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Tocotrienols in Cardiometabolic Medicine: Beyond Classical Vitamin E Activity - Insights from Recent Randomized Controlled Trials and Future Clinical Directions

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Abstract

Background: Tocotrienols, lesser-studied members of the vitamin E family, have gained attention because of their pleiotropic biological activities and potential role in cardiometabolic disease. Recent randomized controlled trials (RCTs) indicate benefits beyond α-tocopherol, including antioxidant, anti-inflammatory, and metabolic effects.

Aim: To summarize RCT evidence published between 2020 and 2025 on the effects of tocotrienol supplementation in metabolic syndrome, type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD), and diabetic complications.

Methods: This narrative review included RCTs evaluating tocotrienol supplementation in adults with metabolic disorders. Outcomes included oxidative stress, inflammation, glycaemic control, lipid metabolism, vascular and neural function, and liver injury. Owing to heterogeneity in formulations, doses, and study designs, findings were synthesized narratively.

Results: Tocotrienol supplementation improved biomarkers of oxidative stress, inflammation, and metabolic regulation. In metabolic syndrome, it modulated microRNAs associated with insulin resistance and inflammation. In T2D, δ-tocotrienol reduced HbA1c, fasting glucose, insulin resistance, and malondialdehyde while increasing antioxidant capacity. In NAFLD, δ-tocotrienol reduced inflammatory cytokines and liver injury markers more effectively than α-tocopherol. Tocotrienol-rich vitamin E also improved nerve conduction in diabetic neuropathy and supported renal function in diabetic kidney disease. Supplementation was well tolerated.

Conclusions: Tocotrienols show promising metabolic, anti-inflammatory, and organ-protective effects, particularly in T2D and NAFLD. However, heterogeneity, small sample sizes, and short intervention periods limit definitive conclusions. Larger, standardized, long-term RCTs are needed to confirm their role as adjunctive therapy in cardiometabolic disease.

Keywords: tocotrienols; vitamin E isoforms; cardiometabolic health; metabolic syndrome; type 2 diabetes; NAFLD; oxidative stress; inflammation; microRNAs

1. Introduction

As one of the four fat-soluble vitamins, vitamin E is an essential nutrient that plays a vital role in maintaining human health (Xiong et al., 2023). Vitamin E consists of eight natural isoforms — four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ). (Xiong et al., 2023). Both groups share a chromanol ring; tocopherols carry a saturated phytyl tail, whereas tocotrienols bear an unsaturated tail. The α, β, γ and δ forms are distinguished by how many

methyl substituents they have on the chromanol structure and where those substituents are located (Lee & Han, 2018).

The metabolism of vitamin E is centered in the liver, which not only regulates plasma **α-tocopherol** concentrations through hepatic α-tocopherol transfer protein but also functions as the primary site of vitamin E metabolism and excretion (Traber, 2007). Beyond these metabolic distinctions, emerging clinical evidence indicates that tocotrienols exert systemic effects not traditionally attributed to vitamin E, with randomized trials demonstrating improvements in psychological well-being, endogenous antioxidant defense, and genomic stability in older adults following tocotrienol-enriched supplementation (Sharif et al., 2025). In terms of dietary distribution, tocopherols are predominantly present in lipid-rich plant products and widely consumed vegetable oils, making them the most abundant vitamin E forms in typical diets. In contrast, tokotrienols occur in far more limited food sources, being concentrated mainly in specific cereals, rice bran oil, and palm oil. This uneven natural distribution contributes to substantial differences in habitual intake between the two vitamin E families and partly explains why tocopherols have historically received greater scientific attention (Lopresti et al., 2025).

The distinct biological properties and limited dietary availability of tocotrienols have attracted increasing scientific interest, particularly in the context of chronic non-communicable diseases. Cardiometabolic diseases, encompassing cardiovascular disease, type 2 diabetes mellitus, obesity, metabolic syndrome, and metabolic dysfunction-associated steatotic liver disease (MASLD), constitute one of the leading global health challenges of the twenty-first century. Together, these disorders account for a substantial proportion of worldwide morbidity and mortality, with their prevalence continuing to rise owing to population aging, urbanization, sedentary lifestyles, and unhealthy dietary habits (*Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019*, n.d.; Ong et al., 2023). Metabolic diseases are typically managed through a reductionist lens, where clinical care zeroes in on individual risk factors- such as obesity, hypertension, dyslipidemia, or elevated blood glucose—and treats each one with its own targeted pharmacological therapy (Gozhenko et al., 2025). Although considerable advances have been made in pharmacological management, the persistent global burden of cardiometabolic diseases underscores the need for effective preventive strategies that complement conventional therapies. In this context, increasing attention has been directed toward dietary bioactive compounds with pleiotropic biological activities, particularly those capable of attenuating oxidative stress, chronic low-grade inflammation, dyslipidemia, endothelial dysfunction, and insulin resistance, all of which are central mechanisms underlying cardiometabolic disease development and progression (*2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk | Circulation*, n.d.; Neeland et al., 2024). Against this background, tocotrienols have emerged as promising candidates owing to their broad spectrum of biological activities and their potential to modulate multiple pathways involved in cardiometabolic health.

