalent metabolic liver disorder encompassing steatosis, metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma. Its pathogenesis involves systemic insulin resistance, dysfunctional adipose tissue, increased hepatic fatty-acid delivery, de novo lipogenesis, lipotoxicity, mitochondrial and endoplasmic-reticulum stress, oxidative injury, adipokine imbalance, inflammation, hepatocyte death, and fibrogenesis. Palm-derived tocotrienols, members of the vitamin-E family, are of growing interest because their unsaturated side chains and isoform-specific biological properties may confer antioxidant, anti-inflammatory, lipid-regulatory, insulin-sensitizing, and cytoprotective effects that address several MASLD mechanisms concurrently. This critical qualitative review integrates recent mechanistic, translational, and clinical evidence concerning tocotrienols in MASLD. Randomized studies suggest that δ-tocotrienol can improve fatty liver indices, insulin resistance, hepatic enzymes, oxidative-stress markers and inflammatory biomarkers, while potentially altering leptin, adiponectin, cytokeratin-18 and disease-associated circulating microRNAs. Nevertheless, current evidence does not establish regression of clinically important fibrosis or prevention of liver-related outcomes. Small samples, limited phenotypic diversity, inconsistent formulations, and dependence on surrogate endpoints remain major limitations. Future trials should incorporate MRI-PDFF, elastography or magnetic resonance elastography, validated fibrosis biomarkers, histology where appropriate, metabolic phenotyping, pharmacokinetic characterization, and longer follow-up. Palm tocotrienols should therefore be regarded as promising adjunctive candidates rather than established MASLD therapeutics.

Keywords: Metabolic dysfunction-associated steatotic liver disease; MASLD; MASH; Tocotrienols; Palm oil; δ-tocotrienol; Insulin resistance; ipotoxicity; Adipokines; Hepatic fibrosis

JEL Classification: I10; I12; I18; Q18; O33

1. INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease has become one of the dominant chronic liver disorders of the twenty-first century. The disease encompasses a continuum beginning with excessive hepatic fat accumulation and extending, in susceptible individuals, through metabolic dysfunction-associated steatohepatitis, progressive fibrosis, cirrhosis and hepatocellular carcinoma. Contemporary epidemiological analyses indicate that steatotic liver disease affects approximately one third of the global adult population, with prevalence increasing alongside obesity, type 2 diabetes mellitus, sedentary behavior and broader changes in food environments[1-5]. The burden is particularly pronounced among people with obesity and type 2 diabetes, in whom both MASH and clinically important fibrosis are substantially more prevalent.

The terminology itself has changed. A multisociety Delphi process introduced the overarching category of steatotic liver disease and replaced non-alcoholic fatty liver disease with MASLD when steatosis coexists with defined cardiometabolic risk factors. The inflammatory progressive phenotype previously termed NASH is correspondingly designated MASH. The change shifts the disease from an exclusion-based concept toward a positive metabolic diagnosis and better reflects its systemic pathophysiology[6,7]. Contemporary European guidelines now use MASLD terminology throughout clinical risk assessment and therapeutic decision making[8].

The clinical significance of MASLD extends well beyond the liver. Cardiovascular disease remains a major cause of morbidity and death, and cardiovascular risk increases as liver disease and particularly fibrosis become more advanced[9]. Type 2 diabetes, chronic kidney disease, sarcopenia and several malignancies also occur disproportionately in affected populations. Importantly, fibrosis stage is one of the most powerful predictors of liver-related and overall mortality, making fibrosis prevention or regression a more clinically consequential treatment goal than isolated reductions in hepatic triglyceride content[10].

MASLD is therefore not adequately characterized as passive fat storage. Systemic insulin resistance promotes adipose-tissue lipolysis and increases delivery of non-esterified fatty acids to hepatocytes. Hyperinsulinemia and dietary carbohydrate simultaneously stimulate hepatic de novo lipogenesis. Once hepatic lipid-handling capacity becomes overwhelmed, biologically active lipid species generate cellular stress, mitochondrial dysfunction, reactive oxygen species, endoplasmic-reticulum stress and inflammatory signals. Hepatocyte injury activates resident and recruited immune cells, while sustained injury stimulates hepatic stellate cells and extracellular-matrix deposition[11,12].

Dysfunctional adipose tissue is particularly important in connecting obesity with progressive liver disease. Adipose insulin resistance increases fatty-acid release, whereas chronic inflammation alters the endocrine profile of adipose tissue. Hyperleptinemia and lower adiponectin concentrations can amplify hepatic insulin resistance, inflammatory signaling and fibrogenic responses[13-15]. This metabolic–adipose–hepatic network explains why therapeutics directed at a single downstream pathway may produce incomplete effects.

Treatment of MASLD has changed rapidly. Weight reduction through calorie restriction, dietary improvement and physical activity remains foundational, and contemporary endocrine guidance emphasizes integrated management of obesity, diabetes and cardiovascular risk[16]. Incretin-based therapies can produce substantial weight loss and reductions in visceral and ectopic liver fat[17]. Semaglutide first demonstrated substantial MASH-resolution activity in phase 2 research[18] and subsequently improved both MASH resolution and fibrosis in the phase 3 ESSENCE trial[19]. Tirzepatide and survodutide have further strengthened the therapeutic rationale for targeting systemic metabolic dysfunction[20,21]. Resmetirom, a liver-directed thyroid hormone receptor-beta agonist, has demonstrated histological efficacy in phase 3 evaluation, establishing a new benchmark for disease-specific pharmacotherapy[22]. Lanifibranor and fibroblast-growth-factor-21 analogues further illustrate the value of simultaneously addressing metabolic, inflammatory and fibrotic biology[23,24].

Despite these developments, a large proportion of patients remain without disease-specific treatment, access to new drugs is uneven, and residual cardiometabolic risk persists. This creates continuing interest in dietary bioactives capable of influencing several interconnected pathways. Among these candidates, tocotrienols are scientifically notable members of the vitamin-E family. Unlike tocopherols, tocotrienols contain an unsaturated isoprenoid side chain. Palm oil is one of the richest natural sources of α-, β-, γ- and δ-tocotrienols, often provided experimentally as a tocotrienol-rich fraction.

Contemporary clinical research has moved tocotrienols beyond generic antioxidant claims. A placebo-controlled trial in patients with NAFLD reported that δ-tocotrienol reduced fatty liver index, HOMA-IR, high-sensitivity C-reactive protein, malondialdehyde and aminotransferases while improving ultrasonographic steatosis[25]. A subsequent 48-week trial comparing δ-tocotrienol with α-tocopherol found improvement in steatosis and insulin-resistance markers in both groups but greater changes with δ-tocotrienol in body weight, TNF-α, IL-6, leptin, adiponectin and cytokeratin-18[26]. Related analyses found modification of circulating microRNAs associated with metabolic dysfunction, inflammation and apoptosis[27].

These findings are provocative but insufficient to establish disease modification. Modern MASH drug development increasingly uses MRI-proton density fat fraction (MRI-PDFF), vibration-controlled transient elastography, magnetic resonance elastography, Enhanced Liver Fibrosis scores, collagen-turnover biomarkers and histological endpoints. A reduction in fatty liver index or aminotransferases cannot automatically be interpreted as prevention of fibrotic progression. MRI-PDFF reduction is associated with histological response, but even MRI-PDFF alone does not substitute for direct assessment of fibrosis[28,29].

