Review Article

Tocotrienol-Rich Fraction from Palm Oil and Cardiovascular Health Outcomes: A Systematic Literature Review of Randomized Controlled Trials

Loso Judijanto*

IPOSS Jakarta, Indonesia

Abstract

On a global level, cardiovascular disease remains a key contributor to health complications and mortality, prompting increasing scientific interest in nutritional bioactive compounds associated with cardiovascular risk modulation. Derived from palm oil and categorized as part of the vitamin E family, TRF has attracted attention for its possible benefits in reducing oxidative stress, suppressing inflammation, and regulating lipid metabolism. This investigation systematically analyzed evidence obtained from randomized controlled trials to clarify the relationship between TRF supplementation and cardiovascular health indicators. A Systematic Literature Review (SLR) following PRISMA recommendations was conducted using secondary data obtained solely from Scopus and PubMed. Article identification and selection were conducted through structured screening, eligibility assessment, and duplicate removal processes. A total of 33 randomized controlled trials published between 2019 and 2025 fulfilled all predefined inclusion criteria. Bibliographic management and data organization were conducted using Mendeley Desktop, while data analysis applied a structured thematic synthesis approach. The findings demonstrated recurring improvements in lipid profile parameters, oxidative stress biomarkers, inflammatory mediators, endothelial function, vascular responsiveness, blood pressure regulation, and metabolic risk indicators following TRF supplementation. Several studies also reported favorable safety and tolerability outcomes within the supplementation range of 50–400 mg/day. Overall, the reviewed evidence indicates growing scientific relevance of palm-derived TRF in cardiovascular and metabolic health research. Future studies should prioritize larger populations, longer intervention durations, and standardized cardiovascular outcome assessments.

Introduction

Globally, CVD remains among the primary contributors to mortality and persistent disability, representing a substantial public health burden across both developed and developing countries. The increasing prevalence of coronary artery disease, hypertension, stroke, atherosclerosis, and metabolic syndrome has been closely associated with demographic transitions, sedentary lifestyles, population aging, dietary imbalance, obesity, and chronic metabolic disturbances. In recent decades, cardiovascular-related morbidity has continued to rise alongside the growing incidence of dyslipidemia, insulin resistance, chronic inflammation, and endothelial dysfunction, all of which are recognized as major risk factors contributing to cardiovascular deterioration. In addition to clinical implications, cardiovascular disorders also generate considerable socioeconomic consequences due to prolonged treatment costs, reduced productivity, and increased healthcare utilization worldwide [1].

SHRINE PUBLISHERS
Crafting your Achievement

Shrine Journal of Research and Sciences (SJRS)

ISSN: 3069-2032

Volume 3 Issue 4, 2026

Article Information
Received date: July 28, 2026
Published date: August 24, 2026

***Corresponding author**
Loso Judijanto, IPOSS Jakarta, Indonesia

DOI: 10.65070/SJRS.2026.832

Keywords
Tocotrienol-rich fraction; Cardiovascular health; Palm oil; Randomized controlled trials; Systematic literature review

Distributed under:
Creative Commons CC-BY 4.0

Copyright © : Judijanto L

The pathophysiology of cardiovascular disease is multifactorial and involves complex interactions among oxidative stress, inflammatory activation, lipid metabolism abnormalities, vascular impairment, and mitochondrial dysfunction. Considerable scientific emphasis has been placed on oxidative stress, as excessive reactive oxygen species (ROS) generation may enhance endothelial cell damage, lipid oxidation, inflammatory vascular changes, and atherosclerotic plaque growth. Chronic inflammatory processes further contribute to vascular remodeling and arterial stiffness through the activation of cytokines, adhesion molecules, and pro-inflammatory signaling pathways. Consequently, increasing emphasis has been directed toward identifying nutritional and bioactive compounds capable of modulating oxidative and inflammatory pathways associated with cardiovascular risk progression [2].

In the context of preventive cardiology and nutritional science, bioactive compounds belonging to the vitamin E family have attracted attention for their antioxidant and functional biological properties. The classification of vitamin E encompasses tocopherols as well as tocotrienols, both of which possess distinct structural and functional characteristics. Compared with tocopherols, tocotrienols contain an unsaturated isoprenoid side chain that may influence membrane penetration, antioxidant distribution, and cellular signaling activity [3]. Previous biochemical and experimental investigations have suggested that tocotrienols may exhibit biological activities associated with lipid regulation, anti-inflammatory responses, antioxidant protection, and vascular modulation. These properties have attracted increasing scientific interest regarding the potential implications of tocotrienol supplementation in cardiovascular health management and metabolic disease prevention [4].

In the context of nutritional and biomedical sciences, palm oil-derived TRF represents one of the most thoroughly examined natural sources of tocotrienols. Several tocotrienol isomers are found in palm-derived TRF, particularly alpha-, beta-, gamma-, and delta-tocotrienol, alongside modest levels of tocopherols. Due to its naturally occurring composition, palm-derived TRF has been utilized in numerous clinical and experimental studies evaluating antioxidant capacity, lipid metabolism, inflammatory modulation, endothelial responses, and metabolic outcomes. In recent years, scientific attention toward palm-derived tocotrienols has increased considerably, particularly in relation to cardiovascular-related biomarkers and chronic disease prevention strategies [5].

Several mechanistic studies have indicated that tocotrienols may contribute to cardiovascular regulation through multiple biological pathways. These mechanisms include suppression of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase activity, reduction of oxidative lipid damage, modulation of inflammatory mediators, improvement of endothelial nitric oxide bioavailability, and attenuation of vascular oxidative stress [6]. Tocotrienols have additionally been associated with regulation of cytokine expression, inhibition of inflammatory signaling cascades, and enhancement of endogenous antioxidant defense systems. Such mechanisms have positioned tocotrienols as compounds of growing interest within the broader context of functional foods, nutraceutical development, and cardiovascular risk management research.

Despite increasing scientific interest, the available evidence concerning tocotrienol-rich fraction and cardiovascular health outcomes remains heterogeneous across clinical investigations. Existing studies vary considerably in terms of intervention dosage, supplementation duration, participant characteristics, baseline cardiovascular conditions, measured biomarkers, and methodological design [7]. Positive outcomes involving low-density lipoprotein cholesterol, oxidative stress markers, inflammatory mediators, and endothelial function have been reported in some randomized controlled trials of TRF supplementation, while other studies yielded conflicting or less substantial results. Variability in study populations, sample sizes, dietary background, and concurrent metabolic conditions further complicates the interpretation of current evidence [8].

In addition to inconsistencies in outcome measurements, previous review studies concerning tocotrienols have frequently combined evidence derived from animal studies, in vitro experiments, observational studies, and mixed nutritional interventions without specifically focusing on randomized controlled trials involving cardiovascular endpoints [9]. Although such reviews contribute valuable mechanistic perspectives, the integration of heterogeneous evidence sources may limit the ability to evaluate clinically relevant outcomes associated with human intervention studies. Moreover, several existing reviews have examined vitamin E compounds collectively without distinguishing the specific effects of palm-derived tocotrienol-rich fraction from other tocopherol-dominant formulations or mixed antioxidant interventions.

The growing number of randomized controlled trials published in recent years highlights the need for a more focused and methodologically structured synthesis of evidence specifically addressing palm-derived TRF and cardiovascular outcomes. Randomized controlled trials represent one of the most reliable clinical research designs for evaluating intervention effectiveness, supplementation safety, and biomarker responses under controlled conditions. Therefore, synthesizing evidence derived exclusively from randomized controlled trials may provide a clearer understanding regarding the consistency, magnitude, and clinical relevance of cardiovascular responses associated with

palm-derived tocotrienol supplementation [10].

Furthermore, the increasing global interest in functional food ingredients and nutraceutical-based preventive strategies has intensified scientific discussions regarding the role of naturally derived bioactive compounds in long-term cardiovascular health maintenance. Within this context, palm-derived tocotrienol-rich fraction continues to receive attention due to its biochemical composition and potential physiological relevance. Nevertheless, scientific interpretation of available findings requires balanced evaluation grounded in clinical evidence rather than generalized assumptions or isolated mechanistic observations. Accordingly, systematic evidence synthesis remains important to clarify current research patterns, identify emerging trends, and evaluate the overall direction of findings reported in contemporary randomized controlled trials [11].

From a methodological perspective, Systematic Literature Review (SLR) approaches provide an important framework for organizing, evaluating, and synthesizing scientific evidence in a transparent and reproducible manner. The implementation of PRISMA-based protocols supports an organized approach to the identification, screening, eligibility assessment, and inclusion of peer-reviewed articles relevant to established research goals. Through systematic synthesis, SLR methodology may facilitate comprehensive evaluation of intervention outcomes, methodological characteristics, and recurring themes emerging across clinical investigations. Notably, the present investigation utilizes exclusively secondary evidence obtained from scientific publications and does not involve direct primary data collection methods such as field observation, interviews, or focus group discussions, thereby ensuring methodological coherence with evidence-based review standards.