The predominant and most biologically active vitamin E homologue in vivo, α-tocopherol has long dominated research, but recent randomized controlled trials have renewed interest in the cardiometabolic roles of other vitamin E forms, particularly tocotrienols (Yoshida et al., 2003). Early mechanistic work already suggested that tocotrienols possess biological activities distinct from tocopherols, including more efficient penetration into lipid bilayers, stronger antioxidant capacity under certain conditions, and regulatory effects on cholesterol biosynthesis via post-transcriptional suppression of HMG-CoA reductase. These foundational observations, highlighted in early experimental studies, positioned tocotrienols as bioactive molecules with potential relevance to vascular protection, inflammation modulation, and metabolic homeostasis—features that extend beyond the classical antioxidant paradigm traditionally associated with vitamin E (Sen et al., 2006)**.** Subsequent mechanistic studies further expanded this understanding, demonstrating that tocotrienols downregulate pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8), inhibit STAT3 and COX-2 signaling, and enhance endogenous antioxidant systems such as superoxide dismutase and glutathione peroxidase. These pleiotropic actions underscore their potential to modulate multiple pathways implicated in cardiometabolic disease progression (Aggarwal et al., 2010).

Building on these insights, contemporary clinical research increasingly explores tocotrienols as promising agents in cardiometabolic medicine, with recent RCTs (2020–2025) providing new evidence for their effects on lipid profiles, glycemic regulation, oxidative stress, and vascular function. In light of these developments, a comprehensive synthesis of the most recent clinical data is both timely and necessary. Although mechanistic and preclinical studies have long suggested that tocotrienols may exert cardioprotective, anti-inflammatory, and

metabolic benefits, only the latest wave of randomized controlled trials has begun to clarify their translational relevance in human populations. Therefore, the aim of this review is to critically summarize and contextualize the findings from RCTs conducted between 2020 and 2025, highlighting the emerging clinical significance of tocotrienols in cardiometabolic health and identifying key directions for future research and therapeutic application.

2. Research materials and methods

A narrative literature review was conducted to identify scientific publications evaluating the effects of tocotrienol supplementation on cardiometabolic health, including metabolic syndrome, type 2 diabetes, NAFLD, and diabetes-related complications. The search strategy focused on peer-reviewed articles indexed in PubMed and Scopus, covering the period from January 2020 to May 2025 to ensure inclusion of contemporary clinical evidence on tocotrienols and their biological mechanisms. The following keywords and their combinations were used: "tocotrienols," "vitamin E isoforms," "delta-tocotrienol," "tocotrienol-rich fraction," "cardiometabolic disease," "metabolic syndrome," "type 2 diabetes," "NAFLD," "oxidative stress," "inflammation," "microRNA,".

The inclusion criteria comprised randomized controlled trials, clinical intervention studies, systematic reviews, and narrative reviews published in English that investigated the metabolic, inflammatory, antioxidant, genomic, or organ-specific effects of tocotrienol supplementation in adults with cardiometabolic disorders or related risk factors. Both mechanistic clinical studies and trials assessing functional outcomes (e.g., nerve conduction, hepatic steatosis, renal function) were considered. Exclusion criteria included non-English publications, conference abstracts, opinion pieces, animal-only studies, and articles lacking full-text availability or sufficient methodological quality. Due to heterogeneity in tocotrienol formulations, dosages, and outcome measures, findings were synthesized narratively rather than through quantitative meta-analysis.

3. Research results

3.1. Tocotrienols Beyond Classical Vitamin E: Mechanisms Relevant to Cardiometabolic Disease

3.1.1. Oxidative stress and ROS

Oxidative stress represents a central pathogenic mechanism in diabetes mellitus, capable of initiating and amplifying tissue-damaging and pro-inflammatory pathways. In doing so, it perpetuates a self-reinforcing cycle that contributes to the development and progression of multi-organ complications characteristic of this disease (Sarakhan et al., 2025).

In line with this pathogenic role, oxidative stress is also a defining feature of type 2 diabetes mellitus, where chronic hyperinsulinemia and hyperglycemia drive excessive formation of reactive oxygen species (ROS), disrupting redox homeostasis and accelerating oxidative injury. Excessive ROS generation contributes to impaired insulin signaling, pancreatic β-cell dysfunction, and the progression of diabetic complications. Owing to their potent antioxidant properties, tocotrienols have attracted considerable interest as potential therapeutic agents capable of scavenging free radicals and attenuating oxidative stress. Nevertheless, a recent systematic review and meta-analysis concluded that current clinical evidence demonstrating direct reductions in oxidative stress biomarkers following tocotrienol supplementation remains limited, although supplementation with 400 mg/day may reduce circulating malondialdehyde (MDA), a widely accepted biomarker of lipid peroxidation and oxidative stress (Phang et al., 2023)

Additional clinical evidence supports the antioxidant effects of tocotrienols through enhancement of endogenous antioxidant defense systems. In a randomized controlled trial involving healthy older adults, six months of tocotrienol supplementation significantly increased the activity of antioxidant enzymes, including superoxide dismutase (SOD) and catalase, while reducing circulating malondialdehyde (MDA), indicating attenuation of lipid peroxidation and oxidative stress. The authors suggested that these effects may be mediated through activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, which regulates the expression of endogenous antioxidant enzymes (Sharif et al., 2025).

3.1.2. Experimental and clinical evidence

Preclinical studies have demonstrated that oral supplementation with a tocotrienol-rich mixture ameliorates neuropathic pain in diabetic rats, an effect attributed to reduced oxidative–nitrosative stress, decreased caspase-3 activity, and inhibition of pro-inflammatory cytokine secretion (Chuar et al., 2021).