Accordingly, the purpose of this critical qualitative review is to integrate contemporary understanding of MASLD pathogenesis with evidence concerning palm-derived tocotrienols; critically examine whether their metabolic, antioxidant, inflammatory and adipokine effects are sufficient to justify clinical development; distinguish improvements in intermediate biomarkers from clinically meaningful disease modification; and propose a modern research agenda for

evaluating tocotrienols in the era of biomarker-driven MASH therapeutics. This translational framing places particular emphasis on quantitative liver-fat assessment, fibrosis risk, treatment durability and clinically meaningful outcomes rather than relying on isolated biochemical improvement.

2. CONCEPTUAL FOUNDATIONS: MASLD AS A METABOLIC–INFLAMMATORY–FIBROTIC DISEASE

2.1 Insulin resistance and hepatic substrate overload

Insulin resistance is central to most—but not all—MASLD phenotypes. In healthy adipose tissue, insulin restrains lipolysis after feeding. When adipocytes become insulin resistant, this suppression weakens and an increased flux of non-esterified fatty acids reaches the liver. Hyperinsulinemia meanwhile stimulates hepatic lipogenesis through transcriptional networks involving sterol regulatory element-binding protein-1c and related pathways. Dietary carbohydrate and fructose can further increase de novo lipogenesis. The liver therefore receives lipid from circulating fatty acids, dietary remnants and endogenous lipid synthesis simultaneously[12,30].

This mechanism also explains why hepatic steatosis can coexist with systemic hyperinsulinemia even when hepatic glucose production remains incompletely suppressed. The metabolic phenotype is better understood as selective hepatic insulin resistance than total failure of insulin signaling. Lipogenic signaling can remain active while regulation of glucose output deteriorates, thereby perpetuating both steatosis and hyperglycemia.

The metabolic burden is especially pronounced among individuals with type 2 diabetes. An updated meta-analysis involving more than 1.8 million people with type 2 diabetes estimated NAFLD prevalence at approximately 65%, with clinically significant fibrosis present in a substantial subset[31]. Prospective screening studies likewise demonstrate appreciable burdens of advanced fibrosis, cirrhosis and hepatocellular carcinoma in this high-risk population[32]. This makes diabetes an especially important target population for future tocotrienol trials because insulin resistance, oxidative injury and adipokine abnormalities are highly expressed in this group.

2.2 Steatosis is not synonymous with lipotoxicity

Hepatic triglyceride accumulation is a defining feature of steatotic liver disease, but triglyceride droplets are not inherently the most injurious lipid species. Esterification of fatty acids into triglycerides can partly buffer hepatocytes against free-fatty-acid toxicity. Disease progression is more closely associated with the production or accumulation of harmful lipid intermediates, including saturated free fatty acids, ceramides, diacylglycerols and oxidized lipids. These species interfere with insulin signaling, membrane function, mitochondrial integrity and cellular survival pathways[11].

The distinction has therapeutic implications. An intervention that modestly reduces liver fat may not necessarily reduce toxic lipid signaling, whereas an intervention capable of redirecting lipid metabolism, improving β-oxidation or reducing oxidative modification might theoretically influence liver injury even without dramatic changes in total

triglyceride content. Tocotrienol studies therefore should not be evaluated exclusively by conventional ultrasonographic steatosis scores.

2.3 Mitochondrial dysfunction and oxidative stress

Mitochondria initially adapt to lipid oversupply by increasing fatty-acid oxidation. With sustained overload, however, respiratory inefficiency, electron leakage and reactive oxygen species can increase. Oxidative stress damages mitochondrial DNA, proteins and membrane lipids and can amplify hepatocyte injury. Lipid peroxidation produces reactive aldehydes, including malondialdehyde, that propagate cellular damage beyond the initial oxidative event[33].

Oxidative stress also interacts with other intracellular organelles. Persistent lipid overload can activate the unfolded-protein response in the endoplasmic reticulum, disrupt autophagic processing and increase apoptotic susceptibility. Endoplasmic-reticulum stress and altered autophagy are now recognized as integral rather than peripheral components of progressive metabolic liver injury[34]. Oxidative stress therefore represents a plausible target for vitamin-E-related molecules, although antioxidant effects alone should not be assumed to produce antifibrotic outcomes[35].

2.4 Adipose tissue, adiponectin and leptin

The adipose organ functions as both a lipid reservoir and endocrine tissue. In metabolically healthy adipose tissue, energy storage limits exposure of ectopic organs to free fatty acids. Adipocyte hypertrophy, local hypoxia, macrophage infiltration and inflammatory signaling progressively impair this buffering function. Increased fatty-acid release then coincides with altered secretion of adipokines[13,30].

Adiponectin generally promotes fatty-acid oxidation, improves insulin sensitivity and suppresses inflammatory signaling. Lower adiponectin is frequently associated with insulin resistance and more adverse metabolic phenotypes. Leptin, conversely, becomes chronically elevated in obesity as leptin resistance develops. Although leptin is physiologically involved in appetite regulation, sustained hyperleptinemia may facilitate inflammatory and fibrogenic responses in the liver. The ratio and interaction between leptin and adiponectin may therefore provide more information about adipose dysfunction than either marker alone[15].

These pathways are directly relevant to tocotrienol research. The 48-week comparison between δ-tocotrienol and α-tocopherol reported a greater reduction in leptin and greater increase in adiponectin with δ-tocotrienol, accompanying changes in inflammatory and apoptotic biomarkers[26]. This raises the possibility that tocotrienols affect inter-organ metabolic signaling rather than acting solely as direct radical scavengers.

2.5 Inflammatory amplification and fibrosis

Lipotoxic hepatocytes release danger-associated signals and extracellular vesicles that activate Kupffer cells and recruit circulating immune cells. NF-κB-dependent pathways increase transcription of inflammatory mediators such as TNF-α and IL-6. Inflammasome activation, oxidative injury and gut-derived endotoxin can amplify these responses. Persistent

inflammatory signaling increases hepatocyte injury and facilitates progression from uncomplicated steatosis toward MASH[11].

Fibrogenesis represents a wound-healing response that becomes maladaptive when injury persists. Hepatic stellate cells transition toward collagen-producing myofibroblast-like cells under the influence of transforming growth factor-β, platelet-derived growth factors, inflammatory mediators and cellular injury signals. Progressive deposition and remodeling of extracellular matrix eventually distort hepatic architecture.[11,12]

The importance of fibrosis is supported clinically. Meta-analytic evidence demonstrates a graded increase in all-cause and liver-related mortality with advancing fibrosis stage, with particularly sharp increases in stage F3 and cirrhosis[10]. Any claim that tocotrienols "treat MASLD" should therefore ultimately be judged against their ability to prevent or reverse fibrotic progression, not simply improve aminotransferases.

2.6 Gut–liver interactions

Gut microbial dysbiosis may contribute to MASLD through altered intestinal permeability, microbial products, bile-acid metabolism, endogenous ethanol production and immune regulation. Reduced microbial diversity and shifts in pro- versus anti-inflammatory taxa have been documented across MASLD populations, although interindividual heterogeneity remains substantial[36-38]. Randomized clinical studies of microbiota-directed interventions are emerging, but heterogeneity in interventions and endpoints currently limits firm therapeutic conclusions[39].

The gut–liver axis is relevant to nutraceutical interventions because orally delivered bioactives interact with intestinal absorption, dietary lipid composition and microbiota before reaching systemic circulation. Whether tocotrienols modify MASLD partly through microbiome-mediated mechanisms remains inadequately studied and constitutes an important research gap.[38,39]

3. TOCOTRIENOL BIOLOGY AND PHARMACOLOGICAL RATIONALE

Tocopherols and tocotrienols share a chromanol ring but differ in their side chains: tocopherols possess a saturated phytyl chain whereas tocotrienols contain three double bonds in an unsaturated isoprenoid chain. Four major isoforms-alpha, beta, gamma and delta-exist according to methyl substitution of the chromanol ring, and these structural differences influence membrane behavior, metabolism, biological activity and tissue distribution[40,41].