In response to these considerations, the current study undertakes a systematic synthesis and evaluation of randomized controlled trials exploring the relationship between palm oil-derived TRF supplementation and cardiovascular health outcomes. This review specifically focuses on clinical findings associated with lipid metabolism, oxidative stress biomarkers, inflammatory responses, vascular function, blood pressure regulation, metabolic parameters, and supplementation safety observed across contemporary human intervention studies. Through a structured PRISMA-based systematic literature review approach, this study is expected to provide a comprehensive overview of current scientific evidence while identifying recurring patterns and research gaps within the existing body of literature.

Accordingly, the present review addresses the following research questions:

RQ1: How does palm oil-derived tocotrienol-rich fraction supplementation influence cardiovascular-related biomarkers and clinical outcomes in randomized controlled trials?

RQ2: What recurring patterns, consistencies, and variations can be identified across contemporary randomized controlled trials investigating the cardiovascular implications of tocotrienol-rich fraction supplementation?

Literature Review

The literature concerning tocotrienol-rich fraction (TRF) and cardiovascular health has expanded considerably in recent years alongside growing scientific interest in functional bioactive compounds derived from natural sources. Previous studies have explored various aspects related to tocotrienol biochemistry, antioxidant activity, lipid metabolism, inflammatory modulation, endothelial regulation, and vascular responses associated with cardiovascular risk factors. Nevertheless, the available evidence remains heterogeneous due to differences in study populations, intervention protocols, supplementation dosages, and evaluated biomarkers. Accordingly, this literature review discusses several major themes relevant to the present study, including the biological characteristics of tocotrienols within the vitamin E family, oxidative stress mechanisms in cardiovascular disease, the properties of palm oil-derived tocotrienol-rich fraction, lipid metabolism regulation, inflammatory and vascular responses, randomized controlled trials in tocotrienol research, and the existing research gap underlying the need for a systematic synthesis of contemporary clinical evidence.

Tocotrienol and the Vitamin E Family

Classified as lipid-soluble bioactive substances, vitamin E compounds are divided into two principal categories: tocopherols and tocotrienols. Variations in the number and location of methyl groups on the chromanol ring give rise to alpha-, beta-, gamma-, and delta-isomers within both subclasses. Even though tocotrienols and tocopherols display similar antioxidant behavior, tocotrienols are structurally defined by an unsaturated isoprenoid side chain, unlike the saturated phytyl tail of tocopherols. These structural distinctions are considered important because they may influence membrane mobility, intracellular distribution, and interaction with lipid bilayers within biological systems [12].

Scientific attention toward tocotrienols has increased substantially during the last two decades due to emerging evidence indicating that tocotrienols may exhibit broader biological activities beyond conventional antioxidant functions. In addition to scavenging free radicals, tocotrienols have been associated with modulation of

inflammatory pathways, cholesterol biosynthesis, endothelial regulation, and cellular signaling mechanisms involved in chronic disease progression. Several biochemical studies have suggested that tocotrienols may demonstrate greater membrane penetration efficiency compared with tocopherols due to their unsaturated side chain configuration, thereby potentially enhancing biological interaction at the cellular level [13].

Considerable scientific interest has been directed toward palm oil-derived TRF, making it one of the most extensively examined natural tocotrienol sources in nutritional and biomedical research. Palm-derived TRF generally contains a mixture of tocotrienol isomers accompanied by lower concentrations of tocopherols. The biochemical composition of palm-derived TRF has generated interest in its potential application within preventive nutrition and functional food development, particularly in relation to oxidative stress-associated disorders and cardiovascular health management [14].

Cardiovascular Disease and Oxidative Stress Mechanisms

Cardiovascular disease remains closely associated with chronic oxidative stress and inflammatory dysregulation. Excessive ROS formation may contribute to vascular endothelial impairment, inflammatory responses, lipid oxidation, and the gradual development of atherosclerotic changes. Oxidative imbalance may additionally impair nitric oxide bioavailability, leading to vascular stiffness and reduced endothelial responsiveness. Consequently, antioxidant-related interventions have increasingly been investigated as potential supportive approaches for maintaining cardiovascular homeostasis [15].

Oxidized low-density lipoprotein (ox-LDL) is considered one of the major contributors to atherogenic progression because oxidized lipids may stimulate macrophage activation, foam cell formation, and vascular inflammatory cascades. Alongside these processes, chronic inflammatory biomarkers including TNF-α, IL-6, and CRP have been implicated in the progression of vascular damage and endothelial impairment. These interconnected mechanisms highlight the multifactorial nature of cardiovascular disease progression and reinforce the importance of examining bioactive compounds capable of modulating oxidative and inflammatory pathways [16].

Due to their reported antioxidant and anti-inflammatory activities, tocotrienols have become a significant subject of scientific interest in this context. Experimental findings have suggested that tocotrienols may inhibit lipid peroxidation, stabilize cellular membranes, reduce oxidative biomarker accumulation, and influence inflammatory signaling activity.

Although mechanistic observations derived from laboratory studies cannot be directly generalized to clinical outcomes, these findings have contributed to growing interest in evaluating tocotrienol-rich fraction supplementation within human cardiovascular research settings.

Palm Oil-Derived Tocotrienol-Rich Fraction

One of the major naturally occurring sources of tocotrienols is palm oil, especially in the form of a tocotrienol-rich fraction derived from palm sources. The oil palm fruit contains various phytonutrients including carotenoids, tocopherols, tocotrienols, and other lipid-soluble compounds that have attracted increasing interest in food science and nutritional research. The tocotrienol-rich fraction extracted from palm oil generally contains gamma- and alpha-tocotrienol as dominant isomers accompanied by smaller quantities of delta- and beta-tocotrienol [17].

Scientific interest in palm-derived TRF has risen partly as a result of its potential contribution to metabolic and cardiovascular research. Evidence from several studies indicates that tocotrienols may influence endogenous cholesterol synthesis by suppressing the activity of HMG-CoA reductase, a crucial enzyme in cholesterol metabolism. In addition, tocotrienols have been investigated for their possible role in modulating oxidative stress biomarkers, inflammatory mediators, endothelial responses, and vascular homeostasis [18].

Scientific investigation concerning palm-derived tocotrienols has also expanded alongside the broader development of nutraceutical and functional food research. In many studies, TRF supplementation has been evaluated as part of dietary intervention strategies involving individuals with hypercholesterolemia, obesity, metabolic syndrome, hypertension, and type 2 diabetes mellitus. These populations are frequently selected because of their close association with elevated cardiovascular risk profiles and chronic metabolic disturbances [19].

Despite increasing scientific interest, current evidence regarding palm-derived TRF remains heterogeneous. Variability in intervention dosage, supplementation duration, participant characteristics, baseline metabolic conditions, and measured cardiovascular endpoints may contribute to differences in reported findings across studies. Such heterogeneity underscores the importance of systematically synthesizing evidence obtained from controlled human intervention studies.

Tocotrienol and Lipid Metabolism

One of the most frequently investigated aspects of tocotrienol research involves lipid metabolism and cholesterol regulation. Several studies have reported that tocotrienols may influence serum lipid profiles through modulation of cholesterol biosynthesis pathways. Experimental evidence has indicated that tocotrienols may suppress HMG-CoA reductase activity through post-transcriptional regulatory mechanisms, potentially contributing to reductions in total cholesterol and low-density lipoprotein cholesterol concentrations [20].

In clinical settings, randomized controlled trials evaluating tocotrienol-rich fraction supplementation have demonstrated varying outcomes regarding lipid profile improvements. Some studies reported reductions in total cholesterol, LDL cholesterol, triglycerides, and lipid oxidation biomarkers following medium-term supplementation periods. However, other intervention studies demonstrated more modest responses or limited changes in high-density lipoprotein cholesterol levels. Differences in dosage, participant metabolic status, dietary intake, and intervention duration may partly explain the variability observed among clinical findings [21].

The relationship between tocotrienols and lipid metabolism has also been explored in relation to metabolic syndrome and obesity-related cardiovascular risk. Cardiovascular susceptibility may rise when dyslipidemia occurs concurrently with insulin resistance, systemic inflammation, and endothelial dysfunction. Consequently, interventions targeting lipid regulation may possess broader implications for cardiovascular risk reduction strategies.

Inflammation, Endothelial Function, and Vascular Responses

Inflammatory activation constitutes another major component of cardiovascular disease progression. Chronic low-grade inflammation has been implicated in endothelial dysfunction, arterial stiffness, plaque instability, and vascular remodeling. Endothelial injury may be aggravated by cytokines such as IL-6 and TNF-α through activation of inflammatory cascades and oxidative stress pathways [22].