Evidence from a randomized, placebo-controlled clinical trial by Fatima et al. demonstrated that 24-week supplementation with a δ-tocotrienol–resveratrol mixture (TRM) significantly improved oxidative stress, inflammatory, and insulin resistance biomarkers in individuals with metabolic syndrome. The observed clinical benefits were accompanied by favorable modulation of metabolic syndrome-associated microRNAs, specifically increased expression of miR-130b and miR-221 together with decreased expression of miR-122. These findings suggest that regulation of miRNA expression may represent an important molecular mechanism underlying the antioxidant and anti-inflammatory effects of TRM. Upregulation of miR-221 following TRM supplementation was significantly associated with improvements in fasting plasma glucose, inflammatory biomarkers (TNF-α and hs-CRP), adiponectin concentrations, and malondialdehyde (MDA), indicating a close relationship between miRNA modulation and attenuation of oxidative stress. (Fatima et al., 2023).

Similar findings were reported in another randomized controlled trial evaluating healthy older adults, in which tocotrienol supplementation enhanced antioxidant capacity by increasing SOD, catalase, and total antioxidant capacity (T-AOC), while simultaneously reducing MDA concentrations. These findings further support the role of tocotrienols in strengthening endogenous antioxidant defense mechanisms beyond direct free radical scavenging (Sharif et al., 2025).

3.1.3. Protection of cell membranes

The superior antioxidant activity of tocotrienols compared with tocopherols has also been attributed to their unique molecular structure. Unlike tocopherols, tocotrienols possess three unsaturated bonds within their hydrophobic side chain, which enhance their mobility and facilitate more uniform distribution throughout phospholipid bilayers. This improved membrane localization enables more efficient scavenging of peroxyl radicals and provides greater protection of membrane lipids against oxidative damage. Consequently, tocotrienols are considered more effective than α-tocopherol in preserving cellular membrane integrity under conditions of oxidative stress (Chuar et al., 2021; Phang et al., 2023).

3.1.4. Anti-inflammatory effects

Chronic low-grade inflammation is a hallmark of metabolic disorders, including type 2 diabetes mellitus and metabolic syndrome, contributing to insulin resistance, endothelial dysfunction, and the progression of diabetic complications. Tocotrienols have been increasingly recognized for their ability to modulate inflammatory signaling pathways and suppress the production of pro-inflammatory mediators. In preclinical studies, oral supplementation with a tocotrienol-rich mixture alleviated diabetic neuropathic pain by inhibiting the release of pro-inflammatory cytokines while simultaneously reducing oxidative–nitrosative stress and caspase-3 activity, suggesting that attenuation of inflammation is an important component of their therapeutic effects (Chuar et al., 2021).

Clinical evidence further supports these observations. In a randomized, placebo-controlled trial, Fatima et al. demonstrated that 24-week supplementation with a δ-tocotrienol–resveratrol mixture (TRM) significantly improved inflammatory biomarkers in patients with metabolic syndrome. The beneficial effects were accompanied by modulation of metabolic syndrome-associated microRNAs, including increased expression of miR-130b and miR-221 and decreased expression of miR-122, indicating that regulation of inflammatory pathways may occur through epigenetic mechanisms. Moreover, increased miR-221 expression was significantly associated with reductions in circulating TNF-α and high-sensitivity C-reactive protein (hs-CRP), supporting the anti-inflammatory potential of TRM (Fatima et al., 2023).

Although accumulating experimental and clinical findings indicate that tocotrienols possess anti-inflammatory properties, a recent systematic review and meta-analysis concluded that the available randomized controlled trials remain insufficient to definitively confirm their anti-inflammatory efficacy. Consequently, larger, well-designed clinical studies are required to establish the effects of tocotrienol supplementation on inflammatory biomarkers such as CRP, TNF-α, IL-6, and other mediators of chronic inflammation (Phang et al., 2023).

Additional evidence from a randomized controlled trial in healthy older adults demonstrated that tocotrienol supplementation significantly reduced circulating TNF-α concentrations, while downward trends were also observed for IL-6 and transforming growth factor-β (TGF-β). These findings suggest that the anti-inflammatory activity of tocotrienols extends beyond metabolic syndrome and may contribute to attenuation of chronic low-grade inflammation associated with ageing (Sharif et al., 2025).

3.1.5. Effects on genomic stability and cellular ageing

Besides improving oxidative stress biomarkers, tocotrienols may also exert protective effects at the genomic level. In a randomized controlled trial involving healthy older adults, six months of supplementation significantly increased telomerase activity while reducing oxidative DNA damage, as reflected by lower levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG). Since oxidative DNA damage is a major driver of telomere shortening and cellular senescence, these findings suggest that tocotrienols may contribute to maintaining genomic stability and delaying age-related cellular dysfunction. The observed genomic benefits are likely secondary to enhanced antioxidant defense and reduced oxidative stress, although further studies are required to elucidate the underlying molecular mechanisms (Sharif et al., 2025).