Palm tocotrienol-rich fraction generally contains multiple tocotrienol isoforms together with varying amounts of tocopherols. Consequently, the terms "tocotrienol," "tocotrienol-rich fraction," "palm tocotrienol" and "δ-tocotrienol" cannot be treated as pharmacologically interchangeable. This issue has contributed to heterogeneity across the clinical literature. A 2025 review of randomized trials involving palm tocotrienol-rich fractions found promising effects in several health domains but emphasized uncertainty regarding optimal dose, formulation and duration [41]

3.1 Antioxidant effects

The chromanol ring permits vitamin-E molecules to interrupt lipid-peroxidation chain reactions. The unsaturated side chain of tocotrienols can alter membrane distribution and potentially facilitate interaction with lipid domains, while experimental and clinical literature supports broader antioxidant and anti-inflammatory activity across tocotrienol isoforms[40,42]. In MASLD, where oxidative damage interacts with mitochondrial dysfunction, endoplasmic-reticulum stress and inflammatory signaling, such activity is biologically relevant but remains dependent on adequate tissue exposure.

Clinical evidence nevertheless requires caution. A reduction in circulating malondialdehyde provides evidence of altered oxidative status but does not prove that mitochondrial function has normalized or fibrosis has regressed. The 2020 δ-tocotrienol trial reported significant reductions in malondialdehyde relative to placebo, and the 48-week trial demonstrated reduction in oxidative stress in both δ-tocotrienol and α-tocopherol groups[25,26].

3.2 Anti-inflammatory signaling

Tocotrienols can modify inflammatory signaling beyond direct antioxidant activity. Experimental studies implicate suppression of NF-κB activation and downstream inflammatory mediators. A systematic synthesis of NF-κB-related research concluded that tocotrienol-mediated regulation extends across several proteins and signaling pathways, though much of the evidence remains preclinical[43].

Human evidence across clinical conditions similarly suggests anti-inflammatory potential but is heterogeneous. A meta-analysis of randomized trials reported effects on selected inflammatory and oxidative-stress markers, while emphasizing variability across tocotrienol formulations and populations[42]. MASLD is therefore a particularly relevant setting because inflammation is integrated with metabolic stress rather than operating as an isolated process.

3.3 Lipid regulation and the mevalonate pathway

Tocotrienols have been linked to regulation of HMG-CoA reductase and the mevalonate pathway, providing a mechanistic rationale for effects on cholesterol metabolism[40]. This is potentially important in MASLD because dyslipidemia, hepatic lipid handling and cardiovascular risk coexist. However, meta-analytic clinical evidence regarding conventional lipid outcomes is inconsistent; pooled randomized trials have not shown uniform reductions in LDL cholesterol or total cholesterol[44]. The discrepancy illustrates the difference between mechanistic potential and reproducible clinical effect.

This inconsistency is relevant when interpreting hepatic findings. If tocotrienols affect intrahepatic lipid flux, changes may not be completely captured by fasting plasma lipid concentrations. Conversely, putative HMG-CoA reductase

effects should not be invoked as established mechanisms unless exposure and clinical metabolic changes are demonstrated.

3.4 Bioavailability

Poor and variable oral bioavailability is one of the most important translational barriers. Tocotrienols have lower affinity than α-tocopherol for α-tocopherol transfer protein, and absorption varies according to isoform, formulation, dose and fed state. A recent pharmacokinetic review highlighted substantial differences between palm and annatto preparations and among individual isoforms[45].

The problem is not trivial. If plasma and hepatic exposure varies substantially across formulations, clinical trials nominally investigating "tocotrienols" may actually test different pharmacological interventions. Future MASLD trials should therefore report full formulation composition, pharmacokinetic exposure, concomitant α-tocopherol content and timing relative to food.

4. METHOD

This article employs a critical qualitative literature-review methodology rather than a systematic literature review. The objective is interpretive synthesis: to integrate mechanistic biology, translational research, clinical trials, contemporary MASLD diagnostic concepts and treatment developments into a coherent assessment of palm-derived tocotrienols.

Literature was prioritized from 2020 through 2026, with particular emphasis on peer-reviewed articles indexed in major biomedical databases and published in established journals. Earlier foundational evidence was considered conceptually where unavoidable, but the principal evidentiary base was deliberately contemporary. Search concepts included combinations of "MASLD," "MASH," "NAFLD," "NASH," "tocotrienol," "palm tocotrienol," "tocotrienol-rich fraction," "delta-tocotrienol," "insulin resistance," "lipotoxicity," "oxidative stress," "adiponectin," "leptin," "inflammation," "NF-kappa B," "mitochondria," "fibrosis," "MRI-PDFF," "elastography," and "vitamin E."

Evidence was organized into interconnected themes rather than pooled statistically. These themes comprised metabolic substrate overload, insulin resistance, lipid metabolism, oxidative and organellar stress, adipokine signaling, inflammation, hepatocyte injury, fibrogenesis, pharmacokinetics and clinical outcomes. Priority was given to randomized trials where available, while mechanistic and review literature was used to interpret biological plausibility.
The approach differs fundamentally from an SLR. No PRISMA flow diagram, formal exhaustive eligibility protocol, risk-of-bias scoring system or meta-analytic pooling was applied. Instead, evidence was triangulated across molecular, animal, biomarker and clinical levels. Contradictions and evidentiary gaps were treated as analytical findings rather than resolved through statistical averaging.

5. RESULTS: THEMATIC SYNTHESIS

5.1 Tocotrienols and insulin resistance

The strongest clinical signal supporting tocotrienols in metabolic liver disease is their association with improvements in insulin-resistance markers. In the 24-week placebo-controlled trial, δ-tocotrienol significantly reduced HOMA-IR relative to placebo together with fatty liver index and inflammatory and oxidative markers[25]. In the later 48-week comparison, both δ-tocotrienol and α-tocopherol improved HOMA-IR, without a statistically important between-group difference in that endpoint[26].

This pattern has two interpretations. First, vitamin-E-related antioxidant effects may improve aspects of metabolic stress regardless of isoform. Second, δ-tocotrienol may possess additional effects expressed more strongly in adipokine, inflammatory and apoptosis markers than in HOMA-IR itself. Consequently, insulin resistance should be treated as one component of a broader response phenotype rather than the sole mediator.

Whether changes in HOMA-IR represent direct hepatic insulin sensitization is uncertain because the index largely reflects fasting glucose and insulin dynamics. Future trials should consider more precise metabolic phenotyping, including oral glucose-tolerance-derived indices, continuous glucose monitoring or, in mechanistic substudies, clamp methodology.

5.2 Hepatic steatosis and hepatocellular injury

Pervez et al.[25] reported significant improvement in fatty liver index and ultrasonographic steatosis with δ-tocotrienol relative to placebo, accompanied by reductions in ALT and AST. The subsequent active-comparator study reported improvement in fatty liver index and liver-to-spleen attenuation ratio with both δ-tocotrienol and α-tocopherol[26].

These results support biological activity but illustrate the central limitation of the evidence. Fatty liver index incorporates body mass index, waist circumference, triglycerides and gamma-glutamyl transferase; consequently, it is partly a metabolic risk score rather than a direct quantitative measurement of intrahepatic triglyceride. Ultrasound is useful clinically but has limited sensitivity for small longitudinal changes. CT attenuation offers quantitative information but is less sensitive than MRI-PDFF for hepatic-fat measurement.