Findings from multiple experimental and clinical studies suggest that tocotrienols may exert effects on inflammatory responses by targeting NF-κB activity and related signaling networks. Moreover, tocotrienols have been connected with lowered inflammatory biomarker levels, including C-reactive protein and selected cytokines. These observations have generated increasing scientific interest in the potential vascular relevance of tocotrienol-rich fraction supplementation [23].

Endothelial function represents another important focus within cardiovascular research. The vascular endothelium plays a central role in regulating vasodilation, vascular tone, thrombosis, and inflammatory responses. Impaired endothelial function is frequently considered an early marker of cardiovascular deterioration and atherosclerotic progression.

Studies investigating endothelial function commonly examine parameters such as flow-mediated dilation, nitric oxide bioavailability, pulse wave velocity, and measures of arterial stiffness [24].

Clinical evidence regarding tocotrienol-related vascular effects remains variable but increasingly prominent. Some randomized controlled trials have reported improvements in endothelial responsiveness and reductions in oxidative stress markers following TRF supplementation. Nevertheless, inconsistencies across study findings remain apparent, emphasizing the importance of comprehensive evidence synthesis to evaluate the consistency and magnitude of reported cardiovascular outcomes [25].

Randomized Controlled Trials in Tocotrienol Research

Randomized controlled trials are widely recognized as one of the most rigorous approaches for evaluating intervention efficacy and clinical outcomes. Within nutritional and cardiovascular research, randomized controlled trial designs enable controlled assessment of supplementation effects while minimizing selection bias and confounding factors. As scientific interest in tocotrienols has expanded, the number of randomized intervention studies examining palm-derived TRF has also increased [27].

Despite the growing body of clinical evidence, several limitations remain evident within the current literature. Existing studies differ substantially in sample size, participant demographics, intervention duration, baseline cardiovascular conditions, dosage administration, and outcome measurements. Some trials involve relatively short intervention periods, whereas others utilize heterogeneous participant populations with varying metabolic characteristics. Such methodological diversity may complicate direct comparison between studies and contribute to inconsistencies in reported outcomes [28].

Moreover, previous review articles concerning tocotrienols frequently integrate findings from animal experiments, cell culture investigations, observational studies, and mixed antioxidant interventions. Although these approaches provide useful mechanistic insight, they may reduce specificity regarding clinically relevant cardiovascular outcomes observed in randomized controlled human studies. Consequently, a more

focused synthesis restricted to randomized controlled trials may contribute to clearer evaluation of current evidence concerning palm oil-derived tocotrienol-rich fraction and cardiovascular health outcomes.

The increasing volume of tocotrienol-related cardiovascular research highlights the need for a systematic and methodologically structured evaluation of current evidence. Although multiple studies have investigated tocotrienol-rich fraction supplementation, the reported outcomes remain dispersed across diverse clinical populations, intervention protocols, and cardiovascular biomarkers. Furthermore, differences in methodological quality, supplementation dosage, treatment duration, and endpoint selection continue to generate variability in the interpretation of available findings.

Existing reviews have often emphasized mechanistic evidence derived from experimental studies rather than focusing specifically on randomized controlled clinical trials involving cardiovascular outcomes. In addition, several review articles examine vitamin E compounds collectively without differentiating palm-derived tocotrienol-rich fraction from tocopherol-dominant formulations

or other antioxidant mixtures. This limitation may reduce clarity regarding the specific cardiovascular relevance of palm-derived TRF supplementation.

Within this context, the application of a Systematic Literature Review approach based on PRISMA principles provides an important framework for organizing and synthesizing evidence in a transparent and reproducible manner. By focusing specifically on randomized controlled trials, the present review seeks to identify recurring patterns, methodological tendencies, and cardiovascular outcomes associated with palm-derived tocotrienol-rich fraction supplementation. Such synthesis is expected to contribute to a broader understanding of contemporary evidence concerning tocotrienols and cardiovascular health within human clinical research settings.

Methodology

Using the PRISMA framework as guidance, the present study conducts a Systematic Literature Review (SLR) to systematically investigate scientific evidence associated with the cardiovascular health effects of palm oil-derived TRF. Scientific interest in tocotrienols has increased considerably in recent years due to their biological properties, particularly their potential involvement in antioxidant activity, lipid metabolism regulation, vascular protection, and inflammatory modulation associated with cardiovascular function. Palm oil represents one of the major natural sources of tocotrienols, especially in the form of tocotrienol-rich fraction, which has been investigated in various nutritional and clinical contexts. Nevertheless, findings across clinical studies remain heterogeneous due to differences in study populations, intervention duration, dosage administration, cardiovascular endpoints, and analytical approaches. Such variability highlights the importance of conducting a structured evidence synthesis capable of integrating randomized controlled trial findings within a transparent and methodologically rigorous review framework. Accordingly, the present review exclusively utilizes secondary data obtained from peer-reviewed scientific publications indexed in Scopus and PubMed without involving primary data collection methods such as field observation, interviews, or focus group discussions, thereby ensuring consistency with evidence-based SLR methodology.

The PRISMA workflow presented in Figure 1 illustrates the sequential stages of identification, screening, eligibility assessment, and final inclusion adopted in this systematic review process. In the initial identification stage, a broad literature search was conducted using the primary keyword combination “tocotrienol AND cardiovascular,” resulting in 290 records retrieved from Scopus and 173 records from PubMed, with a total of 463 identified publications. To improve the specificity and thematic relevance of the retrieved studies, a more focused Boolean search strategy was subsequently implemented using the following query: (“tocotrienol-rich fraction” OR “palm tocotrienols” OR tocotrienols OR “palm oil tocotrienols”) AND (“cardiovascular health” OR “cardiovascular disease” OR cardiovascular OR cardioprotection OR “heart disease” OR “vascular health”) AND (trial OR intervention OR supplementation OR human). This refined search generated 164 records from Scopus and 152 records from PubMed. Following the application of relevance screening criteria, 147 articles were excluded because they did not align with the predefined scope of cardiovascular intervention and human-related outcomes, resulting in 316 articles eligible for further assessment.

Copyright © : Judijanto L

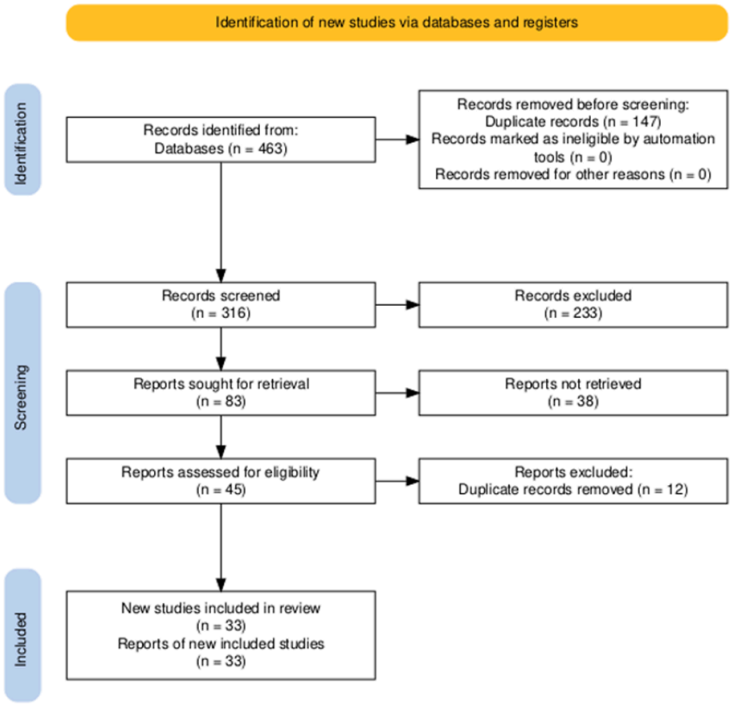

Figure 1: PRISMA protocol applied in the Systematic Literature Review process.

During the screening phase, publication year limitations were applied by restricting eligible studies to those published between 2019 and 2025 in order to ensure the inclusion of recent and scientifically relevant evidence. This stage led to the exclusion of 233 records published outside the selected timeframe, leaving 83 articles for subsequent evaluation. In the eligibility stage, full-text accessibility was assessed to facilitate comprehensive data extraction and detailed analysis. A total of 38 articles were excluded due to unavailable or restricted full-text access, resulting in 45 studies eligible for further review. Subsequently, a final deduplication process identified 12 duplicate articles across the databases that had not been detected during previous stages, and these records were removed accordingly. Consequently, 33 peer-reviewed articles fulfilled all predefined inclusion criteria and were retained for the final qualitative synthesis.

The bibliographic records retrieved throughout the review process were systematically organized and managed using Mendeley Desktop to support citation accuracy, duplicate identification, and reference traceability. All selected articles were examined in full text, and relevant information including study characteristics, intervention design, supplementation duration, measured cardiovascular parameters, and principal findings was extracted and synthesized using a thematic analytical approach. This procedure enabled the integration of evidence derived from heterogeneous randomized controlled trials into a coherent interpretative framework while maintaining methodological transparency and analytical consistency. Through the application of PRISMA-based procedures and a reproducible SLR methodology, the present study provides a structured synthesis of current evidence regarding the potential relationship between palm oil-derived tocotrienol-rich fraction and cardiovascular health outcomes within contemporary clinical research contexts.