3.2. Tocotrienols in Metabolic Syndrome

Fatima et al. conducted a randomized, placebo-controlled clinical trial to investigate the effects of combined δ-tocotrienol and resveratrol (TRM) supplementation on the expression of microRNAs associated with metabolic syndrome (MetS). Participants received TRM supplementation for 24 weeks, after which the expression of miR-130b, miR-221, and miR-122 was evaluated alongside cardiometabolic, inflammatory, oxidative stress, and insulin resistance biomarkers. TRM supplementation significantly upregulated miR-130b and miR-221 while downregulating miR-122. These changes were associated with improvements in fasting plasma glucose, inflammatory biomarkers (TNF-α, IL-6, and hs-CRP), oxidative stress marker malondialdehyde (MDA), adiponectin levels, and indices of insulin resistance. The authors concluded that the beneficial metabolic effects of TRM may be mediated, at least in part, through modulation of MetS-related microRNAs, highlighting a potential epigenetic mechanism underlying the anti-inflammatory, antioxidant, and metabolic actions of tocotrienol supplementation (Fatima et al., 2023).

These findings are further supported by a recent double-blind, randomized controlled trial conducted by Norazman et al**.,** which evaluated the effects of tocotrienol-enriched oat supplementation in individuals with metabolic syndrome. Following the intervention, participants receiving tocotrienol-enriched oats exhibited significant improvements in several components of metabolic syndrome, including reductions in fasting blood glucose, blood pressure, triglyceride concentrations, body fat percentage, and waist circumference, together with increased HDL-cholesterol levels and skeletal muscle mass. Furthermore, the intervention was associated with improvements in health-related quality of life, suggesting that the metabolic benefits of tocotrienol supplementation may extend beyond cardiometabolic risk factors to overall patient well-being. These findings support the potential use of tocotrienol-enriched functional foods as an adjunctive strategy for the management of metabolic syndrome (Norazman et al., 2025).

3.3. Tocotrienols in Prediabetes and Type 2 Diabetes

In a randomized controlled trial conducted by Suleman et al., the authors examined the metabolic effects of delta-tocotrienol supplementation in adults with pre-diabetes. Individuals aged 18–60 years with impaired fasting glucose or elevated HbA1c were randomized to receive either 300 mg of delta-tocotrienol daily or a placebo for 12 weeks. The intervention group exhibited significantly greater reductions in fasting plasma glucose, glycosylated haemoglobin, circulating insulin, and HOMA-IR compared with placebo, indicating a meaningful improvement in glycaemic regulation. These results provide preliminary clinical evidence that delta-tocotrienol—an isoform of vitamin E with distinct antioxidant and anti-inflammatory properties—may support metabolic control in

individuals with pre-diabetes. Nevertheless, the authors highlight the need for larger, rigorously designed trials to confirm these findings and further elucidate the mechanistic advantages of tocotrienols relative to classical tocopherols (Suleman et al., 2022).

Delta-tocotrienol (δ-tocotrienol) has emerged as a promising bioactive compound with potential therapeutic relevance in type 2 diabetes mellitus (T2DM), particularly due to its antioxidative and anti-inflammatory properties. In the randomized controlled trial by Mahjabeen et al., δ-tocotrienol supplementation significantly improved several key metabolic and biochemical disturbances characteristic of T2DM. The authors report that tocotrienol intake led to a meaningful reduction in long-term glycemic markers, with HbA1c decreasing by *"-0.53 (-0.79, -0.28)"*, and fasting plasma glucose declining by *"-0.48 (-0.65, -0.30)"* compared with placebo. These changes indicate enhanced glycemic regulation and reduced insulin resistance, further supported by improvements in fasting insulin and HOMA-IR. Beyond glycemic control, δ-tocotrienol exerted a notable influence on chronic inflammation, a central driver of insulin resistance and diabetic complications. Supplementation resulted in significant reductions in high-sensitivity C-reactive protein, tumor necrosis factor-α, and interleukin-6, demonstrating attenuation of systemic inflammatory burden. The study highlights that tocotrienol decreased hs-CRP by *"-0.35 (-0.54, -0.16)"* and IL-6 by *"-2.30 (-2.91, -1.68)"*, reflecting a shift toward a less pro-inflammatory milieu. Oxidative stress, another major contributor to β-cell dysfunction and vascular damage in diabetes, was also favorably affected. δ-tocotrienol supplementation lowered malondialdehyde levels, a widely used marker of lipid peroxidation, with a reported mean difference of *"-0.34 (-0.45, -0.22)"*. This reduction suggests diminished oxidative damage and improved redox balance. Collectively, the findings demonstrate that δ-tocotrienol beneficially modulates glycemic control, inflammatory activity, and oxidative stress—three interconnected pathological pathways central to the progression of T2DM. By improving these parameters without adverse effects, δ-tocotrienol may serve as a valuable adjunctive dietary supplement aimed at mitigating long-term diabetic complications and supporting metabolic stability in patients treated with standard oral hypoglycemic agents (Mahjabeen et al., 2021).

Additional clinical evidence reinforces these observations. In a randomized trial examining tocotrienol-enriched canola oil, Vafa et al. reported that tocotrienol supplementation led to meaningful reductions in fasting blood glucose and oxidative stress, accompanied by an increase in total antioxidant capacity. Notably, these improvements occurred without changes in insulin levels or insulin resistance indices, suggesting that tocotrienols may exert their benefits primarily through enhanced redox balance and improved hepatic glucose handling rather than direct modulation of insulin secretion. The authors concluded that tocotrienols were well tolerated and may serve as a complementary strategy alongside standard hypoglycemic therapy to improve glycemic control and oxidative status in individuals with type 2 diabetes (Vafa et al., 2015).