MRI-PDFF has become a preferred quantitative endpoint in early-phase MASH research. A relative reduction of approximately 30% is associated with a greater probability of histological response, although it does not guarantee fibrosis improvement [28]. Tocotrienol efficacy would therefore be more convincingly established if replicated using MRI-PDFF.

5.3 Oxidative stress and inflammation

The 2020 placebo-controlled study demonstrated lower high-sensitivity CRP and malondialdehyde with δ-tocotrienol, consistent with the proposed anti-inflammatory and antioxidant mechanisms [25]. The 48-week trial extended this evidence by reporting greater reductions in TNF-α and IL-6 in the δ-tocotrienol group than with α-tocopherol[26].

This pattern is mechanistically coherent with experimental evidence of NF-κB modulation. Nevertheless, cytokine concentrations fluctuate and are influenced by adiposity, infection, exercise and many other factors. Clinical interpretation therefore becomes stronger when cytokine changes coincide with independently measured liver outcomes. The key unanswered question is whether reduction of circulating inflammation is sufficient to alter hepatic stellate-cell activation and fibrogenesis. Current trials did not directly establish such an effect.

5.4 Adipokine remodeling

The reduction in leptin and increase in adiponectin reported during δ-tocotrienol treatment provide an especially interesting mechanistic signal. Adiponectin has insulin-sensitizing and anti-inflammatory properties, whereas chronic hyperleptinemia is associated with obesity, leptin resistance and potentially profibrogenic signaling[15]. A favorable shift could therefore reduce both metabolic substrate delivery and inflammatory amplification.

However, adipokines should not be interpreted as therapeutic endpoints in isolation. Weight reduction itself can lower leptin and raise adiponectin. Because the δ-tocotrienol group also showed greater weight reduction, mediation analyses are needed to determine whether adipokine changes were independent effects of tocotrienol or consequences of altered adiposity.

Future studies should integrate visceral-adipose measurement, body composition, adipokines and liver-fat quantification. Such designs could establish whether tocotrienols meaningfully improve adipose–liver crosstalk.

5.5 Apoptosis and circulating microRNAs

Cytokeratin-18 fragments have historically been investigated as biomarkers of hepatocyte apoptosis and MASH activity. The observed reduction in cytokeratin-18 during δ-tocotrienol therapy is therefore compatible with reduced hepatocellular injury[26].

Circulating microRNA findings provide additional mechanistic depth. Expression of miR-122, miR-21, miR-103a-2, miR-421, miR-375 and miR-34a changed after δ-tocotrienol and α-tocopherol treatment, with stronger effects of δ-tocotrienol on selected microRNAs associated with inflammation and apoptosis[27]. Because microRNAs can participate in metabolic regulation rather than merely reflect injury, these results suggest a potential regulatory mechanism.

Yet microRNA studies remain exploratory. Analytical platforms, normalization techniques and population variability can influence results. Their principal value at present is hypothesis generation and mechanistic stratification rather than routine clinical decision making.

5.6 Evidence for antifibrotic activity remains insufficient

The strongest unmet evidentiary requirement is demonstration that tocotrienols affect fibrosis. Contemporary prognosis studies show that fibrosis stage is closely linked to mortality, and MASLD guidelines increasingly center management on identification of patients with F2–F4 disease[10,46].

Tocotrienol trials have not yet demonstrated histological regression of fibrosis or consistent improvements in validated fibrosis-specific non-invasive endpoints. This is the most important boundary on interpretation. Biochemical improvement, reduced inflammation, and lower steatosis could theoretically reduce future fibrosis risk, but this remains an inference.

Figure 1 illustrates why tocotrienols are conceptually attractive in MASLD: unlike an intervention aimed solely at hepatic triglyceride accumulation, tocotrienols may influence several interconnected "hits" spanning metabolic stress, redox imbalance, inflammation, adipokine dysfunction and hepatocyte injury. The diagram also makes clear that these candidate actions occur upstream of the fibrosis outcomes that ultimately determine clinical prognosis.

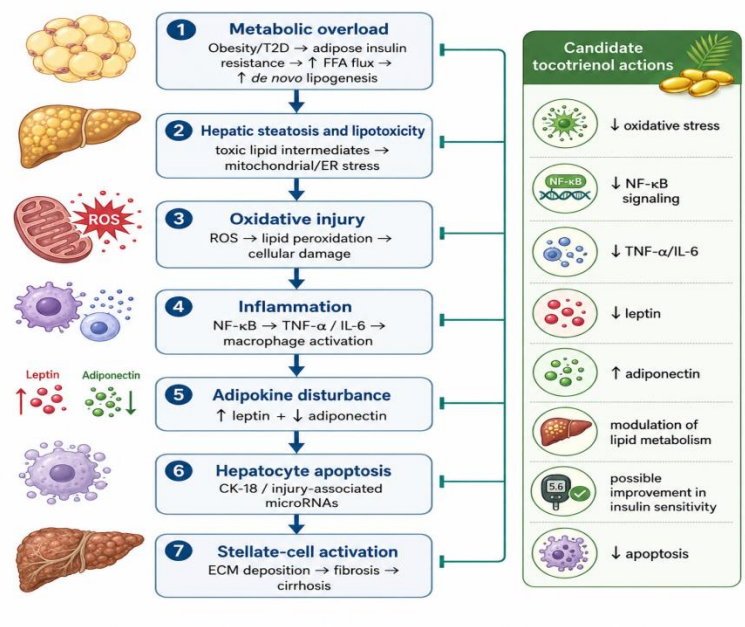

Figure 1: Proposed mechanistic position of palm tocotrienols within the MASLD continuum

The framework should not be interpreted as evidence that every proposed pathway has been validated clinically. The strongest human observations involve insulin-resistance indices, oxidative and inflammatory markers, adipokines, hepatic enzymes, steatosis surrogates and selected microRNAs. The final step from these intermediate effects to fibrosis regression remains unproven.

6. DISCUSSION

6.1 Tocotrienols fit the multiple-hit model unusually well

The principal theoretical advantage of tocotrienols is mechanistic breadth. MASLD emerges from an interconnected network rather than a single biochemical lesion. An intervention that simultaneously modifies lipid handling, oxidative stress, inflammatory signaling and adipose–liver communication could therefore be more biologically coherent than a narrowly targeted antioxidant.

This does not mean that multitarget activity automatically produces clinically meaningful benefit. Many natural compounds show impressive effects in cellular models at concentrations that cannot be achieved safely in human tissues. Pharmacokinetic exposure therefore determines whether a theoretical multi-pathway intervention actually operates as such in patients.

This distinction explains why recent pharmacokinetic research is important. Palm tocotrienol-rich fraction and isolated δ-tocotrienol cannot be assumed to produce equivalent exposure, and α-tocopherol may modify tocotrienol disposition. Formulation science should be integrated into hepatology trials rather than treated as a manufacturing detail [45].

6.2 Tocotrienol versus α-tocopherol is more informative than tocotrienol versus placebo

The placebo-controlled trial establishes that δ-tocotrienol can alter metabolic and liver-associated markers beyond nonspecific trial participation. The active-comparator trial provides a different form of evidence: it asks whether δ-tocotrienol provides advantages over the conventional form of vitamin E already extensively studied in fatty liver disease.

Both δ-tocotrienol and α-tocopherol improved steatosis, HOMA-IR and oxidative stress in the 48-week trial. δ-Tocotrienol produced greater changes in inflammatory mediators, adipokines, body weight and cytokeratin-18[26]. This suggests that the distinction between the molecules may become most apparent in secondary metabolic and inflammatory pathways rather than basic antioxidant activity.