Results

In this systematic literature review, a total of 33 randomized controlled trials published between 2019 and 2025 were systematically analyzed to evaluate the relationship between palm oil-derived tocotrienol-rich fraction (TRF) supplementation and cardiovascular health outcomes in human intervention studies. Through thematic synthesis, seven interrelated domains were identified: (1) lipid profile modulation, (2) oxidative stress and antioxidant responses, (3) inflammatory biomarker regulation, (4) vascular and endothelial function improvement, (5) blood

pressure and hemodynamic responses, (6) metabolic and glycemic regulation associated with cardiovascular risk, and (7) safety and tolerability of TRF supplementation. Several studies contributed simultaneously to multiple themes, reflecting the interconnected biological relationship among dyslipidemia, oxidative stress, inflammation, endothelial dysfunction, and cardiovascular disease progression.

The thematic distribution demonstrated that lipid profile modulation represented the most dominant research focus (27 studies; 81.8%), followed by oxidative stress and antioxidant-related outcomes (24 studies; 72.7%), inflammatory biomarker regulation (20 studies; 60.6%), vascular and endothelial function assessment (16 studies; 48.5%), blood pressure and hemodynamic responses (14 studies; 42.4%), and metabolic or glycemic regulation associated with cardiovascular risk (13 studies; 39.4%). Safety and tolerability evaluations were reported in nearly all intervention studies (29 studies; 87.9%), indicating that most randomized controlled trials incorporated systematic monitoring of adverse effects and biochemical safety markers during supplementation periods. Although several studies focused primarily on one dominant cardiovascular outcome, many trials simultaneously evaluated lipid metabolism, oxidative stress, inflammatory responses, and endothelial biomarkers within the same intervention framework, emphasizing the multidimensional nature of cardiovascular risk modulation.

The predominance of lipid-related and antioxidant-related themes reflects the current research emphasis on fundamental biochemical mechanisms associated with early cardiovascular disease progression. Lipid parameters such as total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and oxidized LDL remain widely investigated because they are established cardiovascular risk indicators that can be quantitatively monitored during medium-term nutritional interventions. Similarly, oxidative stress biomarkers including malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx), and oxidized LDL are frequently prioritized due to their close relationship with endothelial dysfunction, vascular injury, and atherosclerotic processes. In contrast, vascular function outcomes, metabolic responses, and long-term hemodynamic endpoints appeared less frequently because these domains generally require more complex assessment methods, extended intervention durations, and broader clinical monitoring. This thematic distribution suggests that while the mechanistic and biomarker-related foundation concerning palm-derived TRF is becoming increasingly established, additional long-term clinical investigations remain necessary to strengthen translational understanding regarding cardiovascular outcomes in broader human populations.

Effects of Tocotrienol-Rich Fraction on Lipid Profile Parameters

One of the most consistently reported findings across the reviewed studies involved the modulation of lipid profile indicators following TRF supplementation. Several randomized controlled trials demonstrated reductions in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) among participants receiving palm-derived tocotrienol supplementation compared with placebo groups [29]. Reported reductions in LDL-C ranged from approximately 8% to 22% depending on supplementation dose, intervention duration, and baseline cardiovascular risk profile [30]. In studies involving hypercholesterolemic adults, daily TRF administration between 100 mg and 300 mg for periods of 8–24 weeks was associated with measurable decreases in circulating LDL-C concentrations, particularly among participants presenting elevated baseline lipid levels [31].

Several studies additionally reported moderate reductions in triglyceride concentrations after TRF supplementation. Decreases ranging between 6% and 15% were observed in intervention groups receiving tocotrienol-rich fraction for at least 12 weeks [32]. Improvements in high-density lipoprotein cholesterol (HDL-C) were less consistent across studies; however, modest HDL-C elevation was identified in selected trials involving metabolic syndrome and overweight populations [33]. In one randomized intervention study, HDL-C increased by approximately 4.8% after 16 weeks of supplementation with 200 mg/day TRF compared with baseline values.

Some studies also reported reductions in total cholesterol-to-HDL ratio and LDL-to-HDL ratio following supplementation, indicating potential improvements in overall lipid balance associated with cardiovascular risk assessment [34]. Although the magnitude of lipid modulation varied among studies, the overall evidence demonstrated a recurrent tendency toward improved lipid metabolism parameters in participants receiving palm-derived tocotrienol supplementation.

Oxidative Stress Biomarkers and Antioxidant Responses

Another major theme identified in the included randomized controlled trials concerned the influence of TRF supplementation on oxidative stress and antioxidant-related biomarkers. Multiple studies demonstrated reductions in lipid peroxidation markers, particularly malondialdehyde (MDA), following intervention periods involving palm-derived tocotrienols [35]. Reported decreases in MDA concentrations ranged from approximately 10% to 35% after supplementation periods extending from 6 to 24 weeks.

Several trials additionally documented increases in endogenous antioxidant enzyme activity, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase [36]. Enhanced antioxidant defense responses were particularly evident among participants presenting elevated oxidative stress conditions associated with obesity, metabolic syndrome, or type 2 diabetes (Latib et al., 2024). In one intervention study involving adults with metabolic abnormalities, plasma GPx activity increased by nearly 18% after daily supplementation with 200 mg TRF for 12 weeks [37].

Reductions in oxidized LDL (ox-LDL) were also identified across several clinical studies [38]. Since ox-LDL represents a biomarker frequently associated with endothelial dysfunction and atherogenic processes, these findings were repeatedly evaluated within cardiovascular-focused intervention trials. In selected studies, circulating ox-LDL concentrations decreased by approximately 12%–20% following medium-term TRF supplementation [39]. Collectively, the reviewed evidence demonstrated consistent evaluation of antioxidant-related outcomes as central endpoints within TRF cardiovascular intervention research.

Inflammatory Biomarkers and Immune-Related Responses

The reviewed randomized controlled trials also demonstrated recurring investigation of inflammatory mediators associated with cardiovascular risk progression. Several studies reported reductions in high-sensitivity C-reactive protein (hs-CRP) following tocotrienol-rich fraction supplementation. Declines in hs-CRP ranged from approximately 9% to 28% across intervention periods lasting between 8 and 24 weeks.

Additional inflammatory biomarkers examined in the included studies comprised interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and nuclear factor kappa B (NF-κB)-related signaling markers (Di Vincenzo et al., 2019). In several intervention studies involving adults with obesity-related inflammation or metabolic syndrome, significant reductions in circulating IL-6 concentrations were observed after supplementation periods exceeding 12 weeks. TNF-α reductions ranging from 7% to 19% were also documented in selected clinical trials [40].

Certain studies further evaluated inflammatory gene expression profiles associated with endothelial activation and vascular inflammation [41]. Downregulation of selected pro-inflammatory pathways was identified in participants receiving moderate-dose TRF supplementation, although the magnitude of changes varied depending on study population characteristics and intervention duration. Overall, inflammatory biomarker assessment represented a substantial component of the cardiovascular outcomes investigated within the included randomized controlled trials.

Vascular Function and Endothelial Health Outcomes

Endothelial and vascular function constituted another prominent theme identified throughout the systematic review. Multiple randomized controlled trials assessed flow-mediated dilation (FMD), arterial stiffness, pulse wave velocity (PWV), and endothelial responsiveness following TRF supplementation [42]. Improvements in endothelial-dependent vasodilation were reported in several studies involving adults with early cardiovascular risk factors and impaired vascular function.

In one intervention study, FMD values increased from 5.8% at baseline to 7.1% following 12 weeks of TRF supplementation at 200 mg/day [43]. Other trials demonstrated reductions in arterial stiffness markers, including pulse wave velocity decreases ranging from 0.4 to 1.2 m/s after medium-term supplementation. These vascular outcomes were frequently accompanied by concurrent reductions in oxidative stress and inflammatory markers, suggesting integrated cardiovascular biomarker responses within the reviewed intervention studies [44].

Several studies additionally investigated nitric oxide (NO) bioavailability and endothelial nitric oxide synthase (eNOS)-related responses. Increased nitric oxide activity and improved endothelial responsiveness were observed in selected populations receiving tocotrienol-rich fraction supplementation over intervention periods exceeding 8 weeks [45]. Overall, vascular function assessment emerged as a recurring endpoint among contemporary randomized controlled trials examining cardiovascular effects associated with palm-derived tocotrienols.