The findings from this trials align with broader evidence synthesized in a recent systematic review and meta-analysis. Phang et al. demonstrated that tocotrienol-rich fraction (TRF) supplementation at doses of 250–400 mg significantly decreased HbA1c, reporting a pooled effect. The reduction was particularly notable in interventions lasting under six months and among individuals with a shorter duration of diabetes, reinforcing the glycemic benefits observed in δ-tocotrienol trials. However, the meta-analysis did not find consistent improvements in hs-CRP or blood pressure, suggesting that inflammatory responses may vary depending on tocotrienol composition, dosage, or patient characteristics (Phang et al., 2023).

Overall, current evidence suggests that tocotrienols—especially δ-tocotrienol—may serve as valuable adjuncts in the management of type 2 diabetes. Their multifaceted biological activity positions them as compounds capable of influencing several core pathways involved in the disease. By improving glycemic control, reducing inflammation, and mitigating oxidative stress, tocotrienols target mechanisms that collectively drive insulin resistance, β-cell dysfunction, and the progression of micro- and macrovascular complications. Clinical trials demonstrate that δ-tocotrienol can enhance both short- and long-term glycemic regulation and attenuate chronic low-grade inflammation, while tocotrienol-enriched oils have been shown to strengthen antioxidant defenses and reduce lipid peroxidation in individuals with poor glycemic control (Mahjabeen et al., 2021; Vafa et al., 2015). These effects are further supported by systematic evidence indicating that tocotrienol-rich fractions consistently lower HbA1c across diverse patient populations, particularly in shorter interventions and in individuals with a shorter duration of diabetes (Phang et al., 2023).

Taken together, these findings highlight tocotrienols as promising, well-tolerated nutritional compounds that may complement standard oral hypoglycemic therapy by addressing metabolic, inflammatory, and oxidative disturbances central to type 2 diabetes.

3.4.Tocotrienols in Diabetic Complications

3.4.1. Diabetic Neuropathy

Diabetic peripheral neuropathy (DPN) represents one of the most prevalent and disabling microvascular complications of type 2 diabetes, driven by chronic hyperglycemia, oxidative stress, and inflammatory activation. Tocotrienols—particularly in tocotrienol-rich vitamin E formulations—have emerged as promising neuroprotective agents capable of targeting these underlying mechanisms.

Evidence from phase II randomized controlled trials demonstrates that tocotrienol-rich vitamin E (Tocovid) can meaningfully improve nerve conduction parameters, which are objective electrophysiological markers of neuropathy progression. In the multicenter trial by Ng et al., eight weeks of supplementation with 200 mg Tocovid twice daily significantly improved nerve conduction velocity (NCV) across all assessed nerves. The authors reported increases of +1.25 m/s in the median nerve, +1.60 m/s in the sural nerve, and +0.75 m/s in the tibial nerve, all highly significant compared with placebo. Tocovid also elevated circulating nerve growth factor (NGF), a biomarker essential for neuronal maintenance, with significantly higher NGF levels observed in the intervention group after eight weeks. These findings suggest that tocotrienols may exert disease-modifying effects by enhancing neurotrophic support and counteracting hyperglycemia-induced neuronal injury (Ng et al., 2020).

Long-term data reinforce these neuroprotective effects. In a phase II double-blind randomized controlled trial, Chuar et al. investigated the effects of tocotrienol-rich vitamin E on nerve conduction parameters in patients with type 2 diabetes. Supplementation with 400 mg/day of Tocovid for 12 months significantly improved nerve conduction velocity (NCV) in the median and sural sensory nerves, as well as the tibial motor nerve, compared with placebo. Improvements in neurophysiological parameters—including conduction and peak velocity—indicate enhanced peripheral nerve function and reduced electrophysiological impairment associated with chronic hyperglycemia. Although serum biomarkers such as TGF-β1 and VEGF-A remained unchanged, the observed functional recovery suggests that tocotrienols may exert their benefits through antioxidant and anti-inflammatory mechanisms rather than direct modulation of growth factors. Importantly, the effects diminished after a six-month washout, implying that continuous supplementation may be necessary to sustain neuroprotective outcomes. Collectively, these findings support tocotrienols as promising adjuncts for mitigating microvascular and neural complications in type 2 diabetes (Chuar et al., 2021).

Collectively, these trials provide consistent evidence that tocotrienol-rich vitamin E exerts measurable neuroprotective effects in diabetic neuropathy. Improvements in NCV, peak velocity, and NGF levels point toward a multifaceted mechanism involving antioxidant activity, reduced inflammatory signaling, and enhanced neuronal support. Although long-term supplementation did not significantly alter serum biomarkers such as TGF-β1 or VEGF-A, the robust electrophysiological improvements underscore tocotrienols' potential as adjunctive therapy for slowing or modifying the progression of diabetic neuropathy (Chuar et al., 2021; Ng et al., 2020).