Meta-analyses of conventional vitamin E have reported improvements in aminotransferases, steatosis and selected histological outcomes, although substantial heterogeneity exists and long-term benefit remains uncertain[47,48]. Thus, a

future tocotrienol development program should use α-tocopherol as a scientifically meaningful active comparator in selected studies, while placebo-controlled studies remain necessary for definitive efficacy assessment.

6.3 The adipokine findings deserve greater attention

One of the most innovative aspects of existing tocotrienol evidence is not the reduction in liver enzymes but the shift in adiponectin and leptin. MASLD is increasingly understood as an inter-organ disorder. Dysfunctional adipose tissue supplies fatty acids, cytokines and endocrine signals that determine hepatic substrate burden.

A therapy that partially restores adipose endocrine function could therefore exert upstream effects before hepatic inflammation and fibrosis become established. This possibility is particularly attractive for people with early MASLD, obesity and insulin resistance. It may be less effective in established F3 fibrosis, where persistent extracellular-matrix remodeling becomes partly autonomous from the initial metabolic drivers.

Clinical development should consequently distinguish prevention, early disease modification and antifibrotic treatment. A nutraceutical intervention that is useful in metabolically active early MASLD should not be judged against the same expectations as a pharmaceutical agent intended to reverse advanced MASH fibrosis.

6.4 Tocotrienols should be tested against contemporary endpoints

The most important methodological change required is replacement of older surrogate measures with modern quantitative endpoints. Contemporary MASLD drug-development frameworks increasingly integrate imaging, serum fibrosis biomarkers and histological outcomes to strengthen biological interpretation and regulatory relevance[49,50].

MRI-PDFF provides precise liver-fat quantification and is useful for early-phase treatment-response assessment [28]. Vibration-controlled transient elastography and magnetic resonance elastography provide non-invasive information on liver stiffness. Blood-based scores including FIB-4 and ELF can support fibrosis-risk stratification, while emerging markers such as PRO-C3 may provide information on active collagen formation[49,51,52].

A credible phase 2 tocotrienol trial should therefore enroll participants with well-characterized MASLD, preferably with MRI-confirmed steatosis and evidence of metabolically active disease. Randomization should be stratified by diabetes, fibrosis risk and perhaps PNPLA3 genotype. A primary endpoint might use relative change in MRI-PDFF at 24–36 weeks, with prespecified secondary endpoints including liver stiffness, ELF or PRO-C3, ALT, AST, HOMA-IR, HbA1c, inflammatory markers, adiponectin, leptin and body composition.[50]

Histological evaluation should be reserved for populations in which the risk-benefit balance justifies biopsy, particularly patients with suspected F2–F3 MASH. If a tocotrienol formulation progresses to advanced development, demonstration

of MASH resolution without fibrosis worsening and/or ≥1-stage fibrosis improvement without worsening of MASH would permit comparison with contemporary drug trials.[50]

As illustrated in Figure 2, the primary limitation of the literature is not an absence of biological signals but an incomplete evidence chain between those signals and validated disease-modifying outcomes. Closing this bridge requires trials that connect biomarker changes to quantitative imaging, fibrosis measures and, where appropriate, histological response.

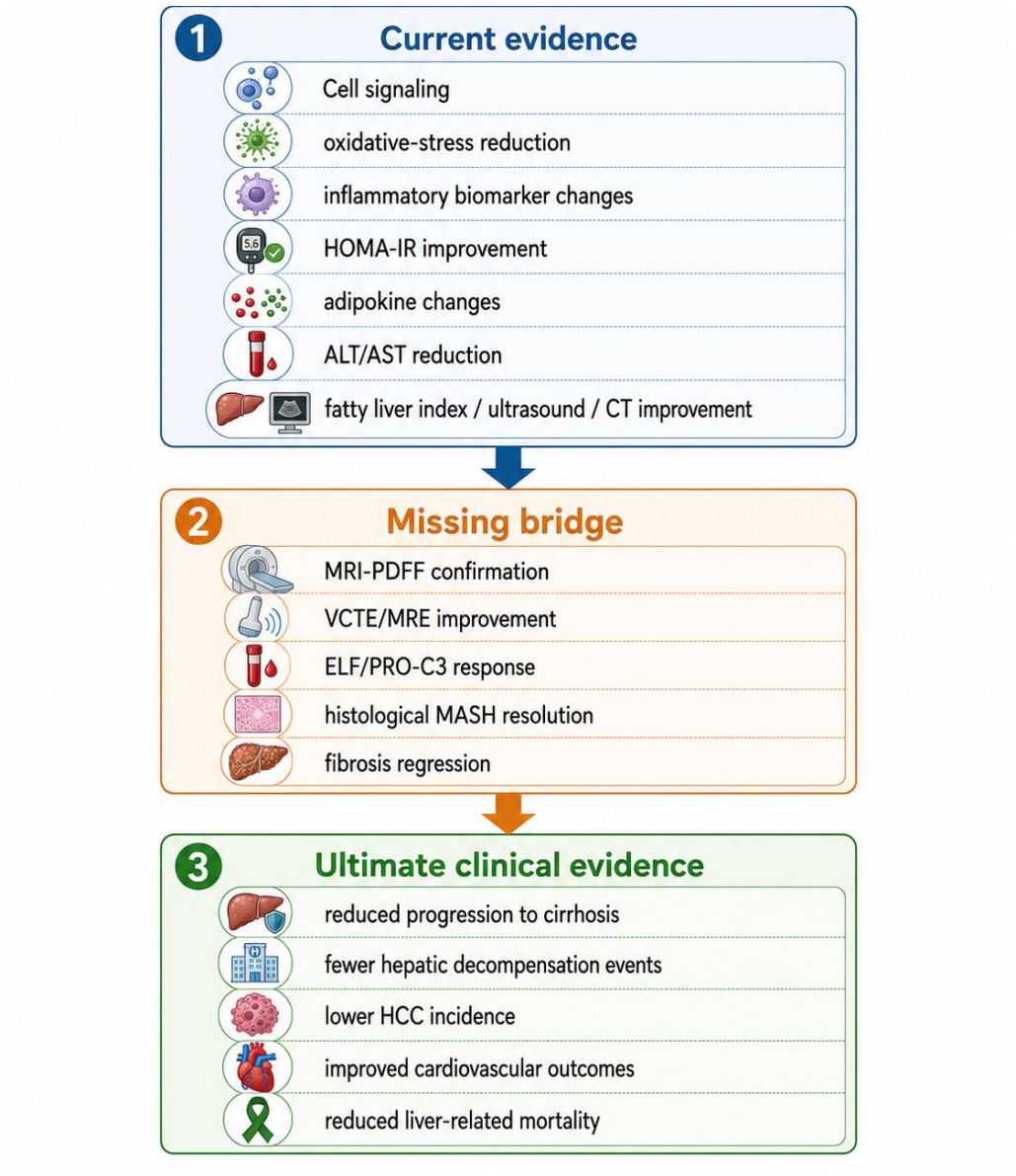

Figure 2: Current tocotrienol evidence versus the evidentiary standard required for MASLD disease modification

Current tocotrienol studies reach approximately the middle of the translational pathway. They demonstrate changes in hepatic and metabolic surrogates but do not establish the downstream outcomes that now define efficacy in MASH drug development. Future trials should be explicitly designed to close this gap.