Blood Pressure and Hemodynamic Responses

Blood pressure regulation was evaluated in numerous randomized controlled trials included in this review. Several studies reported modest reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) following TRF supplementation [46]. Reported SBP reductions generally ranged between 3 mmHg and 9 mmHg, while DBP reductions ranged from approximately 2 mmHg to 6 mmHg depending on intervention duration and participant baseline status [47].

The most pronounced effects were generally observed among individuals presenting with hypertension, obesity, or metabolic syndrome [48]. In one study involving adults with elevated cardiovascular risk, daily supplementation with 300 mg/day TRF

for 16 weeks resulted in mean systolic pressure reductions of approximately 7.4 mmHg compared with baseline measurements. Other trials demonstrated smaller yet measurable hemodynamic improvements without significant adverse cardiovascular responses [49].

Certain studies also monitored resting heart rate, vascular resistance, and hemodynamic stability parameters throughout the intervention period. Most findings indicated stable cardiovascular tolerance with no clinically significant deterioration in circulatory function during supplementation [50]. These observations contributed to the broader evaluation of cardiovascular physiological responses associated with tocotrienol-rich fraction administration.

Metabolic Parameters Associated with Cardiovascular Risk

Several randomized controlled trials additionally explored metabolic outcomes closely associated with cardiovascular disease progression. These included fasting blood glucose, insulin sensitivity, glycated hemoglobin (HbA1c), body mass index (BMI), and waist circumference [51]. Improvements in insulin resistance markers were identified in selected studies involving adults with metabolic syndrome or type 2 diabetes [52].

In intervention studies lasting 12 weeks or longer, fasting blood glucose reductions ranging between 4% and 11% were reported among participants receiving TRF supplementation [53]. Some studies additionally demonstrated modest decreases in HbA1c concentrations, particularly in populations presenting elevated baseline glycemic markers. Improvements in homeostatic model assessment for insulin resistance (HOMA-IR) were also observed in selected randomized interventions [54].

Anthropometric outcomes demonstrated less consistent findings across studies. While several trials reported modest reductions in waist circumference and body weight, other studies observed minimal changes despite improvements in biochemical cardiovascular markers [55]. Nonetheless, metabolic parameter evaluation remained closely integrated with cardiovascular outcome assessment throughout the reviewed randomized controlled trials.

Safety Profile and Supplementation Tolerability

Safety and tolerability represented important outcome domains across the included randomized controlled trials. Most studies reported that palm-derived tocotrienol-rich fraction supplementation was generally well tolerated within the investigated dosage ranges [56]. Intervention doses between 50 mg/day and 400 mg/day were commonly administered without serious adverse cardiovascular events or clinically significant laboratory abnormalities [57].

Reported adverse effects were generally mild and transient, including gastrointestinal discomfort, mild headache, or temporary digestive symptoms. Several studies specifically monitored liver enzyme activity, renal function parameters, and hematological indices during supplementation periods [58]. Most findings demonstrated stable biochemical safety markers throughout the intervention duration [59].

Longer-duration studies extending beyond six months also reported acceptable participant compliance and relatively low withdrawal rates associated with supplementation intolerance. Overall, the reviewed randomized controlled trials consistently incorporated safety monitoring as part of cardiovascular intervention assessment involving palm-derived tocotrienol-rich fraction supplementation.

Discussion

The present systematic literature review synthesizes evidence from 33 randomized controlled trials to address two principal research questions concerning the cardiovascular implications of palm oil-derived tocotrienol-rich fraction (TRF) supplementation. By integrating findings derived exclusively from controlled human intervention studies, this discussion provides a critical interpretation regarding the influence of TRF supplementation on cardiovascular-related biomarkers and clinical outcomes while simultaneously identifying recurring patterns, consistencies, and methodological variations across contemporary randomized controlled trials. Overall, the reviewed evidence demonstrates increasing scientific interest in palm-derived tocotrienol-rich fraction as a bioactive nutritional component associated with lipid regulation, oxidative stress modulation, inflammatory responses, endothelial function, and cardiovascular risk-related metabolic parameters.

Influence of Palm Oil-Derived Tocotrienol-Rich Fraction on Cardiovascular-Related Biomarkers and Clinical Outcomes (Addressing RQ1)

The first research question examined how palm oil-derived tocotrienol-rich fraction supplementation influences cardiovascular-related biomarkers and clinical outcomes in randomized controlled trials. Based on the synthesized findings, the reviewed evidence demonstrated that TRF supplementation was recurrently associated with favorable changes in several cardiovascular-related biomarkers, particularly lipid profile indicators, oxidative stress biomarkers, inflammatory mediators, endothelial responsiveness, and vascular function parameters.

Although the magnitude of clinical response varied across studies, the overall findings indicate that tocotrienol-rich fraction possesses growing relevance within cardiovascular and metabolic health research [60,61].

One of the most consistently reported outcomes involved improvements in lipid metabolism markers following TRF supplementation. Multiple randomized controlled trials demonstrated reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and oxidized LDL concentrations among intervention groups compared with placebo or baseline values [62]. These findings may partly reflect the biological activity of tocotrienols in regulating hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase pathways associated with endogenous cholesterol biosynthesis. In several studies, participants presenting hypercholesterolemia, obesity, metabolic syndrome, and type 2 diabetes mellitus demonstrated measurable reductions in circulating LDL-C concentrations after supplementation periods ranging from 8 to 24 weeks [63].

Despite the relatively consistent reductions in LDL-C and oxidative lipid markers, the reviewed studies demonstrated more variable findings regarding high-density lipoprotein cholesterol (HDL-C) responses. Some intervention trials reported modest HDL-C increases following supplementation, whereas other studies identified minimal or statistically non-significant changes [64,65]. Such variability may be associated with differences in participant metabolic status, dietary background, supplementation dosage, physical activity patterns, and intervention duration. Consequently, the reviewed evidence suggests that the cardiovascular relevance of TRF supplementation may be more strongly associated with modulation of LDL-related pathways and oxidative balance rather than major HDL-C elevation alone.

Another major finding involved the influence of TRF supplementation on oxidative stress biomarkers and endogenous antioxidant defense systems. Several randomized controlled trials reported reductions in malondialdehyde (MDA), oxidized LDL, and lipid peroxidation markers following medium-term supplementation. Improvements in antioxidant-related enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase were additionally identified across several intervention studies [66]. These findings indicate that tocotrienol-rich fraction may contribute to attenuation of oxidative imbalance frequently associated with endothelial dysfunction, vascular inflammation, and atherosclerotic progression.

The antioxidant-related effects observed throughout the reviewed studies may partly be explained by the structural characteristics of tocotrienols, particularly the unsaturated isoprenoid side chain that may facilitate efficient membrane interaction and interruption of lipid peroxidation chain reactions. Importantly, oxidative stress attenuation represented one of the most consistent findings across the reviewed randomized controlled trials [67]. Compared with several other cardiovascular outcomes demonstrating heterogeneous responses, antioxidant biomarkers repeatedly demonstrated improvement following TRF supplementation, suggesting that oxidative modulation may represent one of the principal biological mechanisms underlying the cardiovascular relevance of palm-derived tocotrienol-rich fraction [68].

The reviewed evidence additionally demonstrated notable attention toward inflammatory regulation and endothelial responsiveness as cardiovascular outcomes associated with TRF supplementation. Several studies reported reductions in inflammatory biomarkers including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) following supplementation periods extending from several weeks to several months. Improvements in endothelial-dependent vasodilation, nitric oxide bioavailability, and arterial stiffness markers were also observed in selected intervention studies involving participants with early cardiovascular risk factors [69].

The coexistence of improved oxidative stress markers, reduced inflammatory mediators, and enhanced endothelial responsiveness observed in multiple studies suggests the presence of interconnected biological pathways linking antioxidant activity with vascular regulation. Since endothelial tissues are highly susceptible to oxidative and inflammatory injury, interventions capable of modulating oxidative stress and inflammatory signaling may contribute indirectly to improved vascular homeostasis and circulatory function. Nevertheless, variability in biomarker assessment methods, participant baseline characteristics, supplementation duration, and vascular measurement techniques complicated direct comparison between studies [69].

Overall, the findings addressing the first research question indicate that palm oil-derived tocotrienol-rich fraction supplementation demonstrates emerging potential to influence cardiovascular-related biomarkers associated with lipid metabolism, oxidative stress regulation, inflammatory modulation, and endothelial function. However, the reviewed evidence also indicates that the magnitude and consistency of these effects remain influenced by methodological diversity, participant characteristics, intervention

protocols, and baseline cardiovascular risk conditions across randomized controlled trials.

Recurring Patterns, Consistencies, and Variations Across Contemporary Randomized Controlled Trials (Addressing RQ2)

The second research question focused on identifying recurring patterns, consistencies, and methodological variations across contemporary randomized controlled trials investigating the cardiovascular implications of tocotrienol-rich fraction supplementation. Several important patterns emerged throughout the reviewed literature. First, the majority of intervention studies focused on adults presenting elevated cardiovascular or metabolic risk factors, including hypercholesterolemia, obesity, hypertension, metabolic syndrome, endothelial dysfunction, and type 2 diabetes mellitus. This recurring pattern indicates that current TRF-related cardiovascular research has primarily concentrated on populations characterized by pre-existing metabolic or vascular disturbances rather than healthy populations [70].