3.4.2. Diabetic Kidney Disease

Diabetic kidney disease (DKD) represents one of the most serious microvascular complications of type 2 diabetes, often progressing toward renal failure and substantially increasing morbidity. Tocotrienol-rich vitamin E has been proposed as a potential renoprotective agent due to its antioxidant, anti-inflammatory, and antifibrotic properties. In a Phase IIb randomized controlled trial, Koay et al. investigated the effects of long-term tocotrienol supplementation in patients with DKD and observed clear improvements in renal function markers compared with placebo. The intervention led to a favorable shift in kidney performance, reflected by better filtration capacity and lower biochemical indicators of renal strain. These benefits were most evident in individuals with moderate chronic kidney disease, suggesting that tocotrienols may be particularly effective in earlier stages of renal impairment. Notably, tocotrienol supplementation did not meaningfully alter albuminuria, indicating that its renoprotective

effects may act primarily through mechanisms influencing filtration efficiency rather than structural glomerular damage. The study also found no significant changes in antifibrotic biomarkers such as TGF-β1 or VEGF-A, implying that the functional improvements may arise from pathways independent of classical fibrotic signaling. Importantly, the renal benefits diminished after a washout period, highlighting the need for continuous supplementation to sustain therapeutic effects. Overall, the findings position tocotrienol-rich vitamin E as a promising adjunctive strategy for supporting kidney function in DKD, particularly in patients with early to moderate disease (Koay et al., 2021).

3.5. Tocotrienols in Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) constitutes the leading cause of chronic liver pathology worldwide. Its global prevalence is estimated at approximately 25% in the general population and rises to 65–70% among individuals with type 2 diabetes. Despite its growing burden, no pharmacological therapy has yet been approved for NAFLD, leaving lifestyle modification and weight reduction as the cornerstone of management—interventions that are challenging to achieve and even more difficult to sustain over time (Sudoł et al., 2024).

In a randomized, double-blind active-controlled trial, Pervez et al., compared delta-tocotrienol directly with alpha-tocopherol in adults with moderate to severe NAFLD. Both interventions led to meaningful improvements in hepatic steatosis, oxidative stress, and insulin resistance over the 48-week supplementation period, indicating that vitamin E isoforms share core metabolic benefits in NAFLD management. However, delta-tocotrienol demonstrated a distinctly stronger impact on inflammatory and apoptotic pathways. Patients receiving delta-tocotrienol experienced greater reductions in pro-inflammatory cytokines, leptin, and hepatocyte-injury markers, alongside more favorable increases in adiponectin. These findings align with preclinical evidence showing that tocotrienols possess more potent anti-inflammatory and antioxidant activity than tocopherols, likely due to their superior membrane penetration and broader regulatory effects on lipid metabolism and cellular stress responses. Importantly, both treatments were well tolerated, with no adverse events reported (Pervez, Khan, Mirza, et al., 2022).

These clinical outcomes are complemented by molecular evidence from a subsequent trial by the same research group. In a randomized controlled study, Pervez et al., demonstrated that delta-tocotrienol and alpha-tocopherol both exerted hepatoprotective effects through the modulation of circulating microRNAs dysregulated in NAFLD. Supplementation with either compound led to downregulation of miRNAs involved in hepatic lipid accumulation, insulin resistance, oxidative stress, inflammation, and apoptosis. Notably, delta-tocotrienol produced a more pronounced reduction in miR-375 and miR-34a—two microRNAs strongly linked to inflammatory signaling and hepatocyte apoptosis—suggesting a superior ability to modulate pathways associated with disease progression. Changes in miRNA expression also correlated with improvements in biochemical markers of steatosis, insulin sensitivity, oxidative balance, and inflammatory activity, reinforcing the mechanistic relevance of tocotrienols in restoring hepatic homeostasis (Pervez, Khan, Gilani, et al., 2022)

Earlier placebo-controlled findings further support the hepatoprotective role of δ-tocotrienol. In a 24-week randomized trial, δ-tocotrienol supplementation significantly improved biochemical markers of hepatocellular injury and steatosis compared with placebo. Participants receiving δ-tocotrienol exhibited reductions in liver enzymes, inflammatory biomarkers, oxidative stress markers, and ultrasound-graded steatosis. The trial also reported downregulation of key circulating miRNAs associated with lipid dysregulation and hepatocyte injury, reinforcing the compound's capacity to target multiple pathogenic pathways simultaneously (Pervez et al., 2020).

Together, these three clinical investigations—spanning biochemical outcomes, comparative efficacy against α-tocopherol, and miRNA-level mechanistic regulation- provide converging and increasingly robust evidence that δ-tocotrienol is a promising adjunctive therapy for NAFLD. By improving steatosis, enhancing insulin sensitivity, reducing oxidative and inflammatory stress, and attenuating hepatocyte apoptosis, tocotrienols target multiple interconnected pathways central to NAFLD progression. Their consistent superiority over α-tocopherol in modulating inflammatory and apoptotic mechanisms further supports their potential role in the management of

both early and advanced stages of the disease (Pervez et al., 2020; Pervez, Khan, Gilani, et al., 2022; Pervez, Khan, Mirza, et al., 2022).

Importantly, recent pediatric evidence further strengthens this body of research. A single-blind randomized clinical trial by Al-Baiaty et al. showed that tocotrienol-rich fraction (TRF) vitamin E exerts clear biological benefits in obese children with NAFLD. The authors observed that TRF supplementation reduced markers of oxidative DNA injury and led to a measurable decline in circulating pro-inflammatory cytokines, including IL-6 and TNF-α. In other words, children receiving TRF displayed a shift toward a less inflammatory and less oxidative systemic profile, which mirrors the hepatoprotective effects previously documented in adult tocotrienol trials. These pediatric findings highlight that tocotrienols may offer a safe, well-tolerated adjunctive strategy even in early stages of NAFLD, supporting their potential role across different age groups(Al-Baiaty et al., 2024).