6.5 Contemporary MASH pharmacology raises the evidentiary bar

Tocotrienols now enter a therapeutic landscape very different from that of a decade ago. Semaglutide progressed from phase 2 evidence of MASH resolution[18] to phase 3 evidence demonstrating improvement in both MASH resolution and fibrosis among patients with F2-F3 disease[19]. Tirzepatide also produced substantial MASH-resolution responses and signals of fibrosis improvement in the SYNERGY-NASH trial[20], while lanifibranor demonstrated effects on MASH resolution and fibrosis-related endpoints through pan-PPAR agonism[23].

FGF21 analogues have produced further evidence that combined effects on metabolism and fibrosis are achievable. Early pharmacokinetic and pharmacodynamic studies of pegozafermin were followed by randomized evidence of improvements in fibrosis and MASH-resolution endpoints in biopsy-proven F2-F3 disease[24,53]. Efruxifermin has likewise advanced as a candidate FGF21-based strategy, although definitive long-term clinical-outcome data remain limited[54]. Survodutide, combining glucagon and GLP-1 receptor agonism, has similarly demonstrated substantial histological MASH activity[21].

Most importantly, the phase 3 MAESTRO-NASH trial demonstrated that resmetirom could achieve both MASH resolution without fibrosis worsening and fibrosis improvement without worsening of disease activity [22]. Regulatory and clinical expectations have therefore moved beyond changes in aminotransferases.

Tocotrienols need not outperform these pharmaceuticals to remain clinically relevant. They may ultimately serve a different population: individuals with early disease, people unable to access or tolerate pharmacotherapy, or patients receiving combination treatment. However, such positioning should be evidence-driven and must avoid implying equivalence with approved pharmacotherapy.

6.6 Combination therapy may be more realistic than monotherapy

Because MASLD is heterogeneous, future management is likely to use combinations addressing metabolic drivers and hepatic injury simultaneously. In a patient with obesity and type 2 diabetes, for example, an incretin-based therapy may provide profound weight loss and metabolic improvement. A second agent could theoretically target residual inflammation, oxidative injury or fibrosis.

Tocotrienols may therefore be better conceptualized as adjunctive rather than stand-alone therapy. Their safety profile in published trials is encouraging, but longer exposure and interactions with contemporary medications require evaluation.

Combination studies should not merely add tocotrienols indiscriminately to standard therapy. Factorial or carefully stratified designs could examine whether tocotrienols provide incremental improvements in MRI-PDFF, inflammation or fibrosis markers after accounting for weight loss. This would directly test their clinical value.

6.7 Cardiovascular implications should be incorporated

MASLD management cannot be separated from cardiovascular prevention. Meta-analytic evidence indicates increased cardiovascular-event risk, especially in more advanced liver disease [9]. Tocotrienols have been investigated for effects on lipid metabolism, inflammation and oxidative stress, suggesting possible cardiovascular co-benefits, but randomized evidence for conventional lipid lowering has been inconsistent[44].

Future MASLD trials should therefore include lipoproteins, apoB, blood pressure, glycemia and cardiovascular risk markers rather than evaluating the liver in isolation. This would be especially valuable in long-term pragmatic trials.

6.8 Safety and supplement quality require explicit evaluation

The classification of a compound as a nutraceutical does not remove the need for pharmaceutical-quality safety assessment. Botanical and dietary-supplement products can differ in purity, dose accuracy and formulation. AASLD guidance concerning supplement-associated liver injury illustrates why apparently natural products require careful characterization and pharmacovigilance[55].

Palm-derived tocotrienol trials should specify manufacturing standards, isoform composition, α-tocopherol content, contaminants and stability. Future studies should record concomitant supplement use and systematically monitor adverse events.

7. TOWARD PRECISION TOCOTRIENOL THERAPY

MASLD is highly heterogeneous. Genetic factors including PNPLA3, TM6SF2, MBOAT7 and HSD17B13 can alter susceptibility and progression independently of conventional metabolic risk. Contemporary precision-medicine frameworks increasingly propose combining genetic, metabolic, imaging, biomarker and microbiome information rather than treating every patient with hepatic steatosis identically[52,56,57].

This principle could transform tocotrienol research. The most responsive phenotype may consist of patients with pronounced oxidative stress, hyperinsulinemia and adipose dysfunction but limited established fibrosis. Alternatively, certain genetic or metabolic subgroups may respond differently because the primary drivers of steatosis differ.

Baseline nutrient status may also matter. Patients who are already replete in vitamin E may respond differently from those with lower antioxidant status. Trials rarely incorporate such stratification.

Precision research could therefore investigate whether treatment response is modified by diabetes status, visceral adiposity, PNPLA3 genotype, baseline α-tocopherol, inflammatory phenotype or fibrosis stage. Such analysis may explain why nutraceutical trials often produce heterogeneous average effects.[57]

Figure 3 proposes a staged clinical-development framework that would prevent premature movement from biochemical findings to therapeutic claims. It also highlights the value of patient enrichment and formulation standardization before expensive confirmatory trials are undertaken.

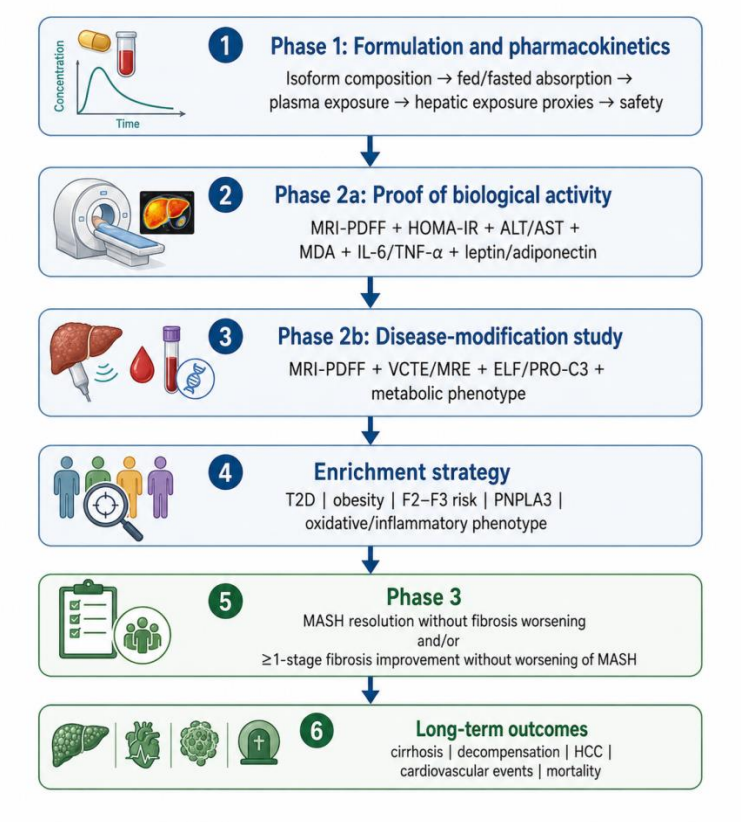

Figure 3: Proposed biomarker-stratified clinical-development pathway for palm tocotrienols

The framework begins with pharmacokinetic standardization because formulation heterogeneity can obscure true efficacy. It then progresses through quantitative liver-fat assessment and fibrosis biomarkers toward histological and long-term clinical outcomes. Biomarker enrichment could reduce heterogeneity and identify populations in whom multi-pathway tocotrienol activity is biologically most plausible.

8. RESEARCH GAPS AND FUTURE DIRECTIONS

First, the tocotrienol evidence base requires independent replication. Several important MASLD studies originate from a limited number of research groups and relatively homogeneous populations. Multicenter trials across Asia, Europe and other regions would improve external validity.

Second, formulation standardization is essential. Investigators should report the exact amount of α-, β-, γ- and δ-tocotrienol, tocopherol content, excipients, delivery technology and pharmacokinetic behavior. “Vitamin E” and “tocotrienol-rich fraction” should not be used as pharmacologically interchangeable categories.