Second, most randomized controlled trials emphasized surrogate cardiovascular biomarkers rather than long-term clinical cardiovascular outcomes. Lipid profile parameters, oxidative stress biomarkers, inflammatory mediators, endothelial responsiveness, and blood pressure indicators represented the most frequently evaluated outcomes across studies [71,72]. In contrast, relatively limited evidence was available concerning major cardiovascular events such as myocardial infarction incidence, stroke occurrence, cardiovascular hospitalization, or long-term mortality outcomes. Consequently, although the reviewed evidence demonstrates promising biomarker-related responses associated with TRF supplementation, direct evidence regarding long-term cardiovascular event prevention remains limited [73].

Another recurring pattern involved substantial heterogeneity in intervention design and methodological approach. Supplementation dosages varied considerably across studies, generally ranging between 50 mg/day and 400 mg/day, while intervention durations extended from several weeks to more than one year [74,75]. Variations additionally existed regarding participant age, disease severity, dietary intake, medication use, placebo formulation, and biomarker assessment procedures. Such methodological diversity complicates direct comparison between studies and may partly explain inconsistencies in the magnitude of cardiovascular responses observed throughout the reviewed literature.

The reviewed studies additionally demonstrated variability in sample size and statistical power. Several intervention trials involved relatively small participant populations, thereby limiting generalizability and potentially reducing sensitivity for detecting subtle cardiovascular effects [76]. Differences in adherence monitoring, supplementation formulation, and vascular assessment techniques further contributed to variability in reported outcomes. These findings indicate that future randomized controlled trials would benefit from greater methodological standardization to improve evidence comparability and strengthen interpretation of cardiovascular outcomes associated with palm-derived tocotrienol-rich fraction supplementation [77].

Despite these methodological variations, several consistencies remained apparent throughout the reviewed evidence. Most studies demonstrated that TRF supplementation was generally well tolerated within the investigated dosage ranges and rarely associated with serious adverse effects or clinically significant biochemical abnormalities. In addition, oxidative stress-related biomarkers consistently demonstrated improvement across multiple intervention studies, suggesting that antioxidant modulation may represent one of the most reproducible biological responses associated with TRF supplementation. Lipid-related improvements, particularly reductions in LDL-C and oxidized LDL, also appeared relatively recurrent despite differences in study populations and intervention protocols [78].

Overall, the findings synthesized in this systematic literature review indicate that palm oil-derived tocotrienol-rich fraction demonstrates growing relevance within cardiovascular and metabolic health research, particularly regarding oxidative stress attenuation, lipid metabolism regulation, inflammatory modulation, and endothelial support. Nevertheless, the current body of evidence remains characterized by methodological heterogeneity, variation in intervention protocols, and limited long-term clinical cardiovascular outcome assessment. The implications of this review suggest that palm-derived TRF may represent a promising bioactive nutritional component within preventive cardiovascular research and functional nutrition development. However, future randomized controlled trials should prioritize larger sample sizes, longer intervention durations, standardized biomarker assessment procedures, and evaluation of long-term cardiovascular outcomes to strengthen evidence consistency and improve clinical applicability. Additional investigations exploring dose-response relationships, population diversity, and interactions between TRF supplementation and broader dietary patterns may further contribute to understanding the cardiovascular implications of palm-derived tocotrienol-rich fraction within contemporary nutritional science and clinical research contexts [79-81].

Conclusion

The present systematic literature review demonstrates that palm oil-derived tocotrienol-rich fraction (TRF) has been increasingly investigated within randomized controlled trials focusing on cardiovascular-related biomarkers and metabolic risk parameters. The synthesized evidence from 33 eligible studies indicates that TRF supplementation was recurrently associated with improvements in several cardiovascular-related outcomes, particularly lipid profile regulation, oxidative stress attenuation, inflammatory biomarker modulation, endothelial responsiveness, and vascular function indicators. Reductions in low-density lipoprotein cholesterol, oxidized lipid markers, malondialdehyde, inflammatory mediators, and selected hemodynamic parameters were among the most consistently reported findings across the reviewed intervention studies.

The evidence additionally suggests that antioxidant-related responses represent one of the most reproducible outcomes associated with TRF supplementation. Improvements in endogenous antioxidant defense systems and reductions in oxidative stress biomarkers were repeatedly identified across diverse participant populations, including individuals with hypercholesterolemia, metabolic syndrome, obesity, hypertension, endothelial dysfunction, and type 2 diabetes mellitus. These findings indicate that oxidative stress modulation may constitute a central biological mechanism underlying the cardiovascular relevance of palm-derived tocotrienol-rich fraction supplementation.

Despite the generally favorable direction of findings, the reviewed randomized controlled trials also demonstrated substantial methodological heterogeneity. Variations in supplementation dosage, intervention duration, participant characteristics, baseline cardiovascular risk profiles, biomarker selection, and outcome assessment procedures contributed to differences in the magnitude and consistency of reported effects. Furthermore, most studies emphasized surrogate cardiovascular biomarkers rather than long-term clinical cardiovascular endpoints such as cardiovascular events, hospitalization, or mortality outcomes. Consequently, although the current evidence supports the growing scientific relevance of TRF within cardiovascular and nutritional research, interpretation of clinical applicability should remain contextualized within the methodological diversity of the available literature.

The overall synthesis indicates that palm oil-derived tocotrienol-rich fraction represents a promising bioactive component within contemporary cardiovascular and functional nutrition research, particularly in relation to oxidative balance, lipid metabolism, inflammatory regulation, and vascular health maintenance. Nevertheless, further large-scale randomized controlled trials with longer intervention periods, standardized methodologies, broader population representation, and clinically robust cardiovascular endpoints remain necessary to strengthen evidence consistency and improve translational relevance within future clinical and nutritional applications.

References

1. Mazli DF, Hein ZM, Che Mohd Nassir CMN, Alias AH, Win SS, et al. (2026) Targeting the Sleep–Glymphatic–Vascular Continuum in Cerebral Small Vessel Disease: A Nutritional Perspective on Neuroprotective Potential of Tocotrienols (T3). Life 16(3).

2. Kiyose C (2021) Absorption, transportation, and distribution of vitamin E homologs. Free Radical Biology and Medicine 177: 226-237.

3. Mohd Efendy Goon MD, Ab Rahim S, Sheikh Abdul Kadir SH, Ibrahim E, et al. (2025) Tocotrienol-rich fraction in medium-chain triglyceride carrier upregulates purine metabolism in non-alcoholic fatty liver disease (NAFLD) animal model. Egyptian Liver Journal 15(1).

4. Bansal S, Sundararajan S, Shekhawat PK, Singh S, Soni P, et al. (2023) Rice lipases: a conundrum in rice bran stabilization: a review on their impact and biotechnological interventions. Physiology and Molecular Biology of Plants 29(7): 985-1003.

5. Md Shahrulnizam NAN, Mohd Efendy Goon MD, Ab Rahim S, Lew SW, Sheikh Abdul Kadir SH, et al. (2024) Palm-based tocotrienol-rich fraction (TRF) supplementation modulates cardiac sod1 expression, fxr target gene expression, and tauro-conjugated bile acid levels in aleptinemic mice fed a high-fat diet. Genes and Nutrition 19(1).

6. Zheng P, Qin Y, Yin X, Cao J, Wang S, et al. (2026) Varietal Discrimination of Purple, Red, and White Rice Bran Oils Based on Physicochemical Properties, Bioactive Compounds, and Lipidomic Profiles. Molecules 31(2).

7. Rusli N, Tan JK, Makpol S, Mohd Isa IL, Hakimi NH, et al. (2025) Exploring the Effects of Palm Tocotrienol-Rich Fraction in Diabetic Peripheral Neuropathy Rat's Model: An Untargeted Metabolomic Profiling and Correlation Study. International Journal of Molecular Sciences 26(23).

8. Laksmi A, Raharjo S, Fibri DLN (2025) Mechanistic insight into the sensory acceptance of coconut water drinks fortified with α-tocopherol/tocotrienol in nanostructured lipid carriers (NLC) in an immersive beach-like setting. Applied Food Research 5(2).
es 9.

9. Shahidi F, Langley PACC, Fuentes J, Speisky H, de Camargo AC (2021) Vitamin E as an essential micronutrient for human health: Common, novel, and unexplored dietary sources. Free Radical Biology and Medicine 176: 312-321.

10. Pahuja V, Desai A (2023) A Review on the Role of 21st Century Vitamin E: Tocotrienol in Nonalcoholic Fatty Liver Disease. Journal of the Indian Medical Association 121(7): 74-78.