3.6. Cardiovascular Effects of Tocotrienols

Evidence from the ongoing randomized controlled trial conducted at the National Heart Institute in Kuala Lumpur suggests that tocotrienols may exert meaningful cardiovascular effects, particularly in the context of cardiac surgery. Post-operative atrial fibrillation (POAF) is a common and clinically significant complication after coronary artery bypass grafting (CABG), driven largely by acute systemic inflammation and oxidative stress triggered by surgical trauma. Musa et al. describe POAF as arising from a “pro-inflammatory and pro-oxidative milieu” created in the mediastinal space after surgery, highlighting the mechanistic rationale for testing tocotrienols as a preventive strategy. Tocotrienols—administered as Tocovid—were selected because of their potent antioxidant and anti-inflammatory properties, which exceed those of classical tocopherols. Although the study remains blinded, interim analysis provides insight into the cardiovascular relevance of tocotrienols. Among all participants, POAF was associated with markedly worse outcomes: a three-fold increase in mortality, longer ICU and hospital stays, and higher rates of re-intubation. These findings underscore the importance of interventions that can modulate perioperative oxidative and inflammatory stress. The trial’s design—pre-operative and early post-operative tocotrienol supplementation—targets the window in which oxidative injury and inflammatory activation are most intense. By attenuating these processes, tocotrienols may help stabilize atrial electrophysiology, reduce oxidative damage to cardiac tissue, and limit inflammatory signaling that contributes to arrhythmogenesis. While final efficacy results await unblinding, the mechanistic rationale and early safety profile support tocotrienols as a promising cardioprotective adjunct in high-risk surgical settings. Overall, the Musa et al. study positions tocotrienols as potential modulators of cardiovascular outcomes through their ability to counteract oxidative stress, dampen inflammation, and possibly reduce the incidence and severity of POAF—one of the most impactful complications following cardiac surgery (Musa et al., 2021).

Additional cardiovascular evidence comes from patients with ischemic stroke or transient ischemic attack (TIA). In a year-long randomized trial, Slivka et al. demonstrated that tocotrienol supplementation reduced the incidence of aspirin resistance in patients receiving dual antiplatelet therapy with aspirin and clopidogrel—an important finding given that inadequate platelet inhibition is associated with recurrent ischemic events . Tocotrienols have been shown to inhibit platelet aggregation, modulate thrombus formation, and suppress HMG-CoA reductase activity, aligning with mechanisms known to improve vascular stability and reduce cardiovascular risk (Slivka et al., 2020).

Together, these studies position tocotrienols as promising cardioprotective agents capable of counteracting oxidative stress, reducing inflammation, improving platelet responsiveness, and potentially lowering the incidence and severity of high-risk cardiovascular complications across both surgical and cerebrovascular settings (Musa et al., 2021; Slivka et al., 2020).

4. Discussion

The current clinical evidence on tocotrienols, although increasingly promising, remains constrained by several important methodological and translational limitations that prevent definitive conclusions about their efficacy in

cardiometabolic disease. Many randomized controlled trials are small, short in duration, and conducted in narrowly defined populations, which limits statistical power and generalizability. Several studies report beneficial effects that diminish after washout periods, indicating that sustained supplementation may be required; as noted, *"the effects diminished after a six-month washout"* (Chuar et al., 2021) Intervention periods of 8–24 weeks are insufficient to evaluate long-term outcomes such as cardiovascular events, renal decline, or progression of diabetic complications, and most trials rely on surrogate biomarkers rather than hard clinical endpoints. Heterogeneity in tocotrienol formulations—including differences in isoform composition, dosing (200–400 mg/day), delivery matrices, and co-supplementation with compounds such as resveratrol—further complicates comparisons across studies and obscures identification of optimal therapeutic regimens. Mechanistic insights remain incomplete, with limited pharmacokinetic data and insufficient exploration of tissue-specific effects, despite indications that *"current clinical evidence demonstrating direct reductions in oxidative stress biomarkers… remains limited"* (Phang et al., 2023) Geographic concentration of trials in Southeast Asia restricts applicability to diverse populations with different dietary patterns, genetic backgrounds, and comorbidities. Additionally, although several studies demonstrate modulation of inflammatory markers, oxidative stress, microRNAs, or nerve conduction parameters, these findings have not yet been linked to long-term clinical improvements or disease modification. Potential conflicts of interest and industry involvement in tocotrienol research also underscore the need for independent replication. Collectively, these limitations highlight that while tocotrienols exhibit multifaceted biological activity and encouraging early clinical effects, the current evidence base is insufficiently robust to support broad therapeutic recommendations, and larger, longer, and more rigorously designed trials are required to establish their true clinical relevance.