Third, advanced imaging should replace low-resolution steatosis assessment in efficacy trials. MRI-PDFF should become the preferred quantitative liver-fat endpoint, complemented by elastography.

Fourth, fibrosis must become an explicit target. The absence of fibrosis-specific evidence is the largest barrier to interpreting tocotrienols as disease-modifying therapy.

Fifth, studies should separate direct pharmacological effects from weight-loss-mediated effects. Body composition and visceral adiposity should be measured and mediation analysis considered where adipokines change concurrently with body weight.

Sixth, microRNA findings should be validated using standardized assays and linked prospectively to imaging and histological outcomes. Such validation is necessary before circulating microRNAs can be considered response biomarkers rather than exploratory correlates of treatment exposure[27].

Seventh, pharmacological interaction studies are needed. Tocotrienols will increasingly be studied in patients receiving GLP-1 receptor agonists, dual incretin therapies, SGLT2 inhibitors, statins and resmetirom. Safety and incremental benefit need direct evaluation.

Eighth, long-term cardiovascular endpoints should not be overlooked. For many patients with MASLD, preventing myocardial infarction or stroke may be as important as preventing cirrhosis.

Finally, health-economic and implementation research could become relevant if efficacy is demonstrated. Palm tocotrienols are linked to an established agricultural supply chain, which could create potential cost or accessibility advantages in producing regions. Such advantages, however, should only be considered after robust clinical efficacy and quality-standardization evidence exists.

9. CONCLUSION

Palm-derived tocotrienols are biologically plausible multi-target candidates for adjunctive management of MASLD because they intersect with several pathways central to disease progression, including oxidative injury, inflammatory signaling, insulin resistance, dysregulated lipid metabolism, adipokine imbalance and hepatocyte apoptosis. Modern randomized trials provide encouraging evidence that δ-tocotrienol can improve biochemical, metabolic, inflammatory and steatosis-related indicators, and comparative data suggest potentially broader effects than conventional α-tocopherol in selected pathways.

The evidence nevertheless remains insufficient to conclude that tocotrienols modify the natural history of MASLD. Existing clinical studies have not established histological MASH resolution, clinically meaningful fibrosis regression or reductions in liver-related events. This distinction is increasingly important because modern pharmacological trials have raised the standard of evidence required for claims of disease modification.

The next generation of research should therefore move beyond generic antioxidant supplementation. Palm tocotrienols should be evaluated as precisely characterized pharmacological-nutritional interventions, with standardized formulations, pharmacokinetic data, quantitative imaging, validated fibrosis markers, metabolic phenotyping and—where justified—histological confirmation. Biomarker-stratified trials in patients with type 2 diabetes, obesity and early fibrotic disease may provide the strongest opportunity to determine whether the biological versatility of tocotrienols can be translated into clinically meaningful hepatoprotection.

If those studies demonstrate incremental benefit and long-term safety, palm-derived tocotrienols could eventually occupy a rational adjunctive position within integrated metabolic-hepatology care. Until then, they should be viewed as promising translational candidates rather than established treatments.

REFERENCES

1. Riazi, K. et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterology & Hepatology 7, 851–861 (2022). https://doi.org/10.1016/S2468-1253(22)00165-0

2. Younossi, Z. M. et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 77, 1335-1347 (2023). https://doi.org/10.1097/HEP.0000000000000004
3. Liu, J. et al. Estimating global prevalence, incidence, and outcomes of non-alcoholic fatty liver disease from 2000 to 2021. Chinese Medical Journal 135, 1682–1691 (2022). https://doi.org/10.1097/CM9.0000000000002277
4. Quek, J., Chan, K.E., Wong, Z.Y., Tan, C. et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterology & Hepatology 8, 20–30 (2023). https://doi.org/10.1016/S2468-1253(22)00317-X
5. Ye, Q., Zou, B., Yeo, Y.H., Li, J., Huang, D.Q. et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterology & Hepatology 5, 739–752 (2020). https://doi.org/10.1016/S2468-1253(20)30077-7
6. Rinella, M.E., Lazarus, J.V., Ratziu, V., Francque, S.M., Sanyal, A.J. et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Journal of Hepatology 79, 1542–1556 (2023). https://doi.org/10.1016/j.jhep.2023.06.003
7. Kanwal, F., Neuschwander-Tetri, B.A., Loomba, R. & Rinella, M.E. Metabolic dysfunction-associated steatotic liver disease: update and impact of new nomenclature on the AASLD practice guidance. Hepatology 79, 1212–1219 (2024). https://doi.org/10.1097/HEP.0000000000000670
8. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) & European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). Journal of Hepatology 81, 492-542 (2024). https://doi.org/10.1016/j.jhep.2024.04.031
9. Mantovani, A. et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. Lancet Gastroenterology & Hepatology 6, 903–913 (2021). https://doi.org/10.1016/S2468-1253(21)00308-3
10. Ng, C.H. et al. Mortality outcomes by fibrosis stage in nonalcoholic fatty liver disease: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology 21, 931–939.e5 (2023). https://doi.org/10.1016/j.cgh.2022.04.014
11. Parthasarathy, G., Revelo, X. & Malhi, H. Pathogenesis of nonalcoholic steatohepatitis: an overview. Hepatology Communications 4, 478-492 (2020). https://doi.org/10.1002/hep4.1479
12. Bansal, S.K. & Bansal, M.B. Pathogenesis of MASLD and MASH—role of insulin resistance and lipotoxicity. Alimentary Pharmacology & Therapeutics 59, S10–S22 (2024). https://doi.org/10.1111/apt.17930
13. Wang, X., Rao, H., Liu, F., Wei, L., Li, H. & Wu, C. Recent advances in adipose tissue dysfunction and its role in the pathogenesis of non-alcoholic fatty liver disease. Cells 10, 3300 (2021). https://doi.org/10.3390/cells10123300
14. Petrescu, M. et al. Chronic inflammation—a link between nonalcoholic fatty liver disease and dysfunctional adipose tissue. Medicina 58, 641 (2022). https://doi.org/10.3390/medicina58050641

15. Francisco, V. et al. Adipokines in non-alcoholic fatty liver disease: are we on the road toward new biomarkers and therapeutic targets? Biology 11, 1237 (2022). https://doi.org/10.3390/biology11081237
16. Cusi, K. et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings. Endocrine Practice 28, 528–562 (2022). https://doi.org/10.1016/j.eprac.2022.03.010
17. Liao, C., Liang, X., Zhang, X. & Li, Y. The effects of GLP-1 receptor agonists on visceral fat and liver ectopic fat in an adult population with or without diabetes and nonalcoholic fatty liver disease. PLoS ONE 18, e0289616 (2023). https://doi.org/10.1371/journal.pone.0289616
18. Newsome, P.N. et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. New England Journal of Medicine 384, 1113–1124 (2021). https://doi.org/10.1056/NEJMoa2028395
19. Sanyal, A. J. et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. New England Journal of Medicine 392, 2089-2099 (2025). https://doi.org/10.1056/NEJMoa2413258
20. Loomba, R. et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. New England Journal of Medicine 391, 299-310 (2024). https://doi.org/10.1056/NEJMoa2401943
21. Sanyal, A. J. et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. New England Journal of Medicine 391, 311-319 (2024). https://doi.org/10.1056/NEJMoa2401755
22. Harrison, S.A., Bedossa, P., Guy, C.D., Schattenberg, J.M., Loomba, R., Taub, R. et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. New England Journal of Medicine 390, 497–509 (2024). https://doi.org/10.1056/NEJMoa2309000
23. Francque, S.M., Bedossa, P., Ratziu, V., Anstee, Q.M., Bugianesi, E., Sanyal, A.J., Loomba, R. et al. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. New England Journal of Medicine 385, 1547–1558 (2021). https://doi.org/10.1056/NEJMoa2036205
24. Loomba, R., Sanyal, A.J., Kowdley, K.V., Bhatt, D.L., Alkhouri, N., Frias, J.P. et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. New England Journal of Medicine 389, 998–1008 (2023). https://doi.org/10.1056/NEJMoa2304286
25. 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. Complementary Therapies in Medicine 52, 102494 (2020). https://doi.org/10.1016/j.ctim.2020.102494
26. 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. Complementary Therapies in Medicine 70, 102866 (2022). https://doi.org/10.1016/j.ctim.2022.102866
27. Pervez, M. A. et al. Hepato-protective effects of delta-tocotrienol and alpha-tocopherol in patients with non-alcoholic fatty liver disease: regulation of circulating microRNA expression. International Journal of Molecular Sciences 24, 79 (2023). https://doi.org/10.3390/ijms24010079