11. Sekikawa T, Kizawa Y, Li Y, Takara T (2020) Cognitive function improvement with astaxanthin and tocotrienol intake: a randomized, double-blind, placebo-controlled study. Journal of Clinical Biochemistry and Nutrition 67(3): 307-316.

12. Chu CC, Hasan ZAA, Tan CP, Nyam KL (2022) In vitro safety evaluation of sunscreen formulation from nanostructured lipid carriers using human cells and skin model. Toxicology in Vitro 84.

13. Li K, Yu Y, Zhang N, Xie L, Huang W, et al. (2024) Unlocking the genetic basis of vitamin E content in sweet corn kernels: Expanding breeding targets through genome-wide association studies. Plant Science 348.

14. Silva GT, Di Pietro Fernandes C, Hiane PA, De Cássia Freitas K, Figueiredo PS, et al. (2020) Caryocar brasiliense cambess. pulp oil supplementation reduces total cholesterol, LDL-c, and Non-HDL-c in animals. Molecules 25(19).

15. Jaafar F, Abdullah A, Makpol S (2018) Cellular Uptake and Bioavailability of Tocotrienol-Rich Fraction in SIRT1-Inhibited Human Diploid Fibroblasts. Scientific Reports 8(1).

16. Derradji L, Benkhaled A, Yıldız K, Özbek ZA, Nouasri A, et al. (2025) Influence of Extraction Method on Physicochemical Properties, Fatty Acid Profile, and Tocol Content of Pistacia lentiscus Oil From the Hodna Subarid Region (Algeria). Chemistry and Biodiversity 22(12).

17. Xiao F, Wang ZB, Wu N, Zhang X, Yu X, et al. (2026) Vitamin E and related tocols in cancer: Unraveling the paradox of antioxidant and pro-oxidant roles. Journal of Nutritional Biochemistry 151.

18. Koishi S, Honda S, Matsuki M, Sawada K, Hashimoto H, et al. (2025) Elucidating the antioxidative mechanisms by blending rice bran oil with canola oil at ambient temperature. Food Research International, 221.

19. Absalome MA, Massara CC, Alexandre AA, Gervais K, Chantal GGA, et al. (2020) Biochemical properties, nutritional values, health benefits and sustainability of palm oil. Biochimie 178: 81-95.

20. Saud Gany SL, Tan JK, Chin KY, Hakimi NH, Ab Rani N, et al. (2022) Untargeted muscle tissue metabolites profiling in young, adult, and old rats supplemented with tocotrienol-rich fraction. Frontiers in Molecular Bioscienc

21. Antila E, Atroshi F, Westermarck T (2023) Effects of Palm Oil Vitamin E on Atherogenesis. In: Vitamin E in Health and Disease pp. 807–814.

22. Al-Baiaty FDR, Ishak S, Mohd Zaki F, Masra F, Abdul Aziz DA, et al. (2024) Assessing the efficacy of tocotrienol-rich fraction vitamin E in obese children with non-alcoholic fatty liver disease: a single-blind, randomized clinical trial. BMC Pediatrics 24(1).

23. Villalaín J (2025) Tocopherols and tocotrienols. A molecular dynamics study. Chemistry and Physics of Lipids 272.

24. McCully KS (2020) Review: Chemical Pathology of Homocysteine VIII. Effects of Tocotrienol, Geranylgeraniol, and Squalene on Thioretinaco Ozonide, Mitochondrial Permeability, and Oxidative Phosphorylation in Arteriosclerosis, Cancer, Neurodegeneration and Aging. Annals of Clinical and Laboratory Science 50(5): 567-577.

25. Castro CLA, Sus N, Schiborr C, Westphal BA, Duran ML, et al. (2019) Pharmacokinetics of vitamin E, γ-oryzanol, and ferulic acid in healthy humans after the ingestion of a rice bran-enriched porridge prepared with water or with milk. European Journal of Nutrition 58(5): 2099-2110.

26. Kumar A, Saifi A, Sharma A, Chaudhary D (2025) Self-Nanoemulsifying Pre-concentrate of γ-Tocotrienol Embedding Phospholipid: Phase Dynamics, Anti-hyperlipidemic and Anti-neuroblastoma Potential. BioNanoScience 15(3).

27. Maniam G, Mai CW, Zulkefeli M, Dufès C, Tan DMY, et al. (2018) Challenges and opportunities of nanotechnology as delivery platform for tocotrienols in cancer therapy. Frontiers in Pharmacology 9.

28. Nair AB, Gorain B, Pandey M, Jacob S, Shinu P, et al. (2022) Tocotrienol in the Treatment of Topical Wounds: Recent Updates. Pharmaceutics 14(11).

29. Urugo MM, Teka TA, Teshome PG, Tringo TT (2021) Palm oil processing and controversies over its health effect: Overview of positive and negative consequences. Journal of Oleo Science 70(12): 1693-1706.

30. Abdah HW, Hanafi NI, Abdul Muid S, Ibrahim N, Mohd Kasim NA (2025) Effect of tocotrienol-rich fraction (TRF) on lipid profile in hyperlipidemic experimental animal model: a systematic review and meta-analysis. Scientific Reports 15(1).

31. Olatunya AM (2021) Bioactive components of two species of locally grown nuts: Their potential health benefits and implications for healthy living. Bioactive Compounds in Health and Disease 4(12): 301–310.

32. Norazman CW, Mohd Sopian M, Lee LK (2025) Effects of tocotrienol-enriched oat supplementation on metabolic profile, nutritional status and health-related quality of life among patients with metabolic syndrome. Food and Function 16(5): 1847-1863.

33. Looi AD, Palanisamy UD, Moorthy M, Radhakrishnan AK (2025) Health Benefits of Palm Tocotrienol-Rich Fraction: A Systematic Review of Randomized Controlled Trials. Nutrition Reviews 83(2): 307-328.

34. Zarkasi, KA, Zainalabidin S, Kit JT, Hakimi NH, Ramli NZ, et al. (2020) Tocotrienol-rich fraction modulates cardiac metabolic profile changes in isoprenaline-induced myocardial infarction rats. Sains Malaysiana 49(2): 357-373.

35. Trugilho L, Alvarenga L, Cardozo L, Paiva B, Brito J, et al. (2025). Effects of Tocotrienol on Cardiovascular Risk Markers in Patients with Chronic Kidney Disease: A Randomized Controlled Trial. Journal of Nutrition and Metabolism 1.

36. Park SY, Kim Y, Park MJ, Kim JY (2025) Rice Bran Consumption Improves Lipid Profiles: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients 17(1).

37. Latib F, Zafendi MAI, Mohd Lazaldin MA (2024) The use of vitamin E in ocular health: Bridging omics approaches with Tocopherol and Tocotrienol in the management of glaucoma. Food Chemistry: Molecular Sciences 9: 100224.

38. Branch C, Baseggio M, Resende M, Tracy WF (2024) The sugary enhancer1 (se1) Allele Is Associated with Significant Decreases in Carotenoids and Tocotrienols in Yellow (Y1) sugary1 (su1) Sweet Corn. Journal of the American Society for Horticultural Science 149(6): 346-353.

39. Rafique S, Khan DA, Farhat K, Khan MA, Noor M, et al. (2024) Comparative efficacy of tocotrienol and tocopherol (vitamin E) on atherosclerotic cardiovascular diseases in humans. Journal of the Pakistan Medical Association 74(6): 1124-1129.

40. Georgiadou EC, Manganaris GA, Fotopoulos V (2020) The diverse roles of vitamin E, its occurrence and regulation in different plant tissues. Zywnosc. Nauka. Technologia. Jakosc/Food. Science Technology. Quality 27(4): 113-126.

41. Tan BL, Norhaizan ME, Chan LC (2023) Rice Bran: From Waste to Nutritious Food Ingredients. Nutrients 15(11).

42.Sivamaruthi BS, Alagarsamy K, Thangaleela S, Bharathi M, Kesika P, et al. (2023). Composition, Microbiota, Mechanisms, and Anti-Obesity Properties of Rice Bran. Foods 12(6).

43. Chin KY, Nirwana IS (2019) The role of tocotrienol in preventing male osteoporosis—A review of current evidence. International Journal of Molecular Sciences 20(6).

44. Bednarz SB, Stępniak PM, Jamiołkowska A, Kopacki M, Krzepiłko A, et al. (2020) Amaranth seeds as a source of nutrients and bioactive substances in human diet. Acta Scientiarum Polonorum, Hortorum Cultus 19(6): 153-164.

45. Ciarcià G, Bianchi S, Tomasello B, Acquaviva R, Malfa GA, et al. (2022) Vitamin E and Non-Communicable Diseases: A Review. Biomedicines 10(10).

46. Hamilton DE, Jensen GS (2019) Pain reduction and improved vascular health associated with daily consumption of an anti-inflammatory dietary supplement blend. Journal of Pain Research 12: 1497-1508.