Future research must prioritize adequately powered, multicenter randomized controlled trials to validate the metabolic, anti-inflammatory, and organ-protective effects of tocotrienols. Existing studies often involve small cohorts and short intervention periods, limiting generalizability and the ability to detect clinically meaningful outcomes. Large trials with follow-up beyond 12 months are essential to determine whether improvements in biomarkers translate into reductions in hard endpoints such as cardiovascular events, renal decline, or neuropathy progression. Expanding research into diverse populations—including Western cohorts, older adults with multimorbidity, and individuals with advanced metabolic disease—will also strengthen external validity. Key next step: large-scale RCT design

Current evidence is limited by substantial heterogeneity in tocotrienol formulations, including differences in isoform composition (α, β, γ, δ), extraction sources, delivery matrices, and dosing strategies. Standardization is necessary to enable meaningful comparisons across studies and to identify optimal therapeutic doses. Future trials should employ well-characterized preparations with consistent δ-tocotrienol content, validated bioavailability profiles, and transparent manufacturing specifications. Harmonizing dosing regimens will also facilitate meta-analyses and regulatory evaluation. Explore further: tocotrienol formulation standards

Emerging evidence suggests that tocotrienols modulate oxidative stress, inflammation, and metabolic pathways through epigenetic mechanisms, including regulation of microRNAs associated with metabolic syndrome, NAFLD, and diabetes. Future studies should incorporate comprehensive biomarker panels—oxidative stress markers, cytokines, lipidomic signatures, and miRNA profiles—to clarify mechanistic pathways and identify responders versus non-responders. Longitudinal miRNA tracking may reveal whether tocotrienols exert disease-modifying effects or primarily short-term biochemical improvements. Learn more: miRNA panels

Given their pleiotropic biological activity and favorable safety profile, tocotrienols are well positioned to serve as adjunctive agents alongside standard pharmacotherapy. Future research should evaluate synergistic effects with metformin, GLP-1 receptor agonists, SGLT2 inhibitors, statins, and antihypertensive medications. Trials should also assess whether tocotrienols enhance quality of life, reduce medication burden, or improve treatment adherence. Clear clinical guidelines will be needed to define when tocotrienols should be recommended—whether for early metabolic dysfunction, persistent inflammation, or organ-specific complications such as neuropathy or steatosis. Next step: adjunctive therapy models

Among all cardiometabolic conditions studied to date, NAFLD and type 2 diabetes show the most consistent and clinically meaningful responses to tocotrienol supplementation. δ-tocotrienol demonstrates superior

anti-inflammatory and anti-apoptotic effects compared with α-tocopherol in NAFLD, while multiple RCTs report improvements in HbA1c, fasting glucose, insulin resistance, and oxidative stress in diabetes. Future research should prioritize these indications, focusing on disease progression, fibrosis risk, hepatic microRNA modulation, and prevention of microvascular complications. Dedicated trials in MASLD/MASH and early diabetic nephropathy may further clarify therapeutic potential.

5. Conclusions

The growing body of randomized controlled trials conducted between 2020 and 2025 provides increasingly compelling evidence that tocotrienols represent a biologically potent and clinically promising class of vitamin E compounds with relevance across multiple domains of cardiometabolic health. Their pleiotropic activity—spanning antioxidant defense, suppression of pro-inflammatory cytokines, modulation of lipid metabolism, enhancement of endothelial function, and regulation of microRNAs—positions them as uniquely capable of targeting the interconnected mechanisms that drive metabolic dysfunction, chronic inflammation, and oxidative stress. Across diverse clinical populations, tocotrienols have demonstrated improvements in glycemic control, insulin resistance, lipid profiles, oxidative stress biomarkers, inflammatory mediators, and organ-specific complications such as neuropathy, kidney disease, and hepatic steatosis. These findings are reinforced by mechanistic observations showing enhanced endogenous antioxidant enzyme activity, reductions in malondialdehyde, modulation of miRNAs linked to metabolic syndrome and NAFLD, and even improvements in genomic stability, including increased telomerase activity and reduced oxidative DNA damage.

Among all investigated indications, type 2 diabetes and NAFLD appear to be the most promising therapeutic targets. δ-tocotrienol consistently outperforms α-tocopherol in reducing inflammatory cytokines, hepatocyte injury markers, and apoptotic pathways in NAFLD, while multiple trials demonstrate meaningful reductions in HbA1c, fasting glucose, insulin resistance, and oxidative stress in diabetes. These effects suggest that tocotrienols may offer advantages beyond classical vitamin E, likely due to their superior membrane penetration, broader regulatory influence on cellular stress responses, and more efficient distribution within phospholipid bilayers. Importantly, tocotrienols have shown favorable tolerability across trials, with no significant adverse events reported, supporting their potential suitability as adjunctive therapies alongside standard pharmacological treatments.

Despite these encouraging developments, the current evidence base remains insufficiently mature to support definitive clinical recommendations. Many trials are limited by small sample sizes, short intervention periods, heterogeneous formulations, and reliance on surrogate biomarkers rather than hard clinical endpoints. The absence of standardized tocotrienol preparations complicates comparisons across studies, while geographic concentration of research in Southeast Asia limits generalizability to broader populations. Furthermore, although early mechanistic insights are promising, the precise pathways through which tocotrienols exert their metabolic and anti-inflammatory effects remain incompletely understood, particularly regarding long-term genomic stability, epigenetic regulation, and tissue-specific actions.

Taken together, the available evidence positions tocotrienols as biologically versatile, safe, and clinically promising compounds with potential to complement existing therapies for metabolic syndrome, type 2 diabetes, NAFLD, and related cardiometabolic disorders. However, their full therapeutic value will only be realized through larger, longer, and more rigorously designed trials that incorporate standardized formulations, advanced biomarker profiling, and evaluation of clinically meaningful outcomes. If these gaps are addressed, tocotrienols may ultimately emerge as a well-defined adjunctive strategy capable of mitigating metabolic dysfunction, reducing chronic inflammation, and improving long-term cardiometabolic health.

Disclosure

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In preparing this work, the author(s) used ChatGPT for language improvement and grammatical correction. After using this tool/service, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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