28. Stine, J. G. et al. Change in MRI-PDFF and histologic response in patients with nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clinical Gastroenterology and Hepatology 19, 2274-2283.e5 (2021). https://doi.org/10.1016/j.cgh.2020.08.061
29. Li, G. et al. Non-invasive tests of non-alcoholic fatty liver disease. Chinese Medical Journal 135, 532-546 (2022). https://doi.org/10.1097/CM9.0000000000002027
30. Lee, W.-H. et al. The physiology of MASLD: molecular pathways between liver and adipose tissues. Clinical Science 139, 1015-1046 (2025). https://doi.org/10.1042/CS20257571
31. Cho, E. E. L. et al. Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: an updated systematic review and meta-analysis. Gut 72, 2138-2148 (2023). https://doi.org/10.1136/gutjnl-2023-330110
32. Ajmera, V. et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. Journal of Hepatology 78, 471-478 (2023). https://doi.org/10.1016/j.jhep.2022.11.010
33. Karkucinska-Wieckowska, A., Simoes, I.C.M., Kalinowski, P. et al. Mitochondria, oxidative stress and nonalcoholic fatty liver disease: a complex relationship. European Journal of Clinical Investigation 52, e13622 (2022). https://doi.org/10.1111/eci.13622
34. Flessa, C.-M. et al. Endoplasmic reticulum stress and autophagy in the pathogenesis of non-alcoholic fatty liver disease: current evidence and perspectives. Current Obesity Reports 10, 134–161 (2021). https://doi.org/10.1007/s13679-021-00431-3
35. Arroyave-Ospina, J.C., Wu, Z., Geng, Y. & Moshage, H. Role of oxidative stress in the pathogenesis of non-alcoholic fatty liver disease: implications for prevention and therapy. Antioxidants 10, 174 (2021). https://doi.org/10.3390/antiox10020174
36. Di Ciaula, A., Bonfrate, L. & Portincasa, P. The role of microbiota in nonalcoholic fatty liver disease. European Journal of Clinical Investigation 52, e13768 (2022). https://doi.org/10.1111/eci.13768
37. Gupta, H. et al. Gut microbiome in non-alcoholic fatty liver disease: from mechanisms to therapeutic role. Biomedicines 10, 550 (2022). https://doi.org/10.3390/biomedicines10030550
38. Zhang, Q. et al. Gut microbiota-mitochondrial inter-talk in non-alcoholic fatty liver disease. Frontiers in Nutrition 9, 934113 (2022). https://doi.org/10.3389/fnut.2022.934113
39. Han, T.-R. et al. Gut microbiota therapy for nonalcoholic fatty liver disease: evidence from randomized clinical trials. Frontiers in Microbiology 13, 1004911 (2023). https://doi.org/10.3389/fmicb.2022.1004911
40. Wong, S. K. et al. Potential role of tocotrienols on non-communicable diseases: a review of current evidence. Nutrients 12, 259 (2020). https://doi.org/10.3390/nu12010259
41. 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. Nutrition Reviews 83, 307–328 (2025). https://doi.org/10.1093/nutrit/nuae061

42. Khor, B.-H. et al. 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
43. Abdul Nasir, N.A., Sadikan, M.Z. & Agarwal, R. Modulation of NFκB signalling pathway by tocotrienol: A systematic review. Asia Pacific Journal of Clinical Nutrition 30, 537–555 (2021). https://doi.org/10.6133/apjcn.202109_30(3).0020
44. Zuo, S. et al. The effects of tocotrienol supplementation on lipid profile: a meta-analysis of randomized controlled trials. Complementary Therapies in Medicine 52, 102450 (2020). https://doi.org/10.1016/j.ctim.2020.102450
45. 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
46. Rinella, M.E. et al. 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
47. Vadarlis, A. et al. Systematic review with meta-analysis: the effect of vitamin E supplementation in adult patients with non-alcoholic fatty liver disease. Journal of Gastroenterology and Hepatology 36, 311-319 (2021). https://doi.org/10.1111/jgh.15221
48. Abdel-Maboud, M. et al. The efficacy of vitamin E in reducing non-alcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. Therapeutic Advances in Gastroenterology 13, 1756284820974917 (2020). https://doi.org/10.1177/1756284820974917
49. Wattacheril, J. J., Abdelmalek, M. F., Lim, J. K. & Sanyal, A. J. AGA clinical practice update on the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease: expert review. Gastroenterology 165, 1080-1088 (2023). https://doi.org/10.1053/j.gastro.2023.06.013
50. Diaz, L. A. et al. Clinical trial design, biomarkers and end points in metabolic and alcohol-related liver disease. Nature Reviews Gastroenterology & Hepatology 22, 866-884 (2025). https://doi.org/10.1038/s41575-025-01120-5
51. Bassal, T., Basheer, M., Boulos, M. & Assy, N. Nonalcoholic fatty liver disease—a concise review of noninvasive tests and biomarkers. Metabolites 12, 1073 (2022). https://doi.org/10.3390/metabo12111073
52. Thakral, N. et al. A precision medicine guided approach to the utilization of biomarkers in MASLD. Seminars in Liver Disease 44, 273–286 (2024). https://doi.org/10.1055/a-2364-2928
53. Loomba, R. et al. Safety, pharmacokinetics, and pharmacodynamics of pegozafermin in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 1b/2a multiple-ascending-dose study. Lancet Gastroenterology & Hepatology 8, 120-132 (2023). https://doi.org/10.1016/S2468-1253(22)00347-8
54. Puengel, T. & Tacke, F. Efruxifermin, an investigational treatment for fibrotic or cirrhotic nonalcoholic steatohepatitis. Expert Opinion on Investigational Drugs 32, 451–461 (2023). https://doi.org/10.1080/13543784.2023.2230115

55. Fontana, R.J. et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. Hepatology 77, 1036–1065 (2023). https://doi.org/10.1002/hep.32689
56. Zhang, X., Chang, K.-M., Yu, J. & Loomba, R. Unraveling mechanisms of genetic risks in metabolic dysfunction-associated steatotic liver diseases: a pathway to precision medicine. Annual Review of Pathology 20, 375–403 (2025). https://doi.org/10.1146/annurev-pathmechdis-111523-023430
57. Caddeo, A. & Romeo, S. Precision medicine and nucleotide-based therapeutics to treat steatotic liver disease. Clinical and Molecular Hepatology 31, S76–S93 (2025). https://doi.org/10.3350/cmh.2024.0438