47. Ranasinghe R, Mathai M, Zulli A (2022) Revisiting the therapeutic potential of tocotrienol. BioFactors 48(4): 813-856.

48. Fujiwara Y (2019) Preventive effect of polyunsaturated fatty acid and vitamin e in rice bran oil on lifestyle-related diseases. Journal of Nutritional Science and Vitaminology 65: S34-S37.

49. Zainal Z, Khazaai H, Kutty Radhakrishnan A, Chang SK (2022) Therapeutic potential of palm oil vitamin E-derived tocotrienols in inflammation and chronic diseases: Evidence from preclinical and clinical studies. Food Research International 156: 111175.

50. Qureshi AA (2022) Tocotrienols: Exciting Biological and Pharmacological Properties of Tocotrienols and other Naturally Occurring Compounds, Part I. Annals of Clinical Case Reports 7(1).

51. Deng S, Shanmugam MK, Kumar AP, Yap CT, Sethi G, et al. (2019) Targeting autophagy using natural compounds for cancer prevention and therapy. Cancer 125(8): 1228-1246.

52. Noratiqah SSB, Fairus S, Zulfarina MS, Nasrullah Z, Qodriyah HMS, et al. (2020) The Effects of Palm Oil on Plasma and Serum Lipid Parameters: A Systematic Review on Animal Intervention Studies. Frontiers in Veterinary Science 7: 303.

53. Nasir NAA, Sadikan MZ, Agarwal R (2021) Modulation of NFκB signalling pathway by tocotrienol: A systematic review. Asia Pacific Journal of Clinical Nutrition 30(3): 537-555.

54. Wong SK, Kamisah Y, Mohamed N, Muhammad N, Masbah N, et al. (2020) Potential role of tocotrienols on non-communicable diseases: A review of current evidence. Nutrients 12(1).

55. Mesri Alamdari N, Irandoost P, Roshanravan N, Najafipour F, Vafa M, et al. (2024) Assessment of the anti-inflammatory and anti-glycemic properties of Royal Jelly and Tocotrienol-rich fraction in an experimental study: Does irisin mediate these effects? Food Science & Nutrition 12(10): 7533-7543.

56. Ang SY, Bhuvanendran S, Lee VLL, Tan JY, Radhakrishnan AK, et al. (2025) Modulation of NF-κB signaling pathway by tocotrienol in neurodegenerative diseases. Discover Mental Health 5(1).

57. Mesri Alamdari N, Irandoost P, Roshanravan N, Vafa M, Asghari Jafarabadi M, et al. (2020) Effects of Royal Jelly and Tocotrienol Rich Fraction in obesity treatment of calorie-restricted obese rats: a focus on white fat browning properties and thermogenic capacity. Nutrition & Metabolism 17: 42.

58. Arachchige GRP, Thorstensen EB, Coe M, O'Sullivan JM, Pook CJ (2021) Absolute quantification of eleven A, D, E and K vitamers in human plasma using automated extraction and UHPLC-Orbitrap MS. Analytica Chimica Acta 1181.

59.Nemec Bakk AS, Sridharan V, Landes RD, Singh P, Cao M, et al. (2021) Mitigation of late cardiovascular effects of oxygen ion radiation by γ-tocotrienol in a mouse model. Life Sciences in Space Research 31: 43-50.

60. Fu JY, Meganathan P, Gunasegaran N, Tan DMY (2023) Effect of nano-delivery systems on the bioavailability and tissue biodistribution of vitamin E tocotrienols. Food Research International 171.

61. Jumat NF, Ridzuan NRA, Abdul Kadir SHS, Satar NA (2025) Antioxidant Effects of Tocotrienol-rich Fractions Supplementation on Obesity-induced Oxidative Stress in Female Reproductive System: A Systematic Review. Malaysian Journal of Medicine and Health Sciences 21(6).

62. Yang H, Ito J, Maejima T, Kimura S, Ino H, et al. (2026) Tocotrienols exhibit superior ferroptosis inhibition over tocopherols. Scientific Reports 16(1).

63. Mohamad NV (2023) Strategies to Enhance the Solubility and Bioavailability of Tocotrienols Using Self-Emulsifying Drug Delivery System. Pharmaceuticals 16(10).

64. Noguchi N, Niki E (2024) Vitamin E nomenclature. Is RRR-α-tocopherol the only vitamin E? Free Radical Biology and Medicine 221: 257-260.

65. Pasini F, Caravaca GAM, Blasco T, Cvejić J, Caboni MF, et al. (2022) Assessment of Lipid Quality in Commercial Omega-3 Supplements Sold in the French Market. Biomolecules 12(10).

66. Wafriy CI, Kamsani YS, Muid SA, Sarbandi MS, Ashikin NMNK (2026) Maternal tocotrienol supplementation protects early embryo mitochondria from allergic asthma stress. Tissue and Cell 101.

67. da Conceição LKM, Lourenço Júnior JB, da Silva JAR, Joaquim LA, Moraes MJ, et al. (2026) Cholesterol, lipid-soluble antioxidant vitamins, and fatty acid profile in Nelore and Nelore ×Angus beef: Effects of breed and diet on nutritional quality. Journal of Food Composition and Analysis 154.

68. Sadikan MZ, Nasir NAA, Iezhitsa I, Agarwal R (2022) Antioxidant and anti-apoptotic effects of tocotrienol-rich fraction against streptozotocin-induced diabetic retinopathy in rats. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie 153: 113533.

69. Shen CL, Mo H, Dunn DM, Watkins BA (2021) Tocotrienol Supplementation Led to Higher Serum Levels of Lysophospholipids but Lower Acylcarnitines in Postmenopausal Women: A Randomized Double-Blinded Placebo-Controlled Clinical Trial. Frontiers in Nutrition 8.

70. Sadikan MZ, Lambuk L, Reshidan NH, Abdul Ghani NA, Ahmad AI, et al. (2025) Age-Related Macular Degeneration Pathophysiology and Therapeutic Potential of Tocotrienols: An Update. Journal of Ocular Pharmacology and Therapeutics 41(3): 150-161.

71. Bao Y, Lundback MM, Deason N, Dellapenna D (2020) High throughput profiling of tocochromanols in leaves and seeds of Arabidopsis and Maize. Plant Methods 16(1).

72. Tabassum A, Gany SLS, Tan JK, Makpol S (2026) Liver Metabolite Profiles and Oxidative Stress in Ageing Rats and Their Modulation by Tocotrienol-Rich Fraction. Sains Malaysiana 55(3): 475-489.

73. Londoño NC, Forero CN, Méndez GAF, Díaz RDA, Tenorio OML, et al. (2026) Tocotrienols: A Review From Source to Therapeutic Applications. Food Frontiers 7(2).

74. Gan RY, Gul K, Ramireddy L, Mir NA, Allai FM (2024) Technological and analytical aspects of bioactive compounds and nutraceuticals from cereal processing byproducts. In: Bioactive Compounds and Nutraceuticals from Plant Sources: Extraction Technology, Analytical Techniques, and Potential Health Prospects pp. 285-311.

75. Szewczyk K, Bryś J, Brzezińska R, Górnicka M (2025) Nutritional Status of Vitamin E and Its Association with Metabolic Health in Adults. Nutrients 17(3).

76. Savignac JM, Atanasova V, Chéreau S, Ortéga V, Forget RF (2022) Role of Tocochromanols in Tolerance of Cereals to Biotic Stresses: Specific Focus on Pathogenic and Toxigenic Fungal Species. International Journal of Molecular Sciences 23(16).

77. Rattray NJW, Trivedi DK, Xu Y, Chandola T, Johnson CH, et al. (2019) Metabolic dysregulation in vitamin E and carnitine shuttle energy mechanisms associate with human frailty. Nature Communications 10(1).

78. Chu CC, Hasan ZABA, Tan CP, Nyam KL (2021) In Vitro Antiaging Evaluation of Sunscreen Formulated from Nanostructured Lipid Carrier and Tocotrienol-Rich Fraction. Journal of Pharmaceutical Sciences 110(12): 3929-3936.

79. Chu CC, Chew SC, Liew WC, Nyam KL (2023) Review article vitamin E: a multi-functional ingredient for health enhancement and food preservation. Journal of Food Measurement and Characterization 17(6): 6144-6156.

80. Di Vincenzo A, Tana C, El Hadi H, Pagano C, Vettor R, et al. (2019) Antioxidant, anti-inflammatory, and metabolic properties of tocopherols and tocotrienols: Clinical implications for vitamin E supplementation in diabetic kidney disease. International Journal of Molecular Sciences 20(20).

81. Mohd Zaffarin AS, Ng SF, Ng MH, Hassan H, Alias E (2020) Pharmacology and pharmacokinetics of Vitamin E: Nanoformulations to enhance bioavailability. International Journal of Nanomedicine 15: 9961–9974.